



Screening for Vascular Disease in Pulmonary Rehabilitation

Sofia Arruda^{1*}, Marty Tam¹, Marianne Vest¹, Joel Hughes², John Gunstad²,
Mary Dolansky^{1,3}, Richard Sukeena¹ and Richard Josephson¹

¹Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, Ohio, United States.

²Department of Psychology, Kent State University, Kent, Ohio, United States.

³Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio, United States.

Authors' contributions

This work was carried out in collaboration between all authors. Author RJ was responsible for the coordination of the overall study, including: the study design, collaboration amongst investigators, data analysis, and manuscript preparation. Author SA wrote the first draft of the manuscript. Authors MT and SA managed the analyses of the study and the literature searches. Authors MD, JH and JG contributed to the study design and selection of cognitive biobehavioral instruments. Author MV and RS assisted with staff training, manuscript review, and study design.

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ABSTRACT

Background: Several of the comorbidities and risk factors associated with COPD and other pulmonary disorders are also similar to those for lower extremity peripheral artery disease (PAD) and cerebrovascular disease. The later condition is often manifested as cognitive impairment, not only from large vessel associated stroke, but also from vascular cognitive impairment (VCI). We hypothesized that pulmonary rehabilitation (PR) would be an appropriate site to discern the prevalence of both PAD and mild cognitive impairment (MCI). Individuals in PR with severe pulmonary disease may have impaired cognition, which could impact learning and treatment adherence while PAD may contribute to functional limitation.

Study Design: In this pilot study of 14 patients enrolled in phase II PR, we describe the prevalence

*Corresponding author: Email: sarruda1@jhu.edu;

of PAD and cognitive impairment, the utility of screening tools, and the potential relationship between PAD, depression, and cognitive impairment.

Results: Twenty-eight percent of patients had an abnormal ABI with two subjects manifesting low (<0.90) and two subjects with abnormally high (>1.40) ABI. The Edinburgh Claudication Questionnaire was negative in all subjects and was not useful in the detection of PAD (sensitivity 0%, specificity 11%, PPV 0%, NPV 78.57%). The Walking Impairment Questionnaire did not differentiate patients with or without abnormal ABIs with respect to walking distance (40.02 vs. 64.46 meters, $P=.154$), speed (27.15 vs. 25.92 miles per hour, $P=.545$), or symptoms (46.88 vs. 63.75, $P=.152$). Furthermore, eleven of the fourteen patients (79%) had an overall score of less than 26 on the Montreal Cognitive Assessment, indicating cognitive impairment. Scores indicating mild to moderate depression or anxiety measured by the PHQ-9 and STAI questionnaires revealed a concurrence between depressive and anxiety symptoms.

Conclusion: Our results have led us to postulate a possible relationship between PAD and MCI, along with that of PAD and depression and anxiety. Future studies, with a large sample size, will provide more insight on ameliorating care for patients whose vascular disease affects cognitive function and mental health.

Keywords: Pulmonary rehabilitation; PAD; COPD; mild cognitive Impairment.

1. INTRODUCTION

Pulmonary disorders are an increasing cause of disability and functional impairment, followed by high rates of mortality [1]. Patients enrolled in a pulmonary rehabilitation (PR) program are provided with individually tailored therapy to minimize their disability, to improve functional impairment and disease specific knowledge, and to decrease the psychological burden of their disorder. A majority of patients enrolled in PR are diagnosed with chronic obstructive pulmonary disease (COPD), the fourth-leading cause of death in the United States [1]. Several of the comorbidities and risk factors associated with this and other pulmonary disorders are notably similar to those for lower extremity peripheral artery disease (PAD) and cerebrovascular disease. Symptomatic and functional consequences of PAD emerge from intermittent or chronic leg ischemia leading to claudication. Cerebrovascular disease is often manifested as cognitive impairment, not only from large vessel associated strokes, but also from vascular cognitive impairment (VCI). This latter condition is a heterogeneous group of disorders including VCI-no dementia, vascular dementia, and cognitive impairment of mixed (Alzheimer's disease and vascular dementia) origin [2]. Additionally, patients with VCI-no dementia have a high risk of progression to dementia, mixed primary neurodegenerative dementia, and vascular dementia, particularly if they have recurrent strokes [2]. Furthermore, structured lower extremity exercise is the fundamental component of treatment for claudication, and there is an increasing amount of evidence

affirming that it may result in improvement of cognitive dysfunction [3]. Therefore, we hypothesized that PR would be an appropriate site to discern the prevalence of both PAD and mild cognitive impairment (MCI), as well as potentially to administer therapeutic interventions targeted to improve both vascular maladies.

PAD is often undetected and untreated, despite the high prevalence of this disease and its significant clinical consequences [3]. The ankle-brachial index (ABI) is a widely used non-invasive and cost effective test for screening, which compares the higher of the brachial artery systolic blood pressures with both the left and right lower extremities (either the *dorsalispedis* or *posterior tibial*) systolic blood pressure in a simple ratio [4]. Standardized questionnaires, validated in settings other than PR have been used as well. The Edinburgh Claudication Questionnaire is one such questionnaire that has been validated as a PAD screening tool with reported 91% sensitivity and 99% specificity for diagnosis in the general populations [5]. Additionally, the Walking Impairment Questionnaire is another validated method that assesses functional limitations by helping identify the degree of walking ability in the PAD populations in comparison to graded treadmill tests [6].

Cognitive impairment is increasingly recognized as common in many medical conditions and may relate to the ability of the cardiovascular system to provide adequate brain perfusion. Reduced cerebral blood flow and structural brain changes including greater global and region-specific

atrophy are often implicated, as past work in patients with COPD or depression has demonstrated a strong relationship between cognitive dysfunction and decreased fitness in patients with COPD or depression [7]. Specifically, the recent Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study concluded that midlife COPD and asthma were associated with an almost two-fold risk of mild cognitive impairment and dementia later in life [8]. Therefore, it may be hypothesized that individuals in PR with severe pulmonary disease may have impaired cognition, and this especially may be the case with those diagnosed with vascular diseases such as PAD.

2. MATERIALS AND METHODS

2.1 Goals

The primary goal of this study was to determine the validity of screening tools in detecting PAD in comparison to ABI status in a representative population of patients in pulmonary rehabilitation. Secondary goals included the detection of cognitive impairment (defined by standardized neuropsychological testing with the Montreal Cognitive Assessment, MoCA) and of depression. Thus, we sought to find a quantitative relationship between these important medical conditions.

2.2 Protocol

This was a prospective observational pilot study of 25 consecutive subjects enrolled in phase II PR at University Hospitals Harrington Heart & Vascular Institute's Pulmonary Rehabilitation Program in Ohio. All patients enrolled in PR between June 21, 2013 and August 27, 2013 were considered for this study. Exclusion criteria included individuals with required use of an assistive device (walker, cane, or wheelchair) for ambulation (n=2), documented dementia (n=0), or failure to provide informed consent (n=10).

The research assistant screened subjects for the study during the course of the patients' rehabilitation sessions. If the subject met the selection criteria, informed consent was obtained the day of screening or at the following session.

The study was conducted with minimal interruption to the course of pulmonary rehabilitation. After consent was obtained, the Walking Impairment Questionnaire, the Edinburgh Claudication Questionnaire, and the

Seton Medical Center Pulmonary Knowledge Test were administered. Following the first set of questionnaires, the research assistant obtained ABI measurements according to the American Heart Association recommendations [9]. At the next scheduled rehabilitation session, the following surveys were administered: the Montreal Cognitive Assessment (MoCA), the State Trait Anxiety Inventory, and the Patient Health Questionnaire 9 (PHQ-9), which were used to screen for anxiety and depression symptoms respectively.

2.3 Data Analysis

The prevalence of peripheral artery disease, defined as an ABI <0.9 or >1.4 was described for the overall study population. Baseline characteristics of subjects with abnormal ABI were compared to those subjects with normal ABI. Furthermore, continuous variables were reported with standard descriptive statistics including mean and standard deviation. Between-group differences were tested for statistical significance with an unpaired t-test, and categorical variables were described as frequency and percentage. The test characteristics of the Edinburgh Claudication Questionnaire for the detection of abnormal ABI in this population were described in terms of sensitivity, specificity, and negative and positive predictive value. Unpaired t-tests were used to compare the walking ability scores on the Walking Impairment Questionnaire of patients with normal ABI to those with abnormal ABI. Additionally, the prevalence of depressive symptoms, assessed by PHQ-9, was described as percentages. Similarly, the overall scores on the MoCA were compared between both groups by percentages. The pulmonary knowledge of the rehabilitation patients was related with standard descriptive statistics. Lastly, the results of the MoCA were correlated with those of the PHQ-9 and STAI questionnaires using chi-square testing and two sample t-tests. All statistical tests were two-sided with a 0.05 significance level. Analyses were performed with SPSS version 20 (IBM SPSS Statistics for Windows, Armonk, NY).

3. RESULTS

3.1 Patient Population

Twenty-five consecutive patients enrolled in phase II pulmonary rehabilitation were assessed

for eligibility and all met criteria; 8 were not consented within the first six exercise sessions and 17 agreed to participate however 3 did not complete testing due to early withdrawal from the program.

The prevalence of PAD in this population of PR patients was 28% (4/14), with two subjects manifesting low (<0.90) and two subjects with abnormally high (>1.40) ABI (Fig. 1).

(Table 1) contains the baseline characteristics of subjects with normal ABI compared to those with abnormal ABI as well as risk factors for PAD.

Table 1. Baseline characteristics and risk factors for PAD in both ABI groups

| Demographic | Normal ABI | Abnormal ABI |
|-----------------------------|---------------|----------------|
| Number | 10(72%) | 4(28%) |
| Age | 66(+/- 7.5) | 66.8(+/- 12.8) |
| Sex | | |
| Male | 4(28.6%) | 2(14.3%) |
| Female | 6(42.8%) | 2(14.3%) |
| Race | | |
| African American | 5(35.7%) | 2(14.3%) |
| White | 5(35.7%) | 2(14.3%) |
| BMI (kg/m ²) | 32.3(+/- 9.2) | 30.4(+/-12.6) |
| Past medical history | | |
| PAD | 0 | 0 |
| DM | 2(20%) | 0 |
| HTN | 4(40%) | 3(75%) |
| DLD | 1(10%) | 1(25%) |
| COPD | 10(100%) | 2(50%) |
| Asthma | 2(20%) | 1(25%) |
| OA | 6(60%) | 2(20%) |
| Smoking history | | |
| Current/former | 9(90%) | 4(100%) |
| Never | 1(10%) | 0 |

DM=Diabetes mellitus; HTN=Hypertension; DLD=Dyslipidemia; COPD= Chronic obstructive pulmonary disorder; OA=Osteoarthritis

3.2 Risk Factors

The total number of traditional risk factors for PAD was assessed in both groups, including the presence of smoking history, diabetes, obesity (BMI>30), hypertension, dyslipidemia, and age >50. Most of the patients in each PR group displayed at least three risk factors, however there was no statistically significant difference between the average numbers of risk factors when comparing subjects with normal ABI to those with abnormal ABI (P=.465).

3.3 Edinburg Claudication Questionnaire (ECQ)

The Edinburg Claudication Questionnaire performed poorly in this population of PR patients, as it was negative in all subjects. Therefore, it was not useful in the detection of PAD in this population (sensitivity 0%, specificity 11%, PPV 0%, NPV 78.57%).

3.4 Walking Impairment Questionnaire (WIQ)

The WIQ also performed poorly in this population, as it did not correlate with the presence of PAD. The questionnaire did not reveal any differences between patients with abnormal compared to normal ABIs with regard to walking distance, speed, or symptoms (Table 2; P=.154, P=.545, P=.152).

Table 2. Average results on the WIQ between patients with abnormal and normal ABIs

| Section | Abnormal ABI (average score) | Normal ABI (average score) | P-value |
|----------------------|------------------------------|----------------------------|---------|
| Walking distance (m) | 40.015 | 64.456 | 0.154 |
| Walking speed (mph) | 27.15 | 25.92 | 0.545 |
| Walking symptoms | 46.875 | 63.75 | 0.152 |

ABI=Ankle-brachial index

3.5 Montreal Cognitive Assessment (MoCA)

Eleven of the fourteen patients (79%) had an overall score of less than 26, indicating cognitive impairment. One of the three patients who scored >26 had an abnormal ABI. Among the sub-scores, lowest performances were found in abstraction, delayed recall, and visuospatial/executive skills, in which 9 of 14 patients completed the alternating trail making incorrectly. Even with a high proportion of patients scoring less than 26, there was not statistically significant evidence of a relationship between low scores and patients with abnormal ABIs (P=.837) (Fig. 2).

3.6 Seton Knowledge Test

The mean score on the Seton Knowledge test in this population was a 19/25 (76%), which would be considered average performance. Six patients scored 19 points or below, whereas 8 patients scored 20 or above. There was a large range of

scores with a minimum of 11 and a maximum of 24. Of the six patients with scores 19 or less, all scored <26 on the MoCA, five scored minimal to mild depression on the PHQ-9, and five scored low to moderate state anxiety on the STAI. Moreover, half of the six patients had abnormal ABIs (Fig. 3).

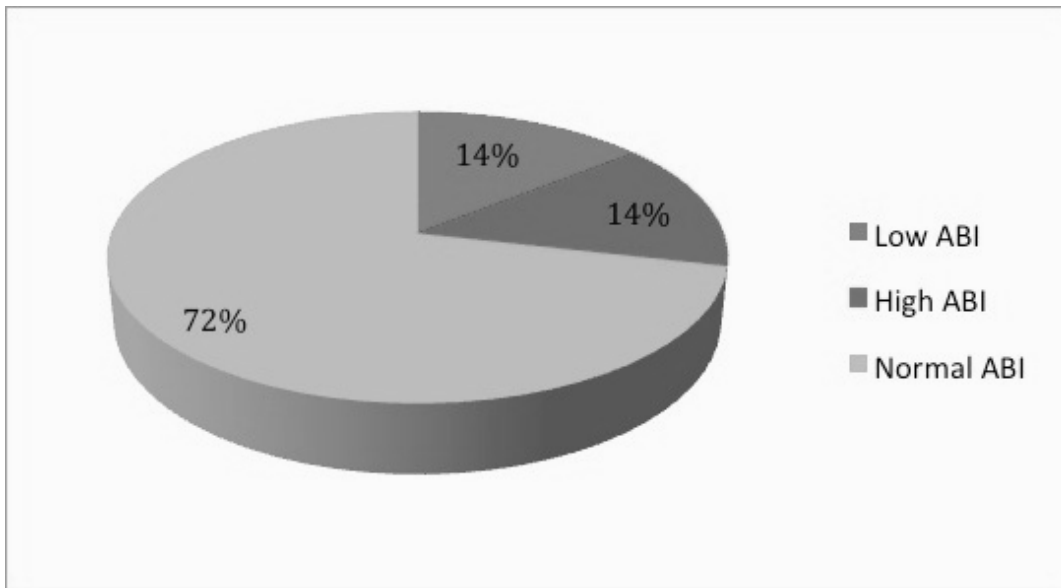


Fig. 1. Prevalence of PAD in PR
PAD=Peripheral artery disease; PR=Pulmonary rehabilitation

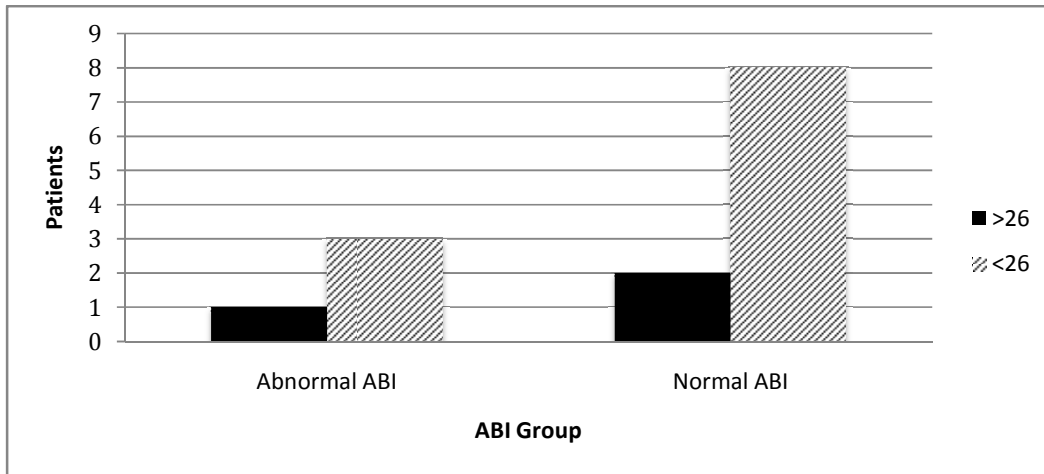


Fig. 2. MoCA results of patients with abnormal and normal ABIs
Scores>26 considered normal

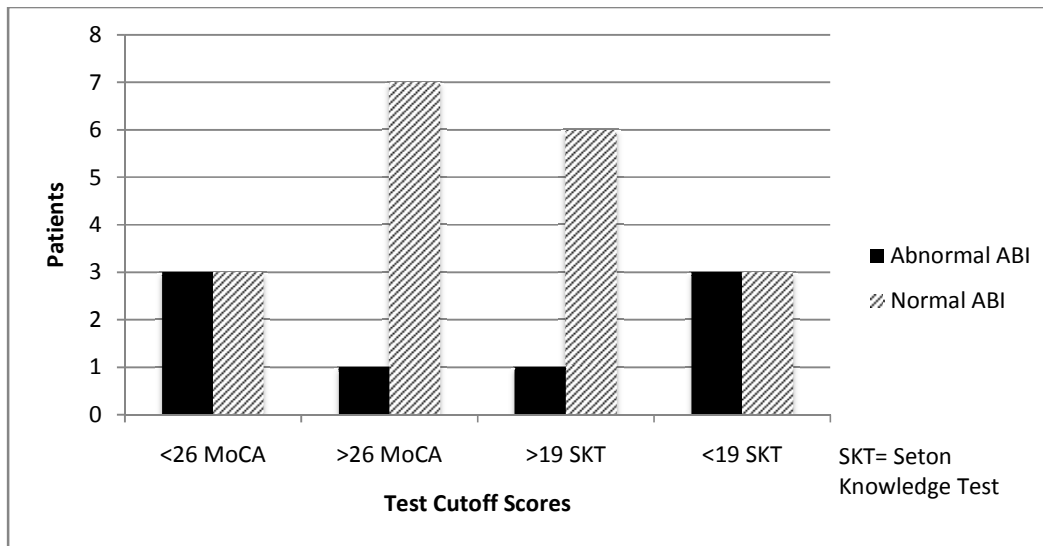


Fig. 3. Performance on the MoCA & seton knowledge test amongst both ABI groups

3.7 STAI/PHQ-9

Most patients' scores correlated to moderate state anxiety on the STAI questionnaire and similarly, those of the PHQ-9 corresponded with none, minimal, or mild depression. Although, one patient scored moderate to severe state anxiety and another scored moderate depression. Three of the four patients with abnormal ABIs that scored low to moderate on the STAI, and minimal to mild depression on the PHQ-9, had an overall score of <26 on the MoCA. Similarly among patients with normal ABIs, 9 of 10 patients that scored none to moderate on the PHQ-9, scored <26 on the MoCA. Despite this trend, there was not a statistically significant correlation with depression and anxiety levels and results of the MoCA among both patient groups ($P=.466$, $P=.075$).

4. DISCUSSION

4.1 Screening for Occult Peripheral Artery Disease

PAD is prevalent in patients with known cardiovascular disease as reported in previous studies, [2] however little is known about its relation to pulmonary disease and its prevalence in the pulmonary rehabilitation population. This study confirms and updates prior studies indicating that lower extremity PAD is prevalent in the pulmonary rehabilitation population. Despite the ability of the Edinburgh Claudication

Questionnaire and other screening modalities to detect PAD in the general population, they are less sensitive in the PR population. These patients are likely to have other functionally limiting co-morbid conditions that may mask the presence of typical claudication symptoms, confounding the clinical detection of PAD. Additionally, selective screening based on risk factor stratification is of limited value in the PR population. As a result, this supports the application of ABI as a simple screening test for all patients enrolled in PR to detect PAD, as many patients are asymptomatic or have atypical symptoms.

4.2 Prevalence of Mild Cognitive Impairment

Cognitive impairment is prevalent in our representative PR population. It has been found that patients with Vascular Cognitive Impairment (VCI) even if they do not have lesions on neuroimaging can have a notably poor prognosis [2]. Additionally, lower scores on the Seton Knowledge test could be related to below normal scores on the MoCA, as all six patients that answered 19 or fewer questions correctly out of 25 on the Seton Knowledge test also scored lower than 26 on the MoCA. Half of these patients had abnormal ABIs. This may reflect an inability to retain information learned in rehabilitation sessions as a consequence of MCI. As a result, there is an emerging concurrence between PAD and cognitive impairment.

4.3 Prevalence of Depressive and Anxiety Symptoms

Past prospective studies have found that depressive symptoms are associated with cognitive decline and that the effect of anxiety on cognitive function is indirectly mediated by depression [10]. Thus, the established relationship between cognitive impairment and depression can be taken into consideration amongst patients with PAD, who have markedly reduced health-related quality of life and higher prevalence of depression [11]. The association between depressive symptoms and reduced cognitive function can be explained by the ruminative processing of negative information that may reduce effort and attention to demanding cognitive tasks [10]. Furthermore, depression in patients with cognitive impairment is marked by abnormalities on neuropsychological tests including impairments in memory, attention, and executive function [12], all of which are assessed in the MoCA. Consequently, our results affirm the existing relationship between depressive and anxiety symptoms and cognitive impairment, and also allude to a relationship between PAD and depression and anxiety.

5. STUDY LIMITATIONS AND IMPLICATIONS

PAD was defined in our study by abnormal ABI. Other less common but more sophisticated, costly, and often higher risk diagnostic methods such as pulse volume recording, computed tomography angiography, and magnetic resonance angiography were not utilized given financial and logistical restrictions. This pilot study was limited by the small sample size, precluding robust multivariate analysis or other analyses such as net reclassification. Future studies, with larger populations, could utilize these techniques to provide additional insight.

As the prevalence of PAD is common in both pulmonary and cardiac rehabilitation [13], our study extends other work for future studies assessing MCI in a larger PR population. Furthermore, inquiry into the prevalence of MCI in patients with PAD would be of great significance as well considering both of their clinical consequences. In a population-based study, progression from VCI-no dementia to incident dementia occurred at the highest rate in patients with both memory and functional

impairment at baseline. Equivalently, up to a third of people change diagnostic category (no cognitive impairment; cognitive impairment-no dementia; dementia) within one year after stroke [2]. Therefore, cognitive impairment has become increasingly common and debilitating, and should be a target for further study in the proposed populations.

Overall, pulmonary rehabilitation serves a broad spectrum of patients, even amongst those with a single index diagnosis such as COPD. Pulmonary therapies such as continuous positive air pressure (CPAP) and corticosteroids along with comorbidities, namely hyperlipidemia, diabetes mellitus, and hypertension, may influence vascular and muscle structure and function [14]. As a result, the listed therapies and comorbidities could potentially influence the development and clinical manifestations of PAD in patients enrolled in pulmonary rehabilitation and could be explored in future work.

6. CONCLUSION

PAD is common in patients in phase II pulmonary rehabilitation and is often clinically occult. It is infrequently detected by standard screening questionnaires in this population, suggesting a need for a broad-based screening strategy including ABI measurements. In fact, unappreciated PAD may correlate with mild cognitive impairment, which was observed in a significant percentage of patients. Overall, our results have affirmed the substantial prevalence of both PAD and cognitive impairment in PR. We found a positive correlation between low Seton Knowledge test scores and low MoCA results, indicating the lack of acquisition of disease related knowledge, which is one of the primary goals of PR. The concurrence between depressive and anxiety symptoms and cognitive impairment was affirmed as well. Individuals with depression have a greater tendency to submit to unhealthy habits and risks, which may lead to increasing the risks of cardiovascular disease, cognitive impairment, or worsening existing conditions [12]. Therefore, our conclusions have led us to postulate a possible relationship between PAD and MCI, along with that of PAD and depression and anxiety. Future studies, with a large sample size, will provide more insight on ameliorating care for patients whose vascular disease affects cognitive function and mental health.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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