ORIGINAL RESEARCH

Analysis of the Predictive Efficacy of Serum suPAR Combined with APN and IgE Test and the Relationship of Patients with CHF and Cardiac Function

Sijia Tu, MD; Li Ye, MD; Chaofeng Shen, MD; Xinghua Bai, MD; Cairong Li, MD

ABSTRACT

Background • Chronic heart failure (CHF) is a complex cardiovascular disorder resulting from prolonged heart disease, leading to structural and functional damage, weakened myocardial contraction, and inadequate cardiac output for daily metabolism. The purpose of study is accurate evaluation and early identification of cardiac function and ventricular remodeling through effective biochemical indicators.

Methods • This study, conducted from April 2020 to March 2021, included 100 CHF patients meeting the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2020 from First People's Hospital of Linping District, ascertaining a confirmed diagnosis based on these established guidelines. The objective of detecting these biomarkers is not for early diagnosis, given that the subjects are already diagnosed according to the guidelines. Instead, our focus is on using these biomarkers to assess disease severity, prognosis, or treatment response in the context of diagnosed CHF patients. Classification comprised 42 ischemic and 58 non-ischemic CHF cases, with NYHA cardiac function grading (I, II, III-IV) and left ventricular ejection fraction (LVEF) categorization (≤ 40%, >40%). A control group of 100 healthy volunteers was selected for comparison. SuPAR, APN, and IgE expressions were analyzed among different groups and LVEF categories. Diagnostic efficacy was assessed through ROC curves, and correlations with cardiac function and LVEF were explored.

Results • SuPAR, APN, and IgE expressions were significantly higher in CHF patients compared to the control group. Increasing cardiac function grades in CHF patients correlated with a gradual elevation in suPAR, APN, and IgE expressions. Comparing LVEF groups, CHF patients with LVEF ≤ 40% exhibited significantly higher suPAR, APN, and IgE expressions. Combined detection of suPAR, APN, and IgE demonstrated superior diagnostic accuracy (AUC of 0.899) compared to individual markers. Positive correlations were observed between suPAR, APN, IgE, and cardiac function grades, while LVEF showed a significant negative correlation with these biomarkers.

Conclusions • SuPAR, APN, and IgE expressions are elevated in CHF patients, and their combined detection serves as a highly efficient auxiliary diagnostic method. The findings offer valuable insights into the diagnosis and treatment of CHF patients. (*Altern Ther Health Med.* 2024;30(4):124-129)

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INTRODUCTION

Chronic heart failure (CHF) is a comprehensive heart disease caused by long-term heart disease that causes damage to the structure and function of the heart to a certain extent, the myocardial contraction ability continues to weaken, and the cardiac output cannot meet the daily metabolism of the human body. It is the late development stage of various heart diseases, manifested by progressive motor capacity loss, ventricular remodeling, ventricular dysfunction, and other symptoms.[1,2] With the aggravation of the aging population in China, the incidence of CHF is increasing yearly. The incidence of the elderly over 70 years old in China is as high as 10%, the fatality rate is 50%, and there are about 500,000 new cases every year, which has been a focus of clinical attention in recent years.[4] In clinical practice, it is necessary to evaluate the cardiac function and ventricular remodeling in patients with heart failure by effective biochemical indicators, and to make them an early identification and diagnosis.[3,4] Studies found that the annual case fatality rate of CHF cardiac function-grade patients is as high as 30% to 40%. soluble urokinase-type plasminogen activator receptor (suPA R) can reflect the activation degree and inflammation level of the body's immune

system, and is closely related to the occurrence of cardiovascular diseases.[24] The serum suPA R level of CHD patients is significantly increased, and it is positively correlated with the degree of coronary artery stenosis.[5,6] Studies have shown that serum adiponectin (APN) is associated with cardiovascular disease, but relatively few studies exist.[7] Immunoglobulin E (IgE) can be used as an inflammatory marker of the cardiovascular system, which is associated with the severity of coronary heart disease. The patients with suPAR, APN, and IgE are currently being diagnosed jointly in CHF patients, and there are few studies in combination with cardiac function grade and prognosis.[8] However, existing literature lacks a comprehensive exploration of the joint assessment of suPAR, APN, and IgE, particularly concerning their interplay with cardiac function grades and prognosis.

Addressing this gap, our study focuses on CHF patients to evaluate the efficacy of serum suPAR, APN, and IgE. This research aims to provide a more nuanced understanding of these biomarkers' significance and potential contribution to advancing prognostic assessments for individuals with CHF.

DATA AND METHODS

General Information

This study included 100 chronic heart failure patients treated by First People's Hospital of Linping District from April 2020 to March 2021. All CHF patients met the criteria of Diagnosis and Treatment of Heart Failure 2020;[25] so the patients were within NYHA cardiac function; after clinical examination, the left ventricular ejection fraction (Left ventricular ejection fraction, LVEF) was <50%; the patients and their families were aware of the study protocol and signed informed consent. This research received ethical approval from First People's Hospital of Linping District of the Institutional Review Board to ensure compliance with ethical standards and safeguard the rights and well-being of all participants.

Patients with acute myocardial infarction or heart disease, liver and renal dysfunction, tumor combined, mental abnormalities, inability to have normal communication, cardiopulmonary combined and other impaired organic function, and incomplete clinical data were excluded. Included patients in the study included 59 men and 41 women with an age range of 61 to 75 years, mean age (68.19±4.12), patient duration from 1 to 12 years, and mean duration (6.25±2.13) years. According to CHF typing, 42 ischemic heart failure and 58 non-ischemic HF were included. During the same period, we selected 100 healthy volunteers from our hospital to constitute the control group. The control group comprised 55 males and 45 females, with ages ranging from 60 to 76 years and an average age of 68.96±8.77. To ensure the comparability of the study groups, we meticulously matched the control group subjects with the patients in group 2 in terms of age and sex ratio, and no significant differences were observed ($P > .05$).

The cardiovascular health of the control group was rigorously assessed, including comprehensive evaluations of their cardiac function, blood pressure, lipid profiles, and any relevant medical history. All participants in the control group were confirmed to be free from any diagnosed cardiovascular conditions or other significant health issues. Additionally, the control group underwent a thorough clinical examination to ensure the absence of any acute or chronic illnesses that could impact the study's objectives. It is noteworthy that all participants included in both the control and study groups provided informed consent before their inclusion in the study. This detailed description of the control group's cardiovascular health aims to establish a solid foundation for meaningful comparisons with the patient group in group 2.

The classification of patients into ischemic and non-ischemic CHF groups was based on a comprehensive evaluation of their medical histories, diagnostic assessments, and clinical presentations. Ischemic CHF was attributed to a history of myocardial infarction or evidence of coronary artery disease, while non-ischemic CHF encompassed cases without a history of myocardial infarction or significant coronary artery disease. This classification aimed to differentiate between CHF cases stemming from ischemic heart disease and those with alternative etiologies, providing a more nuanced understanding of the study population.

Regarding the LVEF classification, patients were categorized into two groups: LVEF > 40% and LVEF ≤ 40%. This distinction was chosen to delineate patients with relatively preserved systolic function (LVEF > 40%) from those with impaired systolic function (LVEF ≤ 40%). The clinical significance lies in identifying different degrees of ventricular dysfunction, aiding in the characterization of heart failure severity and guiding appropriate therapeutic interventions.

It is important to note that these classifications were essential for the research analysis, allowing for a more detailed examination of distinct subgroups within the CHF patient population. The classifications served to uncover potential associations, patterns, and prognostic implications associated with ischemic or non-ischemic etiologies and varying levels of systolic function. All classifications were made with the sole purpose of enhancing the research's clinical relevance and interpretability.

Research Methods

Peripheral venous blood samples (5 mL) were obtained 24 hours after admission from participants in the control group. The blood samples were then subjected to centrifugation at 3000 rpm for 10 minutes. Following centrifugation, 1 mL of the supernatant was carefully preserved and stored at -80^{0}C for subsequent analysis. The serum suPAR levels (Human soluble urokinase-type Plasminogen Activator Receptor kit (suPAR) ELISA detection kit, BS-1955,China), as well as APN (Human adiponectin (APN) ELISA kit, MM-1721H1, China) and IgE (The Human Immunoglobulin E (IgE) ELISA kit, xyA545Hu, China), were determined using kits obtained from Shanghai ELISA. All procedures were conducted in strict adherence to the manufacturer's instructions to ensure accuracy and reliability.

Color Ultrasound LVEF Determination Method: The determination of LVEF involved utilizing a Philips 7500 color Doppler ultrasonic imager equipped with a 4VC ultrasonic probe, operating at a frequency range of 1.7 to 3.5 MHz. In the 2D imaging mode, LVEF was measured, and the average of three values obtained from each patient's cardiac cycle was calculated. This method allowed for a comprehensive assessment of cardiac function.

To minimize potential sources of bias or confounding factors, rigorous protocols were established during the study design and implementation. Uniform procedures were employed for blood sample collection, handling, and storage to ensure consistency. Additionally, efforts were made to control for variables that could impact the study outcomes, and the study design incorporated appropriate statistical analyses to address potential confounding factors. These measures were implemented to enhance the reliability and validity of the study results.

Observation indicators

(1) Comparing the suPAR, APN, and IgE expression conditions in the two groups;
(2) Comparing suPAR, APN, and IgE expression in patients with different cardiac function grades;
(3) Comparing the suPAR, APN, and IgE expression of patients in different LVEF groups;
(4) Analyze the diagnostic efficacy of suPAR, APN and IgE in CHF patients;
(5) Analyze the relationship between suPAR, APN and IgE and cardiac function;
(6) suPAR, APN and IgE and LVEF correlation analysis.

Statistical Methods

To organize the required data for this study, an Excel spreadsheet was created, categorizing the data into groups. Data analysis was conducted using IBM SPSS Statistics version 26.0. For measurement data, normality tests were performed, and the data were presented as mean ± standard deviation ($\bar{x} \pm s$). Groups meeting the criteria for normality underwent a one-way analysis of variance (ANOVA) with *F*-test. Intergroup differences were assessed using an independent sample t-test, while within-group comparisons utilized a paired-sample *t* test. In cases of non-normality, the Mann-Whitney U test was used to analyze the data. The rate data were expressed as percentages and tested using chi-square tests (χ^2). To examine the relationship between suPAR, APN, IgE, heart function, and LVEF in CHF patients, Pearson correlation analysis was conducted. The diagnostic effectiveness of suPAR, APN, and IgE in CHF patients was compared using ROC curves. All statistical analyses were performed with a significance level set at $P < .05$, indicating statistical significance. The transparent reporting of these specific statistical tests and the software used enhances the clarity and rigor of our data analysis approach.

RESULTS

The suPAR, APN, and IgE expressions were compared between the two groups

The expressions of suPAR, APN, and IgE were markedly higher in the study group (n=100) compared to the control group (n=100), with statistically significant differences observed in data comparisons ($P < .05$). Table 1 provides a detailed presentation of the numerical results and associated statistics.

Contrast the suPAR, APN, and IgE expression in patients with different cardiac function grades

According to the NYHA cardiac function grade, including grade, the suPAR, APN and IgE expression were gradually increased with the increase of CHF patients, and the data comparisons were significantly different ($P < .05$), as shown in Table 2.

Contrast suPAR, APN and IgE expression in different LVEF groups

According to the LVEF classification, it can be divided into LVEF>40% (n=46) and LVEF 40% (n=54). Compared with CHF patients, LVEF 40 F patients were significantly higher, and the data differ significantly ($P < .05$), as shown in Table 3.

Analysis of the diagnostic efficacy of suPAR, APN, and IgE in CHF patients

For suPAR, APN and IgE combined detection in CHF, the offline area of ROC curve in diagnostic evaluation was AUC of 0.899, with high specificity, sensitivity, and significantly higher than the offline area of ROC curve in suPAR, APN and IgE alone and the prediction model (Z=2.771, $P < .05$), as shown in Table 4, Figure 1.

Table 1. Comparison of suPAR, APN, and IgE expression between the two groups

group	suPAR (ng/ml)	APN (μg/ml)	IgE (KU/L)
Study Group (n=100)	10.31±2.79	9.71±2.85	21.96±4.67
Control group(n=100)	3.62±1.37	2.73±1.15	6.22±2.17
t	21.524	22.712	30.566
P value	<.001	<.001	<.001

Table 2. Comparison of suPAR, APN, and IgE expression in patients with different cardiac function grades

Group	suPAR (ng/ml)	APN (μg/ml)	IgE (KU/L)
II level (n=36)	4.37±1.58	5.61±1. 63	16.41±3.55
III level (n=44)	9.82±3.17	9.56±3.41	20.53±4.69
Level (n=20)	13.89±4.96	13.69±4.32	24.35±5.87
F	21.526	23.418	22.537
P value	<.001	<.001	<.001

Table 3. Comparison of suPAR, APN, and IgE expression in the different LVEF groups

group	suPAR (ng/ml)	APN (μg/ml)	IgE (KU/L)
LVEF>40% (n=46)	7.89±2.33	7.69±2.51	16.53±3.58
LVEFF≤40% (n=54)	12.53±3.85	12.99±3.88	24.95±4.17
t	-7.134	-7.592	-10.732
P value	<.001	<.001	<.001

Table 4. Diagnostic potency of suPAR, APN, and IgE in patients with CHF

metric	accuracy	sensitivity	specificity	cutoff value	AUC
suPAR	85.00	80.50	85.50	9.56 ng/ml	0.788 (0.748~0.829)
APN	86.00	85.00	86.60	9.77 μg/ml	0.759 (0.662~0.838)
IgE	83.00	87.00	85.50	20.39 KU/L	0.767 (0.702~0.798)
Joint detection	96.00	97.00	95.50	N/A	0.899 (0.823~0.958)

Figure 1. The ROC curves of the diagnostic efficacy of suPAR, APN, and IgE for CHF patients

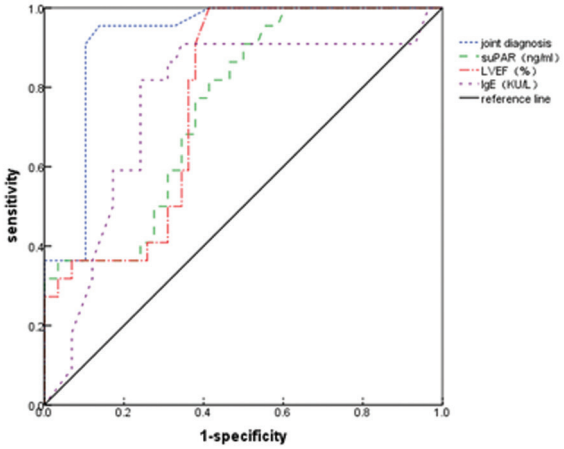

Table 5. suPAR, APN, and IgE with cardiac function, and correlation

	cardiac functional grading	
metric	r	*P* value
suPAR	0.845	<.001
APN	0.796	<.001
IgE	0.831	<.001

Table 6. suPAR, APN, and IgE showed their correlation with LVEF

	cardiac functional grading	
metric	*r*	*P* value
suPAR	-0.779	<.001
APN	-0.786	<.001
IgE	-0.820	<.001

Analysis of suPAR, APN, and IgE with cardiac function, and correlation

The suPAR, APN, IgE, and cardiac function were collected from all patients, and a significant positive correlation was found between the cardiac function grade and suPAR, APN and IgE in CHF patients (all $P < .05$), as shown in Table 5.

Association of suPAR, APN and IgE and LVEF were analyzed

suPAR, APN, IgE and LVEF were collected from all patients, and LVEF showed a significant negative correlation with suPAR, APN and IgE (all $P<0.05$ in CHF patients), as shown in Table 6.

DISCUSSION

CHF is a common clinical disease, and the incidence rate is increasing annually. It is reported that in the past 40 years, the global mortality rate of heart failure cases has increased by about 6-fold, which is one of the main diseases threatening human life and health at present. Therefore, the clinical diagnosis and treatment of CHF have been a focus of research. CHF refers to various causes of heart pump dysfunction or blood filling disorder, progressive myocardial contractility, CO, systemic circulation or pulmonary circulation congestion, causing cases of systemic ischemia hypoxia, gradual loss of exercise ability, ventricular remodeling, ventricular dysfunction and other comprehensive heart disease, is the terminal state of all kinds of heart disease.[8-9] The clinical manifestations are dizziness, weakness, dyspnea, and fluid retention. In the CHF stage, the body develops a series of compensatory changes with the disease, such as sympathetic excitation, myocardial hypertrophy, Frank-Starling compensation, altered vascular endothelial factors, and increased release of inflammatory factors.[10] The hyperactivated neuroendocrine system exacerbates myocardial injury as well as the deterioration of cardiac function. Large amounts of oxygen radicals directly damage cardiac cell membranes, leading to a calcium ions overload state. The increase in the vascular endothelial factor ET-1, as well as the decrease in NO, further aggravated the macroangiopathy. In addition, cardiomyocytes appear energy metabolism disorder, resulting in the energy shortage of the ion pump, calcium ion exchange is blocked, and myocardial electrical activity is affected, further aggravating myocardial diastolic contraction disorder.[11,12] Therefore, it is of great clinical significance to accurately assess the severity of the patient's condition and predict the patient's prognosis, to formulate effective treatment measures as soon as possible, control the change of the patient's condition, and improve the prognosis.[13]

The body's inflammatory response plays an important role in the development of heart failure, and suPA R, a glycosylphosphatidylinositol-fixed glycoprotein, is an inflammatory biomarker involved in the development of inflammation, infection, and tumors.[14] When the body is subjected to inflammatory stimulation, suPA R is cut by proteolysis and released into the blood, increasing the amount of suPA R in the blood; and suPA R gathers a large number of inflammatory cells under the inner membrane through cell adhesion, chemotaxis, and other ways, and promotes the secretion of a large number of inflammatory factors, thus aggravating the inflammatory response of the body and causing serious damage to the patient's heart function.[15] Studies have shown that serum suPA R levels are associated with an increased incidence of atherosclerosis and coronary artery disease, and that elevated serum suPA R levels are an independent risk factor affecting mortality in CHF patients.[16] This study showed that the serum suPA R level of CHF patients was significantly higher than that of healthy controls, that of cardiac function patients was higher than grade and grade patients, and the serum su-PA R level of grade patients was statistically significant, suggesting that suPA R may participate in the disease change process of CHF. Huang Shoulian et al[17] It has been reported that the serum expression of suPAR is significantly increased in patients

with CHF. Furthermore, its serum levels demonstrate a gradual increase corresponding to the patient's cardiac function grade. The existing literature underscores the high prognostic evaluation value of suPAR in predicting patient outcomes in CHF.

It is important to note that while a significant association has been established between elevated suPAR levels and CHF, the current understanding is primarily observational. Further research is needed to elucidate the underlying mechanisms and establish whether suPAR plays a causal role in the development or progression of CHF. Future studies exploring the dynamic interplay between suPAR and CHF could provide valuable insights into the potential utility of suPAR as a predictive and prognostic biomarker for this cardiovascular condition

APN is a protein specifically secreted by adipocytes for regulating glucose and lipid metabolism and reducing insulin resistance[18]. Studies have found that insulin resistance(IR) has a certain relationship with CHF, and appropriate increases in adiponectin levels can antagonize insulin resistance in patients with chronic heart failure. Studies have also found that adiponectin can reverse the myocardial remodeling caused by angiotensin by inhibiting adenylate-activated protein kinase activity and activation of NAD(P)H oxidase to produce reactive oxygen species clusters, thus inhibiting the production of myocardial fibrosis and cardiac hypertrophy.[19,20] In this study, when compared to a control group of a healthy population, the suPAR, APN, and IgE expression were significantly higher in CHF patients in the study group. There are obvious differences in the data; With the increased grade of cardiac function in patients with CHF, The suPAR, APN, and IgE expression showed a trend of gradual increase. Moreover, the data comparisons were significantly different ($P < .05$), It was suggested that patients with HF presented with a depletion status, Poor nutritional status, due to the high-adiponectin status, increased fat mobilization, energy expenditure, and weight loss in HF patients, increased mortality in patients with heart failure, It suggests that HF patients with elevated adiponectin levels have a poor prognosis, It shows that the plasma APN level can be used as a reference index for clinical diagnosis and condition assessment in patients with HF heart failure.[21]

While the observed associations suggest a strong correlation between elevated suPAR, APN, and IgE levels and CHF, it is crucial to note that the current study primarily establishes an observational link. Further research is essential to elucidate whether suPAR, APN, and IgE play a causal role in the development or progression of CHF. Investigating the underlying mechanisms could provide valuable insights into the potential utility of these biomarkers for predictive and prognostic purposes in patients with heart failure.

Serological markers of heart failure mainly include myocardial injury markers, inflammatory markers, oxidative stress markers, and ventricular remodeling markers, which reflect different pathological and physiological processes, respectively. IgE is involved in the development of atopic diseases and systemic allergic reactions and belongs to an inflammatory marker of the cardiovascular system, which is associated with the severity of coronary heart disease. Inflammation has an important role in cardiac remodeling.[22] The immune response acts as a defense mechanism and has an important role in the vascular inflammatory response. Immunized inflammatory response can induce cardiomyocyte hypertrophy and different macrophages can also have different roles in cardiovascular disease, IgE can promote the expression of inflammatory factors, thus promoting atherosclerosis.[23]

The clinical implications of these findings are substantial. Elevated suPAR, APN, and IgE levels could serve as valuable indicators for CHF diagnosis, prognosis, and treatment assessment. Monitoring these markers may provide clinicians with insights into the underlying pathological processes, allowing for more tailored and effective interventions. However, further research is warranted to elucidate the specific mechanisms through which these markers influence CHF progression and to validate their utility in routine clinical practice.

While our study provides valuable insights into the complex landscape of CHF, it is essential to acknowledge certain limitations that may impact the interpretation of our findings. One notable limitation is the relatively modest sample size, which could affect the generalizability of our results. Additionally, potential sources of bias, such as patient selection or data collection methods, may introduce variability in the study outcomes. Confounding factors, inherent in observational studies, could also influence the observed associations.

The clinical manifestations and progression of CHF are multifaceted, and our study focused on specific biomarkers, namely suPAR, APN, and IgE, to explore their potential as diagnostic indicators. However, it is crucial to recognize that CHF involves a complex interplay of various factors, and the exclusive focus on these biomarkers may not capture the full spectrum of the disease.

Moreover, although our study revealed significant differences in the expression of suPAR, APN, and IgE across various grades of cardiac function in CHF patients, it is crucial to recognize that these biomarkers provide only a glimpse into the complex pathophysiological mechanisms involved. The findings from this study suggest several avenues for future research. To further enhance our understanding of CHF, investigating additional biomarkers and expanding the scope of analysis is essential. Future studies could explore the interaction and synergistic effects of a more comprehensive set of biomarkers in larger and more diverse cohorts.

Based on our work, several questions and hypotheses arise, inviting further exploration. For instance, how do these biomarkers interact with other established indicators of heart failure, and what role do they play in the progression of the disease? Additionally, are there specific subpopulations within CHF patients where these biomarkers demonstrate heightened diagnostic or prognostic significance? Addressing

these questions through targeted research endeavors will contribute to a more nuanced understanding of CHF and may pave the way for the development of more effective diagnostic and therapeutic strategies.

To conclude, our study underscores the importance of a careful interpretation of the results, considering the acknowledged limitations. Despite these constraints, the findings hold significant clinical relevance with direct implications for patient care. Understanding the expression patterns of suPAR, APN, and IgE in different grades of cardiac function among CHF patients provides valuable insights for clinicians.

In a clinical setting, [26] the identification of elevated suPAR levels could serve as an early indicator of inflammatory responses, aiding in timely intervention strategies. Similarly, the correlation between APN levels and insulin resistance highlights a potential avenue for targeted therapies in managing chronic heart failure. Furthermore, recognizing the role of IgE in the inflammatory process sheds light on its relevance as a cardiovascular inflammatory marker.

As we navigate the complexities of CHF, our research prompts clinicians to consider a multifaceted approach, incorporating these biomarkers into diagnostic and prognostic assessments. It is also necessary to further implement patients' physical health care and quality of life in clinical medical work.[27] Future studies addressing the identified limitations will undoubtedly refine the clinical applicability of our findings, guiding the development of more precise and effective strategies for the diagnosis and management of CHF patients.

CONCLUSION

In summary, elevated levels of suPAR, APN, and IgE in CHF patients, as indicated by our study, demonstrate substantial diagnostic efficacy, particularly when combined. These biomarkers exhibit a notable positive correlation with cardiac function grade. Our findings suggest that the combined test could serve as a valuable auxiliary diagnostic method for CHF in clinical settings. This insight provides a foundation for enhancing the diagnosis and treatment of CHF patients.

DATA AVAILABILITY

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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None

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