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ORIGINAL ARTICLE

Impact of prone positioning on patients with COVID-19 and ARDS on invasive mechanical ventilation: a multicenter cohort study

Marieta C A Cunha[1], Jociane Schardong, Natiele Camponogara Righi[2,3], Adriana Claudia Lunardi[4], Guadalupe Nery de Sant'Anna[4], Larissa Padrão Isensee[4], Rafaella Fagundes Xavier[4], Kaciane Roberta Brambatti[2], José Eduardo Pompeu[4], Fabiano Frâncio[5], Luiza Martins Faria[6], Rozana Astolfi Cardoso[7], Antonio Marcos Vargas da Silva[2], Camila de Christo Dorneles[8], Roberta Weber Werle[8], Juliana Carvalho Ferreira[1], Rodrigo Della Méa Plentz[2,3], Celso R F Carvalho[4]

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Serviço de Fisioterapia, Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.
3. Departamento de Fisioterapia, Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA – Porto Alegre (RS) Brasil.
4. Departamento de Fisioterapia, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
5. Hospital Tacchini, Bento Gonçalves (RS) Brasil.
6. Departamento de Fisioterapia, Hospital Universitário Polydoro Ernani de São Thiago, Universidade Federal de Santa Catarina, Florianópolis (SC) Brasil.
7. Departamento de Fisioterapia, Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte (MG) Brasil.
8. Hospital Universitário de Santa Maria, Universidade Federal de Santa Maria, Santa Maria (RS) Brasil.

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Study carried out at the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP); Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS); Hospital Tacchini, Bento Gonçalves (RS); Hospital Universitário de Santa Maria, Universidade Federal de Santa Maria, Santa Maria (RS); Hospital Universitário Polydoro Ernani de São Thiago, Universidade Federal de Santa Catarina, Florianópolis (SC); and Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To identify factors that lead to a positive oxygenation response and predictive factors of mortality after prone positioning. **Methods:** This was a retrospective, multicenter, cohort study involving seven hospitals in Brazil. Inclusion criteria were being > 18 years of age with a suspected or confirmed diagnosis of COVID-19, being on invasive mechanical ventilation, having a PaO_2/FIO_2 ratio < 150 mmHg, and being submitted to prone positioning. After the first prone positioning session, a 20 mmHg improvement in the PaO_2/FIO_2 ratio was defined as a positive response. **Results:** The study involved 574 patients, 412 (72%) of whom responded positively to the first prone positioning session. Multiple logistic regression showed that responders had lower Simplified Acute Physiology Score III (SAPS III)/SOFA scores and lower D-dimer levels (p = 0.01; p = 0.04; and p = 0.04, respectively). It was suggested that initial SAPS III and initial PaO_2/FIO_2 were predictors of oxygenation response. The mortality rate was 69.3%. Increased risk of mortality was associated with age (OR = 1.04 [95 CI: 1.01-1.06]), time to first prone positioning session (OR = 1.18 [95 CI: 1.06-1.31]), number of sessions (OR = 1.31 [95% CI: 1.00-1.72]), proportion of pulmonary impairment (OR = 1.55 [95% CI: 1.02-2.35]), and immunosuppression (OR = 3.83 [95% CI: 1.35-10.86]). **Conclusions:** Our results show that most patients in our sample had a positive oxygenation response after the first prone positioning session. However, the mortality rate was high, probably due to the health status and the number of comorbidities of the patients, as well as the severity of their disease. Our results also suggest that SAPS III and the initial PaO_2/FIO_2 predict the oxygenation response; in addition, age, time to first prone positioning, number of sessions, pulmonary impairment, and immunosuppression can predict mortality.

Keywords: Respiratory distress syndrome; Coronavirus infections; Pulmonary medicine; COVID-19; Prone position; SARS-CoV-2.

INTRODUCTION

In severe COVID-19 cases, there is a cytokine storm characterized by a hyperinflammatory state, interstitial edema, hypoxemic respiratory failure, pulmonary perfusion impairment, and multiple organ failure.[(1)] A significant proportion of individuals with COVID-19 presents a deficit in ventilation-perfusion similar to moderate-to-severe ARDS but with an atypical and heterogeneous pathological pattern.[(2-5)]

COVID-19-related ARDS presents a spectrum of clinical phenotypes that vary in degrees of pulmonary infiltration, concomitant thrombotic injury, and lung recruitability and compliance; therefore, heterogeneous respiratory mechanics. Thus, some patients are more or less likely to respond to prone positioning, and subgroups tend to have different behaviors and high mortality.[(6)]

Prone positioning has been recommended as rescue therapy by the WHO and the Surviving Sepsis Campaign in refractory hypoxemia due to COVID-19-related

Correspondence to:
Celso R F Carvalho. Faculdade de Medicina, Universidade de São Paulo, Avenida Doutor Arnaldo, 455, Sala 1210, CEP 01246-903, São Paulo, SP, Brasil.
Tel.: 55 11 3061-7317. E-mail: cscarval@usp.br
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ARDS.[7-9] The main effects of prone positioning are improvement in chest wall compliance, uniformity of pleural pressure gradient, recruitment of dorsal regions, and changes in the distribution of alveolar units.[10]

The recommendation is the association of prone positioning with protective ventilatory strategies, using low VT (6 mL/kg of predicted weight), plateau pressure of the respiratory system (Pplat) < 30 cmH_2O, and neuromuscular blocker infusion.[11,12] Furthermore, there is evidence that prone positioning provides better outcomes when applied earlier (within the first 48 h of disease onset) and maintained for at least 12-16 h.[1,9,11]

Since the beginning of the pandemic, researchers have shown that prone positioning is effective and safe in treating COVID-19-related ARDS. However, we sought to understand which patients would be more susceptible to a better response. The primary goal of the study was to identify factors that would lead to a positive oxygenation response after the use of the prone positioning maneuver. The secondary goal was to identify predictive factors of mortality.

METHODS

This retrospective multicenter study was conducted in seven Brazilian hospitals involving a cohort of 574 intubated, mechanically ventilated patients with severe COVID-19-related ARDS. The clinical research ethics committees of all hospitals involved approved the study (Protocol no. 31881520.3.1001.5335). Patient consent was waived because of the retrospective nature of the study.

Data collection was conducted between the 1st of June and the 30th of December, 2020. The authors had access to electronic medical records of their affiliated institutions. Data were collected using standardized forms, safeguarding the identification of each patient. The main goals were to identify predictive factors of oxygenation improvement and mortality among the patients placed in prone positioning.

Inclusion criteria were individuals having suspected or confirmed COVID-19, requiring invasive mechanical ventilation, presenting with severe ARDS (PaO_2/FIO_2 < 150 mmHg), and being ≥ 18 years of age. Confirmed diagnosis of COVID-19 was based on clinical symptoms and a positive RT-PCR test; highly suspected diagnosis of COVID-19 was based on presenting with a negative RT-PCR test but showing COVID-19 clinical signs such as flu-like symptoms, progressive dyspnea, compatible pulmonary radiological images, and positive epidemiology.

Patients with negative RT-PCR were included due to the high probability of false-negative results. However, patients who were submitted to prone positioning when awake, without invasive mechanical ventilation support, were excluded.

All patients were divided into two groups according to oxygenation response. The PaO_2/FIO_2 ratio was calculated before and after the first prone positioning session. Patients who presented an increase in the PaO_2/FIO_2 ratio ≥ 20 mmHg after the session were allocated in the responder group, whereas those with an increase < 20 mmHg after the session were allocated in the nonresponder group.

The overload caused by the initial peak of the disease in Brazil made laboratory sample collection unfeasible in due time. Therefore, it was not possible to perform blood gas analyses one hour after prone positioning, as recommended. The data considered in the study were the ones obtained closest to the beginning and end of the first prone positioning session. The patients included were followed until hospital discharge. The mortality outcome included the events that occurred during hospitalization.

Availability of study data

The datasets generated and analyzed during the current study are available in the Zenodo repository (https://zenodo.org/badge/DOI/10.5281/zenodo.4667698.svg).

Collected variables

The following data were collected: age, gender, race, comorbidities, and BMI. Pulmonary impairment was assessed by chest CT performed closer to the intubation period. According to the radiologist report in the medical records, the proportion of parenchymal impairment was classified as < 25%, 25-50%, 51-75%, or > 75%. Lung involvement was subclassified into I (< 25%), II (25-50%), III (51-75%), and IV (> 75%) to enable data analysis.

D-dimer levels were evaluated using the HemosIL HS-500 automated immunoassay (Instrumentation Laboratory Company, Bedford, MA, USA). The level considered for statistics was the one closest to the first prone positioning session if the patient had multiple measurements. The Simplified Acute Physiology Score III (SAPS III) and the SOFA score considered for analysis were collected at ICU admission.

The following comorbidities were reported: immunosuppression; arterial hypertension; diabetes; obesity; smoking and alcohol consumption; and neurological, hematological, respiratory, or cardiovascular diseases. Patients with a history of organ transplantation were considered immunosuppressed, as were those with chronic kidney disease, HIV/AIDS, and those undergoing cancer treatment.

Data on ventilator settings, respiratory mechanics (i.e., driving pressure, Pplat, and static compliance of the respiratory system), and arterial blood gas analysis were collected before and after the first prone positioning session. Time to first prone positioning session was defined as the time between the first intubation procedure and the first prone positioning session.

Total duration of the first prone positioning session (in h), number of sessions, and adverse effects were recorded. Patient outcomes were also recorded, including duration of invasive mechanical ventilation, length of ICU and hospital stay, reintubation, and survival.

Statistical analysis

Continuous and categorical variables were expressed as medians (interquartile ranges) and absolute and relative frequencies, respectively. Comparisons between the two groups (responders and nonresponders) were performed using an independent test or the Mann-Whitney test. Logistic regression was used in order to examine factors associated with the response to prone positioning and mortality. A forward stepwise regression was then performed to identify the clinical variables that correlated with the change of oxygenation level. After that, multicollinearity was assessed by examining the variance inflation factor (values > 2 were excluded). The results are presented as odds ratios and 95% confidence intervals. We used the IBM SPSS Statistics software package, version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Significance was set at $p < 0.05$.

RESULTS

During the study period, 574 consecutive patients were included. The median age was 59 years. Male sex and White race were the most prevalent self-responses. The most common comorbidities in both groups were arterial hypertension and diabetes. Being overweight or obese was the third most prevalent comorbidity. The mean BMI was 29.4 kg/m^2 (Table 1).

The mean overall SAPS III was 65, and the mean overall SOFA score was 9. The degree of pulmonary involvement on chest CT was high; most patients were classified as grade III (51-75%). The mean overall D-dimer level was 9.6 µg/m. SAPS III, SOFA score, and D-dimer levels were significantly lower in the responder group. In general, patients had Pplat < 30 cmH$_2$O, and duration of prone positioning was greater than 12-16 h.

The median time to the first prone positioning session was 48 h (24-120 h) and 72 h (24-144 h) in the responder and nonresponder groups, respectively (p = 0.02). In general, patients required 2 (1-3) prone positioning sessions, and there was no difference in the number of sessions performed between the groups.

Most patients received vasoactive drugs and neuromuscular blockade infusion, and a small proportion required tracheostomy and/or reintubation during the follow-up period. The median length of ICU stay was 20 days and that of hospital stay was 27 days (Table 2).

Table 1. Baseline characteristics of patients with COVID-19-related ARDS at ICU admission.[a,b]

Variable	Whole sample (n = 574)	Group: Responder (n = 412)	Group: Nonresponder (n = 162)	p
Age, years	59 [49-69]	59 [49-69]	59 [50-70]	
Male gender	336 (58.5)	237 (57.5)	99 (61.1)	0.43
Self-reported race				
White	348 (60.6)	253 (61.4)	95 (58.6)	0.47
Brown	163 (28.4)	112 (27.2)	51 (31.5)	
Black	37 (6.4)	27 (6.6)	10 (6.2)	
Asian	4 (0.7)	3 (0.7)	1 (0.6)	
Comorbidities				
Arterial hypertension	334 (58.2)	237 (57.5)	97 (59.9)	0.60
Diabetes mellitus	225 (39.2)	161 (39.1)	64 (39.5)	0.88
Obesity	224 (39)	163 (39.6)	61 (37.7)	0.73
Smoker	115 (20)	78 (18.9)	37 (22.8)	0.26
Pneumopathy	75 (13.1)	54 (13.1)	21 (13.0)	0.98
Immunosuppression	62 (10.8)	48 (11.7)	14 (8.6)	0.31
SAPS III	65 [54-77]	63 [52-75]	68 [56-79]	0.01
SOFA score	9 [6-12]	9 [6-12]	10 [7-13]	0.04
Chest CT pulmonary findings				
I (< 25%)	7 (1.2)	6 (1.5)	1 (0.6)	0.91
II (25-50)	60 (10.5)	38 (9.2)	22 (13.6)	
III (51-75)	151 (26.3)	104 (25.2)	47 (29.0)	
IV (> 75%)	45 (7.8)	30 (7.3)	15 (9.3)	
BMI, kg/m^2	29.4 [24.8-32.6]	29.4 [24.8-32.7]	29.2 [24.4-32.3]	0.75
D-dimer, ng/mL	9,634 [943-5,426]	9,224 [891-4,452]	10,534 [1,146-6,376]	0.04

SAPS III: Simplified Acute Physiology Score III. [a]Values expressed as median [IQR] or n (%). [b]Missing data: diabetes mellitus (n = 1); obesity (n = 3); smoker (n = 2); pneumopathy (n = 1); immunosuppression (n = 2); SAPS III (n = 141); SOFA score (n = 159); chest CT (n = 310); BMI (n = 42); and D-dimer (n = 149).

Prone positioning and oxygenation improvement

The PaO_2/FIO_2 ratio improved in 412 patients (72%) after the first prone positioning session. The median difference in PaO_2/FIO_2 after the first prone positioning session was expressively greater in the responder group (84 [41-111] mmHg vs. −9.2 [−20.5 to 7.0] mmHg). As previously mentioned, SAPS III and SOFA scores, as well as D-dimer levels, were significantly lower in the responder group.

Among ventilator settings, the responder group presented lower RR, PaO_2, and $PaCO_2$ but no significant changes in arterial pH. In addition, the initial PaO_2/FIO_2 ratio was lower in the responder group. Regarding the nonresponder group, it was found that the time to the first prone positioning session was longer, and session duration was shorter.

The clinical variables related to oxygenation response studied were the following: SAPS III, number of sessions, static compliance of the respiratory system, baseline PaO_2/FIO_2 ratio, and D-dimer level. After multivariate logistic regression analysis, SAPS III and baseline PaO_2/FIO_2 ratio were significantly associated with oxygenation improvement (Table 3).

Prone positioning and mortality

More than half of the patients had an unfavorable outcome after prone positioning. Although no difference was observed between responders and nonresponders (p = 0.08), responders had lower mortality than did nonresponders (67.2% vs. 74.7%).

Mortality was associated with age, time to first prone positioning session, SOFA score, SAPS III, number of prone positioning sessions, extension of pulmonary

Table 2. Ventilator management, response to prone positioning, and outcomes in the patients studied.

Variable	Whole sample	Group		p*
		Responder	Nonresponder	
	(n = 574)	(n = 412)	(n = 162)	
Pre-prone ventilatory support				
PEEP, cmH_2O	11 [10-12]	11 [10-12]	11 [10-12]	0.66
FIO_2,%	80 [65-100]	80 [65-100]	80 [60-100]	0.11
RR, breaths/min	28 [24-32]	28 [24-32]	30 [25-34]	< 0.001
VT, mL	387 [335-435]	385 [330-440]	390 [350-420]	0.76
Driving pressure	13 [11-16]	13 [11-15]	14 [11-16]	0.69
Pplat, cmH_2O	24 [22-28]	24 [22-28]	24 [22-28]	0.82
Cst, mL/cmH_2O	31.2 [23.0-37.0]	31.2 [23.0-36.5]	31.0 [22.0-37.5]	0.75
Pre-prone blood gas analysis				
Arterial pH	7.31 [7.25-7.38]	7.32 [7.26-7.39]	7.30 [7.25-7.36]	0.05
PaO_2, mmHg	74.7 [64-83]	74 [63-82]	77 [65-84]	0.04
$PaCO_2$, mmHg	53.8 [45-60]	53 [43-59]	56 [47-61]	0.01
HCO_3, mEq/L	27 [23-30]	26.7 [23-30]	28 [23-30]	0.62
Initial PaO_2/FIO_2 ratio, mmHg	100 [79-120]	97 [77-118]	103 [83-123]	0.01
Time to 1st prone maneuver, days	2 (1-5)	2 [1-5]	3 [1-6]	0.02
Duration of 1st prone maneuver, h	18.3 (16.2-20.5)	18.6 [16.5-20.9]	17.6 [16.0-20.0]	0.04
Prone sessions, n	2 [1-3]	2 [1-3]	2 [1-2]	0.74
Post-prone oxygenation/ventilatory response				
$\Delta PaO_2/FIO_2$, mmHg	57.8 [14.7-90]	84 [41–111]	−9.2 [−21 to 7]	< 0.001
ΔPCO_2, mmHg	−3.0 [−10.0 to 5.0]	−2.5 [−9.4 to 5.1]	−3.8 [−11.5 to 4.0]	0.33
Complications	31 (5.4)	10 (2.4)	21 (13.0)	< 0.001
Drug interventions				
Anticoagulants	559 (97.4)	398 (96.6)	161 (99.4)	0.07
Vasopressors	509 (88.7)	361 (87.6)	148 (91.4)	0.16
Duration of MV, days	18 (9-23)	18 (9-22)	18 (10-24)	0.61
Length of ICU stay, days	20 [11-26]	21 [11-26]	20 [10-25]	0.49
Length of hospital stay, days	27[14-35]	28 [14-35]	26 [12-34]	0.05
Reintubation	76 (13.2)	54 (13.1)	22 (13.6)	0.89
Tracheotomy	115 (20.0)	85 (20.6)	30 (18.5)	0.61
In-hospital mortality	398 (69.3)	277 (67.2)	121 (74.7)	0.08

MV: mechanical ventilation; Pplat: plateau pressure of the respiratory system; Cst: static compliance of the respiratory system; and HCO_3: bicarbonate; [a]Values expressed as median [IQR] or n (%). [b]Missing data: PEEP (n = 1); RR (n = 5); VT (n = 4); driving pressure (n = 238); Pplat (n = 233); Cst (n = 253); duration of first prone maneuver (n = 2); complications (n = 8); anticoagulants (n = 1); vasopressors (n = 2); reintubation (n = 5); and tracheostomy (n = 2). *Mann-Whitney test for continuous variables and the chi-square test for categorical variables.

impairment on chest CT, immunosuppression, initial arterial pH, and $PaCO_2$. After multivariate logistic regression analysis, age, time to first session, number of sessions, extension of pulmonary impairment, immunosuppression, and initial arterial pH were independently associated with the risk of mortality (Table 3).

DISCUSSION

We performed a retrospective multicenter study involving seven Brazilian hospitals in a cohort of 574 intubated, mechanically ventilated patients with severe COVID-19-related ARDS. Our results showed that most patients (72%) had their oxygenation improved after the first prone positioning session, and this response was associated with SAPS III and PaO_2/FIO_2 ratio. We also observed a high mortality rate during ICU stays that was associated with age, time to the first prone positioning session, number of sessions, pulmonary impairment, and immunosuppression.

Patients were subdivided according to oxygenation improvement using a cutoff point of 20 in PaO_2/FIO_2. Although PaO_2/FIO_2 has been used to assess oxygenation response in patients with ARDS, no cutoff values have been well established. Most studies have used either an improvement of 10-20 mmHg in PaO_2 or a 10-20% increase in PaO_2/FIO_2.[13] In addition, we identified that the responder group presented lower SAPS III and SOFA score, as well as lower D-dimer levels. The SAPS III and SOFA scores are systems for predicting mortality in patients admitted to the ICU. Also, elevated D-dimer levels in patients with COVID-19 are associated with hemostatic abnormalities and poor outcomes and could predict mortality risk.[6,14-16] Taken together, our results reinforce the clinical relevance of using SAPS III/SOFA score and D-dimer levels to predict mortality in patients with COVID-19-related ARDS.

We found no significant reductions in mortality when comparing responder and nonresponder groups (67.2 vs. 74.7%; p = 0.08). Other studies were also unable to determine this correlation in patients with COVID-19-related ARDS. However, a retrospective study of 648 intubated patients with COVID-19-related ARDS placed in prone positioning showed that oxygenation response could reduce mortality.[10] Our results suggest that age, previous immunosuppression, extension of pulmonary involvement, time to start the first prone positioning session, number of prone sessions, and baseline arterial pH are predictors of mortality.

Overall mortality was 69.3%. We hypothesize that our patients had worse outcomes due to their socioeconomic status and health condition as accessed by age, comorbidities, SAPS III/SOFA score, D-dimer levels, and extension of pulmonary impairment. Weiss et al.[7] found a mortality rate of 21.4% among 42 patients requiring invasive mechanical ventilation and submitted to prone positioning. The mean age of the patients was 58.5 years, and the mean SOFA score was 6.8 at ICU admission. On the other hand, a less socioeconomically favored population neighborhood in New York City had a mortality rate > 75%.[17] Therefore, it is necessary to consider that the present study represents a population lacking resources in an underdeveloped country.

The high mortality rate can also be attributed to the overloaded health care system during the first pandemic peak in Brazil. The mortality rate in Brazil was approximately 80% among 250,000 patients hospitalized with COVID-19 on mechanical ventilation.[18] In addition, the median time to perform the first prone positioning session was 48 h (24-120 h) in the responder group and 72 h (24-144 h) in the nonresponder group. We were unable to identify the reasons why it took some patients a long time to be placed in the prone position.

The study had several limitations. First, because it is a retrospective study, it was not possible to find all of the data in the electronic medical records for analysis. Second, this is an observational study, and, contrary to a clinical trial, the decision and timing of prone positioning could not be controlled. Moreover, it was not possible to assess the strategies adopted by the teams during the prone positioning maneuver. Third, other treatments to improve response to

Table 3. Univariate logistic regression model analysis for predictors of oxygenation improvement and mortality.

Variable	OR	95% CI	p
Oxygenation response[a]			
SAPS III	0.98	0.96-0.99	0.04
Initial PaO_2/FIO_2 ratio, mmHg	0.98	0.97-0.98	< 0.001
Mortality risk[b]			
Age, years	1.04	1.01-1.06	< 0.001
Immunosuppression	3.83	1.35-10.86	0.01
Pulmonary impairment, % chest CT involvement			
Initial arterial pH	0.01	0.01-0.02	< 0.001
Time to first prone positioning session, days	1.18	1.06-1.31	0.01
Prone positioning sessions, n	1.31	1.00-1.72	0.04

SAPS III: Simplified Acute Physiology Score III. [a]Univariate analysis included the following data: SAPS III, number of sessions, static compliance of the respiratory system, initial PaO_2/FIO_2 ratio, and D-dimer level. [b]Univariate analysis included the following data: age, time to first prone positioning session, SOFA score, SAPS III, number of sessions, pulmonary impairment, immunosuppression, initial arterial pH, and $PaCO_2$.

prone positioning, such as the use of extracorporeal membrane oxygenation, hemodialysis, and alveolar recruitment, were not performed. Finally, the criteria that we used to assess the response to prone positioning are not universal; therefore, comparisons with other studies should be carried out with caution.

Our study showed that most patients with COVID-19-related ARDS experienced improved oxygenation after prone positioning. However, the mortality rate was high, probably due to the poor health status of the patients, disease severity, and high number of comorbidities of the patients, as well as the severity of their disease. These results highlight the usefulness of prone positioning to improve gas exchange for patients with COVID-19, mainly when performed early and in subjects with a better health status.

AUTHOR CONTRIBUTIONS

MCAC, JS, NCR, ACL, GNS, and LPI: study design, conception, and planning; data collection; interpretation of evidence; and drafting and revision of the manuscript. KRB, JEP, FF, LMF, RAC, AMVS, CCD, and RWW: study conception and planning; data collection; interpretation of evidence; revision of the manuscript; and approval of the final version. JCF, RDMP, and CRFC: study design, conception, and planning; interpretation of evidence; and revision of the manuscript.

CONFLICT OF INTEREST

None declared.

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