Immunomodulatory Therapy for MIS-C

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abstract

CONTEXT: Studies comparing initial therapy for multisystem inflammatory syndrome in children (MIS-C) provided conflicting results.

OBJECTIVE: To compare outcomes in MIS-C patients treated with intravenous immunoglobulin (IVIG), glucocorticoids, or the combination thereof.

DATA SOURCES: Medline, Embase, CENTRAL and WOS, from January 2020 to February 2022.

STUDY SELECTION: Randomized or observational comparative studies including MIS-C patients <21 years.

DATA EXTRACTION: Two reviewers independently selected studies and obtained individual participant data. The main outcome was cardiovascular dysfunction (CD), defined as left ventricular ejection fraction < 55% or vasopressor requirement ≥ day 2 of initial therapy, analyzed with a propensity score-matched analysis.

RESULTS: Of 2635 studies identified, 3 nonrandomized cohorts were included. The meta-analysis included 958 children. IVIG plus glucocorticoids group as compared with IVIG alone had improved CD (odds ratio [OR] 0.62 [0.42–0.91]). Glucocorticoids alone group as compared with IVIG alone did not have improved CD (OR 0.57 [0.31–1.05]). Glucocorticoids alone group as compared with IVIG plus glucocorticoids did not have improved CD (OR 0.67 [0.24–1.86]). Secondary analyses found better outcomes associated with IVIG plus glucocorticoids compared with glucocorticoids alone (fever ≥ day 2, need for secondary therapies) and better outcomes associated with glucocorticoids alone compared with IVIG alone (left ventricular ejection fraction < 55% ≥ day 2).

LIMITATIONS: Nonrandomized nature of included studies.

CONCLUSIONS: In a meta-analysis of MIS-C patients, IVIG plus glucocorticoids was associated with improved CD compared with IVIG alone. Glucocorticoids alone was not associated with improved CD compared with IVIG alone or IVIG plus glucocorticoids.

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Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a postinfectious syndrome characterized by hyperinflammatory immune dysregulation with multiorgan involvement, frequently including severe cardiovascular dysfunction.[1–4] MIS-C is a leading contributor to SARS-CoV-2 related PICU admission,[5–7] as children have less morbidity and mortality with acute coronavirus disease 2019 (COVID-19) as compared with adults.[8]

Because of the acuity and severity of illness typically seen at presentation of MIS-C, identifying the most effective initial therapy for MIS-C has been a crucial issue for clinicians. The overlapping features of MIS-C with Kawasaki Disease (KD) led physicians to use therapies used in KD, primarily intravenous immunoglobulin (IVIG) and glucocorticoids as first-line therapies.[1] Randomized clinical trials have been initiated to compare these treatments, but enrollment has been somewhat hampered by the rarity of MIS-C and results are not yet available.[9]

In this context, several nonrandomized controlled studies were conducted with propensity score methodology to reduce the risk of selection bias and to balance the baseline characteristics of participants.[10,11] The results of an early study[12] suggested that IVIG plus glucocorticoids may be associated with better outcomes compared with IVIG alone, including less fever and cardiovascular dysfunction. A larger observational study using the propensity score approach also suggested benefits of IVIG plus glucocorticoids over IVIG alone,[13] whereas another large study found no difference between these initial treatments, including glucocorticoids alone.[14] Thus, WHO guidelines suggest using glucocorticoids in addition to standard care,[15] and the optimal initial therapy for MIS-C remains unclear.

Because of the nonrandomized nature of these studies, limiting the risk of selection bias is critical. Propensity score methods have been developed to address this.[10,11] To be applied in a meta-analysis, it requires individual participant-level data.[16,17] In an effort to provide clarity on this important clinical issue, we assembled the 3 consortia of the above-mentioned studies (BATS international consortium, the Overcoming COVID-19 Investigators in USA, and the French Covid-19 Pediatric Inflammation Consortium and Pandor study group, subsequently named "Pandor study") to create the "International MIS-C Treatment Collaborative." The goal of the current study was to perform a systematic review of publications related to MIS-C treatment as well as a meta-analysis of individual patient-level data to compare clinical outcomes across initial therapies for MIS-C, including IVIG alone, IVIG plus glucocorticoids or glucocorticoids alone.

METHODS

We conducted a systematic review and meta-analysis of individual participant data. The protocol of this study was registered on PROSPERO (CRD42021292162) before collecting and analyzing data, and the reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 1).[18] The systematic review aimed at identifying potential other studies fulfilling our eligibility criteria that were not included in the International MIS-C Treatment Collaborative.

Data Sources and Searches

On February 2, 2022, we systematically searched Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science for articles published from January 1, 2020 to February 1, 2022, with no language restriction. An update of this literature search was performed on January 31, 2023. We developed a search algorithm based on a combination of terms related to "MIS-C," "treatments" (intravenous immunoglobulins and/or glucocorticoids), and "child." The full search algorithm is presented in Supplemental Table 3. We completed this search by screening the reference lists of all included articles.

Search Strategy and Selection Criteria

Studies were eligible if: (1) they were designed as randomized or nonrandomized quasi-experimental or observational comparative therapeutic studies, (2) the objective was to formally compare outcomes of children treated with IVIG plus glucocorticoids, glucocorticoids alone, or IVIG alone as initial therapy, and (3) the patient population fulfilled World Health Organization (WHO),[19] Centers for Disease Control and Prevention (CDC)[20] or Royal College of Pediatrics and Child Health criteria for MIS-C[21] (details in Appendix 2).

Exclusion criteria included: (1) noncomparative studies (e.g., cases series, single-arm cohorts, or 2-arm studies with less than 10 patients per arm), (2) nonoriginal studies (e.g., review, systematic review), (3) studies with duplicate patients, (4) studies that did not compare 1 of the 3 initial therapies (IVIG plus glucocorticoids, glucocorticoids alone, or IVIG alone, and (5) in vitro studies.

Two independent reviewers (N.O. and E.V.) screened the titles and abstracts of all publications identified by the search strategy and examined the full text of any potentially eligible article. Disagreements were resolved by discussion with a third author (F.A.) to reach consensus.

Individual Participant Data Collection

Anonymized individual patient data from the 3 consortia were collected in a secure database. Collected data included baseline characteristics needed to develop the propensity score and outcomes.

Risk of Bias and Quality of Evidence Assessment

The risk of bias and quality of evidence assessment followed the previously published living WHO guidance for clinical management of MIS-C, which provided an

independent assessment of the studies included in this meta-analysis.[15] The risk of bias assessment followed the Cochrane risk-of-bias tool for nonrandomized studies of interventions (ROBINS-I),[22] which contains 7 items: confounding, selection of participants into the study, classification of the intervention, deviations from intended interventions, missing data, measurements of outcomes, and selections of the reported result. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool recommended for meta-analysis.[23,24] The certainty of evidence was rated for each outcome as "high," "medium," "low," or "very low."

Meta-analyses

The primary outcome was cardiovascular dysfunction on or after day 2 of initial therapy, defined as either a left ventricular ejection fraction (LVEF) < 55% or the use of vasoactive or inotropic amine. As previously published, this composite cardiovascular outcome was chosen because low LVEF does not always result in the use of vasopressors, and distributive shock requiring hemodynamic support does not consistently accompany low LVEF in MIS-C.[13]

The day the first immunomodulatory treatment was administered was considered day 0. Treatment combination (IVIG plus glucocorticoids) was considered initial therapy when the beginning of administration of the 2 therapies occurred within 1 calendar day. Based on this, 3 treatment groups were analyzed for the primary outcome: IVIG alone, IVIG plus glucocorticoids, and glucocorticoids alone.[12–14]

Secondary Outcomes Included:

- Hemodynamic support on or after day 2 of initial therapy, defined as the use of vasoactive or inotropic amine;
- LVEF< 55% on or after day 2 of initial therapy, through discharge;
- Ventilatory support (invasive or noninvasive) on or after day 2 of initial therapy, through discharge;
- Fever on or after day 2 of initial therapy, through discharge; and
- Second-line therapy, also known as secondary treatment, including glucocorticoids, second doses of IVIG, or biologic medications prescribed for MIS-C at least 24 hours after the initial therapy.

Finally, Subgroup Analyses Were Also Performed for:

- Patients fulfilling WHO versus CDC criteria for MIS-C;
- Patients with or without initial cardiovascular dysfunction (defined as either initial hemodynamic support or initial LVEF< 55%);
- Patients with or without initial hemodynamic support (defined as the use of vasoactive or inotropic amine);
- Patients with or without initial LVEF < 55%;
- Children < or ≥6 years of age;
- Patients with or without criteria for complete KD;
- Patients with or without lower respiratory tract symptoms.

The detailed definition of each subgroup is provided in Appendix 3. Because of sample size limitation, these subgroup analyses were only conducted for the IVIG plus glucocorticoids versus IVIG alone comparison. The age dichotomization was based on a previously published study.[14]

Statistical Analysis

The primary analysis used propensity score matching.[12–14] The propensity score was calculated with a multivariable logistic regression model, allowing to estimate for each patient the probability of receiving 1 of the initial therapies according to baseline characteristics. The baseline characteristics used to build the propensity score were: continent, age, sex, comorbidities (defined by any chronic condition), obesity, gastrointestinal symptoms, lower respiratory tract symptoms, neurologic symptoms, criteria for complete KD,[25] intensity of inflammatory response (C-reactive protein level > or ≤150 mg/L), initial PICU care, and initial hemodynamic support. All baseline characteristics were considered at admission, ie, before or on the day of initial therapy. The detailed definition of each variable is provided in Appendix 3.

Patients from each treatment group were matched by their propensity score using nearest-neighbor matching without replacement, with a minimum caliper of 0.2.[26] The ratio was 1 patient from IVIG plus glucocorticoids group matched with 1 patient receiving IVIG alone. Given the lower number of cases in the glucocorticoids alone group, the ratio was 1 patient from glucocorticoids alone group matched with 2 patients receiving IVIG alone and with 2 patients receiving IVIG plus glucocorticoids. The balance between the treatment groups for each covariate was assessed with a standardized difference less than 0.1 considered acceptable.[10] Individual participant data meta-analyses were conducted as a 1-stage approach of binary outcomes via conditional logistic regression analysis, using the matched cohorts to test the association between each treatment groups and outcomes.[16] Findings were expressed as odds ratios (ORs), and 95% confidence intervals (CIs). The analysis also adjusted for continent and for heterogeneity between studies by using random-effects modeling.[27] As a measure of between study heterogeneity, the between study variance was provided for each outcome.[28,29]

Based on previous publications,[12–14] a low proportion of missing data were expected. Thus, a complete-case analysis was conducted.

A Range of Sensitivity Analyses Were Conducted:

- First, the data were analyzed using inverse probability of treatment weighting (IPTW), which is an alternative

approach to propensity score matching to account for indication bias in nonrandomized design.[10,11] Unlike propensity score matching, this strategy has the advantage of including all patients in the analysis[11];
- Second, a propensity score-matched analysis was performed with fixed effect for continent and study;
- Third, propensity score-matched analysis was performed with a minimum caliper of 0.1, to explore potential remaining unbalance between groups;
- Fourth, a propensity score-matched analysis was conducted with within-study matching to account for potential heterogeneity between studies. Indeed, a recent study compared within and across-study matching for individual participant data meta-analysis and found that across matching reduced the risk of bias if the prevalence of treatment was similar across studies.[28] Another similar study suggested that across-study matching may improve covariate balance.[30] In our meta-analysis, the prevalence of IVIG plus glucocorticoids was similar across studies, ranging from 52% to 69% of cases. This led us to choose matching across studies for the main analysis. However, as within study matching may offer other advantages,[28] and to explore the influence of this approach on the results, a sensitivity analysis using within study matching was also conducted;
- Fifth, a propensity score–matched analysis was conducted with double adjustment on likely confounding variables: initial hemodynamic support and initial LVEF $<$ 55%.[12] This strategy has been proposed to remove residual confounding after propensity score matching for the main potential confounders[31];
- Sixth, an IPTW analysis was conducted with double adjustment on initial hemodynamic support and initial LVEF $<$ 55%[31];
- Seventh, a propensity score–matched analysis was conducted with initial left ventricular dysfunction considered on day 0 or day 1 included in the propensity score, as some patients only had an initial echocardiography on day 1;
- Eighth, a propensity score-matched analysis was conducted with fever duration before first-line therapy as an additional baseline variable to account for potential differences between groups in the delay between disease onset and initial treatments[12];
- Ninth, a logistic multivariable regression analysis adjusted on the variables included in the propensity score was conducted;
- Tenth, for comparisons of glucocorticoids alone versus IVIG alone and glucocorticoids alone versus IVIG plus glucocorticoids, a propensity score-matched analysis using a 1:1 matching was also conducted.

All statistical tests were 2 sided, with $P < .05$ considered statistically significant. Statistical analyses were conducted using using R v4.1.1 (http://www.R-project.org/).

RESULTS

Study Selection

Among the 2635 studies retrieved from Medline, Embase, CENTRAL and Web of Science, 918 duplicates were removed, and 1717 studies were screened by title and abstract. Among them, 76 were potentially eligible. After full text examination, 3 studies were finally included (see detailed PRISMA diagram Fig 1A). The update of the literature search on January 31, 2023 retrieved 628 additional studies, among which a single center retrospective cohort met our inclusion criteria,[32] but could not be included in our individual participant data meta-analysis (individual data not available).

These 3 studies were nonrandomized cohorts. Thus, despite the use of propensity score analysis in all studies, the risk of bias for confounding using the ROBINS-I tool was classified as serious for all included studies. As a result, the level of certainty was very low for all GRADE outcomes (Appendix 4).

Baseline Characteristics

Baseline characteristics of the 958 included children are detailed in Table 1. The median age was 8.1 years, interquartile range (4.2–11.7), sex ratio was 0.7 (female to male), without major differences across studies. Incidence of initial PICU care was 34% (161 of 468) in the BATS study, 45% (158 of 349) in the Overcoming COVID-19 study, and 68% (72 of 106) in Pandor study. Rate of initial LVEF $<$ 55% followed the same trend (23% (61 of 267) in BATS study, 30% (89 of 295) in Overcoming COVID-19 study, and 47% (50 of 106) in Pandor study (Table 1).

The rate of cardiovascular dysfunction on or after day 2 was quite high in children who already had initial cardiovascular dysfunction compared with children without initial cardiovascular dysfunction (46%, 149 of 327 versus 9%, 34 of 378, respectively). Similar observations were seen for hemodynamic support on or after day 2, LVEF $<$ 55% on or after day 2, and ventilatory support on or after day 2 (Supplemental Table 4).

Among the 958 included children with MIS-C, 482 were in the IVIG alone group, 387 in the IVIG plus glucocorticoids group, and 89 in the glucocorticoids alone group (Fig 1B, Supplemental Table 5). No included children had received COVID-19 vaccines because of the timing of the study enrollment period. No child received remdesevir or other antiviral therapy.

Propensity Score-matched Analysis: IVIG Plus Glucocorticoids Versus IVIG Alone

For the main analysis comparing IVIG plus glucocorticoids versus IVIG alone, 311 children were matched in each group. After matching, the balance between the

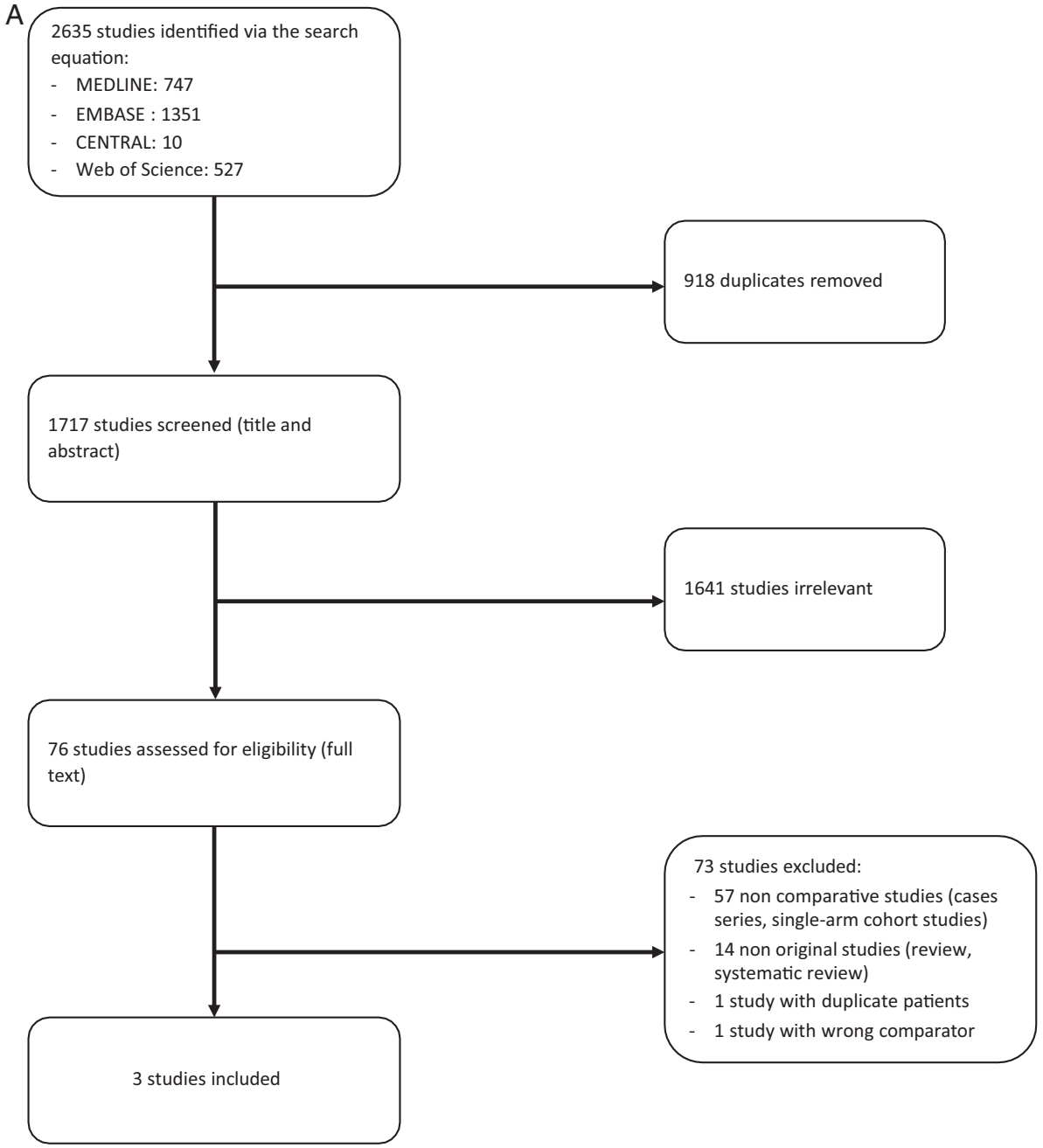

FIGURE 1

Flowchart. (A) PRISMA flow diagram. (B) Flow chart of MIS-C cases. BATS study: among the 614 children included in the original article, 503 received either IVIG plus glucocorticoids, glucocorticoids alone, or IVIG alone as initial therapy in the reporting hospital, and were included in this meta-analysis.[14] Overcoming COVID-19 study: among the 518 children included in the original article, 349 received either IVIG plus glucocorticoids, or IVIG alone as initial therapy, and were included in this meta-analysis.[13] Of note, 40 children received glucocorticoids alone as initial therapy. They were more likely to be PCR positive, have underlying conditions and requirement for mechanical ventilation, raising the possibility of severe acute COVID-19. Thus, this group was not included in this meta-analysis. Pandor study: among the 111 children included in the original article, 106 received either IVIG plus glucocorticoids, glucocorticoids alone, or IVIG alone as initial therapy, and were included in this meta-analysis.[12] CENTRAL, Cochrane Central Register of Controlled Trials; IVIG, intravenous immunoglobulins; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;[18] MIS-C, multisystem inflammatory syndrome in children.

treatment groups for baseline characteristics was satisfactory (Supplemental Fig 3, A and B). The primary outcome (cardiovascular dysfunction on or after day 2) occurred in 58 of 311 (19%) matched children from IVIG plus glucocorticoids group versus 85 of 311 (27%) in the matched IVIG alone group. Patients treated with IVIG plus glucocorticoids had significantly less cardiovascular dysfunction on or after day 2 as compared with those

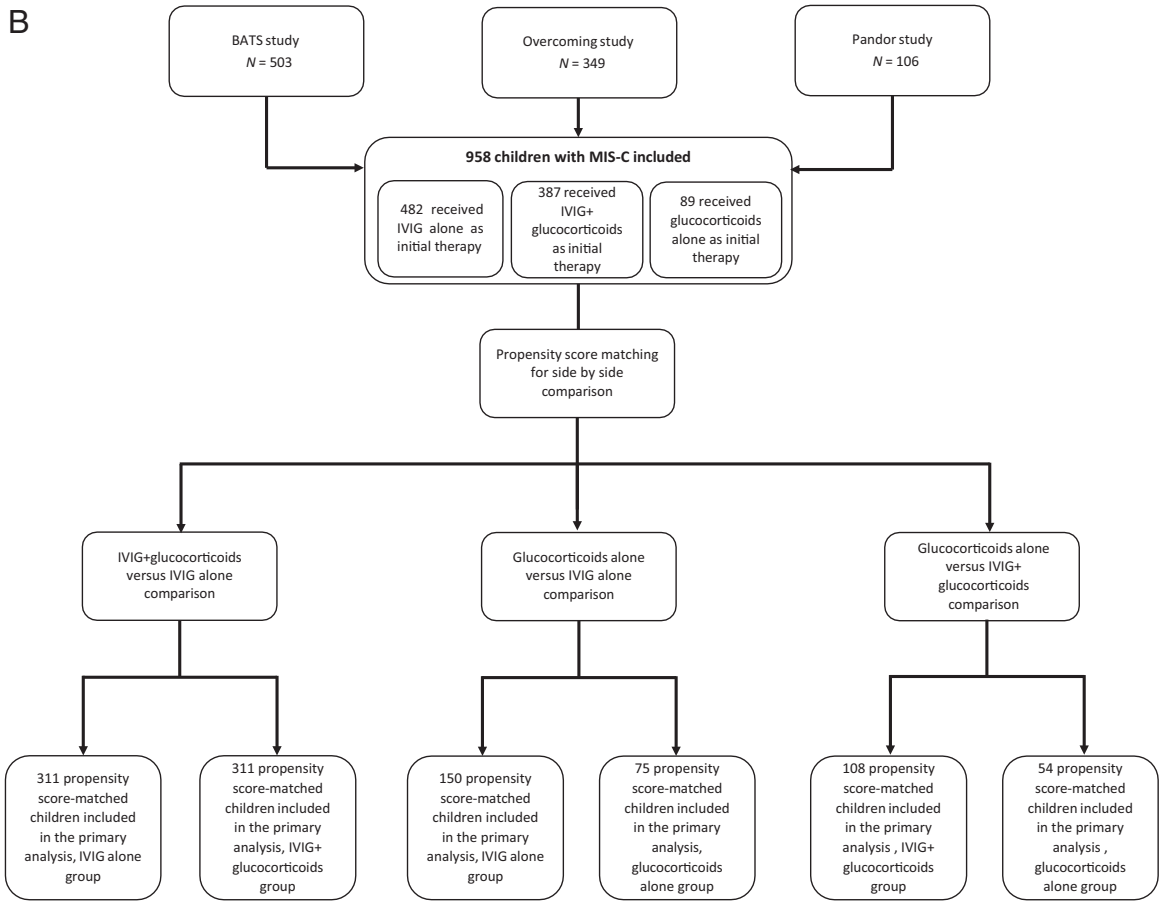

FIGURE 1
Continued

treated IVIG alone as initial therapy (OR = 0.62 [0.42–0.91], $P = .014$).

All secondary outcomes favored the IVIG plus glucocorticoids group, except for ventilatory support on or after day 2 (Fig 2A, Supplemental Table 6A). Similarly, all sensitivity analyses showed improved outcomes for children treated with IVIG plus glucocorticoids compared with IVIG alone, including IPTW and within-study propensity score-matched analysis (Supplemental Table 7A). Subgroup analyses also favored IVIG plus glucocorticoids group, except for those children with initial lower respiratory tract symptoms (OR = 0.77 [0.46–1.30], $P = .33$, Table 2) or full criteria for KD (OR = 0.59 [0.19–1.83], $P = .36$).

Propensity Score-matched Analysis: Glucocorticoids Alone Versus IVIG Alone

For the main analysis, 75 children from the glucocorticoids alone group, who all came from the BATS study, were matched to 150 children from IVIG alone group. The balance between the matched treatment groups for baseline characteristics was satisfactory (Supplemental Fig 3, C and D). The primary outcome of cardiovascular dysfunction on or after day 2 occurred in 10 of 75 (13%) matched children from the glucocorticoids alone group and in 33 of 150 (22%) in the IVIG alone group, with no significant difference between the groups (OR 0.57 [0.31–1.05], $P = .07$, reference: IVIG alone group).

All secondary outcomes analyses showed no significant association between treatment with glucocorticoids alone versus IVIG alone and outcome, except for LVEF < 55% on or after day 2 (OR 0.13 [0.03–0.59], $P = .008$, Fig 2B, Supplemental Table 6B). Sensitivity analyses provided similar nonsignificant results, with the exception of a propensity score-matched analysis that included fever duration before first-line therapy which favored glucocorticoids alone (OR 0.53 [0.28–0.99], $P = .046$, reference: IVIG alone group, Supplemental Table 7B).

Propensity Score-matched Analysis: Glucocorticoids Alone Versus IVIG Plus Glucocorticoids

For the main analysis, 54 children from the glucocorticoids alone group were matched to 108 children from IVIG plus glucocorticoids group. The balance between the matched

TABLE 1 General Characteristics of the Population at Baseline

	BATS(*N* = 503)	Overcoming COVID-19(*N* = 349)	Pandor(*N* = 106)	Total (*N* = 958)[a]
Female sex	192 (38)	145 (42)	56 (52)	393 (41)
Median age, y	8.2 (4.1–11.5)	7.8 (3.9–11.9)	8.6 (4.7–12.2)	8.1 (4.2–11.7)
Continent				
Africa	2 (0)	0 (0)	0 (0)	2 (0)
Americas	148 (29)	349 (100)	0 (0)	497 (52)
Asia	14 (3)	0 (0)	0 (0)	14 (1)
Europe	339 (67)	0 (0)	106 (100)	445 (46)
Comorbidities[d]	16 (3)	51 (15)	23 (22)	90 (9)
Obesity	77 (15)	61 (17)	6 (6)	144 (15)
Year of diagnosis				
2020	434 (68)	349 (100)	106 (100)	889 (93)
2021	69 (32)	0 (0)	0 (0)	69 (7)
Ethnicity (NA = 65)				
Afro-Caribbean or Black	59 (12)	122 (40)	68 (72)	249 (28)
Asian	40 (8)	10 (3)	5 (5)	55 (6)
Hispanic	98 (20)	116 (38)	4 (4)	218 (24)
White	264 (53)	41 (14)	20 (21)	325 (36)
Other	33 (6)	13 (4)	0 (0)	46 (5)
Clinical features				
Fever duration before therapy (days) (NA = 39)	5 (4–7)	5 (4–6)	6 (5–6)	5 (4–6)
Gastrointestinal symptoms (NA = 27)	403 (80)	322 (92)	99 (93)	824 (89)
Respiratory symptoms	169 (34)	216 (62)	27 (25)	412 (43)
Neurologic symptoms	109 (22)	39 (11)	53 (50)	201 (21)
Criteria for complete Kawasaki syndrome	110 (22)	30 (9)	27 (25)	167 (17)
CRP level, mg/L	154 (94–242)	150 (76–217)	182 (115–261)	154 (90–242)
Initial LVEF < 55% (NA = 290)	61 (23)	89 (30)	50 (47)	200 (30)
Initial LVEF < 55% including day 1[c] (NA = 166)	86 (24)	95 (30)	50 (47)	231 (29)
Initial hemodynamic support (NA = 22)	115 (23)	62 (19)	43 (41)	220 (24)
Initial cardiovascular dysfunction[b] (NA = 246)	143 (47)	130 (43)	58 (55)	331 (46)
Initial cardiovascular dysfunction including day 1[b,c] (NA = 150)	159 (41)	135 (42)	58 (55)	352 (44)
Initial coronary dilatation (NA = 282)	26 (8)	26 (12)	6 (6)	58 (9)
Initial ventilatory support (NA = 7)[e]	59 (12)	20 (6)	27 (25)	106 (11)
Initial PICU admission (NA = 35)	161 (34)	158 (45)	72 (68)	391 (42)

Quantitative data are presented as median (interquartile range) and categorical data as number (%). NA, not available. Countries for which patients were recruited are detailed in Appendix 5.

[a] All characteristics are at baseline, i.e., before or on the day of initial therapy.

[b] Cardiovascular dysfunction defined as either hemodynamic support or LVEF < 55%.

[c] With data collected on day 1 considered as baseline.

[d] Comorbidities without obesity.

[e] Invasive or noninvasive ventilatory support.

treatment groups for baseline characteristics was satisfactory (Supplemental Fig 3, E and F). The primary outcome of cardiovascular dysfunction on or after day 2 occurred in 8 of 54 (15%) children in the glucocorticoids alone group versus 23 of 108 (21%) in the IVIG plus glucocorticoids group, with no statistically significant difference between groups (OR 0.67 [0.24–1.86], $P = .43$, reference: IVIG plus glucocorticoids group).

In the secondary outcome analyses, the glucocorticoids alone group was associated with a higher rate of second line therapy (OR 6.95 [3.73–12.95], $P < .0001$) and persistent fever on or after day 2 (OR 2.16 [1.18–3.93], $P = .012$, Fig 2C, Supplemental Table 6C). All sensitivity analyses also found no significant association between treatment and the primary outcome (Supplemental Table 7C).

DISCUSSION

In a meta-analysis of patient-level data from nearly 1000 participants enrolled in 3 observational studies across 5 continents, we found that initial treatment of MIS-C with IVIG plus glucocorticoids was associated with improved cardiovascular dysfunction when compared with IVIG alone. These findings were consistent across sensitivity analyses, secondary outcomes, and subgroups analyses.

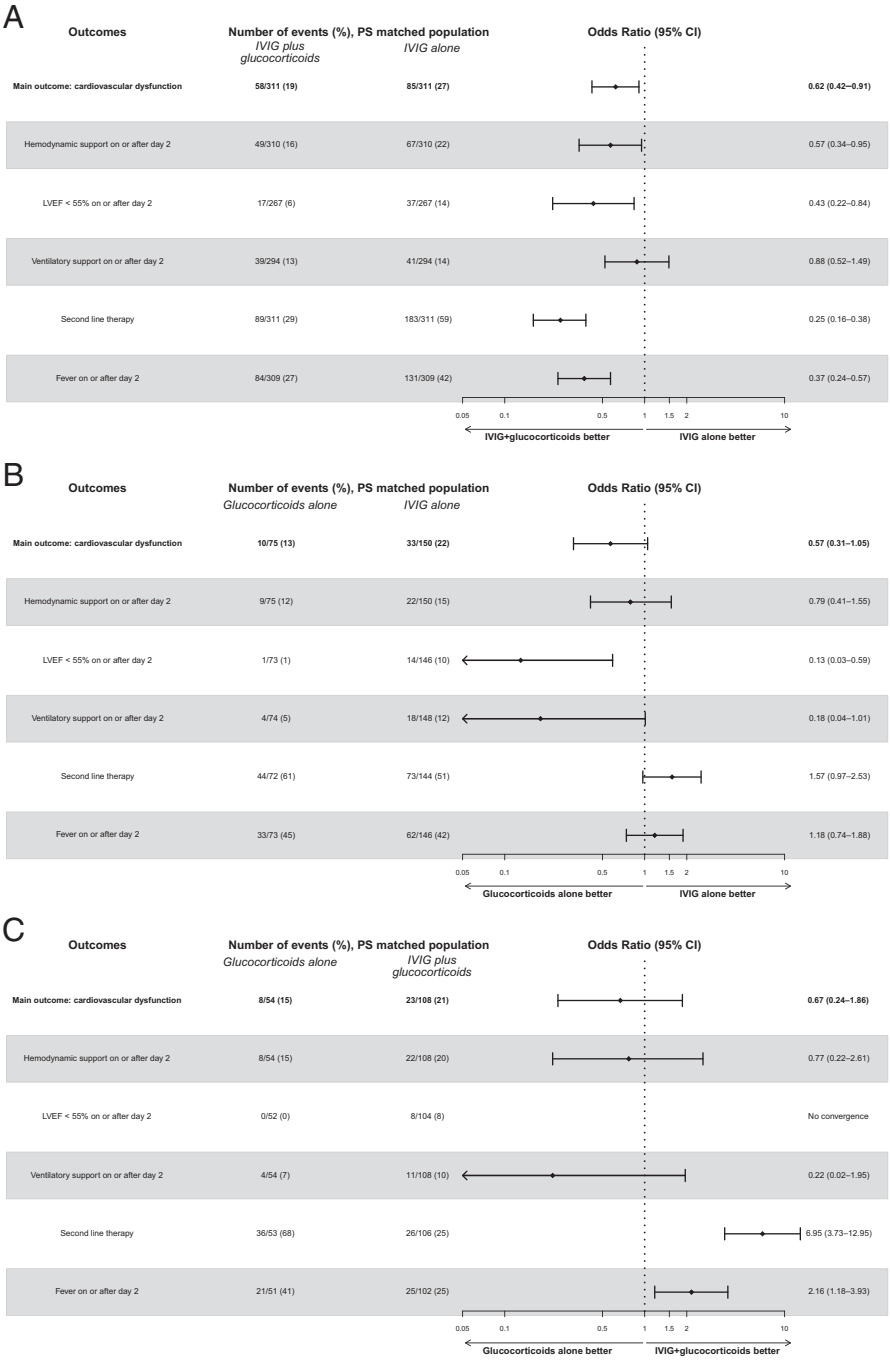

FIGURE 2

Primary and secondary outcome analyses. (A) IVIG plus glucocorticoids versus IVIG alone.* (B) Glucocorticoids alone versus IVIG alone.* (C) Glucocorticoids alone versus IVIG plus glucocorticoids.* The ratio was 1:1 for IVIG + glucocorticoids versus IVIG alone comparison, and 1:2 for glucocorticoids alone versus IVIG alone and glucocorticoids alone versus IVIG + glucocorticoids comparisons. A random effect on study was not included for glucocorticoids alone versus IVIG alone and glucocorticoids alone versus IVIG + glucocorticoids comparisons because only BATS study contributed to the glucocorticoids alone group.* Analysis based on a propensity score matching using nearest neighbor matching, based on complete cases, without replacement, with a minimum caliper of 0.2, with random effect on continent and study.

By contrast, initial treatment with glucocorticoids alone was not associated with improved cardiovascular dysfunction, compared with IVIG alone or glucocorticoids plus IVIG.

The findings regarding glucocorticoids plus IVIG versus IVIG alone diverged in the 3 original studies, as the BATS study found no significant difference in outcomes,[14] whereas Pandor and Overcoming COVID-19 studies showed IVIG plus

TABLE 2 Subgroup Analysis Showing the Association Between Initial Therapy and Treatment Failure, IVIG Plus Glucocorticoids Versus IVIG Alone

	After Propensity Score Matching[a]				
	IVIG Plus Glucocorticoids, *n/N* (%)	IVIG Alone, *n/N* (%)	OR (95% CI) (reference: IVIG alone)	*P*	Between Study Variance
Cases fulfilling MIS-C WHO definition	55/287 (19)	75/287 (26)	0.48 (0.29–0.80)	.005	0.00
Cases fulfilling MIS-C CDC definition	54/295 (18)	80/295 (27)	0.42 (0.26–0.68)	.0005	0.00
Initial cardiovascular dysfunction	45/114 (39)	53/114 (46)	0.59 (0.33–1.06)	.079	0.001
No initial cardiovascular dysfunction	5/121 (4)	17/121 (14)	0.27 (0.09–0.79)	.017	0.412
Initial hemodynamic support	28/63 (44)	35/63 (56)	0.31 (0.12–0.77)	.012	0.552
No initial hemodynamic support	23/227 (10)	35/227 (15)	0.52 (0.28–1.00)	.051	0.549
Initial LVEF $<$ 55%	24/80 (30)	35/80 (44)	0.55 (0.28–1.08)	.084	0.00
No initial LVEF $<$ 55%	17/172 (10)	28/172 (16)	0.52 (0.26–1.05)	.068	0.00
Children $<$ 6 y of age	8/94 (9)	17/94 (18)	0.31 (0.11–0.88)	.028	0.077
Children $\geq$ 6 y of age	45/208 (22)	66/208 (32)	0.55 (0.34–0.90)	.018	0.035
Met criteria for complete Kawasaki disease	9/48 (19)	11/48 (23)	0.59 (0.19–1.83)	.358	0.00
No criteria for complete Kawasaki disease	47/254 (19)	66/254 (26)	0.54 (0.31–0.93)	.028	0.00
Initial lower respiratory tract symptoms	40/127 (31)	48/127 (38)	0.77 (0.46–1.30)	.326	0.055
No initial lower respiratory tract symptoms	8/166 (5)	24/166 (14)	0.24 (0.09–0.64)	.004	0.991

All subgroup analysis considered treatment failure as cardiovascular dysfunction on or after day 2 after the initial therapy, defined as either a LVEF less than 55% or the use of vasoactive or inotropic amine.

[a] Analysis based on a propensity score matching using 1:1 nearest neighbor matching, based on complete cases, without replacement, with a minimum caliper of 0.2, with random-effect on continent and study (BATS, Overcoming COVID-19 and Pandor).

glucocorticoids to be associated with superior outcomes.[12,13] Because these 3 studies were similar in their statistical approach to reduce confounding by indication,[12–14] the statistical approach used seems unlikely to explain divergent findings. However, the initial severity of the illness varied substantially across studies.[33,34] The Pandor and Overcoming COVID-19 studies enrolled more children with initial cardiovascular dysfunction requiring PICU admission,[33,34] and these patients were as at higher risk of persistent organ dysfunction on or after day 2 than those without in our analysis. Based on this, 2 hypotheses could be offered: (1) the benefit of combination therapy could be restricted to the most severely ill children, and (2) the benefit of combination therapy could be present both in severe and mild disease, but inclusion of milder MIS-C may reduce the power to detect differences as these outcomes are less frequent. Our subgroup analyses found that the benefit of the combination therapy compared with IVIG alone was substantial both in children with or without initial cardiovascular dysfunction, suggesting that the benefit of combination therapy may not vary according to initial severity. However, a recent study addressing this question suggested that the most important differences between BATS and Overcoming COVID-19 studies was initial cardiac involvement, PICU care, and vasopressors use.[35] Taken together, these findings suggest that inclusion of children with milder disease in the BATS study may have reduced the power to detect significant differences in populations where outcomes are rare and may have driven the divergent findings of these 3 original studies.[35] It may also indicate that for some children with mild initial illness, a monotherapy with glucocorticoids may be appropriate.

A third source of heterogeneity may be the different primary outcomes selected. Indeed, the Pandor study

used persistent fever as the primary outcome, with organ dysfunction being a secondary outcome.[12] Overcoming COVID-19 studied a primary outcome of cardiovascular dysfunction, as defined in this meta-analysis,[13] whereas the BATS study used a composite outcome (hemodynamic and/or ventilatory support, or death).[14] Of note, in this meta-analysis, ventilatory support was the only secondary outcome without significant difference between IVIG plus glucocorticoids and IVIG alone groups. This should be put in perspective with accumulated evidence suggesting that severe pulmonary involvement may not be a key feature of MIS-C and is not part of the WHO or the new CDC definitions.[19,36] Cardiovascular dysfunction may represent a more specific outcome and may be preferred in future therapeutic studies.[13] A recently published single center study included 68 children treated with glucocorticoid monotherapy and compared them to children treated with IVIG plus glucocorticoids.[32] The primary outcome in that study was failure of initial therapy as evidenced by fever, worsening or lack of improvement of laboratory, cardiac, or clinical factors. They found no significant differences across treatment groups, but comparison with our findings is limited as this study did not compare IVIG alone versus IVIG plus glucocorticoids, and the composite outcome differed from ours.[32] This underlines the need for harmonizing primary outcomes across therapeutic studies to allow comparisons and meta-analyses.

Strengths and Limitations

The main strengths of our meta-analysis include the large number of patients and the individual participant data analysis. This offered several advantages.[29] First, it allowed applying the propensity score method. Indeed, as all included studies were not randomized trials, limiting the risk of bias was critical. The baseline variables used to calculate the propensity score varied across the original studies and outcomes analyzed also differed. Thus, using individual participant data were the only way to calculate a homogeneous propensity score for all included children, allowing adequate balance between groups for baseline covariates and to harmonize outcomes.[29] Second, it allowed conducting sensitivity analyses not present in original studies, reinforcing the robustness of our findings.[29] It also allowed conducting subgroup analyses, which were not possible in original studies because of sample size limitations.

Several limitations were present. First, because of the nonrandomization, the certainty was very low for all GRADE outcomes. Despite the propensity score approach achieving adequate balance for baseline covariates, we can't exclude remaining confounding by indication because of unmeasured covariates. Second, as MIS-C diagnosis relies on clinical criteria, misdiagnosis can't be excluded. Additionally, echocardiographic findings as a clinical criterion were not independently reviewed in all cohorts once sent to the coordinating centers. Subgroup analyses by the degree of initial cardiac dysfunction may require future studies. Third, as most children were enrolled in the respective studies in 2020, MIS-C triggered by Δ and *o* variants was not included. Fourth, potentially evolving treatment norms may have influenced outcomes. However, as most MIS-C cases included in this meta-analysis occurred early in the pandemic, this hypothesis seems unlikely. Fifth, the number of children treated with glucocorticoids alone as initial therapy was low, which may have reduced the power to detect differences for this group and may have increased the risk of type 2 error. As the primary outcome analysis for glucocorticoids alone versus IVIG alone trended toward significance, differences may emerge with increasing the number of participants in future analyses. Sixth, as the pathophysiology of MIS-C remains unclear, the biology underlying the benefit of combination therapy versus IVIG alone requires further investigation. Seventh, the systematic review considered articles published up to February 1, 2022. An update of the literature on January 31, 2023 identified the above-mentioned single center retrospective cohort meeting our inclusion criteria that was not included in our individual participant data meta-analysis.[32] Eighth, different healthcare resources or other treatments depending on WHO region may have influenced outcomes. However, children that received cytokine blockers as initial therapy were not included. No included patient received antiviral therapy. No included children received a COVID-19 vaccine.

Policy Implications

While awaiting results from randomized trials, this meta-analysis offers further support for initial treatment with IVIG plus glucocorticoids as compared with IVIG alone for children who meet criteria for MIS-C, especially for severely ill patients. As the primary outcome analysis found no significant difference between treatment with glucocorticoids alone versus IVIG alone or versus IVIG plus glucocorticoids, monotherapy with glucocorticoids may be considered, especially in settings of limited IVIG availability. However, caution should be taken when using this initial treatment, as exploratory secondary outcome analysis suggested better outcomes for combination therapy compared with glucocorticoids alone.

CONCLUSIONS

In a meta-analysis of nonrandomized trials of MIS-C treatments, IVIG plus glucocorticoids was associated with improved cardiovascular dysfunction compared with IVIG alone. In contrast, glucocorticoids alone were not significantly associated with improved cardiovascular dysfunction compared with immunoglobulins alone or compared with immunoglobulins plus glucocorticoids. Secondary outcome analyses, that should be considered exploratory, suggested better outcomes

associated with glucocorticoids alone compared with IVIG alone and better outcomes associated with glucocorticoids plus IVIG compared with glucocorticoids alone.

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ABBREVIATIONS

CD: cardiovascular dysfunction
CI: confidence intervals
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IPTW: inverse probability of treatment weighting
IVIG: intravenous immunoglobulin
LVEF: left ventricular ejection fraction
MIS-C: multisystem inflammatory syndrome in children
OR: odds ratio

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A complete list of the BATS consortium, the Overcoming COVID-19 Investigators, and the French Covid-19 Pediatric Inflammation Consortium and Pandor study group is provided in the Appendices.

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