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Cardiac abnormalities due to multisystem inflammatory syndrome temporally associated with Covid-19 among children: A systematic review and *meta*-analysis

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ABSTRACT

Background: Cardiac defects due to multisystem inflammatory syndrome in children (MIS-C) have been abundantly reported leading high morbidity among children affected by Covid-19. We aimed to systematically assess the incidence of such cardiac abnormalities due to MIS-C in children suffering Covid-19.
Methods: The manuscript databases including Medline, Web of knowledge, Google scholar, Scopus, and Cochrane were deeply searched by the two blinded investigators for all eligible studies based on the relevant keywords. The risk of bias for each study was assessed according to QUADAS-2 tool. Statistical analysis was performed using the Comprehensive Meta Analysis (CMA) software.
Results: In final, 21 articles (including 916 children) were eligible for the final analysis that all yielded good quality and none of the citation was determined to have high risk of bias. Considering studies focusing different cardiac abnormalities related to MIS-C yielded a pooled prevalence of 38.0% for significant left ventricular dysfunction, 20.0% for coronary aneurism or dilatation, 28.1% for ECG abnormalities or cardiac arrhythmias, 33.3% for raised serum troponin level and 43.6% for raised proBNP/BNP level.
Conclusion: Although cardiac abnormalities among children suffering Covid-19 are uncommon, in the context of the MIS-C can be common and therefore potentially serious and life threatening.

Contents

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1. Introduction

Until the current writing, more than 68 million cases of Covid-19 have been reported worldwide, leading to more than 1.5 million deaths [1]. Apart from the pulmonary effects and disabilities associated with the progression of the infection, cardiovascular disorders have been reported in patients suffering this disorder [2]. Coronary atherosclerosis leading to myocardial infarction, myocarditis, valvular defects, peripheral vascular complications due to increased coagulopathies, and even acute heart failure due to severe left ventricular dysfunction have all been reported complications of the disease [3–5]. The probable mechanisms related to cardiac injuries include both direct invasion of virus leading cardiomyocyte death or indirect myocardial injury due to activation of inflammatory or coagulative cascades, hypoxemia, or metabolic disturbances [6].

Less information is available about children with the disease and its potential complications in childhood, and according to some claims, children are at a much lower risk of contracting

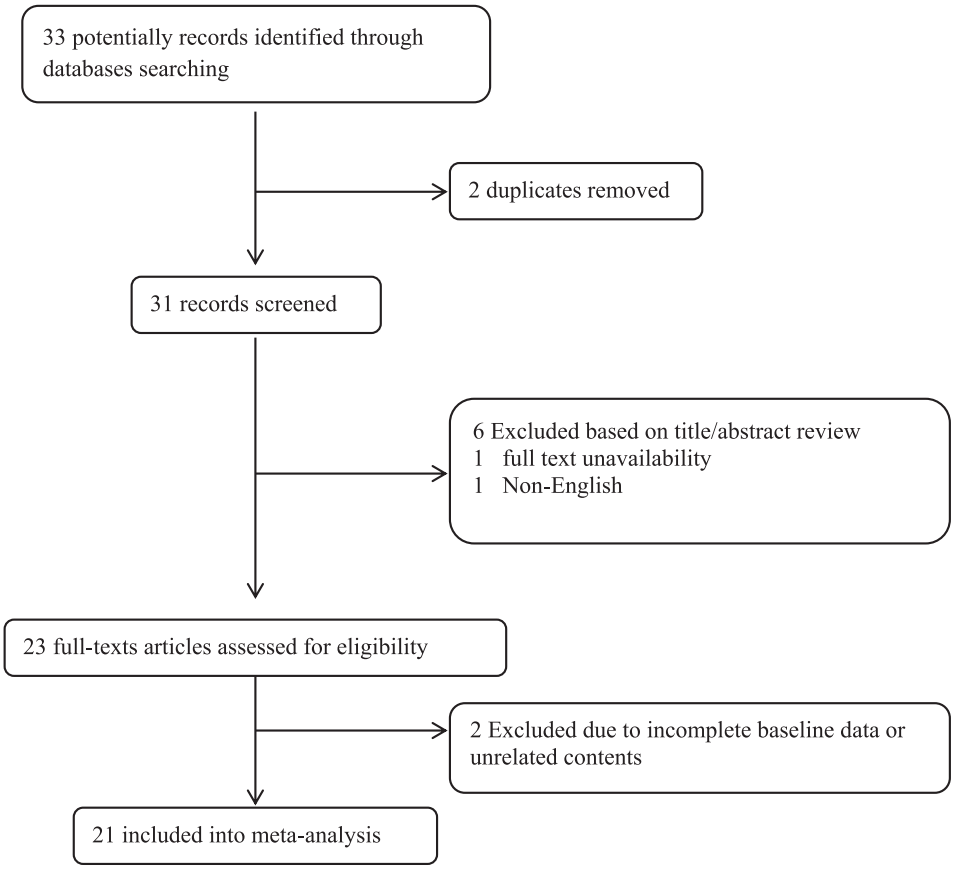

Fig. 1. The flowchart of screening the eligible studies.

Table 1
Baseline characteristics in study population.

Author	Country	Number	Mean age	Male/Female	RT-PCR (+)
Belhadjer et al (13)	Switzerland	35	10	18/17	14/35
Blondiaux et al (14)	France	4	9	1/3	0/4
Cheung et al (15)	USA	17	8	8/9	8/17
Chiotos et al (16)	USA	6	14	1/5	3/6
Dufort et al (17)	USA	99	12	53/46	50/94
Feldstein et al (18)	USA	186	8	115/71	73/186
Gaitonde et al (19)	USA	12	8	9/3	4/12
Grimaud et al (20)	France	20	10	10/10	10/20
Kaushik et al (21)	USA	33	10	20/13	11/33
Matsubara et al (22)	USA	28	11	14/14	14/28
Minocha et al (23)	USA	33	3	19/14	11/33
Pouletty et al (24)	France	16	10	8/8	11/16
Ramcharan et al (25)	UK	15	9	11/4	2/15
Riphagen et al (26)	UK	8	12	5/3	2/8
Theocharis et al (27)	UK	20	10	15/5	2/20
Toubiana et al (28)	France	21	8	9/12	8/21
Valverde et al (29)	UK	286	8	194/92	96/286
Verdoni et al (30)	Italy	10	7	7/3	2/10
Waltuch et al (31)	USA	4	9	3/1	0/3
Whittaker et al (32)	UK	58	9	25/33	15/58
Wolfler et al (33)	Italy	5	7	2/3	5/5

	Patient selection	Index test	Outcomes	Flow and timing
Chiotos et al	+	+	+	+
Waltuch et al	+	+	?	+
Wolfler et al	+	+		+
Grimaud et al	+	?		+
Toubiana et al	+	+	?	+
Whittaker et al	+	+	?	+
Blondiaux et al	+	+	+	+
Cheung et al	+	?	+	+
Ramcharan et al	+	+	+	+
Pouletty et al	+	+	+	+
Kaushik et al	+	?	+	+
Dufort et al	+	+	+	+
Feldstein et al	?	+	+	+
Riphagen et al	+	+	+	+
Verdoni et al	+	?	+	+
Belhadjer et al	+	+	+	+
Matsubara et al	?	+	+	+
Theocharis et al	+	+	+	+
Gaitonde et al	+	?	+	+
Valverde et al	+	+	+	+
Minocha et al	+	+	?	+

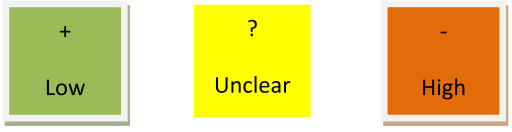

Fig. 2. Assessment of the risk of bias.

and dying from the disease [7]. Also, cardiac abnormalities among children suffering Covid-19 is infrequent finding, however it can be life-threatening and also with permanent heart defects [8]. Although the incidence of cardiac abnormalities related to Covid-19 are uncommon among children (with an overall incidence of 0.6%) [9], the occurrence of such abnormalities in the background of critical situation such as multisystem inflammatory syndrome in children (MIS-C) has been frequently reported [10]. According to the definition released by the World Health Organization (WHO), MIS-C is characterized in Children and adolescents (aged 0 to 19 years) by appearing fever (more than three days) with at least two of the following findings: 1) rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs, 2) hypotension or shock, 3) any evidences of cardiac dysfunction along with raising Troponin and NT-proBNP levels, 4) any evidence of coagulopathy, 5) acute gastrointestinal problems, 6) increasing inflammatory markers such as ESR and CRP, all in the background of Covid-19 disease [11]. As reported in the last months, cardiac defects due to MIS-C have been abundantly reported leading high morbidity among children affected by Covid-19 [12]. However, so far no consensus has been reached on such cardiac complications. We aimed to systematically assess the incidence of such cardiac abnormalities due to MIS-C in children suffering Covid-19 that in this way, it is possible to identify the various dimensions of such cardiac defects and improve the survival of the affected children.

2. Materials and methods

2.1. Study selection

The present systematic review and *meta*-analysis followed the guideline for the Preferred Reporting Items for Systematic review

Table 2
Cardiac manifestations in study population.

Author	Number	LV dysfunction (LVEF < 35)	Coronary aneurism/dilation	Abnormal ECG	Raised troponin	Raised proBNP/BNP
Chiotos et al	6	4	1	–	3	3
Waltuch et al	4	4	3	–	3	3
Wolfler et al	5	3	–	1	–	–
Grimaud et al	20	20	–	–	–	–
Toubiana et al	21	16	5	2	17	14
Whittaker et al	58	18	8	6	–	29
Blondiaux et al	4	1	–	2	4	4
Cheung et al	17	6	7	4	14	15
Ramcharan et al	15	12	14	9	15	15
Pouletty et al	16	7	3	–	11	11
Kaushik et al	33	4	6	–	–	–
Dufort et al	99	51	9	–	63	74
Feldstein et al	186	90	15	12	50	73
Riphagen et al	8	6	1	1	1	8
Verdoni et al	10	5	2	–	5	10
Belhadjer et al	35	10	–	2	1	35
Matsubara et al	28	11	4	–	–	–
Theocharis et al	20	8	3	–	–	–
Gaitonde et al	12	8	–	–	–	–
Valverde et al	286	59	76	101	20	17
Minocha et al	33	4	2	15	7	12

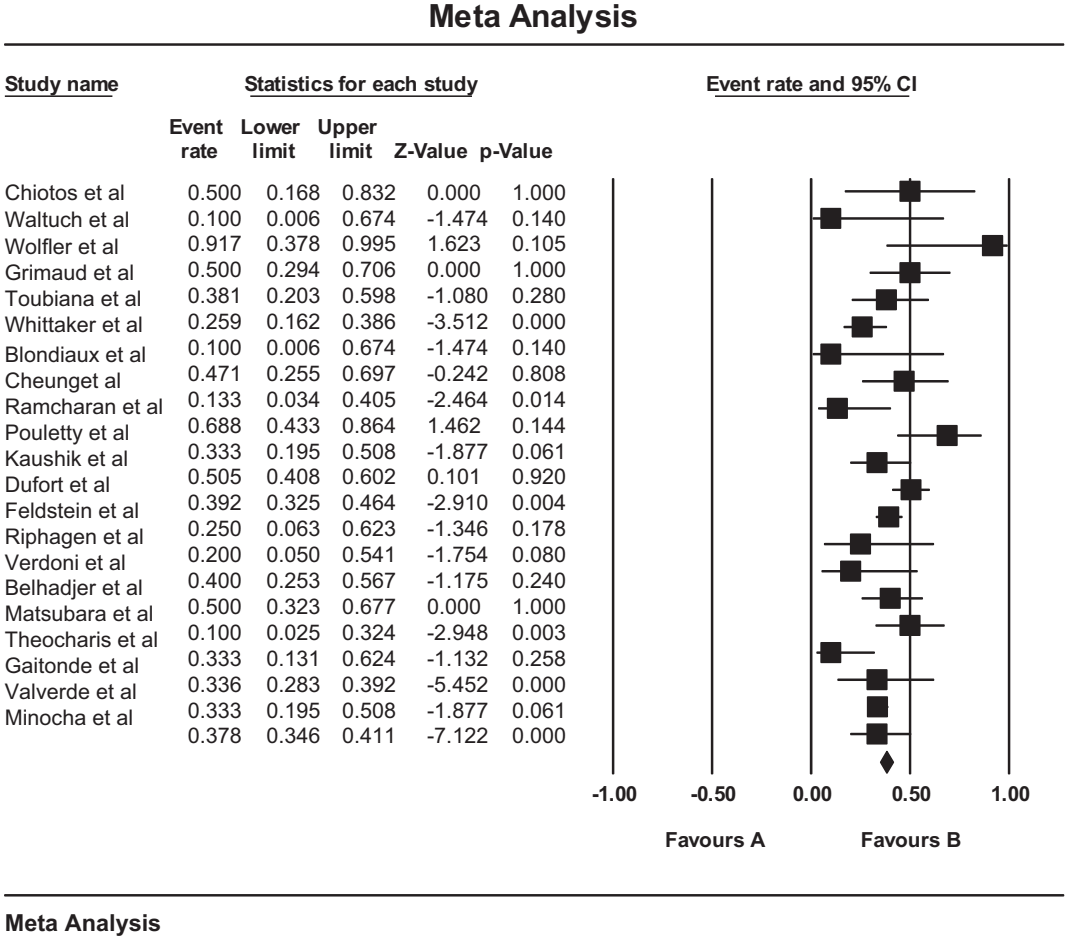

Fig. 3. The pooled prevalence of RT-PCR positivity for Covid-19 genome.

and Meta-Analysis (PRISMA). Firstly, the main study questions was suggested based on the authors purposes as "What is the prevalence of each of the cardiac abnormalities caused by MIS-C in the relation to Covid-19 among children?" In the next step, the manuscript databases including Medline, Web of knowledge, Google scholar, Scopus, and Cochrane were deeply searched by the two blinded investigators for all eligible studies based on the considered keywords including "children", "Covid-19", "multisystem inflammatory syndrome", "heart", and "cardiovascular". The inclusion criteria were considered to retrieve the studies: 1) the studies

finally assessed different aspects of cardiovascular defects related to MIS-C among children suffering Covid-19, 2) The studies were restricted to English language, 3) the studies with unclear or irreproducible results were all excluded, 4) lack of access to the manuscripts full texts was also considered as the inclusion criteria unless the abstracts had enough data for our analysis, 5) case reports and review papers were all excluded. As shown in the flow diagram of the study selection (Fig. 1), 33 articles were initially collected by database searching. After removing 2 articles due to evidences of duplication, 31 records were primarily under-screened. Based on the titles and abstracts, 8 records were excluded and the remaining 23 citations were assessed for further eligibility. Of those, 2 were also excluded due to incompleteness of the data and contents. In final, 21 articles were eligible for the final analysis [13–33] (Table 1).

2.2. Data abstraction and validity assessment

Data abstraction was independently performed by two unblinded reviewers on structure collection forms without divergences in data collection. We resolved disagreements by consensus or by involving a third person. The study quality was evaluated based on the following criteria: 1) the systematic review and *meta*-analysis based on the questions primarily described and formulated; 2) inclusion and exclusion criteria predefined in the studies as eligibility criteria; 3) searching the literature performed on a systematic and comprehensive approach; 4) to minimize the bias, the full texts of the article were dually reviewed; 5) the quality of included studies were rated independently by the reviewers for appraising internal validity; 6) studies' characteristics and findings were comprehensively listed; 7) the publication and risk of bias were listed; and 8) heterogeneity was also assessed. The risk of bias for each study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and also according to QUADAS-2 tool. Any disagreement was resolved by discussion in the whole study team (see Table 2).

2.3. Statistical analysis

Dichotomous variables are reported as proportions and percentages. The pooled prevalence for each cardiac defect was assessed and presented by the pooled prevalence and 95% confidence interval (CI) as summary statistics. Cochran's Q test was used to determine the statistical heterogeneity. This test was complemented with the I2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. Publication bias was assessed by the rank correlation test and also confirmed by the funnel plot analysis. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at p = 0.05. Statistical analysis was performed using the Comprehensive Meta Analysis (CMA) software version 3.0 (Biostat, Englewood, NJ 07,631 USA).

3. Results

To assess the prevalence of cardiac abnormalities related to MIS-C based on applied keywords, in total 21 studies finally assessed that published from different countries between February

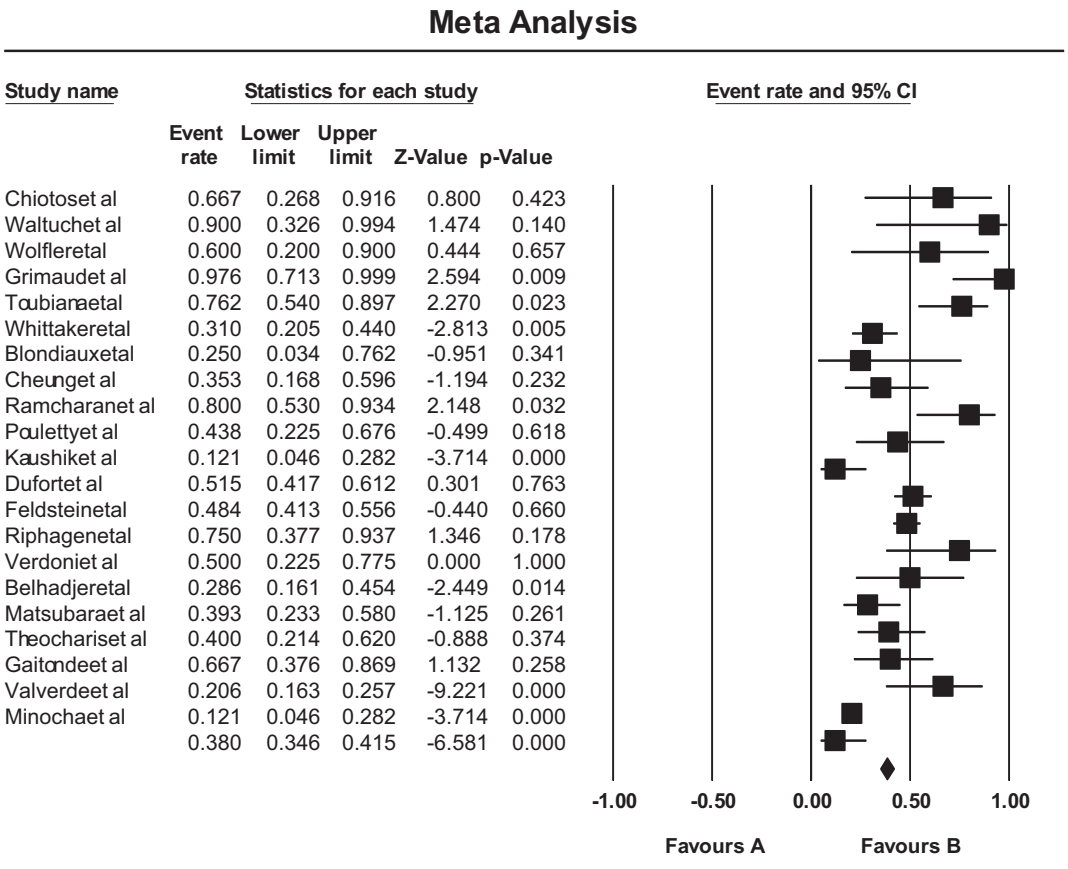

Fig. 4a. The pooled prevalence of left ventricular dysfunction.

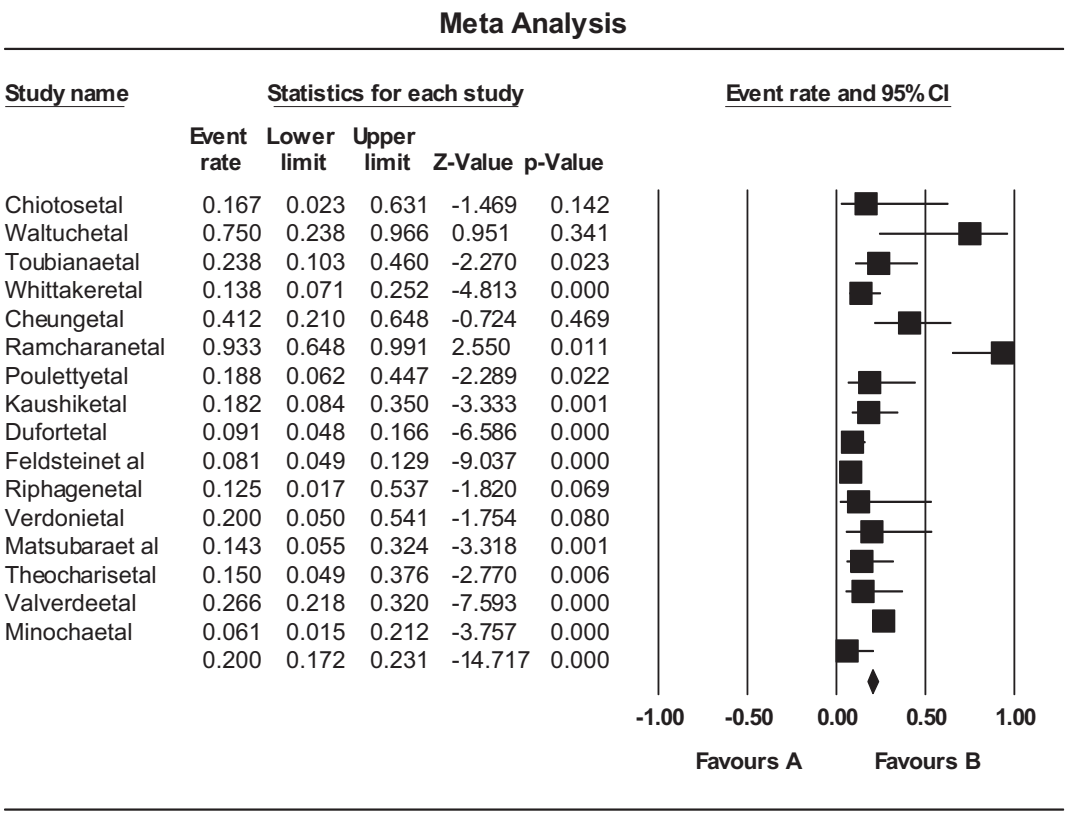

Fig. 4b. The pooled prevalence of coronary artery aneurism/dilatation.

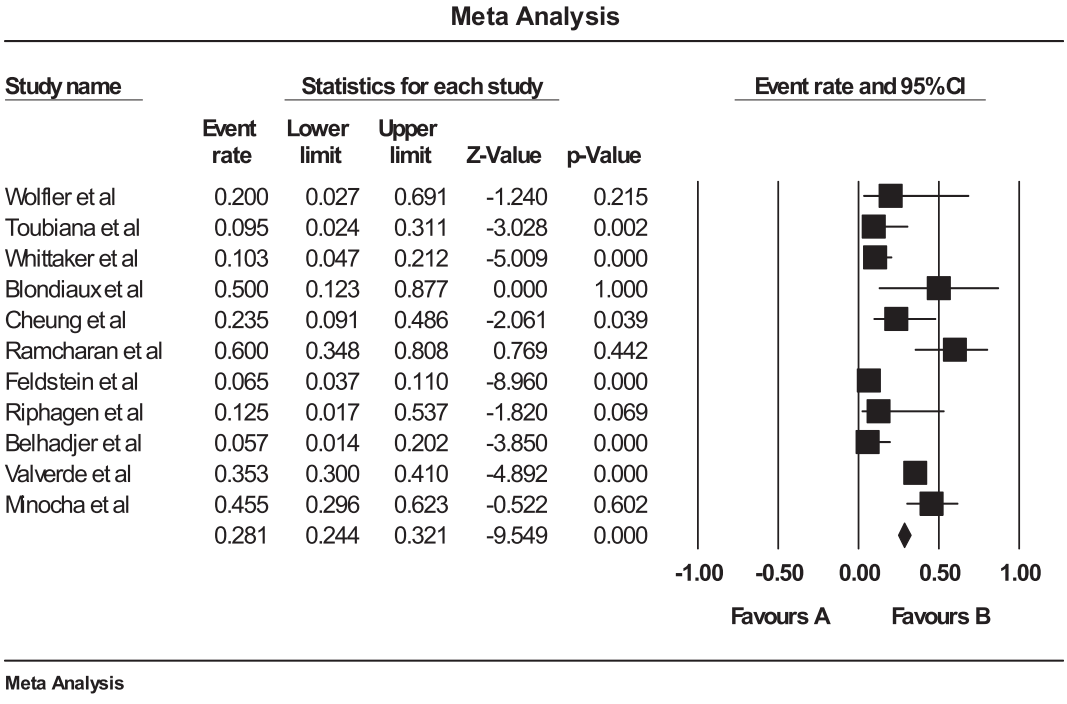

Fig. 4c. The pooled prevalence of ECG abnormalities.

and October 2020 (Table 1). According to our risk of bias assessment, all 21 studies yielded good quality and none of the citation was determined to have high risk of bias and therefore the pooled results should be persuasive (Fig. 2). In total, 916 children were assessed indicating higher rate of boys than girls. The median age of the patients on admission was 9 years ranged 3 to 14 year.

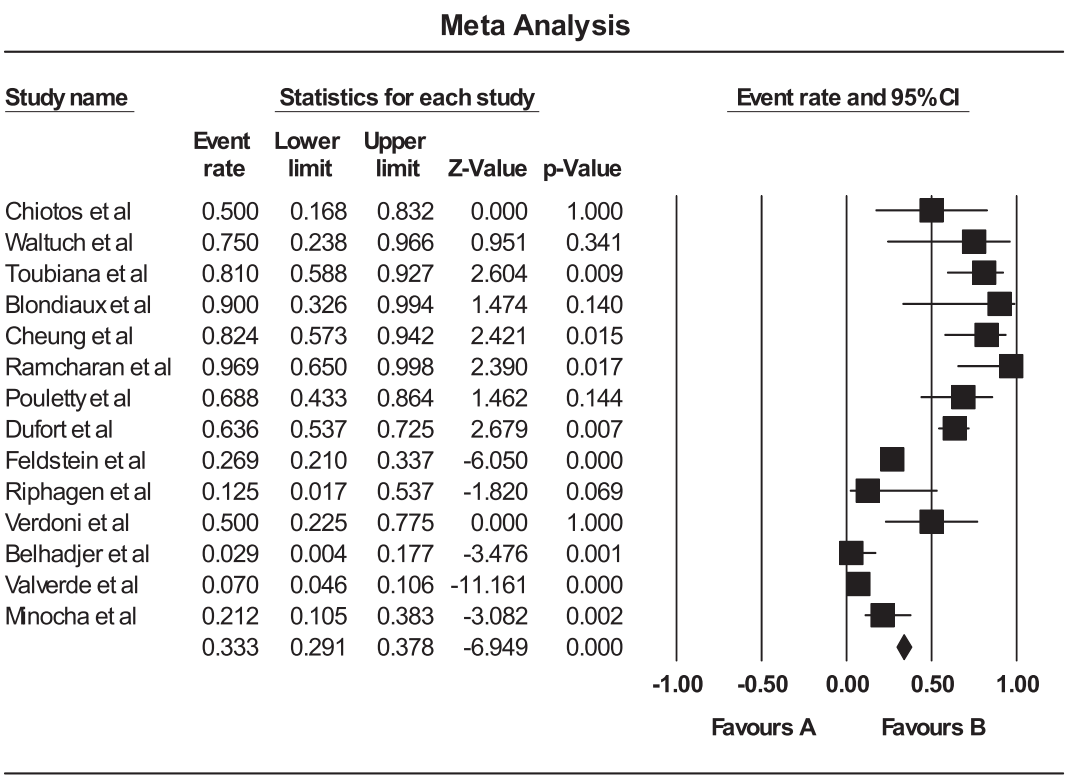

Fig. 4d. The pooled prevalence of raised serum troponin level.

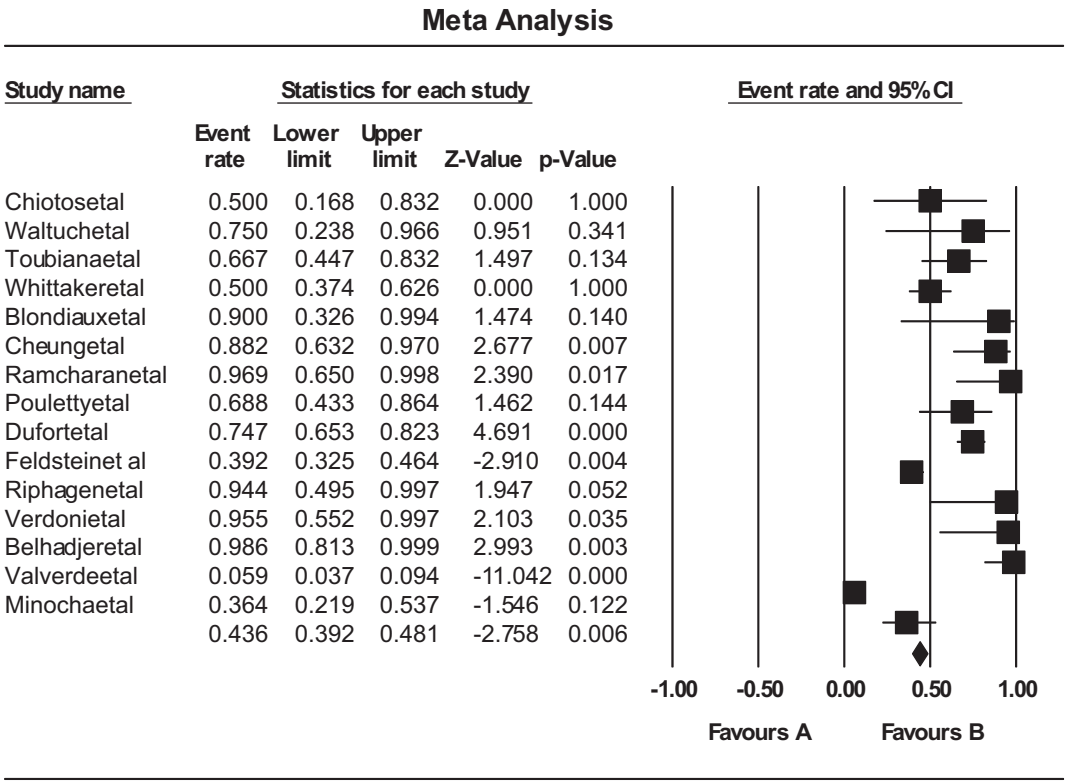

Fig. 4e. The pooled prevalence of raised serum NT-ProBNP level.

Contrary to the impression, the molecular assessment of virus using the RT-PCR (Fig. 3) led to wide positive test results with the pooled positivity of 37.7% (95%CI: 32.2% to 43.7%). Considering studies focusing different cardiac abnormalities related to MIS-C yielded a pooled prevalence of 38.0% (95%CI: 34.6% to 41.5%) for significant left ventricular dysfunction, 20.0% (95%CI: 17.2% to 23.1%) for coronary aneurism or dilatation, 28.1% (95%CI: 24.4% to 32.1%) for ECG abnormalities or cardiac arrhythmias, 33.3% (95%CI: 29.1% to 37.8%) for raised serum troponin level and 43.6% (95%CI: 39.2% to 48.1%) for raised proBNP/BNP level (Figs. 4a–e). The statistical heterogeneity was significant for all events assessment with I^2 values ranged 75.456 to 97.249 ($P < 0.001$). The authors believed that the pointed heterogeneities were sourced from the differences in the interpretation of the ECG or echocardiography by specialists and also the lack of calibration of the instruments used. There was also a significant publication bias as evidenced by either funnel plot asymmetry or Egger test for all assessments due to the publishers' desire to publish articles with significant and positive results. The main echocardiography findings in the studies evaluated were hypokinesia of the left ventricular wall and interventricular septum, left ventricular dilatation, mild to moderate pericardial effusion, mild mitral regurgitation, cardiogenic shock, myocarditis, or coronary artery dilatation/aneurism/ectasia. Regarding ECG abnormalities, the prominent findings included ST-segment elevation or depression, Junctional cardiac rhythm, atrial fibrillation, sinus bradycardia, QT interval prolongation, ventricular arrhythmias, and atrioventricular block.

4. Discussion

According to the findings of the present systematic review and *meta*-analysis, various dimensional and functional changes are expected following MIS-C due to Covid-19 in children. In this regard, both left ventricular myocardial tissue as well as coronary arteries can be affected significantly by such critical situation so that overall more than one-third of the patients may show a degree of such abnormal cardiac conditions. As analyzed finally, about 38.0% of the pointed children suffered from significant (mild to moderate) left ventricular dysfunction which accompanied with diffuse left ventricular hypokinesia along with dilatation, 20.0% from coronary arteries involvement as aneurism, dilatation or ectasia, and 28.1% from different types of ECG abnormalities as atrial or ventricular arrhythmias. Interestingly, such cardiac changes could be accompanied with the raise of both cardiac enzyme (troponin) and also cardiac function-related proteins (NT-proBNP) in 33.3% and 43.6% respectively. The evidences have been shown that mild cardiac changes in those children suffering Covid-19 [7,8], however if accompanied by MIS-C, a notable number of children affected by Covid-19 may suffered from serious cardiac complications may lead to high mortality rates. Of course, it is not yet clear whether the occurrence of such complications is related to the severity and extention of Covid-19 disease. As shown in this study, a significant proportion of patients had a negative result of tracing the genome of the virus and in fact the diagnosis was based mainly on clinical manifestations, but it has been also shown that majority of affected children had high titers of antibodies as well as elevated inflammatory biomarkers and trigger cytokines explaining a close link between the severity of Covid-19 and cardiac complications even among children. As a general guideline, children suffering MIS-C need to intensive cares due to multi-organ dysfunction and thus such caring approaches should be more emphasized in case of appearing any evidences of cardiac involvement. In this regard, continuous hemodynamic and cardiac monitoring, using cardiac inotropes, preserving arterial oxygen saturation, using intravenous immunogolebulin (IVIG) and immunomodulators should be considered in such patients [34,35].

References

[1] WHO Coronavirus Disease (COVID-19) Dashboard. The World Heart Organization, Data last updated: 2020/12/9. Available in: [https://covid19.who.int/]

[2] Francesca Mai, Rita Del Pinto, Claudio Ferri, COVID-19 and cardiovascular diseases, J. Cardiol. 76 (2020) 453–458.

[3] Bansal M. Cardiovascular disease and COVID-19.Diabetes Metab Syndr. 2020 May-Jun;14(3):247-250. doi: 10.1016/j.dsx.2020.03.013. Epub 2020 Mar 25.

[4] K.J. Clerkin, J.A. Fried, J. Raikhelkar, G. Sayer, J.M. Griffin, A. Masoumi, S.S. Jain, D. Burkhoff, D. Kumaraiah, L. Rabbani, A. Schwartz, N. Uriel, COVID-19 and Cardiovascular Disease, Circulation 141 (20) (2020 May 19) 1648–1655, https://doi.org/10.1161/CIRCULATIONAHA.120.046941, Epub 2020 Mar 21.

[5] A. Akhmerov, E. Marbán, COVID-19 and the Heart, Circ Res. 126 (10) (2020 May 8) 1443–1455, https://doi.org/10.1161/CIRCRESAHA.120.317055, Epub 2020 Apr 7.

[6] C. Chen, C. Chen, J.T. Yan, N. Zhou, J.P. Zhao, D.W. Wang, Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19, Zhonghua Xin Xue Guan Bing Za Zhi. 48 (7) (2020 Jul 24) 567–571, https://doi.org/10.3760/cma.j.cn112148-20200225-00123.

[7] J.F. Ludvigsson, Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults, Acta Paediatr. 109 (2020) 1088–1095.

[8] Giulia Sanna, Gaia Serrau, Pier Paolo Bassareo, Paola Neroni, Vassilios Fanos, Maria Antonietta Marcialis. Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. Eur J Pediatr. 2020 May 30 : 1–9.

[9] Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;e20200702

[10] Mubbasheer Ahmed,a Shailesh Advani,b,c,1 Axel Moreira,a Sarah Zoretic,d John Martinez,d Kevin Chorath,e Sebastian Acosta,a Rija Naqvi,a,b,c,d,e Finn Burmeister-Morton,d Fiona Burmeister,d Aina Tarriela,d Matthew Petershack, d Mary Evans,d Ansel Hoang,d Karthik Rajasekaran,e Sunil Ahuja,d and Alvaro Moreirad. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020 Sep; 26: 100527.

[11] Centers for Disease Control and Prevention. Emergency preparedness and response: health alert network. Published May 14, 2020. emergency.cdc.gov/han/2020/han00432.asp (accessed August 5, 2020).

[12] A.H. Rowley, Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children, Nat Rev Immunol. 20 (8) (2020 Aug) 453–454, https://doi.org/10.1038/s41577-020-0367-5.

[13] Belhadjer Z, Méot M, Bajolle F et al., 2020. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 33. https:// doi.org/10.1161/CIRCULATIONAHA.120.048360.

[14] E. Blondiaux, P. Parison, A. Redheuil, et al., Cardiac MRI of children with multisystem inflammatory syndrome (MIS-C) associated with COVID-19: case series Eléonore, Radiology 78 (2012) 1–15.

[15] E.W. Cheung, P. Zachariah, M. Gorelik, et al., Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York city, JAMA J. Am. Med. Assoc. 8–10 (2020), https://doi.org/10.1001/jama.2020.10374.

[16] K. Chiotos, H. Bassiri, E.M. Behrens, et al., Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series, J. Pediatric. Infect. Dis. Soc. (2020), https://doi.org/10.1093/jpids/piaa069.

[17] E.M. Dufort, E.H. Koumans, E.J. Chow, et al., Multisystem inflammatory syndrome in children in New York state, N Engl. J. Med. 1–12 (2020), https://doi.org/10.1056/NEJMoa2021756.

[18] L.R. Feldstein, E.B. Rose, S.M. Horwitz, et al., Multisystem inflammatory syndrome in U.S. children and adolescents, N Engl J Med (2020) 1–13, https://doi.org/10.1056/NEJMoa2021680.

[19] Mansi Gaitonde 1, Daniel Ziebell 1, Michael S Kelleman 2, David E Cox 3, Joan Lipinski 3, William L Border 1, Ritu Sachdeva 1. COVID-19-Related Multisystem Inflammatory Syndrome in Children Affects Left Ventricular Function and Global Strain Compared with Kawasaki Disease. J Am Soc Echocardiogr. 2020 Oct;33(10):1285-1287. doi: 10.1016/j.echo.2020.07.019. Epub 2020 Jul 31.

[20] M. Grimaud, J. Starck, M. Levy, et al., Acute myocarditis and multisystem inflammatory emerging disease following SARSCoV-2 infection in critically ill children, Ann Intensive Care 10 (2020) 1–5, https://doi.org/10.1186/s13613-020-00690-8.

[21] S. Kaushik, S.I. Aydin, K.R. Derespina, et al., Multisystem inflammatory syndrome in children (MIS C) associated with SARSCoV-2 infection: a multi-institutional study from New York City, J. Pediatr. 2–7 (2020), https://doi.org/10.1016/j.jpeds.2020.06.045.

[22] Daisuke Matsubara 1, Hunter L Kauffman 1, Yan Wang 1, Renzo Calderon-Anyosa 1, Sumekala Nadaraj 1, Matthew D Elias 1, Travus J White 1, Deborah L Torowicz 1, Putri Yubbu 1, Therese M Giglia 1, Alexa N Hogarty 1, Joseph W Rossano 1, Michael D Quartermain 1, Anirban Banerjee 2. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. J Am Coll Cardiol. 2020 Oct 27;76(17):1947-1961. doi: 10.1016/j.jacc.2020.08.056. Epub 2020 Sep 2.

[23] Prashant K Minocha 1, Colin K L Phoon 1, Sourabh Verma 2, Rakesh K Singh 1. Cardiac Findings in Pediatric Patients With Multisystem Inflammatory Syndrome in Children Associated With COVID-19. Clin Pediatr (Phila). 2020 Sep 25;9922820961771. doi: 10.1177/0009922820961771.

[24] M. Pouletty, C. Borocco, N. Ouldali, et al., Paediatric multisystem inflammatory syndrome temporally associated with SARSCoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort, Ann. Rheum. Dis. 999–1006 (2020), https://doi.org/10.1136/annrheumdis-2020-217960.

[25] T. Ramcharan, O. Nolan, C.Y. Lai, et al., Paediatric inflammatory multisystem syndrome: temporally associated with SARSCoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital, Pediatr. Cardiol. (2020), 2.https://doi.org/10.1007/s00246-020-02391-2.

[26] S. Riphagen, X. Gomez, C. Gonzalez-martinez, et al., Hyperinflammatory shock in children during COVID-19 pandemic, Lancet 395 (2020) 1607–1608, https://doi.org/10.1016/S0140-6736(20)31094-1.

[27] Paraskevi Theocharis 1, James Wong 1, Kuberan Pushparajah 1 2, Sujeev K Mathur 1, John M Simpson 1, Emma Pascall 1, Aoife Cleary 1, Kirsty Stewart 1, Kaitav Adhvaryu 1, Alex Savis 1, Saleha R Kabir 1, Mirasol Pernia Uy 1, Hannah Heard 1, Kelly Peacock 1, Owen Miller 1 3. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. Eur Heart J Cardiovasc Imaging. 2020 Aug 7;jeaa212. doi: 10.1093/ehjci/jeaa212. Online ahead of print.

[28] J. Toubiana, C. Poirault, A. Corsia, et al., Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study, Br. Med. J. 1–7 (2020), https://doi.org/10.1136/bmj.m2094.

[29] Israel Valverde 1, Yogen Singh 2, Joan Sanchez-de-Toledo 3, Paraskevi Theocharis 4, Ashish Chikermane 5, Sylvie Di Filippo 6, Beata Kucinska 7, Savina Mannarino 8, Amalia Tamariz-Martel 9, Federico Gutierrez-Larraya 10, Giridhar Soda 11. Acute Cardiovascular Manifestations in 286 Children with Multisystem Inflammatory Syndrome Associated with COVID-19 Infection in Europe. Circulation. 2020 Nov 9. doi: 10.1161/CIRCULATIONAHA.120.050065.

[30] L. Verdoni, A. Mazza, A. Gervasoni, et al., An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARSCoV-2 epidemic: an observational cohort study, Lancet 6736 (2020) 1–8, https://doi.org/10.1016/S0140-6736(20)31103-X.

[31] T. Waltuch, P. Gill, L.E. Zinns, R. Whitney, J. Tokarski, J.W. Tsung, J.E. Sanders, Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department, Am. J. Emerg. Med. (2020), https://doi.org/10.1016/j.ajem.2020.05.058.

[32] E. Whittaker, A. Bamford, J. Kenny, et al., Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA –, J. Am. Med. Assoc. (2020) 1–11, https://doi.org/10.1001/jama.2020.10369.

[33] A. Wolfler, S. Mannarino, V. Giacomet, et al., Acute myocardial injury: a novel clinical pattern in children with COVID-19, Lancet Child Adolesc. Heal. 4642 (2020) 1016–1017, https://doi.org/10.1016/S2352-4642(20)30168-1.

[34] American College of Rheumatology. Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARSCoV-2 and Hyperinflammation in COVID-19. Availablefrom: https://www.rheumatology.org/ Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-CHyperinflammation .pdf. Accessed August 7, 2020.

[35] A. Hassoun, E.D. Thottacherry, J. Muklewicz, Q.U. Aziz, J. Edwards, Utilizing tocilizumab for the treatment of cytokine release syndrome in COVID-19, J. Clin. Virol. 128 (2020) 104443.