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REVIEW

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Clinical manifestations of children with COVID-19: A systematic review

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Abstract

Background: The coronavirus disease 2019 (COVID-19) outbreak is an unprecedented global public health challenge, leading to thousands of deaths every day worldwide. Despite the epidemiological importance, clinical patterns of children with COVID-19 remain unclear. The aim of this study was to describe the clinical, laboratorial, and radiological characteristics of children with COVID-19.

Methods: The Medline database was searched between December 1st 2019 and April 6th 2020. No language restrictions were applied. Inclusion criteria were (a) studied patients younger than 18 years old; (b) presented original data from cases of COVID-19 confirmed by reverse-transcription polymerase chain reaction; and (c) contained descriptions of clinical manifestations, laboratory tests, or radiological examinations.

Results: A total of 38 studies (1124 cases) were included. From all the cases, 1117 had their severity classified: 14.2% were asymptomatic, 36.3% were mild, 46.0% were moderate, 2.1% were severe, and 1.2% were critical. The most prevalent symptom was fever (47.5%), followed by cough (41.5%), nasal symptoms (11.2%), diarrhea (8.1%), and nausea/vomiting (7.1%). One hundred forty-five (36.9%) children were diagnosed with pneumonia and 43 (10.9%) upper airway infections were reported. Reduced lymphocyte count was reported in 12.9% of cases. Abnormalities in computed tomography were reported in 63.0% of cases. The most prevalent abnormalities reported were ground-glass opacities, patchy shadows, and consolidations. Only one death was reported.

Conclusions: Clinical manifestations of children with COVID-19 differ widely from adult cases. Fever and respiratory symptoms should not be considered a hallmark of COVID-19 in children.

KEYWORDS

children, coronavirus, COVID-19, SARS-CoV-2

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, Coronavirus disease 2019; CT, Computed tomography; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

1 | INTRODUCTION

In late December 2019, Chinese authorities informed the World Health Organization (WHO) that, due to unknown cause, an outbreak of pneumonia emerged in Wuhan, Hubei province. On 7 January 2020, a new type of coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was isolated, and later named "coronavirus disease 2019" (abbreviated "COVID-19"). The first death caused by COVID-19 was on 9 January 2020, in Wuhan and since then more than 370 000 cases and 16 000 deaths occurred worldwide.[1] Currently, the death toll in Italy has far surpassed the number registered in China, and the United States became the new COVID-19 epicenter.

In spite of stepped-up efforts to contain the pandemic, the number of affected patients and the death toll continue to rise. Elderly patients infected with SARS-CoV-2 are at high risk to have severe acute respiratory syndrome, complications, and death.[2] Due to unknown reasons, children with COVID-19 appear to have a milder clinical course compared to adults, and reports of death are scarce.[3,4] However, the pediatric population may play a major role in the community spread of SARS-CoV-2. In addition to viral shedding in nasal secretions, there is evidence of fecal shedding for several weeks after diagnosis, which poses a challenge for infection control.[5]

Despite the epidemiological importance, clinical patterns of children with COVID-19 remain unclear. The WHO recommends testing all suspected cases, however, children infected with SARS-CoV-2 may not meet all the criteria required in the suspected case definition.[6] The objective of this study is to describe the clinical, laboratorial, and radiological characteristics of children with COVID-19 reported in the literature.

2 | METHODS

This review was performed in accordance with the Preferred Reporting Items for Systematic and Meta-Analysis statement.[7,8] The Medline database was searched using the following search strategy: ((((COVID-19) OR coronavirus) OR SARS-CoV-2)) AND (((((((pediatrics) OR children) OR neonates) OR child) OR neonate) OR infant) OR infants). No language restrictions were applied. Articles published between December 1st 2019 and April 7th 2020 were evaluated for inclusion. No attempts were made to contact the study authors for identifying missing and confusing data. A manual search of the references found in the selected articles and reviews was also performed.

2.1 | Study selection

Two authors (THS and JAN) screened the titles and abstracts independently and in duplicate for potential eligibility. They subsequently read the full texts to determine final eligibility. Discrepancies were resolved through discussion and consensus, and if necessary, the assistance of a third author (MBB) was sought.

Eligible studies fulfilled the following criteria: (a) studied patients younger than 18 years old; (b) presented original data from cases of COVID-19 confirmed by reverse-transcription polymerase chain reaction; (c) contained descriptions of clinical manifestations, laboratory tests, or radiological examinations.

2.2 | Data extraction

A structured data extraction form was piloted and then used to extract data from the reports of all included studies in duplicate and independently by two authors (THS and JAN). Discrepancies in extracted data were resolved through discussion. The following data were extracted, when available, from each selected article: first author, publication year, study design, number of cases, gender, age, clinical manifestations, laboratory tests, radiological examinations, and outcomes (discharged, still hospitalized, or death).

When sufficient data were reported, the cases were classified into the following clinical types[9]:

1. Asymptomatic infection: without any clinical symptoms and signs and the chest imaging is normal, while the SARS-CoV-2 nucleic acid test was positive or the serum-specific antibody was retrospectively diagnosed as infection.
2. Mild: symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows the congestion of the pharynx and no auscultatory abnormalities. Some cases may have no fever or have only digestive symptoms such as nausea, vomiting, abdominal pain, and diarrhea.
3. Moderate: presented as pneumonia. Frequent fever and cough, mostly dry cough, followed by productive cough, some may have wheezing, but no obvious hypoxemia or shortness of breath, and lung auscultation may have rhonchi or dry stertor and/or wet stertor. Some cases may have no.
4. clinical signs and symptoms, but chest computed tomography (CT) shows lung lesions, which are subclinical.
5. Severe: early respiratory symptoms such as fever and cough, may be accompanied by gastrointestinal symptoms such as diarrhea. The disease usually progresses around 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, with other hypoxia manifestations.
6. Critical: children can quickly progress to acute respiratory distress syndrome or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury, including multiple organ dysfunction.

3 | RESULTS

3.1 | Study selection and characteristics

Of 293 potentially relevant articles identified by the search strategy, 38 met the inclusion criteria. A total of 1117 descriptions of pediatric

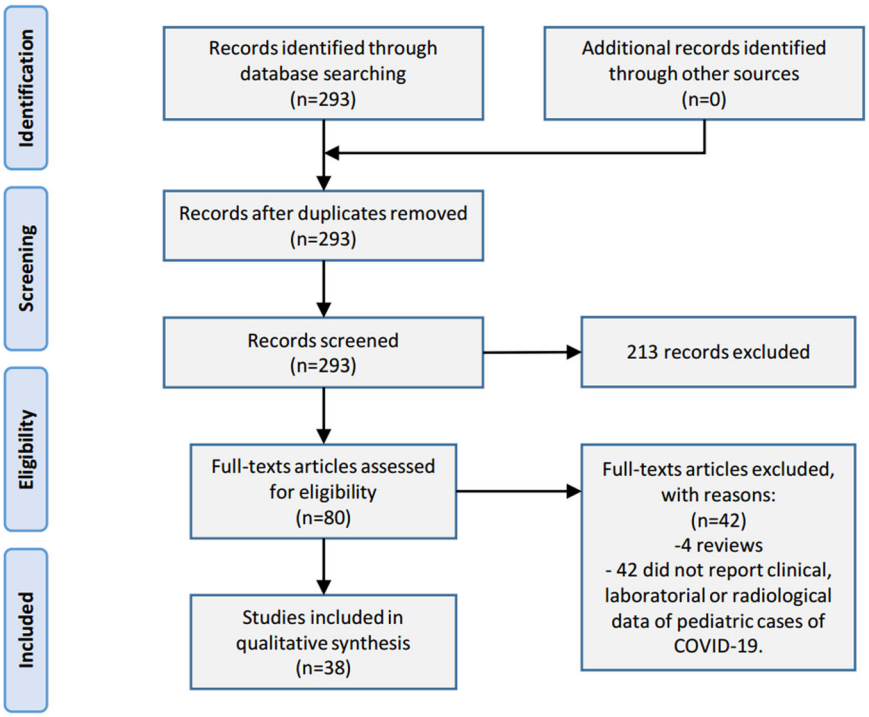

FIGURE 1 PRISMA flow diagram for study selection. PRISMA, Preferred Reporting Items for Systematic and Meta-Analysis [Color figure can be viewed at wileyonlinelibrary.com]

cases[3,5,10-40] and seven neonate cases[41-45] of COVID-19 were obtained, including 643 males, 478 females, and three undisclosed. The flow diagram (Figure 1) summarizes the steps followed to identify the studies meeting the inclusion criteria.

Twenty studies were case reports,[20-28,31,32,35,37-43,45] 11 were case series[5,15-19,29,30,33,34,44] and six were retrospective studies.[3,10-14,36] With the exception of five multicenter studies,[5,10-12,36] all others were unicentric studies. Thirty-three studies were conducted in China,[3,5,10-22,24-27,29,30,32-37,39-44] one in Italy,[38] one in Iran,[45] one in Singapore,[28] one in Korea,[23] and one in Vietnam.[31]

3.2 | Severity of illness

A total of 1117 cases had their severity classified based on the reported clinical data. One hundred fifty-nine (14.2%) cases were asymptomatic, 406 (36.3%) were mild, 514 (46.0%) were moderate, 25 (2.1%) were severe, and 13 (1.2%) were critical cases. The severity of illness of the reported cases is illustrated in Figure 2. Details on the ventilatory support used were described in 10 critical cases (nine children and one newborn).[3,12,16,27,43] Eight children underwent invasive mechanical ventilation and one premature newborn who suffered fetal distress received noninvasive ventilation.

Table 1 summarizes the severity of illness reported in each included study.

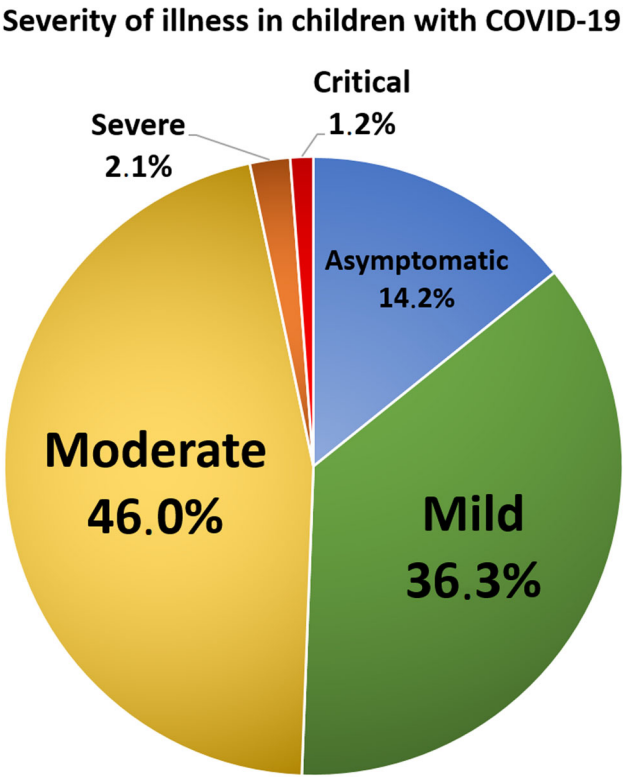

FIGURE 2 Severity of illness of the reported cases. COVID-19, coronavirus disease 2019 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Severity of illness and characteristics of cases reported

			Gender		Severity of illness					
Studies	N	Age	Males	Females	Asymptomatic	Mild	Moderate	Severe	Critical	NR
Dong et al[20]	731	10 y[a]	420	311	94 (12.9%)	315 (43.1%)	300 (41.0%)	15 (2.5%)	3 (0.4%)	1 (0.1%)
Lu et al[3]	171	6 y (1 d-15 y)[a]	104	67	27 (15.7%)	33 (19.3%)	107 (62.6%)	1 (0.6%)	3 (1.7%)	
Qiu et al[29]	36	8 y (1-16 y)[b]	23	13	10 (27.7%)	7 (19.4%)	19 (52.8%)			
Wang et al[31]	31	7 (6 mo-17 y)[b]	15	16	4 (12.9%)	13 (41.9%)	14 (45.1%)			
Zheng et al[35]	25	3 y (3 mo-14 y)[b]	14	11		8 (32.0%)	15 (60.0%)		2 (8.0%)	
Xia et al[36]	20	2 y (1 d-14 y)[a]	13	7			19 (95.0%)	1 (5.0%)		
Feng et al[37]	15	7 (4-14 y)[b]	5	10		3 (20.0%)	12 (80.0%)			
Cai et al[5]	10	74 mo (3-131 mo)[a]	4	6		6	4			
Wei et al[38]	9	6 mo (1-11 mo)[a]	2	7	1	6				2
Su et al[26]	9	4.5 y (11 mo-9 y)[a]	3	6	6	3				
Zhou et al[27]	9	1 y (7 mo-3 y)[b]	4	5	5		4			
Sun et al[39]	8	6.8 y (2 mo-15 y)[a]	6	2				5	3	
Liu et al[40]	6	3 y (1-7 y)[b]	2	4			4	1		1
Hu et al[10]	5	8 y (5-15 y)[a]	3	2	4	1				
Liu et al[23]	5	5.9 y (7 mo-13 y)[a]	4	1	3	2				
Liu et al[11]	4	3 y (2 mo-9 y)[a]	2	2		1	3			
Lou et al[12]	3	6 mo/6 y/8 y	1	2			3			
Zeng et al[43]	3	neonates	3				2		1	
Zhang et al[33]	3	6 y/8 y/9 y	3				3			
Li et al[13]	2	4 y/4 y	1	1	1		1			
Ji et al[14]	2	15 y/9 y	2			2				
Aghdam et al[45]	1	15 d	NR	NR				1		
Canarruto et al[32]	1	32 d	1			1				
Le et al[24]	1	3 mo		1		1				
Lin et al[34]	1	7 y		1		1				
Pan et al[25]	1	3 y	1		1					
Wang et al[42]	1	19 d	1			1				
Zhang et al[28]	1	1 y 2 mo		1		1				
Yu et al[44]	1	neonate	NR	NR	1					
Park et al[15]	1	10 y		1			1			
Cui et al[16]	1	55 d		1				1		
Tang et al[17]	1	10 y	1		1					
Zhang et al[18]	1	3 mo					1			
Cai et al[30]	1	7 y	1				1			
Zeng et al[41]	1	17 d	1				1			
Chen et al[19]	1	1 y	1						1	
Kam et al[21]	1	6 mo	1			1				
Chan et al[22]	1	10 y	1		1					
Total	1121		643	478	159 (14.2%)	406 (36.3%)	514 (46.0%)	25 (2.1%)	13 (1.2%)	4

Note: NR = not reported.

[a]Value expressed as mean (range).

[b]Value expressed as median (range).

3.3 | Clinical manifestations

The most prevalent symptom was fever, reported in 47.5% of the cases, followed by cough (41.5%), nasal symptoms (11.2%), diarrhea (8.1%), nausea/vomiting (7.1%), fatigue (5.0%), and respiratory distress (3.5%). The nasal symptoms described were runny nose and nasal congestion, symptoms of loss of smell were not described. One hundred forty-five (36.9%) children were diagnosed with pneumonia and 43 (10.9%) upper airway infections were reported. Amongst the most common clinical signs described were pharyngeal erythema (20.6%), tachycardia (18.6%), and tachypnea (13.4%) on admission. All the clinical manifestations reported in the selected studies and their relative frequencies are described in Table 2. All clinical manifestations described in each study are presented in E-Table 1 in the Supporting Information.

3.4 | Laboratorial characteristics

Twenty-nine studies detailed the white blood cell count of 174 cases.[11,13,14,16-19,21-43,45] Of these, 13 (7.5%) were elevated, 29 (16.6%) were decreased, and 132 (75.8%) were within normal ranges. Normal or elevated lymphocytes counts were detailed in 28 studies, involving 154 cases.[11,13,16,17,19,21-43,45] Normal lymphocyte counts were reported in 69.5% and elevated in 11.7% of cases. Reduced lymphocyte counts were reported in 45 of 350 (12.9%) cases.[3,11-13,16,17,19,21-43,45] Zheng et al[12] reported a median white blood cell count of 6.2×10^9/L (interquartile range [IQR]: 4.30-9.85) and median lymphocyte count of 2.19×10^9/L (IQR: 1.15-3.31) of 25 pediatric patients.

Normal or decreased platelet counts were detailed in 15 studies, involving 32 cases.[16,23-25,27,29,31-33,35,37,39-41,45] Normal platelet counts were reported in 78.1% (22/32) and decreased in 3.2% (1/32) of cases. Increased platelet counts were reported in 6 of 63 (9.5%) cases.[11,16,23-25,27,29,31-33,35,37,39-41,45]

Elevated C-reactive protein (CRP) levels were described in 59 of 305 cases (19.3%), reported in 25 studies.[3,11,13,16,19-24,26,27,29,31-37,39-42,45] Zheng et al[12] reported a median CRP level of 15.5 mg/dL (IQR: 0.93-25.04) in 25 cases, and Cai et al[5] a median of 7.5 mg/dL in 10 cases.

Procalcitonin levels were elevated in 139 of 279 cases (49.8%), reported in 16 studies.[3,11,13,16,24,26,27,31,33,36,37,39-43] Cai et al[5] reported a median procalcitonin level of 0.07 ng/dL in 10 cases.

Increased liver enzymes were described in 56 of 292 cases (19.2%), reported in 16 studies.[3,11,13,16,21,24,27,29,31,33-37,39-41,43] Zheng et al[12] reported a median alanine aminotransferase of 12 U/L in 25 cases, and Cai et al[5] a median alanine aminotransferase and aspartate aminotransferase level of 18.5 U/L and 27.7 U/L, respectively, in 10 cases.

Nine studies described 70 cases tested for coinfections with other pathogens, of which 19 were positive (27.1%).[5,12,13,16,19,26,34,37,41] Two patients were reported with influenza A, five with influenza B, three with respiratory syncytial virus (RSV), one with cytomegalovirus, seven with *Mycoplasma pneumoniae* and one with *Enterobacter aerogenes*.

TABLE 2 Distributions of clinical manifestations of children with COVID-19 described in the selected studies

Clinical manifestations	Frequency of occurrence[a]
Fever	187 (47.5%)
Cough	163 (41.5%)
Pneumonia	145 (36.9%)
Pharyngeal erythema	81 (20.6%)
Tachycardia on admission	73 (18.6%)
Tachypnea on admission	53 (13.4%)
Nasal symptoms	44 (11.2%)
Upper airway infections	43 (10.9%)
Diarrhea	32 (8.1%)
Nausea/Vomiting	28 (7.1%)
Fatigue	20 (5.0%)
Respiratory distress	14 (3.5%)
Sore throat	10 (2.5%)
Respiratory failure	7 (1.8%)
Creptations	6 (1.5%)
Sputum	6 (1.5%)
Hypoxemia	5 (1.3%)
Abdominal pain	2 (0.5%)
Sneezing	2 (0.5%)
Cyanosis	2 (0.5%)
Lymphadenopathy	1(0.2%)

Abbreviation: COVID-19, coronavirus disease 2019.
[a]Expressed in absolute number and percentage in relation to the total of cases in which clinical manifestations were described (n = 393).

3.5 | Radiological features

Twenty-seven studies reported 184 cases which underwent chest CT.[3,11-14,16-27,29,30,32,34-36,39-42] One hundred sixteen (63.0%) CT scans presented abnormalities. The most prevalent abnormalities reported were ground-glass opacities, patchy shadows, and consolidations. In the study of Lu et al[3] involving 171 cases, ground-glass opacities and patchy shadowings were observed in 32.7% and 31% of cases, respectively.[3] Pleural effusion was observed in a 2-month-old child with simultaneous RSV and SARS-CoV-2 infections.[19]

3.6 | Outcomes

Clinical outcomes of death, discharged or still hospitalized were described for 371 cases in 32 studies.[3,5,11-14,16-18,20-29,31,33-42,44,45] Of these, 62 cases were still hospitalized when studies were submitted, 308 were discharged and one died.

4 | DISCUSSION

In our study, we described the main clinical, laboratorial, and radiological characteristics of children infected with SARS-CoV-2 reported in the literature. It was observed that only a small proportion of infected children became severely or critically ill. About half of the children with COVID-19 were asymptomatic or mild cases, and several were classified as moderate due to radiological abnormalities in spite of their mild clinical manifestations. The prognosis seems to be very good, with recovery described in the vast majority of reported cases. Only one death was reported in the included studies, a 10-month-old child with intussusception.[3]

Since COVID-19 has a favorable clinical course in children, the importance of pediatric cases is mainly due to epidemiological issues.[46] Despite being mild or asymptomatic cases, prolonged viral shedding in stool and nasal secretions made children possible facilitators of viral transmission.[5,47] In the study of Xu et al,[47] 8 of 10 children with SARS-CoV02 had persistently positive rectal swabs even after their nasopharyngeal tests were negative. This raises concerns about the possibility of a fecal-oral route of transmission. The role of children in the transmission chain needs to be urgently clarified to establish social and public health policies for the protection of vulnerable populations, such as the elderly and people with comorbidities.

Testing of people who meet the COVID-19 suspected case definition is essential for clinical management and outbreak control. The Centers for Disease Control and Prevention (CDC) recommends that clinicians should decide to test patients based on the presence of signs and symptoms compatible with COVID-19. The WHO, CDC, and several other government health agencies emphasize fever and respiratory symptoms in the criteria for suspected cases, however, we observed in our study that only 47.5% of pediatric cases had fever.[48,49] Since many are asymptomatic or mild cases, children may not be tested as often as adults, leading to an underestimate of the true numbers of infected people and increased transmission of the virus.

Guan et al[4] demonstrated pronounced lymphopenia in adults with COVID-19, especially in severe cases, where the observed prevalence was 96.1%. Some authors even suggest that lymphopenia is a predictor of prognosis in adult patients with COVID-19.[50] In our study, decreased lymphocyte count was described in only 12.9% of infected children, in contrast to adults, in which 80% of the non-severe cases have lymphopenia. Therefore, lymphopenia may not be a reliable indicator of COVID-19 in children.

We observed that a significant number of children with COVID-19 were also infected with other pathogens. Similar results have been published involving adults.[51] Kim et al[51] observed that 20.7% of the 116 specimens positive for SARS-CoV-2 were positive for one or more additional pathogens. Based on these results, the identification of other respiratory pathogens during the COVID-19 pandemic does not rule out SARS-CoV-2 infection.

Similar to adults, the most prevalent abnormalities on chest CT of children with COVID-19 were ground-glass opacities and patchy shadowings. However, while 86.2% of adults cases presented any abnormalities on chest CT, the same occurred in only 63.0% of children in the selected studies. Descriptions of chest X-rays of pediatric cases are scarce and would be useful for resource-limited settings.

Our study has some limitations. First, data from the same patient may have been presented in more than one included study. Second, the majority of data are from China, and may not be generalized for other populations. Third, the presented results are from patients who presented to medical attention and likely overestimate the severity of illness in children. Fourth, this study could not describe patient comorbidities or hospitalization rates, which would be helpful data for clinicians. Finally, at the time this manuscript was completed there was no report of children with a multisystem inflammatory condition related to SARS-CoV-2 infection.

5 | CONCLUSION

The vast majority of children with COVID-19 have a favorable clinical course and their clinical manifestations differ widely from adult cases. Fever and respiratory symptoms should not be considered a hallmark of COVID-19 in children. Therefore, pediatricians should have a high level of clinical suspicion to diagnose children infected with SARS-Cov-2, as the majority of pediatric cases are asymptomatic or mild. Regardless of the favorable prognosis, it is important that the child's role in the contamination chain is precisely established and considered.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTION

Tiago Henrique de Souza conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Tiago Henrique de Souza and José Antonio Hersan Nadal designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Roberto José Negrão Nogueira, Ricardo Mendes Pereira, and Marcelo Barciela Brandão coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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