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Examine the association between metabolic syndrome and frailty in an older Asian population

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Abstract: Background: There has been evidence that metabolic syndrome (MetS) may increase the risk of frailty. However, there is limited evidence on this association in Asian populations. **Aims**: This study aims to identify the association between MetS and frailty in older people in Vietnam. **Methods**: This is a cross-sectional analysis of a dataset obtained from an observational study on frailty and sarcopenia in patients aged ≥60 at a geriatric hospital in Vietnam. Frailty was defined by the frailty phenotype. Participants were defined as having MetS if they had ≥3 out of 5 criteria from the definition of the National Cholesterol Education Program (NCEP) Adults Treatment Panel (ATP) III. Multiple logistic regression models were performed to estimate the risk of having frailty in patients with MetS. **Results**: There were 669 participants (mean age 71, 60.2% female), 62.3% had MetS and 39.0% was frail. The prevalence of frailty was 42.2% in participants with MetS, 33.7% in participants without MetS (p=0.029). On logistic regression models, MetS was associated with increased likelihood of being frail (adjusted OR 1.52, 95%CI 1.01-2.28), allowing for age, sex, education, nutritional status, history of hospitalisation and chronic diseases. **Conclusion**: There was a significant association between MetS and frailty in this population. Further longitudinal studies are required to confirm this association.

Keywords: metabolic syndrome; diabetes; hypertension; obesity; frailty; older people; Asian.

1. Introduction

In the recent years, with ageing and considerable changes in population structure worldwide, ranging from higher-income regions to the lesser-developed nations, frailty has emerged as a public health interest due to its debilitating impacts on older people.[1,2] Frailty is characterised by a gradual depletion in physiological reserve and homeostatic tolerance following exposure to stressors people.[2] A recent systematic review of studies across 62 countries showed that frailty was present in 12% to 24% in community-dwelling populations.[1] Such common geriatric condition predisposes older people to various adverse health outcomes, including fall, delirium, hospitalisation or even death and thus is regarded as a crucial transition between healthy ageing and disability.[2] Even though frailty can be characterised by a plethora of frameworks proposed by different organisations, Fried's phenotypic classification framework remains prominent owing to its practicality. In 2001, Fried and her colleagues proposed phenotypic frailty criteria for frailty, thus enabling classification of older people based on their frailty status, taking into account five adverse health features: unexplained weight loss, exhaustion, reduced physical activity, low grip strength and slow gait speed.[3]

On the other hand, metabolic syndrome (MetS), or so-called Syndrome X is also a predominant disorder in the elders.[4] MetS describes a constellation of metabolic disorders,

characterised by hypertriglyceridaemia, central adiposity, hypercholesterolaemia, insulin resistance and hypertension[5]. According to the classification framework established by the National Cholesterol Education Program (Adult's Treatment Panel III), the definition of metabolic syndrome warrants the presence of ≥ 3 of the aforementioned adverse features.[6] Several studies have reported the association between frailty and metabolic syndrome. However, the majority of relevant literature regarding this topic focuses on Caucasian population and there is limited evidence on this topic in the context of other ethnic groups, in particular in Asian populations.[7-15]

Therefore, this study aims to explore this discrepancy, by investigating whether there is a significant correlation between MetS and frailty in older people in Vietnam - a country situated in Southeast Asian region. Previous studies in Vietnam showed that the prevalence of frailty was 21.7% in community-dwelling older people [16], and 32%-55% in older hospitalised patients. [17,18] We hypothesised that in older people, MetS is associated with increased risk of acquiring frailty.

2. Methods

2.1. Participants

This study was a secondary analysis, based on a primary study investigating the prevalence of sarcopenia in older patients in Vietnam. The details of this study were described in a previous publication [19]. Consecutive patients aged 60 years or above at a geriatric hospital in Vietnam were recruited from 1/2018 to 10/2018.

2.2. Data collection

Data in the primary study were collected from patients' medical records and measurements. Information from medical records were extracted by the Vietnamese investigators using a pre-defined data collection form, including demographic characteristics and medical history. Comorbidities were obtained based on a pre-defined list. Nutritional status was evaluated using the Mini Nutritional Assessment Short Form (MNA-SF) tool (maximum score of 14 points, and a total score of ≤7 points was indicative of a malnourished status [20]). Participants' weight (in kg) and height (in m) were measured following standard procedures. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and participants were categorised into three groups: underweight (BMI <18.50), normal (BMI 18.50 – 24.99) and overweight (BMI ≥25.00). Participants' handgrip strength was measured using a dynamometer (Jamar TM Hydraulic Hand Dynamometer 5030 J1, made in the USA) when participants were sitting with their elbows flexed at a 90-degree angle. Grip strength measurements were taken once on each hand and the highest value of the two readings was recorded and utilised for analysis.

Metabolic syndrome definition: Metabolic syndrome (MetS) was defined according to the revised framework by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III[6]. The definition incorporates five major metabolic disturbances: abdominal obesity, hyperglycaemia, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol and hypertension. Presence of at least three out of the five factors confers the acquisition of MetS.

(1) Abdominal obesity: defined as waist circumference ≥102 cm in men, and ≥88 cm in women.

(2) Hyperglycaemia: fasting serum blood glucose (BGL) of ≥100 mg/dL or a concurrent history of diabetes

(3) Hypertriglyceridaemia: defined as serum triglyceride (TG) level of ≥150 mg/dL

(4) Low HDL cholesterol: defined as serum HDL cholesterol level of <40 mg/dl in men or <50 mg/dl in women.

(5) Hypertension: defined as having systolic blood pressure (SBP) of ≥130 mmHg or diastolic blood pressure (DBP) of ≥85 mmHg or concurrent history of hypertension.

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All measurements were obtained either through direct measurements by the research staffs (waist circumference, blood pressure) or blood test results (BGL, serum HDL, TG).

Frailty definition: Frailty was defined by the frailty phenotype (Fried's frailty criteria), which was composed of five components: shrinking, weakness, exhaustion, slowness and low physical activity.[3] Patients were classified as being frail if they met 3 or more out of the 5 components (1-2: prefrail, 0: robust). However, for the purpose of this study, frailty was treated as a binary variable, with presence of ≥ 3 features serves as a cut-off for acquisition of frailty.[3]

(1) Shrinking: defined as unintentional weight loss of ≥5% (or 4.5 kg) in the last year or BMI<18.5

(2) Weakness: cut-off points for low grip strength were <28kg in men and <18kg in women, as outlined by the Asian Working Group for Sarcopenia (AWGS) in 2019.[21]

(3) Self-reported exhaustion: In the primary study, participants were asked to complete the Centre for Epidemiological Studies' Depression scale. Self-reported exhaustion was defined if a participant answered "occasionally or a moderate amount of time (3-4 days)", or "all of the time" (7 days) after being asked "whether you felt that everything you did was an effort" for the past week.

(4) Slowness based on walking speed: Gait speed was deemed "slow" if the participants mobilised by ≤ 0.8 m/s in the 4-meter walking test.

(5) Low physical activity: The International Physical Activity Questionnaire (IPAQ) was used to measure physical activity level of the participants.[22] Low physical activity was defined as a total score of <600 MET-minutes per week.[22]

2.3. Statistical analysis

Binary variables are presented as frequency and percentage, and continuous variables are presented as mean and standard deviation. Frailty was treated as a binary variable (yes/no) with the presence of ≥3 adverse features confirming the frailty status. Comparisons between participants with and without frailty were assessed using Chi-square tests for binary variables and Student's t-tests for continuous variables. Two-tailed P values < 0.05 were deemed statistically significant.

To examine the relationship between metabolic syndrome and frailty, univariate logistic regression was conducted with frailty as the dependent variable and metabolic syndrome as the independent variable of interest. Univariate logistic regressions were also performed for other factors that can be associated with frailty, such as age, sex, education, living condition, comorbidities. The relationship between metabolic syndrome and frailty was then examined further in multivariable logistic regression models controlling for factors that had a p-value <0.05 on the univariate logistic regressions. Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). All variables were checked for multicollinearity and interactions. Data analysis was conducted using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA).

Sample size justification: The sample size of this study was estimated based on the Longitudinal Aging Study Amsterdam. Their baseline data showed that the prevalence of frailty in older participants with MetS was 16.7%, and 8.8% in those without MetS. Therefore, we estimated that a sample size of at least 558 participants will enable the detection of a significant difference in frailty prevalence between older people with and without MetS (at 80% power, 5% significance level)

3. Results

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A total of 996 participants were recruited in the primary study. Among these, data of frailty and metabolic syndrome were available for 669 participants (n = 669) whose characteristics were outlined in **Table 1**.

The participants had a mean age of 71.1±8.5. Among the 669 participants, 60.2% were females and 39.0% were classified as being frail. The most common chronic health conditions were chronic kidney disease (CKD, 52.9%), followed by hypertension (47.5%), chronic obstructive pulmonary disease (COPD, 37.5%) and diabetes (19.9%). Chronic health conditions were more prevalent in the frail population; however, such associations were only significant in hypertension, heart failure, stroke, CKD, cancer and dementia ($p<0.05$). Furthermore, the prevalence of low educational status (37.9% in frail versus 16.4% in non-frail) and recent hospitalisations (64.0% in frail versus 33.6% in non-frail) were around two-fold higher in the frail participants compared to their non-frail counterparts ($p<0.001$). Frailty was also associated with a significantly higher rate of malnutrition at 18.0% (compared to 2.5% in non-frail participants, $p<0.001$) within the study population.

Table 1. Participant characteristics.

	All (N=669)	Nonfrail (N=408)	Frail (N=261)	P-values
Age (years)	71.11 ± 8.55	68.88 ± 7.40	74.65 ± 9.04	<0.001
Female	403 (60.2%)	244 (59.8%)	159 (60.9%)	0.774
Body mass index (kg/m^2)	21.77 ± 3.43	22.49 ± 2.86	20.64 ± 3.92	<0.001
Low education	166 (24.8%)	67 (16.4%)	99 (37.9%)	<0.001
Malnutrition (MNA ≤7)	57 (8.5%)	10 (2.5%)	47 (18.0%)	<0.001
Having history of hospitalization in the past year	304 (45.4%)	137 (33.6%)	167 (64.0%)	<0.001
Chronic health conditions:				
Hypertension	318 (47.5%)	177 (43.4%)	141 (54.0%)	0.007
Diabetes	133 (19.9%)	73 (17.9%)	60 (23.0%)	0.107
Myocardial infarction	18 (2.7%)	9 (2.2%)	9 (3.4%)	0.333
Heart failure	10 (1.5%)	3 (0.7%)	7 (2.7%)	0.043
Stroke	25 (3.7%)	10 (2.5%)	15 (5.7%)	0.028
Peripheral vascular disease	30 (4.5%)	16 (3.9%)	14 (5.4%)	0.379
Chronic kidney disease	354 (52.9%)	179 (43.9%)	175 (67.0%)	<0.001
Chronic obstructive pulmonary disease	251 (37.5%)	143 (35.0%)	108 (41.4%)	0.099
Cancer	10 (1.5%)	2 (0.5%)	8 (3.1%)	0.007
Dementia	4 (0.6%)	0 (0)	4 (1.5%)	0.012

Continuous data are presented as mean ± standard deviation. Categorical data are shown as n (%). MNA, Mini Nutritional Assessment. SBP, systolic blood pressure. DBP, diastolic blood pressure. HDL, high-density lipoprotein.

MetS was present in 62.3% of the participants. The prevalence of MetS was significantly higher in frail participants (67.4% compared to 59.1% in non-frail participants, $p=0.029$). The prevalence of MetS and its constitutive components by gender is demonstrated in **Table 2**. Among the individual components of MetS, elevated blood pressure (67.3%) was the most prevalent, followed by low HDL-C (66.8%), high TG (63.2%). elevated fasting plasma glucose (61.3%), and central obesity (25.0%). MetS was more prevalent in women (71.2% vs. 48.9% in men, $p<0.001$). Abdominal obesity, elevated fasting plasma glucose and low HDL cholesterol were more common in women than in men.

Table 2. The prevalence of metabolic syndrome and its components by gender.

	All	Men	Women	P-values

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	(N=669)	(N=266)	(N=403)	
Having metabolic syndrome	417 (62.3%)	130 (48.9%)	287 (71.2%)	<0.001
Abdominal obesity (waist circumference ≥102 cm in men, and ≥88 cm in women)	167 (25.0%)	6 (2.3%)	161 (40.0%)	<0.001
Fasting blood glucose ≥100 mg/dl or having a history of diabetes	410 (61.3%)	147 (55.3%)	263 (65.3%)	0.009
SBP ≥130 mmHg or DBP ≥85 mmHg or having a history of hypertension	450 (67.3%)	174 (65.4%)	276 (68.5%)	0.407
HDL cholesterol <40 mg/dl in men or < 50 mg/dl in women.	447 (66.8%)	147 (55.3%)	300 (74.4%)	<0.001
Triglyceride ≥150 mg/dl	423 (63.2%)	165 (62.0%)	258 (64.0%)	0.601

SBP, systolic blood pressure. DBP, diastolic blood pressure. HDL, high-density lipoprotein.

Figure 1. presents the prevalence of frailty and its components in participants with and without MetS. Overall, the prevalence of frailty was higher in participants with MetS than in participants without MetS (42.2% versus 33.7%, respectively, p=0.029). Among the five components of frailty, slowness was the most prevalent (86.1%), followed by weakness (71.3%) and low physical activity (29.9%). Participants with MetS had significantly higher prevalence of slowness, low physical activity and exhaustion compared to those without MetS.

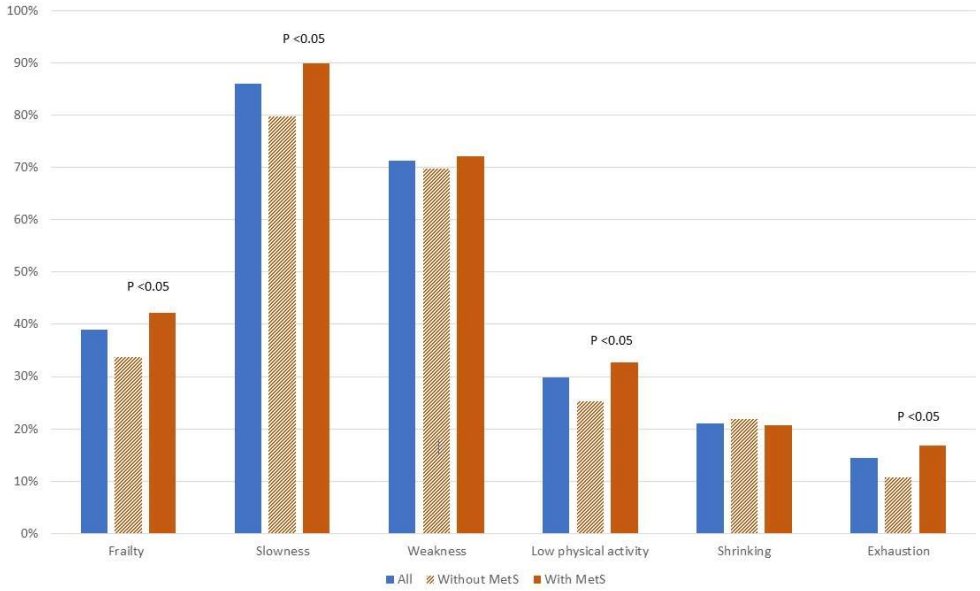

Figure 1. The prevalence of frailty and its components in participants with and without metabolic syndrome (MetS).

On univariate logistic regression, there was a significant relationship between the presence of MetS and an increased risk of frailty (unadjusted OR 1.44, 95%CI 1.04-1.99, p=0.03). This relationship was further explored in multivariate logistic regression, adjusted to age, sex and the variables that were found to demonstrate significant associations with frailty on univariate analyses (**Table 3**).

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Table 3. Univariate logistic regression of potentially associated factors on frailty.

Variables	Unadjusted odds ratios for being frail (95%CI)	P-values
Having metabolic syndrome	1.44 (1.04 – 1.99)	0.030
Age (per year)	1.10 (1.08 – 1.12)	<0.001
Female	1.10 (0.84 – 1.45)	0.499
Recruitment source (inpatients vs. outpatients)	2.92 (2.13 – 3.99)	<0.001
Low education	2.92 (2.15 – 3.97)	<0.001
Malnutrition	9.14 (4.71 – 17.74)	<0.001
History of hospitalization in the last year	2.99 (2.26 – 3.95)	<0.001
Myocardial infarction	0.88 (0.38 – 2.01)	0.760
Heart failure	1.95 (0.80 – 4.75)	0.143
Stroke	2.07 (1.02 – 4.22)	0.045
Peripheral vascular disease	1.07 (0.59 – 1.94)	0.830
Chronic kidney disease	2.66 (1.98 – 3.58)	<0.001
Chronic lung disease	1.05 (0.79 – 1.38)	0.761
Cancer	4.26 (1.12 – 16.15)	0.033
Dementia	3.16 (0.58 – 17.35)	0.185

After adjusting to age, sex, low educational and nutritional statuses, recent hospitalisation, recruitment resources and chronic health conditions (CKD, stroke and cancer), MetS still remained significantly associated with a higher risk frailty (adjusted OR 1.52, 95%CI 1.01 - 2.28, p=0.043) (**Table 4**).

Table 4. Multivariate logistic regression of metabolic syndrome on frailty status.

	Adjusted odds ratios for being frail (95%CI)	P
Model 1	1.42 (1.00 – 2.00)	0.049
Model 2	1.42 (1.00 – 2.02)	0.049
Model 3	1.47 (1.01 – 2.14)	0.045
Model 4	1.62 (1.10 – 2.38)	0.015
Model 5	1.52 (1.01 – 2.28)	0.043

Model 1: adjusted to age Model 2: adjusted to age, education Model 3: adjusted to age, education, nutritional status, hospitalisation in the past year Model 4: adjusted to age, education, nutritional status, hospitalisation in the past year, chronic health conditions (chronic kidney disease, stroke, peripheral vascular disease, cancer) Model 5: adjusted to age, sex, education, nutritional status, hospitalisation in the past year, chronic health conditions (chronic kidney disease, stroke, peripheral vascular disease, cancer) and recruitment sources.

4. Discussion

In this study of 669 older participants, there was a high prevalence of frailty (39.0%) and MetS (62.3%). The presence of MetS was associated with a significantly higher likelihood of being frailty in the participants.

Our findings on the significant association between MetS and frailty coincided with findings from several previous studies. Our literature search revealed that most of the studies on this topic were conducted in Caucasian older populations [7-13], with only two studies reported the association between frailty and metabolic syndrome in Asian populations.[14,15] Chao and colleagues found that among 2862 community-dwelling older adults, the presence of MetS were associated with a significantly higher risk of combined frailty/prefrailty (OR 2.53, 95%CI 1.78-3.60).[14] Lee and colleagues also reported that metabolic syndrome were strongly associated with frailty status (OR 3.2, 95%CI 1.7-6.0).[15] In a

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cross-sectional study of 118 non-institutionalised older people in Italy (mean age 76.1±5.0 years, 60% women), Viscogliosi and colleagues found that the prevalence of frailty was significantly higher in the participants with MetS compared to those without MetS (60.7% vs. 12.9%, respectively), and the adjusted odds ratio of MetS for frailty acquisition was comparable to our study at 1.53 (95%CI 1.33-1.76).[7] Their longitudinal data also showed that baseline MetS increased the risk of reduced handgrip strength and gait speed.[23] An analysis from the Salus in Apulia study in Italy also showed that metabolic syndrome was associated with increased risk of physical frailty (OR 1.42, 95%CI 1.00-2.03).[13] In another cross-sectional study conducted in Germany in 1,486 elderly participants with a mean age of 68.7 years, the odds of being prefrail/frail was significantly increased with the presence of MetS (adjusted OR 1.5, 95%CI 1.2-1.9).[10] Another data analysis from 1247 elderly participants partaking in the Longitudinal Aging Study Amsterdam also reported a significantly higher prevalence of frailty in those with MetS (16.7%) compared to their unaffected counterpart (8.8%).[8] In a longitudinal study by Perez-Tasigchana in Spain, after following 1499 community-dwelling participants (aged ≥ 60 years) for 3.5 years, they found that participants with MetS had higher risk of developing frailty than those without MetS (OR 1.85, 95%CI 1.12-3.05), adjusting for participants' socio-economic factors, healthy behaviours and comorbidities.[9]

Although the pathophysiological linkage between MetS and frailty is still an area of active research, several studies suggested low-grade chronic inflammation state, high circulating inflammatory markers and neuroendocrine dysfunction as common grounds between the two syndromes. A meta-analysis of 32 cross-sectional studies demonstrated significant associations between increased inflammatory markers, in particular IL-6 and C-reactive protein (CRP) with impaired muscle function, predisposing older people to increased risk of frailty.[24] Similarly, pro-inflammatory state induced by adipokines and other inflammatory mediators was also postulated to be central to insulin resistance and thus MetS pathogenesis.[25] The individual components defining MetS were shown to contribute to the presence of frailty in several studies. Hypertension, in particular high systolic blood pressure was shown to have a positive correlation with frailty in studies by Newman, Bastos-Barbosa and their respective colleagues.[26,27] Abdominal obesity, after adjusted for BMI, was demonstrated to increase the risk of frailty, on both frailty index (FI) and phenotypic classifications according to Hubbard and colleagues.[28] Several other studies showed that insulin resistance was amongst the most commonly-documented component of MetS, with respect to its association with frailty.[9,29] Longer duration of insulin resistance or overt diabetes, coupled with poor glycaemic control could have resulted in suboptimal muscle quality and strength, thus directly increasing the odds of falls and frailty.[30]

To the best of our knowledge, this study is the first of its kind to provide evidence on the association between metabolic syndrome and frailty in Vietnam. However, this study has several limitations. First, this was a secondary analysis, and thus, we were limited by the available data. A total of 327 participants, despite meeting criteria for inclusion from the primary study, was excluded from our analysis because of insufficient data to define frailty and MetS. Second, this study was conducted at only one geriatric hospital in Vietnam. Therefore, the studied population may not be representative for all older patients in Vietnam and the results should be interpreted cautiously. Although the ability for generalisation was somewhat limited, owing to its single site nature, our study still remains relevant in a public health point-of-view, serving as a starting point for future studies linking the two prominent risk factors for adverse health outcomes in older people. As metabolic syndrome and its constitutive components are targetable pharmacologically and conservatively through public health directives, a significant relationship between MetS and frailty could aid decision makers, justify the role of MetS management as a primary prevention for frailty syndrome in older people.

5. Conclusion

This study found that metabolic syndrome was present in around two-thirds of the participants and was associated with increased risk of frailty. Further longitudinal studies are required to confirm this association. These findings support routine assessment for frailty in older people with cardio-metabolic disorders.

Competing interests: None

Author Contributions: All authors (Hiep HH Dao, Tu Ngoc Nguyen, Huyen TT Vu, Anh Trung Nguyen) contributed to the study conception and design. Participant recruitment and data curation were performed by Huyen TT Vu and Anh Trung Nguyen. Data analysis were performed by Hiep HH Dao and Tu Ngoc Nguyen. Hiep HH Dao and Tu Ngoc Nguyen wrote the various drafts of the manuscript. All authors contributed to interpretation of data and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the National Geriatric Hospital in Hanoi, Vietnam (protocol code 1235/IRB, date of approval 28/11/2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The study data is available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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