

# Serum amyloid A may be a potential biomarker for vasculitis

## Serum amiloid A vaskülit değerlendirmede potansiyel bir biyobelirteç olabilir

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### Abstract

**Objective:** There are still unmet needs for ideal biomarkers for management of vasculitis. This study aimed to analyze the potential utilities of the S100A12 and Serum Amyloid A (SAA) as diagnostic or activity-specific biomarkers of vasculitis.

**Methods:** A total of 18 clinically active vasculitis patients [giant cell arteritis (n=6), Takayasu arteritis (n=6), and granulomatosis with polyangiitis (n=6)] and 12 healthy controls (HCs) were enrolled. Disease activity was assessed using the Birmingham disease activity score (BVAS). The correlation between SAA, S100A12, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and BVAS was analyzed. Receiver operating characteristics analysis was used to evaluate the diagnostic utility of each marker.

**Results:** Patients with active vasculitis had significantly higher levels of CRP, S100A12, and SAA, and higher ratios of NLR and PLR compared to HCs. S100A12 did not correlate with disease activity and other biomarkers. SAA had the most significant correlation with BVAS ( $r=0.63$ ,  $p<0.05$ ). All biomarkers have the capability of effectively discriminating patients with vasculitis from HCs. The area under the curve (AUC) of CRP, SAA, S100A12, NLR and PLR was 0.95 (95% confidence interval 0.88-0.99), 0.82 (0.65-0.98), 0.77 (0.60-0.95), 0.90 (0.79-0.99) and 0.89 (0.76-0.99), respectively. SAA had better AUC compared to S100A12. A level of 7.5 mg/L (sensitivity 78%, specificity 83%) for SAA and 24 ng/mL (sensitivity 89%, specificity 67%) for S100A12 were found as the optimum cut-off points for defining active vasculitis.

**Conclusion:** SAA could be proposed as a more potential biomarker than S100A12. Both discriminative value for active vasculitis and correlation with disease activity of SAA were more significant than S100A12. Our results point to the need of further longitudinal researches regarding utility of SAA and SAA-like proteins in the assessment of vasculitis.

**Keywords:** Serum amyloid A, S100A12, vasculitis, biomarker

### Öz

**Amaç:** Vaskülitlerin takibinde ideal biyobelirteç için hala karşılanmamış ihtiyaçlar vardır. Bu çalışmada S100A12 ve Serum Amiloid A'nın (SAA) vaskülitlerin tanı veya hastalık aktivasyonunda biyobelirteç olarak geçerliliklerini değerlendirmeyi amaçladık.

**Yöntem:** Klinik olarak aktif 18 vaskülit hastası [dev hücreli arterit (n=6), Takayasu arteriti (n=6) ve granülomatoz polianjit (n=6)] ve 12 sağlıklı kontrol çalışmaya dahil edildi. Hastalık aktivitesi Birmingham hastalık aktivite skoru (BVAS) kullanılarak değerlendirildi. SAA, S100A12, C-reaktif protein (CRP), nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve BVAS arasındaki korelasyon araştırıldı. Her biyobelirteğin tanılabilirliğini değerlendirmek için alıcı işlem karakteristiklerinin analizi yapıldı.

**Bulgular:** Aktif vaskülitli hastalarda, sağlıklı kontrollere kıyasla CRP, S100A12 ve SAA düzeyleri ile NLR ve PLR oranları anlamlı derecede yüksek saptandı. S100A12, hastalık aktivitesi ve diğer biyobelirteçler ile korele değildi. Hastalık aktivitesi ile en anlamlı korelasyona SAA'nın sahip olduğu saptandı ( $r=0.63$ ,  $p<0.05$ ). Tüm biyobelirteçlerin vaskülit hastalarını sağlıklı kontrollerden etkin bir şekilde ayırt edebildikleri saptandı. Eğri altındaki alan (EAA); CRP, SAA, S100A12, NLR ve PLR için sırasıyla 0,95 (%95 güven aralığı 0,88-0,99), 0,82 (0,65-0,98), 0,77 (0,60-0,95), 0,90 (0,79-0,99) ve 0,89 (0,76-0,99) olarak saptandı. SAA, S100A12 ile karşılaştırıldığında daha iyi bir EAA'ya sahipti. SAA için 7,5 mg/L (duyarlılık %78, özgüllük %83) ve S100A12 için 24 ng/mL (duyarlılık %89, özgüllük %67) aktif vaskülit tanımlamak için en uygun değerler olarak saptandı.

**Sonuç:** SAA, S100A12'den daha potansiyel bir biyobelirteç olarak önerilebilir. SAA'nın, hem aktif vaskülit ayırt edici özelliği hem de hastalık aktivitesi ile korelasyonu S100A12'den daha anlamlı olarak saptandı. Sonuçlarımız, SAA ve SAA benzeri proteinlerin vaskülit değerlendirmesinde kullanımıyla ilgili daha ileri araştırmalara ihtiyaç duyulduğunu göstermektedir.

**Anahtar Kelimeler:** Serum amiloid A, S100A12, vaskülit, biyobelirteç

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## Introduction

Vasculitides are a heterogeneous group of diseases, characterized by inflammation of blood vessels, causing severe tissue destruction and organ/system failure. Given the variability of the location and size of the involved vessels, there is a great diversity of clinical presentation and severity. This heterogeneity and insidious natural history make the management of vasculitis challenging.<sup>[1]</sup> Vasculitis related damage causes significant mortality, morbidity and economic burden.<sup>[2]</sup> The prompt and accurate treatment of patients regarding their organ involvement is crucial to prevent damage. Therefore, identifying the disease and relapse is quite important. Despite our increasing knowledge about vasculitis, there are still unmet needs for ideal biomarkers. Available markers, including antineutrophil cytoplasmic antibodies,<sup>[3]</sup> erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are unreliable and inaccurate for diagnosis, assessing disease activity and defining relapse. For instance ESR and CRP can be quite normal in some clinically active Takayasu and histopathologically active giant cell arteritis (GCA) patients.<sup>[4-6]</sup>

Serum amyloid A (SAA) is an acute-phase protein that belongs to the apolipoprotein family. SAA is synthesized primarily in the liver by activated monocytes and macrophages in response to proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>[7]</sup> The S100 protein family is a unique class of calcium-binding proteins which are expressed and released at local sites of inflammation.<sup>[8-10]</sup> Members of the S100 protein family are the most abundant danger-associated molecular patterns (DAMPs), which participated in an inflammatory reaction during stress, and associated with various receptors (e.g. Toll-like receptor 4) and advanced glycosylation end products (RAGE).<sup>[11]</sup> S100A12 is more restricted to granulocytes with several important extracellular roles including activating the NF- $\kappa$ B pathway, which results in the expression of the proinflammatory cytokines and adhesion molecules.<sup>[12,13]</sup> The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have emerged as a markers of inflammation and are found to be a useful indices for estimating the current inflammatory burden and disease activity of vasculitis.<sup>[14,15]</sup>

The capability of neither SAA nor S100A12 in the assessment of vasculitis has not been fully elucidated. In particular, we are not aware of any study that compares S100A12 and SAA in that field. In light of this background, this study analyzed the plasma levels of SAA and S100A12 in patients with active vasculitis and healthy controls (HCs) and we aimed to investigate their correlation with disease activity and other biomarkers, and to identify the potential

utilities as identifying diagnosis or relapse in patients with GCA, Takayasu arteritis, and granulomatosis with polyangiitis (GPA).

## Materials and Methods

Eighty-five consecutive vasculitis patients, whether newly diagnosed or relapsing, were admitted to the clinic during the study period. The inclusion criterion was clinically active disease. Exclusion criteria were refusal to participate, having inactive disease, other autoimmune conditions or malignancies, being under 18 years of age and being pregnant. Sixty-seven of them were excluded because they met the exclusion criteria or reached the target number per group. Total of eighteen consecutive active vasculitis patients (six patients for each) who fulfilled the American College of Rheumatology classification criteria for GCA,<sup>[16]</sup> Takayasu arteritis<sup>[17]</sup> and GPA<sup>[18]</sup> were enrolled in this cross-sectional study. Twelve healthy controls (HCs), who had no signs or symptoms that direct an inflammatory disease, participated in this study (Figure 1). The study was conducted after the ethical approval of the local ethics committee (approval number: 98, date: 27/01/2020) complied with the declaration of Helsinki. Informed consent was obtained from all patients and HCs before the initiation of the study.

Demographic data were collected. The disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS v3), which is composed of nine major items.<sup>[19]</sup> BVAS>0 was accepted as active disease. Conventional inflammatory biomarkers included CRP, NLR and PLR analyzed by use of in-house method. CRP was studied with the nephelometric method and under 5 milligrams per liter (mg/L) is considered normal. Peripheral venous samples were obtained; after clothing, the tubes were centrifuged at 3000x for 5 min, and sera were stored at -80°C for further analyses. S100A12 and SAA were analyzed by enzyme-linked immunosorbent assay (ELISA) methods. Human S100A12 was studied with a commercially available ELISA kit (Boster Immunoleader En Rage PicoKineTMCA, USA). The assay detection range was 31.2 pg/mL-2000 pg/mL and sensitivity was <10 pg/mL. SAA was studied with commercially available SAA ELISA Kit (Assay Pro, MO, USA). The assay detection range was 0.125-2 ug/mL and sensitivity was 6 ug/mL.

## Statistical Analyses

We conducted all statistical analyses with SPSS software (version 15 for Windows; SPSS INC., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine the distribution of data. Continuous variables were expressed as a median

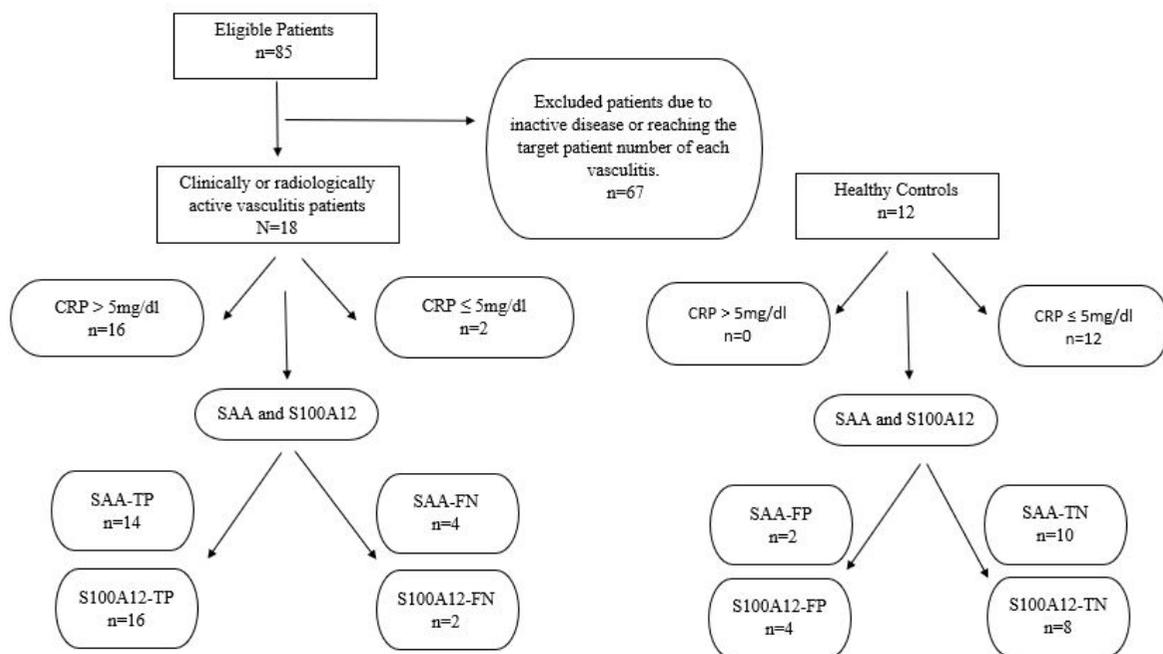
values with minimum-maximum (min-max). Categorical data are summarized as absolute frequencies and percentages. We compared the biomarker levels across different subgroups by either Kruskal-Wallis (>2 groups) or Mann-Whitney U (2 groups) tests, when appropriate. Spearman's correlations were calculated to define the association between biomarkers and disease activity. Receiver operating characteristic (ROC) curve analysis was performed to establish the optimal discriminatory threshold for identifying patients with vasculitis from HCs. A two-tailed p-value <0.05 was considered statistically significant.

## Results

Table 1 details the characteristics and biomarker levels of both groups. Patients were significantly older than HCs

[52 (28-80) vs. 36 (26-56), respectively, p=0.01]. Gender distribution and body mass index (BMI) were comparable. Median BVAS of the patients was 4 (min-max, 1-14). CRP, SAA, S100A12, NLR and PLR were significantly higher in patients than in HCs [61.4 (3-306) vs. 2.2 (1.24-4.15), p<0.001; 26.0 (0.07-42) vs. 2.0 (0.49-15.62), p=0.004; 60.8 (17.1-125.3) vs. 21.4 (16.1-82.2), p=0.013; 5.1 (1.3-20.8) vs. 1.6 (1.2-4.5) p<0.001; and 304.5 (72.2-1322.5) vs. 107.0 (67.8-230.8), p<0.001, respectively].

The patient population comprised six patients with GCA, Takayasu arteritis and GPA. Further subgroup analyses showed a statistical difference between these groups in terms of CRP, SAA, NLR, and PLR, unlike S100A12 (p=0.083) (Table 2). Correlation analysis between biomarkers and BVAS were performed separately for the patients and HCs.



**Figure 1.** Flowchart of the study

CRP: C-reactive protein, FN: False negative, FP: False positive, SAA: Serum amyloid A, TN: True negative, TP: True positive

**Table 1.** Demographics and biomarker levels of active vasculitis patients and the control group

Variable	Patients (n=18)	Healthy controls (n=12)	p-value
Age, years	52 (28-80)	36 (26-56)	0.01
Female, %	56%	50%	0.76
BMI, kg/m <sup>2</sup>	24.8 (18.2-33.2)	27.7 (18.0-37.8)	0.16
CRP (mg/L)	61.4 (3-306)	2.2 (1.24-4.15)	<0.001
SAA (mg/L)	26.0 (0.07-42)	2.0 (0.49-15.62)	0.004
S100A12 (ng/mL)	60.8 (17.1-125.3)	21.4 (16.1-82.2)	0.013
NLR	5.1 (1.3-20.8)	1.6 (1.2-4.5)	<0.001
PLR	304.5 (72.2-1322.5)	107.0 (67.8-230.8)	<0.001

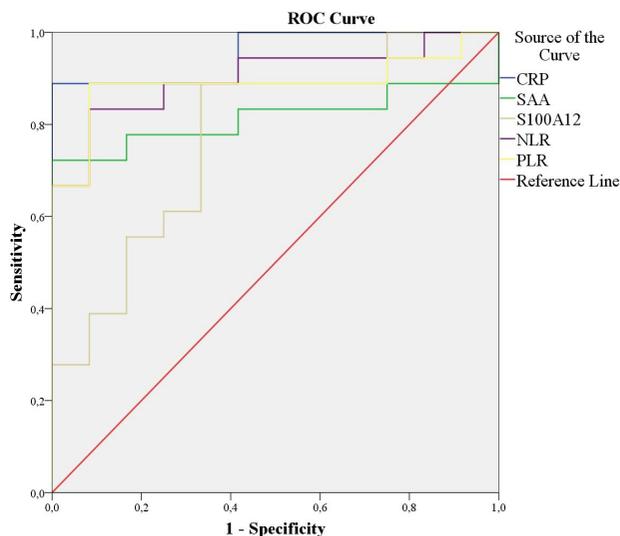
BMI: Body mass index, CRP: C-reactive protein, SAA: Serum amyloid A, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio. p<0.05 is considered as significant. Numerical data was showed as median (min-max)

There was no correlation between biomarkers in the HCs ( $p>0.05$ , data not shown). SAA has a high positive correlation with CRP, whereas NLR and PLR have a moderate positive correlations (Table 3,  $r=0.8$ ,  $p<0.001$ ;  $r=0.5$ ,  $p=0.035$ ; and  $r=0.49$ ,  $p=0.038$ , respectively). S100A12 was highly correlated with CRP only in GCA patients ( $r=0.83$ ,  $p<0.05$ ). Moreover, CRP, SAA and NLR were moderately correlated with BVAS for all patients ( $r=0.57$ ,  $p=0.013$ ;  $r=0.63$ ,  $p=0.005$ ; and  $r=0.52$ ,  $p=0.028$  respectively). There was no correlation between BVAS and S100A12.

The area under the curve (AUC) of CRP, SAA, S100A12, NLR and PLR was found to be significantly greater than the reference line [ $p<0.05$ , AUC (95% CI): 0.95 (0.88-0.99), 0.82 (0.65-0.98), 0.77 (0.60-0.95), 0.90 (0.79-0.99) and 0.89 (0.76-0.99), respectively]. A level of 7.5 mg/L (sensitivity 78%, specificity 83%) for SAA and 24 ng/mL (sensitivity 89%, specificity 67%) for S100A12 were found as the optimum cut-off points for diagnosing vasculitis (Figure 2). There were two patients with active vasculitis who had normal CRP levels. Both of them had GCA and their BVAS was found 2 and 3. SAA was higher than the defined cut off limit in one patient (25.44 mg/L) while S100A12 was higher than the defined cut off limit (81.44 and 37.22 ng/mL) in both patients.

## Discussion

In view of challenges in the management of vasculitis and not having an ideal biomarker to diagnose, and to determine the disease activity and relapses, it is important to study new biomarkers. Especially, biomarkers, which can assess



**Figure 2.** Receiver operating characteristic curves for tested biomarkers for the diagnosis of vasculitis

CRP: C-reactive protein, FN: False negative, FP: False positive, ROC: Receiver operating characteristic, SAA: Serum amyloid A, TN: True negative, TP: True positive

**Table 2.** Demographics, biomarker levels and disease activity of groups

	GCA (n=6)	Takayasu (n=6)	GPA (n=6)	Healthy (n=12)	p-value
Age, years	66 (52-80)	41 (28-52)	51.6 (32-76)	36 (26-56)	0.004
Female, %	17%	100%	50%	50%	0.04
CRP (mg/L)	80.3 (8.9-191.0)	7.5 (3-53.8)	129.5 (51.2-306.0)	2.2 (1.24-4.15)	0.001
SAA (mg/L)	21.8 (0.42-32.0)	10.1 (0.07-39.1)	30.5 (25.1-42.0)	2.0 (0.49-15.62)	0.004
S100A12 (ng/mL)	49.8 (17.1-87.3)	77.9 (17.6-114.8)	55.7 (27.6-97.7)	21.4 (16.1-82.2)	0.08
NLR	3.0 (1.3-20.8)	5.2 (1.6-20.8)	9.5 (4.6-16.1)	1.6 (1.2-4.5)	0.001
PLR	246.1 (72.2-1117.5)	285.5 (99.6-1322.5)	536.9 (169.2-844.4)	107.0 (67.8-230.8)	0.002
BVAS	3.5 (2-5)	3 (1-6)	7 (5-14)	NA	0.006

BVAS: Birmingham vasculitis activity score, CRP: C-reactive protein, GCA: Giant cell arteritis, GPA: Granulomatosis with polyangiitis, NA: not applicable, NLR=Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SAA: Serum amyloid A,  $p<0.05$  is considered as significant. Numerical data was showed as median (min-max)

**Table 3.** Correlations between biomarkers and disease activity

	CRP	SAA	S100A12	NLR	PLR
BVAS	<b>0.57*</b>	<b>0.63*</b>	0.21	<b>0.52*</b>	0.44
CRP	1	<b>0.80</b>	0.33	<b>0.50</b>	<b>0.49</b>
SAA	<b>0.80</b>	1	0.41	<b>0.66</b>	<b>0.60</b>
S100A12	0.33	0.41	1	0.22	0.38

BVAS: Birmingham vasculitis activity score, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SAA: Serum amyloid A. Bold indicating significance of correlation at the 0.05 level (2-tailed)

disease activity reliably and detect relapse, are urgently needed in clinical practice. S100A12 and SAA have not been fully analyzed for this purpose. In particular, this is the first study that compares SAA and S100A12. Here, we report a preliminary study, which analyzed the utility of SAA and S100A12 on discriminating patients with active vasculitis, whether at initial presentation or relapse, from healthy controls, and investigated the correlation between disease activity and S100A12 and SAA.

S100A12 did not correlate with disease activity and had a significant but a lower capability of discriminating active vasculitis from HCs among all biomarkers. This is noteworthy since S100 proteins have received much attention recently. The S100 protein family is a unique class of calcium-binding proteins which are expressed and released at local sites of inflammation.<sup>[7-9]</sup> Besides S100A12 and S100A8/9 proteins have been shown to be useful biomarkers of disease activity in some rheumatic diseases in many studies.<sup>[20-25]</sup> However, there are some conflicts about S100A12. On one hand, S100A12 was found to be elevated in patients with active MPO-ANCA-associated glomerulonephritis, Behçet's disease and GCA compared to vasculitis patients or/and HCs. Moreover, S100A12 was correlated with disease activity and pathologic activity scores<sup>[26]</sup> and was strongly expressed in the pathological examination of GCA, and Behçet's disease.<sup>[26-28]</sup> On the second hand, S100A12 was found similar in active and inactive Takayasu patients.<sup>[29]</sup> Above all, S100A12 was found to be related to aortic aneurysms and wall repair itself, irrespective of inflammatory diseases.<sup>[30,31]</sup> The major concern is the association between S100A12 and vessel wall damage itself, since this makes it impossible to discriminate between the active and inactive patients, which is an urgent need in clinical practice

Both the discriminative capability of active vasculitis from HCs and the correlation with disease activity of SAA was more significant than S100A12. SAA may be a reliable biomarker than S100A12 for assessing patients with vasculitis. This is somehow expected since all available data about SAA, even very few, supported our results; SAA might be related to the pathogenesis of GCA<sup>[32]</sup> and was a more reliable biomarker than CRP in patients with active GCA and MPO-ANCA associated vasculitis.<sup>[33,34]</sup> Moreover, SAA was elevated in Takayasu patients<sup>[35]</sup> and decreased in treatment responders,<sup>[36]</sup> unlike S100A12. Moreover, this study supported the knowledge that CRP can be quite normal in some clinically active Takayasu and histopathologically active GCA patients,<sup>[4-6]</sup> as our two clinically active GCA patients had normal CRP levels. Though SAA was highly correlated with CRP, SAA effectively differentiated one of these patients from healthy controls. Although the

knowledge regarding SAA and vasculitis is more enlightening and precise than S100A12, SAA fell out of favor. However, according to our results, this should be reconsidered and further research should be conducted.

### Study Limitations

A small sample size and lack of follow-up assessment were the major limitations of our study. The main limitations were the lack of diseased controls (mimickers) and inactive vasculitis patients. Moreover, BVAS is not the perfect-activity assessment measure for patients with GCA and Takayasu arteritis.

### Conclusion

Consequently, this is the first study that compares SAA and S100A12 as biomarkers in vasculitis patients and has results to widen the research fields. Both discriminative capability of active vasculitis and correlation with disease activity of SAA were more significant than S100A12. Our results draw attention to the SAA as a biomarker of vasculitis and point to the need of further longitudinal research regarding the diagnostic and assessment utility of SAA and SAA-like proteins for vasculitis.

### Ethics

**Ethics Committee Approval:** The study was conducted after the ethical approval of the local ethics committee (Gazi University Ethics Committee, approval number: 98, date: 27/01/2020) complied with the declaration of Helsinki.

**Informed Consent:** Informed consent was obtained from all patients and HCs before the initiation of the study.

**Peer-review:** Externally and peer reviewed.

**Conflict of Interest:** No conflict of interest was declared by the author.

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