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# Echocardiographic findings of hospitalized children with covid-19: A cross-sectional study in southeast Iran

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## Abstract

**BACKGROUND:** Cardiovascular involvement represents a potentially serious complication associated with novel coronavirus disease 2019 (COVID-19), particularly among pediatric patients. Data regarding echocardiographic findings remain sparse, especially in lowand middle-income countries. The primary objective of this study was to investigate the echocardiographic findings of hospitalized children with COVID-19 in southeast Iran.

**METHODS:** This was a cross-sectional study of hospitalized pediatric COVID-19 patients in Kerman, southeast Iran, between March 2020 and March 2022. Clinical records of patients who had undergone transthoracic echocardiograms were evaluated. Demographic and clinical data, as well as echocardiographic findings—including left ventricular (LV) dysfunction, coronary involvement, valvular abnormalities, and pericardial effusion—were noted. Serum inflammatory markers were also assessed.

**RESULTS:** Data from a total of 188 children were analyzed. The mean age (± standard deviation) was 52.7 ± 4.9 months, and 61.4% were male. In terms of disease severity, 36.1% were categorized as moderate, 47.9% as severe, and 16.0% as multisystem inflammatory syndrome in children (MIS-C). Overall, 92.0% had abnormal echocardiographic findings—most commonly pericardial effusion (55.9%), valvular dysfunction (44.1%), coronary artery involvement (36.7%), and LV dysfunction (19.1%). Mitral regurgitation (36.2%) and tricuspid regurgitation (19.7%) were the most common valvular involvements. Moreover, coronary ectasia (19.7%) and dilatation (13.3%) were the prominent coronary abnormalities. LV dysfunction and valvular abnormalities were associated with increased mechanical ventilation, ICU admission, and mortality. Elevated erythrocyte sedimentation rate (ESR) was associated with valvular dysfunction, while higher NT-proBNP was associated with LV dysfunction.

**CONCLUSION:** Hospitalized children had a high prevalence of echocardiographic abnormalities, with LV and valvular dysfunction correlating with worse prognosis and inflammation. Echocardiography appears valuable for risk stratification in ventilator support and Intensive Care Unit (ICU) admission in pediatric patients; however, further research is needed on long-term cardiac sequelae.

Keywords: COVID-19; Children; Echocardiography; Cardiac Manifestations



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### Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of individuals worldwide since its emergence in late 2019<sup>1,2</sup>. Preliminary data from the onset of the pandemic indicated that the overall case fatality rate was approximately 2.3%, with markedly higher rates among older patients<sup>3</sup>. However, during the initial phase of the pandemic, the prevalence of confirmed COVID-19 cases within the pediatric population was notably limited, to the prevailing perception that children frequently experienced a mild or asymptomatic progression of the disease<sup>4,5</sup>. As the pandemic progressed, increasing evidence reported that a subset of pediatric patients with COVID-19 developed severe forms, as well as multisystem inflammatory syndrome in children (MIS-C), characterized by multi-organ dysfunction<sup>6-8</sup>.

While COVID-19 commonly manifests as a wide range of symptoms involving various organs<sup>9-11</sup>, accumulating evidence suggests that cardiac involvement may be a potentially serious outcome, particularly among pediatric patients<sup>12</sup>. Cardiac injury in COVID-19 is thought arise from various pathophysiological mechanisms. SARS-CoV-2 may induce myocardial damage, manifesting as myocarditis<sup>13</sup>. COVID-19 may also predispose patients to thromboembolic events, leading to increased formation of microthrombi and the potential development of coronary disease<sup>14</sup>. Moreover, dysregulated immune responses and cytokine storms may cause multi-organ failure with hemodynamic instability and cardiac dysfunction<sup>15</sup>.

Echocardiography has proven useful for evaluating cardiac involvement in COVID-19. Common echocardiographic findings in pediatric COVID-19 patients include left ventricular (LV) dysfunction, pericardial effusion, coronary artery involvement, and valvular dysfunction, which are reported to be more prevalent in severe forms of the disease and in MIS-C<sup>16</sup>. These abnormalities may underlie cardiac

symptoms such as tachycardia, hypotension, and heart failure reported in children with COVID-19<sup>17</sup>. Identification of echocardiographic abnormalities can aid prognostication and guide management in this population.

Despite increasing reports of cardiac manifestations in COVID-19, data remain limited on echocardiographic findings among hospitalized children, particularly from lowand middle-income countries. Investigation of these findings in different pediatric populations can enhance understanding of the spectrum of COVID-19 cardiovascular involvement. This study aimed to evaluate echocardiographic abnormalities and their clinical correlations in hospitalized children diagnosed with COVID-19 in southeast Iran.

## **Methods**

# Study design and participants

This was a cross-sectional study conducted on hospitalized children diagnosed with COVID-19 between March 2020 and March 2022 at Afzalipour Hospital, Kerman, Iran. The inclusion criteria were patients under 18 years of age who tested positive for COVID-19 infection according to the Reverse Transcription (RT)–Polymerase Chain Reaction (PCR) for SARS-CoV-2. Patients without transthoracic echocardiographic evaluation or with a history of established cardiac anomaly or confirmed immune deficiency were excluded from the study.

All patients eligible for inclusion in the study during this time period were 188, all of whom were included in the study through a census. The protocol for this study was approved by the ethics committee of Kerman University of Medical Sciences (Ethics code: IR.KMU. AH.REC.1400.174).

# Measures and procedure

Data regarding the demographic characteristics of the patients (including age, sex, and weight), as well as clinical symptoms—including fever, constitutional and organ-specific symptoms at the time of admission—and hospitalization outcomes were extracted from

clinical records. Moreover, cardiac signs and symptoms including tachycardia, hypotension, arrhythmia, gallop rhythm, and murmurs were noted.

In terms of disease severity according to the Centers for Disease Control and Prevention (CDC), patients were categorized as moderate (requiring non-invasive ventilation), severe (requiring invasive ventilation or ICU admission but not meeting criteria for MIS-C), or meeting the criteria for MIS-C at either severity level<sup>18</sup>. Echocardiographic findings were recorded within the first 36 hours of admission by an experienced pediatric cardiologist using a Samsung HS70 machine. These findings included LV dysfunction (defined as an ejection fraction of 54% or below, or fractional shortening less than 28%)<sup>19</sup>; coronary artery involvement (i.e., coronary ectasia or coronary dilatation with abnormality defined as  $\geq$  2 z-score); valvular dysfunction (evidenced by mitral regurgitation of at least mild degree, tricuspid regurgitation of at least mild to moderate degree, and findings suggestive of pulmonary hypertension); and pericardial effusion. All data were extracted according to the echocardiography reports. Moreover, laboratory inflammatory markers—including Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), and N-terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP)—recorded within the first 36 hours of admission were also extracted to assess the potential association between echocardiographic findings and serum inflammatory biomarkers.

## Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 26.0; SPSS Inc., Chicago, IL, USA). Mean and standard deviation (SD) were used to describe quantitative variables, while frequency and percentage were used for categorical variables. A chi-squared test was employed to compare the frequency of echocardiographic findings according to patient outcomes, mechanical ventilation, disease severity, ICU

admission, and sex. Independent samples t-test and Mann–Whitney test were used to compare the mean age of patients according to echocardiographic findings. A p-value less than 0.05 was considered statistically significant.

#### Results

A total of 188 hospitalized pediatric patients with COVID-19 were evaluated. Most of the participants were male (61.4%), and the mean ( $\pm$  SD) age was 52.7  $\pm$  4.9 months, ranging from 1 to 180 months. The mean weight was 19.0  $\pm$  9.5 kg.

The most common non-cardiac manifestations were gastrointestinal symptoms (69.7%),respiratory symptoms (44.1%),symptoms and mucocutaneous (18.1%),followed by neurological/musculoskeletal symptoms (17.6%). The most common cardiac manifestations were tachycardia hypotension (20.7%), weak pulse (19.7%), heart murmurs (9.0%), and gallop rhythm (8.5%), while 19.1% of patients showed heart failure in their echocardiograms. In terms of disease severity, 36.1% were categorized as moderate, 47.9% as severe, and 16.0% as meeting the criteria for MIS-C at any severity stage. The mortality rate was 5.3% (Table 1).

Assessment of echocardiographic findings demonstrated that 173 patients (92.0%) had at least one abnormal result. The most common findings were pericardial effusion (55.9%),valvular dysfunction (44.1%),coronary artery involvement (36.7%), and LV dysfunction (19.1%) (Table 2). According to the echocardiographic reports—and considering concurrent occurrences of valvular involvement within individual patients—the most frequently documented valvular dysfunctions were mitral regurgitation (MR, n = 68, 36.2%), followed by tricuspid regurgitation (TR, n = 37, 19.7%) and pulmonary hypertension (n = 4, 2.1%). Additionally, coronary ectasia (n = 44, 23.4%) and coronary dilatation (n = 25, 13.3%) were the most prominent coronary abnormalities observed (Table 1).

Table 1. Distribution of clinical manifestations in children with COVID-19

| Characteristics             |                              | Total (n=188) |  |  |
|-----------------------------|------------------------------|---------------|--|--|
| Sex                         | Male                         | 115 (61.2%)   |  |  |
| Sex                         | Female                       | 73 (38.8%)    |  |  |
| Age; year                   |                              | 52.71±4.92    |  |  |
|                             | Gastrointestinal             | 131 (69.7%)   |  |  |
|                             | Respiratory                  | 83 (44.1%)    |  |  |
| Non-cardiac manifestations  | Mucocutaneous                | 34 (18.1%)    |  |  |
|                             | Neurological/musculoskeletal | 33 (17.6%)    |  |  |
|                             | Renal                        | 3 (1.6%)      |  |  |
|                             | Tachycardia                  | 167 (88.8%)   |  |  |
|                             | Weak pulse                   | 37 (19.7%)    |  |  |
| Cardiac manifestations      | Hypotension                  | 39 (20.7%)    |  |  |
|                             | Murmur                       | 17 (9.0%)     |  |  |
|                             | Gallop rhythm                | 16 (8.5%)     |  |  |
| Outcome                     | Discharge                    | 178 (94.7%)   |  |  |
| Outcome                     | Death                        | 10 (5.3%)     |  |  |
|                             | Moderate                     | 68 (36.1%)    |  |  |
| Disease severity            | Severe                       | 90 (47.9%)    |  |  |
|                             | MIS-C                        | 30 (16.0%)    |  |  |
|                             | Pericardial effusion         | 105 (55.9%)   |  |  |
|                             | Valvular dysfunction**       | 83 (44.1%)    |  |  |
|                             | MR                           | 68(36.2%)     |  |  |
|                             | TR                           | 37(19.7%)     |  |  |
| Echocardiographic findings* | Pulmonary hypertension       | 4(2.1%)       |  |  |
|                             | Coronary artery involvement  | 69 (36.7%)    |  |  |
|                             | Coronary ectasia             | 44(23.4%)     |  |  |
|                             | Coronary dilatation          | 25(13.3%)     |  |  |
|                             | LV dysfunction               | 36 (19.1%)    |  |  |

<sup>\*:</sup> A patient may have more than one echocardiographic finding.

Data shown mean± SD or n(%)

**Table 2.** Comparison the frequency of echocardiographic findings according to patient outcomes, mechanical ventilation, disease severity, and ICU admission

|                                       |             | Valvular dysfunction |            | Pericardial effusion |            | Coronary Involvement |            | LV dysfunction |            |
|---------------------------------------|-------------|----------------------|------------|----------------------|------------|----------------------|------------|----------------|------------|
|                                       |             | Yes                  | No         | Yes                  | No         | Yes                  | No         | Yes            | No         |
| Sex                                   | Female      | 35(47.9)             | 38(52.1)   | 35(47.9)             | 38(52.1)   | 28(38.4)             | 45(61.6)   | 54(74)         | 19(26)     |
|                                       | male        | 48(41.7)             | 67(58.3)   | 70(60.9)             | 45(39.1)   | 41(35.7)             | 74(64.3)   | 98(85.2)       | 17(14.8)   |
|                                       | P-value     | 0.40                 |            | 0.08                 |            | 0.7                  |            | 0.056          |            |
| Mechanical ventilation Yes No P-value | Yes         | 7(33.3)              | 14(66.7)   | 8(38.1)              | 13(61.9)   | 16(76.2)             | 5(23.8)    | 10(47.6)       | 11(52.4)   |
|                                       | No          | 98(58.7)             | 69(41.3)   | 75(44.9)             | 92(55.1)   | 103(61.7)            | 64(38.3)   | 26(15.6)       | 141(84.4)  |
|                                       | P-value     | 0.020*               |            | 0.550                |            | 0.190                |            | 0.001*         |            |
|                                       | Moderate    | 37(54.4)             | 31(45.6)   | 29.4%                | 48(70.6)   | 47(69.1)             | 21(30.9)   | 16(23.5)       | 52(76.5)   |
| Disease<br>Severity                   | Severe      | 52(57.8)             | 38(42.2)   | 46(51.1)             | 44(48.9)   | 53(58.9)             | 37(41.1)   | 13(14.4)       | 77(85.6)   |
|                                       | MIS-C       | 16(53.3)             | 14(46.7)   | 17(56.7)             | 13(43.3)   | 19(63.3)             | 11(36.7)   | 7(23.3)        | 23(76.7)   |
| •                                     | P-value     | 0.874                |            | 0.008*               |            | 0.418                |            | 0.291          |            |
| ICU<br>Admission                      | Yes         | 39(73.6)             | 14(26.4)   | 32(60.4)             | 21(39.6)   | 18(34.0)             | 35(66)     | 29(54.7)       | 24(45.3)   |
|                                       | No          | 44(32.6)             | 91(67.4)   | 73(54.1)             | 62(45.9)   | 51(37.8)             | 84(62.2)   | 123(91.1)      | 12(8.9)    |
|                                       | P-value     | 0.001*               |            | 0.430                |            | 0.620                |            | 0.001*         |            |
| Outcome                               | Discharge   | 74(41.6)             | 104(58.4)  | 100(56.2)            | 78(43.8)   | 67(37.6)             | 111(62.4)  | 150(84.3)      | 28(15.7)   |
|                                       | Death       | 9(90.0)              | 1(10.0)    | 5(50.0)              | 5(50.0)    | 2(20.0)              | 8(80.0)    | 2(20)          | 8(80)      |
|                                       | P-value     | 0.003*               |            | 0.70                 |            | 0.26                 |            | 0.001*         |            |
| Age; year                             | Mean±<br>SD | 53.18±4.81           | 52.33±4.48 | 47.88±4              | 58.81±5.37 | 62.47±5.4            | 47.05±4.04 | 51.89±3.58     | 56.15±8.06 |
|                                       | P-value     | 0.89                 |            | 0.09                 |            | 0.02*                |            | 0.61           |            |

Data were shown n (%) or Mean $\pm$  SD \* Statistically significant (P<0.05)

Patients with valvular dysfunction (P = 0.020) and LV dysfunction (P = 0.001) had significantly higher rates of mechanical ventilation.

Additionally, patients with valvular dysfunction (P = 0.001) and LV dysfunction (P = 0.001) demonstrated significantly higher rates of ICU

<sup>\*\*:</sup> A patient may have more than one valvular dysfunction.

| Inflammatory<br>markers | Valvular d                | Valvular dysfunction       |                         | Pericardial effusion      |                           | Coronary Involvement       |                             | LV dysfunction          |  |
|-------------------------|---------------------------|----------------------------|-------------------------|---------------------------|---------------------------|----------------------------|-----------------------------|-------------------------|--|
|                         | Yes                       | No                         | Yes                     | No                        | Yes                       | No                         | Yes                         | No                      |  |
| ESR                     | 48.9<br>(4.1)             | 36.1 (3.3)                 | 45.3<br>(3.7)           | 37.2<br>(3.6)             | 44.6<br>(3.8)             | 40.0<br>(3.5)              | 43.6<br>(5.9)               | 41.3<br>(2.9)           |  |
| P-value                 | 0.010*                    |                            | 0.120                   | . ,                       | 0.400                     |                            | 0.730                       | , ,                     |  |
| CRP                     | 57.0<br>(5.1)             | 52.1<br>(5.0)              | 59.8<br>(4.6)           | 47.6<br>(5.6)             | 58.4<br>(6.1)             | 52.0<br>(4.5)              | 66.2<br>(8.9)               | 51.4<br>(3.9)           |  |
| P-value                 | 0.490                     |                            | 0.090                   |                           | 0.390                     |                            | 0.100                       |                         |  |
| NT-proBNP**             | 1637<br>(178.5-<br>16041) | 636.5<br>(117.75-<br>1628) | 618<br>(81.87-<br>1629) | 3666<br>(626-<br>16440.5) | 1629<br>(582-<br>14965.5) | 620<br>(124.75-<br>2668.2) | 627.5<br>(126.5-<br>2122.5) | 4784<br>(1625-<br>4784) |  |
| P-value                 | 0.09                      |                            | 0.06                    | •                         | 0.15                      |                            | 0.008*                      |                         |  |

**Table 3.** Comparison of inflammatory markers in terms of echocardiographic findings

Data shown Mean(SD) and \*\*median (Q1-Q3)

admission. Valvular dysfunction (P = 0.008) and LV dysfunction (P = 0.001) were also significantly associated with mortality. Specifically, 90% of deceased children had valvular dysfunction, and 80% had LV dysfunction.

Regarding disease severity, patients categorized with moderate disease had higher rates of pericardial effusion (P = 0.008). However, disease severity was not correlated with coronary involvement, valvular dysfunction, or LV dysfunction findings (Table 2).

The Patients with valvular dysfunction exhibited significantly higher levels of ESR (P=0.010). Moreover, patients with LV dysfunction had significantly elevated levels of NT-proBNP (p=0.041). However, there was no significant association between CRP levels and either of the echocardiographic findings (Table 3).

#### Discussion

Given that cardiovascular involvement represents a critical facet of severe COVID-19 complications in pediatric patients, investigation of echocardiographic alterations and their associated clinical factors assumes a pivotal role in determining patient prognosis formulating appropriate therapeutic strategies. Overall, our findings demonstrated a high frequency of abnormal echocardiographic results, most commonly pericardial effusion, valvular dysfunction, coronary artery involvement, and LV dysfunction. These abnormalities were associated with greater disease severity, the need for mechanical ventilation, and increased mortality risk.

Exploring the echocardiographic findings of children with COVID-19 in our study demonstrated that most patients had at least one abnormal echocardiographic finding, as observed in 92% of the study population. The most common echocardiographic findings included pericardial effusion (55.9%), valvular dysfunction (44.1%), coronary artery involvement (36.7%), and LV dysfunction (19.1%). The high rate of cardiac involvement likely reflects the focus on hospitalized children with more severe disease course in the current study since all the hospitalized cases in our study were moderate to severe cases who had a possible indication to undergo echocardiography.

Sabri and colleagues, in a longitudinal study of thirty-five pediatric MIS-C patients using Speckle Tracking Echocardiography (STE) in Isfahan, revealed that STE is a more useful method than conventional echocardiography for detecting subclinical cardiac injury in MIS-C patients during both the acute and post-acute phases. Twenty percent of patients exhibited abnormal global strain rate (GLS) despite having normal left ventricular ejection fraction (LVEF). All patients demonstrated reduced segmental myocardial strain in at least one segment. Four out of 26 recovered patients without

<sup>\*</sup> Statistically significant (P<0.05)

comorbidities had abnormal GLS at follow-up, despite normal LVEF. Notably, their report was unique in both echocardiographic methodology and longitudinal design<sup>20</sup>.

In concordance with our study, Diniz et al. reported that 16.6% of hospitalized pediatric COVID-19 cases manifested LV dysfunction, while 25% of the pediatric cohort showed coronary dilatation upon echocardiographic assessment<sup>21</sup>. In another study by Williams et al., 61% of children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or MIS-C exhibited myocardial dysfunction, coronary abnormalities were reported in 39% of cases, and pericardial effusion was observed in 35% of patients<sup>22</sup>. Findings from a study by Rostad et al. demonstrated that myocardial and valvular dysfunctions were present in 64% of children with COVID-19 and MIS-C<sup>23</sup>.

Taken together, valvular dysfunction as observed in a substantial portion of our patients, predominantly as mitral regurgitation (MR, 36.2%) and tricuspid regurgitation (TR, 19.7%)—typically manifests as regurgitation due to valve leaflet thickening or dysfunction secondary to ventricular dilatation. Moreover, the most common coronary involvements evidenced by echocardiographic assessment in our study were coronary ectasia and dilatation, observed in 23.4% and 13.3% of patients, respectively. Coronary artery involvement, seen in over one-third of our patients, may result from vasculitis, generalized hyperinflammation, or extrinsic compression by pericardial effusion. Initial reports of MIS-C shared clinical features with Kawasaki disease, with coronary artery involvement as the most prominent common characteristic<sup>24</sup>. However, MIS-C is currently considered a distinct disease entity from Kawasaki disease<sup>25</sup>.

Overall, the prevalence of coronary artery aneurysms has been reported at 13–26% in the setting of MIS-C<sup>26</sup>, with several studies indicating favorable outcomes<sup>27</sup>. Additionally, LV systolic dysfunction reflects impaired contractility, leading to reduced cardiac output. It signals

a worse prognosis and higher risk of shock and mortality, as demonstrated in our study. Our findings showed that LV dysfunction and valvular abnormalities were associated with more severe in-hospital complications, including increased need for mechanical ventilation and higher rates of ICU admission. Notably, the majority of deceased children in our study exhibited both LV dysfunction and valvular abnormalities, underscoring the prognostic value of echocardiographic assessment.

Consistent with our findings, Acevedo and colleagues reported that 100% of pediatric fatalities attributed to COVID-19 accompanied by cardiovascular complications, with cardiac involvement significantly associated with mortality<sup>28</sup>. Similarly, in the study by Diniz et al., echocardiographic abnormalities were significantly associated with ICU admission, need for respiratory support, and mortality<sup>21</sup>. Therefore, echocardiographic parameters may serve as valuable tools in risk stratification and management of hospitalized pediatric patients. Children with significant myocardial involvement may require closer surveillance and enhanced cardiovascular support.

Our findings also demonstrated that inflammatory markers were correlated with echocardiographic abnormalities. ESR was linked to valvular dysfunction, likely reflecting underlying inflammation. NT-proBNP levels were also higher in patients with LV dysfunction, consistent with its release in response to myocardial stress<sup>29</sup>. Consistent with these observations, Kavurt et al. showed that children with low ejection fraction (EF) had significantly higher levels of NT-proBNP30. In another study, children with elevated NTproBNP levels were found to be at increased risk for a severe course of COVID-19<sup>31</sup>. Furthermore, a case series of hospitalized COVID-19 children revealed that all cases had elevated ESR levels, suggesting an inflammatory trajectory of the disease<sup>32</sup>. Gul et al. similarly demonstrated that COVID-19 patients exhibited higher ventricular dysfunction and elevated levels of ESR and NTproBNP compared to a control group<sup>33</sup>. These findings suggest that serum inflammatory markers may serve as valuable indicators for assessing prognosis and the presence of COVID-19-induced cardiac involvement.

Overall, our results demonstrate significant cardiac involvement in hospitalized children in southeast Iran, as evidenced by high frequencies of echocardiographic abnormalities. This underscores the need for careful cardiac monitoring and evaluation in severe pediatric COVID-19 cases. Some limitations should be acknowledged. As a retrospective study, echocardiographic assessments were not standardized and were performed by multiple operators. Prospective studies with systematic protocols are warranted to obtain more definitive results. Moreover, since this study focused solely on hospitalized children, the findings may not be generalizable to outpatients with a milder disease course.

#### Conclusion

This study identified a high prevalence of echocardiographic abnormalities hospitalized children with COVID-19 in southeast Iran. Pericardial effusion, valvular dysfunction, coronary involvement, and LV systolic dysfunction were frequent findings associated with increased disease severity, ventilation requirement, and mortality risk. Echocardiography remains essential for risk stratification and guiding management in severe pediatric COVID-19. Further research is needed to evaluate long-term cardiac sequelae. Global collaborative efforts are encouraged to improve understanding of COVID-19 cardiovascular manifestations across pediatric populations.

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## **Conflict of interests**

The authors declare no conflict of interest.

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### **Author's Contributions**

Study Conception or Design: MMB; RS; FD; MI; SA

Data Acquisition: FT; RS

Data Analysis or Interpretation: FT

Manuscript Drafting: FT; RS Critical Manuscript Revision: RS

All authors have approved the final manuscript and are responsible for all aspects of the work.

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