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ORIGINAL ARTICLE

Prevalence of pulmonary embolism among patients with recent onset of dyspnea on exertion. A cross-sectional study

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Abstract

Background: Exertional dyspnea is a frequently encountered complaint in clinical practice. However, the prevalence of pulmonary embolism (PE) among patients with dyspnea on exertion has not been reported.

Objective: The objective of this study was to assess the prevalence of objectively confirmed PE among consecutive patients visiting an emergency department because of recent onset of exertional dyspnea.

Methods: Patients aged ≤75 years with recent (<1 month) marked exertional dyspnea had a systematic workup for PE, irrespective of concomitant signs or symptoms of venous thromboembolism and alternative explanations for dyspnea. PE was excluded on the basis of a low pretest clinical probability and normal age-adjusted D-dimer. All other patients had computed tomography pulmonary angiography. An interim analysis after inclusion of 400 patients would stop recruitment if the 95% confidence interval (CI) of the PE prevalence had a lower limit exceeding 20%.

Results: The study was prematurely terminated after the inclusion of 417 patients. In 134 patients (32.1%), PE was excluded based on low clinical probability and normal D-dimer. PE was found in 134 (47.3%) of the remaining 283 patients, for an overall prevalence of 32.1% (95% CI, 27.8-36.8). PE was present in 40 of 204 (19.6%) patients without other findings suspicious for PE and in 94 of 213 patients (44.1%) with such findings. PE involved a main pulmonary artery in 37% and multiple lobes in 87% of the patients.

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Conclusion: The angiographic demonstration of PE is common in patients presenting with recent onset of marked exertional dyspnea, including 20% without other findings suggesting pulmonary embolism.

KEYWORDS
diagnosis, exertional dyspnea, pulmonary angiography, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

A classical presentation of pulmonary embolism (PE) is a patient with abrupt onset of dyspnea, pleuritic chest pain, and perhaps hemoptysis. Diagnostic algorithms for PE have proliferated and have been refined to expedite diagnosis and sometimes gather teams for patient management [1]. However, missteps in both diagnosis and early management were found prevalent in a broad survey of USA emergency department practices [2]. Nonspecific clinical manifestations and absence of typical signs and symptoms can lead to a diagnosis of PE being delayed or missed entirely, causing a complicated clinical course or death [3]. Apart from this, failure to diagnose PE is a common malpractice allegation [4].

Dyspnea on exertion with subacute onset is a symptom of multiple conditions, including cardiac, airways, and pulmonary parenchyma diseases, as well as systemic illnesses affecting oxygen transport, such as anemia [5,6]. Although isolated dyspnea on exertion does not generally lead in a straight line to include suspicion of PE, it is a plausible etiology. Given the extensive cardiopulmonary reserve of previously healthy persons, embolic pulmonary vascular obstruction may not first lead to dyspnea at rest but rather manifest at first only as dyspnea on exertion. However, we found no clinical evidence regarding the proportion of patients consulting with the complaint of recent subacute onset of marked dyspnea in whom an objective diagnosis of PE would be established. In addition, current guidelines omit specific attention to consider PE in patients with dyspnea on exertion only [1].

We hypothesized that PE might be a frequent underlying condition in patients presenting for care complaining of marked dyspnea on exertion of recent onset. We used a systematic diagnostic workup to assess the prevalence of PE in a series of such outpatients referred because of recent onset of dyspnea on exertion, irrespective of other findings suggestive of venous thromboembolism (VTE) or the presence of alternative explanations for dyspnea.

Essentials

- The prevalence of pulmonary embolism (PE) in patients with exertional dyspnea is unknown.
- We assessed the prevalence of PE in 417 patients with recent onset of marked exertional dyspnea.
- PE was found in 134 (32.1%) patients, including 40 of 204 (19.6%) free from findings suspicious for PE.
- A diagnostic workup for PE should be performed in all patients with recent onset of exertional dyspnea.

2 | METHODS

2.1 | Study design

This was a multicenter, prospective, cross-sectional study to determine the prevalence of PE in consecutive patients visiting an emergency department of 14 University or Hospital Centers in Italy between September 2018 and August 2020 with recent onset of marked dyspnea on exertion during previously well-tolerated physical activities, independent of referral diagnosis and additional signs or symptoms. The protocol was approved by the institutional review board at each participating hospital and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

TABLE 1 Severity of exertional dyspnea based on the modified scale of the Medical Research Council [7].

Grades of dyspnea	Features
Grade 0	Not troubled with breathlessness except with strenuous exercise
Grade 1	Troubled by shortness of breath when hurrying on level ground or walking up a slight hill
Grade 2	Walks slower than people of the same age because of breathlessness or has to stop for breath when walking at own pace on the level
Grade 3	Stop for breath after walking about 100 yards (approximately 91 m) or after a few minutes on the level
Grade 4	Too breathless to leave the house or breathless when dressing or undressing

Patients who were referred for outpatient evaluation with recent (<1 month) dyspnea on exertion with a severity of 3 or 4 on the modified Medical Research Council dyspnea scale were potentially eligible for the study (Table 1) [7]. Patients were excluded if they were younger than 18 years or older than 75 years, had previous deep-vein thrombosis (DVT) or PE, used therapeutic anticoagulation, had contraindications to computed tomography pulmonary angiography (CTPA), or were pregnant.

2.2 | Study outcomes

The main study outcome was the prevalence of PE in the entire cohort of patients with recent marked dyspnea on exertion. Secondary study outcomes were the prevalence of PE in relation to the presence of concomitant signs and symptoms suspicious for PE and the prevalence of PE in those without concomitant signs and symptoms suspicious for PE in relation to the presence of alternative explanations for dyspnea.

2.3 | Study assessments

Patients were evaluated for the presence of signs and symptoms of PE, potential explanations for their dyspnea, and risk factors for VTE and had a chest X-ray, an electrocardiogram, and routine blood testing, including D-dimer. Findings suspicious for PE included signs or symptoms of DVT, pleuritic chest pain, syncope, tachycardia, atrial fibrillation, hemoptysis, cough, cyanosis, hypotension, or pleural effusion on chest X-ray. Alternative explanations for dyspnea on exertion included cardiovascular disorders (congestive heart failure, aortic valve stenosis, and/or coronary heart disease), lung diseases, severe anemia, hyperthyroidism, and psychiatric disorders. Risk factors for VTE were defined as surgery, trauma or infectious disease during the last 3 months, ongoing hormonal or antipsychotic treatment, prolonged (>1 week) immobilization, recent (<1 week) long-haul flight, active cancer, known thrombophilia, and family history of VTE.

TABLE 2 Simplified Wells score for the assessment of the pretest clinical probability of pulmonary embolism [9].

Parameters	Points
Clinical signs/symptoms of deep-vein thrombosis	3.0
Alternative diagnosis less likely than pulmonary embolism	3.0
Heart rate greater than 100	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous venous thromboembolism	1.5
Hemoptysis	1.0
Active cancer	1.0

Pulmonary embolism is unlikely with score ≤4.0, and likely with score higher than 4.0.

2.4 | Ascertainment of pulmonary embolism

The presence of PE was assessed using a validated algorithm based on pretest clinical probability and quantitative D-dimer results [8]. The D-dimer concentration was assessed with the quantitative high-quality assay routinely used in each participating center. The pretest clinical probability was assessed by the simplified Wells score and classified as "PE likely" or "PE unlikely" (Table 2) [9]. An abnormal D-dimer was defined as a result of 500 ng/mL or higher for patients up to 50 years and higher than 10 times the patient's age for those older than 50 years [10].

In patients with "PE unlikely" and a normal age-adjusted D-dimer result, PE was considered excluded. Patients with "PE likely", an elevated age-adjusted D-dimer result, or both, underwent CTPA. Diagnostic criterion for the presence of PE was an intraluminal filling defect, and the thrombotic burden was assessed by the most proximal location of the emboli and the number of lobes involved (ie, one versus multiple). A central adjudication committee, unaware of patients' characteristics, evaluated all CTPAs.

2.5 | Statistical analysis

Based on pilot data that demonstrated 10 (20%) cases of PE in a sample of 50 unselected patients with recent onset of dyspnea on exertion (data not published), we assumed a prevalence of PE of 20% in all patients who had dyspnea on exertion among the reasons for referral. To obtain a 2-sided 95% confidence interval (CI) of 2.5% for the prevalence of PE, a sample size of 600 patients was required. An interim analysis was scheduled after enrolment of approximately 400 patients with a stopping rule for recruitment if the lower limit of the 95% CI of the prevalence of PE was higher than 20%. The prevalence of PE and its 95% CIs were calculated for all patients, as well as for those with and without signs and symptoms suspicious for PE, and for those without concomitant signs and symptoms suspicious for PE in relation to the presence of alternative explanations for dyspnea. For comparison of baseline characteristics between patients with and without PE, the chi-square test was used for categorical parameters

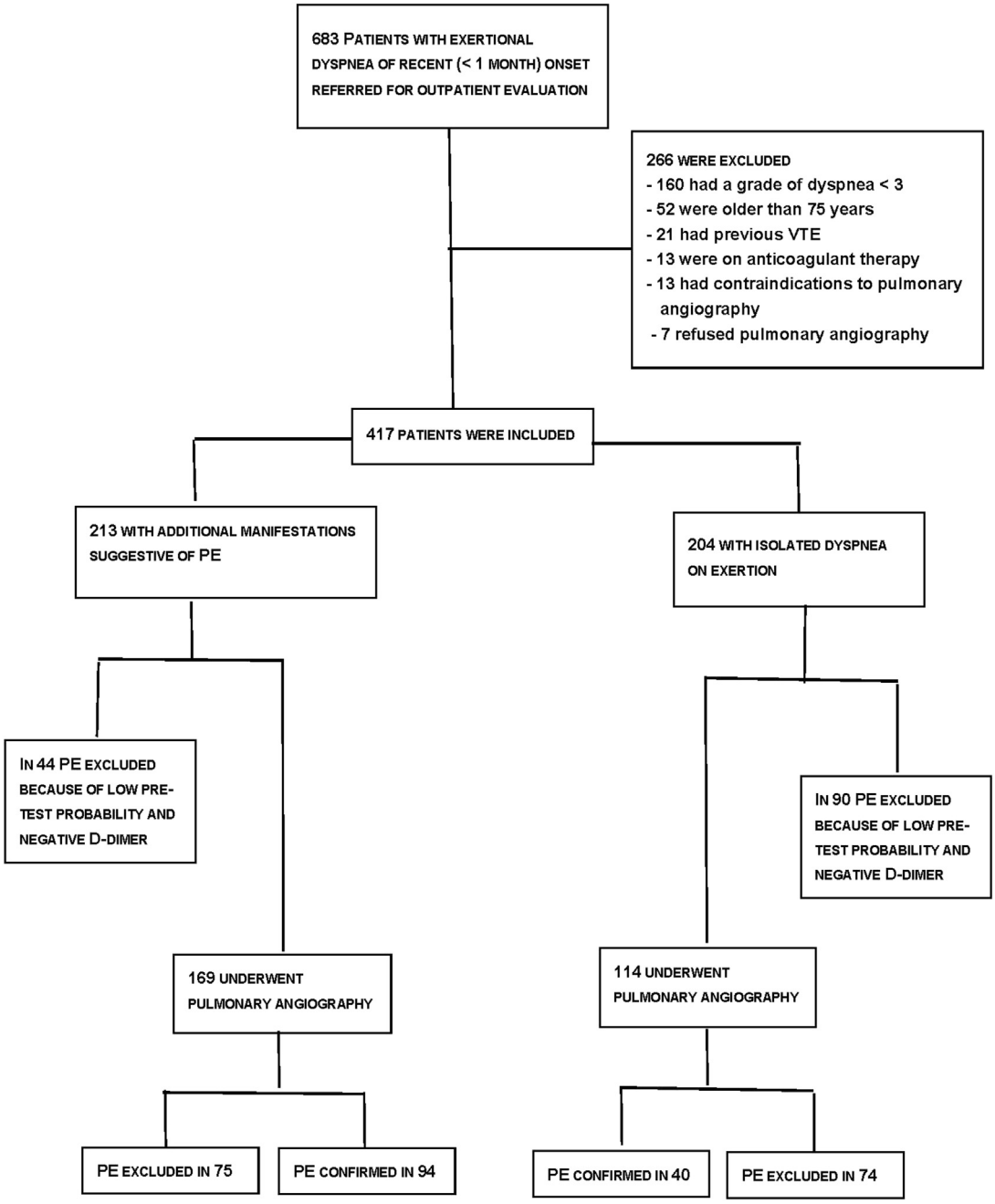

FIGURE Flow diagram of the study.

and the Student's *t* test was used for continuous parameters. The 95% CIs and *p* values were calculated according to the normal approximation of the binomial distribution. All calculations were performed with SPSS Statistics 22.0.

Because the observed frequency of PE was unexpectedly high and more than half of study patients had findings suspicious for DVT or PE, it was decided to perform a prospective validation study using the same protocol, again including only patients with recent marked dyspnea on exertion but excluding those with likely alternative explanation for dyspnea and with findings suspicious for DVT or PE.

3 | RESULTS

3.1 | Patients

As shown in Figure reporting the flow diagram, during the study period 683 patients were seen at the emergency department because of dyspnea on exertion of recent (<1 month) onset. Of these, 166 (39.8%) patients were referred by their general physicians, whereas the remaining patients self-referred. 266 patients (38.9%) were excluded because of a modified Medical Research Council dyspnea

TABLE 3 Main demographic and clinical characteristics of study patients.

	All patients (*n* = 417)	PE confirmed (*n* = 134)	PE excluded (*n* = 283)	Odds ratio	95% CI	*p* value
Variable						
Mean age—y ± SD	57.7 ± 15.6	54.0 ± 15.5	59.5 ± 15.4			0.001
Males—(%)	208 (49.9)	53 (39.6)	155 (54.8)	0.54	0.36-0.82	0.005
Body mass index ≥30—no. (%)	44 (10.6)	19 (14.2)	25 (8.8)	1.70	0.90-3.22	0.124
Systolic blood pressure <110 mmHg—no. (%)	85 (20.4)	55 (41.0)	30 (10.6)	5.87	3.52-9.79	<0.001
Heart rate >100/min—no. (%)	176 (42.2)	86 (64.2)	90 (31.8)	3.84	2.49-5.92	<0.001
Oxygen saturation <90%—no. (%)	171 (41.0)	68 (50.7)	103 (36.4)	1.80	1.19-2.73	0.008
Clinical signs or symptoms of VTE—no. (%)						
Clinical signs and symptoms of PE	168 (40.3)	60 (44.8)	108 (38.2)	1.31	0.87-1.99	0.20
Clinical signs and symptoms of DVT	45 (10.8)	34 (25.4)	11 (3.9)	8.41	4.10-17.23	<0.001
Acquired risk factors of VTE[a]—no. (%)	127 (30.5)	69 (51.5)	58 (20.5)	4.10	2.63-6.40	<0.001
Familiar history for VTE—no. (%)	28 (7.0)	15 (11.5)	13 (4.8)	2.57	1.18-5.57	0.020
Active cancer—no. (%)	54 (12.9)	13 (9.7)	41 (14.5)	0.63	0.33-1.23	0.212
Known thrombophilia[b]—no. (%)	37 (11.9)	29 (28.7)	8 (3.8)	10.22	4.47-23.38	<0.001
Onset of symptoms						
Less than one week—no. (%)	336 (80.6)	113 (84.3)	223 (78.8)	1.45	0.84-2.50	0.233
One week or more—no. (%)	81 (19.4)	21 (15.7)	60 (21.2)	0.69	0.40-1.19	

Abbreviations: CI, confidence interval; DVT, deep-vein thrombosis; PE, denotes pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

[a]One or more of the following: recent trauma, surgery or infectious disease, ongoing hormonal or antipsychotic treatment, prolonged immobilization, and recent long-haul flight.

[b]Factor V Leiden, prothrombin mutation, deficiency in the natural anticoagulants, and antiphospholipid syndrome.

score of 2 or lower (n = 160), age older than 75 years (n = 52), previous VTE (n = 21), use of anticoagulants (n = 13), contraindications to CTPA (n = 13), or refusal of informed consent (n = 7). Thus, 417 patients with recent marked dyspnea on exertion were included. The main demographic and clinical characteristics of the patients are provided in Table 3. Additional clinical manifestations suspicious for PE were found in 213 of the 417 patients (51.1%), including 45 with suspected DVT. Of the remaining 204 patients with isolated dyspnea on exertion, alternative explanations for dyspnea were present in 96 (47.1%) patients, of whom 40 had lung disorders, 39 had cardiovascular disorders (heart failure, aortic valve stenosis, and/or coronary artery disease), 15 had severe anemia, and 2 had hyperthyroidism.

3.2 | Prevalence of pulmonary embolism

In 134 (32.1%) of the 417 patients, PE was excluded based on the combination of a low pretest clinical probability of PE and normal D-dimer result. Among the remaining 283 patients, PE was found in 134 (47.3%) patients. Hence, in the entire cohort, the prevalence of PE was 32.1% (95% CI, 27.8-36.8). The prevalence of PE was high in all participating centers (ie, between 27.6% and 56.7%). As at the interim analysis, the lower limit of the 95% CI was well above 20%, the study was prematurely terminated, according to the defined stopping rule.

Patients with PE were younger, were more likely to be women, have a systolic blood pressure lower than 110 mm Hg, a heart rate higher than 100 per minute, an oxygen saturation lower than 90%, and were more likely to have risk factors for VTE, including a family history of VTE or thrombophilia (Table 3).

In the 213 patients with dyspnea on exertion who had concomitant findings suspicious for PE, PE was found in 94 (44.1%) patients, whereas in the 204 patients without these signs and symptoms, PE was found in 40 (19.6%) patients. Among these 204 patients, the prevalence of PE was 14.6% (n = 14) in the 96 patients with an alternative explanation for dyspnea and 24.1% (n = 26) in the 108 patients without an alternative explanation for dyspnea. PE was detected in 113 of the 337 (33.5%) patients with dyspnea on exertion with a duration of less than one week and in 21 of the 80 (26.3%) patients who had dyspnea with a duration between 1 week and 1 month.

3.3 | Thrombotic burden

In the 134 patients with PE, the most proximal location of the embolus was in a main pulmonary artery in 49 patients (36.6%), a lobar artery

in 54 (40.3%) patients, a segmental artery in 30 (22.4%) patients, and a subsegmental artery in 1 (0.7%) patient. PE involved a single lobe in 17 patients (12.7%) and multiple lobes in the remaining 117 (87.3%) patients. In all cases, the thrombotic burden was found by the independent adjudication committee to be compatible with the recent apposition of fresh thrombotic material.

3.4 | Validation study

Between November 2020 and November 2021, a total of 61 patients with a recent (<1 month) onset of dyspnea on exertion with a modified Medical Research Council dyspnea score of 3 or 4 but no other sign or symptom suspicious for PE and no likely alternative explanation for their symptoms were included in the validation study. Of these, 36 (59.0%) patients were women, with a mean age of 59.5 (SD ± 13.4) years, and 24 (39.3%) patients had risk factors for VTE. Dyspnea on exertion was present for less than one week in 30 (49.2%) of them. PE was excluded in 25 (41.0%) patients by the Wells clinical probability score and D-dimer result. The prevalence of PE was 47.2% (n = 17) in the remaining 36 patients. Hence, the prevalence of PE in the entire validation cohort was 27.9% (95% CI, 18.2%-40.2%).

4 | DISCUSSION

Our study demonstrated a high prevalence of PE among outpatients who visited an emergency department (either spontaneously or referred by their general practitioners) with recent onset, marked (grade 3 or 4 on the modified Medical Research Council scale) dyspnea on exertion. The prevalence of PE was highest (44%) in patients who had concomitant signs or symptoms suspicious for PE or underlying DVT. However, in patients without these concomitant signs and symptoms, PE was still detected in almost 20% of the patients. A validation study in patients who presented with dyspnea on exertion of recent onset, without these concomitant signs or symptoms, and who had no likely alternative diagnosis confirmed this high proportion. The pulmonary emboli detected were significant: almost all such patients had segmental or more proximal emboli involving multiple lobes. Our findings suggest that regardless of the diagnostic algorithm in use, physicians should rule in or out PE in patients who solely report recent onset of marked dyspnea on exertion.

The observed 32% prevalence of PE in our study may seem to contrast with the low prevalence of 7% to 13% found in contemporary studies in patients with suspected PE [11–13]. However, in earlier studies that required invasive testing in all patients with conventional pulmonary angiography, lung scintigraphy, or CTPA [14–18], the prevalence of PE varied between 18% and 33%. In later studies that selected patients for invasive testing based on D-dimer and clinical decision rule, the prevalence of PE in all included patients dropped over time from 26% to 7% [8,10–13]. This is likely explained by lowering of the threshold for suspicion of PE in all presenting patients, since the proportion of patients in whom invasive testing could be obviated increased from 31% to 66%. Of interest, compared with North America countries, the prevalence of PE among emergency department cohorts in European countries is generally higher, as is the diagnostic yield from CTPA [19]. We think that our high prevalence of PE is largely explained by differences in applied thresholds for suspicion of PE [3]. Of the aforementioned studies, only one explicitly allowed inclusion of patients with dyspnea only on exertion without specifying the prevalence of PE in this subgroup [18]. Therefore, we do not have prior evidence on the prevalence of PE among patients presenting with significant exertional dyspnea to which we can compare our results.

Our data acquisition was robust, as they came from prospective observations in a large number of patients at multiple hospitals. The diagnostic workup for PE was performed according to accepted international guidelines [1], and a central adjudication committee reviewed all CTPAs unaware of clinical signs and symptoms. Furthermore, to minimize the risk of chronic thromboembolic obstruction as a cause of dyspnea [20,21], patients with longstanding symptoms or previous VTE were excluded. Limitations of our study include that our results are not applicable to patients older than 75 years or patients with chronic (more than 1 month) symptoms of dyspnea or less severe dyspnea (modified Medical Research Council dyspnea score of 2 or lower). Moreover, no attempt was performed to stratify the clinical relevance of PE. Finally, exploration of other causes of dyspnea was left to the discretion of attending physicians and may have been underreported. Finally, information on treatment decisions and follow-up was not collected.

Some other aspects of our study warrant comment. Although 10.8% of patients were determined to have signs or symptoms of DVT, none were specifically referred for these complaints. The proportion of patients with PE varied plausibly in patients with (44%) and without (20%) concomitant signs and symptoms of VTE: in patients without, the proportion with PE varied with the presence (15%) or absence (24%) of a likely alternative diagnosis. Our validation study in a new subgroup of patients with marked dyspnea on exertion of recent onset without concomitant signs or symptoms of PE or DVT or a likely alternative diagnosis showed a strikingly similar prevalence of PE, with a lower 95% confidence limit of 18.2%.

In conclusion, the angiographic demonstration of PE was found in one-third of patients younger than 75 years referred solely for recent onset of marked dyspnea on exertion. The rate was higher among patients with concomitant complaints consistent with VTE and those without a likely alternative explanation for dyspnea. Regardless of the diagnostic algorithm in use, physicians should suspect PE and conduct appropriate workup in patients reporting recent onset of marked dyspnea on exertion.

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AUTHOR CONTRIBUTIONS

P.P. and G.P. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: P.P., A.W.A.L., M.H.P., M.L., B.L.D. *Acquisition of data*: M.C., S.P., F.P., Visonà, W.A., F.B., M.L.M., E.B., L.D., C.B., N.C., C.C. *Drafting of the manuscript*: P.P., A.W.A.L., M.H.P. *Critical revision of the manuscript for important intellectual content*: All authors. *Statistical analysis*: F.N., M.H.P. *Administrative, technical, or material support*: C.B., L.M., G.P. *Supervision*: P.P., A.W.A.L., G.P.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

APPENDICES

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