

## REVIEW

# Oral manifestations of multisystemic inflammatory syndrome in children (MIS-C) and Kawasaki disease associated to COVID-19: A systematic review

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## Abstract

**Aims:** Multisystemic inflammatory syndrome in children (MIS-C) is a condition noted in some children asymptomatic but positive to Sars-cov-2 antibody and it presents clinical and laboratory changes similar to Kawasaki disease (KD). Oral changes have also been observed. This systematic review evaluated oral manifestations detected in children with MIS-C and KD associated to COVID-19.

**Methods and Results:** This work was registered at PROSPERO (#CRD42020225909), following PRISMA guidelines. A comprehensive research was conducted in MEDLINE, Web of Science, EMBASE, LILACS, Scopus, and Grey Literature through August 2021, based on original research evaluating children diagnosed with MIS-C or KD related to COVID-19. Two authors independently screened all retrieved references. Twenty five selected studies evaluated 624 children, mean age 8.78 years. The assessment of the risk of bias (ROB) showed that most of them presented low ROB. Oral manifestations were erythematous mucous membrane, oral ulcers lesions, dry, swollen and cracked lips, and strawberry tongue.

**Conclusion:** MIS-C and KD share the same oral manifestations and their identification may lead to an early diagnosis.

## KEYWORDS

COVID-19, Kawasaki disease, multisystem inflammatory syndrome in children, oral manifestations, pediatric multisystem inflammatory syndrome

## 1 | INTRODUCTION

The reports of hyperinflammatory shock in previously healthy children in spring 2020 appear to be associated to the coronavirus disease-19 (COVID-19) pandemic. Manifestations of this syndrome share clinical and laboratory features with Kawasaki disease (KD) or toxic shock syn-

drome, and they tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies.<sup>1</sup> Initially termed inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS), this syndrome is also called multisystem inflammatory syndrome in children (MIS-C), and it is a rare complication of asymptomatic SARS-CoV-2 infection in children.<sup>2</sup>

The role of COVID-19 in the pathogenesis of MIS-C is unclear.<sup>3</sup> Normally, this syndrome occurs late to COVID-19 infection and, in general, patients present positive IgG and IgM but negative PCR to Sars-Cov-2.<sup>4,5</sup> Commonly they are treated as they have KD with IV immunoglobulin (IVIg).<sup>5</sup>

Center of Disease Control and Prevention (CDC) defined criteria for MIS-C: serious illness leading to hospitalization, less than 21 years, fever (body temperature, >38.0°C) or report of subjective fever lasting at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement (involving at least two systems), and laboratory confirmed SARS-CoV-2 infection (positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction [RT-PCR] or antibody test during hospitalization) or an epidemiologic link to a person with COVID-19.<sup>6</sup> In this context, patients present 4–5 days of fever, rash, conjunctivitis, oral mucosal changes, gastrointestinal symptoms (vomiting and diarrhea), and laboratory changes as neutrophilia, lymphopenia, elevated serum of inflammatory markers (CRP), and ferritin concentrations, that are evidence of significant inflammation.<sup>1,2</sup> Patients can also present hypercoagulable state and pancarditis, an inflammation of pericardium, myocardium and endocardium, and others complex problems like dysfunction of the left ventricular, hyperechoic coronary arteries. More complex complications have been reported in children with this syndrome, such as systemic thrombosis and coronary artery aneurysms. Despite the low rate, some cases evolve to death.<sup>2</sup> Initially, these children were diagnosed as incomplete KD because they met the criteria set by the American Heart Association in 2017.<sup>3,5,7</sup>

Oral changes are noted in children with KD, and they have also been observed as a manifestation of MIS-C such as dry, erythematous or cracked lips, erythema of the oropharyngeal mucosa, strawberry tongue (prominent lingual papillae), and others less frequent oral symptoms.<sup>4,5,7,8</sup> Oral changes were reported in isolated studies that observed systemic manifestations in patients with PMIS-TS<sup>4,5,7</sup>; however, there are few studies summarizing these oral manifestations; and there is still a question about whether these lesions are due to coronavirus infection or secondary manifestations resulting from the patient's systemic condition. Thus, the early diagnosis of oral manifestations of COVID-19 to better profile the role of pediatric dentists should be emphasized, considering the need for support, pain control, and quality of life. In addition, the dentist's relevance as part of the multidisciplinary team in supporting critical of these patients should be highlighted. In this context, the aim of this study is to perform a systematic review (SR) for evaluating oral manifestations associated to MIS-C and KD related to emergent COVID-19 in children.

## 2 | SYSTEMATIC REVIEW

### 2.1 | 1 Register protocol

An SR was written and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA Statement) checklist recommendations and was registered on PROSPERO (International prospective register of systematic reviews; protocol number #CRD42020225909).<sup>9</sup> This SR was developed aiming to identify and characterize oral manifestations in children with a diagnosis of either MIS-C or KD associated to COVID-19.

### 2.2 | Eligibility criteria

The acronym PECO (Population/context, Exposition, Control and Outcomes) was used to formulate the focused question of this Integrative Review: "What are the oral manifestations of Multisystemic Inflammatory Syndrome in Children (MIS-C) and Kawasaki disease associated to COVID-19?". According to these criteria: P, children who developed multisystemic inflammatory syndrome or KD; E, the exposition was the COVID-19; C, control was not applied; O, oral manifestations.

Eligible studies included original research studies published in peer-reviewed journals, mainly focusing on epidemiology, burden, prevalence, risk factors, or incidence of oral manifestations of MIS-C or KD. All primary studies, including case reports, that positively identified children defined as age less than 18 years with potential diagnosis of MIS-C in addition to a positive SARS-coV-2 PCR test result, SARS-coV-2 serum antibody assay, or epidemiologic link to person who tested positive were included. Only reports published or accepted after December 2019 were eligible, as MIS-C or KD prior to this date is not related to SARS-coV-2. Exclusion criteria were studies that reported patients with negative SARS-coV-2 PCR or negative SARS-coV-2 serum antibody, literature or SR papers, letter to the editor, monographs, thesis, interviews, conference papers, and studies that did not describe in detail the study population. In addition, analysis in patients with any systemic disease was not considered.

### 2.3 | Search strategy and study selection

An electronic database search was performed in advanced mode of the PubMed/MEDLINE, Web of Science, Embase, Scopus, and LILACS up to August 2021. The search protocols for the different databases were constructed to be similar and customized according to the requirements of each

database that was searched (Supplementary file 1). Grey literature was also searched in OpenGrey ([www.opengrey.eu](http://www.opengrey.eu)). To complement this review, the reference lists of the included studies were hand searched to retrieve all possible eligible papers that could not have been identified during the database search. There were no restrictions on the language and date of publication to include studies. All references were managed and duplicates were removed using a reference manager software Mendeley (Mendeley, London, UK).

Article screening was performed independently by two reviewers (R.B.N. and N.S.A.). Disagreement was resolved by discussion, and the measurement of inter-review agreement (Kappa statistic) was calculated. Study selection was performed in a two-phase process: first, the reviewers independently applied the eligibility criteria for titles and abstracts of all identified references, whereas, in phase-2, the same eligibility criteria were applied to the full-text studies. Care was taken to ensure that any studies reported more than once were not counted twice; if a study had been more than one, the most complete reporting of the relevant population was considered for inclusion.

## 2.4 | Risk of bias (RoB)

The same reviewers independently assessed the methodological quality of the selected studies according to their level of evidence, as proposed by the Joanna Briggs Institute Methodological Index,<sup>10</sup> with some adjustments, according to the study design proposed in each article selected. Doubts and discrepancies between the reviewers were also discussed. In the final analysis, studies were categorized as “high RoB (Risk of Bias)” when the study achieved up to a 49% “yes” score; “Moderate RoB” when the study reached 50%–69% “yes” score; and “low RoB” when the study reached over 70% “yes” score.

## 2.5 | Data collection and analysis

Data extracted from the articles were classified as quantitative or qualitative by one of the reviewers (N.S.A.) and then checked by another (R.B.N.). The data were collected from the papers selected, and then organized in structured tables. Demographics including age, location and design of study, oral manifestations, laboratory investigations, and treatments provided were recorded for each study. The case reports were combined into one data set and the number of patients, in each study, with treatment were recorded.

## 3 | RESULTS

A total of 361 potentially relevant references were identified in the search; 37 were considered duplicated and were therefore removed. No manuscripts were identified through grey literature. After titles and abstracts screening, 37 studies remained. Reading these study texts resulted in exclusion of 19 more studies due to: (3) study design as letter to the editor,<sup>3,11,12</sup> (5) review article,<sup>13–17</sup> (8) because they did not evaluate or report or have the oral manifestations,<sup>18,19</sup> (2) due to patients being older than 18-year-old,<sup>20,21</sup> and (1) the patients had underlying diseases.<sup>22</sup> A manual search for articles identified eight more studies. Overall, 25 studies were selected for the analysis (Tables 1 and 2). Details of the search strategy are presented in Figure 1.<sup>4,5,7,8,23–38</sup>

The Kappa inter-investigator agreement for articles that were selected ( $K \geq 0.85$ ) from showed an acceptable level of agreement.

The main characteristics of the included studies are presented in Table 1. Fifteen studies were case report ( $n = 23$  children),<sup>4,5,7,8,23,30–32,35,36,38–42</sup> two was a case series ( $n = 68$ ),<sup>27,43</sup> five were prevalence studies ( $n = 277$ ),<sup>25,28,29,33,37</sup> two were cohort studies ( $n = 26$ ),<sup>24,26</sup> and one was a case-control study (MIS-C group = 44; KD = 7; control = 181).<sup>34</sup>

### 3.1 | Risk of bias of included studies

The bias risk assessment showed that among the included papers, 23 presented as a good-quality study according to JBI criteria whereas two presented moderated RoB (Table 3). Overall, the main biases identified were (1) small sample size, (2) did not assess clear the presence of confounding factors and/or did not report a strategy to deal with them, (3) did not provide sufficient information about diagnosis criteria, and (4) unclear answers regarding the post-intervention clinical condition.

### 3.2 | Synthesis of results

The study population was composed of 624 children including 322 boys and 263 girls (some cases were not informed by the author), mean age 8.78 years, presenting clinical and laboratory features associated to KD or MIS-C during COVID-19 pandemic. Most studies were case

TABLE 1 Characteristics of selected studies

Study	Country	Study design/ sample (n)	SARS-coV-2 testing			COVID-19 exposure <sup>a</sup>	Diagnostic criteria MIS-C	FR KD	QR
			Nasopharyngeal or fecal RT-PCR	Serum antibody assay	FR KD				
Falah et al. (2020)	Pakistan	Observational study (10)	8	1	1	---	American Heart Association (AHA) criteria	No	LR
Carlin et al. (2020)	USA	Case-control study (44 <sup>b</sup> ; 7 <sup>c</sup> ; 181 <sup>d</sup> )	9 <sup>b</sup> ; 1 <sup>c</sup> ; 2 <sup>d</sup>	40 <sup>b</sup> ; 2 <sup>c</sup> ; 3 <sup>d</sup>	25 <sup>b</sup> ; 3 <sup>c</sup> ; 49 <sup>d</sup>	Patients who were treated with corticosteroid and IVIg, rheumatologists and infectious disease physicians determined cases as MIS-C	AHA criteria and clinical judgment	NR	LR
Al Ameer et al. (2020)	Saudi Arabia	Case report (1)	1	0	0	Based on CDC criteria – PMIS-C	-	No	LR
Chiu et al. (2020)	USA	Case report (1)	1	0	0	-	Symptoms – seven-day fever, fatigue, diarrhea, dry cough, rash, and conjunctivitis	No	MR
Feldstein et al. (2020)	USA	Observational study (186)	73	58	55	Based on CDC criteria	-	Yes	LR
Del Greco et al. (2020)	USA	Case report (4)	1	0	3	Based on CDC criteria	-	No	LR
Heidemann et al. (2020)	USA	Case report (3)	2	2	2	Then they considered Incomplete Kawasaki Disease as MIS-C	Incomplete Kawasaki disease – AHA criteria, physical attributes, and laboratory evidence	No	LR
Jones et al. (2020)	USA	Case report (1)	1	0	0	-	Based on symptoms: Five-day of fever, limbic sparing conjunctivitis, prominent tongue papilla, a blanching, polymorphous, maculopapular rash, and swelling of the hands and lower extremity	No	LR

(Continues)

TABLE 1 (Continued)

Study	Country	Study design/ sample (n)	SARS-coV-2 testing			COVID-19 exposure <sup>a</sup>	Diagnostic criteria MIS-C	FR KD	QR
			Nasopharyngeal or fecal RT-PCR	Serum antibody assay	MIS-C				
Licciardi et al. (2020)	Italy	Case report (2)	2	2	0	-	Kawasaki like Hyperinflammatory syndrome (SICKH) – persistent fever, rash, and conjunctivitis	No	LR
Pouletty et al. (2020)	France	Cohort study (16)	12	8	2	-	AHA criteria	No	MR
Spencer et al. (2020)	USA	Case report (1)	1	0	0	-	Based on symptoms: ≥5 days of fever and were found to have mucosal changes, rash, conjunctival injection, and gastrointestinal involvement	No	LR
Tam et al. (2020)	Canada	Case report (1)	1	1	1	-	Symptoms: cardiogenic shock, myocarditis, liver dysfunction, acute kidney injury, and evolving macrophage activation syndrome	Yes	LR
Toubiana et al. (2020)	France	Observational study (21)	8	19	0	-	AHA criteria (II patients fulfilled the complete criteria while 10 presented incomplete KD)	No	LR
Verdoni et al. (2020)	Italy	Cohort study (19 B; 10A)	2	8	5	-	AHA criteria: 5 patients presented classical KD and 5 presented incomplete KD	No	LR
Whittaker et al. (2020)	United King- dom	Case series (58)	15	40	ND	-	PMIS-TS – based on UK, CDC or World Health Organization (WHO) criteria, without requiring proof of SARS-CoV-2 exposure	Yes	LR

(Continues)

TABLE 1 (Continued)

Study	Country	Study design/ sample (n)	SARS-coV-2 testing			COVID-19 exposure <sup>a</sup>	Diagnostic criteria	FR KD	QR
			Nasopharyngeal or fecal RT-PCR	Serum antibody assay	MIS-C				
Carbajal et al. (2020)	France	Cross sectional study (7)	1	7	5	Own definition from University Pediatric Hospital Armand Trousseau in Paris	-	No	LR
Cattalini et al. (2021)	Italy	Observational study (53)	136	-	-	Royal College of Paediatrics and Child Health. Guidance	AHA criteria	No	LR
Makiello et al. (2020)	UK	Case report (1)	1	1	0	Royal College of Paediatrics and Child Health Guidance	-	No	LR
Onyeaghala et al. (2021)	Nigeria	Case report (1)	1	0	0	WHO preliminary case definition (WHO, 2020) and the RCPCH and CDC criteria	-	No	LR
Tabaac et al. (2020)	USA	Case report (1)	1	1	1	CDC and WHO criteria	-	No	LR
Marino et al. (2021)	Italy	Case report (1)	0	1	0	-	AHA criteria	No	LR
Fraser et al. (2021)	Italy	Case report (1)	1	0	0	-	“Atypical KD” based on symptoms: history of malaise, dry cough, strawberry tongue, rash and jaundice, mild hepatitis, and fever	No	LR
Parsons et al. (2021)	USA	Case report (1)	1	0	0	Based on CDC criteria	-	No	LR
Beşar et al. (2021)	Turkey	Case series (10)	7	16	1	WHO or CDC diagnostic criteria	-	No	LR
Ashraf et al. (2021)	Pakistan	Case report (1)	0	1	0	Symptoms: generalized erythematous maculopapular rash and conjunctivitis, high grade fever.	-	No	LR

A, group of patients diagnosed after beginning of pandemic; B, group of patients diagnosed with a Kawasaki-like disease before the beginning of the SARS-CoV-2 epidemic. Abbreviations: AHA, American Heart Association; CDC, Centers for Disease Control; FR, financial relationships; HR, high ROB; KD, Kawasaki disease; LR, low ROB; MR, moderate ROB; ND, not described; NR, not reported; QR, quality rating; ROB, risk of bias; RT-PCR, reverse transcription polymerase chain reaction test; UK, United Kingdom.

<sup>a</sup>Exposure to suspected/confirmed COVID-19 case within 4 weeks prior to onset of symptoms.  
<sup>b</sup>MIS-C group.  
<sup>c</sup>Kawasaki disease group.  
<sup>d</sup>Control group.

TABLE 2 Oral manifestations of multisystemic inflammatory syndrome in children and Kawasaki disease

Study	General characteristics			Oral manifestations			Treatment strategies	Outcomes
	Age (mean or median)	Boy	Girl	Local	Characteristics			
Falah et al. (2020)	6 years	8	2	Lips	ND		Intravenous immunoglobulin (IVIg) therapy, acetylsalicylic acid. Antibiotics, oxygen, steroids, monoclonal antibody, anticoagulation, plasma therapy, or antivirals	Seven patients required admission to a critical unit care, but no mortality occurred
Carlin et al. (2020)	99 months <sup>a</sup> (8.2 years)	21	23	Oral cavity Oral cavity	ND Mucosal irritation		ND	ND
	29 months <sup>b</sup> (2.4 years)	2	5	Oral cavity	ND			
	61 months <sup>c</sup> (5 years)	86	72	Oral cavity	ND			
	27 months <sup>d</sup> (2.2 years)	13	10	Oral cavity	ND			
Al Ameer et al. (2020)	13 years	0	1	Lips	Erythematous and cracked		IVIg and corticosteroid. COVID-19 management protocol in Saudi Arabia, including antiviral, monoclonal antibody interleukin-6 (IL-6) blockers, and low molecular weight heparin	Death
Chiu et al. (2020)	10 years	1	0	Oropharynx	Minimally erythematous without exudate or lesions		Orally nonsteroidal anti-inflammatory drug, dopamine	At the time of the writing, the patient continues to be critically ill with outcome yet to be determined
Feldstein et al. (2020)	8.3 years	115	71	Lips Oral mucosal changes (78 patients)	Cracked ND		Most of them (144 patients) received IVIg and almost half (91 patients) also received glucocorticoids	At the time of writing, 130 patients recovered, 52 were still hospitalized and 4 died
Del Greco et al. (2020)	10.7 years	1	3	Oral cavity	Erythema		Intravenous immunoglobulin (IVIg) and corticosteroids	Symptoms remission. Patients were kept on ASA and/or prednisone

(Continues)



TABLE 2 (Continued)

Study	General characteristics			Oral manifestations			Treatment strategies	Outcomes
	Age (mean or median)	Boy	Girl	Local	Characteristics			
Heidemann et al. (2020)	6 years	2	1	Lips Tongue Oral cavity	Dry and cracked Erythema Erythema		Intravenous immunoglobulin and high-dose aspirin	All of the cases recovered
Jones et al. (2020)	6 months (0.5 years)	0	1	Lips	Lips Dry and cracked		Single dose of 2 g/kg intravenous immunoglobulin (IVIg) and high dose acetylsalicylic acid (ASA) 20 mg/kg four times daily	Symptoms remission. Patient was kept on low dose ASA (3 mg/kg daily) with plans to follow-up
Licciardi et al. (2020)	9.5 years	2	0	Tongue Lips	Prominent papilla Cracked		Patient 1 – corticosteroids patient 2 – IVIg and corticosteroid	All of the cases recovered
Pouletty et al. (2020)	10 years	8	8	Tongue Oral cavity Lips	De-epithelialization Apthous stomatitis Dry, erythematous, and cracked		Most of them were treated by IVIg (one or two infusion) and some of them also received steroids.	All patients were in symptoms remission and were discharged on anti-aggregate aspirin treatment
Spencer et al. (2020)	7 years	0	1	Lips	Swelled, red, and cracked		Corticosteroids	There was significant improvement in the symptoms, although later the patient had recurrence of her rash and at the moment of publication, she was under treatment
Tam et al. (2020)	10 years	1	0	Tongue	Form of strawberry		IVIg (one dose) and corticosteroid	The patient was weaned off steroids after 3 weeks of treatment, and he remains on interleukin antagonists at the time of writing
				Lips	Red and cracked			(Continues)



TABLE 2 (Continued)

Study	General characteristics			Oral manifestations		Treatment strategies	Outcomes
	Age (mean or median)	Boy	Girl	Local	Characteristics		
Toubiana et al. (2020)	7.9 years	9	12	Lips and Oral cavity	ND	21 received IVIg and 10 also received corticosteroids	All of the cases recovered
Verdomi et al. (2020)	7.5 years	7	3	Lips and oral cavity	ND	All patients were administered IVIg at 2 g/kg. Some of them also received corticosteroids	ND
Whittaker et al. (2020)	9 years	25	33	Lips	Cracked	Most of them were treated by IVIg and some of them also by corticosteroids. Three patients received interleukin antagonists and eight tumor necrosis factor- $\alpha$ inhibitors	Few of them recovered with only supportive care. ND
Carbajal et al. (2020)	7.5 years	2	5	Oral cavity	ND	IVIg; Tracheal intubation, Inotropes, Corticosteroids	The outcomes were favorable in all seven children
Cattalini et al. (2021)	7 years	53 <sup>c</sup>	Pharyngeal and/or oral cavity	Cheilitis, erythema and strawberry tongue	IVIg, intravenous glucocorticoids, acetylsalicylic acid, hydroxychloroquine, interleukin antagonists, interleukin-6 (IL-6) blockers, anti-viral agents, antibiotics, vasoactive agents, and heparins	Patients had an excellent response to treatment and a good outcome, with few complications and no deaths	
Makiello, et al. (2020)	11 years	1	0	Lips	cracked lips	Initially an empirical cephalosporin and nitroimidazole antibiotics. IVIg, which terminated his fevers, and completed a 5-day course of intravenous glucocorticoids. Antibiotics	The patient was discharged home with low dose acetylsalicylic acid and proton pump inhibitors (omeprazole); follow-up in 3 months' time

(Continues)

TABLE 2 (Continued)

Study	General characteristics			Oral manifestations			Treatment strategies	Outcomes
	Age (mean or median)	Boy	Girl	Local	Characteristics			
Onyeaghala et al. (2021)	12 years	0	1	Mouth	Dried peeled lips and hyperemic oral mucosa	Blood transfusion with intravenous (IV) diuretics, cephalosporin antibiotic, hydrocortisone, subcutaneous heparins, macrolide antibiotics, analgesic. Hydroxychloroquine twice a day for 24 h then twice a day for 4 days, A and C vitamins	Discharged after 14 days of hospitalization, with a long-term follow-up plan and echocardiography request for cardiac evaluation	
Tabaac et al. (2020)	9 years	1	0	Lips and oral cavity	cracked lips, strawberry tongue without oropharyngeal exudates, erythema, or swelling	Lincomycin, glycopeptide, and cephalosporin antibiotics. Fluid boluses. One dose of IVIg and low-dose of acetylsalicylic acid	Symptoms remission. Discharged on low-dose of acetylsalicylic acid and a steroid taper	
Marino et al. (2021)	5 years	1	0	Lips	Cracked lips	Intravenous immuno-globulins (IVIg), ylprednisolone, and aspirin (ASA) at anti-inflammatory dosage	Symptom remission and rapid normalization of cardiac findings	
Fraser et al. (2021)	15 years	0	1	Tongue	Strawberry tongue	Intravenous immunoglobulin (IVIg) and Aspirin	Discharged without symptoms.	
Parsons et al. (2021)	9 years	1	0	Mouth	Oral mucositis	Ceftriaxone, doxycycline, and intravenous immunoglobulin	Discharged without symptoms.	
Başar et al. (2021)	111 months	14	10	Oral changes	Inflammation	All the patients received IVIg, prophylactic low-molecular-weight heparin and discharged with an antiaggregant dose of acetylsalicylic. In some cases, methylprednisolone	Two died. Others had symptoms remission	
Ashraf et al. (2021)	7 years	1	0	Lips	Cracked lips	IV ceftriaxone and supportive treatment of shock. IVIg, high dose aspirin, methylprednisolone	Discharged on low dose aspirin and a follow-up	

Abbreviations: IVIg, IV immunoglobulin; ND, not described; PICU, pediatric critical care unit

<sup>a</sup>MIS-C group.

<sup>b</sup>Kawasaki disease group.

<sup>c</sup>Control (output patient) group.

<sup>d</sup>Control (from emergency departments) group.

<sup>e</sup>Data not informed separately for each group.

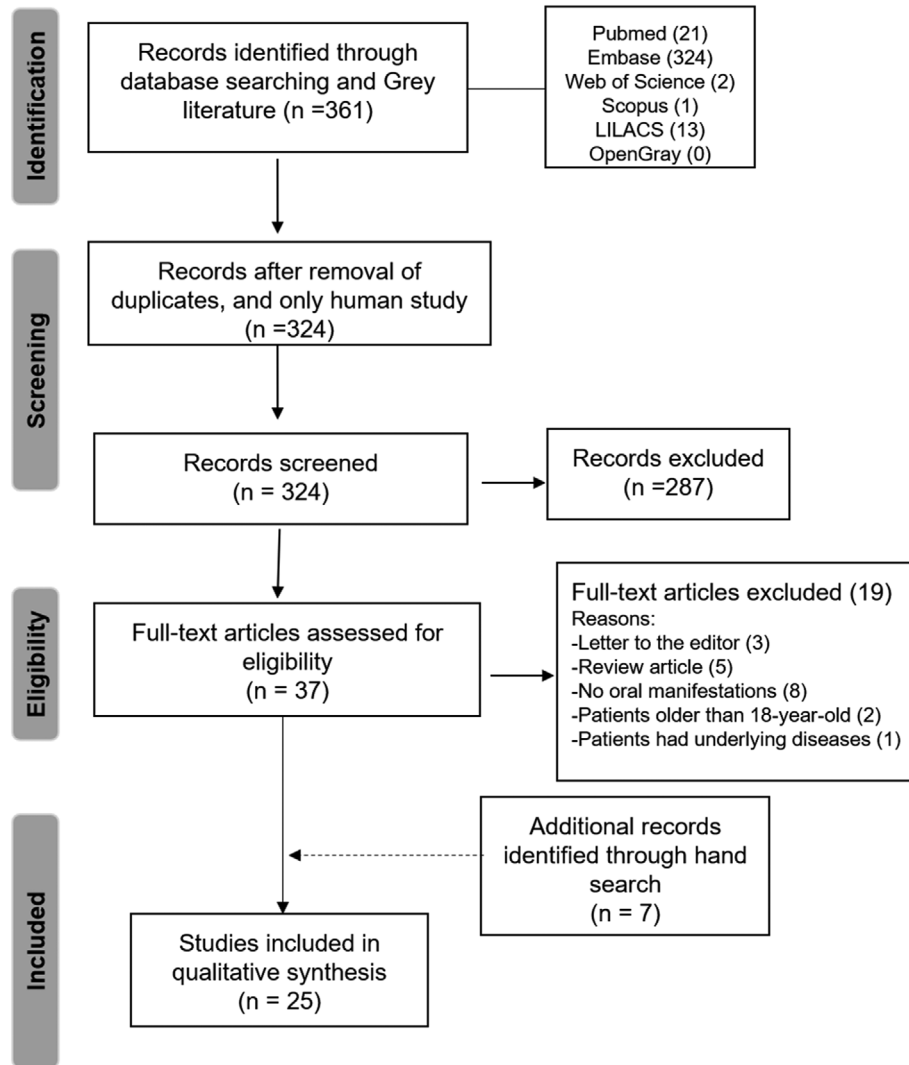


FIGURE 1 Flow chart of review conduction

reports of children assisted in pediatric centers that have been diagnosed to MIS-C or KD in most of cases based on CDC and AHA criteria, although some authors based on UK or World Health Organization (WHO) criteria. COVID-19 was diagnosed by the positive RT-PCR test to the virus or by the identification of anti-Sars-Cov-2 antibodies (IgG and IgM) and, in some cases, due to exposure to a COVID-19 positive person.

Hospitalized children due to MIS-C or KD were treated by infusion of IVIGs associated or not with the use of corticosteroids. In general, remission of the symptoms occurred after IVIG infusion but in some cases a second infusion was necessary. Few deaths have been reported. Most of patients were recovered.

Oral manifestations were noticed as one of the most common symptoms of MIS-C. These oral changes are similar in both KD and MIS-C reported in patients with KD and MIS-C covered lips, tongue, and other mucous

membranes. Authors identified erythematous, dry and/or cracked lips, erythematous mucous membranes and sometimes ulcers as aphthous stomatitis, and erythematous tongue, sometimes presenting strawberry shape.

#### 4 | DISCUSSION

MIS-C is an emergent disease identified during COVID-19 pandemic. KD and MIS-C share clinical and laboratory features that made many authors initially diagnose as “Incomplete Kawasaki disease” because they met the criteria set by the American Heart Association in 2017. These criteria include (1) fever lasting more than 5 days, (2) erythema of the palms and soles or more commonly edema of the hands and feet, (3) periungual peeling, (4) diffuse rash, (5) conjunctival injection, (6) erythema of lips and oral cavity, (7) cervical lymphadenopathy, and (8)

**TABLE 3** Analysis of methodological quality (risk of bias) according the Joanna Briggs Institute Methodological Index critical appraisal checklist

Study	Instrument items – JBI critical appraisal checklist											Rating overall confidence	
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11		%
Ashraf et al. (2021)	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Başar et al. (2021)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	–	90	LR
Falah et al. (2020) <sup>a</sup>	Y	Y	N	Y	Y	Y	Y	NA	Y	–	–	87.5	LR
Carlin et al. (2020) <sup>b</sup>	Y	Y	Y	Y	N	U	U	Y	Y	Y	–	90	LR
Al Ameer et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Chiu et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	U	N	N	–	–	–	62.5	MR
Feldstein et al. (2020) <sup>a</sup>	Y	Y	NA	Y	Y	Y	Y	Y	Y	–	–	100	LR
Fraser et al. (2021)	Y	Y	Y	U	Y	Y	Y	Y	–	–	–	87.5	LR
Del Greco et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Heidemann et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Jones et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	U	Y	–	–	–	87.5	LR
Licciardi et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Pouletty et al. (2020) <sup>d</sup>	Y	Y	Y	N	U	NA	Y	Y	NA	NA	Y	66.9	MR
Spencer et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	U	Y	–	–	–	87.5	LR
Tam et al. (2020) <sup>e</sup>	Y	Y	Y	Y	Y	Y	U	Y	–	–	–	87.5	LR
Makiello et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	N	Y	–	–	–	87.5	LR
Marino et al. (2021)	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Onyeaghala et al. (2021) <sup>c</sup>	Y	Y	Y	Y	Y	Y	N	U	–	–	–	75	LR
Parsons et al. (2021)	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	100	LR
Tabaac et al. (2020) <sup>c</sup>	Y	Y	Y	Y	Y	Y	N	Y	–	–	–	87.5	LR
Toubiana et al. (2020) <sup>a</sup>	Y	Y	NA	Y	Y	Y	Y	Y	Y	–	–	100	LR
Carbajal et al. (2020) <sup>a</sup>	Y	Y	Y	Y	Y	N	Y	Y	–	–	–	87.5	LR
Cattalini et al. (2021) <sup>a</sup>	Y	Y	Y	N	Y	Y	Y	Y	–	–	–	87.5	LR
Verdoni et al. (2020) <sup>c</sup>	Y	NA	Y	N	U	NA	Y	Y	NA	NA	Y	71.4	LR
Whittaker et al. (2020) <sup>e</sup>	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	–	90	LR

Questions were adjusted, according to the study design proposed in each article selected.

Abbreviations: HR, high ROB; LR, low ROB; MR, moderate ROB; NA, not applicable; ROB, risk of bias; U, unclear.

<sup>a</sup>Prevalence study.

<sup>b</sup>Case–control Study.

<sup>c</sup>Case report.

<sup>d</sup>Cohort study.

<sup>e</sup>Case series.

exclusion of other diseases. Coronary artery abnormalities including dilation of coronary arteries and aneurysms may also occur. Evidence of myocarditis is commonly seen but patients rarely present with hemodynamic instability and shock.<sup>7,44</sup>

The emerging number of children presenting a multisystem inflammatory syndrome led the CDC to define criteria for its diagnosis, which were used by most authors as a basis for the diagnosis of this disease. CDCs criteria are: (1) age < 21 years presenting with fever ( $\geq 38.0^{\circ}\text{C}$  for  $\geq 24$  hours, or report of subjective fever lasting  $\geq 24$  hours), laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem ( $\geq 2$ ) organ involvement;(2) no alternative

plausible diagnoses; and (3) positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.<sup>6</sup>

The diagnose of COVID-19 was mainly reported by positive identification of virus on RT-PCR test and by the identification of anti-Sars-Cov-2 antibodies (IgG and IgM). In some patients, tests were negative but diagnosis of COVID-19 was considered when the patient had exposure to a positive person, which is recommended by CDC.

Oral manifestations are often noted in patients with KD,<sup>45,46</sup> and they have also been observed in patients with MIS-C. In the present study, cases of studies that

did not present oral involvement were excluded according to eligibility criteria. Since, during the selection of articles, most of the published cases presented these oral changes. In these cases, oral manifestations frequently noted in MIS-C patients do not differ from those identified on KD patients. In both disease, children may present erythematous mucous membranes and tongue with or without lesions like ulcers (aphthous stomatitis), lips may be erythematous, swollen, dry, and/or cracked. Usually, these symptoms are accompanied by burning and/or pain and reduced oral intake.<sup>5,8,23,27,35</sup> In general, oral manifestations were observed as one of the first symptoms of the disease. In some cases, due to the delay in the diagnosis with consequent worsening of the clinical condition, the disease evolved to a more severe condition, requiring intubation. The identification of oral manifestations associated to other clinical signs and a history of positivity for the COVID-19 virus can help in early diagnosis and prevent sequelae and deaths from this disease.

The treatment of oral conditions has not been reported in any case presented in the articles analyzed in this current review. However, signs and symptoms of MIS-C or KD usually regressed after treatment with IVIg associated to corticosteroids and/or aspirin, so probably there was remission of oral manifestations, although the authors did not clearly report this information. Papers published before COVID-19 pandemic showed that oral manifestations of KD also regressed after systemic treatment with IVIg.<sup>45,46</sup> In addition, it was noted that no research has been developing focusing on oral cavity manifestations, and recently one letter to the editor has been published summarizing oral changes reported by authors that evaluate systemic condition.<sup>47</sup>

Most of the cases analyzed in this review were case reports, which is due to the emergent COVID-19 pandemic, and despite the speed of publication, it was noted that the analyzed studies presented low to moderated RoB. However, at the moment of their publication, some of these papers had not yet ended the treatment and had no outcome or did not make the outcome clear, which probably happened after the article has been published.<sup>4,8,36,37</sup> In this context, it is important to reinforce the role of dental professionals in the early detection of the oral manifestations and referral for further investigation. The rapid detection of COVID-19 is crucial to control outbreaks; only using early identification of oral manifestations and consequent early diagnosis, it is possibly effective and rapid isolation of cases and the appropriate contact tracing. Thus, it should be highlighted that other studies and reports about this topic are surely required.

## 5 | CONCLUSION

MIS-C and KD may have high mortality and morbidity rate if not treated early, and hence an early diagnosis and treatment are important because children are at increased risk of deterioration. The oral findings, mainly erythematous mucous membranes, lesions like ulcers, dry and cracked lips, and strawberry tongue, are a characteristic feature of both diseases and can occur earlier than systemic manifestations. Many cases might first report to the dental clinician so dentists should always remain alert in handling patients presenting those oral manifestations and to associate to COVID-19.

## AUTHOR CONTRIBUTIONS

The responsibility of Rebeca Barros Nascimento was to conceive the idea, to conduct the systematic review, and to write – original draft. The responsibility of Nara Santos Araujo was to conceive the idea, to conduct the systematic review, and to write – original draft. The responsibility of Jamerson Carvalho Silva was to conduct the systematic review and to write - original draft. The responsibility of Flávia Caló Aquino Xavier was to orient and supervision the work and to write – review and editing. All authors made substantial contributions to acquisition of data, drafting the article, revising it critically, and have approved the final version to be submitted. These authors contributed equally.

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## CONFLICT OF INTERESTS

The authors declared that there is no conflict of interest. No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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