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Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2: a case series quantitative systematic review

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Abstract

Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS) is infrequent, but children might present as a life-threatening disease. In a systematic quantitative review, we analyzed 11 studies PIMS-TS, including 468 children reported before Jul 1st. We found a myriad of clinical features, but we were able to describe common characteristics: previously healthy school-aged children, persistent fever and gastrointestinal symptoms, lymphopenia, and high inflammatory markers. Clinical syndromes like myocarditis and Kawasaki disease were present in only one-third of cases each one. PICU admission was frequent, although LOS was less than one week, and mortality was low. Most patients received immunoglobulin or steroids, although the level of evidence for that treatment is low. PIMS-ST was recently described, and the detailed quantitative pooled data will increase clinicians' awareness, improve diagnosis, and promptly start treatment. This analysis also highlights the necessity of future collaboratives studies, given the heterogeneous nature of PIMS-TS.

Background

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread worldwide, from the initial outbreak in Wuhan, China, to Southeast Asia and Oceania, Europe, and then the Americas [1–3].

During April 2020 and the following months, several small case series were published, describing children with an abnormal systemic inflammatory response, temporally related to SARS-CoV-2 [4-22]. These children required hospitalization and frequently presented a life-threatening disease requiring pediatric intensive care unit (PICU) admission. This syndrome shares characteristics with other pediatric inflammatory conditions, including Kawasaki disease (KD), staphylococcal and streptococcal toxic shock syndromes, sepsis, and macrophage activation syndrome. Authors are trying to classify these syndromes according to the predominant signs and symptoms, leading to confusing terminology, not very useful to the clinician at the bedside [23–26]. This syndrome has been called by many names and acronyms, like PIMS-TS (Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2), MIS-C (Multisystem Inflammatory Syndrome in Children), hyperinflammatory shock, cytokine storm, among others.

We present a systematic review of the cases of inflammatory syndromes associated with SARS-CoV-2 infection published until Jul 1, 2020. For this review, we will ascribe to PIMS-TS denomination.

Methods

We evaluated relevant studies in PubMed, LILACS, and Embase, published between May 1 to Jul 1, 2020, using combinations of the terms "pediatrics", "coronavirus," "COVID-19", "SARS-CoV-2", "pediatric intensive care", "pediatric inflammatory multisystem syndrome", "Kawasaki disease," "Hyper-inflammatory · Kawasaki · PIMS-TS · MIS-C · COVID-19 · SARS-CoV-2". We retrieved studies with at least three patients, and pediatric age was considered younger than 21 years old. We excluded studies that had duplicate patients from other reports. Quality of measures was assessed by the tool developed by Murad et al (27). Data extraction was performed by two independent reviewers (RB and JCJ). Data was initially described by study using the presented measurement of distribution on the original paper. A meta-analysis was carried out if the variable of interest was present in more than 50% of studies. Detailed method for quantitative meta-analysis is available in supplementary file 1.

Results

We found 184 potentially relevant articles. Eleven case series were selected for this review (supplementary file 2). The quality score of the included studies is shown in Supplementary file 3. Supplementary file 4 and 5 shows detailed clinical and laboratory data of the analyzed studies. Reported cases came from 196 centers describing a total of 468 children. Clinical characteristics are shown in Table 1. The average age was 9.2 years (95% CI 8.5-9.9) and all patients were febrile at presentation. Rash was reported in 58% (95% CI 52-63%), conjunctivitis in 56% (95% CI 42-69%), and shock in 76% (95% CI 55-93%). A positive test for SARS CoV-2 was available in RT-PCR 38% (95% CI 29-46%), serology 68% (95% CI 50-84%), and a known positive contact in 29% (95% CI 14-47%). Twenty-six percent (95% CI 13-40%) of cases fulfilled the American Heart Association Kawasaki Disease criteria, while 29% (95 CI 3%-66%) developed myocarditis. Pooled laboratory test data are shown in Table 2. Markers of inflammation and cardiac injury were frequently elevated.

Chest -X-ray or lung CT-scan showed pulmonary infiltrates in 41% (95% CI 36-47%). Left ventricular dysfunction by echocardiogram was found in 72% (95 % CI 52-89%), abnormalities in the coronary arteries in 24% (95% CI 11-39%), pericardial effusion or pericarditis in 24% (95% CI 12-39%). Thirty-seven percent (95% CI 3 to 60%) reported electrocardiographic alterations.

Overall, 82% (95% CI 68-93%) of patients required intensive care (figure 1 A), 62% (95% CI 250-73%) received vasoactive drugs (figure 1B) and 59% (95% CI 40-77%) respiratory support (figure 1C), such as invasive mechanical ventilation (IMV) in 27% (95% CI 15-41%) (figure 1D), non-invasive ventilation (NIV) in 9% (95% CI 2-20%) and high-flow nasal cannula (HFNC) in 6% (95% CI 0-17%). 25 patients were placed on extracorporeal membrane oxygenation (ECMO). Only one patient required renal replacement therapy.

Intravenous immune globulin (IVIG) was used in 79% (95% CI 66-90%) of patients, followed by steroids in 47% (95% CI 34-59%). Other therapies where use more inconsistently like aspirin (36% studies, range 20-100% of cases), anticoagulants (27% studies, range 47-100%), tocilizumab/siltuximab (36% studies, range 5-80%), infliximab (18% studies, range 5-14%), anakinra (45% studies, 5%-33%)

and antibiotics (45% studies, 67-100%). Remdesivir use was not reported in the analyzed studies. Standardized ICU length of stay was six days (95% CI 4-7 days) with an overall hospital stay of 9 days (95% CI 7-11 days). A total of 7 deaths occurred, 5 of them during ECMO run.

Eighty-one children (17.6%) were still hospitalized at the time the case series were reported.

Discussion

In this systematic review of PIMS-TS cases in the literature, we found a great deal of heterogeneity. The cases reported are numerous, from several centers, but there is no standardized description of the variables of interest. We analyzed 11 case series, including 468 children from 196 centers. Instead of listing studies and patients, we performed a quantitative analysis according to the weighed cases of the studies. Our main findings can be summarized as follows:

1) We were able to define the most frequent clinical characteristics of patients: previously healthy school-aged children, presenting with persistent fever and gastrointestinal symptoms.
2) Clinical syndromes like myocarditis and KD were present only one-third of cases each one.
3) High level of care (PICU) was very frequent, although LOS was less than one week, and mortality was very low.
4) Most patients received immunoglobulin or steroids, although the level of evidence for that treatment is low.

Given the current hypotheses [28,29] of the physiopathology of PIMS-TS, viral infection versus a post-infectious disease, it is important to note that RT-PCR was positive in 38%, and serology in 68% of cases. An alternative hypothesis might be that these symptoms and clinical syndromes are also present in non-SARS-CoV2 coronaviruses. For instance, there are some cases of myocarditis and Kawasaki disease associated with human coronavirus exposure. Thus, the clusters of PIMS-TS observed may be secondary to massive exposure to a trigger in a susceptible population, but not specifically to SARS-CoV2 [30,31]. Most of the patients were previously healthy school-age children. Remarkably, all patients had fever. Gastrointestinal symptoms were frequent, as well as rash and mucositis. Regards laboratory examination, all inflammatory markers were elevated, being the most consistent C-reactive protein. C-reactive protein is very unspecific, but it is disproportionally elevated, about 20 times the normal value. Lymphopenia was also commonly found. Cases of PIMS-TS fulfilling criteria for KD and myocarditis were not reported frequently, about one-third of cases each one. Respiratory and neurological symptoms were usually mild, and AKI accounted for one third. There was a high number of patients with shock criteria, explaining the frequent requirement of PICU admissions. In our study, less than 50% of children with PIMS-TS had abnormal chest x-ray or CT-scan.

Left ventricular dysfunction was reported in about half on the patients, explaining the high frequency of shock and vasoactive support requirements. Coronary abnormalities were described in one-fourth of cases during the acute phase, so we cannot extrapolate our results to mid and long-term sequelae [32,33].

Regards treatments, most PIMS-TS patients received intravenous immunoglobulin or steroids. Surprisingly, despite the severity of cases, antiviral therapy was very uncommon. Most of the children with PIMS-TS were admitted to PICU and required invasive interventions. However, ECMO and CRRT

were very uncommon. Despite the severity of admission and life support requirements, the overall prognosis of PIMS-TS was good. The average PICU length of stay was less than a week, and mortality is very low.

Our study has some limitations. First, there are subtle differences in diagnosis criteria (RCPH, CDC, WHO) that can lead to a bias in the selection of patients in different countries and regions. No specific information was requested to authors, and case by case review was not done, contributing to the heterogeneity of parameters reported. Patients described in the analyzed studies were only from Europe and North America. Risk factors to develop PIMS-TS, like socio-economic deprived or genetically susceptible children, are still not well understood, which make the behavior of the pandemic unpredictable in regions such as Latin America and Africa. Second, many small series were added to build larger cohorts. To avoid duplication of data, case reports and some small series were not included. A large cohort has more power in the analysis, but usually, some specific data is lost. Third, PIMS-TS is a new syndrome, and our understanding is still limited. Many non-epidemiological factors, like disease awareness, media, and academic pressure, and loose criteria for diagnosis, may lead to overdiagnosis as pandemic develops. Although, we analyzed the quality of the studies with a standardized validated tool.

In summary, PIMS-TS is an infrequent and heterogeneous disease. It can mimic some pediatric inflammatory syndromes, like KD, MAS, and myocarditis, but only in one-third of cases can fulfill strict criteria. Clinical characteristics are very distinctive when compared to pediatric COVID-19 infections, frequently presenting as a severe disease. Given the recent description of PIMS-TS, there are still many questions regards its physiopathology, although, with the current empirical treatment, it has a good prognosis.

Table 1. Overall pooled effects of demographics and clinical characteristics of 486 children with PIMS-TS.

Table 2. Overall pooled effects of Laboratory results of 486 children with PIMS-TS.

Figure 1. Forrest plots of analyzed studies. A) Intensive care admission. B) Vasoactive support C) Advanced respiratory support (any) D) Invasive Mechanical Ventilation.

Supplementary file 1. Expanded methods for the quantitative meta-analysis.

Supplementary file 2. Selection of the studies included in the quantitative meta-analysis.

Supplementary file 3. Quality score of analyzed studies according to Murad MH et al (30).

Supplementary file 4. Demographic, clinical and outcome data of the eleven studies included in the quantitative metanalysis

Supplementary file 5. Laboratory data of the eleven studies included in the quantitative metanalysis

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Table 1-2 Fig 1

Table 1.- Overall pooled effects of demographics and clinical characteristics of 486 children with PIMS-TS

Demographics	**Studies n/N**	**Cases n/N**	**Pooled effects* (95%CI; I^2)**
Age (years)	11/11	468/468	9.2 (8.5 - 9.9; 53%)
Male sex	11/11	263/468	54% (48% - 61%; 28%)
Previously healthy	10/11	337/453	78% (66% - 88%; 81%)
Obesity	6/11	90/360	24% (16% - 33%; 52%)
Any respiratory comorbidity	9/11	56/443	6% (2% - 12%; 58%)
Known contact	9/11	151/405	29% (14% - 47%; 89%)
Positive RT-PCR SARS-CoV-2	11/11	188/468	38% (29% - 46%; 56%)
Positive serology SARS-CoV-2	11/11	269/468	68% (50% - 84%; 91%)
Clinical	**Studies n/N**	**Cases n/N**	**Pooled effects * (95%CI; I^2)**
Any GI symptom	11/11	468/468	85% (74% - 94%; 81%)
Shock criteria	10/11	163/218	76% (55% - 93%; 91%)
Rash	10/11	268/453	58% (52% - 63%; 10%)
Conjunctivitis	9/11	231/418	56% (42% - 69%; 78%)
Any respiratory symptoms	6/11	81/216	37% (19% - 56%; 80%)
Neurological symptoms	11/11	117/468	33% (18% - 51%; 91%)
AKI	7/11	69/473	33% (14% - 55%; 93%)
Myocarditis criteria	8/11	95/242	29% (3% - 66%; 96%)
Kawasaki disease criteria	9/11	149/428	26% (13% - 40%; 85%)

*Variable must be present in more than 50% of studies. Standardized means by transformation approach. For pooled proportions, we used the metaprop module.

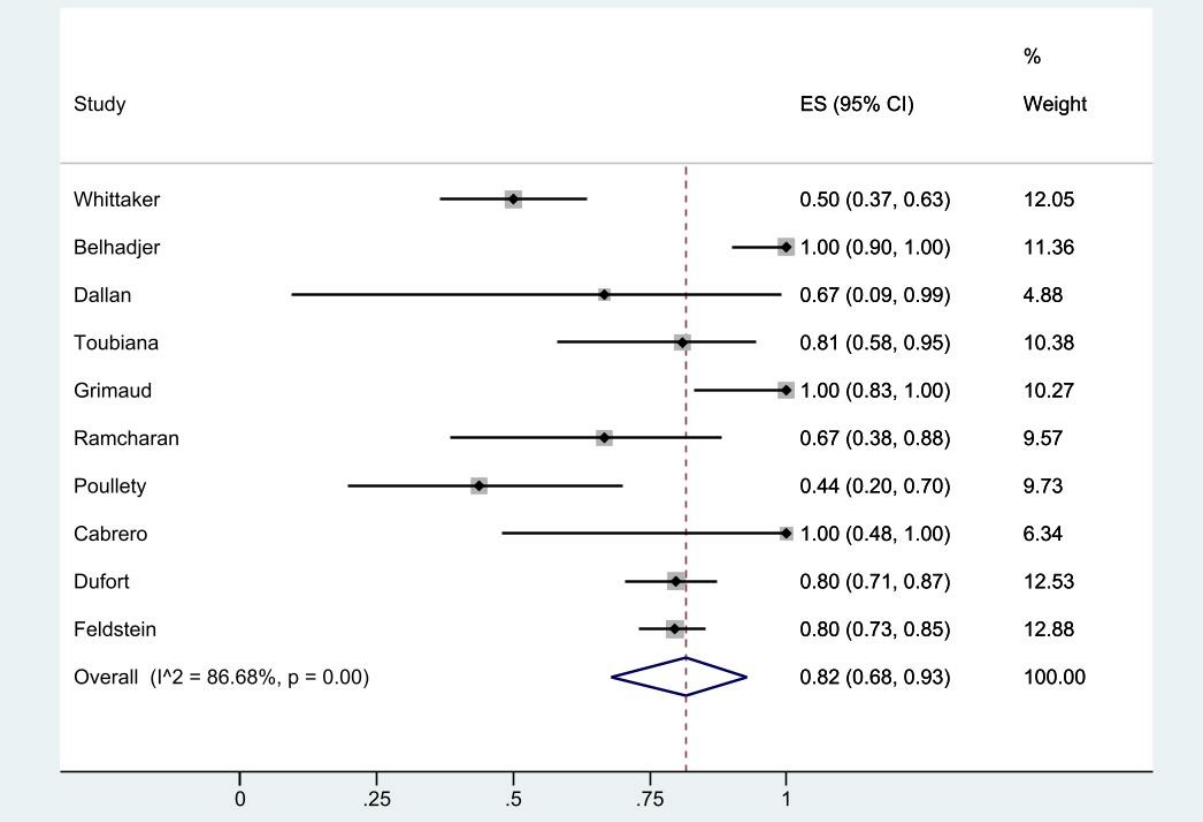
Table 2 Overall pooled effects of Laboratory results of 486 children with PIMS-TS

Laboratory test	**Studies n/N**	**Cases n/N**	**Pooled effetcs* (95%CI; I^2)**
C-Reactive protein (mg/L)	11/11	468/468	*226 (206 - 246; 84%)*
Procalcitonin (ng/mL)	7/11	199/199	*58 (34 - 83; 70%)*
Ferritin (ng/mL)	8/11	392/392	*727 (593 - 860; 60%)*
D-dimer (ng/mL)	9/11	432/432	*4230 (2311 - 6148; 41%)*
Lymphocyte count ($x10^9$/L)	8/11	232/232	*1.04 (0.74 - 1.34; 92%)*
Platelet count ($x10^9$/L)	8/11	413/413	*207 (135 - 279; 98%)*
Albumin (gr/dL)	7/11	410/410	*2.5 (2.0 - 2.9; 49%)*

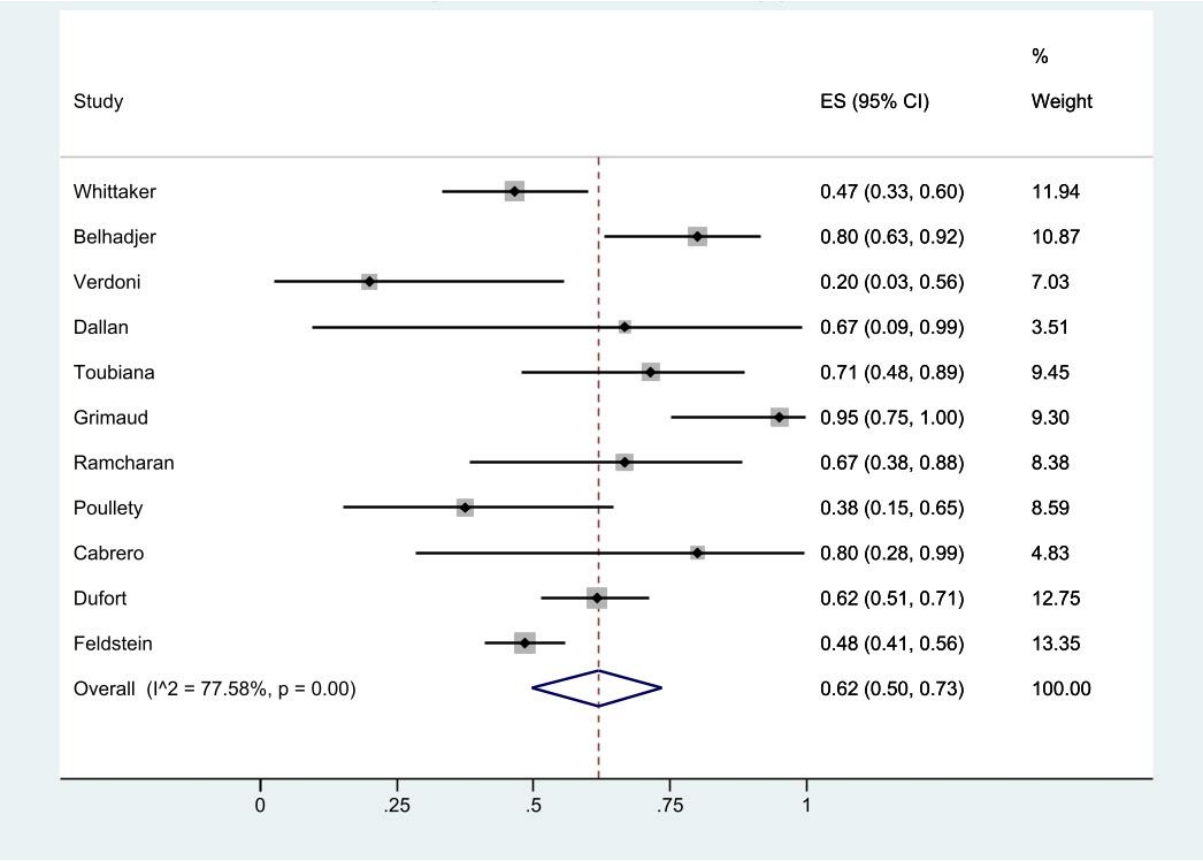
*Variable must be present in more than 50% of studies. Standardized means by transformation approach. For pooled proportions, we used the metaprop module.

Figure 1. Forrest plots of analyzed studies. A) Intensive care admission. B) Vasoactive support C) Advanced respiratory support (any) D) Invasive Mechanical Ventilation

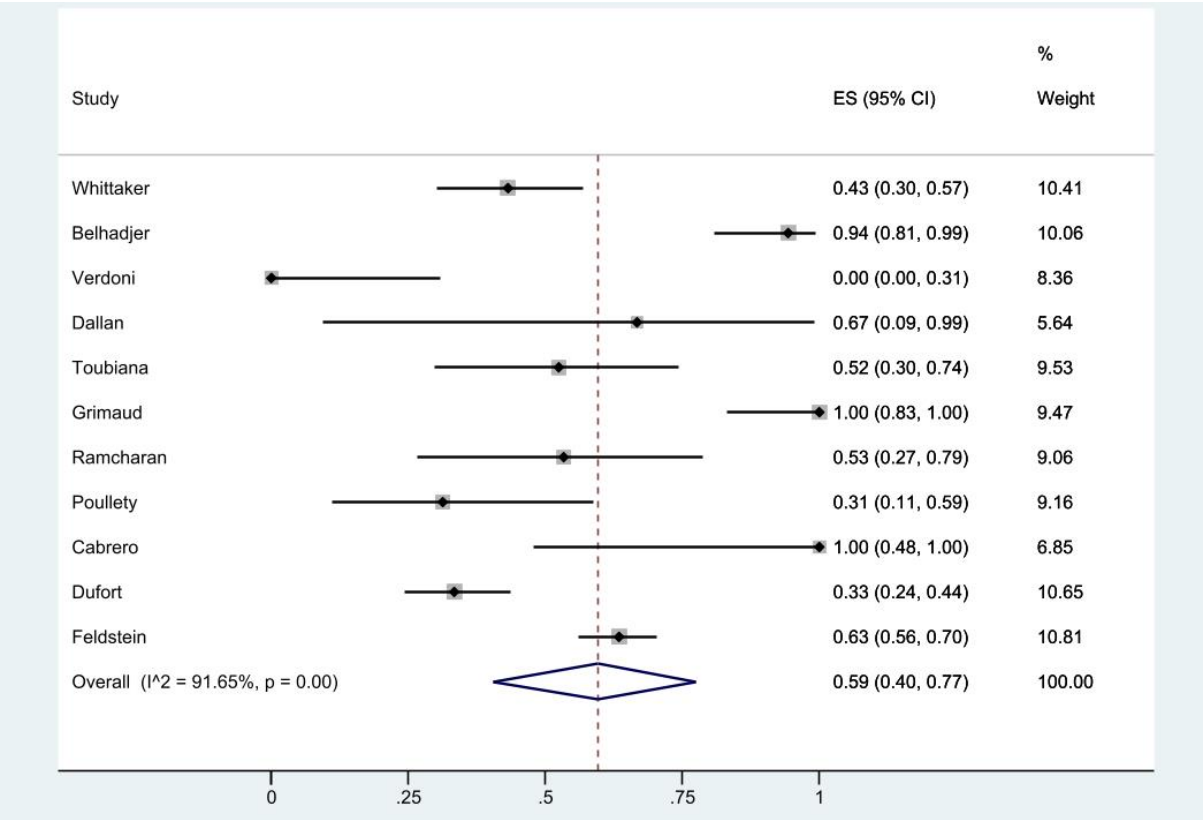
A.



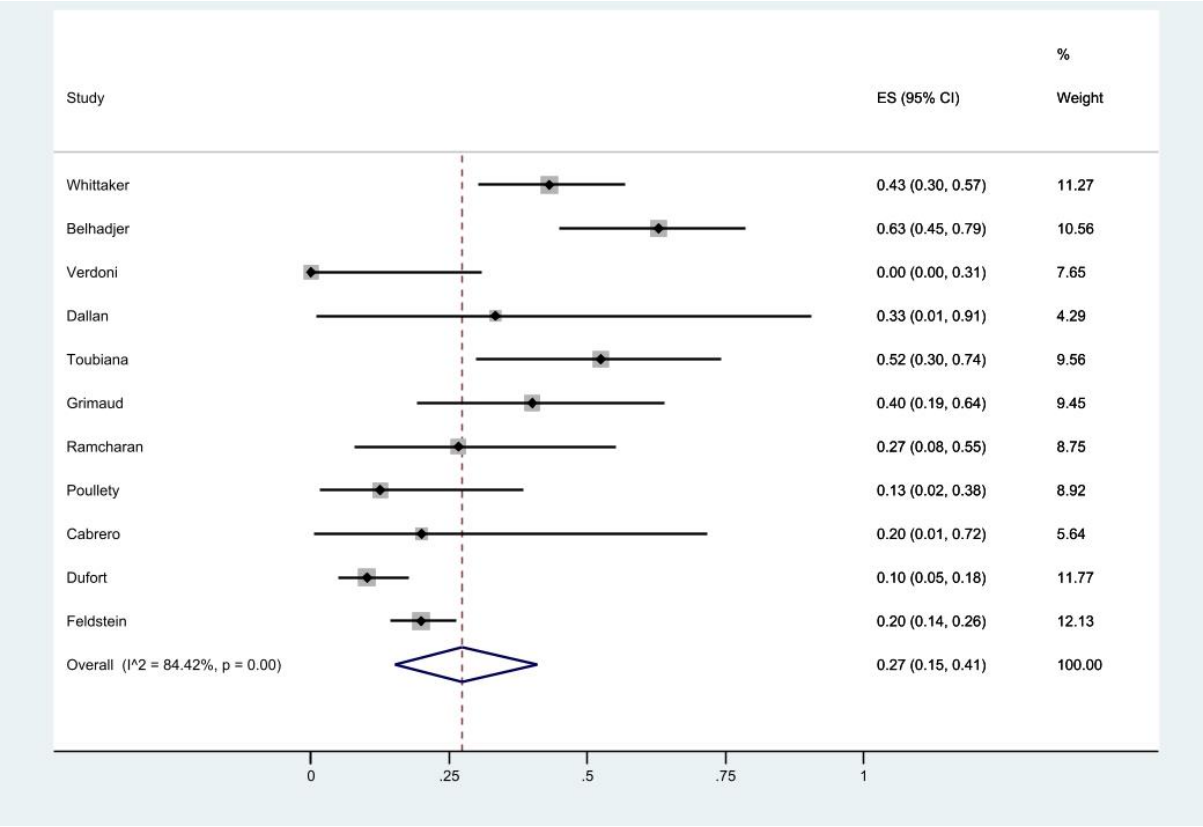
B


Study
ES (95% CI)
%
Weight
Whittaker
0.47 (0.33, 0.60)
11.94
Belhadjer
0.80 (0.63, 0.92)
10.87
Verdoni
0.20 (0.03, 0.56)
7.03
Dallan
0.67 (0.09, 0.99)
3.51
Toubiana
0.71 (0.48, 0.89)
9.45
Grimaud
0.95 (0.75, 1.00)
9.30
Ramcharan
0.67 (0.38, 0.88)
8.38
Poullety
0.38 (0.15, 0.65)
8.59
Cabrero
0.80 (0.28, 0.99)
4.83
Dufort
0.62 (0.51, 0.71)
12.75
Feldstein
0.48 (0.41, 0.56)
13.35
Overall (I^2 = 77.58%, p = 0.00)
0.62 (0.50, 0.73)
100.00
0
.25
.5
.75
1

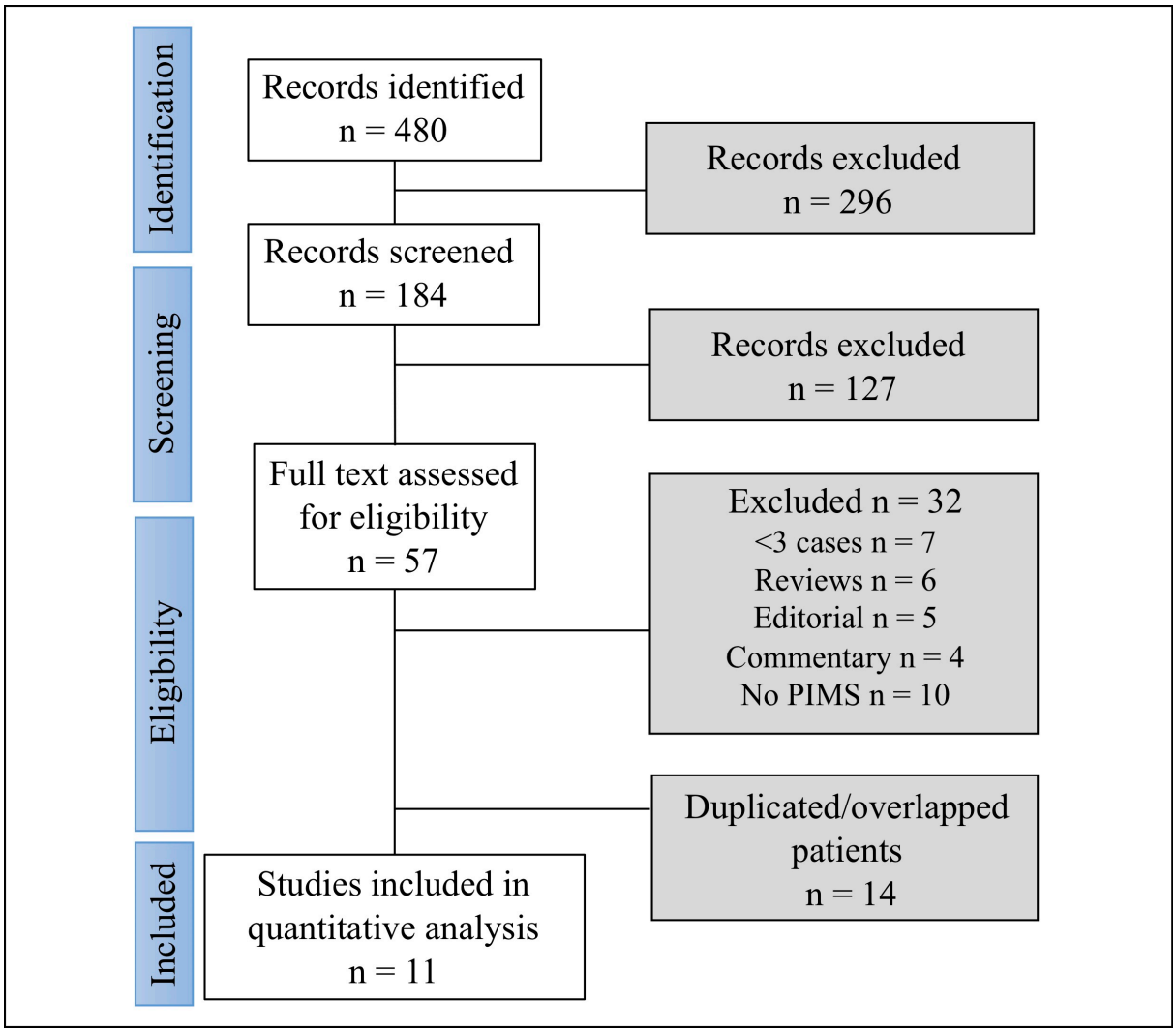
C.


Study
ES (95% CI)
%
Weight
Whittaker
0.43 (0.30, 0.57)
10.41
Belhadjer
0.94 (0.81, 0.99)
10.06
Verdoni
0.00 (0.00, 0.31)
8.36
Dallan
0.67 (0.09, 0.99)
5.64
Toubiana
0.52 (0.30, 0.74)
9.53
Grimaud
1.00 (0.83, 1.00)
9.47
Ramcharan
0.53 (0.27, 0.79)
9.06
Poullety
0.31 (0.11, 0.59)
9.16
Cabrero
1.00 (0.48, 1.00)
6.85
Dufort
0.33 (0.24, 0.44)
10.65
Feldstein
0.63 (0.56, 0.70)
10.81
Overall (I^2 = 91.65%, p = 0.00)
0.59 (0.40, 0.77)
100.00
0
.25
.5
.75
1

D.


Study
ES (95% CI)
%
Weight
Whittaker
0.43 (0.30, 0.57)
11.27
Belhadjer
0.63 (0.45, 0.79)
10.56
Verdoni
0.00 (0.00, 0.31)
7.65
Dallan
0.33 (0.01, 0.91)
4.29
Toubiana
0.52 (0.30, 0.74)
9.56
Grimaud
0.40 (0.19, 0.64)
9.45
Ramcharan
0.27 (0.08, 0.55)
8.75
Poullety
0.13 (0.02, 0.38)
8.92
Cabrero
0.20 (0.01, 0.72)
5.64
Dufort
0.10 (0.05, 0.18)
11.77
Feldstein
0.20 (0.14, 0.26)
12.13
Overall (I^2 = 84.42%, p = 0.00)
0.27 (0.15, 0.41)
100.00
0
.25
.5
.75
1

Supplementary file 1. Selection of the studies included in the quantitative meta-analysis.



Supplementary file 2. Expanded methods for the quantitative meta-analysis.

Methods

Study selection

We evaluated relevant studies in PubMed, LILACS, and Embase, published between May 1 to Jul 1, 2020, using combinations of the terms "pediatrics", "coronavirus," "COVID-19", "SARS-CoV-2", "pediatric intensive care", "pediatric inflammatory multisystem syndrome", "Kawasaki disease," "Hyper-inflammatory · Kawasaki · PIMS-TS · MIS-C · COVID-19 · SARS-CoV-2". We retrieved studies with at least three patients, and pediatric age was considered younger than 21 years old. We excluded studies that had duplicate patients from other reports. A special mention is the study of Toubiana et al. (17), which was conducted at the Necker-Enfants-Malades University Hospital. This center also participated in a larger case series (16), but we did not exclude it because we noticed that dates of the inclusion criteria did not overlap.

Quality measures.

To date, no universal framework for conducting synthesis of evidence when only case reports or series are available, due to the weak inferences and high likelihood of bias. To address this gap in knowledge, Murad MH et al. (1) proposed a tool to appraise the overall quality of included cases by removing items that do not apply to case reports from the Newcastle Ottawa scale. We used this approach, which contains four domains: selection, ascertainment, causality, and reporting.

Data extraction

Two independent reviewers (RB and JCJ) extracted data on demographics, clinical presentation, laboratory and imaging studies, treatments, PICU hospitalization, and respiratory and circulatory support. The pharmacological therapy used, and the ICU outcomes were also analyzed.

Analysis

Data is initially described by study using the presented measurement of distribution on the original paper (absolute and relative frequencies, categories, or means and standard deviation (SD) or medians with quartiles, minimum and maximal values). If the variable of interest was present in more than 50% of studies, a meta-analysis was carried for that variable. For continuous data, as most data was presented in medians, we used a transformation approach using *median2mean* excel calculator. (2) This calculator uses three scenarios depending on what variability measure is available using Luo et al. (3) approach to do a transformation to means and either Wan et al. (4) or Shi et al. (5) to find the transformed SD. For proportions, we used the metaprop module (Victoria Nyaga and Marc Arbyn, Brussels, Belgium) for Stata. We used the Freeman-Tukey Double Arcsine Transformation and the exact binomial (Clopper-Pearson) procedures to find the 95% confidence intervals. A representative forest plots meta-analyses

graphs were built. (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. 2019). For all calculations, we included the I-square (I^2) to quantify the degree of heterogeneity among studies. A suggested rough interpretation is as follows: 0% to 40% low (unimportant) heterogeneity; 30%-60% moderate; 50%-90% substantial; 75-100%: considerable. (6)

Additional references

1. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid-Based Med. 2018 Apr;23(2):60–3.

2. Estimating the sample mean and standard deviation [Internet]. 2020. Available from: http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html

3. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018 Jun;27(6):1785–805.

4. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol [Internet]. 2014 Dec [cited 2020 Aug 6];14(1). Available from: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-14-135

5. Shi J, Luo D, Weng H, Zeng X, Lin L, Chu H, et al. Optimally estimating the sample standard deviation from the five-number summary. Res Synth Methods [Internet]. 2020 Jul 25 [cited 2020 Aug 6]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jrsm.1429

6. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane [Internet]. 2019; Available from: www.training.cochrane.org/handbook

Suplementary file 3. Quality score of analyzed studies according to Murad MH et al (30).

	Study	Dates	Selection	Ascertainment	Causality	Reporting	Score	Observations
1	Verdoni et al.[10]	02/18 - 04/20	Adequate	Adequate	Adequate	Adequate	4/4	
2	Belhadjer et al.[11]	03/22 - 04/30	Adequate	Adequate	Inadequate	Adequate	3/4	Specific work up to rule out other causes is not mentioned (i.e. cultures, PCR for respiratory virus)
3	Whittaker et al. [12]	03/23 - 05/16	Adequate	Adequate	Adequate	Adequate	4/4	
4	Dallan et al.[15]	NA	Inadequate	Adequate	Adequate	Adequate	3/4	No specific crietria for diagnosis and selection is mentioned
5	Grimaud et al.[16]	04/15 - 04/27	Adequate	Adequate	Adequate	Adequate	4/4	
6	Toubiana et al.[17]	04/27 - 05/11	Adequate	Adequate	Adequate	Adequate	4/4	
7	Ramcharan et al.[20]	04/10 - 05/09	Adequate	Adecuate	Adequate	Adequate	4/4	
8	Pouletty et al[21]	03 - 04	Adequate	Adequate	Inadequate	Adequate	3/4	PCR for respiratory virus was done, but specific work up to rule out other causes is not mentioned (i.e. cultures, viral serology)
9	Cabrero-Hernández et al.[22]	ND	Inadequate	Adequate	Adequate	Adequate	3/4	No specific criteria for diagnosis and selection is mentioned
10	Dufort et al.[24]	03/01 - 05/10	Adequate	Adequate	Adequate	Adequate	4/4	
11	Feldstein et al.[25]	03/15 - 05/20	Adequate	Adequate	Inadequate	Adequate	4/4	Specific work up to rule out other causes is not mentioned (i.e. cultures, PCR for respiratory virus)