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Systematic Review/Meta-analysis

Kawasaki Disease Shock Syndrome vs Classical Kawasaki Disease: A Meta-analysis and Comparison With SARS-CoV-2 Multisystem Inflammatory Syndrome

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ABSTRACT

Contexte : À l’échelle mondiale, de plus en plus d’enfants sont touchés par un processus inflammatoire grave avec état de choc mimant le syndrome de choc de la maladie de Kawasaki (Kawasaki disease shock syndrome ou KDSS). Cette situation nous a incités à mieux caractériser le KDSS en préambule à une comparaison systématique des deux pathologies.

Méthodologie : Nous avons passé systématiquement en revue les cas de KDSS et effectué une méta-analyse comparant les cas déclarés de KDSS à des témoins atteints de la maladie de Kawasaki.

Context: The emergence of increasing reports worldwide of a severe inflammatory process and shock in pediatric patients resembling Kawasaki disease shock syndrome (KDSS)—and, more specifically, Kawasaki disease—prompted us to explore KDSS in a preamble of a systematic comparison between the two conditions.

Methods: We completed a systematic review of KDSS and performed a meta-analysis comparison between reported KDSS cases and KD controls.

Kawasaki disease (KD) is the leading cause of acquired childhood heart diseases in developed countries, mostly affecting children below the age of 5. It is classified among the acute immune vasculitis and may result in coronary-artery aneurysms, as they account for the most severe complication; they occur in 25% of untreated cases of KD. A single high dose of intravenous immunoglobulin (IVIG), combined with aspirin, is the most efficient primary treatment for KD, as it reduces the risk of coronary-artery abnormalities and resolves inflammation. The generalized aspect of KD sometimes implies a multiorgan involvement, which might include cerebral involvement (eg, aseptic meningitis, cerebral stroke), renal involvement (eg, proteinuria, hematuria, sterile pyuria, renal failure), gastrointestinal involvement (eg, diarrhea, vomiting, abdominal pain), hepatic involvement (raised liver enzymes), and other organs. This multiorgan dysfunction is also observed in a rare form of KD called Kawasaki disease shock syndrome (KDSS). Cases of KDSS were reported over the last 15 years but remain rare, representing 1% to 7% of KD. KDSS is described as KD involving a patient with complete or incomplete criteria who requires resuscitation, inotropic or support with vasoactive agents, or extracorporeal membrane oxygenation (ECMO), with the shock being unrelated to an acute coronary event.

From another perspective, the etiology of KD remains unknown, but the widely accepted hypothesis is that KD is a result of immunologic response to nonspecific infection. Previous studies have shown associations between viral respiratory infections and KD. Thus, preceding exposure to an...
Results: A total of 10 case-control series were included in the meta-analysis. Patients with KDSS were older (38.4 ± 30.6 vs 21.9 ± 19.5 months; P < 0.001) compared with standard KD with equal sex distribution and completeness of clinical diagnostic criteria. KDSS present higher C-reactive protein (59.4 ± 29.2 mg/dL vs 20.8 ± 14.8 mg/dL; P < 0.001), lower albumin (2.7 ± 0.5 g/dL vs 3.3 ± 0.5 g/dL; P < 0.01), and lower platelets (255 ± 149 109/L vs 394 ± 132 109/L; P < 0.001) but only borderline higher white blood cells (P = 0.06). Differences in alanine transaminase, aspartate aminotransferase, and erythrocyte sedimentation rate were nonsignificant. The odds of intravenous immunoglobulin resistance (44.4% vs 9.6%; P < 0.001) and the hospital length of stay (10.9 ± 5.8 vs 5.0 ± 3.0 days; P < 0.001) were higher in KDSS, as were the odds of coronary-artery abnormalities (33.9% vs 8.6%; P < 0.001).

Conclusions: This first meta-analysis on KDSS vs KD represents a basis for future works on KDSS and opens the opportunity for future multicentre studies in the search of causal relationships between presenting elements and the eventual complications of KDSS. The similarities between SARS-CoV-2 multisystem inflammatory syndrome in children and KDSS open new horizons to the understanding of the etiology and pathophysiology related to KDSS.

Methods
For the KDSS systematic review, and to perform the meta-analysis, we searched PubMed for case reports and case series reporting Kawasaki disease with shock. The search terms used were “Kawasaki disease,” “Kawasaki disease shock syndrome,” “Kawasaki disease + shock,” and “Kawasaki disease + hypotension.” Abstracts were reviewed to identify relevant articles. Studies were excluded if they were not in English or if they did not present sufficient information about their patients with shock (eg, shock intervention and treatment). The following data were collected from each article: patient demographics (including age, sex, ethnicity), clinical criteria for KD (complete or incomplete), elements of shock (low blood pressure, low perfusion, myocardial dysfunction), laboratory findings, treatment received for KD and shock, intensive care unit (ICU) length of stay and outcome, cardiac complications (coronary-artery aneurysms or dilatation, residual cardiac dysfunction). A total of 70 publications relating to KDSS were identified, including 52 case reports and 18 case series. After review, 39 case reports presenting 47 patients were included in the aggregated data collection, whereas 14 case reports were excluded (2 were not in English [1 was in Chinese and the other in German], and 11 included patients without shock). There were 18 case series, 4 of which were excluded for insufficient KDSS before the SARS-CoV-2 pandemic as a basis for a better understanding of KDSS and future comparison between the 2 entities. The objective of this paper was to describe the features of KDSS by performing a systematic review and a meta-analysis comparing KDSS with their KD controls. As the immunogenic triggers of the 2 conditions (KDSS/KD and MIS-C/SARS-CoV-2) bear some similarities, this article displays qualitative comparison between the 2 entities.
information. Of the remaining 14 case series, 4 case series did not have KD controls and were excluded from the meta-analysis but used for the aggregated data collection and presented a total of 85 patients with KDSS.23-26 The following 10 case series comprised the elements for meta-analysis5,27-35 (Fig. 1). The KDSS group was composed of 280 patients, and the control group was composed of 9943 patients (9350 controls from Lin et al.35) KDSS diagnostic criteria used across the 10 studies were either patients with KD admitted to the ICU for hypotension or shock or patients with KD presenting with systolic hypotension for age following Kanegaye’s definition.36

We only included case-control studies for our meta-analysis. Therefore, the KDSS/control comparison includes only data from the 10 reports that included a control group from the same population.5,27-35 Data from the 4 case series without KD controls were excluded from meta-analysis.24-26,36 For the meta-regression, a sensitivity analysis was done without the series by Lin et al.; given the high control N, the standard error of the difference is very low. The results are comparable, and thus the sensitivity analysis is not reported. Meta-regression was performed only if at least 5 of 10 studies reported a specific parameter. Meta-regressions were performed using the Metafor package for R. For each parameter, we report separately the weighted average for the 10 reports that are included in the KDSS/control comparisons and the weighted average for the 14 series and the combined case reports. A weighted average was performed for the aggregated data, which included the case reports and the excluded case series from the meta-analysis. When necessary, mean and standard deviations were estimated from median and interquartile range (IQR) or median and minimum/maximum, using the method proposed in Wan et al.37 Mean, standard deviation (SD), median, and frequencies were extracted and presented as number (percentage), median (range), or mean ± SD. The combined effect $P$ value was calculated. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for appropriate meta-analysis methodology.38 This study was exempt from ethics review.

**Results**

**Patient characteristics**

Patients with KDSS are, on average, older than their KD control counterparts, with an average age of 38.4 ± 30.6 months compared with 21.9 ± 19.5 months (Fig. 2A). There seems to be no association between sex and KDSS, as female patients represent 35.7% of patients with KDSS and 38.2% of KD ($P$ = 0.95). Overall, 9 publications originate from East Asia, whereas 4 case reports do not report ethnicity. Only 2 studies report data from a diverse group of patient ancestry-wise, and therefore it is not possible to conduct an unbiased analysis. There was no association between the type of KD based on the classical diagnostic clinical criteria (complete vs incomplete) and KDSS ($P$ = 0.37) (Figs. 2 and 3).

**Clinical manifestations and laboratory results**

The admitting diagnosis of KDSS cases is not KD in general, possibly leading to longer hospital stay, with the lowest study27 having 22% of their patients presenting with KD as initial diagnosis and the highest study31 presenting with 65%. KDSS is associated with slightly higher white blood cells (WBCs) and significantly lower platelet counts than controls (Fig. 3, A and B), lower serum albumin levels (Fig. 3C), and higher C-reactive protein (CRP) (Fig. 3D). KDSS was not associated with higher erythrocyte sedimentation rate (ESR) ($P$ = 0.78), alanine transaminase (ALT) ($P$ = 0.22), or aspartate aminotransferase (AST) ($P$ = 0.15) (Table 1). Other
cardiac biomarkers, such as troponin, were only reported in 2 studies, and γ-glutamyl transferase was only reported in a single study. Elevated D-dimers, although rarely reported owing to unavailable data, were particularly present in KDSS, accompanying the cytokine storm. Only recent reports presented patients with the macrophage-activation syndrome (MAS).31

**Multiorgan components**

Multiorgan dysfunction and myocardial systolic dysfunction were reported in a small number of studies and were therefore insufficient for comparative analysis. In general, patients with KDSS were reported to develop higher proportions of depressed left-ventricular systolic function (12.4%), pericardial effusions (22.2%), or aorticvalve regurgitation (32.8%) compared with KD (Table 1). Because of an overall low reporting on cardiac involvement in the references, we did not perform statistical comparison. From the pathophysiology perspective, 5 patients presented with a cardiogenic shock, whereas 3 presented with a distributive shock, suggesting that KDSS might cause various mechanisms of shock.25 The series from the Children’s Hospital of Mexico City established that 90% of KDSS cases presented with gastrointestinal (GI) abnormalities (abdominal pain, vomiting, diarrhea, GI bleeding).29

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**Figure 2.** Meta-regression results reporting clinical aspects of Kawasaki disease shock syndrome/Kawasaki disease(observed outcome) by incorporated study and by combined effect representing significant factors (P values for combined effect). IVIG, intravenous immunoglobulin; RE, random-effect.
Treatment and outcome

KDSS was associated with increased odds of occurrence of coronary-artery abnormality (CAA) compared with controls (prevalence of 33.9% vs 8.6%) (Table 1, Fig. 2D). The definition of CAA was not uniformly defined among the source series, however, which limits the qualitative discrimination between aneurysms and dilatation as well as the quantitative determination of size of the CAA. For instance, Gamez-Gonzalez et al.39 reported a very high prevalence of CAA in the control group (58%), which makes the CAA rate in that group questionable.

IVIG therapy was reported in all but 1 study for KDSS. In many studies, treatment with IVIG was among the inclusion criteria, and, as such, the rate of IVIG is universally high. No meta-regression analyses were performed for the use of IVIG, aspirin, and corticosteroid because of insufficient variance among studies. Overall, patients with KDSS received IVIG in 98.9% (n = 280), aspirin in 98.8% (n = 252), and corticosteroids in 36.7% (n = 98), whereas KD controls received IVIG in 99.9% (n = 9593), aspirin in 100% (n = 9514), and corticosteroids in 11.0% (n = 219). KDSS was associated with increased odds of IVIG resistance (44.4%) compared with controls (9.6%) (Fig. 2B). The length of hospital stay was significantly higher in KDSS 10.9 ± 5.8 days compared with 5.0 ± 3.0 days (Table 1, Fig. 2C). In terms of shock, when specific management was detailed, 97.1% received fluid resuscitation, 50% mechanical ventilation, 63.2% inotropic support, 63.8% vasopressors, and 78.6% a combination of treatment.
Aggregated data

The 38 case reports and the 4 case series were combined (Fig. 1) to present aggregated data on 132 patients with KDSS (Table 2). In general, these patients presented a very similar profile to the patients with KDSS from our meta-analysis. There was identical male predominance (58%, 77 of 132); high IVIG resistance (44%); similar shock treatment, with a predominance of fluid resuscitation and inotropic support; systolic dysfunction in 15%, specifying dilatations and aneurysms in 15%, and coronary artery abnormalities in 32%.

Discussion

KD, in its acute phase, can lead to KDSS, a relatively rare entity summarized in 15 studies and 39 case reports published since 1993 on the subject. The cumulative information from the 10 papers included in the meta-analysis established the following features that enable distinguishing KDSS from the usual KD case presentation: (1) Usually, the admitting diagnosis of KDSS cases is not KD, leading possibly to longer hospital stay; (2) patients with KDSS are older than the usual patient with KD and have a higher prevalence and severity of GI symptoms; (3) patients with KDSS present with worse biological and inflammatory markers, (4) exhibit a higher resistance rate to IVIG, (5) have a higher rate of CAA, and (6) have greater number of reported cases of ventricular systolic dysfunction and atriointerventricular valve regurgitation.

There are no explanations or attempts to explaining causal reasons for KDSS to occur beyond the observational clinical and laboratory features. Until now, only few papers report MAS and multiorgan failure in association with KDSS, suggestive of cytokine storm. Given the featured similarities with MIS-C, the current SARS-CoV-2 pandemic is a valuable opportunity to better understand enigmatic features of an old disease from the exhaustive dynamic research on a current new disease and vice versa.

Our meta-analysis on KDSS and KD highlights a few important points that can be taken into account by physicians to better distinguish those diseases in a clinical setting. There are no explanations or attempts to explaining causal reasons for KDSS to occur beyond the observational clinical and laboratory features. Until now, only few papers report MAS and multorgan failure in association with KDSS, suggestive of cytokine storm. Given the featured similarities with MIS-C, the current SARS-CoV-2 pandemic is a valuable opportunity to better understand enigmatic features of an old disease from the exhaustive dynamic research on a current new disease and vice versa.

Our meta-analysis on KDSS and KD highlights a few important points that can be taken into account by physicians to better distinguish those diseases in a clinical setting. Therefore, we present a few clinical investigations that should be performed routinely when evaluating patients with KD, KDSS, or MIS-C. First of all, when evaluating a patient presenting to the clinic or the hospital with shock, it is important to include KD as differential diagnosis, as it is often missed.
leading to longer hospitalization and severe complications. The same is to be done with patients admitted with MIS-C. It is also important to assess for previous infections or viral triggers that could have potentially started the inflammation. To obtain a better profile of patients with KD and KDSS across various locations, it is important to order the appropriate laboratory tests when presented with a patient with shock or a patient with features of KD. Albumin, WBC, platelets, and ESR are essential to assess inflammation, CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; KDSS, KD shock syndrome; SD, standard deviation; TSS, toxic shock syndrome; WBC, white blood cell.

### Table 2. Characteristics of aggregated data of 132 patients with KDSS from 39 case reports and 4 case series

| Characteristics                                      | Mean ± SD, n (%)                     |
|------------------------------------------------------|--------------------------------------|
| Age (months)                                         | 41.9 ± 31.3                          |
| Male / total                                         | 77/132 (58%)                         |
| Ethnicity                                            |                                       |
| White                                                | 3/132 (2%)                           |
| Asian                                                | 90/132 (68%)                         |
| African American                                     | 2/132 (2%)                           |
| Hispanic                                             | 1/132 (1%)                           |
| Other                                                | 3/132 (2%)                           |
| Not specified                                        | 33/132 (25%)                         |
| Incomplete KD                                        | 29/58 (50%)                          |
| Type of shock                                        |                                       |
| KDSS, not specified otherwise                       | 117/132 (89%)                        |
| Myocardial                                           | 10/132 (8%)                          |
| TSS                                                  | 4/132 (3%)                           |
| Treatment                                            |                                       |
| IVIG                                                  | 113/115 (98%)                        |
| Aspirin                                               | 41/115 (36%)                         |
| Corticosteroids                                       | 18/115 (16%)                         |
| Other immunosuppressive therapy                      | 12/115 (10%)                         |
| IVIG resistance                                       | 51/115 (44%)                         |
| Admitted ICU                                         | 128/132 (97%)                        |
| Treatment for shock                                  |                                       |
| Ventilation support                                  | 20/65 (31%)                          |
| Fluid resuscitation                                  | 41/65 (63%)                          |
| Inotropic support                                    | 38/65 (58%)                          |
| Vasoactive agents                                    | 25/65 (38%)                          |
| ECMO                                                 | 2/65 (3%)                            |
| Combination of treatment                             | 45/65 (69%)                          |
| Multigorgan dysfunction                              | 53/69 (77%)                          |
| Uveitis                                               | 3/69 (5%)                            |
| Irritability                                         | 5/69 (9%)                            |
| Gastrointestinal symptoms                            | 22/69 (38%)                          |
| Diarrhea                                             | 13/69 (22%)                          |
| Vomiting                                             | 23/69 (40%)                          |
| Abdominal pain                                       | 14/65 (24%)                          |
| Hepatomegaly                                         | 10/69 (17%)                          |
| Ascites                                              | 2/69 (3%)                            |
| Renal dysfunction/failure                            | 15/69 (26%)                          |
| Respiratory difficulties                             | 23/69 (40%)                          |
| Cardiac involvement                                  |                                       |
| Coronary abnormality                                  | 20/132 (15%)                         |
| Coronary dilatation                                  | 41/132 (31%)                         |
| Coronary aneurysm                                    | 29/132 (22%)                         |
| Giant coronary aneurysm                              | 0/132 (0%)                           |
| Systolic dysfunction                                 | 20/58 (34%)                          |
| Mitral/tricuspid regurgitation                       | 9/132 (13%)                          |
| Laboratory findings                                  |                                       |
| Albumin (g/dL)                                       | 2.28 ± 0.51                          |
| WBC (109/L)                                          | 15.2 ± 6.6                           |
| Platelets (109/L)                                    | 309 ± 148                            |
| ESR (mm/h)                                           | 71.3 ± 38.2                          |
| CRP (mg/dL)                                          | 87.6 ± 76.3                          |
| ALT (U/L)                                            | 120 ± 81                             |
| AST (U/L)                                            | 130.8 ± 96.8                         |
| Death                                                | 4/132 (3%)                           |

Mean ± SD, n (%), or median (range). ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; KDSS, KD shock syndrome; SD, standard deviation; TSS, toxic shock syndrome; WBC, white blood cell.

The initial circumstantial evidence suggesting a causal link between MIS-C and COVID-19 is now supported by serology data and immunologic mechanisms. Patients initially presented with MIS-C within 2 to 6 weeks following the outbreak of the pandemic. The main characteristics of MIS-C present many similarities with KDSS, which have been qualitatively compared in Table 3. Although MIS-C is reportedly associated with lymphopenia, reports on KDSS do not provide lymphocyte counts.
A comprehensive comparison between KDSS and MIS-C was reported on the UK series vs a series of patients with KDSS diagnosed between 2002 and 2019 in San Diego, California. Accordingly, MIS-C and KDSS are thought to be 2 different entities. Although we agree, in general, with the latter, one should be conscious of the fact that the 2 series are drawn from 2 different populations, with different social-ethnic makeup, in 2 remote geographic areas, which were exposed to totally different infectious and environmental triggers. The comparison between the results from our meta-analysis and MIS-C literature identified striking similarities, with higher inflammatory response compared with KD, elevated myocardial markers, and both reporting MAS and elements of cytokine storm response. As lymphopenia is not typically searched for in KD, there are no available data in the KDSS literature to verify whether this occurs, in what frequency, and at what intensity. At this state of knowledge surrounding the various case definitions of MIS-C, the lack of precision discerning KD and KD-like presentation associated to SARS-CoV-2, and the potential mixing between the 2 entities in this early MIS-C reporting, we elected to refrain from quantitive comparison between KDSS and MIS-C. It would be more appropriate to perform in-depth quantitative comparison once the case definition of MIS-C is upgraded to higher standards of certainty. The clinical pictures of MIS-C and KDSS are also very similar, with a few differences, such as older age, sex distribution as well as ethnic backgrounds and race. The latter observation, including the relative rarity in the Asian populations, raises questions concerning the etiology and genetic component of both conditions. Clinical outcome related to the impact on the coronary arteries (dilatations or aneurysms) and the myocardial function (typically responsive to IVIG), poor perfusion and shock, as well as the low mortality rate are other common grounds of similarities between MIS-C and KDSS.

The association between KD and respiratory viruses have always existed, including corona viruses in particular. For instance, pathology specimen from deceased patients with KD were extensively studied by Rowley et al., advancing that RNA respiratory viruses could be the infectious trigger of KD. In 2004, van Der Hoek et al. discovered HCoV-NL63, a small series of KD. The association between HCoV-NH and KD was refuted in the following years in Japan, the United States, and Taiwan, as the association between HCoV-NL63 and KD was likewise refuted. Since then, in 2014 Chang et al. proposed that patients with KD had higher chances of being infected by coronavirus than temporal local controls, and their hypothesis was supported by Shirato et al., who found a possible association between another strain of coronavirus (HCoV-229E or the Sendai-H serotype) and KD. In this line of thought, KDSS should be maintained in the list of differential diagnoses of MIS-C or shock with or without presenting features of KD, notwithstanding the circumstantial association between the clinical presentation and the exposure and or infection with SARS-CoV-2.

Table 3. Comparison between KDSS and MIS-C according to the MMWR CDC report41

| KDSS41 | MIS-C |
|--------|-------|
| **Clinical** | **MIS-C** |
| KDSS older than KD controls, but younger than MIS-C | Older age median ~8 years |
| 62.4% male (similar to KD controls 61.8% males) | 55.4% male |
| 1% to 7% of KD cases | 35.6% of SARS-CoV-2 (CDC); 5.8% of COVID-19 (China) |
| Gastrointestinal symptoms (occasional in most series) | Gastrointestinal symptoms common (91%) |
| Lower prevalence in Asian vs Western countries | Predominantly in Asian Western countries |
| Higher in Hispanic origin (1 study) | ~40% Hispanic, ~33% black, ~13% white |
| Incomplete KD criteria (1 of 3) in KDSS vs (1 of 4) in KD (ns) | KD-like symptoms, rare complete criteria 4.9% (3% to 6.6%) |
| Admitting diagnoses often other than KD | A mix of admitting diagnoses (GI, shock, respiratory) |
| Poor perfusion/shock by definition | Poor perfusion/shock 35.4% (9% to 75.9%) |
| Myocardial dysfunction present | Myocardial dysfunction 40.6%, myocarditis 22.8% |
| PICU stay ~6 days | PICU stay ~5 days (IQR: 3-7) |
| Higher resistance to IVIG (44.4%) than KD controls (9.6%) | Unknown prevalence of IVIG resistance |
| Coronary abnormalities (39.8%) than KD controls (8.6%) | Coronary dilatation and aneurysms (18.6%) |
| Longer hospitalization (11 days) than KD controls (5 days) | Length of hospitalization ~6 days (IQR: 4-9) |
| Longer duration of fever compared with KD controls | Duration of fever ~5 days (IQR: 3-6) |
| 1.3% mortality | 1.8% mortality |

| Biological | MIS-C |
|------------|-------|
| Elevated CRP (higher in KDSS compared to KD controls) | Elevated CRP |
| Elevated interleukins, TNF-α | Elevated interleukins, TNF-α |
| Elevated troponin (rarely tested) | Elevated troponin |
| Lower platelet count in KDSS compared with KD controls | Thrombocytopenia |
| Elevated WBC count, (unreported lymphocyte count) | Elevated WBC count with lymphopenia |
| Elevated D-dimers (reported) | Elevated D-dimer |
| Elevated BNP/NT-proBNP (when tested) | Elevated BNP/NT-proBNP |
| Macrophage-activation syndrome (reported) | Macrophage activation syndrome (frequently reported) |

BNP/NT-proBNP, B-type natriuretic peptide-N-terminal pro-BNP; CDC, US Centers for Disease Prevention and Control; CRP, C-reactive protein; GI, gastrointestinal; IQR, interquartile range; IVIG, Intravenous immunoglobulin; KD, Kawasaki disease; KDSS, KD shock syndrome; MIS-C, Multisystem inflammatory syndrome in children; MMWR, Morbidity Mortality Weekly Report; PICU, pediatric intensive care unit; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2 TNF, tumour necrosis factor; WBC, white blood cell.

*Age, male to female ratio, and complete vs incomplete diagnostic criteria for KD are based on the current meta-analysis.

1. As reported by the CDC.
2. Of 2143 Chinese children diagnosed with laboratory-verified or clinically diagnosed COVID-19, 5.2% had severe disease, and 0.6% had critical disease. From 2.6 to 6.95% in Western countries (vs) 1.45% and 1.9% in Taiwan.
Risk of bias

KDSS data are from retrospective series of consecutive cases in single institutions, which exclude selection bias. Controls varied between random selection,5,31,34,35,39 seasonal, sex and age matching,27,30 or date of admission.28,32,33

Limitations

The main limitation of the meta-analysis is related to the rarity of KDSS and therefore the number of eligible studies. As such, some information is not readily available for proper statistics. The case definition of coronary lesions and precision among dilatation, aneurysm, and giant aneurysm are not uniformly considered in the reports. The numbers for coronary artery “abnormalities” may be overestimated, as a result of the mix of types of lesions in some reports. Finally, we could not perform a cause-to-effect analysis in the meta-analysis because basic characteristics and baseline biological and laboratory data were not available in association with outcomes in a patient-by-patient—tabulated format in most series. We intend, however, to study cause-to-effect relationship further in a multicentre retrospective study.

Conclusions

This first meta-analysis represents a basis for future works on KDSS and opens the opportunity for future multicentre studies in the search of causal relationships between presenting elements and the eventual complications of KDSS. KDSS is currently acknowledged to be a subentity of KD. However, the similarities among the new pediatric manifestations of SARS-CoV-2, MIS-C, and KDSS opens new horizons to the understanding of the etiology and pathophysiology related to KDSS.

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The authors have no conflicts of interest to disclose.

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