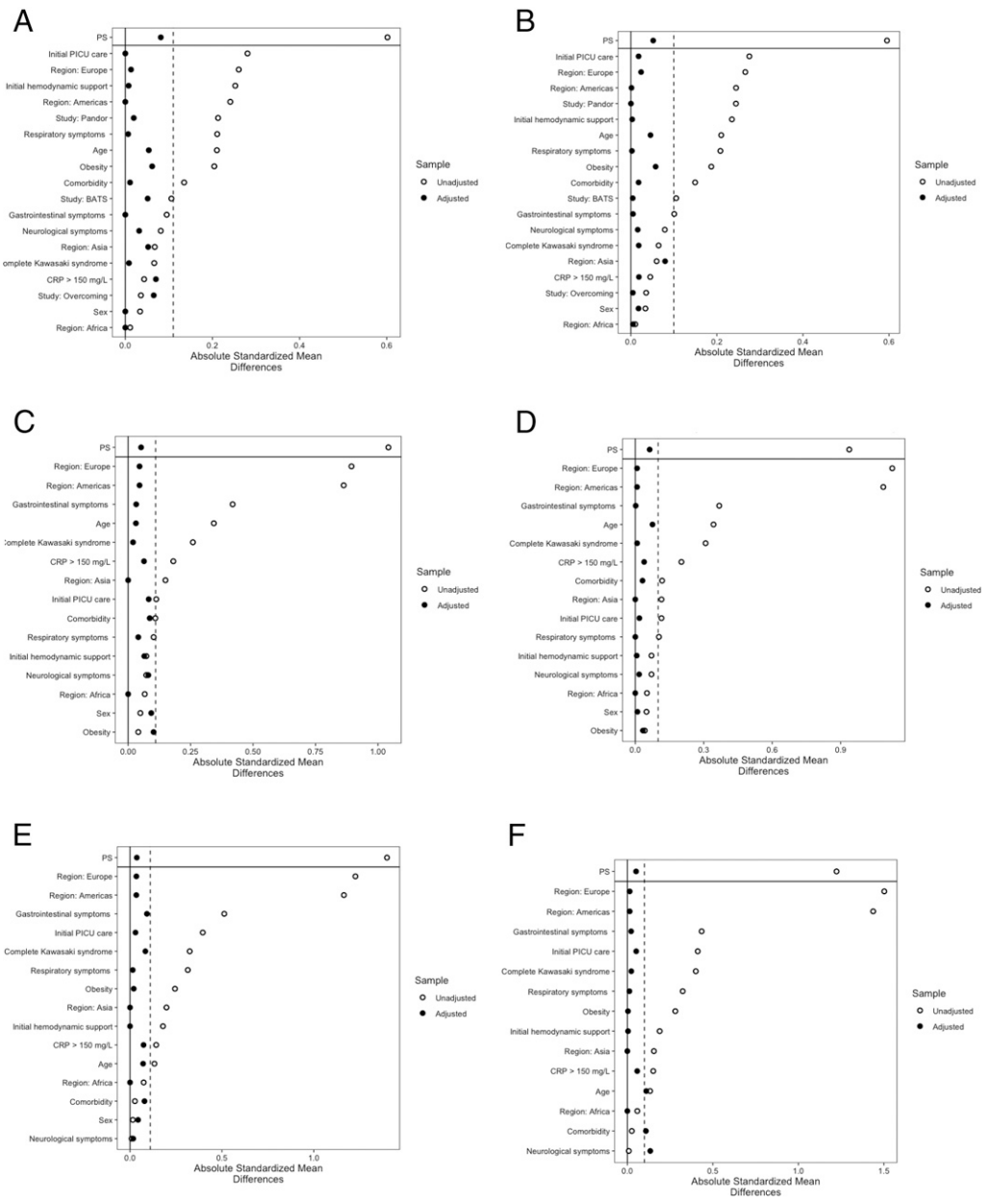
Supplemental Information



SUPPLEMENTAL FIGURE 3

Covariate balance of the main propensity score matching model and the inverse probability of treatment weighting model. (A) IVIG + glucocorticoids versus IVIG alone, Propensity score matching.* (B) IVIG + glucocorticoids versus IVIG alone, inverse probability of treatment weighting. (C) Glucocorticoids alone versus IVIG alone, propensity score matching.† (D) Glucocorticoids alone versus IVIG alone, inverse probability of treatment weighting. (E) Glucocorticoids alone versus IVIG + glucocorticoids, Propensity score matching.† (F) Glucocorticoids alone versus IVIG + glucocorticoids, inverse probability of treatment weighting. PS, propensity score.* Propensity score matching using 1:1 nearest neighbor matching, based on complete cases, without replacement, with a minimum caliper of 0.2.† Propensity score matching using 2:1 nearest neighbor matching, based on complete cases, without replacement, with a minimum caliper of 0.2.

SUPPLEMENTAL TABLE 3 Electronic Search Strategies		
	Search Strategy	**Results**
MEDLINE (Ovid), 1946 to February 1, 2022; date of search: February 2, 2022		
1	exp Systemic Inflammatory Response Syndrome/	142 371
2	(MISC or MIS-C or PIMS or KD or Kawasaki-like or childhood multisystem inflammatory syndrome or COVID-19 associated Kawasaki-like multisystem inflammatory disease or COVID-19 associated multisystem inflammatory syndrome or COVID-19 Kawasaki-like syndrome or COVID-19 related multisystem inflammatory syndrome or Kawa-COVID-19 or Kawasaki like disease or Kawasaki-like multisystem inflammatory syndrome or multi-inflammatory syndrome in children or multi-system inflammatory syndrome in children or multiorgan inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammation syndrome in children or multisystem inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammatory syndrome in children or p?ediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 or p?ediatric multi-system inflammatory syndrome or p?ediatric multisystem inflammatory syndrome or p?ediatric multisystem inflammatory syndrome temporally associated with COVID-19 or p?ediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 or PIMS-TS or PMIS-TS or SARS-CoV-2 associated multisystem inflammatory syndrome or SARS-CoV-2 induced Kawasaki-like hyperinflammatory syndrome or SARS-CoV-2 mimicking Kawasaki disease).mp.	68 359
3	or/1-2	209 757
4	exp Glucocorticoids/	202 711
5	exp Immunoglobulins, Intravenous/	14 855
6	(corticosteroid* or corticoid* or predniso* or dehydrocortison* or predni* or corti* or methlypred* or dexa* or dexameth* or hydrocorti* or cortisol cortef or hydrocorton* or glucocort* or cortico* or steroid* or IVIG* or immunoglob* or immune glob* or (intraven* adj2 glob*)).mp.	1 429 092
7	or/4-6	1 444 572
8	3 and 7	17 390
9	(teen* or adolescen* or youth or child* or p?ediatr* or juvenile or minor* or less than 18).mp.	4 231 246
10	8 and 9	3723
11	limit 8 to “all child (0 to 18 years)”	3518
12	10 or 11	4252
13	12 not ((exp animal/ or nonhuman/) not exp human/)	4159
14	limit 13 to yr=”2020 -Current”	747
EMBASE (Ovid), 1947 to February 1, 2022; date of search: February 2, 2022		
1	exp pediatric multisystem inflammatory syndrome/	1496
2	(MISC or MIS-C or PIMS or KD or Kawasaki-like or childhood multisystem inflammatory syndrome or COVID-19 associated Kawasaki-like multisystem inflammatory disease or COVID-19 associated multisystem inflammatory syndrome or COVID-19 Kawasaki-like syndrome or COVID-19 related multisystem inflammatory syndrome or Kawa-COVID-19 or Kawasaki like disease or Kawasaki-like multisystem inflammatory syndrome or multi-inflammatory syndrome in children or multi-system inflammatory syndrome in children or multiorgan inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammation syndrome in children or multisystem inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammatory syndrome in children or p?ediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 or p?ediatric multi-system inflammatory syndrome or p?ediatric multisystem inflammatory syndrome or p?ediatric multisystem inflammatory syndrome temporally associated with COVID-19 or p?ediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 or PIMS-TS or PMIS-TS or SARS-CoV-2 associated multisystem inflammatory syndrome or SARS-CoV-2 induced Kawasaki-like hyperinflammatory syndrome or SARS-CoV-2 mimicking Kawasaki disease).mp.	68 649
3	or/1-2	68 649
4	exp Glucocorticoids/	787 478
5	exp Immunoglobulin/	546 248
6	(corticosteroid* or corticoid* or predniso* or dehydrocortison* or predni* or corti* or methlypred* or dexa* or dexameth* or hydrocorti* or cortisol cortef or hydrocorton* or glucocort* or cortico* or steroid* or IVIG* or immunoglob* or immune glob* or (intraven* adj2 glob*)).mp.	2 445 633
7	or/5-6	2 464 916
8	3 and 7	10 618
9	(teen* or adolescen* or youth or child* or p?ediatr* or juvenile or minor* or less than 18).mp.	4 347 650
10	8 and 9	3975
11	limit 10 to (infant or child or preschool child <1 to 6 y> or school child <7 to 12 y> or adolescent <13 to 17 y>)	3070
12	10 or 11	3975
13	12 not ((exp animal/ or nonhuman/) not exp human/)	3899
14	limit 13 to yr=”2020 -Current”	1351

SUPPLEMENTAL TABLE 3 Continued

	Search Strategy	Results
Controlled Trials (Wiley), inception to February 1, 2022; date of search: February 2, 2022		
1	(MISC or MIS-C or PIMS or KD or Kawasaki-like or childhood multisystem inflammatory syndrome or COVID-19 associated Kawasaki-like multisystem inflammatory disease or COVID-19 associated multisystem inflammatory syndrome or COVID-19 Kawasaki-like syndrome or COVID-19 related multisystem inflammatory syndrome or Kawa-COVID-19 or Kawasaki like disease or Kawasaki-like multisystem inflammatory syndrome or multi-inflammatory syndrome in children or multi-system inflammatory syndrome in children or multiorgan inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammation syndrome in children or multisystem inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammatory syndrome in children or p?ediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 or p?ediatric multi-system inflammatory syndrome or p?ediatric multisystem inflammatory syndrome or p?ediatric multisystem inflammatory syndrome temporally associated with COVID-19 or p?ediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 or PIMS-TS or PMIS-TS or SARS-CoV-2 associated multisystem inflammatory syndrome or SARS-CoV-2 induced Kawasaki-like hyperinflammatory syndrome or SARS-CoV-2 mimicking Kawasaki disease).mp.	1123
2	(corticosteroid* or corticoid* or predniso* or dehydrocortison* or predni* or corti* or methlypred* or dexa* or dexameth* or hydrocorti* or cortisol cortef or hydrocorton* or glucocort* or cortico* or steroid* or IVIG* or immunoglob* or (immune adj2 glob*)).mp.	119 046
3	(teen* or adolescen* or youth or child* or p?ediatr* or juvenile or minor* or less than 18).mp.	308 796
4	limit 4 to yr="2020-Current"	10
Web of science (Clarivate), Inception to February 1, 2022; date of search: February 2, 2022		
1	(((TS=(MISC or MIS-C or PIMS or KD or Kawasaki-like or childhood multisystem inflammatory syndrome or COVID-19 associated Kawasaki-like multisystem inflammatory disease or COVID-19 associated multisystem inflammatory syndrome or COVID-19 Kawasaki-like syndrome or COVID-19 related multisystem inflammatory syndrome or Kawa-COVID-19 or Kawasaki like disease or Kawasaki-like multisystem inflammatory syndrome or multi-inflammatory syndrome in children or multi-system inflammatory syndrome in children or multiorgan inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammation syndrome in children or multisystem inflammatory syndrome associated with SARS-CoV-2 or multisystem inflammatory syndrome in children or p?ediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 or p?ediatric multi-system inflammatory syndrome or p?ediatric multisystem inflammatory syndrome or p?ediatric multisystem inflammatory syndrome temporally associated with COVID-19 or p?ediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 or PIMS-TS or PMIS-TS or SARS-CoV-2 associated multisystem inflammatory syndrome or SARS-CoV-2 induced Kawasaki-like hyperinflammatory syndrome or SARS-CoV-2 mimicking Kawasaki disease)) AND TS=(corticosteroid* or corticoid* or predniso* or dehydrocortison* or predni* or corti* or methlypred* or dexa* or dexameth* or hydrocorti* or cortisol cortex or hydrocorton* or glucocort* or cortico* or steroid* or IVIG* or immunoglob* or immune NEAR/3 glob*)) AND TS=(teen* or adolescen* or youth or child* or p?ediatr* or juvenile or minor* or less than 18))	527
Grey literature search strategy available upon request.		

SUPPLEMENTAL TABLE 4 Crude Outcome Depending on Baseline Characteristics

	Initial Cardiovascular Dysfunction[a] (*N* = 331)	No Initial Cardiovascular Dysfunction[a] (*N* = 381)	Initial Hemodynamic Support (*N* = 220)	No Initial Hemodynamic Support (*N* = 716)	Initial LVEF < 55% (*N* = 200)	No Initial LVEF < 55% (*N* = 468)
Cardiovascular dysfunction on or after day 2[a]	149/327 (46)	34/378 (9)	119/217 (55)	73/712 (10)	79/197 (40)	75/463 (16)
Hemodynamic support on or after day 2	129/323 (40)	27/375 (7)	115/217 (53)	46/707 (7)	59/193 (31)	67/459 (15)
LVEF < 55% on or after day 2	44/305 (14)	19/323 (6)	22/205 (11)	45/628 (7)	39/188 (21)	24/396 (6)
Ventilatory support on or after day 2	65/316 (21)	30/359 (8)	54/210 (26)	46/687 (7)	36/191 (19)	44/439 (10)
Fever on or after day 2	97/319 (30)	139/369 (38)	66/214 (31)	252/694 (36)	56/189 (30)	159/451 (35)
Second line therapy	145/330 (44)	172/379 (45)	93/219 (42)	320/712 (45)	86/199 (43)	207/466 (44)

Data presented as *n/N* (%) unless noted otherwise. Missing data: cardiovascular dysfunction on or after day 2: NA = 8; hemodynamic support on or after day 2: NA = 20; LVEF < 55% on or after day 2: NA = 108; ventilatory support on or after day 2: NA = 49; fever on or after day 2: NA = 34; second line therapy: NA = 5.
[a] Cardiovascular dysfunction defined as either hemodynamic support or LVEF < 55%.

SUPPLEMENTAL TABLE 5 Crude Outcomes Depending on Initial Therapy

	IVIG ($N = 482$)	IVIG + steroids ($N = 387$)	Steroids ($N = 89$)	Total ($N = 958$)
Cardiovascular dysfunction on or after day 2[a]	106/480 (22)	81/382 (21)	11/88 (13)	198/950 (21)
Hemodynamic support on or after day 2	84/470 (18)	71/380 (19)	10/88 (11)	165/938 (18)
LVEF < 55% on or after day 2	49/415 (12)	20/346 (6)	1/89 (1)	70/850 (8)
Ventilatory support on or after day 2	50/447 (11)	49/374 (13)	5/88 (6)	104/909 (11)
Fever on or after day 2	194/464 (42)	94/373 (25)	36/87 (41)	324/924 (35)
Second line therapy	271/481 (56)	104/384 (27)	49/88 (56)	424/953 (44)
Death	3/478 (1)	5/374 (1)	3/83 (4)	11/935 (1)

Data presented as *n/N* (%) unless noted otherwise. Missing data: Cardiovascular dysfunction on or after day 2: NA = 8. Hemodynamic support on or after day 2: NA = 20. LVEF < 55% on or after day 2: NA = 108. Ventilatory support on or after day 2: NA = 49. Fever on or after day 2: NA = 34. Second line therapy: NA = 5. Death: NA = 23.
[a] Cardiovascular dysfunction defined as either hemodynamic support or LVEF < 55%.

SUPPLEMENTAL TABLE 6A Primary and Secondary Outcome Analysis, IVIG + Glucocorticoids Versus IVIG Alone*

	After Propensity Score Matching				
	IVIG + Glucocorticoids, $N = 311$	IVIG Alone, $N = 311$	OR (95% CI) (reference: IVIG alone)	*P*	Between Study Variance
Primary outcome, main analysis[a]					
Treatment failure[b]	58/311 (19)	85/311 (27)	0.62 (0.42–0.91)	.014	0.176
Secondary outcomes					
Hemodynamic support on or after day 2	49/310 (16)	67/310 (22)	0.57 (0.34–0.95)	.032	0.00
LVEF < 55% on or after day 2	17/267 (6)	37/267 (14)	0.43 (0.22–0.84)	.013	0.633
Ventilatory support on or after day 2	39/294 (13)	41/294 (14)	0.88 (0.52–1.49)	.635	0.128
Second line therapy	89/311 (29)	183/311 (59)	0.25 (0.16–0.38)	<.0001	0.267
Fever on or after day 2	84/309 (27)	131/309 (42)	0.37 (0.24–0.57)	<.0001	0.001

Data presented as *n/N* (%) unless noted otherwise.
[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 region and study (BATS, Overcoming and Pandor).
[b] Cardiovascular dysfunction on or after day 2 after the initial therapy, defined as either a left ventricular ejection fraction (LVEF) less than 55% or the use of vasoactive or inotropic amine.

SUPPLEMENTAL TABLE 6B Primary and Secondary Outcome Analysis, Glucocorticoids Alone Versus IVIG Alone

	After Propensity Score Matching			
	Glucocorticoids Alone, *N* = 75	**IVIG Alone, *N* = 150**	**OR (95% CI) (reference: IVIG alone)**	***P***
Primary outcome, main analysis[a]				
Treatment failure[b]	10/75 (13)	33/150 (22)	0.57 (0.31–1.05)	.069
Secondary outcomes				
Hemodynamic support on or after day 2	9/75 (12)	22/150 (15)	0.79 (0.41–1.55)	.498
LVEF < 55% on or after day 2	1/73 (1)	14/146 (10)	0.13 (0.03–0.59)	.008
Ventilatory support on or after day 2	4/74 (5)	18/148 (12)	0.18 (0.04–1.01)	.052
Second line therapy	44/72 (61)	73/144 (51)	1.57 (0.97–2.53)	.066
Fever on or after day 2	33/73 (45)	62/146 (42)	1.18 (0.74–1.88)	.637

Data presented as *n/N* (%) unless noted otherwise. A random effect on study was not included because only BATS study contributed to the glucocorticoids alone group. The between study variance was not provided because only BATS study contributed to the glucocorticoids alone group.

[a] Analysis based on a propensity score matching using 2:1 nearest neighbor matching, based on complete cases, without replacement, with a minimum caliper of 0.2, with random effect on region.

[b] Cardiovascular dysfunction on or after day 2 after the initial therapy, defined as either a left ventricular ejection fraction (LVEF) less than 55% or the use of vasoactive or inotropic amine.

SUPPLEMENTAL TABLE 6C Primary and Secondary Outcome Analysis, Glucocorticoids Alone Versus IVIG + Glucocorticoids

	After Propensity Score Matching			
	Glucocorticoids Alone, *N* = 54	**IVIG + Glucocorticoids, *N* = 108**	**OR (95% CI) (reference: IVIG + glucocorticoids)**	***P***
Primary outcome, main analysis[a]				
Treatment failure[b]	8/54 (15)	23/108 (21)	0.67 (0.24–1.86)	.432
Secondary outcomes				
Hemodynamic support on or after day 2	8/54 (15)	22/108 (20)	0.77 (0.22–2.61)	.663
LVEF < 55% on or after day 2	0/52 (0)	8/104 (8)	No convergence	
Ventilatory support on or after day 2	4/54 (7)	11/108 (10)	0.22 (0.02–1.95)	.173
Second line therapy	36/53 (68)	26/106 (25)	6.95 (3.73–12.95)	<.0001
Fever on or after day 2	21/51 (41)	25/102 (25)	2.16 (1.18–3.93)	.012

Data presented as *n/N* (%) unless noted otherwise. A random effect on study was not included because only BATS study contributed to the glucocorticoids alone group. The between study variance was not provided because only BATS study contributed to the glucocorticoids alone group.

[a] Analysis based on a propensity score matching using 2:1 nearest neighbor matching, based on complete cases, without replacement, with a minimum caliper of 0.2, with random effect on region.

[b] Cardiovascular dysfunction on or after day 2 after the initial therapy, defined as either a left ventricular ejection fraction (LVEF) less than 55% or the use of vasoactive or inotropic amine.

SUPPLEMENTAL TABLE 7A Sensitivity Analyses, IVIG + Glucocorticoids Versus IVIG Alone

	After Propensity Score Matching				
	IVIG + Glucocorticoids, *N* = 311	**IVIG Alone, *N* = 311**	**OR (95% CI) (reference: IVIG alone)**	***P***	**Between Study Variance**
PS matching with double adjustment[a]	58/311 (19)	85/311 (27)	0.42 (0.26–0.68)	.0004	0.176
PS matching with fixed effect on region and study	58/311 (19)	85/311 (27)	0.42 (0.26–0.69)	.004	0.176
PS matching with a minimum caliper of 0.1	55/308 (18)	84/308 (27)	0.59 (0.40–0.87)	.008	0.175
PS matching including fever duration before first-line therapy	53/294 (18)	82/294 (28)	0.55 (0.37–0.83)	.004	0.367
PS matching with initial LVEF < 55% including day 1 following first-line therapy	49/270 (18)	81/270 (30)	0.51 (0.34–0.78)	.002	0.095
Within-study PS matching	56/309 (18)	77/309 (25)	0.64 (0.43–0.94)	.024	0.195
IPTW	Weighted failure rate (*N* = 363): 21%	Weighted failure rate (*N* = 453): 28%	0.65 (0.46–0.91)	.013	0.082
IPTW with double adjustment[$]	Weighted failure rate (*N* = 363): 21%	Weighted failure rate (*N* = 453): 28%	0.44 (0.28–0.67)	.002	0.131
Multivariate logistic regression	—	—	0.60 (0.39–0.91)	.017	—

Data presented as *n/N* (%) unless noted otherwise. PS, propensity score; —, XXX.

[a] Double adjustment on initial hemodynamic support and initial left ventricular dysfunction.

SUPPLEMENTAL TABLE 7B Sensitivity Analyses, Glucocorticoids Alone Versus IVIG Alone

	After Propensity Score Matching			
	Glucocorticoids Alone, *N* = 75	**IVIG Alone, *N* = 150**	**OR (95% CI) (reference: IVIG alone)**	***P***
PS matching with double adjustment[a]	10/75 (13)	33/150 (22)	0.57 (0.22–1.49)	.253
PS matching with fixed effect on region	10/75 (13)	33/150 (22)	0.57 (0.31–1.05)	.069
PS matching with a minimum caliper of 0.1	10/69 (14)	29/138 (21)	0.64 (0.34–1.19)	.158
PS matching including fever duration before first-line therapy	10/62 (16)	33/124 (27)	0.53 (0.28–0.99)	.046
PS matching with initial LVEF < 55% including day 1 following first-line therapy	8/45 (18)	19/90 (21)	0.81 (0.39–1.69)	.572
PS with 1:1 matching	11/77 (14)	14/77 (18)	0.75 (0.32–1.78)	.513
IPTW	Weighted failure rate (*N* = 83): 13%	Weighted failure rate (*N* = 453): 21%	0.57 (0.24–1.30)	.188
IPTW with double adjustment[$]	Weighted failure rate (*N* = 83): 13%	Weighted failure rate (*N* = 453): 21%	0.44 (0.10–1.65)	.247
Multivariate logistic regression	—	—	0.46 (0.19–1.05)	.075

Data presented as *n/N* (%) unless noted otherwise. The between study variance was not provided because only BATS study contributed to the glucocorticoids alone group. PS, propensity score.; —, not applicable.

[a] Double adjustment on initial hemodynamic support and initial left ventricular dysfunction.

SUPPLEMENTAL TABLE 7C Sensitivity Analyses, Glucocorticoids Alone Versus IVIG + Glucocorticoids

	After Propensity Score Matching			
	Glucocorticoids Alone, *N* = 54	**IVIG + Glucocorticoids, *N* = 108**	**OR (95% CI) (reference: IVIG + glucocorticoids)**	***P***
PS matching with double adjustment[a]	8/54 (15)	23/108 (21)	1.05 (0.31–2.90)	.924
PS matching with fixed effect on region	8/54 (15)	23/108 (21)	1.05 (0.34–3.31)	.925
PS matching with a minimum caliper of 0.1	8/51 (16)	22/102 (22)	0.61 (0.27–1.37)	.233
PS matching including fever duration before first-line therapy	7/48 (15)	21/96 (21)	0.57 (0.26–1.27)	.170
PS matching with initial LVEF < 55% including day 1 following first-line therapy	7/37 (19)	15/74 (20)	0.91 (0.39–2.13)	.829
PS using 1:1 matching	10/70 (14)	13/70 (19)	0.67 (0.24–1.87)	.443
IPTW	Weighted failure rate (*N* = 83): 13%	Weighted failure rate (*N* = 363): 16%	0.81 (0.33–1.93)	.632
IPTW with double adjustment[$]	Weighted failure rate (*N* = 83): 13%	Weighted failure rate (*N* = 363): 16%	1.13 (0.27–4.61)	.864
Multivariate logistic regression	—	—	0.71 (0.27–1.75)	.470

Data presented as *n/N* (%) unless noted otherwise. The between study variance was not provided because only BATS study contributed to the glucocorticoids alone group. PS, propensity score; —, XXX.

[a] Double adjustment on initial hemodynamic support and initial left ventricular dysfunction.

APPENDIX 1 PRISMA Checklist

Section or Topic	#	Checklist Item	Reported on Page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
Abstract			
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.	Page 3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	Page 4
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplemental Table 3
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7 and 8, Fig 1
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 8
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	Page 8, Appendix 3
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.	Page 8
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	Pages 9, 10, and 11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	Pages 9, 10 and 11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	Page 8
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	Pages 9–13
Results			
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.	Page 14 and Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Fig 1, Appendix 4
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).	Appendix 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 2, Table 2, Supplemental Table 7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	Appendix 5

APPENDIX 1 Continued

Section or Topic	#	Checklist Item	Reported on Page #
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression) (see item 16).	Fig 2, Table2, Supplemental Table 7
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	Pages 18 and 21
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	Pages 20–21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pages 18–20
Funding			
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.	Page 26

Hand searched citations of included articles.

APPENDIX 2 MIS-C CASE DEFINITIONS

Several MIS-C definitions have been proposed to date by WHO, the CDC and the Royal College of Paediatrics and Child Health:

(A) MIS-C WHO case definition[19]

- Children and adolescents 0 to 19 years of age with fever > 3 days
- And 2 of the following:
  - o Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet).
  - o Hypotension or shock.
  - o Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated Troponin/NT-proBNP),
  - o Evidence of coagulopathy (by prothrombin time, partial thromboplastin time, elevated d-Dimers).
  - o Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).
- And elevated markers of inflammation such as erythrocyte sedimentation rate, 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 (reverse transcription polymerase chain rection (RT-PCR), antigen test or serology positive), or likely contact with patients with COVID-19.

(B) MIS-C CDC case definition[20]

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation†, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic).
- And no alternative plausible diagnoses;
- And positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms.

Additional comments some individuals may fulfil full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

(C) Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 Royal College of Paediatrics and Child Health definition[21]:

- A child presenting with persistent fever, inflammation (neutrophilia, elevated C-reactive protein and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurologic disorder) with additional features.‡ This may include children meeting full or partial criteria for Kawasaki disease.
- 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).
- SARS-CoV-2 PCR testing may be positive or negative.

As the 3 main therapeutic studies published to date used slightly different definitions for MIS-C,[12–14] the primary analysis included patients fulfilling 1 of the3 above MIS-C cases definitions. Sensitivity analyses were conducted for patients fulfilling only WHO or CDC MIS-C case definitions. All patients whose initial therapy was in the days before transfer to the reporting unit were excluded.

* Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.

† Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin.

‡ See details at https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf.

APPENDIX 3 DETAILED DEFINITION OF BASELINES CHARACTERISTICS USED TO BUILD THE PROPENSITY SCORE AND CONDUCT SUBGROUP ANALYSES

The baseline characteristics used to build the propensity score included:

- Continent (Europe, Americas, Africa, Asia, Oceania);
- Age;
- Sex;
- Comorbidities, defined by any chronic condition or coexisting illness (including malignancy, chronic neurologic condition, chronic lung disease, primary or secondary immunodeficiency, HIV, autoimmune disease and juvenile idiopathic arthritis);
- Gastrointestinal symptoms (defined as the presence of diarrhea, vomiting and/or abdominal pain);
- Lower respiratory tract symptoms (defined as the presence of dyspnea, increased work of breath, oxygenotherapy, invasive or noninvasive ventilatory support);
- Neurologic symptoms, defined by the presence of headache, seizure, awareness;
- Abnormalities and/or meningeal syndrome;
- Criteria for Kawasaki syndrome (following American Heart Association guidelines);[25]

- Intensity of inflammatory syndrome (C-reactive protein level $>$ or $\leq$150 mg/L);
- Initial PICU care (at any time before or on the day of initial therapy);
- Initial hemodynamic support (defined as the use of vasoactive or inotropic amine, at any time before or on the day of initial therapy); and
- Obesity, defined by weight for age Z score $>$ 2.

All these baseline characteristics are considered at admission, ie, before or on the day of initial therapy. For CRP level, we considered the highest value before or on the day of initial therapy.

APPENDIX 4A Risk of Bias and Quality of Evidence Assessment, Risk of Bias Assessment Following the Cochrane Risk-of-bias Tools for Nonrandomized Studies of Interventions (ROBINS-I)22

Study	Confounding (all outcomes)	Selection of Participants	Classification of the Intervention	Deviation From Intended Interventions (assignment)	Missing Data (all outcomes)	Measurement of Outcomes (all outcomes)	Selection of Reported Results (all outcomes)	Overall
McArdle et al[14]	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Ouldali et al[12]	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Son et al[13]	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious

Following the ROBINS-I tool, the categories for risk of bias judgements are "Low risk," "Moderate risk," "Serious risk," and "Critical risk" of bias.

APPENDIX 4B Level of Certainty Assessment Following the GRADE Tool, Based on the WHO Guidance for MIS-C Clinical Management,[15] Glucocorticoids Plus IVIG Versus IVIG Alone

Outcome	Certainty of Evidence	Comment
Cardiovascular dysfunction (primary outcome)	⊕⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies)
Hemodynamic support on or after day 2	⊕⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies)
LVEF $<$ 55% on or after day 2	⊕⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies)
Ventilatory support on or after day 2	⊕⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies)
Second line therapy	⊕⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies)
Fever on or after day 2	⊕⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies)

APPENDIX 4C Glucocorticoids Alone Versus IVIG Alone		
Outcome	**Certainty of Evidence**	**Comment**
Cardiovascular dysfunction (primary outcome)	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Hemodynamic support on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
LVEF $<$ 55% on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Ventilatory support on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Second line therapy	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Fever on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).

APPENDIX 4D Glucocorticoids Alone Versus Glucocorticoids Plus IVIG		
Outcome	**Certainty of Evidence**	**Comment**
Cardiovascular dysfunction (primary outcome)	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Hemodynamic support on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
LVEF $<$ 55% on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Ventilatory support on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Second line therapy	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).
Fever on or after day 2	⨁⊖⊖⊖ Very low	Because of serious risk of bias (downgraded 2 levels for serious risk of confounding in all studies) and serious imprecision (downgraded 2 levels because of small sample size: $n < 100$ in 1 treatment group).

APPENDIX 5 LIST OF THE BATS CONSORTIUM, THE OVERCOMING COVID-19 INVESTIGATORS, AND THE FRENCH COVID-19 PEDIATRIC INFLAMMATION CONSORTIUM AND PANDOR STUDY GROUP

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