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Association Between Age and CD68 Expression in Patients with Adenomyosis

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ABSTRACT

This study explores the relationship between CD68 expression, a macrophage marker involved in inflammation, and clinical outcomes in patients with adenomyosis across different age groups. A descriptive analytic retrospective cross-sectional comparative study was conducted at Undata Palu General Hospital from 2024 to 2025. CD68 expression was assessed using immunohistochemical (IHC) staining of uterine tissue samples obtained from 46 patients with adenomyosis, who were categorized into adult (19–44 years) and pre-elderly (45–59 years) age groups. The association between age groups and CD68 expression categories was analyzed using the Chi-square test, while the strength of the association was evaluated using Cramer's V coefficient. Positive CD68 expression was observed in 58.7% of patients. Statistical analysis demonstrated a significant association between age and CD68 expression ($p = 0.027$), although the strength of the association was weak (Cramer's V = 0.326). The adult group showed a higher proportion of positive CD68 expression (59.3%) compared with the pre-elderly group (where 73.7% showed negative expression). These findings suggest that age is associated with macrophage infiltration in adenomyosis, with younger patients exhibiting greater CD68 expression, potentially reflecting a more active innate immune response. In contrast, lower CD68 expression in older patients may be related to age-associated changes in immune function, including immunosenescence. Given the weak strength of the association, adenomyosis progression should be considered a multifactorial process influenced by age, hormonal status, and disease duration. Understanding age-related variations in inflammatory responses may contribute to a better understanding of adenomyosis pathophysiology and support the development of individualized management strategies.

Key Messages:

- Younger adenomyosis patients (19-44 years) demonstrate significantly higher CD68 macrophage expression compared to older patients (45-59 years).
- The decline in CD68 expression in older patients suggests that immunosenescence modulates the local inflammatory response within the uterine myometrium.

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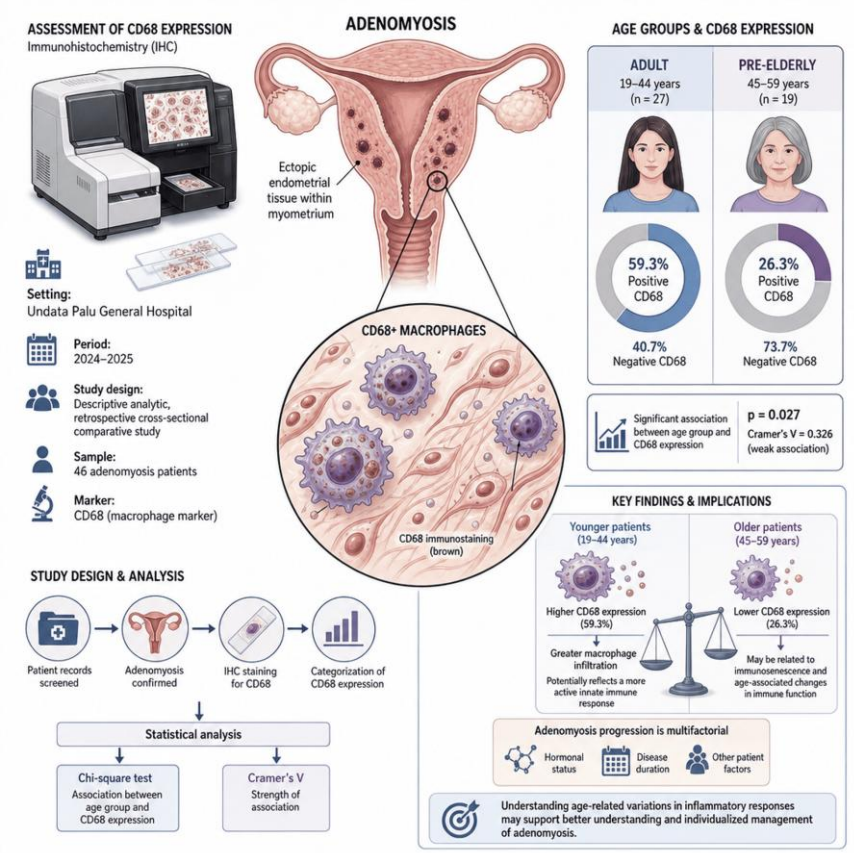
GRAPHICAL ABSTRACT



INTRODUCTION

Adenomyosis is a gynecological condition defined by the benign invasion of endometrial tissue, including glands and stroma, into the uterine myometrium (1). This ectopic tissue often leads to significant clinical symptoms such as severe menstrual pain (dysmenorrhea) and heavy menstrual bleeding (menorrhagia) (2). These manifestations substantially reduce the quality of life for affected individuals (3). Historically, a definitive diagnosis required histopathological examination after a hysterectomy, although modern imaging techniques such as ultrasound and MRI now allow more accurate non-invasive identification.

The prevalence of adenomyosis is rising globally, affecting a significant portion of the female population. Recent data from Italy indicates a prevalence of 34% among women aged 18-30 (4), while studies in Korea show a sharp increase in incidence rates over the last two decades (5). This upward trend is frequently linked to women delaying their first pregnancy until their late 30s or early 40s (6). This demographic shift creates a critical clinical urgency: older reproductive-aged patients face a compounding double-burden of age-related fertility decline and adenomyosis-induced uterine dysfunction (7). In these older cohorts, chronic tissue remodeling not only severely impairs embryo implantation and increases miscarriage rates, but also, in rare cases, elevates the risk of malignant transformation into endometrial cancer (8).

The pathogenesis of this condition involves complex cellular mechanisms, including epithelial-to-mesenchymal transition (EMT) and chronic inflammatory responses (9). Macrophages play a critical role as primary immune cells in these processes. CD68, a transmembrane glycoprotein expressed in monocytes and macrophages, is a reliable marker for quantifying macrophage infiltration in tissues (10). Higher CD68 expression in adenomyosis tissue is associated with increased symptom severity, as macrophages enhance neurogenic inflammation and sensitize pain receptors in the myometrium (11). Crucially, the biological rationale for evaluating CD68 in relation to age lies in the phenomenon of immunosenescence and "inflammaging." As women age, baseline pelvic immune microenvironments undergo a shift toward chronic, dysregulated macrophage polarization and altered phagocytic activity (8). In older patients, this

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altered macrophage behavior can exacerbate fibrotic changes and sustain a hyper-inflammatory state compared to younger counterparts, directly impacting disease progression (12).

Current research has begun to use biomarkers such as CD68 and the Neutrophil-to-Lymphocyte Ratio (NLR) to understand systemic and local inflammation (13). However, evidence comparing the expression of these inflammatory biomarkers across different age groups remains limited. Consequently, there is a clear imperative to evaluate CD68 not merely as an indicator of presence, but specifically as a prognostic biomarker (14). Defining age-dependent profiles of CD68 expression is vital to predict disease trajectories, assess reproductive prognosis, and anticipate therapeutic responsiveness (14–16). This knowledge gap hinders the development of age-specific therapeutic strategies.

This study aims to investigate the relationship between CD68 expression and clinical outcomes in patients with adenomyosis, focusing on differences between younger and older age groups. By exploring how age modulates macrophage-mediated inflammation, the research seeks to provide a deeper understanding of the disease's biological variability. By establishing the role of CD68 as a prognostic indicator across distinct age cohorts, these findings are expected to refine risk stratification, optimize fertility-preserving counseling, and advance targeted, age-specific therapeutic interventions for patients at different stages of their reproductive lives.

METHODS

This study employed a retrospective, cross-sectional comparative design to analyze patients at RSUD Undata Palu over a 24-month period from January 2024 to December 2025. The study population comprised all patients diagnosed with adenomyosis during this period. A total sample size of 46 patients was selected using a total sampling technique (exhaustive sampling), enrolling all consecutive cases that met the predefined selection criteria during the specified study duration to ensure maximum reproducibility. Ethical clearance for this study was officially reviewed and approved by the Research Ethics Committee of Universitas Tadulako (Approval Number: 5452/UN28.10/KL/2025; Approval Date: May 16, 2025). Research on clinical biological tissue was conducted in strict accordance with the Declaration of Helsinki, and written informed consent for the diagnostic and research use of archived biological specimens was obtained from all participants or their legal guardians prior to hysterectomy surgery.

Participants were selected based on specific inclusion criteria, including a confirmed histopathological diagnosis of adenomyosis (defined by the presence of ectopic endometrial glands and stroma within the myometrium, separated by at least 2.5 mm from the endometrial–myometrial junction on standard hematoxylin and eosin [H&E]-stained sections) and completeness of medical record data. Patients with other gynecological malignancies, co-existing pelvic endometriosis, pelvic inflammatory disease (PID), or those undergoing preoperative hormonal or immunosuppressive therapy within the last 3 months were excluded to ensure the accuracy of the local inflammatory marker analysis. The subjects were then categorized into two groups: an adult reproductive group (19–44 years) and a pre-elderly group (45–59 years).

Data collection involved gathering clinical information from archived medical records, including age, marital status, and medical history. Archived formalin-fixed, paraffin-embedded (FFPE) uterine tissue samples obtained from hysterectomies were processed for immunohistochemistry (IHC). The detailed IHC protocol was executed as follows: FFPE tissues were sectioned at a thickness of 4 μ, deparaffinized in xylene, and rehydrated through a graded series of ethanol. Antigen retrieval was performed via heat-induced epitope retrieval (HIER) in a citrate buffer (pH 6.0) using a microwave at 95°C for 15 minutes. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide (H_2O_2) for 10 minutes. The sections were then incubated overnight at 4°C with a mouse monoclonal anti-CD68 primary antibody. Detection was performed using a biotinylated secondary antibody and visualized using 3,3'-diaminobenzidine (DAB) chromogen, followed by Mayer's hematoxylin counterstaining.

To minimize observer bias, the semi-quantitative assessment of CD68 expression was performed independently by two board-certified pathologists blinded to the clinical and age data. Macrophage infiltration was quantified using a validated histoscore (H-score) method, combining staining intensity (0 = negative, 1 = weak/pale brown, 2 = moderate/moderate brown, 3 = strong/dark brown) and the

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percentage of positive cells (0%–100%) scattered around ectopic endometrial glands and stroma. The mathematical formulation used was:

$$H - score = \sum (Intensity\ score\ \times Percentage\ of\ positive\ celss)$$

resulting in a continuous scale from 0 to 300. Inter-observer discrepancies (<5%) were resolved by re-evaluation via a multi-head discussion microscope. Based on receiver operating characteristic (ROC) curve analysis and median values, a definitive cut-off value of was established, stratifying CD68 expression into two definitive operational categories: Negative (≤ cut-off) and Positive (> cut-off).

Statistical analysis was conducted using IBM SPSS Statistics software (Version 26.0; IBM Corp., Armonk, NY, USA) to perform univariate and bivariate tests. The distribution of demographic characteristics and categorical CD68 expression was described through univariate analysis. The association between age groups and CD68 expression categories was tested using the Pearson Chi-square test, with a significance threshold set at $p < 0.05$. Additionally, Cramer's V coefficient was calculated to determine the strength of the relationship between the categorical variables.

RESULTS

Table 1 details the univariate demographic and clinical characteristics of the 46 respondents. The age distribution shows that the majority of patients were in the pre-elderly category (45–59 years), comprising 54.3% (n=25) of the cohort, while the remaining 45.7% (n=21) were classified as adults (19–44 years). Clinically, immunohistochemical evaluation demonstrated that most patients (58.7%, n=27) exhibited positive CD68 expression, whereas 41.3% (n=19) yielded negative results. Socio-demographically, the study population was predominantly married individuals (87.0%, n=40), with the majority working as homemakers (43.5%, n=20), and the most frequent highest educational attainment was senior high school (34.8%, n=16).

Table 1. Demographic and Clinical Characteristics of the Respondents

Characteristics	*n*	%
Age (years)		
Adult (19–44)	21	45.7
Pre-elderly (45–59)	25	54.3
CD68 IHC Expression		
Positive	27	58.7
Negative	19	41.3
Marital Status		
Unmarried	5	10.9
Married	40	87.0
Divorced	1	2.2
Occupation		
Unemployed	13	28.3
Homemaker	20	43.5
Private Sector Employee	1	2.2
Entrepreneur	1	2.2
Midwife	1	2.2
Civil Servant	10	21.7
Educational Attainment		
No Formal Education	9	19.6
Elementary School	5	10.9
Junior High School	6	13.0
Senior High School	16	34.8
Associate's degree (D3)	4	8.7
Bachelor's Degree (S1)	5	10.9
Master's Degree (S2)	1	2.2
Total	**46**	**100**

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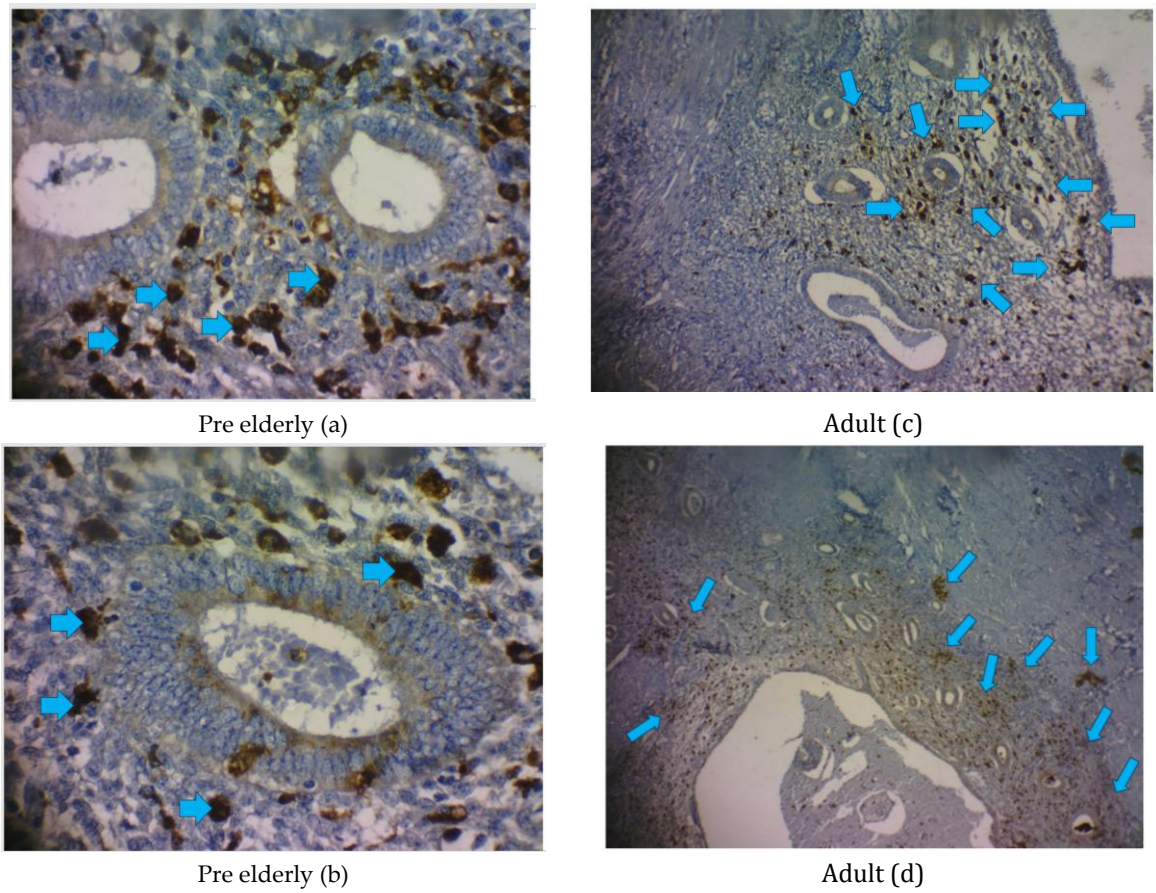
Table 2. Bivariate Analysis of Age and CD68 IHC Expression

Age	CD68 IHC Positive		CD68 IHC Negative		Total		*P*-value	Cramer's V
	n	%	*n*	%	*n*	%		
Adult (19–44 years)	16	59.3	5	26.3	21	45.7	0.027	0.326
Pre-elderly (45–59 years)	11	40.7	14	73.7	25	54.3		
Total	27	100	19	100	46	100		

To determine whether local tissue inflammation scales with chronological shifts, a Pearson Chi-square test was executed to assess the association between age groups and categorical CD68 expression (Table 2). Statistical analysis revealed a significant relationship between the variables ($p = 0.027$). A higher percentage of patients within the adult reproductive group (59.3%) presented with positive CD68 expression. In contrast, the pre-elderly group was characterized mostly by negative CD68 expression (73.7%). To quantify the magnitude of this effect, Cramer's V coefficient was calculated. The resulting value (Cramer's V = 0.326) indicates that while the association is statistically verified, its overall strength falls within the weak category, demonstrating that tissue macrophage distribution in adenomyosis is a multifactorial dynamic rather than an age-dependent continuum.



Pre elderly (a) Adult (c)

Pre elderly (b) Adult (d)

Figure 1. Immunohistochemical staining of CD68 expression in macrophages within adenomyosis tissue. Comparative panels illustrate representative sections across the different age groups: (a, b) Pre-elderly group demonstrating a visibly sparser and more localized macrophage distribution within the periglandular stroma; (c, d) Adult reproductive group showcasing a dense, widespread infiltration of labeled cells throughout the invading stroma. Positive expression is morphologically identified by distinct granular brown cytoplasmic staining (indicated by blue arrows). Nuclei are counterstained with hematoxylin (Representative high-power fields).

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Immunohistochemical staining allowed for the localization and spatial characterization of CD68-positive macrophages within the microenvironment of histologically confirmed adenomyosis tissue (Figure 1). Positive macrophage expression was morphologically identified by distinct, granular brown cytoplasmic staining surrounding the ectopic endometrial glands and within the invading stroma of the myometrium. To ensure technical reliability and rule out background artifact noise, staining runs were verified via tissue controls; standard positive control tissue exhibited robust immunoreactivity, whereas the omission of the primary antibody in negative controls yielded no signal. As illustrated in the comparative panels of Figure 1, a noticeable spatial difference in cell density was captured between the age cohorts under high-power field examination. Tissue sections from the younger adult group (Figure 1c and 1d) demonstrated a dense, widespread infiltration of CD68-positive cells scattered throughout the local stroma. Conversely, tissue sections from the pre-elderly group (Figure 1a and 1b) displayed a visibly sparser and more restricted distribution of labeled macrophages. These structural variations and local tissue density differences across the distinct age cohorts are explicitly highlighted by clear blue directional arrow indicators within the annotated figures.

DISCUSSION

The primary finding of this study demonstrates a statistically verified association between age categories and local tissue inflammation, as measured by CD68 immunohistochemical expression (p = 0.027). Specifically, our data in Table 2 reveals a clear divergence in macrophage infiltration patterns between the two studied cohorts: the majority of patients within the adult reproductive group (19–44 years) exhibited positive CD68 expression (59.3%), whereas the pre-elderly group (45–59 years) was predominantly characterized by negative CD68 expression (73.7%). This structural difference is visually corroborated by the spatial microenvironment captured in Figure 1, where tissue sections from younger adult patients show a dense, widespread accumulation of labelled macrophages compared to the sparser distribution observed in the pre-elderly tissue panels. Taken together, these current findings indicate that local pelvic immune activity and macrophage recruitment around ectopic endometrial glands are significantly more pronounced during the earlier reproductive life stages of adenomyosis patients.

While general literature frequently links peripheral macrophage shifts to broad physiological dynamics such as immunosenescence or "inflammaging," it is a critical distinction that specific cellular aging markers were not directly quantified in this cross-sectional experiment (17). Therefore, the observed age-related drop in uterine CD68 positivity within our pre-elderly cohort must be interpreted through the explicit reproductive and clinical parameters of our actual study population rather than abstract textbook pathways. A robust baseline hormonal status is a key local driver; women in their reproductive prime typically maintain higher and more stable estrogen levels than perimenopausal or pre-elderly individuals (18). Estrogen acts as a potent local immunomodulator that actively enhances the recruitment, proliferation, and activation of tissue macrophages within inflammatory uterine lesions (19,20). Consequently, the significantly higher rate of positive CD68 expression seen in our 19–44 age group directly reflects a tissue microenvironment heavily stimulated by active reproductive hormones, whereas the fluctuating or lower estrogen exposure characteristic of the 45–59 age group aligns with a reduced local immune cell infiltration (21).

Despite the verified statistical significance, the calculation of Cramer's V coefficient yielded a value of 0.326, classifying the strength of this relationship as a weak association. This low effect size serves as direct statistical evidence that local macrophage infiltration in adenomyosis is not dictated by chronological age alone, but is instead an intensely multifactorial pathogenic process governed by overlapping parameters (22,23). Pathophysiologically, factors such as the exact duration of the disease, variation in individual hormone receptor densities, and specific histological subtypes of the lesions can drive macrophage expression independently of patient age (24,25).

Furthermore, this weak association can be directly clarified by examining the baseline socio-demographic variations among our respondents detailed in Table 1, which were not controlled in a multivariate statistical model and likely acted as background confounding noise. Our univariate data reveals that the cohort is predominantly composed of married individuals (87.0%), with homemakers representing the largest occupational bracket (43.5%) and senior high school being the most frequent highest educational attainment (34.8%). In gynecological epidemiology, these socio-economic and

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demographic indicators are closely linked to variations in lifestyle stress, physical activity, dietary habits, and parity status, all of which are established independent modulators of systemic and pelvic inflammation (26,27). Because these baseline variables were not matched or adjusted between our adult and pre-elderly groups, their collective unmeasured presence likely introduced confounding background noise that diluted the direct statistical strength of age on tissue CD68 expression.

Ultimately, our current findings confirm that while chronological age uncovers a definitive trend in local macrophage density, adenomyosis progression is a complex web of biological and demographic traits. CD68 staining provides critical cross-sectional insights into the varying local immune activity of our patients, establishing its relevance as a supplementary marker to chart tissue inflammation profiles across different clinical age groups.

Limitations and Future Directions

Several limitations of this study must be acknowledged. First, the retrospective cross-sectional design restricts our ability to track fluid macrophage kinetics over time or establish a definitive causal loop between aging and local disease progression. Second, because our sample size (n = 46) was derived from a single institution (Undata Palu Hospital), advanced multivariate regression models could not be executed to statistically control for the clinical and socio-demographic confounders identified in Table 1, such as marital status and occupation. Finally, our technical reliance on general CD68 staining limits our capacity to differentiate between pro-inflammatory M1 and anti-inflammatory/pro-fibrotic M2 macrophage phenotypes within the tissue sections.

Future prospective studies utilizing larger, multi-center cohorts are warranted to validate these trends. To overcome the confounding variables indicated by our low Cramer's V value, future protocols should collect precise data on disease duration, body mass index (BMI), parity, and visual analog scale (VAS) pain scores to allow for adjusted multi-variable data processing. Additionally, incorporating dual-immunoflourescence tracking (combining CD68 with specific polarization markers like CD86 or CD163) will be crucial to map the exact quality of age-related pelvic immune shifts without relying on speculative textbook assumptions.

CONCLUSION

In conclusion, this study demonstrates a statistically significant association between age groups and macrophage infiltration, measured via CD68 expression, in patients with adenomyosis (p = 0.027). The adult reproductive group (19–44 years) presents a predominantly positive CD68 expression (59.3%), whereas the pre-elderly group (45–59 years) exhibits a mostly negative expression (73.7%). However, because the overall strength of this association is weak (Cramer’s V = 0.326), macrophage distribution across these distinct age cohorts should be viewed as a multifactorial pathogenic process rather than a standalone age-dependent continuum

DECLARATION OF THE USE OF AI

The authors declare that no artificial intelligence (AI), AI-assisted technologies, or large language models (LLMs) were used in the conception of the study, data analysis, or the drafting, writing, and editing of this manuscript. The only exception is the graphical abstract, which was created using the design platform Illustrae (https://illustrae.co/). The authors take full responsibility for the content and accuracy of the graphical abstract and the entire manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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