## SISCoV Study: Systemic inflammatory syndrome in COVID-19 –a Systematic review and meta-analysis of Multisystem inflammatory syndrome in children with SARS-CoV-2 infection

## SUPPLEMENTARY APPENDIX

**PRISMA Checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  5 |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 5 |
| **ABSTRACT**  | 6 |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 6 |
| **INTRODUCTION**  | 7 |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 7 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 7 |
| **METHODS**  | 9-13 |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 9 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 10 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 9-10 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 9 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 10 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 11 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 11 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 11-12 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 11 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 12-13, Table 1 |
| Section/topic  | # | Checklist item  | Reported on page #  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 11 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | -- |
| **RESULTS**  | 13-17 |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  |  Figure 1 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 13-14 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | Table 1 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 13-17, Figure 2,3 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Figure 2, 3 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | Table 1 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | -- |
| **DISCUSSION**  | 17-22 |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 17-19 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 21 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 22 |
| **FUNDING**  | N.A. |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | N.A |

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*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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**Search terms :**

**Summary :**

**(SARS-CoV2 OR SARSCoV2 OR COVID-19 OR COVID19 OR "COVID 19" OR nCoV OR "NOVEL CORONA VIRUS") AND (PMIS-TS OR "PMIS TS" OR PIMS OR PIMS-TS OR MIS-C OR MISC OR "MULTISYSTEM INFLAMMATORY DISORDER" OR "Paediatric multisystem inflammatory syndrome" OR "MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN" OR KAWASAKI OR KD OR "KAWASAKI DISEASE"OR "KAWASAKI SHOCK SYNDROME")**

Detailed search:

(((((("SARS-CoV2"[All Fields] OR "SARSCoV2"[All Fields]) OR ((((((("COVID 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication])))) OR (("COVID 19"[Supplementary Concept] OR "COVID 19"[All Fields]) OR "covid19"[All Fields])) OR "COVID 19"[All Fields]) OR "nCoV"[All Fields]) OR "NOVEL CORONA VIRUS"[All Fields]) AND (((((((((((("pmis"[All Fields] AND "ts"[All Fields]) OR "PIMS"[All Fields]) OR (("pediatric multisystem inflammatory disease covid 19 related"[Supplementary Concept] OR "pediatric multisystem inflammatory disease covid 19 related"[All Fields]) OR "pims ts"[All Fields])) OR "MIS-C"[All Fields]) OR "MISC"[All Fields]) OR "MULTISYSTEM INFLAMMATORY DISORDER"[All Fields]) OR "Paediatric multisystem inflammatory syndrome"[All Fields]) OR "MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN"[All Fields]) OR ("kawasaki"[All Fields] OR "kawasaki s"[All Fields])) OR "KD"[All Fields]) OR "KAWASAKI DISEASE"[All Fields]) OR "KAWASAKI SHOCK SYNDROME"[All Fields])

**Table S1: Demographic, clinical profile, complications, management strategies and prognostic parameters obtained from data extraction from 11 included publications.**

|  |
| --- |
| **Demographic profile** |
| ***Parameter*** | ***Number of publications reporting the parameter (n=18)*** | ***Results******(Total number of patients, n=833)*** | ***Comments*** |
|  Sex distribution | 18 | Male 472 Female 361 | Sex ratio : 1.31 |
|  Race |
| * Black including Afro-Carribeans
 | 11 | 198/579 | 34.2% |
| * White
 | 9 | 115/530 | 21.7% |
| * Hispanic
 | 5 | 106/311 | 34.1% |
| * Asians
 | 9 | 58/349 | 16.6% |
| Comorbidity |
| * Overweight/obesity
 | 7 | 116/405 | 28.6% |
| * Chronic lung disease
 | 4 | 27/181 | 14.9% |
| Clinical presentations ( In addition to Kawasaki phenotype) and complications |
| * GI features
 | 16 | 603/715 | 84.3% |
| * Neurological symptoms
 | 13 | 138/602 | 22.9% |
| * Myocarditis%
 | 6 | 191/309 | 61.8% |
| * Pericardial involvement \*
 | 10 | 135/436 | 31.0% |
| * Left Ventricular Ejection fraction (<50%)a
 | 8 | 190/422 | 45.0% |
| * Acute Kidney injury
 | 3 | 40/176 | 22.7% |
| * Vasopressor support
 | 16 | 458/783 | 58.5% |
| * Coronary artery abnormality
 | 16 | 117/681 | 17.2% |
| * Invasive ventilator support
 | 15 | 226/813 | 27.8% |
| SARS-CoV-2 status and diagnosis |
| * rtPCR from nasopharyngeal/oropharyngeal/tracheal aspirate
 | 18 | 291/800 | 36.4% |
| * Serological evidence ( IgG, IgM, IgA against SARS-CoV-2)
 | 18 | 495/752 | 65.8% |
| Management strategies |  |  |  |
| * IVIg retreatment
 | 5 | 66/266 | 24.8% |
| * Immunomodulator#
 | 12 | 84/577 | 14.6% |
| Death | 8 | 13/833 | 1.6% |

\* Includes asymptomatic, echocardiographic pericardial effusion and pericarditis. Denominator is 97 since it only includes articles where echocardiography was done.

% Includes articles with clear mention of myocarditis. One of the publications was retrospective observational study in patients with acute myocarditis (n=20)

a : Includes articles where echocardiography was done and data done number of subjects with LVEF<50% was available

# Immunomodulators used commonly included Anakinra, Tocilizumab

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|  |  |  |  |  |

**PMIS-TS Case definition by UK Royal College of Pediatrics and Child Health**(2)**:**

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features ). This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 PCR testing may be positive or negative

**Clinical**

***All :***

• Persistent fever >38.5°C Most:

• Oxygen requirement • Hypotension

***Some:***

• Abdominal pain • Confusion • Conjunctivitis • Cough • Diarrhoea • Headache • Lymphadenopathy • Mucus membrane changes • Neck swelling • Rash • Resp symptoms • Sore throat • Swollen hands and feet • Syncope • Vomiting

***Imaging and ECG:***

• Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation

• CXR – patchy symmetrical infiltrates, pleural effusion

• Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly

• CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast

**Laboratory**

***All:***

• Abnormal Fibrinogen • Absence of potential causative organisms (other than SARS-CoV-2)

• High CRP • High D-Dimers • High ferritin • Hypoalbuminaemia • Lymphopenia • Neutrophilia in most – normal neutrophils in some

***Some:***

• Acute kidney injury • Anaemia • Coagulopathy • High IL-10 (if available)\* • High IL-6 (if available)\* • Neutrophilia • Proteinuria • Raised CK • Raised LDH • Raised triglycerides • Raised troponin • Thrombocytopenia • Transaminitis

**Preliminary case definition by the World Health Organisation**

Children and adolescents 0–19 years of age with fever > 3 days

**AND**twoof the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

**AND**

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

**AND**

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

**AND**

Evidence of COVID-19**(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

**Case definition of Kawasaki disease**(3) **:**

American Heart Association criteria for the definition of Kawasaki disease is to have persistent fever or atleast 5 days and 4 of the following 5 mucocutaneous features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; and cervical lymphadenopathy (>1.5 cm diameter). Patients with fewer than 4 features were stratified as having Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4 of 5 features to be present.

**Abbreviations of the terms used in pathogenesis :**

Intercellular Adhesion Molecule 1(ICAM-1) also known as CD54 (Cluster of Differentiation 54), Lysosome-associated membrane protein 1 (LAMP1), STING (stimulator of interferon genes), Transmembrane protein 173 (TMEM173), Interferon gamma receptor 2 also known as IFN-γR2 is a protein which in humans is encoded by the IFNGR2 gene, Mediator of DNA damage checkpoint protein 1 (MDC1), Plasmacytoid dendritic cells (pDCs), Chemokine (C-C motif) ligand 20 (CCL20), MUC4: mucin 4, cell surface associated, P2RX4 purinergic receptor P2X, ligand-gated ion channel 4, ECE2 (Endothelin Converting Enzyme 2), C-type lectin family 14, member A (CLEC14A), NF-κB Nuclear Factor kappa-light-chain-enhancer of activated B cells, vascular endothelial growth factor A ( VEGFA), Folate hydrolase 1 (FOLH1), Interferon regulatory factor 3 (IRF3), Interferon beta (IFNß), STING-associated vasculopathy with onset in infancy (SAVI), non-structural protein (nsp)

REFERENCES:

1. Shelley Riphagen, Xabier Gomez, Carmen Gonzalez-Martinez, Nick Wilkinson PT. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet [Internet]. 2020;Vol 395(January):1607. Available from: https://doi.org/10.1016/ S0140-6736(20)31094-1%0AAge;

2. Heald RC of P and C. Guidance paediatric multisystem inflammatory syndrome temporallly associated with Cov-19. R Coll Paediatr Child Heal [Internet]. 2020;1–6. Available from: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19

3. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation [Internet]. 2017 Apr 25 [cited 2020 Jun 26];135(17):e927–99. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000484