

RESEARCH ARTICLE

Combined serum biomarker analysis for diagnosis of periprosthetic joint infection: A retrospective cohort study

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Abstract

Objective: Periprosthetic joint infection (PJI) is a serious complication after total joint arthroplasty. Because diagnosis remains difficult, readily available serum biomarkers may provide a practical adjunct. We evaluated whether combining conventional inflammatory markers with cell-count-derived indices improved diagnostic performance compared with individual markers. **Methods:** This single-center retrospective cohort study included 176 patients who underwent hip or knee revision between May 2017 and March 2022. Eighty-six patients were diagnosed with PJI and 90 with aseptic loosening (AL). PJI was defined according to the Musculoskeletal Infection Society (MSIS) criteria. Preoperative C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and pan-immune-inflammation value (PIV) were compared between groups. Receiver operating characteristic (ROC) analyses were performed for individual markers and logistic-regression-based combinations. **Results:** CRP, ESR, PLR, NLR, and PIV were significantly higher in the PJI group, whereas LMR was significantly lower (all $P < 0.005$). ESR (AUC=0.843, 95% CI: 0.781-0.894) and CRP (AUC=0.833, 95% CI: 0.769-0.885) showed the highest discrimination. The AUCs for PLR, PIV, NLR, and LMR were 0.729, 0.697, 0.682, and 0.628, respectively. CRP+ESR achieved an AUC of 0.856 (95% CI: 0.795-0.904), and CRP+ESR+PLR achieved an AUC of 0.860 (95% CI: 0.800-0.908). The three-marker model increased sensitivity to 86.05% but reduced specificity to 73.33%, indicating a modest numerical gain in discrimination with a sensitivity-specificity trade-off. **Conclusions:** The combined use of CRP, ESR, and PLR should be considered a supplementary tool for current PJI diagnostic criteria, rather than a substitute.

Keywords: Platelet-to-lymphocyte ratio, Pan-immune-inflammation value, Diagnosis, Periprosthetic joint infection

1 INTRODUCTION

Total joint arthroplasty (TJA) is a highly successful surgical intervention for treating advanced hip and knee conditions [1]. However, periprosthetic joint infection (PJI) poses a significant

risk following TJA, which is a devastating potential complication. It is estimated that PJI occurs in approximately 1% to 3% of patients undergoing primary total hip or knee arthroplasty (THA/TKA) and in 3% to 5% of patients undergoing revision surgery [2, 3]. Musculoskeletal Infection Society (MSIS) intro-



Table 1. Definition of periprosthetic joint infection†

Diagnostic criteria	Concrete contents
Major criteria	1) Two positive periprosthetic cultures with phenotypically identical organisms; 2) A sinus tract communicating with the joint.
Minor criteria	1) Elevated serum CRP and ESR values; 2) Elevated synovial fluid white blood cell (WBC) counts OR ++changes on leukocyte esterase test strip; 3) An elevated polymorphonuclear neutrophil percentage (PMN%) in the synovial fluid; 4) Positive histological analyses of the periprosthetic tissue; 5) A single positive culture.

Note: †According to the MSIS criteria, PJI is diagnosed when a patient meets one of the two major criteria or three of the five minor criteria. PJI, periprosthetic joint infection; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

duced minor diagnostic criteria for periprosthetic joint infection (PJI) in 2013, which included serum C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) [4]. Since then, there have been significant advancements in the capability and accuracy of PJI diagnostics. However, no single diagnostic test is able to provide 100% sensitivity and specificity. A major benefit of serum biomarkers, compared to synovial fluid biomarkers, is their availability. While synovial fluid biomarkers such as Alpha-defensin have demonstrated excellent diagnostic value, their clinical application is often limited by higher costs, technical challenges, potential for false-positive results in cases of soft tissue reactions [5]. Therefore, exploring novel serum biomarkers that can enhance PJI diagnostic efficiency without imposing additional burdens on patients is of paramount importance.

Inflammation and immune response play pivotal roles in the occurrence and progression of PJI [6, 7]. The identification of effective biomarkers for PJI diagnosis is of great importance. Recent studies have highlighted the potential value of novel blood biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), in detecting PJI [8, 9]. Novel biomarkers have been constructed based on routine blood test results, thus providing clinicians with more valuable diagnostic information without increasing healthcare costs. However, the ability of novel biomarkers to diagnose PJI is controversial, and evidence regarding the incremental diagnostic value of combining these biomarkers remains limited and inconsistent. Thus, the objectives of this study are twofold: (1) to determine the diagnostic value, sensitivity, and specificity of these novel biomarkers in diagnosing PJI; and (2) to explore the potential improvement in diagnostic accuracy through the combination of multiple biomarkers. This research aims to provide valuable insights for the development of more accurate and reliable diagnostic tools for PJI.

2 MATERIALS AND METHODS

2.1 Research design

This study was a single-center retrospective cohort investigation conducted at Henan Provincial People’s Hospital. The data

collection period spanned from May 2017 to March 2022, encompassing various patient demographics such as age, gender, and preoperative biomarkers such as CRP, ESR, PLR, NLR, LMR, and PIV. Ethical approval for this study was obtained from the ethics board of Henan Provincial People’s Hospital under the reference number 2020.80.

2.2 Inclusion and exclusion criteria

The study employed specific inclusion criteria, which are outlined as follows: (i) Patients included in the study were diagnosed with PJI or AL subsequent to undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA). (ii) systematic evaluation and treatment at our institution between May 2017 and March 2022; (iii) complete data for CRP, ESR, LMR, PLR, NLR, and PIV; and (iv) classification of PJI according to the 2013 International Consensus Meeting (ICM)-modified MSIS criteria (Table 1) [4]. Aseptic loosening diagnosis relied on radiographic evaluation of circumferential radiolucency, prosthetic subsidence, changes in stem or cement position, or fractures in the cement mantle, in conjunction with patient-reported clinical symptoms of pain and instability [10, 11]. PJI was excluded in patients classified as having AL based on preoperative infection screening and intraoperative microbiological culture results, in accordance with the MSIS diagnostic criteria.

Patients were excluded if they had a periprosthetic fracture, joint dislocation, a known systemic inflammatory disease, a documented history of malignancy, or incomplete clinical data.

2.3 Laboratory evaluations of biomarkers

Fasting venous blood samples were collected from all patients on the morning of the second day after admission as part of routine clinical care and analyzed within 2 hours. CRP was measured using a PA-990 specific protein analyzer (Lifotronic Technology Co., Ltd., China), ESR using an Alifax TEST1 analyzer (Alifax, Italy), and hematologic parameters using an XN-9100 automated hematology analyzer (Sysmex, Japan).

Table 2. Baseline characteristics of the participants (N=176)

Characteristic	PJI (N=86)	AL (N=90)	Statistics
Age, (Years, Mean ± SD)	66.06±11.29	67.36±11.18	t=-0.770; P=0.442
Gender, n (%)			χ²=0.423; P=0.515
Male	35 (40.70%)	41 (45.56%)	
Female	51 (59.30%)	49 (54.44%)	
Affected joint			χ²=19.339; P<0.001
Hip, n (%)	37 (43.02%)	68 (75.56%)	
Knee, n (%)	49 (56.98%)	22 (24.44%)	

Note: PJI, periprosthetic joint infection; AL, aseptic loosening.

Table 3. Biomarker values in the PJI and AL groups (N=176), median (P25, P75)

Biomarker	PJI (N=86)	AL (N=90)	Statistics
CRP (mg/L)	20.04 (7.52, 42.75)	1.70 (0.58, 6.85)	Z=7.619; P<0.001
ESR (mm/h)	54.50 (32.75, 80.00)	15.50 (7.00, 32.00)	Z=7.864; P<0.001
LMR	3.84 (2.89, 5.60)	5.08 (3.67, 6.73)	Z=-2.929; P<0.005
PLR	185.21 (133.84, 243.93)	129.36 (91.73, 171.06)	Z=5.252; P<0.001
NLR	2.47 (1.83, 3.63)	1.89 (1.41, 2.47)	Z=4.166; P<0.001
PIV	274.60 (159.56, 551.21)	136.02 (86.56, 273.19)	Z=4.515; P<0.001

Note: PJI, periprosthetic joint infection; AL, aseptic loosening; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value.

LMR was calculated as lymphocyte count/monocyte count; PLR as platelet count/lymphocyte count; NLR as neutrophil count/lymphocyte count; and PIV as neutrophil count × mono-
cyte count × platelet count/lymphocyte count.

3 STATISTICAL ANALYSES

Statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess normality. Normally distributed continuous variables are presented as mean ± standard deviation (SD), non-normally distributed continuous variables as median (25th percentile, 75th percentile), and categorical variables as frequencies and percentages. Normally distributed continuous variables were compared using the independent-samples t test, non-normally distributed continuous variables using the Mann-Whitney U test, and categorical variables using the chi-square test. Statistical significance was defined as P<0.05. ROC analyses were performed using MedCalc version 19.0.4 (MedCalc Software, Ostend, Belgium) to estimate sensitivity, specificity, AUC, and 95% confidence intervals (CIs). Optimal cutoffs were selected using Youden’s index. For combined-marker models, binary logistic regression was used to generate predicted probabilities, which were then analyzed as composite variables in ROC analysis [12]. For the CRP+ESR+PLR model, the predicted probability of PJI was calculated as $P=1/(1+e^{-Z})$, where $Z=\beta_0+\beta_1\times\text{CRP}+\beta_2\times\text{ESR}+\beta_3\times\text{PLR}$, with β_0 representing the intercept and β_1 , β_2 , and β_3 representing the regression coefficients for CRP, ESR, and PLR, respectively. The optimal cutoffs for the combined-marker models represent predicted

probability thresholds, with higher predicted probabilities indicating a positive result for PJI.

4 RESULTS

A total of 176 patients were included: 86 in the PJI group and 90 in the AL group. Age and sex distributions did not differ significantly between groups. The distribution of the affected joint differed significantly, with a higher proportion of knee cases in the PJI group and a higher proportion of hip cases in the AL group (P<0.001). Baseline characteristics are presented in Table 2.

All evaluated biomarkers differed significantly between groups (Table 3). Compared with the AL group, the PJI group had higher median CRP, ESR, PLR, NLR, and PIV values and a lower median LMR value (all P<0.005).

The diagnostic performance of individual biomarkers is summarized in Table 4. ESR showed the highest AUC (0.843, 95% CI: 0.781-0.894), followed by CRP (0.833, 95% CI: 0.769-0.885) (Figure 1). PLR had an AUC of 0.729, whereas PIV, NLR, and LMR had lower AUCs of 0.697, 0.682, and 0.628, respectively (Figure 1).

The performance of combined models is shown in Table 5. CRP+ESR yielded an AUC of 0.856 (95% CI: 0.795-0.904), with 79.07% sensitivity and 78.89% specificity. Adding LMR produced an AUC of 0.857 without changing sensitivity or specificity. Adding PLR increased the AUC to 0.860 and sen-

Table 4. Diagnostic performance of individual biomarkers

Biomarker	AUC (95% CI)	Youden index	Optimal cut-off	Sensitivity	Specificity
CRP (mg/L)	0.833 (0.769-0.885)	0.5643	11.50	69.77%	86.67%
ESR (mm/h)	0.843 (0.781-0.894)	0.5225	32.00	75.58%	76.67%
LMR	0.628 (0.552-0.699)	0.2628	4.63	66.28%	60.00%
PLR	0.729 (0.657-0.793)	0.3894	182.58	51.16%	87.78%
NLR	0.682 (0.608-0.750)	0.3527	2.10	68.60%	66.67%
PIV	0.697 (0.623-0.764)	0.3643	189.02	69.77%	66.67%

Note: A positive result for PJI was defined as a biomarker value above the optimal cutoff for CRP, ESR, PLR, NLR, and PIV, and below the optimal cutoff for LMR. PJI, periprosthetic joint infection; AL, aseptic loosening; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value.

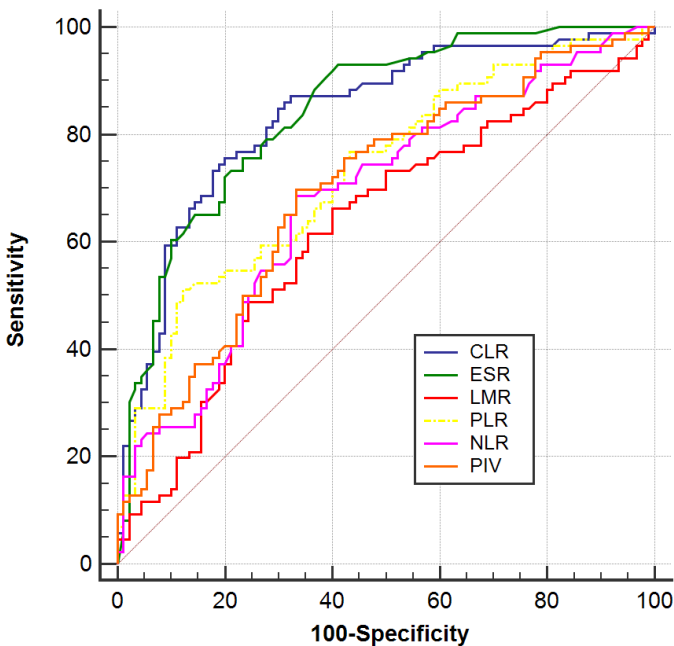


Figure 1. Receiver operating characteristic curves of individual blood biomarkers for the diagnosis of PJI. PJI, periprosthetic joint infection; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value.

sitivity to 86.05%, but specificity decreased to 73.33%. The CRP+ESR+NLR and CRP+ESR+PIV models yielded AUCs of 0.855 and 0.856, respectively. The model containing only LMR+PLR+NLR+PIV had an AUC of 0.750 (Figure 2).

5 DISCUSSION

This study compared conventional inflammatory markers with four cell-count-derived indices and evaluated their combinations for diagnosing PJI. ESR and CRP showed the strongest individual discrimination. PLR provided moderate discrimination, whereas LMR, NLR, and PIV showed lower diagnostic performance. Adding PLR to CRP+ESR increased the AUC only from 0.856 to 0.860. Although sensitivity increased to

86.05%, specificity decreased to 73.33%. Thus, the principal effect of adding PLR was a sensitivity-specificity trade-off rather than a substantial improvement in overall discrimination.

Serum biomarkers remain attractive because they are inexpensive, widely available, and do not require joint aspiration or specialized testing. By comparison, alpha-defensin testing, next-generation sequencing, and mass spectrometry may provide additional diagnostic information but generally require greater technical resources and cost [13]. Because PLR is derived from a routine complete blood count, it can be incorporated without additional blood collection or laboratory expenditure. Nevertheless, its limited standalone AUC and the reduction in specificity observed in the combined model indicate that it should complement, rather than replace, established diagnostic frameworks such as the MSIS or European Bone and Joint Infection Society criteria.

Systemic immune dysregulation is involved in the pathophysiology of PJI, which can be partially indicated by peripheral blood cells, such as neutrophils, lymphocytes, platelets and monocytes [14, 15]. Neutrophils, as the primary responders of innate immunity, show a significant increase in number, which serves as a critical immune indicator [16]. Monocytes coordinate immune responses by phagocytizing bacteria, recruiting other inflammatory cells, and presenting antigens [17]. Lymphocytes play a central role in adaptive immunity, though their function may be suppressed due to increased apoptosis [18]. In addition, platelets actively participate in the inflammatory process by releasing inflammatory mediators and interacting with immune cells [19]. Thus, the interaction of the various cells in the blood and changes in their numbers reflect the state of the host immune system. However, blood cell counts are influenced by a number of factors, and a single indicator does not accurately reflect systemic inflammation. The calculation of inflammation-related ratio markers based on white blood cell counts (monocyte count, neutrophil count, lymphocyte count) and platelet count includes LMR, NLR, PLR, and PIV. These markers, which reflect the inflammatory status of the body, have been extensively studied and found valuable in predicting

Table 5. Diagnostic performance of combined serologic parameters for PJI

Biomarker	AUC (95% CI)	Youden index	Optimal cut-off	Sensitivity	Specificity
CRP+ESR	0.856 (0.795-0.904)	0.5796	0.39	79.07%	78.89%
CRP+ESR+LMR	0.857 (0.796-0.905)	0.5796	0.39	79.07%	78.89%
CRP+ESR+PLR	0.860 (0.800-0.908)	0.5938	0.35	86.05%	73.33%
CRP+ESR+NLR	0.855 (0.794-0.904)	0.5649	0.50	70.93%	85.56%
CRP+ESR+PIV	0.856 (0.795-0.904)	0.5891	0.48	75.58%	83.33%
LMR+PLR+NLR+PIV	0.750 (0.679-0.812)	0.3930	0.50	59.30%	80.00%

Note: The optimal cutoffs represent predicted probability thresholds derived from the corresponding logistic regression models. Predicted probabilities above the respective cutoffs were considered positive for PJI. PJI, periprosthetic joint infection; AL, aseptic loosening; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value.

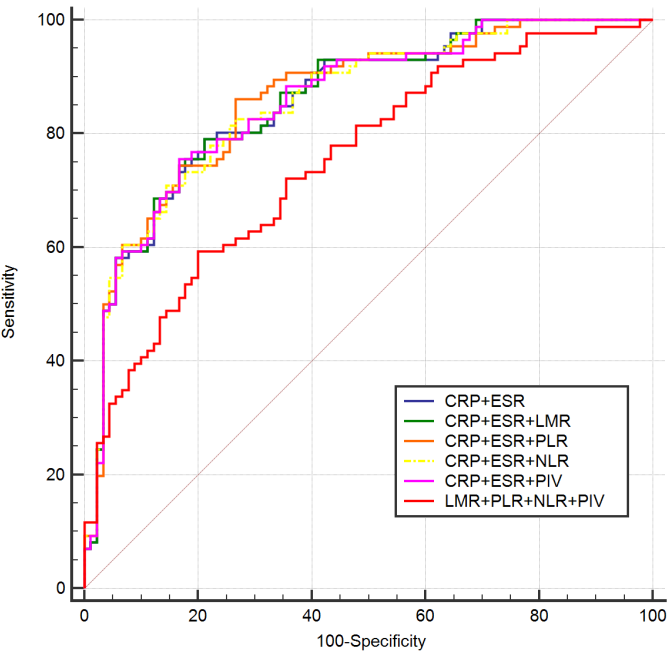


Figure 2. Receiver operating characteristic curves for the combined serum biomarker models in the diagnosis of PJI. PJI, periprosthetic joint infection; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value.

outcomes or prognosis of various diseases, including neoplastic diseases, inflammatory diseases, and infectious diseases [8, 20-23].

Published findings regarding LMR, PLR, and NLR in PJI are heterogeneous, but the apparent discrepancies occur across different clinical settings. Zhao et al. evaluated early postoperative PJI occurring 2–4 weeks after arthroplasty and measured postoperative blood-cell ratios at the time of clinical suspicion; NLR showed strong discrimination, with an AUC of 0.93 [8]. In contrast, Burchette et al. evaluated chronic PJI and reported substantially lower diagnostic performance for NLR (AUC=0.625) and LMR (AUC=0.633), concluding that these

ratios provided limited diagnostic value [9]. In a broader cohort of patients undergoing hip or knee revision surgery, Maimaiti et al. reported intermediate discrimination for NLR (AUC=0.736) and PLR (AUC=0.785) [24]. Differences in infection timing, pathogen virulence, case definition, comparator groups, and cutoff selection may explain these discrepancies.

Infection chronicity is likely to be particularly important. Acute PJI commonly produces a rapid innate immune response with prominent neutrophilia and increased acute-phase proteins, whereas chronic PJI caused by indolent organisms may produce a lower-grade and more heterogeneous inflammatory profile [25]. Because the present cohort was not stratified into acute and chronic PJI, pooling these phenotypes may have attenuated the apparent performance of NLR, LMR, PLR, and PIV. Future studies should prespecify infection timing and report stratified diagnostic estimates.

Previous studies of combined biomarkers have also produced mixed results. Bottner et al. reported high diagnostic accuracy for CRP and interleukin-6, whereas Qin et al. found that combining D-dimer with CRP increased sensitivity at the expense of specificity [26]. Conversely, Klim et al. found no additional benefit from combining several serum biomarkers [27]. In clinical practice, while combined testing improves diagnostic performance, it inevitably necessitates more biomarker information, leading to additional costs (time, money, and additional specimens, etc.). Utilizing combined detection of multiple biomarkers can be challenging for doctors lacking statistical knowledge. Developing an application that automatically generates the combined detection result with only the input of individual test results appears to be a potential solution.

6 LIMITATIONS

This study has several limitations. First, the retrospective, single-center design limits generalizability and may introduce selection bias. Second, comorbidity data were not recorded comprehensively. Although known systemic inflammatory diseases were exclusion criteria, incomplete retrospective documentation may have left conditions such as rheumatoid arthritis

or systemic lupus erythematosus unmeasured or under-ascertained, and other immunocompromising conditions may also have affected systemic inflammatory markers. Third, acute and chronic PJI were not analyzed separately despite their distinct inflammatory profiles. Fourth, the combined models were developed and evaluated in the same dataset without cross-validation or an independent validation cohort, increasing the risk of overfitting. Larger prospective multicenter studies with detailed confounder assessment and predefined infection-chronicity subgroups are needed. Fifth, incorporation bias is a concern. CRP and ESR are part of the MSIS reference standard and were also evaluated as index tests, which may overestimate their diagnostic accuracy and that of combined models containing them.

7 CONCLUSIONS

The combination of CRP, ESR, and PLR may serve as an adjunct to, rather than a replacement for, current diagnostic criteria.

ABBREVIATIONS

AUC, area under the receiver operating characteristic (ROC) curve; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value.

DECLARATIONS

Authors' contributions

All authors contributed to the conception and design of the study. Study design and data analysis were performed by Zhenyu Song, Jincheng Huang, and Shuhui Liang. Data collection was performed by Qiwan He and Shuhui Liang. The first draft was written by Zhenyu Song and Kailin Jiang, and the final version was revised by Yi Jin and Hongkai Wang. All authors reviewed previous versions of the manuscript and approved the final manuscript.

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Data availability

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

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Henan Provincial People's Hospital (approval No. 2020.80) and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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