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ORIGINAL INVESTIGATION

Frailty status and the risk of fractures in older people: the Pro.V.A. Longitudinal study

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Background and aims. Frailty has been associated with an increased risk of fractures in older people, but the mechanisms behind this relationship have yet to be fully elucidated. We aimed to investigate which frailty criteria were more closely associated with the risk of fractures in community-dwelling older people.
Methods. This study analyzed data from 2,113 older men and women enrolled in the Progetto Veneto Anziani (ProVA) study and with no fractures at baseline. Frailty was assessed at baseline and defined as the presence of at least three out of five Fried criteria, pre-frailty was the presence of one or two criteria, while non-frailty was the presence of none of the criteria. Fractures after a mean 4-year follow-up were assessed on the basis of medical records, self-reports, and radiographic examinations.
Results. At follow-up, we identified 233 (11%) new cases of fracture, with an age- and gender-specific incidence rate of 22/1000 person-years (95% CI: 11-36). Compared with the non-frail, frail and pre-frail individuals carried a significant 59% (OR = 1.59, 95% CI: 1.31-1.93) and 21% (OR = 1.21, 95% CI: 1.09-1.34) higher risk of fractures, respectively. Among the frailty determinants, slow gait raised the likelihood of fractures by 56%, physical inactivity by 46%, exhaustion by 32%, and weakness by 31%. No significant associations with unintentional weight loss emerged after adjusting for potential confounders.
Conclusions. Frailty may predict the occurrence of fractures in older people, probably through mechanisms mediated by impaired physical performance and exhaustion. Slow gait seems to be the most relevant factor in increasing the risk of fractures in advanced age.

Key words: Frailty, Bone fractures, Older age, Prospective study

INTRODUCTION

Bone fractures represent one of the main causes of morbidity and disability in the elderly population, with consequent high costs for the healthcare system [1]. The incidence of fractures increases exponentially with age, particularly for hip fractures, for which it reportedly rises by 1% a year for women over 80 with some geographical variations [1]. The wrist, vertebra and distal forearm are other common sites of fracture in older people, though their incidence may be underestimated because patients are less likely to need hospitalization.
The recognized major factors predisposing older adults to fractures are bone strength and recurrent falls [2 3]. Both these conditions are strongly influenced by features typical of aging, such as sarcopenia, cognitive and functional impairments, depression and inflammatory

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states – which also describe the phenotype of frailty syndrome [4 5].

A two-way relationship between fractures and frailty has emerged from the current literature. In fact, frailty status may predispose individuals to falls [2 6], and a history of fractures has been associated with the onset of frailty [7 8]. Moreover, a recent systematic review and meta-analysis including five prospective studies showed that the pooled risk of fractures was increased by 67% in frail and by 30% in pre-frail individuals, compared with non-frail people [9].

While the link between frailty and bone fractures has been demonstrated in a large body of literature, little attention has been paid to which aspects of frailty could be more influential than others. Rothman et al. assessed the impact of frailty determinants on the occurrence of injurious falls in a cohort of community-living older individuals, finding slow gait speed at baseline the most significant predictor [10]. To the best of our knowledge, however, no studies have investigated which determinants of frailty are the most associated with the risk of fractures. Identifying the frailty determinants more strongly associated with the onset of fractures may enable targeted preventive action to reduce the risk of falls and bone fractures.

Based on these considerations, the aim of our study was to investigate the impact of frailty syndrome and its determinants on the incidence of bone fractures in a cohort of older persons over a 4.4-year follow-up.

SUBJECTS AND METHODS

Data source and subjects

The study population consisted of individuals included in the Progetto Veneto Anziani (Pro.V.A.), an observational cohort study that involved 3099 age- and sex-stratified community-dwelling adults aged 65 years and over (1245 men and 1854 women) living in northern Italy. Participants were randomly selected between 1995 and 1997 using a multi-stage stratified sampling method [11]. The study data were collected by trained physicians and nurses at two out-patients' clinics or at participants' homes if they were housebound.

For the purposes of the present study, we analyzed participants' baseline data to identify cases of frailty syndrome, and then examined the cases of fracture after a mean follow-up of 4.4 ± 1.2 years.

Of the 3,099 participants initially enrolled in the study, 326 were excluded because they reported a history of fractures at baseline, 651 died before the follow-up, and 9 lacked sufficient follow-up data, so the final sample consisted of 2,113 older men and women.

The ethical committees of the University of Padua and the Veneto Region's Local Health Units (USSL) no. 15 and 18 approved the study protocol, and participants gave their written informed consent.

Anthropometric, demographic and clinical characteristics

Trained physicians and nurses conducted face-to-face interviews with study participants, and recorded information on their educational level, physical activity, and smoking and drinking habits. Participants' educational level was classified as ≤ 5 or > 5 years (primary school in Italy lasts 5 years), and monthly income as ≤ 500 or > 500 € (equivalent to one million lire), considering as a cut-off the mean pension of Italian retired people during the study period. Smoking status was classified as "never", "former" (for at least a year in the past) and "current" smokers. Drinking habits, defined as any use of any alcoholic beverage in the previous month, was categorized as yes/no. Body weight and height were measured, and the body mass index was calculated (BMI, kg/m^2). Waist circumference was measured midway between the lowest rib and the iliac crest (with participants standing) and expressed in centimeters.

Functional status was evaluated with the Activities of Daily Living (ADL, score from 0 for complete dependence to 6 for total self-sufficiency) and the Instrumental Activities of Daily Living (IADL, score from 0 for total dependence to 8 for complete independence) [12] scales. Depressed mood was assessed using the 30-item Geriatric Depression Scale (GDS), a method validated for the elderly population, which indicates depressive symptoms for scores higher than 10 [13]. Cognitive status was assessed by means of the Mini-Mental State Examination (MMSE) [14]. Lower extremity physical performance was tested by means of the Short Physical Performance Battery (SPPB), which evaluates gait speed, static balance, and time to rise from a chair. The total score on these three tests ranged from 0 (poor) to 12 (good) physical performance [15]. Handgrip strength was assessed using a JAMAR hand-held dynamometer (BK-7498, Fred Sammons, Inc.), and the highest score obtained with three technically-acceptable tests on the dominant side was considered in our analyses.

The participants' medical and hospital records, comorbidities, self-reported symptoms, and records of physical examinations and blood tests were collected by trained physicians and nurses. For the purpose of our analyses, we considered the presence of hypertension, diabetes, cardiovascular diseases (CVD), chronic obstructive pulmonary diseases (COPD), osteoporosis, cancer, lower limb osteoarthritis (OA), and cognitive impairment. Any use of calcium and vitamin D supplements, and bisphosphonates (assessed as yes/no) was also recorded. Diabetes was defined as fasting plasma

glucose levels ≥ 7.0 nmol/L, glycosylated hemoglobin (HbA1c) ≥ 6.5%, the use of glucose-lowering drugs, or a history of a 2 h post-load glucose ≥ 11.1 nmol/L [16]. CVD was defined as any of the following: congestive heart failure, angina requiring a stent, angioplasty or hospitalization, myocardial infarction and stroke. Osteoporosis was identified on participants' medical history or dual X-ray absorptiometry (DXA) scans, defining the disease as the presence of a T-score of -2.5 or lower at the hip, femoral neck, or spine [17]. Lower limb OA was assessed during the interviews with physicians and nurses by means of a clinical examination and participants' medical records, previous X-ray reports, and use of analgesics. A diagnosis of OA was subsequently confirmed by a rheumatologist using a standardized algorithm that also considered records of hospital admissions for OA and prostheses intended to relieve OA-related complications. Renal function was assessed from the estimated glomerular filtration rate (eGFR), calculated with the MDRD (Modification of Diet in Renal Diseases) formula [18].

Biochemical parameters were also considered as potential confounders in our analyses. Serum concentrations of 25-hydroxyvitamin D (25[OH]D) and parathormone (PTH) were assessed. Serum 25OHD levels were measured by radioimmunoassay (RIA kit; DiaSorin) with intra- and inter-assay coefficients of variation (CV) of 8.1 and 10.2%, respectively. Serum intact PTH levels were measured using a two-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin): the intra- and inter-assay CV were 3.0 and 5.5%, respectively.

Frailty assessment and definition

At baseline we assessed the presence of frailty and frailty determinants on the basis of Fried frailty criteria [4]. In particular, we defined frailty as the presence of at least three criteria of Fried frailty phenotype, and pre-frailty as the presence of one or two criteria [4], among:

- self-reported unintentional weight loss of 5 kg or more over the previous year;
- exhaustion, defined as a GDS score higher than 10, and the answer "no" to the item "Do you feel full of energy?" (since data based on the Center for Epidemiological Studies scale for depression [CES-D] were unavailable). The GDS has been used to estimate and predict fatigue and exhaustion in other similar studies [19];
- physical activity level, measured by estimating the energy expenditure on daily activities with a cutoff of 383 kcals/week, and 270 kcals/week for men and women [4], respectively, to define low physical activity;
- gait speed, measured during a 4-meter walk, and adjusting for gender and height to define appropriate cut-offs for frailty [4];
- grip strength, adopting specific cut-offs by gender and BMI to define the presence of weakness [4].

Assessment of fractures

Information on fractures was obtained at the end of the study period from medical and hospital records, self-reports, and X-rays taken during the 4.4-year follow-up of any incident fractures involving the wrist, radius, or femoral or vertebral regions.

Statistical analysis

The Pro.V.A. sample was generalized to the population in the two geographical areas where the participants lived, using a set of weights based on the gender and age distribution of the reference population (Italy, Census 1991) and the sample fraction.

Normal distributions of continuous variables were tested using the Shapiro-Wilk test. The data are shown as means ± standard deviations for quantitative measures and as frequency percentages for all discrete variables. Differences in baseline characteristics between individuals classified by frailty status were compared through the ANOVA test, for continuous variables, and the Chi-square test, for the categorical ones. Levene's test was used to test the homoscedasticity of the variances, and Welch's ANOVA was used whenever its assumption was violated.

Multivariate logistic regression analyses were run, considering baseline frailty status as the independent variable and the onset of fractures during the follow-up as the dependent variable. Participants who were not frail were taken for reference in all analyses. Variables that significantly differed between baseline frailty groups and that could be potential confounders in the association between frailty and fractures were considered for inclusion in the fully-adjusted model. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between baseline frailty status and frailty criteria with the onset of frailty at follow-up.

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed, and a p-value < 0.05 was assumed to be statistically significant.

RESULTS

The data on 2,113 participants (798 M, 1315 F, unweighted data) were included for the purposes of our study. Across the sample as a whole, the mean age was 74.4 ± 7.0 years and the mean BMI was 27.9 ± 4.5 kg/m^2. At the baseline assessment, 216 (10.2%) participants, the majority of them women (79.6%), met at least three of the frailty criteria and were defined as

frail. Compared with the participants who reached the follow-up assessment, those who died during the study period were more likely to be older (mean age 81.5 ± 7.6 years) and to report higher prevalence of diabetes (21.5%), CVD (41.2%), COPD (17.1%), cancer (11.7%), cognitive impairment (26.7%), and frailty (41.9%). They were more likely to have lower BMI values (26.6 ± 4.5 kg/m^2), to be dependent in activities of daily living and physically impaired. No significant differences were found instead on educational level, socioeconomic status, and drinking habits (data not shown). The characteristics of the sample as a whole, and divided by baseline frailty status are reported in Table I. Compared with non-frail and pre-frail subjects, those who were frail were significantly older, less physically active and more dependent in ADL. They reported lower educational levels and monthly incomes, and were less likely to be drinkers and smokers. As regards comorbidities, the frail group had a higher prevalence of CVD, osteoporosis, cancer, lower limb OA, cognitive impairment and depressed mood.

After 4.4 years of follow-up, we found 233 (11%) new cases of fracture, with an age- and gender-specific incidence rate of 22/1000 person-years (95% CI: 11-36) in the sample as a whole. Figure 1 shows the cumulative rate of fractures reported at follow-up among participants divided by baseline frailty status. Significant differences emerged in the rate of new fractures between the groups, with 78 cases among the non-frail (8.7%), 118 among the pre-frail (11.8%), and 37 among the frail individuals (17.1%; $p < 0.0001$). Similarly, the presence at baseline of all determinants of frailty was associated with a higher incidence of fractures at follow-up ($p < 0.0001$ for all, Fig. 1).

Table I. Baseline characteristics of the sample as a whole, and by frailty status. Numbers are mean values (and standard deviations) or percentages (%), as appropriate (unweighted data).

	Frailty status				
Variables	**All (n = 2113)**	**Non-frailty (n = 894)**	**Pre-frailty (n = 1003)**	**Frailty (n = 216)**	**P-values**
Age (years)	74.4 ± 7.0	71.8 ± 5.5	75.4 ± 7.1	80.8 ± 7.0	< 0.001
Sex (women, %)	62.2	51.1	68.4	79.6	< 0.001
BMI (kg/m^2)	27.9 ± 4.5	27.7 ± 4.0	28.1 ± 4.8	27.4 ± 5.4	0.04
Waist (cm)	96.8 ± 11.6	96.5 ± 10.4	97.3 ± 12.2	95.6 ± 13.1	0.09
Diabetes (%)	15.1	14.3	15.2	18.5	0.30
CVD (%)	18.2	13.6	19.4	31.5	< 0.001
Osteoporosis (%)	39.6	32.7	43.3	51.4	< 0.001
Cancer (%)	6.8	4.9	8.0	8.8	0.01
COPD (%)	7.4	5.8	8.7	7.9	0.06
Lower limb OA (%)	24.4	15.3	28.4	43.5	< 0.001
Cognitive impairment (%)	4.2	0.2	2.9	26.9	< 0.001
Educational level > 5 years (%)	14.2	19.0	12.1	8.0	< 0.001
Current smokers (%)	9.4	12.5	7.5	5.2	< 0.001
Former smokers (%)	28.5	35.1	25.0	17.4	< 0.001
Monthly income > 500 € (%)	39.9	43.1	35.7	33.0	0.01
Drinking habits (%)	69.1	75.1	66.9	55.1	< 0.001
ADL (score)	5.3 ± 1.2	5.8 ± 0.5	5.2 ± 1.1	3.5 ± 2.0	< 0.001
IADL (score)	6.3 ± 1.8	7.2 ± 1.0	6.2 ± 1.6	3.5 ± 2.0	< 0.001
GDS (score)	9.4 ± 5.3	7.8 ± 3.6	10.4 ± 5.3	11.5 ± 8.3	< 0.001
MMSE (score)	24.3 ± 5.0	26.0 ± 3.3	24.0 ± 4.4	18.3 ± 8.4	< 0.001
SPPB (score)	8.5 ± 3.3	10.4 ± 1.5	8.0 ± 3.0	3.2 ± 3.0	< 0.001
25(OH)D (nmol/l)	83.2 ± 54.1	96.5 ± 55.9	77.3 ± 51.9	51.8 ± 36.1	< 0.001
PTH (ng/l)	40.3 ± 23.8	36.7 ± 18.9	42.2 ± 26.2	46.9 ± 28.2	< 0.001
GFR (ml/min)	69.9 ± 18.3	71.9 ± 16.9	69.1 ± 18.2	65.7 ± 23.2	< 0.001
Use of calcium supplements (%)	1.8	1.9	1.6	1.9	0.87
Use of vitamin D supplements (%)	1.0	0.7	1.2	1.4	0.43
Use of bisphosphonates (%)	1.4	1.5	1.4	0.9	0.83

Abbreviations. BMI: body mass index; CVD: cardiovascular diseases; COPD: chronic obstructive pulmonary disease; ADL: activities of daily living; IADL: instrumental activities of daily living; GDS: geriatric depression scale; MMSE: mini mental state examination; SPPB: short physical performance battery; 25(OH)D: 25-hydroxyvitamin D; PTH: parathormone; GFR: glomerular filtration rate.

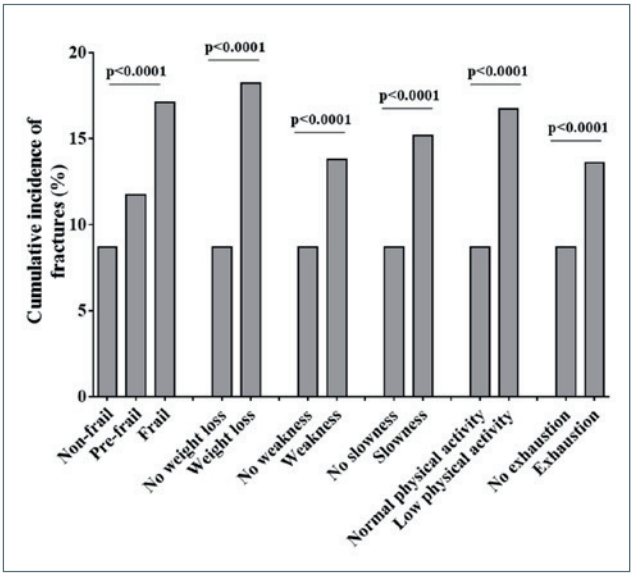

Figure 1. Cumulative incidence of fractures occurring during the 4.4-year follow-up in participants divided by frailty status and presence/absence of frailty criteria at baseline.

Logistic regression analyses confirmed the association between baseline frailty status and fractures at follow-up also after adjusting for potential confounders, with the fracture risk 20% higher for the pre-frail, and 56% higher for the frail individuals (OR = 1.56, 95% CI: 1.31-1.87, p < 0.001), compared with those who were not frail (Tab. II). When the frailty criteria were considered separately, the risk of fractures was significantly associated with low baseline walking speed (OR = 1.51, 95% CI: 1.34-1.70, p < 0.001), low physical activity (OR = 1.62, 95% CI: 1.31-2.00, p < 0.001), weakness (OR = 1.35, 95% CI: 1.22-1.51, p < 0.001), and exhaustion (OR = 1.23, 95% CI: 1.09-1.39, p = 0.001). No significant results emerged for the association between unintentional weight loss and fractures at follow-up.

DISCUSSION

Our longitudinal study confirmed that frailty and pre-frailty significantly increased risk of fractures occurring over a period of 4.4 years in a cohort of community-dwelling older adults. The determinants of frailty most strongly associated with fractures were slow gait, physical inactivity, exhaustion and weakness.

The sample considered in our study revealed a higher prevalence of frailty than in similar samples of older people (10.2 *vs* 6.9% [4] and 8.8% [20]), while large cohorts of women showed an even higher prevalence of frailty than ours, ranging from 16% in two American works [21 22] to 22% in the GLOW international study [23]. These differences in frailty prevalence may be attributable to a variability of the participants' characteristics depending on the inclusion criteria adopted and/or on the different tools used to assess frailty, particularly weight loss, physical activity and exhaustion.

When we investigated the association between the occurrence of fractures and the presence of frailty phenotype, we found a 56 and 20% higher risk of fractures in frail and pre-frail individuals, respectively, compared with their non-frail counterparts. Our results confirm the findings of previous studies [6 8 9 22 24 25]. In particular, similar prospective studies on older women showed an increase in the risk of fractures ranging from 11-31% for the pre-frail, and from 25-57% for frail subjects [21-23], with a marked variability due mainly to the site of fracture considered. Consistently, the risk of falls – a factor that, combined with declining bone strength, may significantly influence the risk of fractures – seems to rise in frail individuals too [4 7 8 26 22-24]. However, the results of a recent study that compared the simplified Women's Health Initiative and the standard Cardiovascular Health Study frailty phenotypes in predicting adverse health-related outcomes in older women found that both phenotypes were associated with increased rates of falls and mortality, but neither could predict incident hip fractures [27].

In addition to bone strength [28], other well-recognized factors promoting falls and fractures in older people are also common features of the frailty syndrome, such as poor physical performance, impaired balance and mobility, low body mass index and reduced lean mass, loss of vision, cognitive decline and polypharmacy [29]. The overall impact of these factors on the likelihood of fractures was demonstrated in our study too when frailty determinants were analyzed separately, with slow gait, physical inactivity, weakness and exhaustion all associated with a higher risk of fractures.

Many authors have identified low walking speed as the strongest predictor of such adverse outcomes as cardiovascular diseases, chronic disability and mortality [10 30]. Rothman et al. also found that this factor was the only frailty criterion capable of predicting injurious falls [10], since it is an indicator of impaired mobility and physical inactivity, both conditions potentially predisposing older people to fractures [31]. Weakness is another marker of scarce physical performance that could raise the risk and consequences of falls in older people [32]. Loss of muscle strength, together with a reduction in muscle mass, are the hallmarks of sarcopenia, a condition closely associated with osteoporosis and higher risk of falls [28 33]. Our study confirmed that weakness increases the chances of fractures, even after adjusting for any presence of osteoporosis, suggesting that this

Table II. Association between the baseline frailty status and frailty determinants with the presence of fractures at follow-up.

Odds ratios and 95% Confidence Intervals of Incident Fractures				
	Age- and sex-adjusted model	**P-value**	**Fully-adjusted model***	**P-value**
Baseline frailty status				
Non-frailty	1 [ref]		1[ref]	
Pre-frailty	1.19 (1.08-1.31)	< 0.001	1.20 (1.09-1.33)	< 0.001
Frailty	1.67 (1.44-1.94)	< 0.001	1.56 (1.31-1.87)	< 0.001
Unintentional weight loss	1.69 (1.16-2.46)	0.01	1.34 (0.91-1.98)	0.14
Weakness	1.37 (1.23-1.51)	< 0.001	1.35 (1.22-1.51)	< 0.001
Slowness	1.50 (1.35-1.67)	< 0.001	1.51 (1.34-1.70)	< 0.001
Low physical activity	1.79 (1.50-2.13)	< 0.001	1.62 (1.31-2.00)	< 0.001
Exhaustion	1.29 (1.15-1.44)	< 0.001	1.23 (1.09-1.39)	0.001

*Adjusted for: sex (male/female), age, body mass index (20-24.9 *vs* < 20/25-29.9/≥ 30 kg/m^2), cardiovascular diseases, osteoporosis, lower limb osteoarthritis, cancer, cognitive impairment (all as yes *vs* no), educational level (≤ 5 *vs* > 5 years), smoking habits (never *vs* current *vs* former), monthly income (< *vs* > 500 euros), drinking habits (yes *vs* no), serum levels of parathormone (≤ 55 *vs* > 55 ng/l), serum levels of 25-hidroxivitamin D (< 75 *vs* ≥ 75 nmol/l), activities of daily living (as continuous variable).

frailty criterion has an independent role in raising the risk of fractures, probably through endocrine-immune mechanisms involved in the musculoskeletal frailty typical of advanced age [33 34]. The incidence of fractures in our sample also rose for people reporting exhaustion at baseline. The feeling of tiredness and depression have been associated with a higher likelihood of falls due to a worse physical performance, slow reaction time and gait, and an impaired balance, mediated by both cognitive and physical mechanisms [35 36]. Falls and the fear of falling can negatively affect motor and psychological well-being, adding to the risk of fractures [37]. Finally, when we considered unintentional weight loss, we found no significant independent association with the onset of fractures, although there are reports of reductions in lean mass and BMI being associated with higher risks of falls and fractures [38 39].

The present study has some limitations. First of all, our not having assessed vertebral fractures by means of morphometric measurements means that we may have underestimated the incidence of such fractures in our sample because most mild and early vertebral body deformations are asymptomatic in older people. Second, we did not consider a history of falls as a potential confounder in the association between frailty and the occurrence of new fractures, though having excluded individuals reporting fractures at baseline minimizes this potential bias. Third, our assessment of frailty syndrome may be biased because self-reported information was considered regarding weight loss and daily physical activities, and the GDS scale was used to define exhaustion.

On the other hand, a strength of our work lies in the prospective design of the study and the inclusion of a large sample of older subjects living in the community. Having adjusted our analyses for multiple covariates also strengthens our results, ruling out any influence of confounders on the association between frailty and the occurrence of fractures. A novel aspect of our study lies in that we investigated how frailty status was associated with the risk of fractures by focusing on single frailty determinants.

In conclusion, frail and pre-frail older adults carry a higher risk of fractures than their non-frail peers. Physical inactivity and slow gait, in particular, but also weakness and exhaustion seem to exacerbate the fracture risk in older people. Assessing older people for any presence of these factors may help to identify those at higher risk of fractures and enable targeted preventive action.

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None of the authors have any financial arrangements, organizational affiliations or other relationships that might give rise to any conflict of interest regarding the subject matter of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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