Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. DOI: 10.1056/NEJMoa2102968

SUPPLEMENTARY APPENDIX

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The Best Available Treatment Study (BATS) Consortium

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Supplementary Methods

Patient Recruitment

BATS invited recruitment of children with a wide, inclusive definition of MIS-C. The instructions to participating centres, including the various definitions in use, are contained in the 'BATS handbook' which is available as supplementary material.

The protocol and study information were translated into Spanish by Gabriela Ivankovich-Escoto and Rolando Ulloa-Gutierrez and into Portuguese by Rolando Andres Paternina-de la Ossa. Enrolment at individual study sites was undertaken by local investigators. The statistical group (listed in Consortium Membership) wrote the statistical analysis plan.

Data preparation

Data were entered in RedCap version 6.14.2. All subsequent processing and analysis were undertaken in R version 4.0.2. The included patients were finalized on 24 February 2021, with data changes restricted to correction of errors and missing data. Validation and correction of admission, discharge and immunomodulatory treatment dates was undertaken. Data were processed such that repeated clinical, laboratory and treatment variables were represented in a table with one row per patient-day.

Clinicians included the patients on their judgement of the patient meeting one or more of the international definitions for MIS-C.[1–3] Patients were excluded from analysis if an admission date was unavailable, data was not entered on the treatment form, there was no daily data and no discharge date, or the date of first immunomodulatory treatment was unclear. Only patients treated on or after the day of admission or transfer could contribute adjusted outcomes. Unadjusted death and complication rates were reported on all included patients.

Level of care variables, including respiratory support and inotropes, and the clinical variable fever were interpolated for missing daily data where preceding and following values were identical. Where missing data for respiratory support and inotropes followed a final value, if the final value indicated no support was needed, subsequent daily values were considered to be the same. Further, where total number of days of invasive ventilation, non-invasive ventilation, oxygen and inotropic support were available, missing data was entered assuming no discontinuous periods of treatment (supported by a low frequency of multiple episodes of inotropes, ventilation or oxygen usage in complete data).

Where multiple hospitals within one location reported patients, we inspected plots of admissions and ages to identify possible adjoining admissions. Two pairs of admissions in London were identified likely corresponding to the same patient based on age, gender, weight, admission periods and compatible laboratory and clinical variables. The data were merged and original records excluded.

Each site reported laboratory variables in units prespecified in the data collection tool, or with alternative units. Conversion to the same units was undertaken. Manual inspection of result distributions from individual sites was undertaken to identify and correct incorrect or discrepant units. Extreme outliers were inspected on a per individual basis and corrected when the value was discrepant with the rest of the biomarker time course.

For each day of admission, clinical severity was assessed on an ordinal scale:

1. Ventilated (invasive or non-invasive) and on inotropic support
2. Ventilated (invasive or non-invasive)
3. Inotropic support

4. Receiving oxygen
5. No supportive therapy last CRP ≥ 50 | No supportive therapy CRP unknown
6. No supportive therapy last CRP < 50 | No supportive therapy CRP unknown
7. Discharged

Additional levels were added for graphical presentation: death, ECMO and transferred (Figure S9B). This ordinal scale was developed by clinical consensus because there are no existing clinical severity scales for this condition. It would be inappropriate to use scales intended for acute COVID-19, which is initially a respiratory illness progressing to systemic disease, whereas MIS-C is a systemic illness with cardiovascular compromise predominating, and secondary respiratory compromise. Our scale considers escalating levels of clinical support, and in those not on support differentiates by level of CRP and admission status. This accords with clinical priorities when caring for patients: for those receiving organ support, coming off support is a key sign of improvement. For those not receiving organ support, improvement in inflammation is very important, and following that being fit for discharge.

Age was recorded in years and additional months. Where additional months were missing, they were assumed to be zero. Age in years was always present.

Patients' weight-for-age Z scores were calculated from the WHO reference data using the UK Royal College of Paediatrics and Child Health (RCPCH) Growth API[4]. The World Bank lending group classification was used for economic status.

Significant past medical history was recorded as primary or secondary immunodeficiency, HIV, autoimmune disease, chronic lung disease, chronic neurological disorder or malignancy.

Primary outcome definitions:

Inotropic support, ventilation and death (dichotomous)

Inotropic support and ventilation (invasive or non-invasive) at any time from the second day post-treatment, or death at any time. Inotropic support and ventilation were regarded as not available if the patient was transferred or died on day one or two, without report of support being received on day 2. If the patient was discharged on day 1 or 2, the outcome was regarded as negative. Death was regarded as missing for all patients transferred to other hospitals, and as negative for all patients whose destination was not recorded.

Improvement at day 2 (dichotomous)

Improvement at day 2 was reported relative to day 0 for:

- Any patient who was discharged on or before day 2
- Patients stepped down from ventilation or inotropic support
- Patients not ventilated or on inotropes who stepped down from oxygen
- Patients not receiving organ support whose CRP fell from above 50 mg/l on or before the day of treatment to below 50 mg/l.

Improvement was regarded as unknown if a patient was transferred on or before day 2, and negative for a patient who died on or before day 2.

Sensitivity analysis

- One planned sensitivity analyses was undertaken: Defining primary treatment as first treatments over two consecutive days (day 0-1)

Subgroup analysis

One planned subgroup analysis was undertaken (referred to as a sensitivity analysis in the protocol and statistical analysis plan):

- Patients fully meeting the WHO criteria for MIS-C

Secondary outcomes:

Failure of primary treatment

Defined as the addition of any immunomodulator from the first day after primary treatment. For patients receiving glucocorticoids within primary treatment, an escalation of more than 5 mg/kg prednisolone equivalent in total daily dose was required for further glucocorticoid usage to class as failure. If transferred before the fifth day following primary treatment, failure was regarded as not available.

Time to improvement in clinical severity

For each patient the time to improvement in clinical severity was calculated as:

- Time to come off ventilator or inotropes for patients receiving both therapies
- Time to come off ventilator for patients ventilated
- Time to come off inotropes for patients receiving inotropes
- Time to come off oxygen for patients receiving oxygen
- Time for CRP to fall below 50 mg/l for patients with final CRP on day of treatment or earlier of greater than or equal to 50 mg/l
- Time until discharge for all patients where preceding other event

Death / Inotropic support / Ventilation

As defined in composite primary outcome.

Fever

Presence of fever at any point from day 2. If no fever reported, but missing data, outcome regarded as not available.

Increase in level of support:

This was based on any commencement of:

- ECMO for patients not on ECMO on day 0
- Ventilation for patients not ventilated on day 0
- Inotropic support for patients not ventilated on day 0
- Oxygen for patients not on oxygen on day 0

Where none of the above led to classification of deterioration, death was regarded as deterioration and transfer was regarded as the outcome being unavailable. Patients discharged home or with unreported discharge destination were regarded as not having increased support.

Persisting coronary artery dilatation

The presence of a coronary artery with Lopez z-score ≥ 2.5 or a report of aneurysm without z-score on the final echocardiogram, undertaken on the second or subsequent days following treatment.[5] Regarded as not available if no echocardiogram reported, and negative if echocardiogram reported with no aneurysm or z-score ≥ 2.5.

Inflammatory markers and troponin

Time courses of CRP, ferritin and troponin were analysed for each treatment group.

Complications of drug therapy

Complications deemed to be the result of immunomodulatory treatment, including but not limited to: allergy/anaphylaxis, cataracts, gastric perforation, gastric ulceration, hip necrosis, hyperglycaemia, hyperlactataemia, opportunistic infection, profound bradycardia, psychosis and glucocorticoid-induced hypertension.

Left ventricular dysfunction

The presence of left ventricular dysfunction on any echocardiogram from the second day after commencement of primary immunomodulatory treatment. For this analysis, the presence of left

ventricular dysfunction prior to starting immunomodulatory treatment was added as an additional covariate for calculation of propensity scores (see below) to control for confounding due to differences in the prevalence of left ventricular dysfunction prior to treatment in each of the treatment arms.

Analysis

Confounding
All primary outcomes, sensitivity analyses, and secondary outcomes (excluding drug complications) underwent analysis following unstandardized inverse probability weighting by multinomial covariate-balanced propensity scores to control for baseline confounding factors, as implemented by WeightIt version 0.11.0, using the "just-identified" approach. The Average Treatment Effect (ATE) was estimated, except when comparing inflammatory markers between treated and untreated patients, when the Average Treatment Effect in the Untreated (ATU) was calculated (equivalent to the Average Treatment Effect in the Treated with the untreated group as the reference. In this way, treated patients were weighted to ensure covariates balanced with the untreated patients).

The analysis plan detailed the following variables could be considered for balancing:

1. Transfer vs. admission (dichotomous)
2. Treated in referring hospital (dichotomous)
3. Age (continuous)
4. Sex (binary)
5. Weight-for-age z-score greater than 2 (binary with missingness indicator)
6. Significant comorbidity (binary)
7. Days since fever at admission (continuous with missingness indicator)
8. Days of admission at treatment (continuous)
9. Total number of important clinical features reported up to day 0 (continuous)
10. COVID status: PCR positive, serology positive (if not PCR positive) or no positive result
11. Peak clinical severity to day of treatment (categorical)
12. Direction of change in clinical severity at day of treatment: increasing, stable, decreasing or unavailable (categorical)
13. Peak CRP up to day of treatment (quartile, or missing)
14. Direction of change in CRP at day of treatment (increasing, decreasing or unavailable)
15. Peak troponin up to day of treatment (quartile, or missing)
16. Peak BNP up to day of treatment (quartile, or missing)
17. Peak D-dimer up to day of treatment (quartile, or missing)
18. Coronary artery status up to day of treatment: last Z score ≥ 2.5, last Z score < 2.5, or not available

This was rationalised based on data availability and likely importance as determinants of treatment and outcome. For example, pre-treatment peak BNP and troponin were available less often than D-dimers (58 and 24% vs 72% respectively), and change in inflammatory markers and clinical severity was more often unavailable. The reduced covariates comprise:

1. Age
2. Sex
3. Weight-for-age z-score greater than 2
4. Significant comorbidity
5. Days of fever at admission
6. Days of admission at treatment
7. Total number of clinical features reported up to day of treatment
8. COVID status
9. Peak clinical severity to day of treatment
10. Peak CRP to day of treatment

11. Peak D dimer to day of treatment

The World Bank resource group was also added based on the importance of resource level to treatment availability. Important covariates were added for certain secondary analyses. When comparing patients receiving and not receiving immunomodulator therapy, variables reporting features up to the day of treatment were replaced with corresponding variables on admission (variables 7, 9, 10 and 11), and days of admission at treatment was removed, due to the lack of a corresponding first treatment day for those not receiving any immunomodulator. Balancing was repeated for every analysis on the population providing the outcome. No imputation for missing outcome data was undertaken.

We aimed for absolute standardized mean differences of 0.1 in continuous variables, and below, and Kolmogorov-Smirnov distances of 0.1 and below. Love plots were used to examine the extent of imbalance and consider the potential impact. We tolerated some deviation since covariates were also included in generalized linear outcome models. Weight distributions and propensity model coefficients are presented in Figure S11 and Tables S8-11.

Models
Modelling approaches producing robust sandwich standard errors were used. Dichotomous outcomes were estimated using weighted generalized linear models (quasibinomial family) as implemented within the survey package, adding all covariates used in covariate balancing, to produce doubly-robust estimates.

Time to event analyses were undertaken using weighted Cox proportional hazards model[6] estimated average hazard ratios. Covariates were reduced to resource group, age, peak clinical severity and peak CRP to day of treatment for ventilation due to low numbers.

Hypothesis testing
P values for primary hypotheses are corrected for multiple hypothesis testing with the Bonferroni-Holm procedure. All other outcomes are presented with 95% confidence intervals alone.

Sensitivity analysis
E-values are presented for primary outcomes as per the method of vanDerWeele and Ding[7].

Clinical severity over time
Clinical severity over time was presented as proportional column charts from two days before treatment to 10 days after treatment. Only patients treated after day 1 of admission contributed severity data for preceding days. Small numbers of patients had missing clinical severity data (maximum 4% on any day). The charts are presented weighted by the covariate-balanced propensity score.

Baseline comparison of treatment groups
Blood results, the proportion of patients ventilated and on inotropes and clinical features of Kawasaki disease were compared across treatment groups at the point of starting the first immunomodulator treatment, or the day of admission for patients who did not receive immunomodulatory treatment.

Inflammatory markers and troponin
Inflammatory markers were plotted as percentages of the peak value, per patient, throughout the course of their admission for each treatment group. Line plots were weighted by covariate-balancing propensity scores as described in Confounding. Smoothed curves with confidence intervals were plotted using a generalized additive model (geom_smooth from the ggplot2 package in R). Comparisons were also made within each treatment group for age and for patients who fulfilled the 2017 AHA criteria for Kawasaki Disease. Patients whose treatment commenced on day 7 of admission or beyond were excluded, as time courses would principally

represent the natural course.

Supplementary Tables

Table S1| Details of additional treatments given by initial immunomodulatory therapy groups.

Initial immunomodulatory therapy	Number of patients	No additional treatment	Additional treatment	Details of specific additional treatment						Glucocorticoid duration median days (IQR)
				IVIG	Glucocorticoid	Anti-IL1	Anti-IL6	Anti-TNF	Other immunomodulator	
IVIG	217	103	114	25	99	0	4	9	1	4 (3-6.5)
IVIG + Glucocorticoid	197	158	39	18	0	0	11	6	0	5 (3-7.75)
Glucocorticoid	89	40	49	47	0	0	2	0	1	7 (4-10)

Table S2 | Unabridged clinical features, demographic information, and blood results for all patients included in analysis.
Descriptive table of demographic features, clinical features and blood markers on admission, and Kawasaki Disease features during admission. Patients were divided by treatment arm on day 0 (IVIG alone, glucocorticoid alone, IVIG+Glucocorticoid, no treatment, and other (any other treatment combination including biologicals)). SARS-CoV-2 PCR data refer to tests taken during admission. Missing data are given as raw values and (%) where applicable.
Abbreviations: Ab: Antibody; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; BCG: Bacillus Calmette–Guérin; BNP: brain natriuretic peptide; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; KD: Kawasaki Disease; LDH: lactate dehydrogenase; PCR: polymerase chain reaction; PT: prothrombin time, WBC: white blood cell count.

	Everyone (N=614)	IVIG (N=246)	Glucocorticoid (N=99)	IVIG and Glucocorticoid (N=208)	Other (N=22)	No treatment (N=39)
[+]Age	8.3 [4.2 - 12]	7.0 [3.7 - 11]	8.8 [5.0 - 12]	8.8 [4.6 - 12]	13 [9.5 - 15]	9.6 [4.4 - 13]
[^]Proportion male at birth	376 (61.2%)	157 (63.8%)	59 (59.6%)	127 (61.1%)	15 (68.2%)	18 (46.2%)
[^]Overweight (age-adjusted z score ≥ 2)	90 (14.7%)	28 (11.4%)	10 (10.1%)	45 (21.6%)	4 (18.2%)	3 (7.69%)
[^]Ethnicity						
White	310 (50.5%)	124 (50.4%)	64 (64.6%)	95 (45.7%)	9 (40.9%)	18 (46.2%)
Latino	112 (18.2%)	33 (13.4%)	11 (11.1%)	60 (28.8%)	5 (22.7%)	3 (7.69%)
Black	75 (12.2%)	30 (12.2%)	2 (2.02%)	33 (15.9%)	4 (18.2%)	6 (15.4%)

	Everyone (N=614)	IVIG (N=246)	Glucocorticoid (N=99)	IVIG and Glucocorticoid (N=208)	Other (N=22)	No treatment (N=39)
Asian	49 (7.98%)	28 (11.4%)	6 (6.06%)	8 (3.85%)	2 (9.09%)	5 (12.8%)
Other or not known	68 (11.1%)	31 (12.6%)	16 (16.2%)	12 (5.77%)	2 (9.09%)	7 (17.9%)
^Significant comorbidity	21 (3.42%)	5 (2.03%)	7 (7.07%)	5 (2.40%)	1 (4.55%)	3 (7.69%)
^Home country economic status						
High-income economies	474 (77.2%)	209 (85.0%)	49 (49.5%)	158 (76.0%)	21 (95.5%)	37 (94.9%)
Upper-middle income economies	105 (17.1%)	32 (13.0%)	34 (34.3%)	37 (17.8%)	0 (0%)	2 (5.13%)
Lower-middle income economies	35 (5.70%)	5 (2.03%)	16 (16.2%)	13 (6.25%)	1 (4.55%)	0 (0%)
^SARS-CoV-2 PCR positive						
Yes	133 (21.9%)	36 (14.8%)	26 (26.5%)	53 (26.0%)	8 (36.4%)	10 (26.3%)
Tested but negative	427 (70.5%)	186 (76.2%)	67 (68.4%)	135 (66.2%)	14 (63.6%)	25 (65.8%)
Not tested	46 (7.59%)	22 (9.02%)	5 (5.10%)	16 (7.84%)	0 (0%)	3 (7.89%)
Missing	8 (1.3%)	2 (0.8%)	1 (1.0%)	4 (1.9%)	0 (0%)	1 (2.6%)
^SARS-CoV-2 Ab positive						
Yes	424 (70.4%)	163 (67.6%)	68 (70.1%)	163 (80.3%)	16 (72.7%)	14 (35.9%)
Tested but negative	89 (14.8%)	49 (20.3%)	7 (7.22%)	16 (7.88%)	4 (18.2%)	13 (33.3%)
Not tested	89 (14.8%)	29 (12.0%)	22 (22.7%)	24 (11.8%)	2 (9.09%)	12 (30.8%)
Missing	12 (2.0%)	5 (2.0%)	2 (2.0%)	5 (2.4%)	0 (0%)	0 (0%)
^At admission level of care						
No support	424 (69.1%)	191 (77.6%)	65 (65.7%)	124 (59.6%)	12 (54.5%)	32 (82.1%)
Oxygen	52 (8.47%)	17 (6.91%)	14 (14.1%)	18 (8.65%)	2 (9.09%)	1 (2.56%)
Inotropes	73 (11.9%)	18 (7.32%)	11 (11.1%)	40 (19.2%)	2 (9.09%)	2 (5.13%)
Ventilation	9 (1.47%)	3 (1.22%)	1 (1.01%)	3 (1.44%)	0 (0%)	2 (5.13%)
Inotropes and ventilation or ECMO	56 (9.12%)	17 (6.91%)	8 (8.08%)	23 (11.1%)	6 (27.3%)	2 (5.13%)
^Clinical features on admission						
Fever	580 (94.5%)	237 (96.3%)	92 (92.9%)	196 (94.2%)	20 (90.9%)	35 (89.7%)
Sore throat	149 (27.9%)	62 (30.1%)	23 (25.6%)	50 (26.2%)	3 (17.6%)	11 (35.5%)
Missing	79 (12.9%)	40 (16.3%)	9 (9.1%)	17 (8.2%)	5 (22.7%)	8 (20.5%)
Cough	124 (21.8%)	49 (21.4%)	24 (25.3%)	38 (19.6%)	7 (35.0%)	6 (19.4%)
Missing	45 (7.3%)	17 (6.9%)	4 (4.0%)	14 (6.7%)	2 (9.1%)	8 (20.5%)

	Everyone (N=614)	IVIG (N=246)	Glucocorticoid (N=99)	IVIG and Glucocorticoid (N=208)	Other (N=22)	No treatment (N=39)
Respiratory distress	88 (15.3%)	29 (12.8%)	12 (12.5%)	36 (18.2%)	6 (28.6%)	5 (14.3%)
Missing	38 (6.2%)	20 (8.1%)	3 (3.0%)	10 (4.8%)	1 (4.5%)	4 (10.3%)
Abdominal pain	365 (63.7%)	142 (63.7%)	48 (51.6%)	138 (69.0%)	16 (72.7%)	21 (60.0%)
Missing	41 (6.7%)	23 (9.3%)	6 (6.1%)	8 (3.8%)	0 (0%)	4 (10.3%)
Diarrhea	281 (48.0%)	100 (43.3%)	36 (38.3%)	120 (58.8%)	7 (31.8%)	18 (51.4%)
Missing	28 (4.6%)	15 (6.1%)	5 (5.1%)	4 (1.9%)	0 (0%)	4 (10.3%)
Vomiting	324 (56.1%)	118 (52.0%)	43 (45.7%)	135 (66.5%)	13 (65.0%)	15 (44.1%)
Missing	36 (5.9%)	19 (7.7%)	5 (5.1%)	5 (2.4%)	2 (9.1%)	5 (12.8%)
Headache	164 (31.6%)	66 (33.3%)	22 (25.6%)	61 (33.2%)	7 (35.0%)	8 (25.8%)
Missing	95 (15.5%)	48 (19.5%)	13 (13.1%)	24 (11.5%)	2 (9.1%)	8 (20.5%)
Encephalopathy	19 (3.39%)	5 (2.30%)	4 (4.40%)	8 (4.02%)	2 (10.0%)	0 (0%)
Missing	54 (8.8%)	29 (11.8%)	8 (8.1%)	9 (4.3%)	2 (9.1%)	6 (15.4%)
Irritability	116 (20.9%)	39 (18.1%)	22 (23.9%)	47 (23.9%)	1 (5.56%)	7 (21.9%)
Missing	60 (9.8%)	31 (12.6%)	7 (7.1%)	11 (5.3%)	4 (18.2%)	7 (17.9%)
Lethargy	222 (39.4%)	89 (40.8%)	46 (47.9%)	64 (32.3%)	11 (55.0%)	12 (37.5%)
Missing	50 (8.1%)	28 (11.4%)	3 (3.0%)	10 (4.8%)	2 (9.1%)	7 (17.9%)
^Kawasaki Disease features during admission						
Rash	396 (64.5%)	177 (72.0%)	63 (63.6%)	126 (60.6%)	11 (50.0%)	19 (48.7%)
Oral mucosal changes	327 (53.3%)	152 (61.8%)	51 (51.5%)	110 (52.9%)	9 (40.9%)	5 (12.8%)
Conjunctival injection	365 (59.4%)	164 (66.7%)	52 (52.5%)	132 (63.5%)	8 (36.4%)	9 (23.1%)
Edema or erythema of extremities	233 (37.9%)	94 (38.2%)	35 (35.4%)	89 (42.8%)	9 (40.9%)	6 (15.4%)
Skin peeling	75 (12.2%)	36 (14.6%)	11 (11.1%)	26 (12.5%)	1 (4.55%)	1 (2.56%)
Lymphadenopathy	224 (36.5%)	101 (41.1%)	31 (31.3%)	77 (37.0%)	6 (27.3%)	9 (23.1%)
BCG reactivity	24 (3.91%)	11 (4.47%)	2 (2.02%)	10 (4.81%)	1 (4.55%)	0 (0%)
+Blood results on admission						
WBC (10^9/L)	10 [7.0 - 14]	9.9 [7.1 - 14]	10 [6.8 - 15]	9.9 [7.0 - 14]	10 [8.2 - 12]	12 [6.6 - 14]
Missing	46 (7.5%)	20 (8.1%)	10 (10.1%)	10 (4.8%)	2 (9.1%)	4 (10.3%)
Neutrophils (10^9/L)	7.5 [5.1 - 11]	7.1 [5.1 - 10]	8.0 [4.7 - 13]	7.5 [5.1 - 11]	8.4 [6.6 - 9.8]	8.9 [5.3 - 11]
Missing	85 (13.8%)	38 (15.4%)	21 (21.2%)	20 (9.6%)	2 (9.1%)	4 (10.3%)
Lymphocytes (10^9/L)	1.2 [0.74 - 1.9]	1.4 [0.80 - 2.2]	1.1 [0.76 - 1.7]	1.1 [0.70 - 1.7]	0.81 [0.48 - 1.5]	1.1 [0.78 - 2.3]

	Everyone (N=614)	IVIG (N=246)	Glucocorticoid (N=99)	IVIG and Glucocorticoid (N=208)	Other (N=22)	No treatment (N=39)
Missing	74 (12.1%)	35 (14.2%)	13 (13.1%)	20 (9.6%)	2 (9.1%)	4 (10.3%)
Hemoglobin (g/L)	120 [110 - 130]	120 [110 - 130]	120 [110 - 130]	110 [100 - 120]	110 [100 - 120]	120 [110 - 130]
Missing	39 (6.4%)	16 (6.5%)	11 (11.1%)	6 (2.9%)	2 (9.1%)	4 (10.3%)
Platelets (10^9/L)	180 [120 - 260]	190 [130 - 290]	160 [120 - 240]	180 [130 - 240]	150 [91 - 230]	250 [150 - 320]
Missing	47 (7.7%)	21 (8.5%)	11 (11.1%)	8 (3.8%)	2 (9.1%)	5 (12.8%)
PT (sec)	15 [13 - 17]	15 [13 - 17]	15 [13 - 17]	15 [13 - 17]	16 [14 - 23]	13 [12 - 15]
Missing	253 (41.2%)	111 (45.1%)	46 (46.5%)	66 (31.7%)	7 (31.8%)	23 (59.0%)
APTT (sec)	32 [28 - 37]	33 [29 - 38]	33 [29 - 38]	30 [26 - 36]	35 [30 - 37]	29 [26 - 35]
Missing	223 (36.3%)	97 (39.4%)	41 (41.4%)	59 (28.4%)	6 (27.3%)	20 (51.3%)
Fibrinogen (g/L)	5.6 [4.5 - 6.8]	5.6 [4.5 - 6.4]	5.6 [4.6 - 6.4]	5.8 [4.5 - 7.0]	5.7 [4.7 - 6.9]	5.9 [3.4 - 7.2]
Missing	243 (39.6%)	108 (43.9%)	35 (35.4%)	70 (33.7%)	7 (31.8%)	23 (59.0%)
D Dimer (ng/mL)	2200 [1000 - 4200]	2300 [1000 - 4400]	2200 [1000 - 4000]	2100 [980 - 4000]	2500 [1600 - 4700]	1300 [480 - 4500]
Missing	232 (37.8%)	108 (43.9%)	38 (38.4%)	59 (28.4%)	4 (18.2%)	23 (59.0%)
Troponin (ng/L)	42 [10 - 190]	18 [8.0 - 55]	50 [16 - 150]	50 [30 - 260]	200 [13 - 2900]	11 [7.3 - 120]
Missing	310 (50.5%)	126 (51.2%)	63 (63.6%)	90 (43.3%)	4 (18.2%)	27 (69.2%)
BNP (ng/L)	130 [35 - 650]	74 [20 - 400]	380 [86 - 750]	160 [65 - 820]	150 [68 - 430]	18 [12 - 75]
Missing	477 (77.7%)	191 (77.6%)	81 (81.8%)	156 (75.0%)	14 (63.6%)	35 (89.7%)
CRP (mg/L)	150 [90 - 230]	150 [82 - 210]	130 [50 - 250]	150 [90 - 250]	160 [120 - 260]	160 [67 - 200]
Missing	84 (13.7%)	33 (13.4%)	20 (20.2%)	25 (12.0%)	2 (9.1%)	4 (10.3%)
Ferritin (ug/L)	460 [230 - 860]	410 [200 - 620]	530 [230 - 1100]	560 [300 - 920]	640 [310 - 1300]	230 [140 - 330]
Missing	237 (38.6%)	93 (37.8%)	53 (53.5%)	69 (33.2%)	2 (9.1%)	20 (51.3%)
LDH (U/L)	340 [260 - 470]	350 [280 - 460]	320 [250 - 470]	330 [250 - 480]	290 [250 - 570]	400 [260 - 480]
Missing	302 (49.2%)	129 (52.4%)	51 (51.5%)	87 (41.8%)	8 (36.4%)	27 (69.2%)
Creatinine (μmol/L)	47 [36 - 66]	43 [34 - 55]	55 [44 - 71]	52 [36 - 73]	55 [44 - 86]	53 [37 - 66]
Missing	94 (15.3%)	44 (17.9%)	21 (21.2%)	21 (10.1%)	2 (9.1%)	6 (15.4%)
ALT (U/L)	29 [18 - 52]	28 [16 - 45]	32 [20 - 56]	32 [20 - 54]	44 [20 - 140]	27 [15 - 59]
Missing	122 (19.9%)	51 (20.7%)	29 (29.3%)	29 (13.9%)	5 (22.7%)	8 (20.5%)
Albumin (g/L)	33 [28 - 38]	34 [29 - 40]	31 [27 - 34]	32 [28 - 38]	32 [29 - 37]	34 [30 - 39]
Missing	177 (28.8%)	72 (29.3%)	41 (41.4%)	47 (22.6%)	3 (13.6%)	14 (35.9%)

^Clinical and demographic features given as raw values and (%).

Table S3 | Clinical features, demographic information, and blood results for all patients included in analysis and subgroups meeting more restricted criteria

Descriptive table of demographic features, clinical features on admission, Kawasaki Disease features during admission, and blood markers on admission. All patients included in the analysis were classified as "Clinician diagnosed MIS-C". This population was subdivided by those who met the full WHO MIS-C criteria, those who met full WHO MIS-C criteria with presence of bacteremia or toxic shock syndrome, and those who were missing one or more mandatory criteria (fever >3 days; 2 of more of rash/non-purulent conjunctivitis, or mucocutaneous signs/hypotension or shock/features of myocardial dysfunction/evidence of coagulopathy/acute gastrointestinal symptoms; elevated markers of inflammation; evidence of Covid-19). All "Clinician diagnosed MIS-C" cases were further divided by patients that met the definition of Kawasaki Disease as set out by the American Heart Association (persistent fever, and at least 4 of the 5 following mucocutaneous features: erythema and cracking lips; strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral non-purulent conjunctivitis; rash; erythema and edema of the hands and feet and/or skin peeling; and lymphadenopathy). Patients with coronary artery aneurysms were also classified as Kawasaki Disease, even if they did not have at least 4 mucocutaneous features. Atypical KD was defined as patients with persistent fever, CRP >30, and meeting at least 2 or 3 mucocutaneous features. 37 % of all patients included in the analysis met the definition of KD by American Heart Association guidelines[8]. SARS-CoV-2 PCR data refer to tests taken during admission.

Abbreviations: ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; BCG: Bacillus Calmette–Guérin; BNP: brain natriuretic peptide; KD: Kawasaki Disease; LDH: lactate dehydrogenase; PCR: polymerase chain reaction; PT: prothrombin time, TSS: toxic shock syndrome; WBC: white blood cell count.

	Clinician diagnosed MIS-C matched on WHO criteria					**All patients with clinician diagnosed MIS-C**		
	Overall (N=614)	**MIS-C (full WHO criteria) (N=490)**	**MIS-C with bacteremia or TSS (N=7)**	**MIS-C missing 1 other criterion (N=92)**	**MIS-C missing >1 criteria (N=25)**	**KD (N=225)**	**Atypical KD (N=186)**	**Not KD (N=203)**
+Age (years)	8.3 [4.2 - 12]	8.6 [4.7 - 12]	9.9 [5.6 - 12]	7.2 [4.1 - 11]	4.1 [1.2 - 8.9]	6.5 [3.3 - 10]	8.8 [4.7 - 12]	10 [5.5 - 14]
^Proportion male at birth	376 (61.2%)	307 (62.7%)	4 (57.1%)	49 (53.3%)	16 (64.0%)	141 (62.7%)	113 (60.8%)	122 (60.1%)
^Overweight (age-adjusted z score ≥ 2)	90 (14.7%)	82 (16.7%)	1 (14.3%)	7 (7.61%)	0 (0%)	30 (13.3%)	27 (14.5%)	33 (16.3%)
^Ethnicity								
White	310 (50.5%)	239 (48.8%)	4 (57.1%)	52 (56.5%)	15 (60.0%)	110 (48.9%)	99 (53.2%)	101 (49.8%)
Latino	112 (18.2%)	102 (20.8%)	1 (14.3%)	8 (8.70%)	1 (4.00%)	42 (18.7%)	34 (18.3%)	36 (17.7%)
Black	75 (12.2%)	65 (13.3%)	2 (28.6%)	5 (5.43%)	3 (12.0%)	24 (10.7%)	21 (11.3%)	30 (14.8%)
Asian	49 (7.98%)	38 (7.76%)	0 (0%)	7 (7.61%)	4 (16.0%)	21 (9.33%)	16 (8.60%)	12 (5.91%)
Other or not known	68 (11.1%)	46 (9.39%)	0 (0%)	20 (21.7%)	2 (8.00%)	28 (12.4%)	16 (8.60%)	24 (11.8%)

	Clinician diagnosed MIS-C matched on WHO criteria					All patients with clinician diagnosed MIS-C		
	Overall (N=614)	**MIS-C (full WHO criteria) (N=490)**	**MIS-C with bacteremia or TSS (N=7)**	**MIS-C missing 1 other criterion (N=92)**	**MIS-C missing >1 criteria (N=25)**	**KD (N=225)**	**Atypical KD (N=186)**	**Not KD (N=203)**
^Significant comorbidity	21 (3.42%)	9 (1.84%)	1 (14.3%)	8 (8.70%)	3 (12.0%)	2 (0.889%)	4 (2.15%)	15 (7.39%)
^Home country economic status								
High-income economies	474 (77.2%)	366 (74.7%)	5 (71.4%)	82 (89.1%)	21 (84.0%)	164 (72.9%)	145 (78.0%)	165 (81.3%)
Upper-middle income economies	105 (17.1%)	94 (19.2%)	0 (0%)	8 (8.70%)	3 (12.0%)	49 (21.8%)	26 (14.0%)	30 (14.8%)
Lower-middle income economies	35 (5.70%)	30 (6.12%)	2 (28.6%)	2 (2.17%)	1 (4.00%)	12 (5.33%)	15 (8.06%)	8 (3.94%)
^SARS-CoV-2 PCR positive								
Yes	133 (21.9%)	113 (23.3%)	1 (14.3%)	13 (14.4%)	6 (25.0%)	39 (17.5%)	38 (20.8%)	56 (28.0%)
Tested but negative	427 (70.5%)	335 (69.1%)	6 (85.7%)	69 (76.7%)	17 (70.8%)	171 (76.7%)	125 (68.3%)	131 (65.5%)
Not tested	46 (7.59%)	37 (7.63%)	0 (0%)	8 (8.89%)	1 (4.17%)	13 (5.83%)	20 (10.9%)	13 (6.50%)
^SARS-CoV-2 Ab positive								
Yes	424 (70.4%)	390 (80.6%)	6 (85.7%)	23 (26.1%)	5 (21.7%)	168 (76.4%)	137 (74.9%)	119 (59.8%)
Tested but negative	89 (14.8%)	42 (8.68%)	1 (14.3%)	38 (43.2%)	8 (34.8%)	30 (13.6%)	27 (14.8%)	32 (16.1%)
Not tested	89 (14.8%)	52 (10.7%)	0 (0%)	27 (30.7%)	10 (43.5%)	22 (10.0%)	19 (10.4%)	48 (24.1%)
^At admission level of care								
No support	424 (69.1%)	327 (66.7%)	1 (14.3%)	74 (80.4%)	22 (88.0%)	159 (70.7%)	139 (74.7%)	126 (62.1%)
Oxygen	52 (8.47%)	41 (8.37%)	4 (57.1%)	7 (7.61%)	0 (0%)	14 (6.22%)	14 (7.53%)	24 (11.8%)
Inotropes	73 (11.9%)	68 (13.9%)	0 (0%)	5 (5.43%)	0 (0%)	28 (12.4%)	23 (12.4%)	22 (10.8%)
Ventilation	9 (1.47%)	6 (1.22%)	1 (14.3%)	0 (0%)	2 (8.00%)	4 (1.78%)	2 (1.08%)	3 (1.48%)
Inotropes and ventilation or ECMO	56 (9.12%)	48 (9.80%)	1 (14.3%)	6 (6.52%)	1 (4.00%)	20 (8.89%)	8 (4.30%)	28 (13.8%)
^Clinical features on admission								
Fever	580 (94.5%)	472 (96.3%)	7 (100%)	83 (90.2%)	18 (72.0%)	218 (96.9%)	181 (97.3%)	181 (89.2%)
Sore throat	149 (27.9%)	124 (28.0%)	3 (50.0%)	18 (26.1%)	4 (23.5%)	57 (28.2%)	59 (34.9%)	33 (20.1%)

	Clinician diagnosed MIS-C matched on WHO criteria					All patients with clinician diagnosed MIS-C		
	Overall (N=614)	**MIS-C (full WHO criteria) (N=490)**	**MIS-C with bacteremia or TSS (N=7)**	**MIS-C missing 1 other criterion (N=92)**	**MIS-C missing >1 criteria (N=25)**	**KD (N=225)**	**Atypical KD (N=186)**	**Not KD (N=203)**
Cough	124 (21.8%)	102 (22.0%)	2 (40.0%)	16 (19.5%)	4 (22.2%)	42 (19.4%)	39 (21.8%)	43 (24.9%)
Respiratory distress	88 (15.3%)	71 (15.4%)	3 (50.0%)	10 (11.2%)	4 (21.1%)	31 (14.4%)	21 (11.8%)	36 (19.8%)
Abdominal pain	365 (63.7%)	316 (67.7%)	2 (33.3%)	42 (50.0%)	5 (31.3%)	125 (59.8%)	125 (69.8%)	115 (62.2%)
Diarrhea	281 (48.0%)	243 (51.3%)	4 (57.1%)	30 (35.3%)	4 (20.0%)	91 (41.7%)	93 (52.0%)	97 (51.3%)
Vomiting	324 (56.1%)	275 (58.8%)	2 (33.3%)	43 (50.6%)	4 (21.1%)	126 (57.3%)	101 (57.1%)	97 (53.6%)
Headache	164 (31.6%)	140 (33.2%)	2 (50.0%)	20 (26.0%)	2 (12.5%)	54 (28.3%)	52 (32.5%)	58 (34.5%)
Encephalopathy	19 (3.39%)	17 (3.74%)	0 (0%)	0 (0%)	2 (10.5%)	9 (4.27%)	4 (2.35%)	6 (3.35%)
Irritability	116 (20.9%)	95 (21.1%)	1 (20.0%)	15 (19.5%)	5 (22.7%)	61 (28.5%)	28 (16.8%)	27 (15.6%)
Lethargy	222 (39.4%)	183 (39.8%)	2 (33.3%)	35 (43.2%)	2 (11.8%)	94 (42.9%)	70 (41.7%)	58 (32.8%)
^Kawasaki Disease features during admission								
Rash	396 (64.5%)	323 (65.9%)	5 (71.4%)	56 (60.9%)	12 (48.0%)	208 (92.4%)	134 (72.0%)	54 (26.6%)
Oral mucosal changes	327 (53.3%)	272 (55.5%)	3 (42.9%)	42 (45.7%)	10 (40.0%)	208 (92.4%)	97 (52.2%)	22 (10.8%)
Conjunctival injection	365 (59.4%)	305 (62.2%)	3 (42.9%)	46 (50.0%)	11 (44.0%)	202 (89.8%)	118 (63.4%)	45 (22.2%)
Edema or erythema of extremities	233 (37.9%)	199 (40.6%)	2 (28.6%)	23 (25.0%)	9 (36.0%)	143 (63.6%)	66 (35.5%)	24 (11.8%)
Skin peeling	75 (12.2%)	60 (12.2%)	1 (14.3%)	11 (12.0%)	3 (12.0%)	54 (24.0%)	13 (6.99%)	8 (3.94%)
Lymphadenopathy	224 (36.5%)	184 (37.6%)	1 (14.3%)	33 (35.9%)	6 (24.0%)	159 (70.7%)	50 (26.9%)	15 (7.39%)
BCG reactivity	24 (3.91%)	20 (4.08%)	0 (0%)	2 (2.17%)	2 (8.00%)	12 (5.33%)	8 (4.30%)	4 (1.97%)
+Bloods on admission								
WBC (10^9/L)	10 [7.0 - 14]	9.9 [7.0 - 14]	9.8 [4.7 - 13]	11 [7.6 - 16]	8.2 [5.0 - 13]	10 [7.1 - 14]	9.8 [7.3 - 14]	10 [6.5 - 15]
Neutrophils (10^9/L)	7.5 [5.1 - 11]	7.5 [5.1 - 11]	9.8 [5.2 - 12]	8.3 [5.5 - 12]	4.4 [2.7 - 8.7]	7.8 [5.1 - 11]	7.4 [5.4 - 11]	7.3 [4.2 - 12]
Lymphocytes (10^9/L)	1.2 [0.74 - 1.9]	1.1 [0.70 - 1.8]	1.3 [0.70 - 1.4]	1.4 [0.90 - 2.3]	2.6 [1.4 - 3.7]	1.3 [0.75 - 2.1]	1.2 [0.74 - 1.8]	1.2 [0.73 - 1.8]

	Clinician diagnosed MIS-C matched on WHO criteria					All patients with clinician diagnosed MIS-C		
	Overall (N=614)	**MIS-C (full WHO criteria) (N=490)**	**MIS-C with bacteremia or TSS (N=7)**	**MIS-C missing 1 other criterion (N=92)**	**MIS-C missing >1 criteria (N=25)**	**KD (N=225)**	**Atypical KD (N=186)**	**Not KD (N=203)**
Hemoglobin (g/L)	120 [110 - 130]	120 [100 - 130]	110 [99 - 110]	110 [110 - 130]	120 [110 - 120]	120 [100 - 120]	120 [110 - 130]	110 [110 - 130]
Platelets (10^9/L)	180 [120 - 260]	170 [120 - 240]	150 [140 - 170]	250 [170 - 340]	270 [230 - 370]	170 [120 - 240]	180 [120 - 260]	200 [140 - 280]
PT (sec)	15 [13 - 17]	15 [13 - 17]	16 [12 - 19]	15 [12 - 17]	14 [13 - 16]	15 [13 - 17]	15 [13 - 17]	15 [12 - 18]
APTT (sec)	32 [28 - 37]	32 [28 - 37]	34 [33 - 42]	34 [28 - 37]	31 [20 - 39]	33 [27 - 37]	32 [28 - 36]	33 [28 - 39]
Fibrinogen (g/L)	5.6 [4.5 - 6.8]	5.7 [4.6 - 6.8]	6.0 [4.5 - 7.0]	5.6 [4.0 - 6.9]	4.9 [4.6 - 5.4]	5.6 [4.7 - 6.7]	5.8 [4.6 - 6.9]	5.7 [4.2 - 6.8]
D Dimer (ng/mL)	2200 [1000 - 4200]	2300 [1000 - 4300]	4000 [2800 - 5200]	1700 [1000 - 3600]	980 [540 - 9100]	2200 [1000 - 4200]	2100 [1100 - 4200]	2200 [930 - 4500]
Troponin (ng/L)	42 [10 - 190]	46 [12 - 200]	48 [30 - 61]	22 [5.0 - 170]	4.0 [3.4 - 9.3]	42 [10 - 120]	27 [10 - 90]	51 [12 - 300]
BNP (ng/L)	130 [35 - 650]	150 [42 - 700]	2700 [1500 - 4000]	62 [19 - 150]	7.5 [6.3 - 8.8]	170 [33 - 660]	82 [36 - 480]	130 [43 - 660]
CRP (mg/L)	150 [90 - 230]	150 [90 - 230]	300 [200 - 410]	130 [62 - 210]	51 [12 - 120]	150 [90 - 220]	170 [110 - 250]	140 [61 - 220]
Ferritin (ug/L)	460 [230 - 860]	480 [250 - 900]	1400 [1100 - 1500]	320 [190 - 580]	160 [93 - 380]	530 [260 - 910]	440 [240 - 860]	420 [180 - 800]
LDH (U/L)	340 [260 - 470]	340 [260 - 470]	740 [710 - 880]	290 [240 - 380]	330 [310 - 450]	320 [250 - 440]	340 [260 - 490]	350 [280 - 510]
Creatinine (µmol/L)	47 [36 - 66]	48 [37 - 68]	93 [88 - 110]	40 [33 - 53]	41 [24 - 53]	43 [33 - 56]	50 [39 - 68]	53 [37 - 72]
ALT (U/L)	29 [18 - 52]	31 [19 - 54]	60 [31 - 100]	22 [11 - 45]	18 [14 - 31]	30 [19 - 54]	31 [19 - 52]	27 [17 - 51]
Albumin (g/L)	33 [28 - 38]	32 [28 - 38]	30 [29 - 33]	33 [28 - 39]	41 [35 - 43]	32 [28 - 37]	33 [29 - 39]	33 [28 - 39]

[^]Clinical and demographic features given as raw values and (%).
[+]Numerical values given as median values and [interquartile ranges].

Table S4 | Distribution of patients meeting WHO criteria subdivided by Kawasaki Disease status and initial treatment given.
Table showing patients matched on MIS-C WHO criteria and divided by whether they met the definition of Kawasaki Disease set out by the American Heart Association (persistent fever, and at least 4 of the 5 following mucocutaneous features: erythema and cracking lips; strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral non-purulent conjunctivitis; rash; erythema and edema of the hands and feet and/or skin peeling; and lymphadenopathy). Patients with coronary artery aneurysms were also classified as Kawasaki Disease, even if they did not have at least 4 mucocutaneous features. Atypical KD was defined as patients with persistent fever, CRP >30, and meeting at least 2 or 3 mucocutaneous features. These columns are compared with the primary treatments received on day 0, and whether they were under 6 or over 6. IVIG is used proportionately more in those meeting AHA criteria. Values given as raw values and (%). Abbreviations: KD: Kawasaki Disease; TSS: toxic shock syndrome.

	MIS-C (full WHO criteria)			**MIS-C with bacteremia or TSS**			**MIS-C missing 1 other criterion**			**MIS-C missing >1 criteria**			**All patients**		
	KD (N=193)	**Atypical KD (N=160)**	**Not KD (N=137)**	**KD (N=1)**	**Atypical KD (N=3)**	**Not KD (N=3)**	**KD (N=24)**	**Atypical KD (N=19)**	**Not KD (N=49)**	**KD (N=7)**	**Atypical KD (N=4)**	**Not KD (N=14)**	**KD (N=225)**	**Atypical KD (N=186)**	**Not KD (N=203)**
Age (years)															
Over 6	105 (54.4%)	120 (75.0%)	103 (75.2%)	1 (100%)	1 (33.3%)	3 (100%)	12 (50.0%)	8 (42.1%)	34 (69.4%)	2 (28.6%)	0 (0%)	7 (50.0%)	120 (53.3%)	129 (69.4%)	147 (72.4%)
Under 6	88 (45.6%)	40 (25.0%)	34 (24.8%)	0 (0%)	2 (66.7%)	0 (0%)	12 (50.0%)	11 (57.9%)	15 (30.6%)	5 (71.4%)	4 (100%)	7 (50.0%)	105 (46.7%)	57 (30.6%)	56 (27.6%)
First immunomodulator given															
IVIG	83 (43.0%)	61 (38.1%)	48 (35.0%)	0 (0%)	1 (33.3%)	0 (0%)	18 (75.0%)	12 (63.2%)	13 (26.5%)	5 (71.4%)	2 (50.0%)	3 (21.4%)	106 (47.1%)	76 (40.9%)	64 (31.5%)
Glucocorticoid	25 (13.0%)	29 (18.1%)	24 (17.5%)	0 (0%)	2 (66.7%)	1 (33.3%)	4 (16.7%)	1 (5.26%)	12 (24.5%)	1 (14.3%)	0 (0%)	0 (0%)	30 (13.3%)	32 (17.2%)	37 (18.2%)
IVIG and glucocorticoid	79 (40.9%)	56 (35.0%)	51 (37.2%)	1 (100%)	0 (0%)	0 (0%)	1 (4.17%)	3 (15.8%)	11 (22.4%)	1 (14.3%)	0 (0%)	5 (35.7%)	82 (36.4%)	59 (31.7%)	67 (33.0%)
Other	5 (2.59%)	6 (3.75%)	5 (3.65%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (10.2%)	0 (0%)	0 (0%)	1 (7.14%)	5 (2.22%)	6 (3.23%)	11 (5.42%)
No treatment	1 (0.518%)	8 (5.00%)	9 (6.57%)	0 (0%)	0 (0%)	2 (66.7%)	1 (4.17%)	3 (15.8%)	8 (16.3%)	0 (0%)	2 (50.0%)	5 (35.7%)	2 (0.889%)	13 (6.99%)	24 (11.8%)

Table S5 | Primary Outcomes and Sensitivity Analyses
Table showing the odds ratios and 95% confidence intervals for the primary outcomes in patients who received a combination of IVIG and glucocorticoids as primary treatment vs IVIG alone and patients who received glucocorticoids alone as primary treatment vs IVIG. Crude numbers are shown in the second column as the numerator/denominator for those providing the outcome, and the number where the outcome is unavailable in parentheses. Weighted proportions are also shown. The E-value for the strength of unmeasured confounding necessary to move a point estimate to the null value is shown for primary outcomes.

Primary Outcomes					
	Raw and weighted proportions (missing)	Odds Ratio	Confidence Interval (95%)	Adj. p value	E-value
IVIG+Glucocorticoids vs IVIG					
On Inotropes/Ventilated D2+ or Death	IVIG: 44/211 (20.9%; 6 missing). Weighted: 31.2% IVIG+S: 56/180 (31.1%; 17 missing). Weighted: 28.1%	0.77	0.33 - 1.82	p=1	1.5
Improvement D2	IVIG: 54/191 (28.3%; 26 missing). Weighted: 29.6% IVIG+S: 54/166 (32.5%; 31 missing). Weighted: 28.3%	0.9	0.48 - 1.69	p=1	1.3
Glucocorticoids vs IVIG					
On Inotropes/Ventilated D2+ or Death	IVIG: 44/211 (20.9%; 6 missing). Weighted: 31.2% S: 17/83 (20.5%; 6 missing). Weighted: 26.4%	0.54	0.22 - 1.33	p=0.7	2.1
Improvement D2	IVIG: 54/191 (28.3%; 26 missing). Weighted: 29.6% S: 20/77 (26%; 12 missing). Weighted: 30.6%	0.93	0.43 - 2.04	p=1	1.2

Table S5 | Secondary Outcomes and Time to Event Analyses
A: Table showing the odds ratio and 95% confidence interval for each of the secondary outcomes for patients who received a combination of IVIG and glucocorticoids as primary treatment vs IVIG alone and patients who received glucocorticoids alone as primary treatment vs IVIG. Crude numbers for dichotomous outcomes are shown in the second column as the numerator/denominator for those providing the outcome, and the number where the outcome is unavailable in parentheses. Weighted proportions are also given.
B: Results of sensitivity analyses in subsets of patients that met the WHO MIS-C criteria and those where primary treatments were defined as first treatments over two consecutive days (day 0-1).
C: Table showing the average hazard ratios and 95% confidence intervals for time to stop inotropes, ventilation, oxygen and time to improvement for patients who received a combination of IVIG and glucocorticoids as primary treatment vs IVIG alone and patients who received glucocorticoids alone as primary treatment vs IVIG.

5A

Secondary Outcomes			
	Raw and weighted proportions (missing)	Odds Ratio	Confidence Interval (95%)
IVIG+Glucocorticoid vs IVIG			
Inotropes D2+	IVIG: 38/216 (17.6%; 1 missing). Weighted: 22.9% IVIG+S: 49/189 (25.9%; 8 missing). Weighted: 24.9%	1.43	0.57 - 3.62
Ventilation D2+	IVIG: 21/208 (10.1%; 9 missing). Weighted: 9% IVIG+S: 30/183 (16.4%; 14 missing). Weighted: 11.8%	1.1	0.39 - 3.09
Improvement D3	IVIG: 105/202 (52%; 15 missing). Weighted: 53.4% IVIG+S: 96/166 (57.8%; 31 missing). Weighted: 52.9%	0.97	0.54 - 1.73
Treatment Escalation	IVIG: 114/216 (52.8%; 1 missing). Weighted: 54.8% IVIG+S: 39/194 (20.1%; 3 missing). Weighted: 21.2%	0.18	0.10 - 0.33
Treatment Escalation D0/1	IVIG: 41/143 (28.7%; 2 missing). Weighted: 25.7% IVIG+S: 32/275 (11.6%; 4 missing). Weighted: 12.5%	0.33	0.16 - 0.71
Fever D2+	IVIG: 86/182 (47.3%; 35 missing). Weighted: 48% IVIG+S: 55/149 (36.9%; 48 missing). Weighted: 37.5%	0.6	0.31 - 1.17
Fever D3+	IVIG: 31/172 (18%; 45 missing). Weighted: 18.2% IVIG+S: 32/143 (22.4%; 54 missing). Weighted: 19.3%	1.1	0.46 - 2.63
Death	IVIG: 3/213 (1.4%; 4 missing). Weighted: 3.6% IVIG+S: 5/184 (2.7%; 13 missing). Weighted: 1.2%	0.32	0.05 - 1.86
Any Deterioration	IVIG: 23/213 (10.8%; 4 missing). Weighted: 10%	1.22	0.55 - 2.71

Secondary Outcomes			
	Raw and weighted proportions (missing)	Odds Ratio	Confidence Interval (95%)
	IVIG+S: 28/187 (15%; 10 missing). Weighted: 11.9%		
LV Dysfunction D2+	IVIG: 23/215 (10.7%; 2 missing). Weighted: 8.5% IVIG+S: 28/188 (14.9%; 9 missing). Weighted: 13.6%	1.65	0.78 - 3.49
Aneurysm	IVIG: 10/143 (7%; 74 missing). Weighted: 5.4% IVIG+S: 6/115 (5.2%; 82 missing). Weighted: 4.3%	0.32	0.03 - 3.21
Glucocorticoid vs IVIG			
Inotropes D2+	IVIG: 38/216 (17.6%; 1 missing). Weighted: 22.9% S: 16/87 (18.4%; 2 missing). Weighted: 23.6%	1.38	0.54 - 3.51
Ventilation D2+	IVIG: 21/208 (10.1%; 9 missing). Weighted: 9% S: 7/87 (8%; 2 missing). Weighted: 10.1%	0.83	0.28 - 2.49
Improvement D3	IVIG: 105/202 (52%; 15 missing). Weighted: 53.4% S: 34/78 (43.6%; 11 missing). Weighted: 50.3%	0.87	0.43 - 1.75
Treatment Escalation	IVIG: 114/216 (52.8%; 1 missing). Weighted: 54.8% S: 49/88 (55.7%; 1 missing). Weighted: 59.9%	1.31	0.64 - 2.68
Treatment Escalation D0/1	IVIG: 41/143 (28.7%; 2 missing). Weighted: 25.7% S: 19/58 (32.8%; 1 missing). Weighted: 32%	1.42	0.54 - 3.73
Fever D2+	IVIG: 86/182 (47.3%; 35 missing). Weighted: 48% S: 36/75 (48%; 14 missing). Weighted: 46.7%	0.95	0.43 - 2.09
Fever D3+	IVIG: 31/172 (18%; 45 missing). Weighted: 18.2% S: 25/71 (35.2%; 18 missing). Weighted: 31.4%	2.44	0.93 - 6.42
Death	IVIG: 3/213 (1.4%; 4 missing). Weighted: 3.6% S: 3/83 (3.6%; 6 missing). Weighted: 9%	2.64	0.36 - 19.58
Any Deterioration	IVIG: 23/213 (10.8%; 4 missing). Weighted: 10% S: 13/84 (15.5%; 5 missing). Weighted: 18.7%	1.92	0.79 - 4.67
LV Dysfunction D2+	IVIG: 23/215 (10.7%; 2 missing). Weighted: 8.5% S: 7/87 (8%; 2 missing). Weighted: 7.7%	0.85	0.24 - 2.96
Aneurysm	IVIG: 10/143 (7%; 74 missing). Weighted: 5.4%	0.95	0.24 - 3.74

Secondary Outcomes			
	Raw and weighted proportions (missing)	Odds Ratio	Confidence Interval (95%)
	S: 4/68 (5.9%; 21 missing). Weighted: 5.6%		

5B

Secondary Analyses - Patients who met WHO MIS-C criteria			
	Raw and weighted proportions (missing)	Odds Ratio	Confidence Interval (95%)
IVIG+Glucocorticoid vs IVIG			
On Inotropes/Ventilated D2+ or Death	IVIG: 40/169 (23.7%; 4 missing). Weighted: 30.2% IVIG+S: 54/162 (33.3%; 15 missing). Weighted: 28.6%	0.95	0.37 - 2.45
Improvement D2	IVIG: 43/152 (28.3%; 21 missing). Weighted: 26.8% IVIG+S: 52/152 (34.2%; 25 missing). Weighted: 28.4%	1.09	0.53 - 2.23
Glucocorticoid vs IVIG			
On Inotropes/Ventilated D2+ or Death	IVIG: 40/169 (23.7%; 4 missing). Weighted: 30.2% S: 12/68 (17.6%; 2 missing). Weighted: 19%	0.3	0.10 - 0.85
Improvement D2	IVIG: 43/152 (28.3%; 21 missing). Weighted: 26.8% S: 16/60 (26.7%; 10 missing). Weighted: 40.8%	1.95	0.83 - 4.60
Sensitivity Analyses - D0/1 as day of starting primary treatment			
	Raw and weighted proportions (missing)	Odds Ratio	Confidence Interval (95%)
IVIG+Glucocorticoid vs IVIG			
On Inotropes/Ventilated D2+ or Death	IVIG: 21/140 (15%; 5 missing). Weighted: 23.9% IVIG+S: 81/260 (31.2%; 19 missing). Weighted: 26.8%	1.27	0.51 - 3.12
Improvement D2	IVIG: 38/126 (30.2%; 19 missing). Weighted: 36.4% IVIG+S: 71/240 (29.6%; 39 missing). Weighted: 26.1%	0.54	0.27 - 1.05
Glucocorticoid vs IVIG			
On Inotropes/Ventilated D2+ or Death	IVIG: 21/140 (15%; 5 missing). Weighted: 23.9% S: 9/55 (16.4%; 4 missing). Weighted: 15.9%	0.33	0.09 - 1.14
Improvement D2	IVIG: 38/126 (30.2%; 19 missing). Weighted: 36.4% IVIG+S: 71/240 (29.6%; 39 missing). Weighted: 26.1%	1.01	0.41 - 2.48

5C

Time to Event Analyses

	Groups and censoring	Average Hazard Ratio	Confidence Interval (95%)
IVIG+Glucocorticoid vs IVIG			
Time to stop inotropes^	IVIG: n=32; 3 censored. IVIG+S: n=62; 12 censored.	1.23	0.646 - 2.339
Time to stop ventilation^	IVIG: n=21; 9 censored. IVIG+S: n=24; 6 censored.	1.52	0.506 - 4.565
Time to stop oxygen^	IVIG: n=30; 3 censored. IVIG+S: n=51; 12 censored.	0.93	0.502 - 1.739
Time to improvement^	IVIG: n=216; 16 censored. IVIG+S: n=196; 21 censored.	0.89	0.665 - 1.185
Glucocorticoid vs IVIG			
Time to stop inotropes^	IVIG: n=32; 3 censored. S: n=18; 2 censored.	1.31	0.71 - 2.407
Time to stop ventilation^	IVIG: n=21; 9 censored. S: n=8; 3 censored.	1.41	0.375 - 5.288
Time to stop oxygen^	IVIG: n=30; 3 censored. S: n=22; 2 censored.	1.60	0.840 - 3.058
Time to improvement^	IVIG: n=216; 16 censored. S: n=89; 6 censored.	1.03	0.727 - 1.460

Table S6 | Coronary artery aneurysms by initial immunomodulatory therapy groups

Initial immunomodulatory therapy	Number of patients	Aneurysms pre-treatment	Aneurysms after treatment	Timing of last post-treatment echocardiogram median days (IQR)
IVIG	246	16/65 (181 unknown)	19/201 (45 unknown)	5 (2-8)
IVIG+ Glucocorticoid	208	16/77 (131 unknown)	11/149 (59 unknown)	5 (3-9)
Glucocorticoid	99	0/16 (83 unknown)	4/84 (15 unknown)	6 (3-10.25)
No immunomodulator	39	0/0 (39 unknown)	0/29 (10 unknown)	4 (3-7)
Other treatment combination	22	5/13 (9 unknown)	4/20 (2 unknown)	3.5 (2.75-5.25)

Table S7 | Treatment related complications
Treatment related complications reported by clinicians.

Treatment	Complication	Number of patients
Glucocorticoid	Profound Bradycardia	1
	Hyperglycaemia	7
	Glucocorticoid-induced hypertension	7
	Other complication not specified	1
	Total (% of patients receiving glucocorticoids)	16/411 (3.9%)
IVIG	Mild rash and lip swelling	1
	Other complication not specified	8
	Total (% of patients receiving IVIG)	9/508 (1.8%)
Anakinra	Superficial cutaneous skin reaction	1
Anticoagulant	Significant bleeding	1
	Mild bleeding	1
ECMO	Cerebrovascular accident	1
Vancomycin	Acute kidney injury	1

Table S8 | Coefficients for covariate-balancing propensity score multinomial model
Primary outcome: inotropes/ventilation day 2+ or death

J - statistic: 0.6427698 Log-Likelihood: -459.3349	Estimate	Std. Error	z value	Pr(>|z|)
IVIG: (Intercept)	9.1273488	3.2637292	2.7966012	0.0051643
IVIG: baseline_resource_groupHigh.income.economies	0.7105361	0.1346049	5.2786797	0.0000001
IVIG: baseline_resource_groupLower.middle.income.economies	-1.0793630	0.1487181	-7.2577802	0.0000000
IVIG: baseline_age	0.2885691	0.1686887	1.7106609	0.0871437
IVIG: baseline_weight_z_over_2	-0.6335239	0.1364810	-4.6418469	0.0000035
IVIG: baseline_weight_z_missingTRUE	-2.0015045	0.1335843	-14.9830823	0.0000000
IVIG: baseline_sig_comorbidityYes	-0.9945116	0.1752417	-5.6750842	0.0000000
IVIG: baseline_fever_days_at_treating_admission	0.2177913	0.1266418	1.7197427	0.0854792
IVIG: baseline_fever_days_missingTRUE	0.1188209	0.1207425	0.9840847	0.3250739
IVIG: genderMale	-0.1179749	0.1671981	-0.7055998	0.4804370
IVIG: baseline_number_clin_feat	0.0939253	0.1431293	0.6562270	0.5116781
IVIG: baseline_admission_day_at_treatment	-0.1173088	0.2014868	-0.5822160	0.5604212
IVIG: baseline_covid_positivePCR	-1.0568009	0.1546772	-6.8323006	0.0000000
IVIG: baseline_covid_positiveSerology	0.3088184	0.1410060	2.1901085	0.0285164
IVIG: baseline_peak_levin_LOCNo.support.CRP...50	-2.1685618	0.1811456	-11.9713769	0.0000000
IVIG: baseline_peak_levin_LOCNo.support.CRP.unknown	-0.4008751	0.2486952	-1.6119135	0.1069808
IVIG: baseline_peak_levin_LOCNo.support.CRP....50	-0.0170510	0.2727179	-0.0625227	0.9501466
IVIG: baseline_peak_levin_LOCOxygen	-0.1874003	0.2220194	-0.8440720	0.3986292
IVIG: baseline_peak_levin_LOCInotropes	1.1078531	0.2209830	5.0132943	0.0000005
IVIG: baseline_peak_levin_LOCVentilation	-1.2116638	0.1864877	-6.4972843	0.0000000
IVIG: baseline_peak_CRP.75th	-0.1412343	0.1602199	-0.8815024	0.3780459
IVIG: baseline_peak_CRP25.50th	-0.4762655	0.1584424	-3.0059229	0.0026478
IVIG: baseline_peak_CRP50.75th	0.3055584	0.1582154	1.9312814	0.0534483
IVIG: baseline_peak_CRPMissing	-0.5614239	0.2281199	-2.4610918	0.0138515
IVIG: baseline_peak_ddimer.75th	0.2302374	0.1987300	1.1585437	0.2466422
IVIG: baseline_peak_ddimer25.50th	0.2034261	0.1958822	1.0385126	0.2990315
IVIG: baseline_peak_ddimer50.75th	-0.7322349	0.1926503	-3.8008500	0.0001442
IVIG: baseline_peak_ddimerMissing	0.5034953	0.2207765	2.2805655	0.0225742
IVIG+G: (Intercept)	4.2697071	5.2837250	0.8080865	0.4190408
IVIG+G: baseline_resource_groupHigh.income.economies	2.5823048	0.2432365	10.6164361	0.0000000
IVIG+G: baseline_resource_groupLower.middle.income.economies	-1.6934589	0.2549718	-6.6417501	0.0000000
IVIG+G: baseline_age	0.9965438	0.3440187	2.8967718	0.0037702
IVIG+G: baseline_weight_z_over_2	0.8686548	0.1964212	4.4224082	0.0000098
IVIG+G: baseline_weight_z_missingTRUE	-1.6943983	0.2305578	-7.3491267	0.0000000
IVIG+G: baseline_sig_comorbidityYes	-1.9618243	0.2887382	-6.7944743	0.0000000
IVIG+G: baseline_fever_days_at_treating_admission	0.3873925	0.1927034	2.0103039	0.0443990
IVIG+G: baseline_fever_days_missingTRUE	-1.2798756	0.1912329	-6.6927592	0.0000000
IVIG+G: genderMale	-0.2115380	0.2885544	-0.7330958	0.4635000
IVIG+G: baseline_number_clin_feat	-1.5966681	0.2315833	-6.8945738	0.0000000
IVIG+G: baseline_admission_day_at_treatment	0.0330626	0.3487229	0.0948106	0.9244653
IVIG+G: baseline_covid_positivePCR	-1.6921022	0.2238540	-7.5589531	0.0000000
IVIG+G: baseline_covid_positiveSerology	0.7081940	0.2157062	3.2831412	0.0010266
IVIG+G: baseline_peak_levin_LOCNo.support.CRP...50	-1.1079819	0.2830362	-3.9146297	0.0000905
IVIG+G: baseline_peak_levin_LOCNo.support.CRP.unknown	0.5444296	0.3888916	1.3999522	0.1615276
IVIG+G: baseline_peak_levin_LOCNo.support.CRP....50	1.2637763	0.3971384	3.1822065	0.0014616
IVIG+G: baseline_peak_levin_LOCOxygen	1.3649816	0.3373189	4.0465608	0.0000520
IVIG+G: baseline_peak_levin_LOCInotropes	-0.4881318	0.3711278	-1.3152661	0.1884205
IVIG+G: baseline_peak_levin_LOCVentilation	2.4988654	0.2717252	9.1962961	0.0000000
IVIG+G: baseline_peak_CRP.75th	-1.8028860	0.2244911	-8.0309892	0.0000000
IVIG+G: baseline_peak_CRP25.50th	-1.1610928	0.2188572	-5.3052524	0.0000001
IVIG+G: baseline_peak_CRP50.75th	-1.0317221	0.2264094	-4.5568873	0.0000052
IVIG+G: baseline_peak_CRPMissing	-0.8985850	0.3451813	-2.6032262	0.0092351
IVIG+G: baseline_peak_ddimer.75th	1.2642562	0.3070198	4.1178328	0.0000382
IVIG+G: baseline_peak_ddimer25.50th	-1.1656636	0.3119981	-3.7361246	0.0001869
IVIG+G: baseline_peak_ddimer50.75th	-0.5809624	0.3279889	-1.7712864	0.0765131
IVIG+G: baseline_peak_ddimerMissing	0.6587579	0.3431995	1.9194607	0.0549261

Table S9 | Coefficients for covariate-balancing propensity score multinomial model
Primary outcome: improvement by day 2

J - statistic: 1.021868 Log-Likelihood: -426.1468	Estimate	Std. Error	z value	Pr(>|z|)
IVIG: (Intercept)	6.2087905	4.4554055	1.3935411	0.1634562
IVIG: baseline_resource_groupHigh.income.economies	1.0256911	0.1570956	6.5290896	0.0000000
IVIG: baseline_resource_groupLower.middle.income.economies	-0.4974489	0.1566625	-3.1752909	0.0014969
IVIG: baseline_age	0.3224193	0.1487008	2.1682421	0.0301403
IVIG: baseline_weight_z_over_2	-0.8039662	0.1807795	-4.4472192	0.0000087
IVIG: baseline_weight_z_missingTRUE	-2.6181433	0.1585445	-16.5136178	0.0000000
IVIG: baseline_sig_comorbidityYes	-1.1843598	0.2182033	-5.4277804	0.0000001
IVIG: baseline_fever_days_at_treating_admission	0.4004949	0.1828159	2.1907008	0.0284735
IVIG: baseline_fever_days_missingTRUE	-0.6343413	0.2209236	-2.8713156	0.0040877
IVIG: genderMale	0.0645182	0.2012557	0.3205783	0.7485300
IVIG: baseline_number_clin_feat	0.0536852	0.1795748	0.2989570	0.7649729
IVIG: baseline_admission_day_at_treatment	-0.0352195	0.1453885	-0.2422442	0.8085910
IVIG: baseline_covid_positivePCR	-0.9682758	0.1819756	-5.3209104	0.0000001
IVIG: baseline_covid_positiveSerology	0.5020153	0.1610568	3.1170075	0.0018270
IVIG: baseline_peak_levin_LOCNo.support.CRP...50	-2.7504627	0.1940379	-14.1748702	0.0000000
IVIG: baseline_peak_levin_LOCNo.support.CRP.unknown	0.0358762	0.2705509	0.1326041	0.8945065
IVIG: baseline_peak_levin_LOCNo.support.CRP....50	0.1880336	0.2866932	0.6558704	0.5119075
IVIG: baseline_peak_levin_LOCOxygen	-0.5790028	0.2091684	-2.7681186	0.0056381
IVIG: baseline_peak_levin_LOCInotropes	1.4360265	0.2113477	6.7946159	0.0000000
IVIG: baseline_peak_levin_LOCVentilation	-0.6814367	0.1935498	-3.5207311	0.0004304
IVIG: baseline_peak_CRP.75th	0.1141795	0.1844924	0.6188846	0.5359924
IVIG: baseline_peak_CRP25.50th	-0.2273779	0.1796400	-1.2657424	0.2056053
IVIG: baseline_peak_CRP50.75th	0.1512790	0.1729420	0.8747381	0.3817164
IVIG: baseline_peak_CRPMissing	1.7382398	0.1403379	12.3861026	0.0000000
IVIG: baseline_peak_ddimer.75th	0.4937935	0.2378905	2.0757179	0.0379201
IVIG: baseline_peak_ddimer25.50th	0.4379791	0.2262901	1.9354759	0.0529319
IVIG: baseline_peak_ddimer50.75th	-0.3195057	0.2244334	-1.4236099	0.1545594
IVIG: baseline_peak_ddimerMissing	0.8966589	0.2335803	3.8387600	0.0001237
IVIG+G: (Intercept)	2.9272363	6.8766626	0.4256769	0.6703433
IVIG+G: baseline_resource_groupHigh.income.economies	2.5751756	0.2624052	9.8137384	0.0000000
IVIG+G: baseline_resource_groupLower.middle.income.economies	-1.3400022	0.1798357	-7.4512598	0.0000000
IVIG+G: baseline_age	1.0941010	0.2668695	4.0997603	0.0000414
IVIG+G: baseline_weight_z_over_2	0.2004048	0.2504993	0.8000214	0.4236984
IVIG+G: baseline_weight_z_missingTRUE	-4.0567488	0.2732349	-14.8471118	0.0000000
IVIG+G: baseline_sig_comorbidityYes	-2.5214488	0.3387671	-7.4430149	0.0000000
IVIG+G: baseline_fever_days_at_treating_admission	0.2540829	0.2674601	0.9499844	0.3421202
IVIG+G: baseline_fever_days_missingTRUE	-1.1136317	0.3343701	-3.3305359	0.0008668
IVIG+G: genderMale	-0.1555245	0.2985997	-0.5208460	0.6024741
IVIG+G: baseline_number_clin_feat	-1.1577452	0.2449999	-4.7254926	0.0000023
IVIG+G: baseline_admission_day_at_treatment	0.1754861	0.2153247	0.8149835	0.4150817
IVIG+G: baseline_covid_positivePCR	-1.3040940	0.2884215	-4.5214860	0.0000061
IVIG+G: baseline_covid_positiveSerology	0.4947898	0.3037595	1.6288870	0.1033369
IVIG+G: baseline_peak_levin_LOCNo.support.CRP...50	-1.0915887	0.3129929	-3.4875824	0.0004874
IVIG+G: baseline_peak_levin_LOCNo.support.CRP.unknown	0.9080603	0.3873030	2.3445736	0.0190489
IVIG+G: baseline_peak_levin_LOCNo.support.CRP....50	0.8871051	0.4220534	2.1018788	0.0355639
IVIG+G: baseline_peak_levin_LOCOxygen	0.6429781	0.3119923	2.0608778	0.0393147
IVIG+G: baseline_peak_levin_LOCInotropes	0.5768457	0.3485192	1.6551333	0.0978975
IVIG+G: baseline_peak_levin_LOCVentilation	3.1125208	0.3303072	9.4231090	0.0000000
IVIG+G: baseline_peak_CRP.75th	-0.6711493	0.2585840	-2.5954791	0.0094459
IVIG+G: baseline_peak_CRP25.50th	-0.3699440	0.2397466	-1.5430625	0.1228156
IVIG+G: baseline_peak_CRP50.75th	-0.4361976	0.2404264	-1.8142668	0.0696367
IVIG+G: baseline_peak_CRPMissing	-0.0933997	0.1976525	-0.4725451	0.6365378
IVIG+G: baseline_peak_ddimer.75th	2.0472264	0.3386930	6.0444901	0.0000000
IVIG+G: baseline_peak_ddimer25.50th	-0.6182960	0.3438155	-1.7983368	0.0721237
IVIG+G: baseline_peak_ddimer50.75th	-0.4813378	0.3386380	-1.4213932	0.1552025
IVIG+G: baseline_peak_ddimerMissing	0.7455251	0.3476955	2.1441894	0.0320177

Table S10 | Coefficients for covariate-balancing propensity score multinomial model
WHO MIS-C: inotropes/ventilation day 2+ or death

J - statistic: 0.8325656 Log-Likelihood: -383.392	Estimate	Std. Error	z value	Pr(>|z|)
IVIG: (Intercept)	6.7570607	4.8937413	1.3807556	0.1673541
IVIG: baseline_resource_groupHigh.income.economies	0.7579875	0.2071986	3.6582653	0.0002539
IVIG: baseline_resource_groupLower.middle.income.economies	-2.5026254	0.1615026	-15.4958872	0.0000000
IVIG: baseline_age	0.1764513	0.1889932	0.9336380	0.3504906
IVIG: baseline_weight_z_over_2	-0.5165437	0.2374051	-2.1757899	0.0295710
IVIG: baseline_weight_z_missingTRUE	-1.7344596	0.2256947	-7.6849827	0.0000000
IVIG: baseline_sig_comorbidityYes	-2.3055166	0.1945926	-11.8479137	0.0000000
IVIG: baseline_fever_days_at_treating_admission	0.4675929	0.2083437	2.2443343	0.0248109
IVIG: baseline_fever_days_missingTRUE	-0.4361620	0.2142856	-2.0354232	0.0418083
IVIG: genderMale	0.0208245	0.1442207	0.1443932	0.8851900
IVIG: baseline_number_clin_feat	0.2462560	0.1886408	1.3054232	0.1917488
IVIG: baseline_admission_day_at_treatment	-0.2158588	0.1580558	-1.3657121	0.1720293
IVIG: baseline_covid_positivePCR	-0.1906752	0.2623994	-0.7266600	0.4674343
IVIG: baseline_covid_positiveSerology	-0.5367068	0.2582702	-2.0780826	0.0377018
IVIG: baseline_peak_levin_LOCNo.support.CRP...50	-2.4132790	0.1990227	-12.1256472	0.0000000
IVIG: baseline_peak_levin_LOCNo.support.CRP.unknown	0.6409686	0.2686110	2.3862336	0.0170219
IVIG: baseline_peak_levin_LOCNo.support.CRP....50	0.6186316	0.2859891	2.1631298	0.0305312
IVIG: baseline_peak_levin_LOCOxygen	0.1905222	0.2649242	0.7191572	0.4720440
IVIG: baseline_peak_levin_LOCInotropes	1.0738660	0.2425416	4.4275534	0.0000095
IVIG: baseline_peak_levin_LOCVentilation	-0.6482202	0.1424515	-4.5504622	0.0000054
IVIG: baseline_peak_CRP.75th	0.0733777	0.2688172	0.2729650	0.7848801
IVIG: baseline_peak_CRP25.50th	-0.4292321	0.2634300	-1.6293968	0.1032291
IVIG: baseline_peak_CRP50.75th	0.7225624	0.2304757	3.1350913	0.0017180
IVIG: baseline_peak_CRPMissing	1.1915781	0.1837588	6.4844696	0.0000000
IVIG: baseline_peak_ddimer.75th	1.0623448	0.2327594	4.5641334	0.0000050
IVIG: baseline_peak_ddimer25.50th	0.2362024	0.1729005	1.3661180	0.1719019
IVIG: baseline_peak_ddimer50.75th	-0.5869631	0.1738248	-3.3767523	0.0007335
IVIG: baseline_peak_ddimerMissing	0.8651297	0.2189859	3.9506178	0.0000779
IVIG+G: (Intercept)	17.1556074	9.1096727	1.8832298	0.0596692
IVIG+G: baseline_resource_groupHigh.income.economies	2.8102455	0.2895786	9.7046032	0.0000000
IVIG+G: baseline_resource_groupLower.middle.income.economies	-2.8157735	0.2294032	-12.2743423	0.0000000
IVIG+G: baseline_age	0.9922981	0.4939373	2.0089555	0.0445419
IVIG+G: baseline_weight_z_over_2	0.6166618	0.5156704	1.1958449	0.2317571
IVIG+G: baseline_weight_z_missingTRUE	-1.9018983	0.4266601	-4.4576427	0.0000083
IVIG+G: baseline_sig_comorbidityYes	-3.4968213	0.3539877	-9.8783697	0.0000000
IVIG+G: baseline_fever_days_at_treating_admission	0.8586581	0.3757605	2.2851208	0.0223057
IVIG+G: baseline_fever_days_missingTRUE	-2.5546394	0.4438105	-5.7561490	0.0000000
IVIG+G: genderMale	0.1850045	0.4762645	0.3884491	0.6976837
IVIG+G: baseline_number_clin_feat	-1.4955455	0.3221473	-4.6424267	0.0000034
IVIG+G: baseline_admission_day_at_treatment	-0.2823823	0.3131069	-0.9018717	0.3671250
IVIG+G: baseline_covid_positivePCR	-0.9129338	0.4467291	-2.0435960	0.0409935
IVIG+G: baseline_covid_positiveSerology	-0.1676171	0.4370840	-0.3834895	0.7013569
IVIG+G: baseline_peak_levin_LOCNo.support.CRP...50	-4.8601043	0.3409385	-14.2550748	0.0000000
IVIG+G: baseline_peak_levin_LOCNo.support.CRP.unknown	-1.9456557	0.4224032	-4.6061578	0.0000041
IVIG+G: baseline_peak_levin_LOCNo.support.CRP....50	-0.8345144	0.4893711	-1.7052793	0.0881423
IVIG+G: baseline_peak_levin_LOCOxygen	-0.5161434	0.4515802	-1.1429716	0.2530504
IVIG+G: baseline_peak_levin_LOCInotropes	1.8540887	0.4782456	3.8768549	0.0001058
IVIG+G: baseline_peak_levin_LOCVentilation	0.5345090	0.2475489	2.1592059	0.0308342
IVIG+G: baseline_peak_CRP.75th	-2.6601369	0.4384927	-6.0665472	0.0000000
IVIG+G: baseline_peak_CRP25.50th	-1.9665872	0.4879568	-4.0302486	0.0000557
IVIG+G: baseline_peak_CRP50.75th	-1.4004961	0.4000502	-3.5008014	0.0004639
IVIG+G: baseline_peak_CRPMissing	1.3404591	0.3276091	4.0916414	0.0000428
IVIG+G: baseline_peak_ddimer.75th	2.4073701	0.3184987	7.5584931	0.0000000
IVIG+G: baseline_peak_ddimer25.50th	-1.4617189	0.2547130	-5.7386892	0.0000000
IVIG+G: baseline_peak_ddimer50.75th	-0.6514437	0.2825733	-2.3053976	0.0211443
IVIG+G: baseline_peak_ddimerMissing	0.5009076	0.4020522	1.2458769	0.2128096

Table S11 | Coefficients for covariate-balancing propensity score multinomial model
WHO MIS-C: improvement by day 2

J - statistic: 1.624243 Log-Likelihood: -367.0137	Estimate	Std. Error	z value	Pr(>|z|)
IVIG: (Intercept)	6.9214310	4.7033819	1.4715860	0.1411327
IVIG: baseline_resource_groupHigh.income.economies	0.9219918	0.1620957	5.6879480	0.0000000
IVIG: baseline_resource_groupLower.middle.income.economies	-2.3185373	0.1775774	-13.0564876	0.0000000
IVIG: baseline_age	0.2081126	0.2733497	0.7613421	0.4464528
IVIG: baseline_weight_z_over_2	-0.4545378	0.1887692	-2.4079021	0.0160445
IVIG: baseline_weight_z_missingTRUE	-2.2467441	0.1842572	-12.1935239	0.0000000
IVIG: baseline_sig_comorbidityYes	-3.1235955	0.2283978	-13.6761206	0.0000000
IVIG: baseline_fever_days_at_treating_admission	0.6404073	0.2315007	2.7663303	0.0056691
IVIG: baseline_fever_days_missingTRUE	-1.6029855	0.2202776	-7.2771165	0.0000000
IVIG: genderMale	0.2842586	0.2370032	1.1993875	0.2303773
IVIG: baseline_number_clin_feat	0.1777595	0.2025471	0.8776205	0.3801497
IVIG: baseline_admission_day_at_treatment	-0.2476265	0.1643947	-1.5062920	0.1319922
IVIG: baseline_covid_positivePCR	0.2783239	0.2748842	1.0125134	0.3112927
IVIG: baseline_covid_positiveSerology	-0.7302890	0.2619896	-2.7874732	0.0053121
IVIG: baseline_peak_levin_LOCNo.support.CRP...50	-2.8290638	0.2206877	-12.8193076	0.0000000
IVIG: baseline_peak_levin_LOCNo.support.CRP.unknown	0.7511316	0.3046027	2.4659390	0.0136655
IVIG: baseline_peak_levin_LOCNo.support.CRP....50	0.7051259	0.2760760	2.5541003	0.0106463
IVIG: baseline_peak_levin_LOCOxygen	-0.1383207	0.2576387	-0.5368786	0.5913515
IVIG: baseline_peak_levin_LOCInotropes	1.1774950	0.2683684	4.3876074	0.0000115
IVIG: baseline_peak_levin_LOCVentilation	-0.1744537	0.1971529	-0.8848650	0.3762295
IVIG: baseline_peak_CRP.75th	0.2270121	0.2757454	0.8232671	0.4103561
IVIG: baseline_peak_CRP25.50th	-0.2251256	0.2940386	-0.7656328	0.4438948
IVIG: baseline_peak_CRP50.75th	0.5399641	0.2540901	2.1250890	0.0335792
IVIG: baseline_peak_CRPMissing	2.2462739	0.1763733	12.7359082	0.0000000
IVIG: baseline_peak_ddimer.75th	1.2772028	0.2276389	5.6106527	0.0000000
IVIG: baseline_peak_ddimer25.50th	0.2074110	0.1791286	1.1578885	0.2469096
IVIG: baseline_peak_ddimer50.75th	-0.4800391	0.2139387	-2.2438161	0.0248442
IVIG: baseline_peak_ddimerMissing	1.4249262	0.1836085	7.7606752	0.0000000
IVIG+G: (Intercept)	15.9536251	9.2853723	1.7181460	0.0857700
IVIG+G: baseline_resource_groupHigh.income.economies	3.2990419	0.5063786	6.5149707	0.0000000
IVIG+G: baseline_resource_groupLower.middle.income.economies	-2.6882377	0.4113593	-6.5350120	0.0000000
IVIG+G: baseline_age	1.2276587	0.5560856	2.2076795	0.0272666
IVIG+G: baseline_weight_z_over_2	-0.3086173	0.3340857	-0.9237667	0.3556078
IVIG+G: baseline_weight_z_missingTRUE	-4.2251966	0.3629301	-11.6419030	0.0000000
IVIG+G: baseline_sig_comorbidityYes	-2.3465135	0.4260041	-5.5081943	0.0000000
IVIG+G: baseline_fever_days_at_treating_admission	0.6329291	0.5005709	1.2644146	0.2060813
IVIG+G: baseline_fever_days_missingTRUE	-2.2287431	0.4747304	-4.6947556	0.0000027
IVIG+G: genderMale	0.2459523	0.4620678	0.5322862	0.5945278
IVIG+G: baseline_number_clin_feat	-0.6902951	0.3534257	-1.9531548	0.0508013
IVIG+G: baseline_admission_day_at_treatment	-0.6547799	0.5024081	-1.3032828	0.1924782
IVIG+G: baseline_covid_positivePCR	-0.6594455	0.5465511	-1.2065578	0.2276025
IVIG+G: baseline_covid_positiveSerology	-0.3566245	0.4971788	-0.7172963	0.4731913
IVIG+G: baseline_peak_levin_LOCNo.support.CRP...50	-4.9043613	0.3772517	-13.0002381	0.0000000
IVIG+G: baseline_peak_levin_LOCNo.support.CRP.unknown	-1.5537708	0.5140837	-3.0224081	0.0025077
IVIG+G: baseline_peak_levin_LOCNo.support.CRP....50	-0.1978904	0.5367914	-0.3686541	0.7123856
IVIG+G: baseline_peak_levin_LOCOxygen	-0.7743659	0.4894305	-1.5821775	0.1136091
IVIG+G: baseline_peak_levin_LOCInotropes	1.9643395	0.4259248	4.6119393	0.0000040
IVIG+G: baseline_peak_levin_LOCVentilation	-1.0700221	0.4026325	-2.6575650	0.0078707
IVIG+G: baseline_peak_CRP.75th	-2.5428766	0.4950475	-5.1366320	0.0000003
IVIG+G: baseline_peak_CRP25.50th	-1.8892584	0.4889947	-3.8635562	0.0001117
IVIG+G: baseline_peak_CRP50.75th	-1.4697895	0.4119465	-3.5679140	0.0003598
IVIG+G: baseline_peak_CRPMissing	3.8401372	0.4377577	8.7722891	0.0000000
IVIG+G: baseline_peak_ddimer.75th	2.9546530	0.3407864	8.6701012	0.0000000
IVIG+G: baseline_peak_ddimer25.50th	-0.6406178	0.3744696	-1.7107338	0.0871303
IVIG+G: baseline_peak_ddimer50.75th	-0.7934098	0.3906214	-2.0311479	0.0422400
IVIG+G: baseline_peak_ddimerMissing	0.5982886	0.3513954	1.7026076	0.0886415

Supplementary Figures

Figure S1 | World map displaying the location of countries registered to the Best Available Treatment Study.
BATS patients were enrolled from across five continents (Europe, Asia, Africa, North America, and South America). Each blue dot may correspond to more than 1 site.

Figure S2a | Number of enrolment sites registered per country.
Data used in this figure is following exclusions. (countries in reverse alphabetical order)

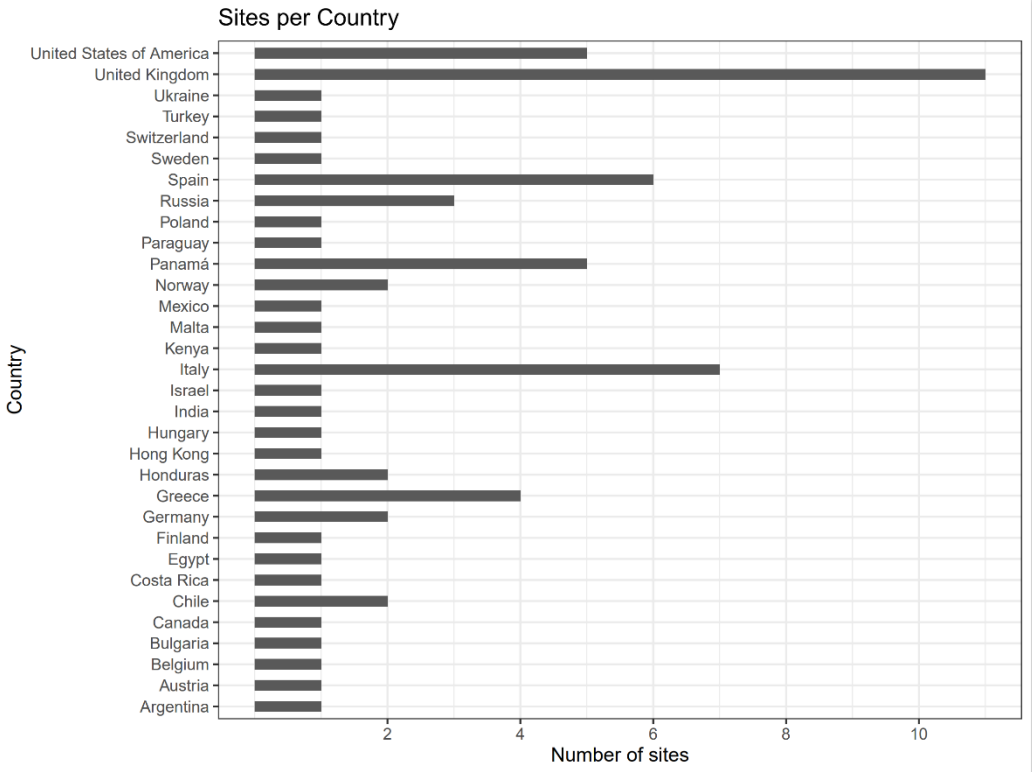


Figure S2b | Number of patients enrolled in BATS per country.
Data used in this figure is following exclusions. (countries in reverse alphabetical order)

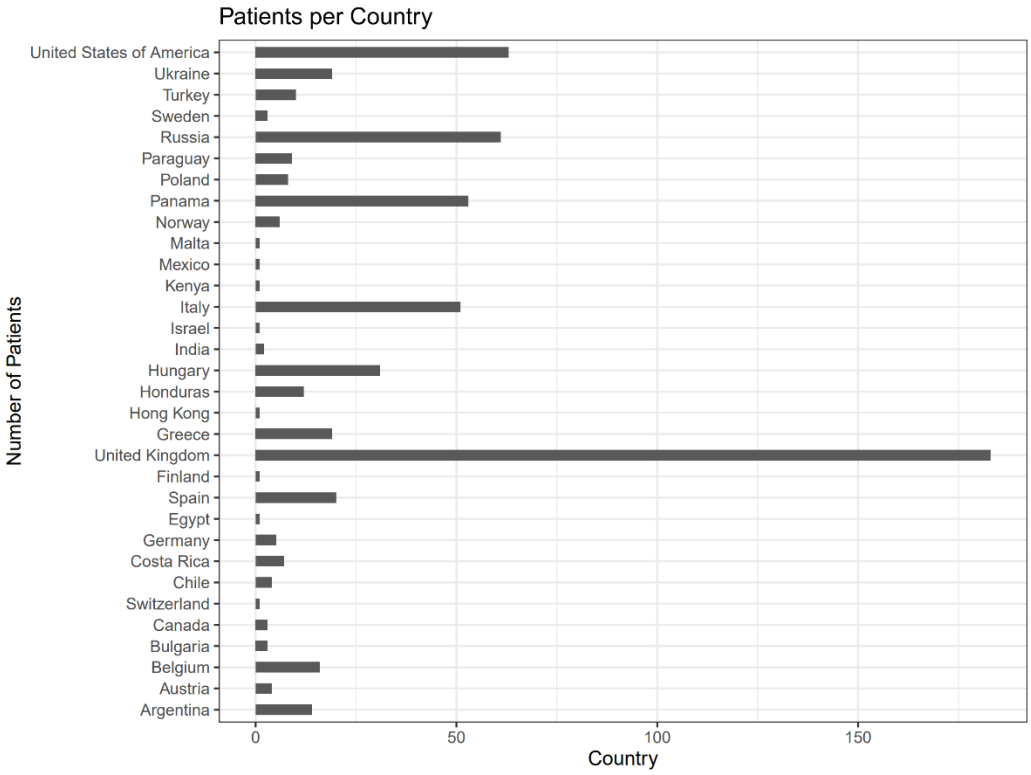


Figure S2c | Number of patients enrolled in BATS by sites in each country.
Data used in this figure is following exclusions. (countries in reverse alphabetical order)

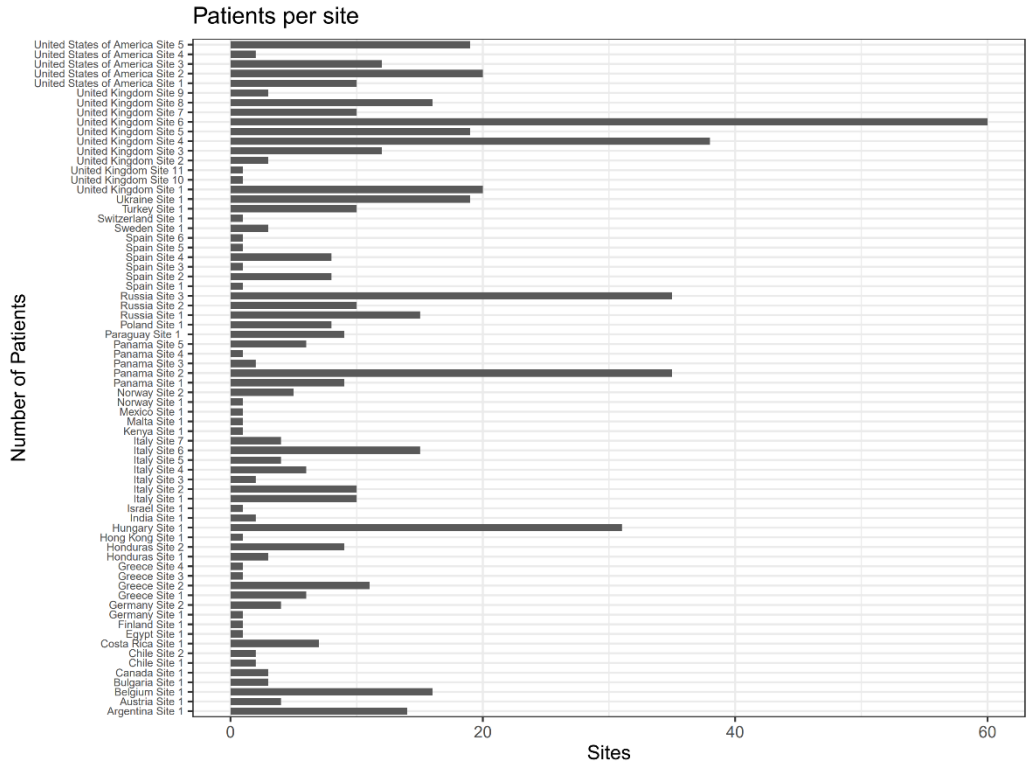


Figure S3 | BATS registration by month between May 2020 and February 2021.

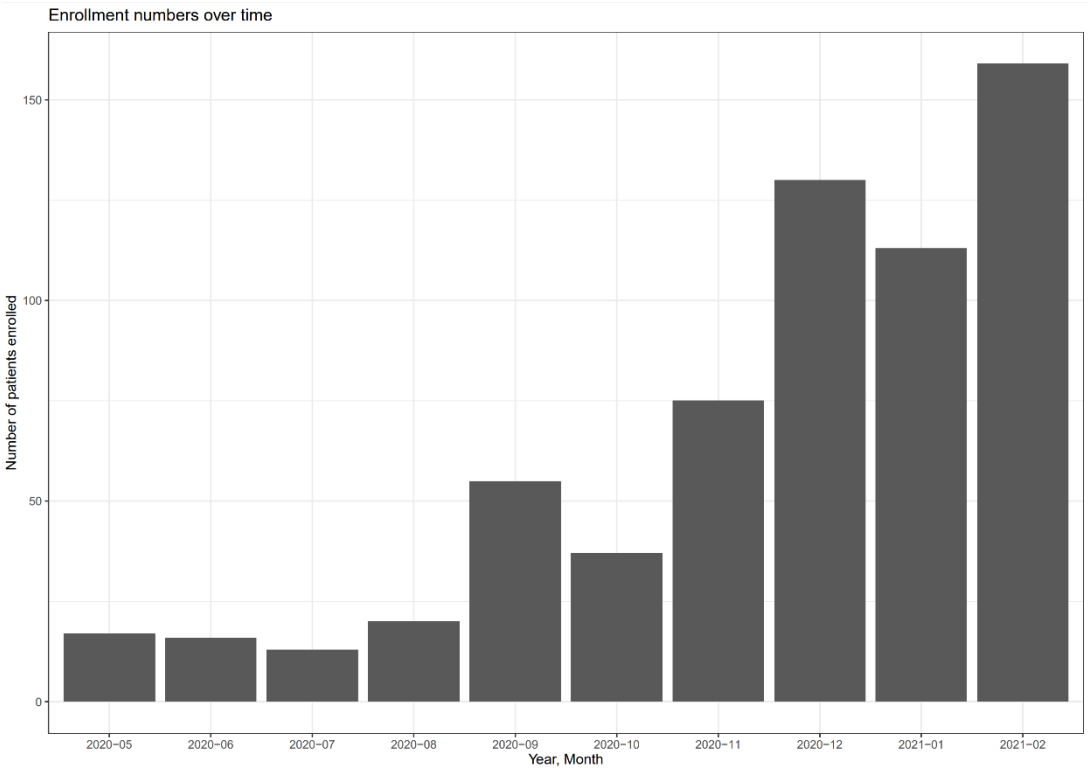


Figure S4 | Comparison of blood results across treatment groups at day 0.
Comparison of blood results by first immunomodulator treatment given at day 0. Statistical significance was calculated using the t-test comparing the blood results in each group versus all other groups. ns: P > 0.05; *: P ≤ 0.05; **: P ≤ 0.01; ***: P ≤ 0.001

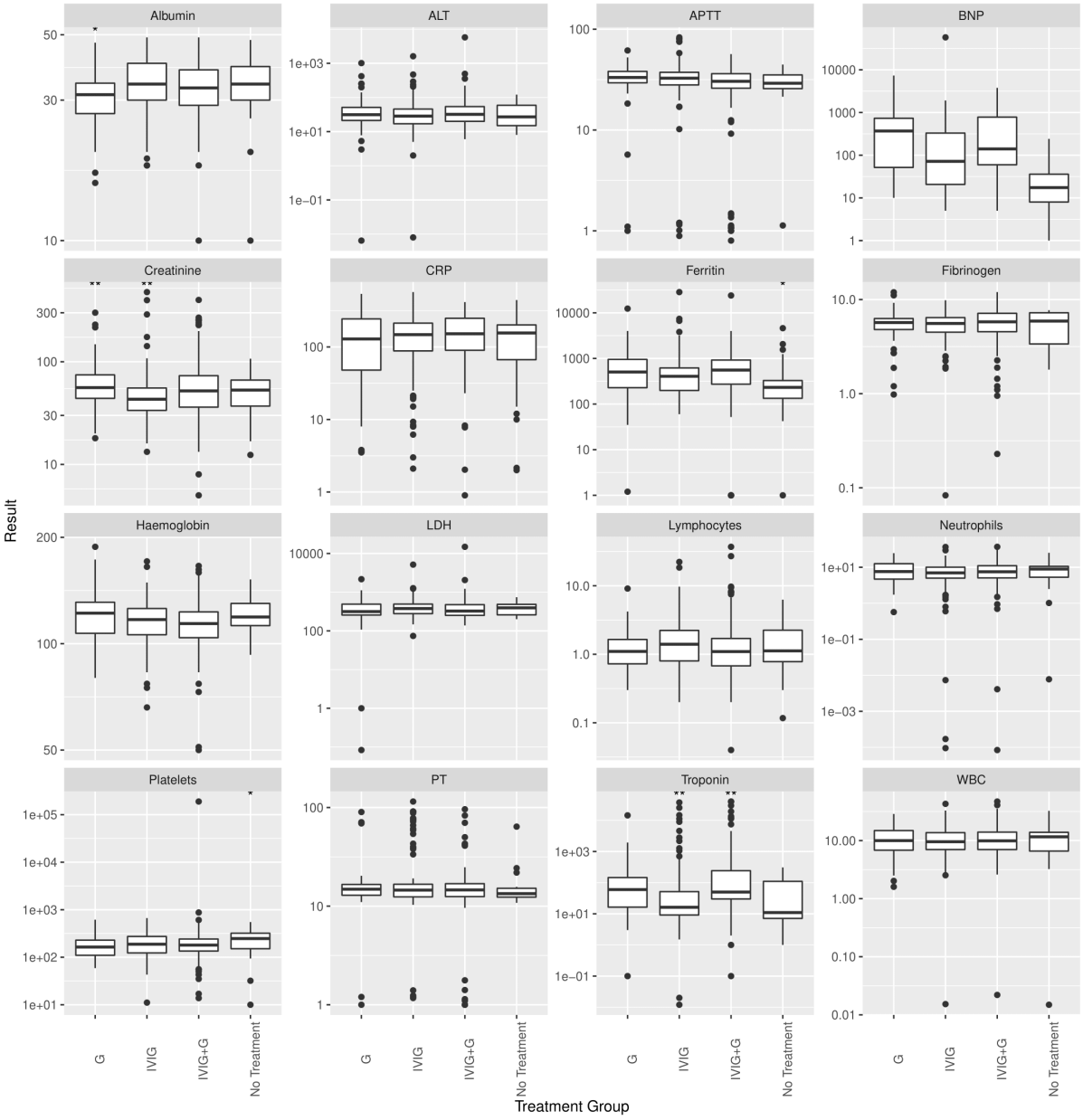


Figure S5 | Comparison of baseline CRP and troponin across treatment groups between day 0 and day 2

Comparison of baseline CRP and baseline troponin by treatment group at day 2. If a patient did not change primary treatment between day 0 and 2, they were classified by that primary treatment (IVIG, IVIG+Glucocorticoid, or glucocorticoid). Patients that changed treatment arm (of IVIG, IVIG+Glucocorticoid, or glucocorticoid) between day 0 and day 2, were classified as "switched Rx arm". Patients who started on primary treatments (IVIG, IVIG+Glucocorticoid, or glucocorticoid) but switched to a biological agent, or a biological agent was added, was classified as "switched to biological". Statistical significance was calculated using the t-test comparing the blood results in each group versus all other groups ns: P > 0.05; *: P ≤ 0.05; **: P ≤ 0.01; ***: P ≤ 0.001.

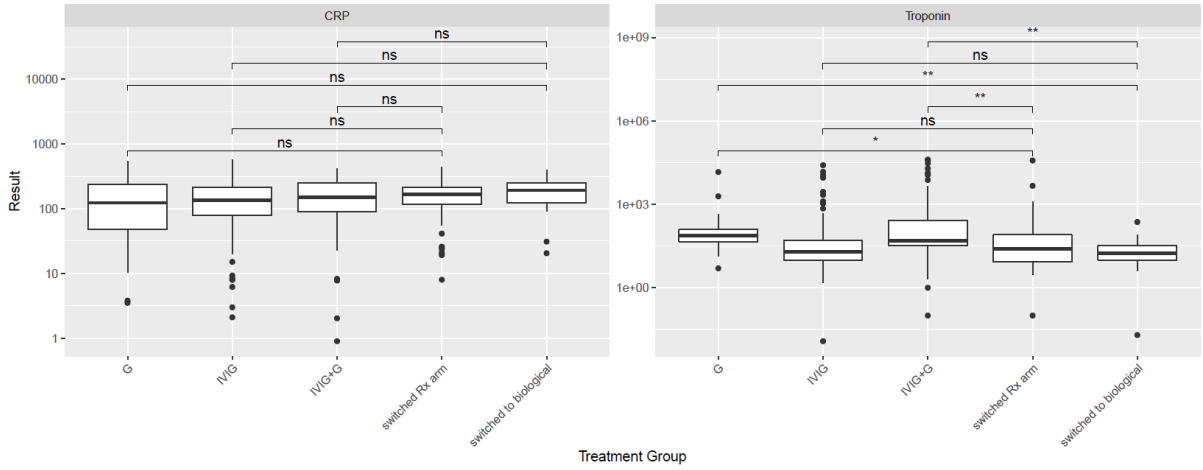


Figure S6A | Proportion of patients on inotropes or ventilated at baseline across treatment arms at day 0.

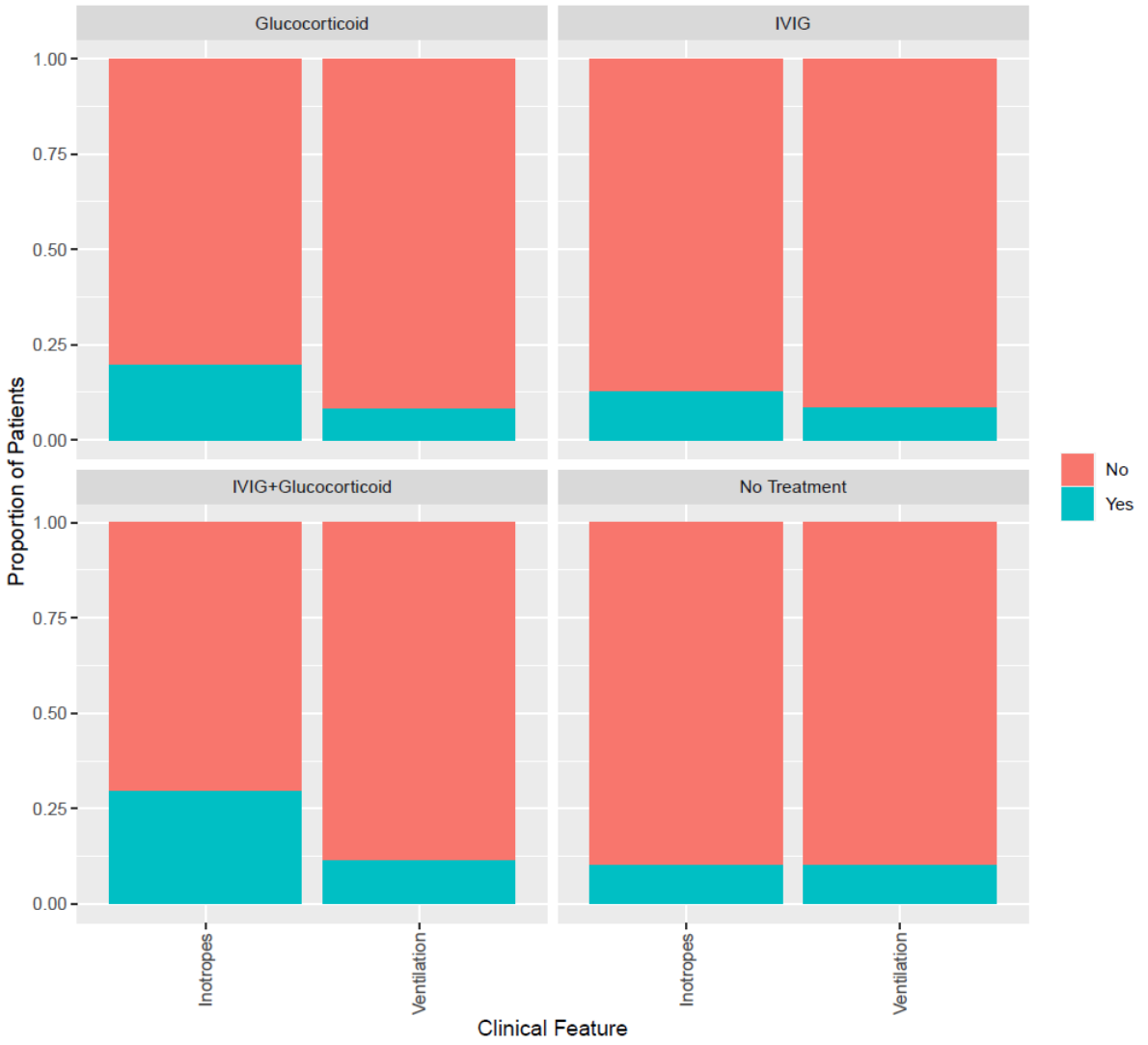


Figure S6B | Proportion of patients on inotropes or ventilated at baseline across treatment groups between day 0 and day 2.
Proportion of patients on inotropes or requiring inotropes at baseline grouped by treatment group at day 2. If a patient did not change primary treatment between day 0 and 2, they were classified by that primary treatment (IVIG, IVIG+Glucocorticoid, or glucocorticoid). Patients that changed treatment arm (of IVIG, IVIG+Glucocorticoid, or glucocorticoid) between day 0 and day 2, were classified as "switched Rx arm". Patients who started on primary treatments (IVIG, IVIG+glucocorticoid, or glucocorticoid) but switched to a biological agent, or a biological agent was added, was classified as "switched to biological".

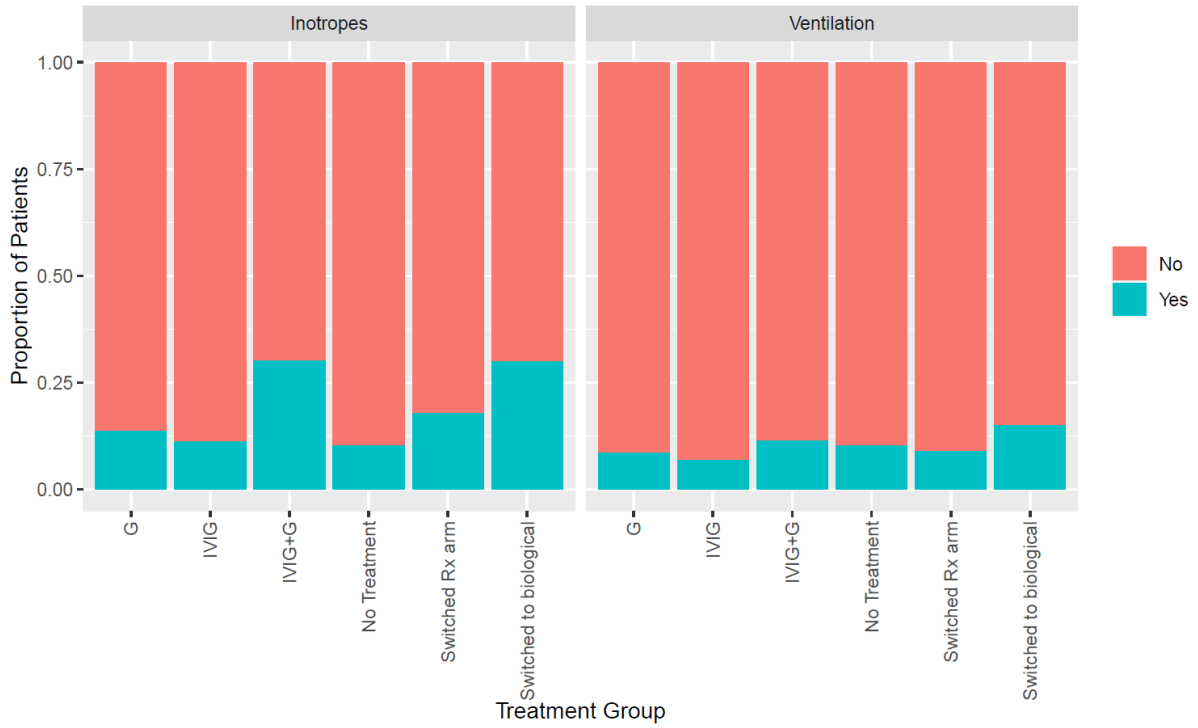


Figure S7 | Missing components in patients with all but one component of the WHO MIS-C criteria

Patients not meeting the full WHO criteria were subsetted by mandatory criteria to assess the most common reasons that they missed full classification. The COVID-19 criterion was defined as evidence of SARS-CoV-2 on RT-PCR, positive antibody result, or likely contact with COVID-19 patients.

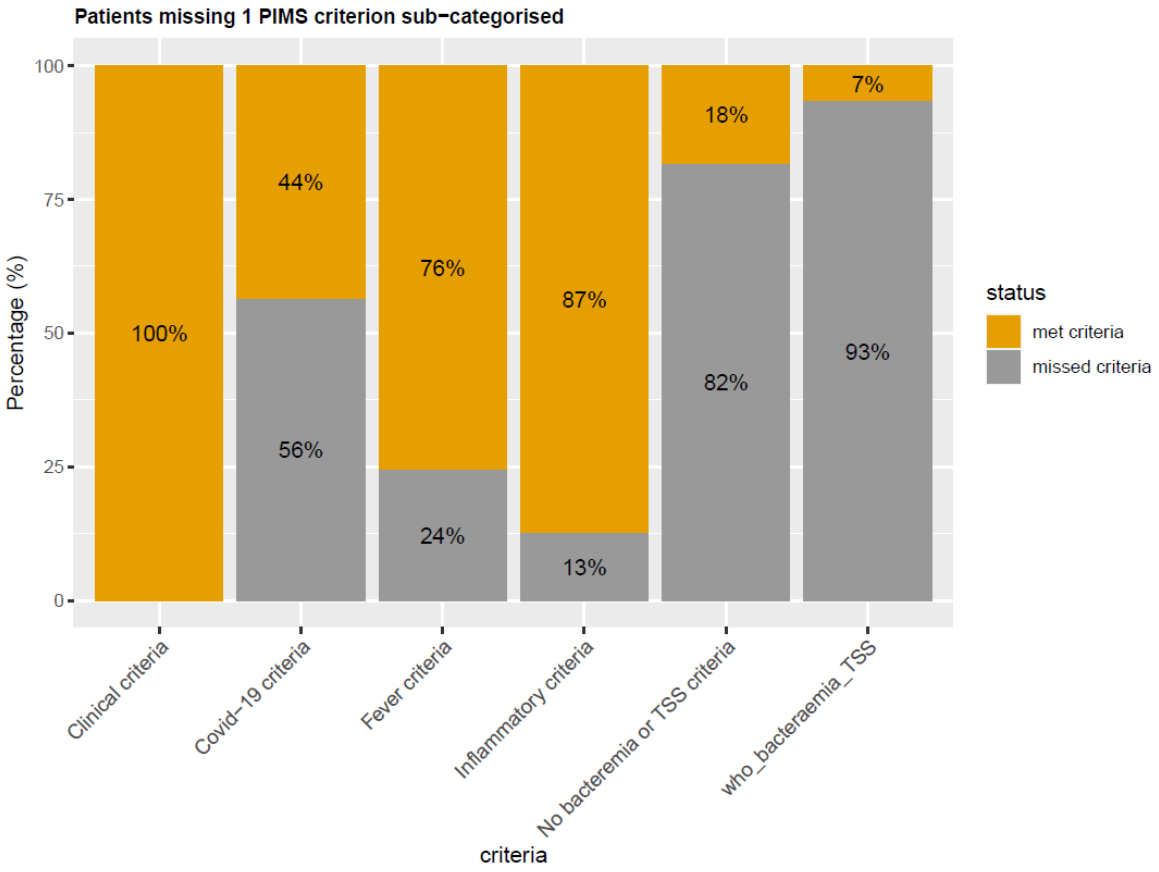


Figure S8 | Proportion of patients with clinical features of Kawasaki disease across treatment groups at day 0

Proportion of patients with clinical features of Kawasaki disease and those that met the criteria for classical and typical Kawasaki Disease across treatment groups at day 0.

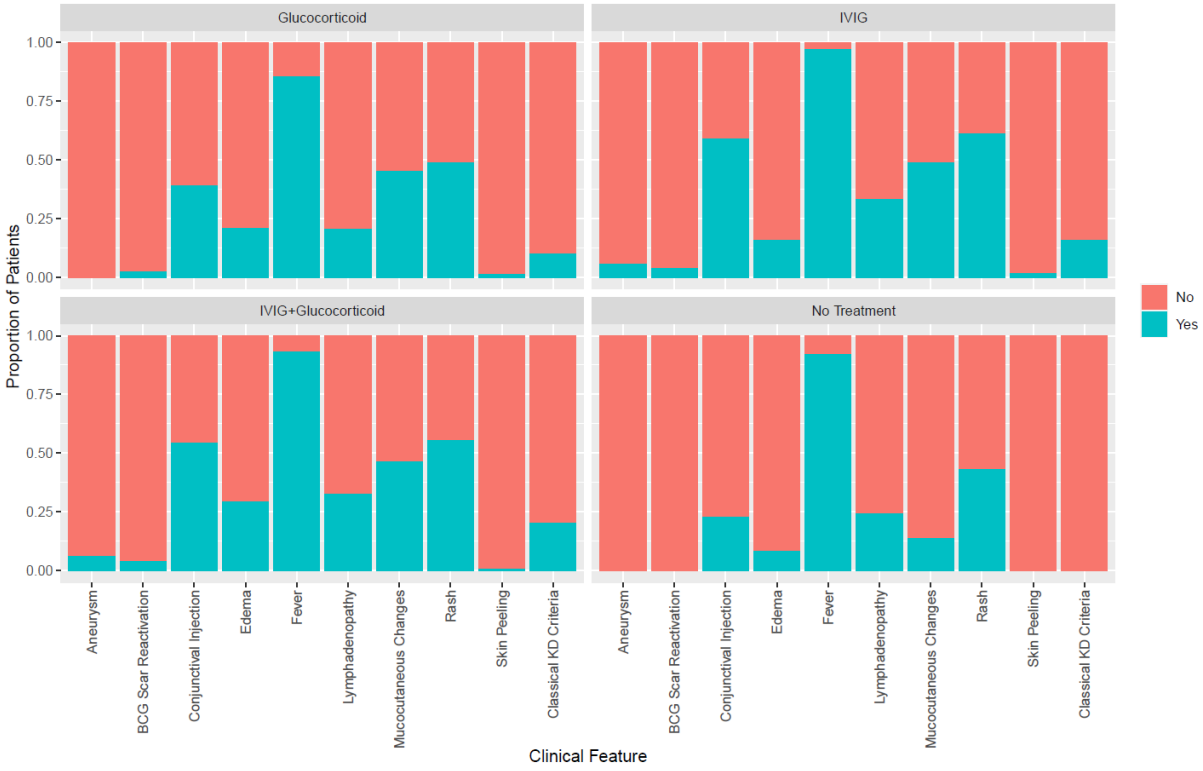
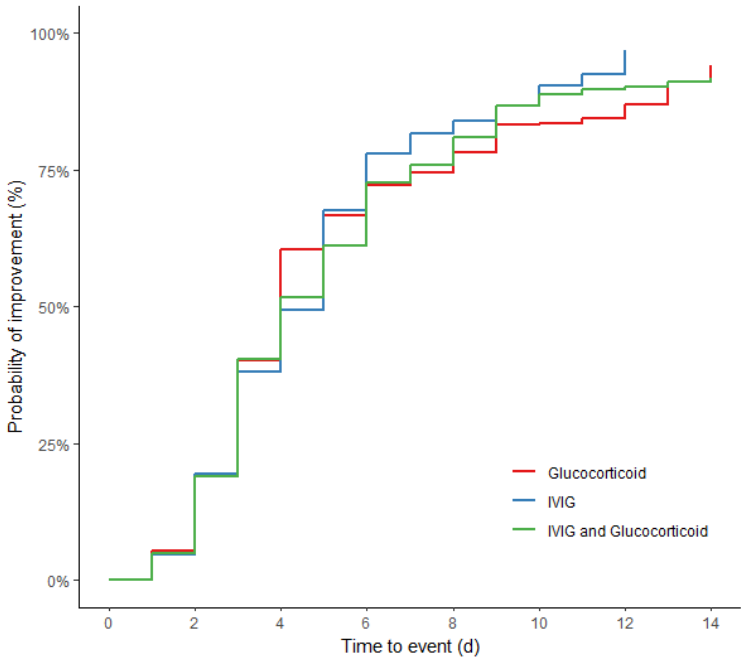


Figure S9 | Clinical improvement over time

(A) Kaplan-Meier chart showing time to one-point improvement in clinical severity on ordinal scale weighted by inverse probability of treatment. (B) Clinical severity shown by day relative to first treatment for patients by treatment group, with weighting by inverse probability of treatment.

A



B

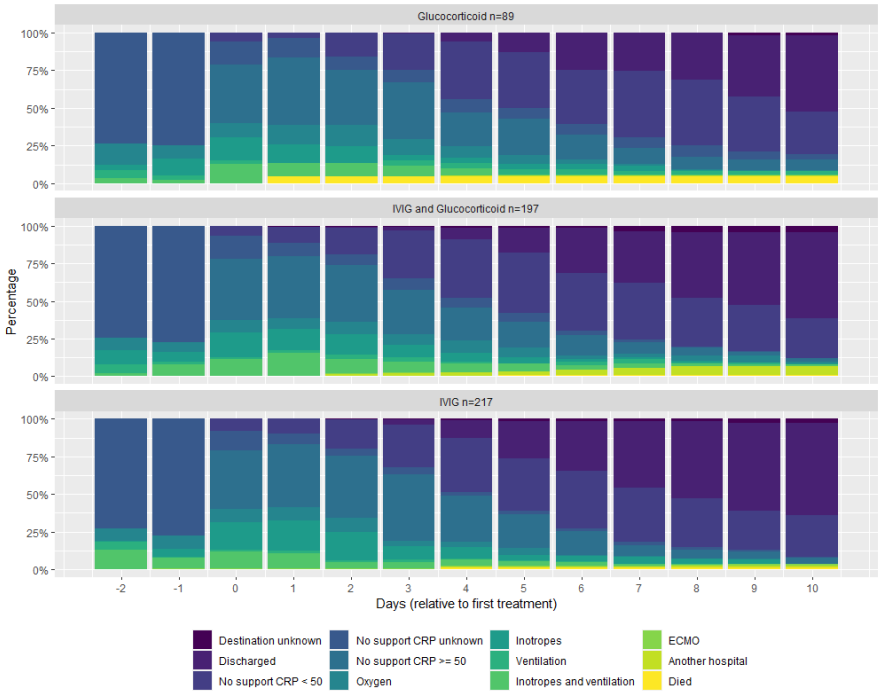


Figure S10 | Percentage of the CRP peak value by admission day for three primary treatments (IVIG, glucocortioids and IVIG and glucocorticoids combined).

Percentage of the CRP peak value by admission day for three primary treatments (IVIG, glucocorticoid and IVIG and glucocorticoid combined). CRP was plotted for each patient and at each time point (day) as a line, weighted by covariate-balancing propensity scores (CBPS) and fitted by a generalized additive model (GAM) for each treatment group. Panel A shows the fitted curves for CRP of children receiving IVIG, glucocorticoid and IVIG+glucocorticoid on the day of admission, younger versus older than 6 years old. Panel B shows the fitted curves for CRP of children who were given IVIG, glucocorticoid or IVIG and glucocorticoid combined, on the day of admission. The fitted curves represent children who meet the KD AHA criteria and are younger than 6 years old, and children who do not meet the KD AHA criteria or are older than 6 years old. Panel C shows the fitted curves for CRP of children who were given glucocorticoids or IVIG alone and whose treatment remained the same between the day of admission and day 3. The fitted curves represent children who meet the KD AHA criteria and are younger than 6 years old, and children who do not meet the KD AHA criteria or are older than 6 years old.

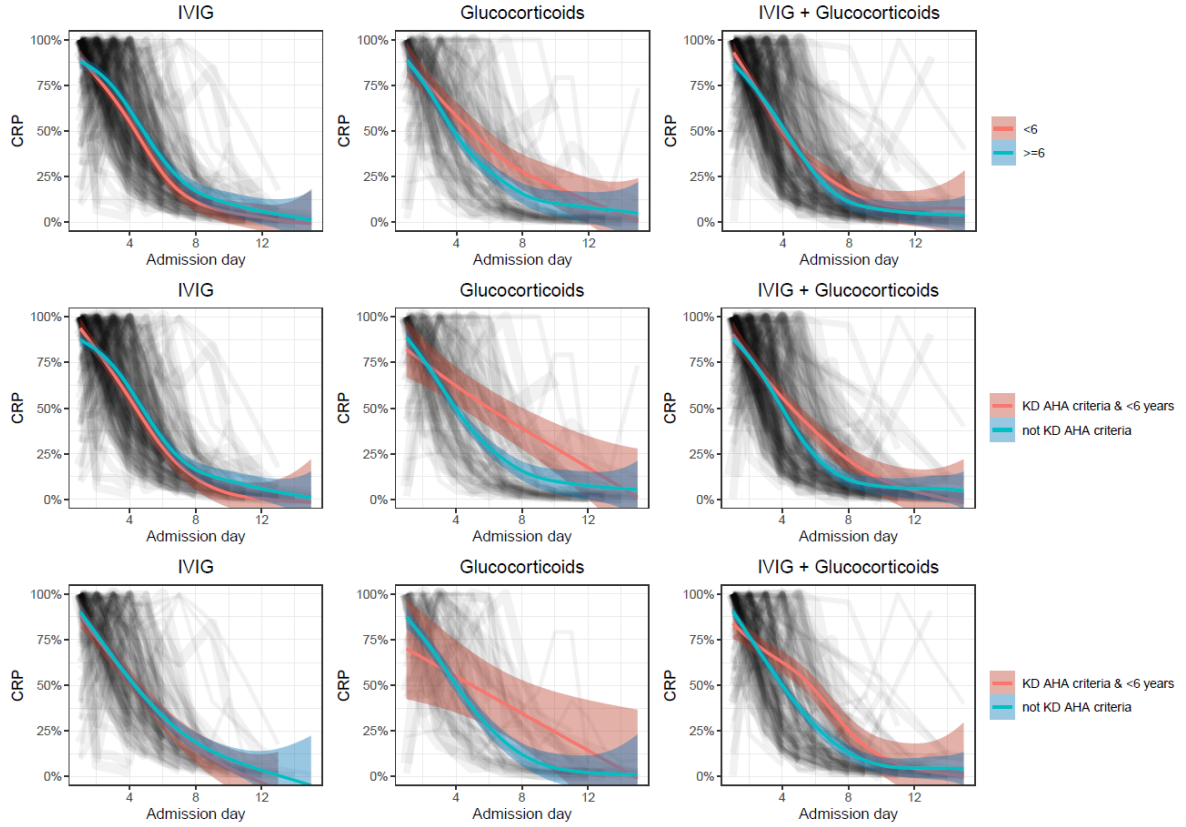
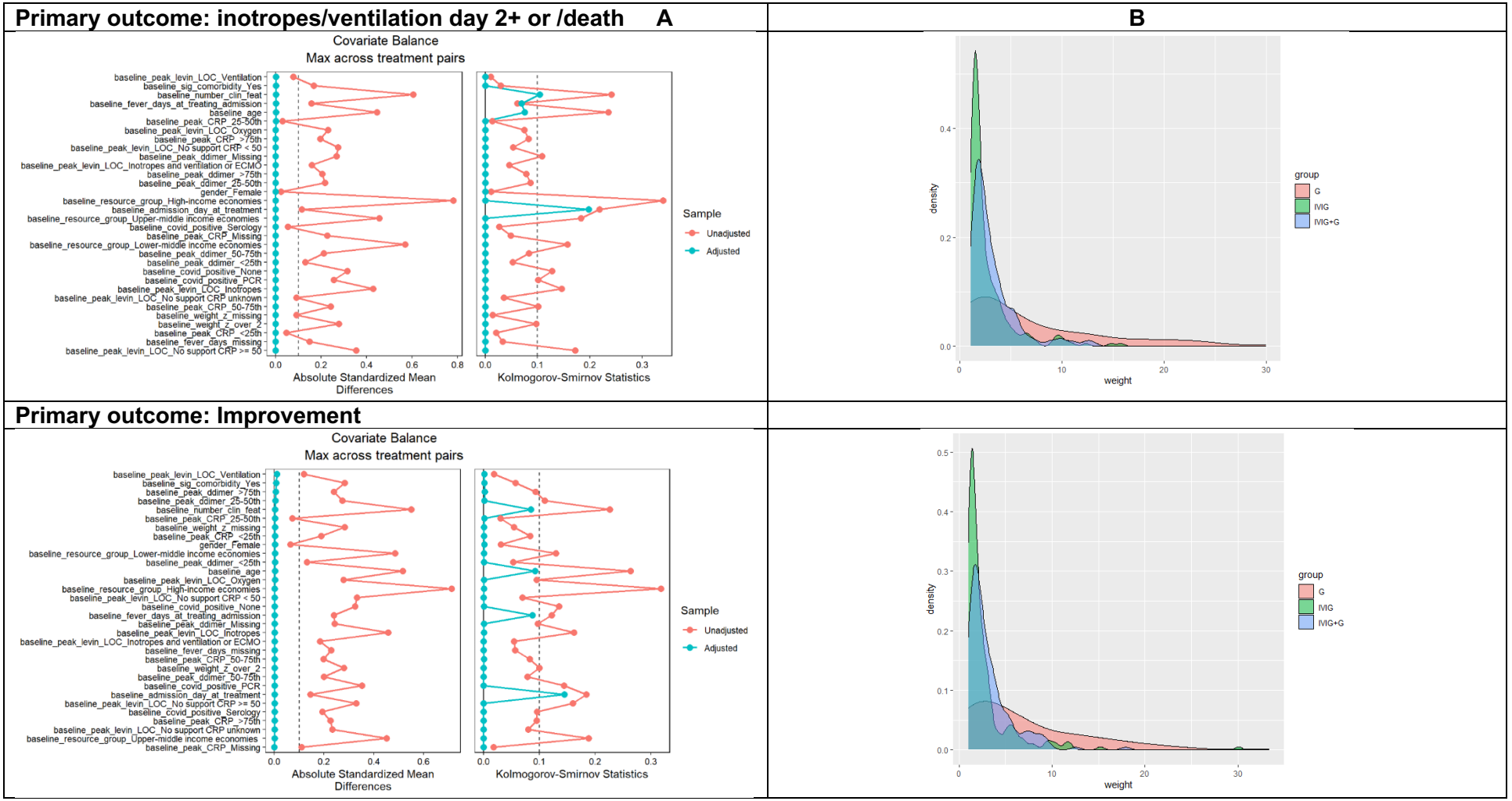
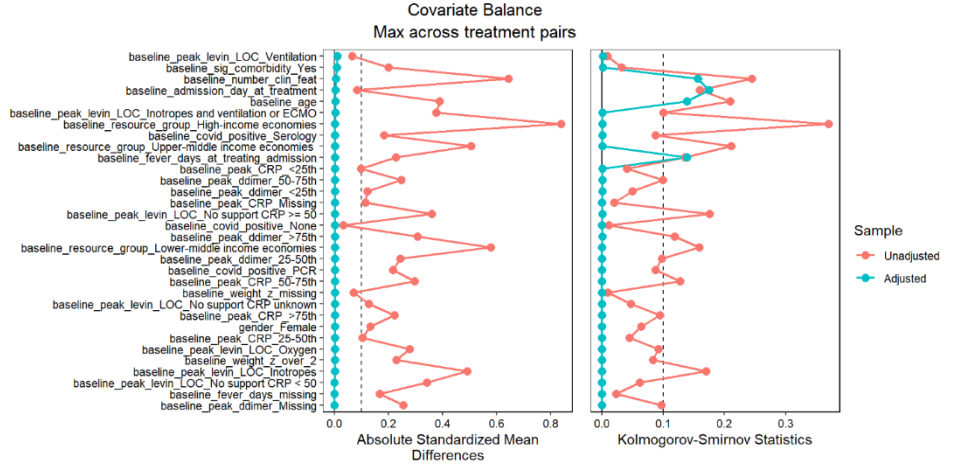


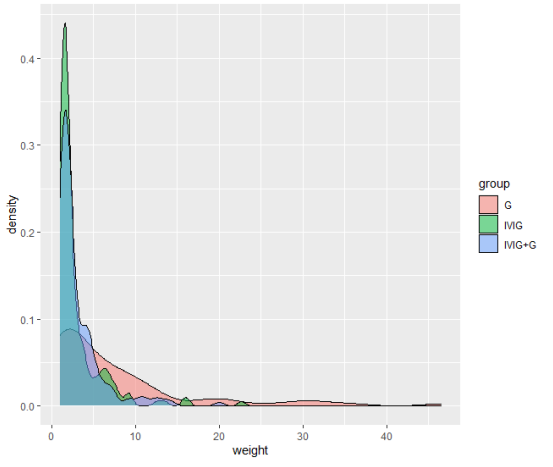
Figure S11 | Inverse probability weight distributions and covariate balance plots

Column A contains unstandardized inverse probability weight distributions for the three treatment groups derived from the covariate-balancing propensity score models. Column B contains covariate balance plots. Red coloured points show unadjusted absolute standardized mean differences; blue coloured line reflects absolute standardized mean differences following covariate-balancing propensity score weighting.

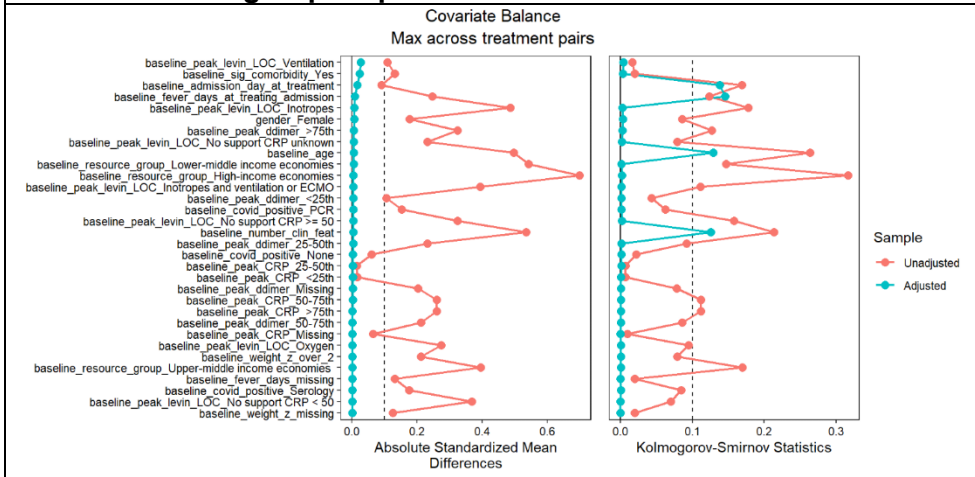


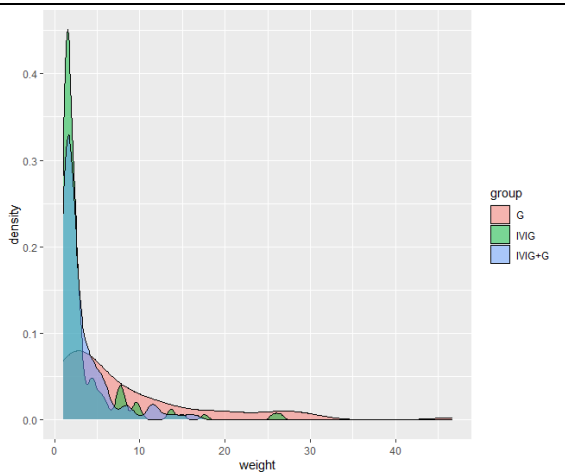
WHO MIS-C subgroup: inotropes/ventilation day 2+ or /death





WHO MIS-C subgroup: improvement





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