Understanding the Concept of Health Care-Associated Pneumonia in Lung Transplant Recipients

Federico Palacio, MD; Luis F. Reyes, MD; Deborah J. Levine, MD, FCCP; Juan F. Sanchez, MD, FCCP; Luis F. Angel, MD, FCCP; Juan F. Fernandez, MD; Stephanie M. Levine, MD, FCCP; Jordi Rello, MD, PhD; Ali Abedi, MD; and Marcos I. Restrepo, MD, FCCP

BACKGROUND: Limited data are available regarding the etiologic impact of health care-associated pneumonia (HCAP) in lung transplant recipients. Therefore, our aim was to evaluate the microbiologic differences between HCAP and hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) in lung transplant recipients with a radiographically confirmed diagnosis of pneumonia.

METHODS: We performed a retrospective cohort study of lung transplant recipients with pneumonia at one transplant center over a 7-year period. Eligible patients included lung transplant recipients who developed a first episode of radiographically confirmed pneumonia ≥ 48 h following transplantation. HCAP, HAP, and VAP were classified according to the American Thoracic Society/Infectious Diseases Society of America 2005 guidelines. χ^2 and Student *t* tests were used to compare categorical and continuous variables, respectively.

RESULTS: Sixty-eight lung transplant recipients developed at least one episode of pneumonia. HCAP (n = 42; 62%) was most common, followed by HAP/VAP (n = 26; 38%) stratified in HAP (n = 20; 77%) and VAP (n = 6; 23%). *Pseudomonas aeruginosa* was the predominantly isolated organism (n = 22; 32%), whereas invasive aspergillosis was uncommon (< 10%). Multiple-drug resistant (MDR) pathogens were less frequently isolated in patients with HCAP compared with HAP/VAP (5% vs 27%; *P* = .009). Opportunistic pathogens were less frequently identified in lung transplant recipients with HCAP than in those with HAP/VAP (7% vs 27%; *P* = .02). Lung transplant recipients with HCAP had a similar mortality at 90 days (n = 9 [21%] vs n = 4 [15%]; *P* = .3) compared with patients with HAP/VAP.

CONCLUSIONS: HCAP was the most frequent infection in lung transplant recipients. MDR pathogens and opportunistic pathogens were more frequently isolated in HAP/VAP. There were no differences in 30- and 90-day mortality between lung transplant recipients with HCAP and those with HAP/VAP.

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ABBREVIATIONS: HAP = hospital-acquired pneumonia; HCAP = health care-associated pneumonia; IQR = interquartile range; LOS = length of stay; LT = lung transplant; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; VAP = ventilator-associated pneumonia

AFFILIATIONS: From the South Texas Veterans Health Care System (Drs Palacio, S. M. Levine, and Restrepo), San Antonio, TX; the University of Texas Health Science Center at San Antonio (Drs Palacio, Reyes, D. J. Levine, Angel, Fernandez, S. M. Levine, Abedi, and Restrepo), San Antonio, TX; Scott and White Health Care System (Dr Sanchez), Temple, TX; the Hospital Universitari Vall d'Hebron (Dr Rello), Vall d'Hebron Institute of Research, CIBERES, Universitat Autonoma de Barcelona, Barcelona, Spain; and the Universidad de La Sabana (Dr Reyes), Bogota, Colombia.

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CORRESPONDENCE TO: Marcos I. Restrepo, MD, FCCP, South Texas Veterans Health Care System, Audrey L. Murphy Division, 7400 Merton Minter Blvd, San Antonio, TX 78229; e-mail: restrepom@uthscsa.edu

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Development of new immunosuppressive agents and advances in surgical technology in solid organ transplantations have significantly improved outcomes in lung transplantation.[1] Survival rates have improved from 70% in 1990 to 81% in 2012, but complications, especially infections, remain common.[1,2] Infections in lung transplant (LT) recipients are one of the major causes of early and late morbidity and mortality, accounting for > 50% of deaths.[3-5] Pneumonia is the most frequent infection seen in LT recipients, reportedly accounting for 35% to 82.7% of all infections in this setting.[1,4,6] In addition, pneumonia following lung transplantation bears a high risk for multidrug-resistant (MDR) pathogens, including *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Acinetobacter* species.[6]

Clinical practice guidelines from the Infectious Diseases Society and American Thoracic Society classify pneumonia as either health care-associated (HCAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP), with HCAP introduced due to similarities in MDR pathogens observed in patients with HAP or VAP.[7,8]

HCAP as a subtype of pneumonia is defined as a respiratory infection associated with specific health-care risk factors that include hospitalization for ≥ 2 days in the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy (including antibiotics), chronic dialysis within 30 days, home wound care, and family member(s) with an MDR pathogen.[7,9] By virtue of this, all LT recipients, who are immunosuppressed, are considered at risk for MDR pathogens. However, data regarding the association of MDR pathogens with pneumonia in LT recipients are lacking, which limits appropriate antimicrobial therapy and assessment of clinical outcomes of HCAP in LT recipients. Therefore, our aim was to evaluate the microbiologic differences between HCAP compared with HAP/VAP in LT recipients with a radiographically confirmed diagnosis of pneumonia.

Materials and Methods

This was a retrospective cohort study of patients hospitalized with HCAP, HAP, and VAP at one academic tertiary care hospital in San Antonio, Texas. The institutional review board of the University Health Science Center at San Antonio classified this project as an exempt study.

Study Sites and Inclusion and Exclusion Criteria

We identified all patients admitted to the study hospitals with a primary discharge diagnosis of pneumonia (*International Classification of Diseases-9* codes 480.0-483.99 or 485-487.0) or secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (code 518.81) over a 7-year period (January 1, 2001, to December 31, 2008). In addition, we reviewed all positive microbiology cultures from respiratory and blood samples.

Subjects were included if (1) they were older than 18 years; (2) had received a LT; (3) their first episode of pneumonia after transplantation was classified as HCAP, HAP, or VAP, with symptoms of lower respiratory tract infection (at least one of the following: fever, cough, sputum production, dyspnea, chest pain); and (4) had radiographically confirmed opacities or other findings consistent with pneumonia on chest radiographs or CT scans of the chest obtained during the hospitalization. For HCAP, radiographic diagnosis of pneumonia was done within 48 h of admission. We excluded patients who received "comfort measures" at the time of admission. In subjects admitted more than once during the study period, only the first pneumonia event was abstracted. MDR pathogens included proven resistance on the susceptibility patterns for MRSA, *P aeruginosa*, and *Acinetobacter* species resistant to at least two classes of antibiotics, and extended spectrum β-lactamase phenotype *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Citrobacter* species, *Achromobacter xyloxosidans*, and *Burkholderia* species.

Outcomes

Primary outcome was the incidence of MDR pathogens. Secondary outcomes included mortality at 30 and 90 days and length of hospital stay (LOS).

Diagnostic Criteria

Microbiologic data were reviewed, and a microbiologic cause was assigned independently by one of the investigators (F. P.). Microbiologic diagnosis was made if one of the following conditions was met: (1) positive blood cultures for bacterial pathogens (in the absence of extrapulmonary source of infection), (2) pleural fluid cultures yielding a bacterial pathogen, (3) endotracheal aspirates with moderate or heavy growth of bacterial pathogens, (4) significant quantitative culture growth from bronchoscopic respiratory samples (protected specimen brush cultures of at least 10^3 colony-forming unit (CFU)/mL, or BAL of at least 10^4 CFU/mL), and (5) positive *Legionella* urinary antigen. When two or more microbiologic causes were present, the patient was considered to have a polymicrobial infection. A patient was considered to have HCAP, HAP, or VAP of unknown cause if microbiologic studies were not performed or were inconclusive. As part of the local policies, every LT recipient who presents with symptoms suggestive of a lower respiratory tract infection will have a comprehensive microbiology evaluation that includes invasive bronchoscopy or, if unavailable, sputum collection, but this was not standardized during the study.

Statistical Analyses

The data collected in this project were descriptive. All analyses were performed using SPSS, version 20 (IBM Corp). Data were presented as frequencies, proportions (with 95% CIs), or median with interquartile range (IQR). ORs and their 95% CIs were calculated. Significance was defined as $P < .05$. A propensity score technique was used to balance covariates associated with HCAP diagnosis between groups.[10] Use of the propensity score technique in this nonrandomized study allowed for control of pretreatment differences by defining sets of comparable patients. The propensity score was derived from a logistic regression model. A dichotomous indicator variable indexing whether a patient had a diagnosis of HCAP was used as our response variable. The covariates used in the propensity score model were pulmonary hypertension, guideline concordant antibiotic therapy, ICU admission, need for mechanical ventilation, and acute rejection. We then created an ordered categorical variable based on a quintile stratification of the propensity score to include in the regression models.

Results

We identified a cohort of 68 LT recipients with a documented first episode of pneumonia from 170 lung transplantations performed during the study period. Forty-eight subjects (71%) had undergone unilateral transplantation and 20 (29%) bilateral lung transplantation. The three most common indications for lung transplantation were COPD (n = 28; 41%), followed by idiopathic pulmonary fibrosis (n = 21; 30.9%) and cystic fibrosis (n = 3; 4.4%) (Table 1). The most common type of pneumonia in LT recipients was HCAP (n = 42; 62%). Patients with HAP/VAP consisted mostly of HAP

TABLE 1] Comparison of Demographic and Clinical Characteristics Among Lung Transplant Recipients With HCAP and HAP/VAP

Variable	HCAP (n = 42)	HAP/VAP (n = 26)	*P* Value
Age, y (interquartile range)	56 (50-61)	53 (47-62)	.5
Men	18 (43)	16 (47)	.3
Type of transplant			
Right-side single lung transplant	16 (38)	9 (35)	.8
Left-side single lung transplant	16 (38)	7 (27)	.3
Bilateral lung transplant	10 (24)	10 (38)	.2
Racial origin			.1
White	29 (69)	12 (43)	
Black	4 (10)	8 (31)	
Hispanic	9 (21)	6 (23)	
Indication for transplant			.3
COPD	18 (43)	10 (38)	
Idiopathic pulmonary fibrosis	13 (31)	8 (31)	
Cystic fibrosis	2 (5)	1 (4)	
Other[a]	9 (21)	7 (27)	
Transplant immunosuppression			
Cyclosporine	30 (59)	21 (41)	.4
Tacrolimus	12 (29)	4 (15)	.2
Mycophenolate mofetil	40 (95)	25 (96)	.9
Azathioprine	2 (5)	1 (4)	.9
Preexistent comorbid conditions			
Pulmonary arterial hypertension	0 (0)	4 (15)	.009
Chronic renal insufficiency	1 (2)	0 (0)	.4
Diabetes mellitus	9 (21)	7 (27)	.6
Complications			
ICU admission	12 (29)	21 (81)	< .01
Mechanical ventilation	12 (29)	15 (58)	.02
Antimicrobial coverage			
Antibiotics against MRSA	26 (62)	20 (77)	.2
Broad-spectrum antibiotics	35 (83)	24 (92)	.3
Double coverage for *Pseudomonas*	24 (57)	14 (54)	.8
Adequate antibiotic coverage	19/21 (90)	21/21 (100)	.1
Guideline-concordant therapy	16 (38)	11 (42)	.7

Data given as No. (%) unless otherwise indicated. HAP = hospital-acquired pneumonia; HCAP = health care-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

[a]Other indications for transplant: bronchiolitis obliterans with organizing pneumonia, bronchiolitis obliterans syndrome, nonspecific interstitial pneumonia, sarcoidosis, scleroderma, pulmonary arterial hypertension, interstitial lung disease, chronic thromboembolic pulmonary hypertension-scleroderma.

(n = 20; 77%), with the remainder having VAP (n = 6; 23%). The median age of LT recipients with HCAP was 56 years (IQR, 50-61 years) compared with 53 years (IQR, 47-62 years) ($P = .5$) in LT recipients with HAP/VAP. Groups were similar with respect to sex, race, comorbidities, type of LT, and indication for transplant (Table 1). Differences in immunosuppression between HCAP and HAP/VAP are summarized in Table 1. Patients with HCAP were less likely to have pulmonary arterial hypertension as a comorbidity (zero patients [0%] vs four [15%]; $P = .009$). LT recipients with HCAP were less likely to be admitted to ICU (12 [29%] vs 15 [81%]; $P \leq .01$) or require mechanical ventilation (12 [29%] vs 15 [58%]; $P = .02$). Regarding antimicrobial therapy, fewer than one-half of the patients received complete guideline concordant therapies (38% for HCAP and 42% for HAP/VAP; $P = .7$) (Table 1). However, most patients (95%) received adequate antimicrobial therapies that were active against bacteria isolated from their respiratory secretions (90% of HCAP and 100% of HAP/VAP; $P = .1$).

Pneumonia Etiology

Specific microbiologic etiology was established in 60% (41 of 68) of LT recipients (Table 2). The most commonly isolated pathogens in both groups were *P aeruginosa* (n = 22; 32%), *Aspergillus* species (n = 6; 8.8%), and methicillin-sensitive *S aureus* (MSSA) (n = 5; 7.3%) (Table 2). No pneumococcal pneumonia was documented. Positive cultures of respiratory secretions identified at least one pathogen in 55% of patients with HCAP compared with 69% of patients with HAP/VAP ($P = .2$). Four of the six isolated *Aspergillus* species were confirmed by BAL, protected sample brush, or both and two were isolated in sputum. Similar rates of both *P aeruginosa* (n = 12 [28%] vs n = 6 [23%]; $P = .8$) and MSSA (n = 2[5%] vs n = 1 [4%]; $P = .9$) were seen among groups. MRSA was isolated only once (1.5%) in a patient with HAP/VAP. There were only two documented bacteremias with MSSA and *P aeruginosa*; however, only eight patients (12%) had bacterial blood cultures drawn at the time of pneumonia. Opportunistic pathogens were significantly less frequent in LT recipients with HCAP compared with HAP/VAP (7% vs 27%; $P = .02$). Culture-negative pneumonia occurred in 19 patients (45%) with HCAP vs eight patients (31%) with HAP/VAP ($P = .3$). Among the patients with negative cultures, evidence of acute and chronic rejection was not statistically significantly different in patients with HCAP compared with HAP/VAP (three [19%] vs zero [$P = .2$] and three [16%] vs zero [$P = .2$], respectively).

TABLE 2] Microbiologic Results Among Lung Transplant Recipients With HCAP and HAP/VAP[a]

Organism	HCAP[b] (n = 42)	HAP/VAP[b] (n = 26)
Culture negative	19 (45.2)	8 (30.8)
Monomicrobial		
Staphylococcus aureus		
MSSA	2 (5)	1 (4)
MRSA	0 (0)	1 (4)
Streptococcus pneumoniae	0 (0)	0 (0)
Nocardia	1 (2)	0 (0)
Enterobacteriaceae		
Enterobacter cloacae	0	1 (4)
Enterobacter aerogenes	1 (2)	0 (0)
Escherichia coli	1 (2)	0 (0)
Serratia marcescens	1 (2)	0 (0)
Non-Enterobacteriaceae		
Pseudomonas aeruginosa	12 (28)	6 (23)
Burkholderia cepacia	0 (0)	1 (4)
Fungal		
Aspergillus species	1 (2)	0 (0)
Trichosporon beigelii	1 (2)	0 (0)
Viral infections		
Influenza	1 (2)	0 (0)
Respiratory syncytial virus	2 (5)	0 (0)
Polymicrobial		
Pseudomonas stutzeri, Enterobacter cloacae with *Aspergillus* species	0 (0)	1 (4)
Achromobacter xylosoxidans with *S marcescens*	0 (0)	1 (4)
MSSA with *Aspergillus* species	0 (0)	1 (4)
P stutzeri, Citrobacter species with *Aspergillus* species	1 (2)	0 (0)
MSSA with *E aerogenes*	0 (0)	1 (4)
P aeruginosa with *Aspergillus* species	0 (0)	2 (8)
P aeruginosa with *S marcescens*	0 (0)	1 (4)
P aeruginosa with *A xylosoxidans*	0 (0)	1 (4)

Data given as No. (%) unless otherwise indicated. MSSA = methicillin-sensitive *S aureus*. See Table 1 legend for expansion of other abbreviations.

[a]$P < .05$ (no values were statistically significant different).

[b]Percentages have been rounded and may not sum 100.

Outcomes

MDR pathogens were less frequently isolated in patients with HCAP when compared with HAP/VAP (5% vs 27%; $P = .009$). Overall 90-day mortality was 19% for LT recipients with pneumonia, being accumulated over the first month after pneumonia onset. HCAP compared with HAP/VAP had similar 30-day (n = 6 [14%] vs n = 4 [15%]; $P = .5$) and 90-day mortality (n = 9 [21%] vs n = 4 [15%]; $P = .3$). The median LOS, however, was 20 days longer for patients with HAP/VAP than for HCAP patients (7 days [IQR, 4-15] vs 27 days [IQR, 15-31]; $P \leq .001$). In the univariate and multivariate analyses, there were no significant statistical differences in mortality at 30 or 90 days between HCAP and HAP/VAP LT recipients (Table 3).

Discussion

This study suggests that HCAP is the most common type of pneumonia in LT recipients. In contrast with HAP/VAP, the percentage of opportunistic infections (including aspergillosis) was significantly lower in HCAP, where management strategies should include antipseudomonal antibiotics. Our study showed similar mortality rates at 30 and 90 days for LT recipients who developed HCAP when compared with those who developed HAP/VAP. This was in contrast to our hypothesis that HAP/VAP (driven by VAP data) would produce higher mortality.[7,11,12] Guideline compliance using triple antimicrobial therapy was low. Interestingly, however, the antibiotics administered had a broad enough spectrum of coverage to adequately target pathogens identified in LT recipients. Empirical use of antipseudomonal β-lactams appeared to be the main reason for this observed adequacy in antimicrobial therapy. Our results are unique, due to currently limited information regarding microbiology, antibiotic use, and clinical outcomes among LT recipients at risk for developing HCAP and HAP/VAP infections.

TABLE 3] Propensity Score of Primary and Secondary Outcomes for Lung Transplant Recipients With HCAP and HAP/VAP

Variable	OR	95% CI	*P* Value
MDR pathogens[a]	1.363	0.789-2.353	.3
Mortality at 30 d	1.375	0.722-2.618	.3
Mortality at 90 d	1.188	0.682-2.068	.5

MDR = multidrug resistant. See Table 1 and 2 legends for expansion of other abbreviations.
[a]MDR pathogens: MRSA, *P aeruginosa*, *Acinetobacter* species, *E coli*, *Klebsiella* species, or *Enterobacter* species. Those with extended-spectrum β-lactamase phenotype are *Citrobacter* species, *A xyloxosidans*, and *Burkholderia* species.

We initially anticipated LT recipients acquiring pathogens outside the hospital setting to have a microbiologic spectrum of organisms closer to community-acquired pneumonia rather than HAP/VAP.[13] However, we found similarly high rates of isolation for *Pseudomonas* species and *S aureus* among LT recipients with HCAP or HAP/VAP. In contrast, no pneumococcal-related pneumonia events were identified in this cohort of LT recipients. Similar results were reported by Campos et al[14] in 108 episodes of pneumonia in LT recipients, where *P aeruginosa* was isolated in 33.3% of the patients and *S aureus* was isolated in 26.8%. Our study results add to the literature highlighting antimicrobial resistance patterns observed in patients with HCAP or HAP/VAP, with higher rates of MDR pathogens observed in the HAP/VAP group.[13,15] However, the statistical significance of the MDR rates observed among groups disappeared after performing multivariable analysis (ie, propensity score).

It is also interesting that no *Streptococcus pneumoniae* was isolated from any of the LT recipients with pneumonia. Pneumoccocal pneumonia was previously associated with excess mortality in patients with HCAP associated with bacteremia.[16] Few data are available and debate exists on the pathogenicity of coagulase-negative *Staphylococcus* in the lungs of immunocompromised patients, although several cases of coagulase-negative *Staphylococcus* infection are reported in the literature among immunosuppressed patients.[17-20] We considered that in the two LT recipients who had coagulase-negative *Staphylococcus*, as determined from BAL and protected sample brush specimens, it was not pathogenic or the source of infection.

HCAP has been classified as a subtype of pneumonia for immunocompromised patients.[9] However, immunosuppression was also recognized in 2005 American Thoracic Society/Infectious Diseases Society guidelines as a risk factor for MDR pathogens. Therefore, we attempted to use a cohort of LT recipients as a well-recognized group of immunosuppressed patients in whom pneumonia is a frequent post-transplant complication.[9] This association has an important implication in the appropriate selection of antimicrobial agents and its impact on clinical outcomes. Current clinical practice guidelines recommend that in HCAP/HAP/VAP, where risk for MDR pathogens exists, a three-antibiotics scheme be used. This includes coverage for MRSA, and double coverage for MDR gram-negative rods including *P aeruginosa* with an anti-*Pseudomonas* β-lactam plus either an aminoglycoside or an anti-*Pseudomonas* fluoroquinolone.[9] Our findings question the generalization of this statement.

The low incidence of guideline-concordant therapy (38% in HCAP and 42% in HAP/VAP) identified in this study is also important and somewhat unexpected. The lack of double coverage with a second antipseudomonal agent observed in our cohort, aided by the presence of highly susceptible strains observed among nonlactose fermenter gram-negative rods, did not limit therapeutic adequacy in the large majority of cases, with no impact on mortality at 30 or 90 days. Another interesting finding was the LOS in HAP/VAP compared with HCAP in LT recipients. In our study, most HCAPs occurred ≥ 1 year after lung transplantation, compared with HAP/VAPs, which occurred mostly during the first month after lung transplantation. A longer LOS in LT recipients with HAP/VAP, therefore, might reflect a complicated hospitalization rather than a direct morbidity effect of HAP/VAP. This finding contrasts with previous studies that reported an increased hospital LOS in patients with HAP/VAP compared with those with HCAP.[7]

Our study has several limitations that are important to acknowledge. First, this was a retrospective cohort study, and there are inherent problems related to this design, including selection bias. However, we were able to verify that all patients had a radiologic diagnosis of pneumonia and symptoms suggesting a lower respiratory infection. It is also possible that patients may have received care at an institution other than our LT center. It is unlikely, however, that this may have affected the primary outcome of this study. Second, microbiologic confirmation of a bacterial diagnosis was not standardized among patients with pneumonia. Third, information regarding pretransplant colonization and infection including donor cultures was not available to us at the time of the study. Fourth, immortal time bias may have affected our results, as patients with HCAP needed to survive the initial hospitalization to acquire a new pneumonia. Fifth, molecular biologic techniques and galactomannan were not used in assisting in the diagnosis of viral or *Aspergillus* infections, other than for cytomegalovirus infection. The diagnosis of viral pathogens was done by viral culture, which may have underestimated the incidence of viral pneumonias in LT recipients.

Other limitations of this study include the difficulty in determining the contribution of the native lung to infection. Although there were no differences found between single and bilateral LT recipients, it is possible that patients who receive a single LT are at higher risk for pneumonia, due to pathogens typically harbored in the native lung of patients with chronic lung diseases. Sinus infections can similarly be a source of pneumonia, particularly in the cystic fibrosis population, with unclear implications in this subset of patients.

The clinical implications of our results are an important strength of our study, and suggest that the use of anti-pseudomonal antimicrobial therapy is justified in our setting. This also emphasizes the need to customize clinical practice recommendations to local susceptibility data. Finally, not all the LT recipients with culture-negative pneumonia had transbronchial biopsies or donor-specific antibody testing to evaluate the impact of rejection.

In conclusion, our study suggests that HCAP represents two-thirds of pneumonia episodes in LT recipients. There were no differences in mortality when comparing LT recipients with HCAP and HAP and VAP, provided anti-pseudomonal agents were prescribed as empirical therapy. Further studies using newer molecular diagnostic techniques may be able to identify other nonbacterial causes of pneumonia.

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Author contributions: M. I. R. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M. I. R. contributed to data analysis and writing the manuscript; F. P., L. F. R., D. J. L., J. F. S., L. F. A., J. F. F., S. M. L., J. R., A. A., and M. I. R. contributed to the study design, data interpretation, revision of the manuscript, and final approval of the manuscript.

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