Supplementary appendix – BATS second analysis

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Supplementary Methods

Introduction and changes from previous analysis

The Best Available Treatment Study (BATS) was initiated in May 2020 in the early months after first recognition of the clinical syndrome of MIS-C. BATS aimed to provide evidence for treatment recommendations for MIS-C by systematic collection, and analysis of outcomes of the treatments chosen by individual paediatricians responsible for patient care. In view of the urgent need to provide clinicians with evidence to support treatment recommendations, an analysis of the first 614 patients enrolled in BATS was reported in the Journal in July 2021.[1] Recruitment has continued, with the knowledge that larger sample sizes were needed to be able to make more definitive recommendations, and we now report data from a substantially larger cohort of patients.

Recruitment and study methodology remain largely unchanged, however minor modifications were made in view of additional accumulated information about the disease. An updated analysis plan was published at the study clinical trials site (https://doi.org/10.1186/ISRCTN69546370, Statistical Analysis Plan – version 2) prior to the start of any analysis being undertaken. We report here additional details for the final analysis undertaken, paying specific attention to any alterations in methodology from the published analysis plan.

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 and at the trial registration site (https://doi.org/10.1186/ISRCTN69546370). The case report form used in BATS included only limited data on coronary artery aneurysm resolution on follow up. In view of the significance of coronary artery outcomes to management decisions we therefore supplemented the previously reported CRF with an additional targeted follow up questionnaire on resolution of coronary artery aneurysms (Appendix A, page 68).

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 study management team and international advisory board (consortium membership, pages 3-11) wrote the statistical analysis plan.

Data preparation and non-outcome definitions

Data entry and processing

Data were entered in RedCap version 6.14.2. The included patients were finalized on 25th April 2022, including all patients admitted to hospital before 1st March 2022. All subsequent processing and analysis were undertaken in R version 4.1.2.[2] A list of R packages used can be found in Appendix C (page 70). Validation and correction of admission, discharge and immunomodulatory treatment dates was undertaken. Subsequent data changes were restricted to correction of obvious errors and missing data, with the database finalized on 6th June 2022. Data were processed such that repeated clinical, laboratory and treatment variables were represented in a table with one row per patient-day.

Inclusion and exclusion criteria

Clinicians included the patients on their judgement of the patient meeting one or more of the international definitions for MIS-C.[3–5] Patients were excluded from analysis for the following reasons:

- No admission date
- No data entered onto treatment form
- No discharge date and absence of any daily data (level of care, KD features, blood results, cardiac investigations)
- Unclear date of first immunomodulatory therapy
- Suspected data misalignment with no confirmation of data validity from recruiting site (see below)
- Neonates, aged <1-month

Inclusion for weighted analysis

Only patients treated from the day of admission or transfer contributed outcomes for weighted analyses, as determination of matching covariates and outcomes was not possible for patients treated before transfer to the recruiting centre. Where recruiting sites entered complete data (enabling both covariate balancing and outcome assessments) from the referring centre we treated this as one single admission for weighted analysis. All patients meeting the above criteria were included for weighted analysis, unless stated in specific subgroup and sensitivity analyses.

Treatment definitions

Primary treatment was defined as the immunomodulatory agent(s) initiated on the same calendar day before any other treatments ("Day 0"). Where two agents were commenced on the same calendar day this was considered a combination treatment. Thus, primary treatment was either single agent or multi-agent therapy. Immunomodulators administered on subsequent days were considered secondary treatments. Patients who only received immunomodulator therapy with low dose oral glucocorticoids were excluded from the glucocorticoid primary treatment group and reclassified as receiving no treatment for the purposes of establishing treatment effects. Low-dose glucocorticoids were defined as an equivalent dose (as per BNFc)[6] of less than 1mg/kg or 40mg-total of prednisolone, whichever was lower. Low dose IV hydrocortisone is commonly used as an adjunct to inotropic therapy in sick children with MIS-C. We therefore classified courses of IV hydrocortisone as non-glucocorticoid therapy where the administered dose was low, as defined above.

Missing data, interpolation, and imputation

To reduce the volume of missing data we communicated with the recruiting sites to address missing or inconsistent data for key fields required for the analysis (Appendix D, page 71). Level-of-care and supportive treatment variables, including respiratory support and inotropes, 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 will be interpolated as no support needed. Further, where total number of days of invasive ventilation, non-invasive ventilation, oxygen, and inotropic support are available, missing data were imputed assuming no discontinuous periods of treatment (supported by a low frequency of multiple episodes of inotropes, ventilation, or oxygen usage in complete data in the previous analysis).

In addition, for a particular level of care, if the final outcome data reported a patient had no support (e.g., no days of respiratory support) and the daily data for each day was either missing or entered as no support needed, then we interpolated the patient to have no support needed on all days of daily data whenever missing. Finally, where missing values of respiratory support followed a period of ventilatory support, with the reported individual days of ventilatory support identical to the reported total days of ventilatory support, we imputed the missing respiratory support values to be no support if

the total days of oxygen therapy are reported as zero, otherwise we imputed to a value of “Oxygen or air” for the purpose of outcome assignments. Where patients were missing fever data on the day of discharge only and were recorded as not having a fever the previous day we imputed “no fever” for the final day.

Merging consecutive admissions

Where multiple hospitals within one location (city/town/country) report patients, we inspected plots of admissions and ages to identify possible consecutive admissions of the same patient. More detailed comparison of age, sex, weight, reported ethnicity, admission periods and laboratory and clinical variables were used to confirm, and recruiting sites contacted to confirm details. Consecutive admissions were merged into a single record by splicing daily data and taking previous admission baseline data and final admission outcomes, with original records excluded.

Assessing for misalignment

During data validation there was a suspicion of data misalignment. This could occur because dates of treatments were recorded by date, but timings of other data were recorded by days relative to admission, and the dates were calculated for comparison with treatments based on recorded admission date. In our definition “day 0” corresponded to the day of admission, and “day 1” to the first full day in hospital. If sites entered admission data incorrectly as day 1 data, then misalignment could occur. Excess daily data for some patients alerted us to this issue. We inspected each patient for discrepancies between the entered daily data and admission length, and overly similar daily data for distinct days, to assess for potential misalignment. We then contacted recruiting sites for clarification of data entry processes and corrected for any misalignment as instructed by recruiting sites.

Laboratory values

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, and it is clear how to resolve the discrepancy (e.g., a single haemoglobin value out by a factor of 10, indicating an error in recording units). Extreme outliers were those visibly far outside the range of most results. Where it was not possible to correct these outliers, contacted recruiting sites for confirmation, and excluded results which could not be resolved.

Definition of clinical severity scale

For each day of admission, clinical severity was calculated 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
6. No supportive therapy, last CRP < 50

5.5 No supportive therapy, CRP unknown

7. Discharged

Additional levels were added for graphical presentation: death, extracorporeal membrane oxygenation (ECMO), pre-admission, transferred, discharged and level-of-care unknown. This ordinal scale was

used in the previous analysis and was developed by clinical consensus because there were no existing clinical severity scales for this condition when the BATS clinical database form was developed. As previously described, 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 in the majority of patients. Our scale considered 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 particularly important, and following that being fit for discharge.

Demographics & baseline clinical data

Age was collected in years and additional months. Where additional months were missing, they were assumed to be zero. If the child was under 2-years old, we contacted recruiting sites to clarify age in months (not required for any patients). If age in years was missing and the data could not be obtained, the child's age was replaced with the predicted age based on sex and weight of other children in the cohort using multiple linear regression for imputation (not required for any patients). Patients' weight-for-age Z scores were calculated from the WHO reference data using the RCPCH Growth API.[7]

The World Bank lending group classification was used for country economic status. Significant past medical history was defined as any of: primary or secondary immunodeficiency; HIV; autoimmune disease; chronic lung disease; congenital heart disease; chronic neurological disorder; or malignancy.

Patients meeting WHO MIS-C criteria and KD criteria

For specific analyses we required a robust method of ensuring patients would meet the WHO MIS-C criteria.[4] We used the extensive data collected on clinical features and laboratory markers both at presentation and during admission to generate data-driven classifications, grouping patients as follows:

1. Meet WHO MIS-C criteria
2. Meet WHO MIS-C criteria except for one criterion
3. Missing > 1 criteria for WHO MIS-C
4. Meet WHO MIS-C criteria but with bacteraemia or toxic-shock syndrome

We similarly used a data-driven approach to determine if patients would meet the 2017 AHA criteria for Kawasaki Disease,[8] grouping patients into one of three groups:

1. Meet complete KD criteria
2. Atypical KD
3. Not KD

Outcome definitions

Primary Outcome Definitions

1. Inotropic support or ventilation or death (dichotomous)

Inotropic support or 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 1 or 2, 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 transferred patients, and as negative for all patients whose destination was not recorded.

2. Time-to-improvement in clinical severity (time-to-event analysis)

Improvement was defined as a one-point improvement on the above ordinal clinical severity scale. For each patient, the time-to-improvement was calculated in days as the first time the patients had improved without subsequent deterioration in clinical severity. If the patient improved but subsequently deteriorated their time-to-improvement was defined by the first time they improved after the deterioration. This equates to improvement being defined by:

- Time to come off ventilator or inotropes for patients receiving both therapies (without subsequently requiring both ventilation and inotropes on further days)
- Time to come off ventilator for patients ventilated (without requiring further ventilation)
- Time to come off inotropes for patients receiving inotropes (without requiring further inotropes)
- Time to come off oxygen for patients receiving oxygen (without requiring further 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 (without CRP rising to ≥ 50 mg/L on a later day)
- Time until discharge for all patients, where preceding other event

Time-to-improvement was defined as not available for patients who died, or where baseline clinical severity was unclear due to missing data. If the patient was transferred and they required any level of support in the two-days prior to transfer (ECMO, inotropes or ventilation) then time-to-improvement was defined as not available. Otherwise, if the patients improved prior to transfer without subsequent deterioration their time-to-improvement was defined as the time-to-improvement as above. When a patient had definitely improved at some point, but missing data led to unclear exact times to improvement we right-censored the patient for time-to-event analysis, using the last date the patient had not improved as the right-censored time. We included this right-censoring for improvement based on a reduction in CRP, which led to greater numbers of censored patients in this analysis compared to the previous analysis as measurement of CRP was not performed daily for many patients. A post-hoc sensitivity analysis using the known time-to-improvement in CRP without right-censoring for days without CRP measurements was performed to determine the impact the additional right-censoring would impact results. This shows no significant difference between these two approaches (page 65).

For time-to-event analysis, the origin (time when patients are first deemed to be at risk) was the first day after treatment initiation, whilst the end point was the time to improvement (defined above) or alternatively the patients is right censored.

Secondary Outcome Definitions

1. No improvement at day 2 (dichotomous)

Patients were defined as not having improved by day 2 if their clinical severity on the ordinal scale on day 2 was at least as bad as day 0. 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.

2. Failure/escalation of primary treatment

Defined as the addition of any new immunomodulator from the first day after primary treatment, or an additional dose of IVIG after primary treatment which includes IVIG, or an escalation in glucocorticoid therapy after primary treatment which includes glucocorticoids. Escalation in glucocorticoid therapy was defined as an increase of more than 5 mg/kg prednisolone equivalent in total daily dose, as

defined by BNFc. If transferred to another hospital before the fifth day following primary treatment, failure will be regarded as not available if they have not escalated in care up to time of transfer.

3. Death or Inotropic support or Ventilation

We treated the individual components of the composite primary outcome, as defined above, as individual secondary outcomes.

4. Fever

Defined as presence of fever at any point from day 2. If no fever reported, but missing data, the outcome was regarded as not available, except for the rare cases of final-day imputation (described above).

5. Increase in level of support

This was defined as any commencement of:

- ECMO for patients not on ECMO on day 0
- Any ventilation for patients not ventilated on day 0
- Invasive ventilation for patients receiving non-invasive ventilation on day 0
- Inotropic support for patients not on inotropes 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.

6. Persisting/new coronary artery dilation at discharge

The presence of a coronary artery with Lopez z-score ≥ 2.5 or a report of aneurysm without z-score on the final in-hospital echocardiogram, undertaken on the second or subsequent days following treatment. Outcome was regarded as not available if no echocardiogram reported, and negative if echocardiogram reported with no aneurysm or z-score < 2.5. Presence of pre-treatment coronary artery dilatation was added as a balancing covariate for weighted analysis (see analysis section pages 18-20).

7. Left ventricular dysfunction

Defined as the presence of left ventricular dysfunction on any echocardiogram from day 2 after commencement of primary immunomodulatory treatment. For this analysis, the presence of left ventricular dysfunction on or during the 2-days prior to starting immunomodulatory treatment was added as an additional balancing covariate for weighted analysis (see analysis section pages 18-20) to control for confounding due to potential differences in pre-treatment prevalence in each of the treatment arms.

8. Persisting Coronary artery dilatation after discharge

We collected follow up data on coronary artery aneurysm only for patients with CAA present on their final echocardiogram during admission. We therefore were missing follow up data from patients who did not develop CAA during admission, or where CAA resolved prior to discharge. We were therefore unable to perform IPTW analysis of the longer-term resolution data due to high degree of missingness. We instead report descriptive analysis, stratified by primary treatment group, of presence of aneurysms during admission, both pre- and post-treatment initiation, and resolution of aneurysms following discharge. We present absolute numbers and percentages of those with

resolution at any time, and also within 6-weeks and 12-weeks of treatment initiation. This combined approach was needed as the exact date of resolution is generally unclear, with typically many days/weeks between follow-up echocardiograms. We also present similar data for patients in the glucocorticoid alone primary treatment group, separated into those who did or did-not receive subsequent treatment with IVIG.

9. Inflammatory markers and other biomarkers

Inflammatory markers were plotted as percentages of the peak value, per patient, throughout the course of their admission relative to treatment initiation for each treatment group. Line plots were weighted by covariate-balancing propensity scores as described in confounding section. Smoothed curves with confidence intervals were plotted using a generalized additive model (geom_smooth with the "gam" method, from the ggplot2 package in R).[9] Comparisons were also made within each treatment group for age and for patients who fulfilled the 2017 AHA criteria for Kawasaki Disease. To ensure time course plots reflected clinically relevant changes over time, patients were only included if they had relevant blood result available both before and after treatment initiation, and only if their last value up to treatment initiation was abnormal (cut-offs defined in relevant figures).

10. Complications of drug therapy

Complications deemed by the treating clinician 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. These are reported descriptively.

Analysis

Sample-size estimations

We performed a pre-analysis sample-size estimation calculation that was published with our updated statistical analysis plan (Appendix B, page 69). When drafting the analysis plan, we performed a scoping analysis of the primary treatments received by this larger cohort, to determine which treatment groups we would have reasonable power to compare. This was undertaken with no examination of outcomes by treatment group, and hence did not compromise comparison of different treatments in any way.

Confounding

All primary outcomes, sensitivity analyses and subgroup analyses (planned and post-hoc), and secondary outcomes (excluding persisting coronary artery dilatation > 6-weeks from treatment initiation, and complications) underwent analysis following Inverse probability of treatment weighting (IPTW) to control for baseline confounding factors, followed by treatment effect estimation using the same list of confounders, to provide doubly robust estimates. This was implemented using weighting by multinomial covariate-balanced propensity scores,[10] as implemented by WeightIt version 0.12.0,[11] 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 Treated (ATT) was calculated with the untreated group as the reference due to the likely dissimilarity of a smaller untreated group and the need to preserve the full sample. Due to some excessive weights and exceptional covariate balancing in most analyses we implemented additional steps of weight stabilization, and truncation to the upper 99th centile weight for large weights, as long as covariate balancing was still acceptable based on the criteria below. This reduces weight variability and hence can increase estimated sample sizes whilst maintaining adequate covariate balancing.

Clinical and demographic covariates were adjusted from those used in the previous analysis, based on consensus opinion within the study team and international advisory board, aiming to define key variables related to both treatment decisions and outcomes. Covariates were used in both covariate balancing and treatment effect estimation to produce doubly-robust estimates.

The following variables were used for balancing:

1. Age, continuous
2. Sex, binary
3. Weight-for-age z-score greater than 2, binary (imputation was undertaken for missing values: patients with “severe obesity” checked in the list of comorbidities were assigned to weight-for-age z-score >2, whereas patients without this comorbidity were assigned to the <2 group)
4. Significant comorbidity, binary
5. Resource group, three categories were considered: High income, Upper-middle income, Low and Lower-middle income (low and lower-middle were grouped as very few sites from low-income countries recruited patients to BATS). High income as the largest category, was the reference group, with two binary covariates coding the other two categories
6. KD features, binary (meeting criteria for complete KD at any time up to treatment day)
7. Requiring inotropes up to treatment day, binary
8. Requiring mechanical ventilation or ECMO up to treatment day, binary
9. Maximum CRP up to treatment day (baseline CRP), continuous

Balancing was repeated for every analysis on the population providing the outcome. This list was reduced for specific analyses based on data availability and area of common support across treatment groups. Important covariates were added for certain secondary analyses as described in the secondary outcome definitions. No imputation for missing outcome data was undertaken except for that already described above. 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 due to a lack of corresponding first treatment day for those not receiving any immunomodulator.

We aimed for absolute standardised mean differences of 0.1 and below in continuous variables, 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 are also included in outcome models, prioritizing the target of absolute standardized mean differences of 0.1 and below.

In our updated analysis plan we stated our intention to attempt to impute missing baseline CRP values. In the previous analysis we instead used an additional dichotomous baseline variable for missingness of CRP, but since this missingness indicator may not be related to outcome this may have led to increased variance of treatment effect estimates, which led us to attempt imputation methods. We tested our imputation models within each main primary treatment group, using samples with known baseline CRP values (maximum up to treatment day) split into 75-25% training and test sets. We attempted imputation using median imputation and K-nearest neighbours, using various combinations of other demographic and baseline variables as predictors. All imputation methods had very poor accuracy to predict the true values, based on root mean square error, R^2 and visual inspection of fitted values against actual values. We therefore did not impute baseline CRP values, and patients without baseline CRP values were instead excluded from weighted analyses. Sensitivity

analyses using median imputation of missing baseline CRP values (Fig2A-D, main paper) and removing baseline CRP from the list of covariates (pages 64-65) showed no difference in treatment effect estimates for the two primary outcomes between any of these models.

Models for treatment effect estimation

We used weighted logistic-regression methods to analyse dichotomous outcomes. Robust sandwich standard errors were used, with dichotomous outcomes analysed using the survey package,[12] adding all covariates used in covariate balancing, to produce doubly-robust estimates. To account for overdispersion quasibinomial regression with a logit link function (a generalised linear model) was used to estimate odds ratios and 95% confidence intervals. Time to event analyses were undertaken using weighted Cox proportional hazards model estimates of average hazard ratios.[13] Right censoring for missing outcome data was used, and is described above in the primary outcome definitions. The assumption of linearity for quantitative predictors (age and CRP) for both quasibinomial and Cox-regression models was assessed by visual inspection of each predictor against the linear predictors from each more (for example, the logit of the outcome for quasibinomial regression). We assessed the proportional hazards assumption by 1) Schoenfeld tests for non-proportionality both for individual covariates and a global Schoenfeld test; and 2) assessing plots of the scaled Schoenfeld residuals versus time.[14]

Confounding with matched models

We performed a planned sensitivity analysis through implementing propensity score matching instead of propensity weighting, again with IVIG as the reference treatment. We used the nearest neighbour matching method with “glm” distance measure and 1:1 ratio without replacement. Due to model specification limitations in the software package used[15] we were unable to estimate the treatment effect using the planned target of Average Treatment Effect (ATE). We therefore estimated and report results using the Average Treatment Effect in the Treated (ATT) estimand. A post-hoc sensitivity analysis using the Average Treatment Effect in the Controls (ATC) was also explored, which demonstrated no significant change in our findings. We conducted separate matching procedures for each pair of comparators and each primary outcome. Observations with incomplete baseline covariate data were removed from the analysis. For each matching, cases missing the outcome of interest were removed. Binomial logistic regression analysis was conducted for each matched sample separately.

Adequate covariate balance was achieved, based on maximum absolute standardised mean difference not exceeding 0.1 with the corresponding calipers of 0.15 for the first primary outcome comparison of Glucocorticoids vs IVIG, and 0.2 for each of the other 3 matchings. The robustness of the results was checked by varying caliper size and observing the changes in effect sizes and confidence intervals. Moderate changes in caliper values did not affect conclusions of the analysis. Adjusted odds ratios and average hazard ratios are reported in Figure 2 of the main paper. Raw values are reported in pages 32-34. A love-plot of the covariate balancing can be found on page 66.

Correction for multiple hypothesis testing

Correction for multiple hypothesis testing was undertaken using the Bonferroni-Holm method for the two primary outcomes and the two primary treatment comparisons. All other outcomes are presented with 95% confidence intervals and unadjusted p-values.

Subgroup, sensitivity, and other analyses

Unadjusted death and complication rates were reported on all included patients. E-values are presented for primary outcomes as per the method of VanderWeele and Ding.[16]

The following planned subgroup analyses were undertaken for all primary outcomes:

- Patients fully meeting the WHO criteria for MIS-C
- Meeting WHO criteria except for presence of bacteremia
- Missing WHO classification by one criterion
- Patients from High- and Upper-middle-income countries
- Stratified by age-group as follows: Under 6-years; 6-11-years; Over 11-years
- Restricting to patients without significant comorbidities
- Stratifying patients based on degree of inflammatory response, separating by peak CRP before treatment into tertiles.

The following planned sensitivity analyses were performed for all primary outcomes:

- Defining primary treatment as all immunomodulatory treatments administered over two consecutive days (days 0-1) (as per previous analysis)
- Using propensity matching model rather than covariate-balancing propensity score weighted analysis
- For the 2nd primary outcome, time to improvement in clinical severity, we undertook an additional sensitivity analysis requiring a 2-point improvement in clinical severity on the ordinal scale.
- For secondary outcome 7, Left ventricular dysfunction from day-two following treatment, we performed a sensitivity analysis including maximal troponin to treatment day as an additional covariate, excluding samples without a troponin measurement before treatment.

A planned secondary analysis was also performed comparing primary treatments of glucocorticoids alone with IVIG & glucocorticoids, using glucocorticoids as the reference group with the same methodology described above (for primary and secondary outcomes).

We were unable to perform weighted analysis for the following planned subgroups, predominantly due to small numbers and therefore were unable to balance covariates:

- Patients from Low- and Lower-middle-income countries (N = 103 total patients)
- Missing WHO classification by >1 criterion (N = 54 total patients)
- For the 2nd primary outcome, time to improvement in clinical severity, we intended to perform subgroup analyses for each baseline severity category on the ordinal scale. For example, we intended to analyse the time to improvement for patients who were ventilated at the time of starting primary treatment as one subgroup analysis, and then repeating this for the other severity categories. Due to small numbers in most groups, we instead aggregated baseline clinical severity groups into two baseline severity groups: those requiring intensive support (ventilation and/or inotropes) and those not requiring intensive support.

To interrogate the data further after reviewing results from our planned analyses we undertook the following additional post-hoc analyses:

- Post-hoc subgroup and sensitivity analyses for two primary outcomes:
  - Restricting to patients who met the complete KD criteria during admission
  - Excluding patients who met the complete KD criteria during admission

    - Excluding patients who received additional therapies after the first day of treatment
    - Removing single covariates from both covariate balancing and treatment effect estimation in leave-one-out analyses
- Post-hoc sensitivity and subgroup analyses for secondary outcomes (main outcome in brackets)
    - No improvement by day 3 (Secondary outcome 1, no improvement by day 2)
    - Escalation in therapy from day 2 onwards (secondary outcome 2, failure/escalation in therapy from any point after treatment initiation)
    - Escalation in therapy excluding patients from Low and lower-middle income countries (secondary outcome 2)
    - Fever from day 3 onwards (Secondary outcome 4, fever from day 2 onwards)
    - Fever from day 2 onwards, restricting to patients meeting complete KD criteria (secondary outcome 4)
    - Increase in level of support excluding patients from Low and lower-middle income countries (secondary outcome 5)
    - Increase in level of support, restricting to patients with no support (inotropes or ventilation) at baseline (secondary outcome 5)
    - CAA at discharge, restricting to patients with no CAA at baseline (secondary outcome 6)
    - CAA at discharge, restricting to patients meeting complete KD criteria (secondary outcome 6)
    - CAA at discharge, excluding patients meeting complete KD criteria (secondary outcome 6)
    - LVD from day 1 onwards (Secondary outcome 7, LVD From day 2 onwards)

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.

Supplementary tables

Table S1: Details of additional treatments given by primary treatment group

Other immunomodulatory treatments include: cytokine adsorber (CytoSorb), granulocyte colony stimulating factor, colchicine, mesenchymal stem cells, convalescent plasma, cyclophosphamide, plasmapheresis and hydroxychloroquine. Further days of glucocorticoids in patients receiving glucocorticoids as part of primary therapy is not considered as additional treatment.

Abbreviations: IVIG: Intravenous immunoglobulin; IL1: Interleukin-1; IL6: Interleukin-6; TNF: Tumour necrosis factor

	Number of patients			Numbers receiving additional therapies						
Primary Immunomodulatory Therapy	Total	No additional treatment	Additional treatments (%)	Further IVIG	Glucocorticoids	Anti-IL1	Anti-IL6	Anti-TNF	Ciclosporin	Other Immunomodulators
IVIG	680	262	468 (68.2%)	216	381	28	23	21	2	2
Glucocorticoids	487	234	253 (52.0%)	230	-	16	25	9	1	2
IVIG+G	698	462	236 (33.8%)	185	-	40	31	13	0	3

Table S2: Unabridged demographic information, clinical features, and blood results for all patients included in the analysis

	Everyone (N=2009)	IVIG (N=680)	Glucocorticoids (N=487)	IVIG and Glucocorticoids (N=698)	Other (N=59)	No treatment (N=85)
[+]Age	8.0 [4.2 - 11]	6.8 [3.6 - 10]	8.8 [5.1 - 12]	8.4 [4.5 - 11]	11 [6.1 - 13]	7.3 [3.3 - 12]
[^]Proportion male	1191 (59.3%)	416 (61.2%)	288 (59.1%)	410 (58.7%)	44 (74.6%)	33 (38.8%)
[^]Overweight (age-adjusted z score ≥ 2)	299 (14.9%)	91 (13.4%)	70 (14.4%)	120 (17.2%)	10 (16.9%)	8 (9.41%)
[^]Ethnicity						
White	825 (41.1%)	290 (42.6%)	210 (43.1%)	272 (39.0%)	27 (45.8%)	26 (30.6%)
Latino	518 (25.8%)	161 (23.7%)	94 (19.3%)	222 (31.8%)	9 (15.3%)	32 (37.6%)
Black	212 (10.6%)	81 (11.9%)	34 (6.98%)	75 (10.7%)	13 (22.0%)	9 (10.6%)
Asian	131 (6.52%)	55 (8.09%)	36 (7.39%)	30 (4.30%)	4 (6.78%)	6 (7.06%)
Other or not known	323 (16.1%)	93 (13.7%)	113 (23.2%)	99 (14.2%)	6 (10.2%)	12 (14.1%)
[^]Significant comorbidity	108 (5.38%)	30 (4.41%)	32 (6.57%)	33 (4.73%)	4 (6.78%)	9 (10.6%)
[^]Home country economic status						
High-income economies	1186 (59.0%)	485 (71.3%)	224 (46.0%)	380 (54.4%)	48 (81.4%)	49 (57.6%)
Upper-middle income economies	710 (35.3%)	181 (26.6%)	197 (40.5%)	287 (41.1%)	10 (16.9%)	35 (41.2%)
Lower-middle income economies	113 (5.62%)	14 (2.06%)	66 (13.6%)	31 (4.44%)	1 (1.69%)	1 (1.18%)
[^]SARS-CoV-2 PCR positive						
Yes	415 (20.8%)	131 (19.4%)	97 (20.0%)	148 (21.4%)	13 (22.0%)	26 (31.7%)
Tested but negative	1397 (70.1%)	484 (71.7%)	349 (71.8%)	473 (68.5%)	44 (74.6%)	47 (57.3%)
Not tested	181 (9.08%)	60 (8.89%)	40 (8.23%)	70 (10.1%)	2 (3.39%)	9 (11.0%)
[^]SARS-CoV-2 Ab positive						
Yes	1321 (66.5%)	412 (61.2%)	344 (71.4%)	492 (71.6%)	43 (72.9%)	30 (35.3%)
Tested but negative	259 (13.0%)	126 (18.7%)	41 (8.51%)	65 (9.46%)	10 (16.9%)	17 (20.0%)
Not tested	406 (20.4%)	135 (20.1%)	97 (20.1%)	130 (18.9%)	6 (10.2%)	38 (44.7%)
[^]At admission level of care						
No support	1100 (54.8%)	434 (63.8%)	243 (49.9%)	330 (47.3%)	22 (37.3%)	71 (83.5%)
Oxygen	203 (10.1%)	58 (8.53%)	57 (11.7%)	79 (11.3%)	5 (8.47%)	4 (4.71%)
Inotropes	347 (17.3%)	68 (10.0%)	109 (22.4%)	156 (22.3%)	13 (22.0%)	1 (1.18%)
Ventilation	30 (1.49%)	12 (1.76%)	1 (0.205%)	13 (1.86%)	1 (1.69%)	3 (3.53%)
Inotropes and ventilation or ECMO	158 (7.86%)	37 (5.44%)	17 (3.49%)	83 (11.9%)	15 (25.4%)	6 (7.06%)
[^]Clinical features on admission						
Fever	1863 (92.7%)	653 (96.0%)	439 (90.1%)	649 (93.0%)	52 (88.1%)	70 (82.4%)
Sore throat	464 (25.5%)	159 (26.5%)	104 (22.9%)	175 (27.0%)	11 (21.6%)	15 (21.1%)
Cough	404 (21.1%)	125 (19.4%)	120 (25.3%)	131 (19.6%)	16 (30.8%)	12 (16.0%)
Respiratory distress	258 (13.3%)	70 (10.9%)	57 (11.9%)	112 (16.4%)	13 (23.6%)	6 (7.59%)
Abdominal pain	1211 (63.2%)	408 (63.9%)	289 (62.3%)	438 (64.8%)	37 (63.8%)	39 (48.1%)
Diarrhea	882 (44.8%)	290 (43.9%)	195 (40.6%)	340 (49.4%)	23 (39.7%)	34 (41.5%)
Vomiting	1057 (54.0%)	330 (50.6%)	251 (52.3%)	408 (59.2%)	34 (60.7%)	34 (42.5%)
Headache	592 (32.8%)	199 (34.1%)	155 (35.0%)	203 (31.4%)	21 (38.9%)	14 (18.4%)
Encephalopathy	74 (3.94%)	15 (2.37%)	21 (4.67%)	30 (4.49%)	6 (11.3%)	2 (2.63%)
Irritability	355 (18.8%)	127 (20.2%)	69 (14.9%)	135 (20.2%)	10 (18.5%)	14 (18.4%)
Lethargy	655 (34.5%)	211 (33.3%)	186 (40.1%)	215 (32.1%)	23 (41.8%)	20 (26.7%)
[^]Kawasaki Disease features during admission						
Rash	1306 (65.0%)	484 (71.2%)	306 (62.8%)	441 (63.2%)	35 (59.3%)	40 (47.1%)
Mucocutaneous changes	1087 (54.1%)	420 (61.8%)	241 (49.5%)	379 (54.3%)	28 (47.5%)	19 (22.4%)
Conjuctival injection	1235 (61.5%)	467 (68.7%)	270 (55.4%)	450 (64.5%)	27 (45.8%)	21 (24.7%)
Edema or erythema of extremities	753 (37.5%)	271 (39.9%)	170 (34.9%)	281 (40.3%)	17 (28.8%)	14 (16.5%)
Skin peeling	245 (12.2%)	96 (14.1%)	55 (11.3%)	87 (12.5%)	4 (6.78%)	3 (3.53%)
Lymphadenopathy	675 (33.6%)	269 (39.6%)	137 (28.1%)	228 (32.7%)	22 (37.3%)	19 (22.4%)
BCG reactivity	27 (1.34%)	11 (1.62%)	0 (0%)	16 (2.29%)	0 (0%)	0 (0%)
[+]Blood results on admission						
WBC (10^9/L)	10 [7.1 - 15]	10 [7.0 - 15]	10 [7.3 - 15]	10 [7.2 - 15]	9.4 [5.6 - 13]	11 [6.4 - 15]
Neutrophils (10^9/L)	7.9 [5.2 - 12]	7.8 [5.0 - 11]	7.9 [5.1 - 12]	7.9 [5.4 - 12]	7.3 [4.5 - 10]	7.1 [3.7 - 10]
Lymphocytes (10^9/L)	1.2 [0.70 - 2.0]	1.3 [0.76 - 2.2]	1.2 [0.70 - 1.8]	1.1 [0.66 - 1.9]	0.86 [0.52 - 1.6]	1.8 [1.1 - 2.9]
Hemoglobin (g/L)	120 [100 - 130]	120 [100 - 120]	120 [110 - 130]	110 [100 - 120]	110 [100 - 120]	120 [110 - 130]
Platelets (10^9/L)	180 [120 - 270]	190 [130 - 290]	170 [120 - 260]	170 [120 - 240]	160 [100 - 240]	240 [160 - 330]
PT (sec)	15 [13 - 17]	15 [13 - 17]	15 [13 - 17]	15 [13 - 16]	15 [14 - 17]	14 [13 - 16]
APTT (sec)	32 [27 - 38]	33 [28 - 38]	32 [27 - 37]	32 [27 - 37]	34 [29 - 37]	31 [27 - 37]
Fibrinogen (g/L)	5.5 [4.3 - 6.7]	5.5 [4.4 - 6.5]	5.5 [4.4 - 6.6]	5.4 [4.3 - 6.8]	5.7 [4.4 - 6.9]	4.7 [3.0 - 6.4]
D Dimer (ng/mL)	2700 [1400 - 4700]	2500 [1200 - 4400]	2600 [1300 - 4500]	2900 [1500 - 5000]	2900 [2000 - 5600]	1800 [780 - 4000]
Troponin (ng/L)	25 [6.1 - 83]	13 [5.0 - 43]	31 [9.8 - 100]	40 [10 - 110]	48 [10 - 270]	10 [2.0 - 38]
BNP (ng/L)						
CRP (mg/L)	150 [85 - 220]	150 [85 - 210]	160 [75 - 220]	160 [90 - 230]	180 [97 - 280]	85 [23 - 180]
Ferritin (ug/L)	440 [230 - 860]	370 [210 - 650]	480 [260 - 970]	520 [260 - 960]	560 [340 - 1700]	280 [140 - 460]
LDH (U/L)	320 [250 - 430]	320 [250 - 420]	310 [260 - 410]	320 [250 - 440]	290 [260 - 370]	350 [270 - 490]
Creatinine (umol/L)	47 [35 - 65]	42 [32 - 56]	53 [42 - 70]	50 [36 - 69]	54 [40 - 72]	46 [30 - 57]
ALT (U/L)	32 [19 - 57]	28 [16 - 48]	34 [19 - 64]	35 [21 - 63]	43 [20 - 76]	28 [15 - 49]
Albumin (g/L)	32 [28 - 37]	34 [28 - 39]	32 [27 - 36]	32 [27 - 36]	32 [27 - 36]	35 [30 - 41]

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 biologics)). 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.

Table S3: Demographic information, clinical features, and blood results for all patients included in the analysis, and subgroups meeting specific criteria

	Clinician diagnosed MIS-C matched on WHO criteria					All patients with clinician diagnosed MIS-C		
	Overall (N=2009)	MIS-C (full WHO criteria) (N=1602)	MIS-C with bacteremia/TSS (N=26)	MIS-C missing 1 criterion (N=284)	MIS-C missing >1 criteria (N=97)	KD (N=629)	Atypical KD (N=682)	Not KD (N=698)
^Age (years)	8.0 [4.2 - 11]	8.2 [4.5 - 11]	7.9 [3.2 - 11]	7.8 [3.8 - 12]	4.7 [2.0 - 9.0]	6.4 [3.4 - 9.7]	8.8 [4.8 - 12]	8.8 [4.6 - 13]
^Proportion male	1191 (59.3%)	962 (60.0%)	11 (42.3%)	170 (59.9%)	48 (49.5%)	377 (59.9%)	397 (58.2%)	417 (59.7%)
^Weight (age-adjusted z score ≥ 2)	299 (14.9%)	257 (16.0%)	3 (11.5%)	32 (11.3%)	7 (7.22%)	77 (12.2%)	103 (15.1%)	119 (17.0%)
^Ethnicity								
White	825 (41.1%)	668 (41.7%)	10 (38.5%)	104 (36.6%)	43 (44.3%)	274 (43.6%)	283 (41.5%)	268 (38.4%)
Latino	518 (25.8%)	404 (25.2%)	5 (19.2%)	80 (28.2%)	29 (29.9%)	167 (26.6%)	133 (19.5%)	218 (31.2%)
Black	212 (10.6%)	164 (10.2%)	7 (26.9%)	32 (11.3%)	9 (9.28%)	47 (7.47%)	83 (12.2%)	82 (11.7%)
Asian	131 (6.52%)	101 (6.30%)	1 (3.85%)	21 (7.39%)	8 (8.25%)	46 (7.31%)	48 (7.04%)	37 (5.30%)
Other or not known	323 (16.1%)	265 (16.5%)	3 (11.5%)	47 (16.5%)	8 (8.25%)	95 (15.1%)	135 (19.8%)	93 (13.3%)
^Significant comorbidity	108 (5.38%)	74 (4.62%)	3 (11.5%)	20 (7.04%)	11 (11.3%)	20 (3.18%)	26 (3.81%)	62 (8.88%)
^Home country economic status								
High-income economies	1186 (59.0%)	930 (58.1%)	18 (69.2%)	183 (64.4%)	55 (56.7%)	347 (55.2%)	444 (65.1%)	395 (56.6%)
Upper-middle income economies	710 (35.3%)	574 (35.8%)	5 (19.2%)	91 (32.0%)	40 (41.2%)	230 (36.6%)	206 (30.2%)	274 (39.3%)
Lower-middle income economies	113 (5.62%)	98 (6.12%)	3 (11.5%)	10 (3.52%)	2 (2.06%)	52 (8.27%)	32 (4.69%)	29 (4.15%)
^SARS-CoV-2 PCR positive								
Yes	415 (20.8%)	337 (21.2%)	5 (19.2%)	44 (15.7%)	29 (30.9%)	108 (17.3%)	120 (17.7%)	187 (27.1%)
Tested but negative	1397 (70.1%)	1110 (69.7%)	18 (69.2%)	212 (75.4%)	57 (60.6%)	464 (74.2%)	490 (72.4%)	443 (64.1%)
Not tested	181 (9.08%)	145 (9.11%)	3 (11.5%)	25 (8.90%)	8 (8.51%)	53 (8.48%)	67 (9.90%)	61 (8.83%)
^SARS-CoV-2 Ab positive								
Yes	1321 (66.5%)	1219 (76.8%)	21 (87.5%)	58 (20.8%)	23 (24.2%)	436 (70.7%)	489 (72.3%)	396 (57.1%)
Tested but negative	259 (13.0%)	135 (8.50%)	1 (4.17%)	101 (36.2%)	22 (23.2%)	80 (13.0%)	81 (12.0%)	98 (14.1%)
Not tested	406 (20.4%)	234 (14.7%)	2 (8.33%)	120 (43.0%)	50 (52.6%)	101 (16.4%)	106 (15.7%)	199 (28.7%)
^Baseline level of care								
No support	1100 (54.8%)	857 (53.5%)	11 (42.3%)	163 (57.4%)	69 (71.1%)	369 (58.7%)	376 (55.1%)	355 (50.9%)
Oxygen	203 (10.1%)	174 (10.9%)	3 (11.5%)	21 (7.39%)	5 (5.15%)	70 (11.1%)	54 (7.92%)	79 (11.3%)
Inotropes	347 (17.3%)	307 (19.2%)	7 (26.9%)	32 (11.3%)	1 (1.03%)	87 (13.8%)	150 (22.0%)	110 (15.8%)
Ventilation	30 (1.49%)	20 (1.25%)	0 (0%)	6 (2.11%)	4 (4.12%)	11 (1.75%)	9 (1.32%)	10 (1.43%)
Inotropes and ventilation or ECMO	158 (7.86%)	125 (7.80%)	2 (7.69%)	29 (10.2%)	2 (2.06%)	31 (4.93%)	50 (7.33%)	77 (11.0%)
^Clinical features on admission								
Fever	1863 (92.7%)	1526 (95.3%)	24 (92.3%)	243 (85.6%)	70 (72.2%)	605 (96.2%)	656 (96.2%)	602 (86.2%)
Sore throat	464 (25.5%)	378 (25.6%)	10 (40.0%)	61 (25.7%)	15 (18.1%)	171 (30.3%)	166 (26.5%)	127 (20.1%)
Cough	404 (21.1%)	316 (20.5%)	7 (28.0%)	57 (22.1%)	24 (27.6%)	127 (20.9%)	125 (19.1%)	152 (23.2%)
Respiratory distress	258 (13.3%)	211 (13.5%)	4 (16.0%)	37 (13.9%)	6 (6.74%)	72 (11.7%)	77 (11.7%)	109 (16.4%)
Abdominal pain	1211 (63.2%)	1044 (67.4%)	16 (66.7%)	136 (52.9%)	15 (17.4%)	371 (62.5%)	428 (65.5%)	412 (61.5%)
Diarrhea	882 (44.8%)	749 (47.3%)	16 (64.0%)	107 (39.6%)	10 (11.1%)	247 (40.2%)	319 (47.6%)	316 (46.3%)
Vomiting	1057 (54.0%)	892 (56.7%)	14 (56.0%)	139 (51.5%)	12 (13.5%)	322 (52.5%)	380 (56.7%)	355 (52.7%)
Headache	592 (32.8%)	502 (34.5%)	6 (30.0%)	72 (29.3%)	12 (14.5%)	194 (35.1%)	201 (32.8%)	197 (30.9%)
Encephalopathy	74 (3.94%)	60 (3.98%)	0 (0%)	9 (3.47%)	5 (5.56%)	23 (3.85%)	21 (3.33%)	30 (4.60%)
Irritability	355 (18.8%)	290 (19.0%)	4 (18.2%)	46 (18.2%)	15 (16.5%)	165 (27.4%)	104 (16.2%)	86 (13.3%)
Lethargy	655 (34.5%)	545 (35.6%)	11 (47.8%)	86 (33.6%)	13 (15.1%)	226 (37.4%)	236 (37.3%)	193 (29.3%)
^Kawasaki Disease features during admission								
Rash	1306 (65.0%)	1077 (67.2%)	14 (53.8%)	178 (62.7%)	37 (38.1%)	609 (96.8%)	475 (69.6%)	222 (31.8%)
Mucocutaneous changes	1087 (54.1%)	909 (56.7%)	12 (46.2%)	138 (48.6%)	28 (28.9%)	599 (95.2%)	372 (54.5%)	116 (16.6%)
Conjuctival injection	1235 (61.5%)	1033 (64.5%)	13 (50.0%)	152 (53.5%)	37 (38.1%)	598 (95.1%)	465 (68.2%)	172 (24.6%)
Edema or erythema of extremities	753 (37.5%)	645 (40.3%)	6 (23.1%)	78 (27.5%)	24 (24.7%)	459 (73.0%)	210 (30.8%)	84 (12.0%)
Skin peeling	245 (12.2%)	193 (12.0%)	5 (19.2%)	37 (13.0%)	10 (10.3%)	165 (26.2%)	58 (8.50%)	22 (3.15%)
Lymphadenopathy	675 (33.6%)	561 (35.0%)	6 (23.1%)	84 (29.6%)	24 (24.7%)	420 (66.8%)	178 (26.1%)	77 (11.0%)
BCG reactivity	27 (1.34%)	18 (1.12%)	1 (3.85%)	7 (2.46%)	1 (1.03%)	20 (3.18%)	4 (0.587%)	3 (0.430%)
^Bloods on admission								
WBC (10^9/L)	10 [7.1 - 15]	10 [7.1 - 15]	12 [6.4 - 16]	11 [7.3 - 15]	9.1 [6.1 - 15]	10 [7.0 - 15]	10 [7.4 - 14]	10 [6.7 - 15]
Neutrophils (10^9/L)	7.9 [5.2 - 12]	7.9 [5.2 - 12]	10 [4.4 - 11]	7.9 [5.0 - 11]	6.2 [3.6 - 10]	8.0 [5.3 - 11]	7.9 [5.4 - 11]	7.6 [4.7 - 12]
Lymphocytes (10^9/L)	1.2 [0.70 - 2.0]	1.1 [0.69 - 1.9]	0.98 [0.69 - 2.4]	1.4 [0.81 - 2.6]	1.8 [0.99 - 3.2]	1.2 [0.70 - 2.1]	1.1 [0.68 - 1.7]	1.3 [0.76 - 2.2]
Hemoglobin (g/L)	120 [100 - 130]	120 [100 - 130]	110 [100 - 110]	120 [110 - 130]	120 [100 - 120]	120 [100 - 120]	110 [100 - 130]	120 [110 - 130]
Platelets (10^9/L)	180 [120 - 270]	170 [120 - 250]	210 [170 - 280]	210 [140 - 310]	290 [180 - 390]	170 [120 - 250]	170 [120 - 250]	200 [140 - 290]
PT (sec)	15 [13 - 17]	15 [13 - 17]	15 [15 - 17]	14 [13 - 16]	13 [13 - 15]	15 [13 - 16]	15 [13 - 16]	15 [13 - 17]
APTT (sec)	32 [27 - 38]	32 [28 - 38]	33 [30 - 42]	31 [26 - 37]	30 [26 - 35]	33 [28 - 38]	32 [28 - 37]	31 [27 - 37]
Fibrinogen (g/L)	5.5 [4.3 - 6.7]	5.5 [4.4 - 6.6]	6.3 [3.7 - 7.1]	5.5 [4.2 - 6.9]	5.1 [4.5 - 6.4]	5.4 [4.3 - 6.4]	5.5 [4.4 - 6.7]	5.5 [4.2 - 6.8]
D Dimer (ng/mL)	2700 [1400 - 4700]	2700 [1400 - 4800]	2400 [1300 - 3800]	2500 [1300 - 4400]	1500 [620 - 3600]	2800 [1700 - 5000]	2800 [1300 - 4400]	2400 [1200 - 4600]
Troponin (ng/L)	25 [6.1 - 80]	27 [7.0 - 85]	40 [10 - 85]	16 [5.0 - 59]	6.7 [3.1 - 12]	18 [5.0 - 50]	28 [9.0 - 98]	29 [6.0 - 110]
BNP (ng/L)	180 [47 - 720]	210 [47 - 730]	240 [91 - 800]	100 [45 - 560]	82 [16 - 160]	180 [58 - 650]	190 [69 - 700]	180 [36 - 830]
CRP (mg/L)	150 [85 - 220]	160 [90 - 230]	190 [87 - 280]	140 [58 - 200]	66 [17 - 150]	150 [86 - 210]	160 [96 - 230]	140 [62 - 220]
Ferritin (ug/L)	440 [230 - 860]	460 [260 - 880]	610 [220 - 1100]	270 [140 - 810]	170 [110 - 300]	460 [260 - 880]	440 [260 - 900]	430 [180 - 820]
LDH (U/L)	320 [250 - 430]	320 [250 - 430]	380 [310 - 410]	310 [250 - 440]	330 [270 - 470]	310 [250 - 410]	310 [250 - 430]	330 [260 - 450]
Creatinine (umol/L)	47 [35 - 65]	48 [36 - 65]	58 [37 - 87]	46 [31 - 62]	42 [27 - 59]	44 [33 - 57]	48 [36 - 66]	51 [37 - 70]
ALT (U/L)	32 [19 - 58]	32 [19 - 57]	33 [21 - 66]	32 [17 - 62]	27 [14 - 41]	33 [20 - 65]	32 [18 - 53]	30 [17 - 57]
Albumin (g/L)	32 [28 - 37]	32 [27 - 37]	32 [27 - 37]	32 [26 - 37]	37 [33 - 41]	32 [27 - 37]	32 [28 - 37]	33 [27 - 38]

Descriptive table of blood markers, demographic & clinical features on admission, and Kawasaki Disease features during 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[8] (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. SARSCoV-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.

Table S4: Distribution of patients meeting WHO criteria subdivided by Kawasaki Disease status, age, and primary treatment

Table showing patients matched on WHO MIS-C criteria and divided by whether they met the definition of Kawasaki Disease set out by the American Heart Association during admission (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. Values given as raw values and (%).

Abbreviations: KD: Kawasaki Disease; TSS: toxic shock syndrome

	MIS-C (full WHO criteria)			MIS-C with bacteremia			MIS-C missing 1 criterion			MIS-C missing >1 criteria			All patients		
	KD (N=544)	Atypical KD (N=596)	Not KD (N=462)	KD (N=6)	Atypical KD (N=7)	Not KD (N=13)	KD (N=63)	Atypical KD (N=66)	Not KD (N=155)	KD (N=16)	Atypical KD (N=13)	Not KD (N=68)	KD (N=629)	Atypical KD (N=682)	Not KD (N=698)
Age (years)															
Over 6	298 (54.8%)	432 (72.5%)	322 (69.7%)	3 (50.0%)	4 (57.1%)	9 (69.2%)	29 (46.0%)	33 (50.0%)	110 (71.0%)	4 (25.0%)	2 (15.4%)	32 (47.1%)	334 (53.1%)	471 (69.1%)	473 (67.8%)
Under 6	246 (45.2%)	164 (27.5%)	140 (30.3%)	3 (50.0%)	3 (42.9%)	4 (30.8%)	34 (54.0%)	33 (50.0%)	45 (29.0%)	12 (75.0%)	11 (84.6%)	36 (52.9%)	295 (46.9%)	211 (30.9%)	225 (32.2%)
First immunomodulator given															
IVIG	210 (38.6%)	187 (31.4%)	127 (27.5%)	3 (50.0%)	3 (42.9%)	4 (30.8%)	40 (63.5%)	36 (54.5%)	32 (20.6%)	12 (75.0%)	9 (69.2%)	17 (25.0%)	265 (42.1%)	235 (34.5%)	180 (25.8%)
Glucocorticoids	110 (20.2%)	155 (26.0%)	134 (29.0%)	0 (0%)	2 (28.6%)	5 (38.5%)	7 (11.1%)	8 (12.1%)	43 (27.7%)	2 (12.5%)	1 (7.69%)	20 (29.4%)	119 (18.9%)	166 (24.3%)	202 (28.9%)
IVIG and Glucocorticoids	208 (38.2%)	221 (37.1%)	167 (36.1%)	2 (33.3%)	2 (28.6%)	2 (15.4%)	13 (20.6%)	16 (24.2%)	58 (37.4%)	2 (12.5%)	0 (0%)	7 (10.3%)	225 (35.8%)	239 (35.0%)	234 (33.5%)
Other	9 (1.65%)	19 (3.19%)	16 (3.46%)	1 (16.7%)	0 (0%)	1 (7.69%)	2 (3.17%)	3 (4.55%)	6 (3.87%)	0 (0%)	0 (0%)	2 (2.94%)	12 (1.91%)	22 (3.23%)	25 (3.58%)
No treatment	7 (1.29%)	14 (2.35%)	18 (3.90%)	0 (0%)	0 (0%)	1 (7.69%)	1 (1.59%)	3 (4.55%)	16 (10.3%)	0 (0%)	3 (23.1%)	22 (32.4%)	8 (1.27%)	20 (2.93%)	57 (8.17%)

Table S5A: Details for first primary outcome - inotropes/ventilation from day 2 or death

Table showing the total number of patients included for analysis of the first primary outcome (inotropes/ventilation from day 2 or death) after exclusions for missing baseline covariates. Crude numbers are shown in the "Raw outcomes" as the numerator/denominator for those providing the outcome, with the proportion in parentheses. Inverse probability of treatment weighted proportions of the outcome are also shown. Adjusted Odds ratios and 95% confidence intervals are provided for primary treatment groups, with IVIG as the reference treatment. All four p-values calculated for the two primary outcomes and two primary comparisons are reported adjusted for multiple hypothesis testing. 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 Therapy	Number of patients	Missing outcome	Raw outcomes	Weighted % with outcome	Odds ratio (relative to IVIG)	Confidence interval (95%)	Adj. p-value	E-value
IVIG	579	11	103/568 (18.1%)	24.0%	-	-	-	-
Glucocorticoid	382	11	81/371 (21.8%)	23.5%	0.93	0.58 - 1.47	1.00	1.24
IVIG and Glucocorticoid	625	17	187/608 (30.8%)	25.5%	1.09	0.75 - 1.58	1.00	1.26

Table S5B: Details for second primary outcome – Time-to-improvement in ordinal scale of clinical severity

Table showing the total number of patients included for analysis of the second primary outcome (time-to-improvement in ordinal scale of clinical severity) after exclusions for missing baseline covariates. The number of patients who improved and right-censored are reported. Those who did not improve or where the outcome could not be calculated are reported as missing this outcome. Adjusted average hazard ratios and 95% confidence intervals are provided for primary treatment groups, with IVIG as the reference treatment. All four p-values calculated for the two primary outcomes and two primary comparisons are reported adjusted for multiple hypothesis testing. 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 Therapy	Number of patients	Improved (censored)	Missing outcome	Average Hazard Ratio (relative to IVIG)	Confidence interval (95%)	Adj. p-value	E-value
IVIG	579	358 (207)	14	-	-	-	-
Glucocorticoid	382	240 (133)	9	0.84	0.70 - 1.00	0.22	1.51
IVIG and Glucocorticoid	625	434 (174)	17	1.04	0.91 - 1.20	1.00	1.21

Table S5C: Raw and weighted dichotomous secondary outcomes by primary treatment group

Table showing the total number of patients included for each dichotomous secondary outcome, including planned and post-hoc *sensitivity and subgroup analyses. The total number of patients included for each separate analysis are shown after exclusions for missing baseline covariates and subgrouping. Crude numbers are shown in the "Raw outcomes" column as the numerator/denominator for those providing the outcome and (%). Inverse probability of treatment weighted proportions of the outcomes are also shown. *post-hoc analysis. **Planned analysis*

Secondary Outcome	Primary Therapy	Number of patients after exclusions	Missing outcome	Raw outcomes	Weighted % with outcome
Death	IVIG	579	16	5/563 (0.9%)	1.4%
	Glucocorticoid	382	13	6/369 (1.6%)	2.4%
	IVIG and Glucocorticoid	625	24	7/601 (1.2%)	0.9%
Inotropes from day 2	IVIG	579	9	89/570 (15.6%)	21.5%
	Glucocorticoid	382	5	76/377 (20.2%)	22.0%
	IVIG and Glucocorticoid	625	7	164/618 (26.5%)	21.9%
Ventilation from day 2	IVIG	579	7	49/572 (8.6%)	10.0%
	Glucocorticoid	382	1	29/381 (7.6%)	11.3%
	IVIG and Glucocorticoid	625	1	93/624 (14.9%)	11.4%
No improvement by day 2	IVIG	579	14	409/565 (72.4%)	70.5%
	Glucocorticoid	382	5	268/377 (71.1%)	73.1%
	IVIG and Glucocorticoid	625	7	414/618 (67%)	67.8%
*No improvement by day 3	IVIG	579	18	275/561 (49%)	48.8%
	Glucocorticoid	382	7	185/375 (49.3%)	49.9%
	IVIG and Glucocorticoid	625	11	284/614 (46.3%)	46.0%
Escalation of primary treatment	IVIG	579	9	334/570 (58.6%)	61.2%
	Glucocorticoid	382	8	187/374 (50%)	52.3%
	IVIG and Glucocorticoid	625	15	125/610 (20.5%)	19.9%
*Escalation, from day 2 onwards	IVIG	579	14	169/565 (29.9%)	30.5%
	Glucocorticoid	382	9	102/373 (27.3%)	28.5%
	IVIG and Glucocorticoid	625	20	90/605 (14.9%)	14.3%
*Escalation, exclude L/LM-IC	IVIG	569	9	328/560 (58.6%)	61.8%
	Glucocorticoid	338	8	160/330 (48.5%)	51.4%
	IVIG and Glucocorticoid	600	15	119/585 (20.3%)	19.7%
Fever from day 2 onwards	IVIG	579	71	228/508 (44.9%)	43.3%
	Glucocorticoid	382	56	128/326 (39.3%)	38.2%
	IVIG and Glucocorticoid	625	101	151/524 (28.8%)	28.2%
*Fever from day 3 onwards	IVIG	579	106	115/473 (24.3%)	24.2%
	Glucocorticoid	382	65	87/317 (27.4%)	27.6%
	IVIG and Glucocorticoid	625	124	101/501 (20.2%)	19.2%
*Fever from day 2, Complete KD criteria	IVIG	222	22	103/200 (51.5%)	50.6%
	Glucocorticoid	87	7	42/80 (52.5%)	46.9%
	IVIG and Glucocorticoid	200	27	58/173 (33.5%)	33.2%

Table S5C: Raw and weighted dichotomous secondary outcomes by primary treatment group (*continued)*

Secondary Outcome	Primary Therapy	Number of patients after exclusions	Missing outcome	Raw outcomes	Weighted % with outcome
Increase in level of support	IVIG	579	14	65/565 (11.5%)	12.4%
	Glucocorticoid	382	12	55/370 (14.9%)	14.3%
	IVIG and Glucocorticoid	625	22	85/603 (14.1%)	13.7%
*Increase in support, exclude L/LM-IC	IVIG	569	14	65/555 (11.7%)	12.9%
	Glucocorticoid	338	12	44/326 (13.5%)	13.4%
	IVIG and Glucocorticoid	600	22	84/578 (14.5%)	14.5%
*Increase in support, baseline no support	IVIG	470	6	50/464 (10.8%)	10.8%
	Glucocorticoid	262	5	41/257 (16%)	15.3%
	IVIG and Glucocorticoid	384	11	43/373 (11.5%)	11.4%
Coronary Artery Aneurysms (CAA) at discharge	IVIG	415	160	21/255 (8.2%)	6.7%
	Glucocorticoid	227	83	9/144 (6.2%)	8.0%
	IVIG and Glucocorticoid	492	186	20/306 (6.5%)	5.6%
*CAA at discharge, no CAA at baseline	IVIG	380	150	11/230 (4.8%)	3.7%
	Glucocorticoid	218	79	7/139 (5%)	5.2%
	IVIG and Glucocorticoid	440	171	11/269 (4.1%)	3.9%
*CAA at discharge, Complete KD criteria	IVIG	148	51	4/97 (4.1%)	4.5%
	Glucocorticoid	50	14	3/36 (8.3%)	10.9%
	IVIG and Glucocorticoid	129	51	2/78 (2.6%)	3.2%
*CAA at discharge, exclude complete KD criteria	IVIG	261	108	16/153 (10.5%)	7.1%
	Glucocorticoid	177	69	6/108 (5.6%)	8.7%
	IVIG and Glucocorticoid	342	129	16/213 (7.5%)	6.2%
LV-dysfunction (LVD) from day 2	IVIG	568	6	66/562 (11.7%)	13.7%
	Glucocorticoid	363	8	47/355 (13.2%)	15.2%
	IVIG and Glucocorticoid	613	18	89/595 (15%)	12.8%
**LVD from day 2, baseline-troponin as covariate	IVIG	437	3	66/434 (15.2%)	18.3%
	Glucocorticoid	207	4	38/203 (18.7%)	22.1%
	IVIG and Glucocorticoid	455	10	102/445 (22.9%)	20.2%
*LVD from day 1	IVIG	568	3	83/565 (14.7%)	17.1%
	Glucocorticoid	363	5	61/358 (17%)	19.6%
	IVIG and Glucocorticoid	613	14	123/599 (20.5%)	18.2%

Table S5D: Raw and weighted outcomes for subgroup and sensitivity analyses of first primary outcome by primary treatment group

*Table showing the total number of patients included for each subgroup and sensitivity analysis for the first primary outcome (inotropes/ventilation from day 2, or death) including planned analyses. The total number of patients included for each separate analysis are shown after exclusions for missing baseline covariates and subgrouping. Crude numbers are shown in the "Raw outcomes" column as the numerator/denominator for those providing the outcome, and (%). Inverse probability of treatment weighted proportions of the outcomes are also shown. *Number matched for propensity matched analysis. **Outcomes in matched cohorts after removing unmatched cases.*

Subgroup/Sensitivity analysis	Primary Therapy	Number of patients after exclusions	Missing outcome	Raw outcomes	Weighted % with outcome
Planned sensitivity analyses					
Primary-therapy on days 0 & 1	IVIG	390	8	33/382 (8.6%)	14.2%
	Glucocorticoid	283	13	30/270 (11.1%)	13.6%
	IVIG and Glucocorticoid	899	28	174/871 (20%)	17.0%
Propensity matched analysis: Glucocorticoids vs IVIG	IVIG	291*	0	63/291 (21.7%)**	
	Glucocorticoid	291*	0	65/291 (22.3%)**	
Propensity matched analysis: IVIG+G vs IVIG	IVIG	487*	0	99/487 (20.3%)**	
	IVIG and Glucocorticoid	487*	0	117/487 (24%)**	
Impute CRP (median by treatment group)	IVIG	609	11	111/598 (18.6%)	24.5%
	Glucocorticoid	428	12	94/416 (22.6%)	24.2%
	IVIG and Glucocorticoid	662	17	193/645 (29.9%)	24.9%
Planned subgroup analyses					
Full WHO MIS-C criteria	IVIG	456	10	92/446 (20.6%)	25.4%
	Glucocorticoid	333	6	71/327 (21.7%)	22.6%
	IVIG and Glucocorticoid	552	16	165/536 (30.8%)	25.8%
Full WHO MIS-C criteria + bacteraemia/TSS	IVIG	464	10	92/454 (20.3%)	25.4%
	Glucocorticoid	337	6	72/331 (21.8%)	22.9%
	IVIG and Glucocorticoid	558	16	168/542 (31%)	25.9%
Missing up-to 1 WHO MIS-C criteria	IVIG	542	11	102/531 (19.2%)	24.5%
	Glucocorticoid	368	8	79/360 (21.9%)	23.5%
	IVIG and Glucocorticoid	613	17	183/596 (30.7%)	25.7%
Exclude Low & Lower-middle Income countries	IVIG	569	11	101/558 (18.1%)	24.6%
	Glucocorticoid	338	11	73/327 (22.3%)	23.2%
	IVIG and Glucocorticoid	600	17	181/583 (31%)	26.0%
Age < 6 years	IVIG	255	5	31/250 (12.4%)	20.7%
	Glucocorticoid	110	1	21/109 (19.3%)	20.5%
	IVIG and Glucocorticoid	207	5	45/202 (22.3%)	18.1%
Age 6-11 years	IVIG	233	3	49/230 (21.3%)	26.2%
	Glucocorticoid	164	4	37/160 (23.1%)	24.9%
	IVIG and Glucocorticoid	283	8	89/275 (32.4%)	27.4%
Age > 11 years	IVIG	91	3	23/88 (26.1%)	30.7%
	Glucocorticoid	95	6	20/89 (22.5%)	26.2%
	IVIG and Glucocorticoid	128	4	50/124 (40.3%)	33.2%

Table S5D: Raw and weighted outcomes for subgroup and sensitivity analyses of first primary outcome by primary treatment group (*continued*)

Subgroup/Sensitivity analysis	Primary Therapy	Number of patients after exclusions	Missing outcome	Raw outcomes	Weighted % with outcome
Planned subgroup analyses					
No significant comorbidities	IVIG	555	10	99/545 (18.2%)	24.2%
	Glucocorticoid	357	8	77/349 (22.1%)	23.9%
	IVIG and Glucocorticoid	595	16	175/579 (30.2%)	24.8%
Baseline CRP < 118.0	IVIG	202	3	20/199 (10.1%)	13.1%
	Glucocorticoid	127	3	14/124 (11.3%)	10.1%
	IVIG and Glucocorticoid	197	3	36/194 (18.6%)	13.9%
Baseline CRP 118.0 - 206.5	IVIG	191	3	34/188 (18.1%)	24.5%
	Glucocorticoid	129	4	28/125 (22.4%)	25.7%
	IVIG and Glucocorticoid	211	6	58/205 (28.3%)	23.9%
Baseline CRP >= 206.5	IVIG	186	5	49/181 (27.1%)	34.0%
	Glucocorticoid	126	4	39/122 (32%)	32.2%
	IVIG and Glucocorticoid	217	8	93/209 (44.5%)	38.4%
Post-hoc subgroup analyses					
Meet complete KD criteria	IVIG	215	0	30/215 (14%)	18.2%
	Glucocorticoid	87	1	16/86 (18.6%)	15.7%
	IVIG and Glucocorticoid	175	3	44/172 (25.6%)	21.9%
Do not meet complete KD criteria	IVIG	357	10	69/347 (19.9%)	25.4%
	Glucocorticoid	295	10	65/285 (22.8%)	26.1%
	IVIG and Glucocorticoid	425	14	124/411 (30.2%)	25.8%
Exclude changes in treatment group	IVIG	263	6	19/257 (7.4%)	16.7%
	Glucocorticoid	198	9	24/189 (12.7%)	15.2%
	IVIG and Glucocorticoid	553	16	150/537 (27.9%)	23.6%

Table S5E: Additional details for subgroup and sensitivity analyses of second primary outcome by primary treatment group

*Table showing the total number of patients included for all sensitivity and subgroup analyses of the second primary outcome (time-to-improvement in ordinal scale of clinical severity) after exclusions for missing baseline covariates and subgrouping. The number of patients who improved and were right-censored are reported. Those who did not improve or where the outcome could not be calculated are reported as missing this outcome. *Number matched for propensity matched analysis. **Outcomes in matched cohorts after removing unmatched cases.*

Subgroup/Sensitivity analysis	Primary Therapy	Number of patients after exclusions	Improved (censored)	Missing outcome
Planned sensitivity analyses				
Primary-therapy on days 0 & 1	IVIG	390	251 (127)	12
	Glucocorticoid	283	191 (82)	10
	IVIG and Glucocorticoid	899	659 (217)	23
Propensity matched analysis: Glucocorticoids vs IVIG	IVIG	304*	291 (13)**	0
	Glucocorticoid	304*	292 (12)**	0
Propensity matched analysis: IVIG+G vs IVIG	IVIG	495*	471 (24)**	0
	IVIG and Glucocorticoid	495*	482 (13)**	0
Two-point Time-to-Improvement	IVIG	579	521 (44)	14
	Glucocorticoid	382	349 (24)	9
	IVIG and Glucocorticoid	625	563 (45)	17
Impute CRP (median by treatment group)	IVIG	609	385 (210)	14
	Glucocorticoid	428	281 (134)	13
	IVIG and Glucocorticoid	662	470 (174)	18
Planned subgroup analyses				
Requiring intensive support at baseline	IVIG	100	89 (3)	8
	Glucocorticoid	111	103 (2)	6
	IVIG and Glucocorticoid	224	214 (2)	8
Requiring no intensive support at baseline	IVIG	428	222 (204)	2
	Glucocorticoid	227	97 (130)	0
	IVIG and Glucocorticoid	332	158 (172)	2
Full WHO MIS-C criteria	IVIG	456	275 (169)	12
	Glucocorticoid	333	210 (117)	6
	IVIG and Glucocorticoid	552	385 (154)	13
Full WHO MIS-C criteria + bacteraemia/TSS	IVIG	464	280 (172)	12
	Glucocorticoid	337	213 (117)	7
	IVIG and Glucocorticoid	558	390 (155)	13
Missing up-to 1 WHO MIS-C criteria	IVIG	542	337 (191)	14
	Glucocorticoid	368	230 (130)	8
	IVIG and Glucocorticoid	613	427 (170)	16
Exclude Low & Lower-middle Income countries	IVIG	569	352 (203)	14
	Glucocorticoid	338	208 (123)	7
	IVIG and Glucocorticoid	600	416 (168)	16

Table S5E: Additional details for subgroup and sensitivity analyses of second primary outcome by primary treatment group (*continued*)

Subgroup/Sensitivity analysis	Primary Therapy	Number of patients after exclusions	Improved (censored)	Missing outcome
Planned subgroup analyses				
Age < 6 years	IVIG	255	149 (101)	5
	Glucocorticoid	110	61 (45)	4
	IVIG and Glucocorticoid	207	127 (74)	6
Age 6-11 years	IVIG	233	144 (85)	4
	Glucocorticoid	164	108 (55)	1
	IVIG and Glucocorticoid	283	200 (73)	10
Age > 11 years	IVIG	91	65 (21)	5
	Glucocorticoid	108	71 (33)	4
	IVIG and Glucocorticoid	135	107 (27)	1
No significant comorbidities	IVIG	555	345 (197)	13
	Glucocorticoid	357	227 (123)	7
	IVIG and Glucocorticoid	595	413 (168)	14
Baseline CRP < 118.0	IVIG	202	116 (81)	5
	Glucocorticoid	127	89 (35)	3
	IVIG and Glucocorticoid	197	144 (50)	3
Baseline CRP 118.0 - 206.5	IVIG	179	118 (58)	3
	Glucocorticoid	128	74 (53)	1
	IVIG and Glucocorticoid	184	110 (70)	4
Baseline CRP >= 206.5	IVIG	186	113 (67)	6
	Glucocorticoid	126	77 (45)	4
	IVIG and Glucocorticoid	217	155 (54)	8
Post-hoc subgroup analyses				
Meet complete KD criteria	IVIG	215	124 (87)	4
	Glucocorticoid	87	46 (41)	0
	IVIG and Glucocorticoid	175	112 (57)	6
Do not meet complete KD criteria	IVIG	357	228 (119)	10
	Glucocorticoid	295	194 (92)	9
	IVIG and Glucocorticoid	425	299 (117)	9
Exclude changes in treatment group	IVIG	263	145 (110)	8
	Glucocorticoid	198	113 (79)	6
	IVIG and Glucocorticoid	553	375 (166)	12

Table S6A: Timing of coronary artery aneurysms by primary treatment group

Table showing the numbers and % of patients with aneurysms detected at any time during admission, up to and after initiation of primary treatment, stratified by primary treatment group. We have subdivided those receiving other combinations of primary treatment into those whose primary treatment did or did not include IVIG.

Primary treatment group	Number of patients	Aneurysms at any time during admission	Aneurysms pre-treatment	Aneurysms post-treatment
IVIG	680	89/660 - 13.5% (No recorded echo 20)	37/436 - 8.5% (No recorded echo 244)	68/521 - 13.1% (No recorded echo 159)
Glucocorticoid	487	40/458 - 8.7% (No recorded echo 29)	9/241 - 3.7% (No recorded echo 246)	36/385 - 9.4% (No recorded echo 102)
IVIG and Glucocorticoid	698	88/680 - 12.9% (No recorded echo 18)	53/518 - 10.2% (No recorded echo 180)	61/507 - 12% (No recorded echo 191)
Other combination - including IVIG	43	11/41 - 26.8% (No recorded echo 2)	9/33 - 27.3% (No recorded echo 10)	8/37 - 21.6% (No recorded echo 6)
Other combination - excluding IVIG	16	6/15 - 40% (No recorded echo 1)	3/9 - 33.3% (No recorded echo 7)	4/13 - 30.8% (No recorded echo 3)
No immunomodulator treatment	85	0/57 - 0% (No recorded echo 28)	0/19 - 0% (No recorded echo 66)	0/45 - 0% (No recorded echo 40)

Table S6B: Coronary artery aneurysm detection and resolution at any time by primary treatment group

Table showing the numbers and % of patients with aneurysms detected at any time (including those where aneurysm status was reported post-discharge) and resolution at any time, stratified by primary treatment group. Only patients with aneurysms recorded on their final inpatient echocardiogram contributed additional post-discharge follow-up. Patients with aneurysms on their final inpatient echocardiogram were classified as not having follow-up if the host sites either did not provide additional follow-up data, or if the follow-up data provided was for less than 6-weeks after initiation of primary treatment. We have subdivided those receiving other combinations of primary treatment into those whose primary treatment did or did not include IVIG.

Primary treatment group	Number of patients	Aneurysms at any time	Aneurysms resolved at any time
IVIG	680	90/663 (13.6% - 17 no echo recorded)	70/76 (92.1% - 14 no follow-up data)
Glucocorticoid	487	41/460 (8.9% - 27 no echo recorded)	33/35 (94.3% - 6 no follow-up data)
IVIG and Glucocorticoid	698	88/682 (12.9% - 16 no echo recorded)	64/68 (94.1% - 20 no follow-up data)
Other combination - including IVIG	43	11/41 (26.8% - 2 no echo recorded)	10/11 (90.9% - 0 no follow-up data)
Other combination - excluding IVIG	16	6/15 (40% - 1 no echo recorded)	5/6 (83.3% - 0 no follow-up data)
No immunomodulator treatment	85	0/57 (0% - 28 no echo recorded)	-
All	2009	236/1918 (12.3% - 91 no echo recorded)	182/196 (92.9% - 40 no follow-up data)

Table S6C: Coronary artery aneurysm resolution at 6-weeks from treatment initiation by primary treatment group

Table showing the number of patients with aneurysms detected at any time, and the number where aneurysm resolution was confirmed to be within 6-weeks of initiation of primary treatment (defined as patients with an echocardiogram before or up-to 6-weeks showing CAA resolution). Patients were defined as not being resolved within 6-weeks if they had an echocardiogram after 6-weeks demonstrating CAA. The percentage resolution by 6-weeks was calculated as the percentage of those definitely resolved by 6-weeks with the denominator as those definitely resolved by 6-weeks and those definitely not resolved by 6-weeks. Patients were defined as having unclear timings if they did not fit into these categories, and then subdivided into those with CAA resolution (but timing not clearly before 6-weeks) and those without resolution but with follow-up less than 6-weeks.

Primary treatment group	Number of CAAs	Number resolved within 6-weeks	Number not resolved within 6-weeks	Percentage resolved within 6-weeks (where outcome certain)	Number resolved, unclear timings	Number not resolved, but follow-up less than 6-weeks
IVIG	90	51	7	87.9 (51/58)	17	15
Glucocorticoid	41	22	3	88.0 (22/25)	10	6
IVIG and Glucocorticoid	88	51	5	91.1 (51/56)	11	21

Table S6D: Coronary artery aneurysm resolution at 12-weeks from treatment initiation by primary treatment group

Table showing the number of patients with aneurysms detected at any time, and the number where aneurysm resolution was confirmed to be within 12-weeks of initiation of primary treatment (defined as patients with an echocardiogram before or up-to 12-weeks showing CAA resolution). Patients were defined as not being resolved within 12-weeks if they had an echocardiogram after 12-weeks demonstrating CAA. The percentage resolution by 12-weeks was calculated as the percentage of those definitely resolved by 12-weeks with the denominator as those definitely resolved by 12-weeks and those definitely not resolved by 12-weeks. Patients were defined as having unclear timings if they did not fit into these categories, and then subdivided into those with CAA resolution (but timing not clearly before 12-weeks) and those without resolution but with follow-up less than 12-weeks.

Primary treatment group	Number of CAAs	Number resolved within 12-weeks	Number not resolved within 12-weeks	Percentage resolved within 12-weeks (where outcome certain)	Number resolved, unclear timings	Number not resolved, but follow-up less than 12-weeks
IVIG	90	62	5	92.5 (62/67)	8	15
Glucocorticoid	41	25	2	92.6 (25/27)	8	6
IVIG and Glucocorticoid	88	58	5	92.1 (58/63)	4	21

Table S6E: Coronary artery aneurysm incidence and resolution in patients receiving primary treatment with glucocorticoids alone

Table showing the number of patients with aneurysms detected at any time, restricted to patients whose primary treatment was with glucocorticoids alone. These have been stratified into those who did and did not receive additional treatment with IVIG at a later date (first column). We also present the number who had echocardiograms during admission, the percentage of these with CAA, and the number and percentage of those with CAA remaining on the final echocardiogram before discharge. The final three columns show the number of those with post-discharge follow-up and the number and percentage of these demonstrating resolution during follow up.

Did patients subsequently receive IVIG?	Number of patients	Had any echo during admission	Had CAA	Percentage with CAA	Had CAAs at discharge	Percentage with CAA at discharge	Has follow-up data	Resolved during follow-up	Percentage Resolved
No	257	239	17	7.1	5	2.1	15	14	93.3
Yes	230	221	24	10.9	9	4.1	20	19	95.0
Yes - before CAA detected	14	14	14	100	6	42.9	13	12	92.3
Yes - on/after CAA detected	10	10	10	100	3	30	7	7	100
Yes - no CAAs	206	197	0	0	0	0			

Table S7A: Maximum coronary artery aneurysm z-scores by primary treatment group

Table shows the number of patients in each z-score band separated by primary treatment group. This includes only patients who were reported to have CAA, and had at least one z-score reported. Percentages indicate the proportions within a specific treatment group.

	Maximal z-score		
Primary treatment group	**2.5-5.0**	**5.0-10.0**	**>=10**
IVIG	56 (77.8%)	9 (12.5%)	7 (9.7%)
Glucocorticoid	33 (89.2%)	3 (8.1%)	1 (2.7%)
IVIG and Glucocorticoid	60 (80%)	13 (17.3%)	2 (2.7%)

Table S7B: Maximum coronary artery aneurysm z-scores by primary treatment group and age

Table reports the median z-scores [IQR] for patients separates by age band and primary therapy. Number inside the parentheses indicates total number of patients in each group with CAA and reported z-scores.

	Age band		
Primary treatment group	**<6 years**	**6-11 years**	**>12 years**
IVIG	3.6 [3.1-6] (37)	3 [2.7-4.3] (24)	3.2 [2.7-3.6] (11)
Glucocorticoid	3.4 [3-4.9] (11)	2.9 [2.7-3.2] (17)	2.9 [2.8-3] (9)
IVIG and Glucocorticoid	3.5 [2.8-5.1] (28)	3.6 [3.1-4.7] (28)	3.3 [2.9-3.9] (19)

Table S8: Treatment related complications

Table shows reported inpatient drug-complications for all patients. Denominators for percentages include all patients who received the specific drug at any point during admission.

Treatment	Complication	Number of patients
Glucocorticoid		
	Glucocorticoid induced hypertension	23
	Hyperglycaemia	14
	Profound bradycardia	6
	Psychosis	2
	Opportunistic infection	1
	Hypothermia	1
	Gastro-oesophageal reflux	1
	Other unspecified	11
Total (% of patients receiving glucocorticoids)		**59/1623 (3.6%)**
IVIG		
	Mild reaction	2
	Anaphylaxis	2
	Hypertension	2
	Extravasation injury / skin necrosis	2
	Headache	2
	Vomiting	1
	Profound bradycardia	1
	Other unspecified	13
Total (% of patients receiving IVIG)		**25/1658 (1.5%)**
Anakinra		
	Opportunistic infection	1
	Profound bradycardia	1
	Superficial cutaneous skin reaction	1
	Other unspecified	1
Anticoagulant		
	Significant bleeding	1
	Mild bleeding	1
	Other unspecified	2
Antimicrobials		
Vancomycin	AKI	1
Phenoxymethylpenicillin	Other unspecified	1
Lopinavir / Ritonavir	Other unspecified	1
Linezolid	Other unspecified	1
Sulfamethoxazole/Trimethoprim	Other unspecified	1
Cefotaxime	Other unspecified	1
ECMO		
	Cerebrovascular accident	1
Poor sedation under paralysis		
	Hypertension	1

Table S9A: Steroid drugs and doses for primary treatment

Table shows steroid doses by route and drug at initiation of primary treatment, for patients with primary treatment of Glucocorticoids alone or IVIG and Glucocorticoids. As described in the supplementary methods, patients receiving low-dose oral steroids alone were excluded from the glucocorticoid alone arm, and low-dose intravenous hydrocortisone was not included in the definition of primary treatment groups (see supplementary methods). Doses are presented as median raw-dose in mg/kg (IQR) and median prednisolone-equivalent doses (IQR) (details on page 13).

Route of administration	Drug name	Number of courses	Median raw dose in mg/kg (IQR)	Median prednisolone equivalent dose in mg/kg (IQR)
Intravenous	Methylprednisolone	860	2.0 (2.0-10.0)	2.5 (2.5-12.5)
	Dexamethasone	174	0.6 (0.3-0.7)	3.8 (1.9-4.6)
	Not reported	62	-	-
	Prednisolone	51	2.0 (2.0-2.0)	2.0 (2.0-2.0)
	Hydrocortisone	10	4.0 (4.0-4.4)	1.0 (1.0-1.1)
Oral	Prednisolone	22	1.2 (1.0-2.0)	1.2 (1.0-2.0)
	Dexamethasone	6	0.4 (0.2-0.6)	2.8 (1.2-4.0)

Table S9B: IVIG doses for primary treatment

Table shows IVIG doses at initiation of primary treatment, for patients with primary treatment of IVIG alone or IVIG and Glucocorticoids. Doses are presented as median raw-dose in g/kg (IQR).

Drug name	Number of courses with reported dose	Median raw dose in g/kg (IQR)
IVIG	1305	2.0 (2.0-2.0)

Table S10: Coefficients for covariate-balancing propensity score multinomial model – Primary outcome: inotropes/ventilation day 2+ or death

	Estimate	Estimate 95% Confidence Interval	Pr(>|z|)
IVIG: (Intercept)	1.90	[0.91 , 2.89]	0.00017
IVIG: Resource Group: Upper-Mid = FALSE	0.77	[0.65 , 0.89]	<0.0001
IVIG: Resource Group: Lower-Mid/Lower = TRUE	-1.09	[-1.23 , -0.96]	<0.0001
IVIG: Age	0.21	[0.07 , 0.34]	0.0038
IVIG: Weight z-score > 2 = TRUE	-0.25	[-0.37 , -0.12]	0.00011
IVIG: Baseline significant comorbidity = TRUE	-0.08	[-0.22 , 0.05]	0.23
IVIG: Baseline Sex = Male	-0.07	[-0.20 , 0.06]	0.29
IVIG: Complete KD criteria = TRUE	0.13	[0.01 , 0.26]	0.036
IVIG: Baseline requiring inotropes = TRUE	-0.94	[-1.07 , -0.80]	<0.0001
IVIG: Baseline requiring ventilation = TRUE	-0.08	[-0.22 , 0.05]	0.23
IVIG: Baseline peak CRP	-0.05	[-0.17 , 0.08]	0.49
IVIG+Glucocorticoid: (Intercept)	0.61	[-0.49 , 1.72]	0.28
IVIG+Glucocorticoid: Resource Group: Upper-Mid = FALSE	1.05	[0.90 , 1.20]	<0.0001
IVIG+Glucocorticoid: Resource Group: Lower-Mid/Lower = TRUE	-2.45	[-2.61 , -2.30]	<0.0001
IVIG+Glucocorticoid: Age	0.37	[0.17 , 0.56]	0.00027
IVIG+Glucocorticoid: Weight z-score > 2 = TRUE	-0.07	[-0.21 , 0.06]	0.30
IVIG+Glucocorticoid: Baseline significant comorbidity = TRUE	-0.55	[-0.70 , -0.40]	<0.0001
IVIG+Glucocorticoid: Baseline Sex = Male	-0.12	[-0.28 , 0.03]	0.12
IVIG+Glucocorticoid: Complete KD criteria = TRUE	1.01	[0.86 , 1.16]	<0.0001
IVIG+Glucocorticoid: Baseline requiring inotropes = TRUE	-1.04	[-1.20 , -0.88]	<0.0001
IVIG+Glucocorticoid: Baseline requiring ventilation = TRUE	1.64	[1.48 , 1.80]	<0.0001
IVIG+Glucocorticoid: Baseline peak CRP	0.01	[-0.17 , 0.19]	0.93

Table S11: Coefficients for covariate-balancing propensity score multinomial model – Primary outcome: Time-to-improvement in clinical severity scale

	Estimate	Estimate 95% Confidence Interval	Pr(>|z|)
IVIG: (Intercept)	2.13	[1.15 , 3.11]	<0.0001
IVIG: Resource Group: Upper-Mid = FALSE	0.75	[0.60 , 0.91]	<0.0001
IVIG: Resource Group: Lower-Mid/Lower = TRUE	-1.03	[-1.17 , -0.89]	<0.0001
IVIG: Age	0.23	[0.11 , 0.35]	0.00011
IVIG: Weight z-score > 2 = TRUE	-0.33	[-0.45 , -0.20]	<0.0001
IVIG: Baseline significant comorbidity = TRUE	-0.13	[-0.25 , -0.02]	0.026
IVIG: Baseline Sex = Male	-0.11	[-0.23 , 0.01]	0.067
IVIG: Complete KD criteria = TRUE	0.11	[-0.02 , 0.23]	0.089
IVIG: Baseline requiring inotropes = TRUE	-0.99	[-1.14 , -0.85]	<0.0001
IVIG: Baseline requiring ventilation = TRUE	-0.16	[-0.31 , -0.01]	0.039
IVIG: Baseline peak CRP	-0.07	[-0.20 , 0.07]	0.32
IVIG+Glucocorticoid: (Intercept)	0.59	[-0.52 , 1.71]	0.30
IVIG+Glucocorticoid: Resource Group: Upper-Mid = FALSE	1.10	[0.93 , 1.28]	<0.0001
IVIG+Glucocorticoid: Resource Group: Lower-Mid/Lower = TRUE	-2.39	[-2.57 , -2.21]	<0.0001
IVIG+Glucocorticoid: Age	0.43	[0.29 , 0.57]	<0.0001
IVIG+Glucocorticoid: Weight z-score > 2 = TRUE	-0.15	[-0.30 , 0.01]	0.066
IVIG+Glucocorticoid: Baseline significant comorbidity = TRUE	-0.66	[-0.79 , -0.53]	<0.0001
IVIG+Glucocorticoid: Baseline Sex = Male	-0.15	[-0.28 , -0.03]	0.015
IVIG+Glucocorticoid: Complete KD criteria = TRUE	0.96	[0.80 , 1.11]	<0.0001
IVIG+Glucocorticoid: Baseline requiring inotropes = TRUE	-1.08	[-1.24 , -0.93]	<0.0001
IVIG+Glucocorticoid: Baseline requiring ventilation = TRUE	1.87	[1.69 , 2.04]	<0.0001
IVIG+Glucocorticoid: Baseline peak CRP	0.02	[-0.19 , 0.23]	0.86

Table S12: Coefficients for covariate-balancing propensity score multinomial model – Subgroup meeting WHO MIS-C Criteria: inotropes/ventilation day 2+ or death

	Estimate	Estimate 95% Confidence Interval	Pr(>|z|)
IVIG: (Intercept)	1.78	[0.76 , 2.81]	0.00065
IVIG: Resource Group: Upper-Mid = FALSE	0.52	[0.40 , 0.64]	<0.0001
IVIG: Resource Group: Lower-Mid/Lower = TRUE	-0.94	[-1.07 , -0.80]	<0.0001
IVIG: Age	0.14	[-0.02 , 0.30]	0.082
IVIG: Weight z-score > 2 = TRUE	-0.15	[-0.28 , -0.01]	0.030
IVIG: Baseline significant comorbidity = TRUE	-0.19	[-0.33 , -0.05]	0.0077
IVIG: Baseline Sex = Male	-0.13	[-0.27 , 0.01]	0.064
IVIG: Complete KD criteria = TRUE	0.16	[0.02 , 0.30]	0.029
IVIG: Baseline requiring inotropes = TRUE	-0.87	[-1.02 , -0.71]	<0.0001
IVIG: Baseline requiring ventilation = TRUE	0.04	[-0.10 , 0.18]	0.54
IVIG: Baseline peak CRP	-0.01	[-0.15 , 0.12]	0.84
IVIG+Glucocorticoid: (Intercept)	0.16	[-0.92 , 1.24]	0.77
IVIG+Glucocorticoid: Resource Group: Upper-Mid = FALSE	0.67	[0.53 , 0.82]	<0.0001
IVIG+Glucocorticoid: Resource Group: Lower-Mid/Lower = TRUE	-2.08	[-2.23 , -1.93]	<0.0001
IVIG+Glucocorticoid: Age	0.29	[0.09 , 0.48]	0.0040
IVIG+Glucocorticoid: Weight z-score > 2 = TRUE	-0.01	[-0.17 , 0.15]	0.90
IVIG+Glucocorticoid: Baseline significant comorbidity = TRUE	-0.68	[-0.84 , -0.52]	<0.0001
IVIG+Glucocorticoid: Baseline Sex = Male	-0.22	[-0.38 , -0.07]	0.0057
IVIG+Glucocorticoid: Complete KD criteria = TRUE	0.99	[0.81 , 1.16]	<0.0001
IVIG+Glucocorticoid: Baseline requiring inotropes = TRUE	-0.88	[-1.06 , -0.69]	<0.0001
IVIG+Glucocorticoid: Baseline requiring ventilation = TRUE	2.04	[1.89 , 2.19]	<0.0001
IVIG+Glucocorticoid: Baseline peak CRP	0.07	[-0.13 , 0.27]	0.50

Table S13: Coefficients for covariate-balancing propensity score multinomial model – Subgroup meeting WHO MIS-C Criteria: Time-to-improvement in clinical severity scale

	Estimate	Estimate 95% Confidence Interval	Pr(>|z|)
IVIG: (Intercept)	2.00	[0.92 , 3.07]	0.00027
IVIG: Resource Group: Upper-Mid = FALSE	0.52	[0.35 , 0.69]	<0.0001
IVIG: Resource Group: Lower-Mid/Lower = TRUE	-0.86	[-1.00 , -0.72]	<0.0001
IVIG: Age	0.17	[0.04 , 0.31]	0.010
IVIG: Weight z-score > 2 = TRUE	-0.22	[-0.35 , -0.09]	0.0011
IVIG: Baseline significant comorbidity = TRUE	-0.22	[-0.36 , -0.08]	0.0024
IVIG: Baseline Sex = Male	-0.17	[-0.30 , -0.03]	0.020
IVIG: Complete KD criteria = TRUE	0.13	[-0.01 , 0.27]	0.059
IVIG: Baseline requiring inotropes = TRUE	-0.88	[-1.03 , -0.74]	<0.0001
IVIG: Baseline requiring ventilation = TRUE	-0.10	[-0.24 , 0.04]	0.18
IVIG: Baseline peak CRP	-0.03	[-0.18 , 0.11]	0.65
IVIG+Glucocorticoid: (Intercept)	0.28	[-0.94 , 1.49]	0.66
IVIG+Glucocorticoid: Resource Group: Upper-Mid = FALSE	0.70	[0.51 , 0.90]	<0.0001
IVIG+Glucocorticoid: Resource Group: Lower-Mid/Lower = TRUE	-2.05	[-2.21 , -1.89]	<0.0001
IVIG+Glucocorticoid: Age	0.31	[0.14 , 0.48]	0.00048
IVIG+Glucocorticoid: Weight z-score > 2 = TRUE	-0.08	[-0.25 , 0.08]	0.33
IVIG+Glucocorticoid: Baseline significant comorbidity = TRUE	-0.59	[-0.75 , -0.43]	<0.0001
IVIG+Glucocorticoid: Baseline Sex = Male	-0.20	[-0.37 , -0.03]	0.018
IVIG+Glucocorticoid: Complete KD criteria = TRUE	0.91	[0.74 , 1.08]	<0.0001
IVIG+Glucocorticoid: Baseline requiring inotropes = TRUE	-0.94	[-1.11 , -0.78]	<0.0001
IVIG+Glucocorticoid: Baseline requiring ventilation = TRUE	1.95	[1.77 , 2.13]	<0.0001
IVIG+Glucocorticoid: Baseline peak CRP	0.06	[-0.13 , 0.25]	0.54

Table S14: Numbers of patients censoring for time-to-improvement primary outcome analysis

Table showing the number of patients right censored for different reasons during time-to-event analysis for the time-to-improvement primary outcome, separated by primary treatment group.

Baseline ordinal severity score	Reason for censoring	IVIG	Glucocorticoid	IVIG and Glucocorticoid
1) Ventilated and on inotropic support	Unclear when came off either ventilation or inotropes due to missing data	1	1	0
2) Ventilated	Unclear when came off ventilation due to missing data	1	0	1
3) Inotropic support	Unclear when came off inotropes due to missing data	1	1	1
4) Receiving oxygen	Unclear when came off oxygen due to missing data	0	1	0
5) No supportive therapy, last CRP > 50	Unclear when CRP fell below 50 due to missing data	202	129	172
6) No supportive therapy, last CRP < 50	Unclear discharge date	2	1	0

Table S15: Summary of missing data for imputed/interpolated variables

Table showing the number of missing values for imputed/interpolated variables (see page 13) of respiratory support, inotropic support, and presence of fever, before and after imputation/interpolation were performed. We present the total number (%) of patients with at least one missing variable, followed by the total number (%) of patient-days with missing values for the entire BATS cohort.

	Imputation/ Interpolation	Respiratory support	Inotropic support	Fever
Patients with at least one missing value	Before	41 (2.0%)	30 (1.5%)	551 (27.4%)
	After	7 (0.3%)	8 (0.4%)	434 (22.1%)
Total days missing value	Before	387 (1.9%)	314 (1.5%)	3322 (16.1%)
	After	87 (0.4%)	123 (0.6%)	3205 (15.6%)

Supplementary figures

Figure S1: World map displaying the location of countries registered to the Best Available Treatment Study and recruiting at least one patient

BATS patients were enrolled from across five continents (Europe, Asia, Africa, North America, and South America). Each yellow dot represents a different country, and the size of the dot is proportional to the number of patients recruited from the country, and may correspond to more than 1 site.

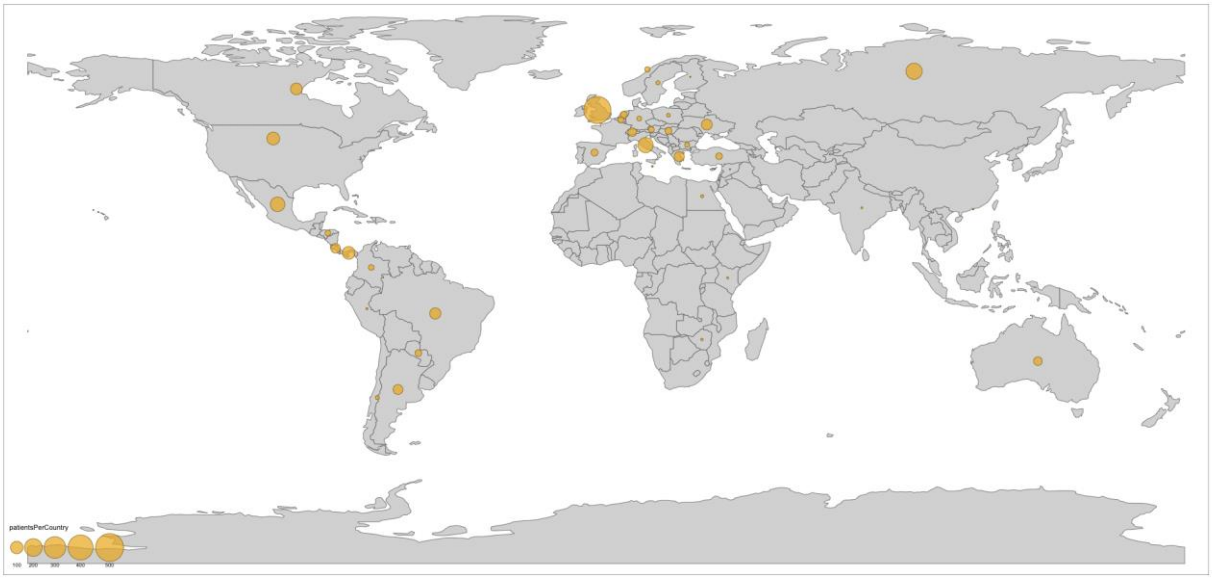


Figure S2A: Number of enrolment sites registered per country

Data used in this figure is following exclusions, with countries ordered in reverse by number of enrolment sites

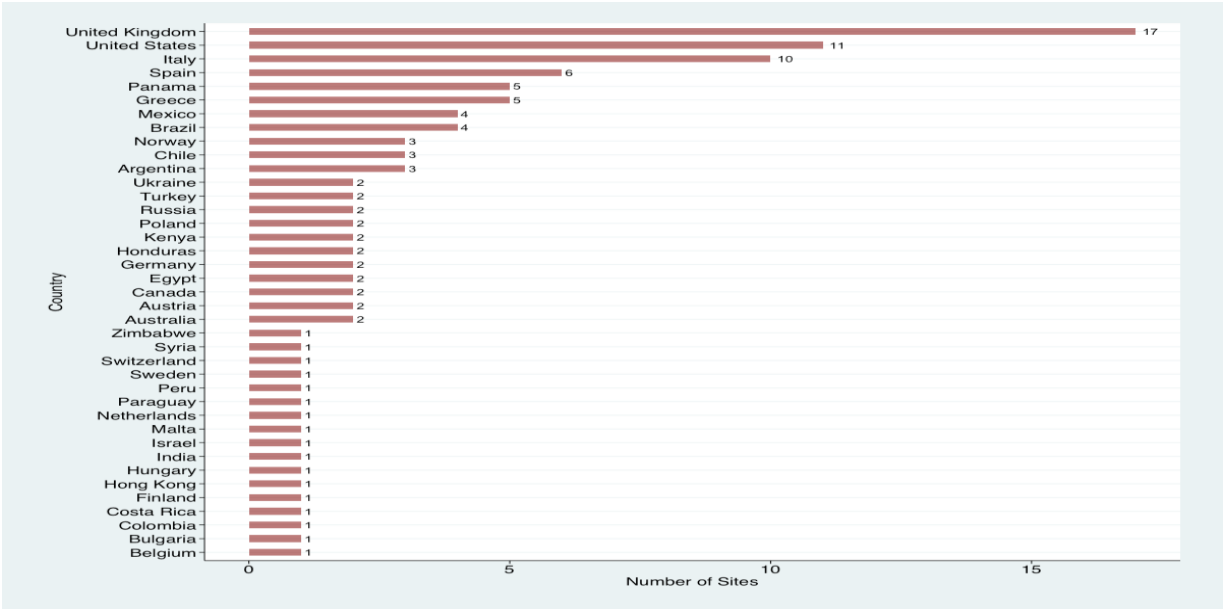


Figure S2B: Number of patients enrolled in BATS per country

Data used in this figure is following exclusions, with countries ordered in reverse by number of patients enrolled

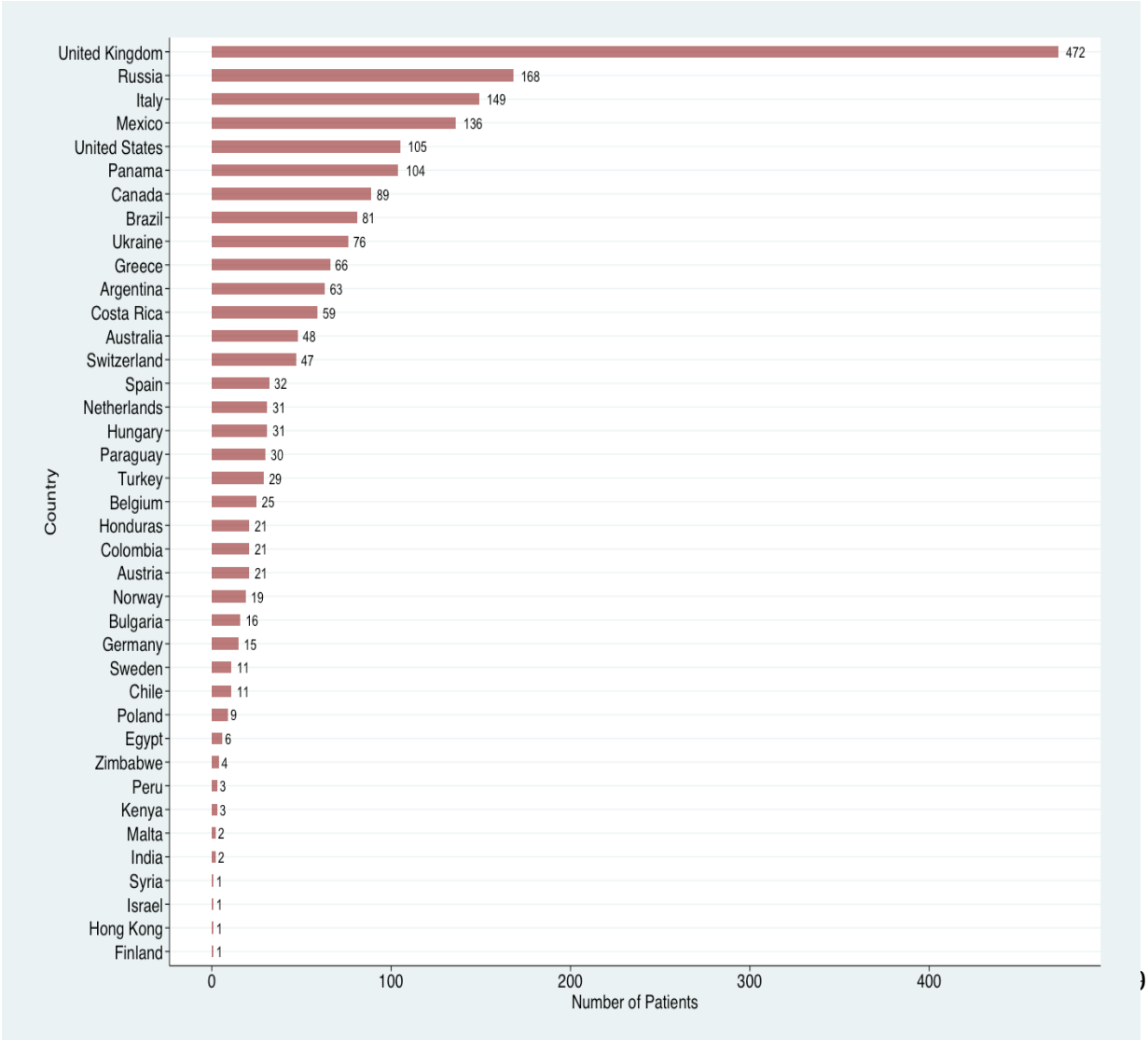


Figure S2C: Number of patients enrolled in BATS by site in each country

Data used in this figure is following exclusions

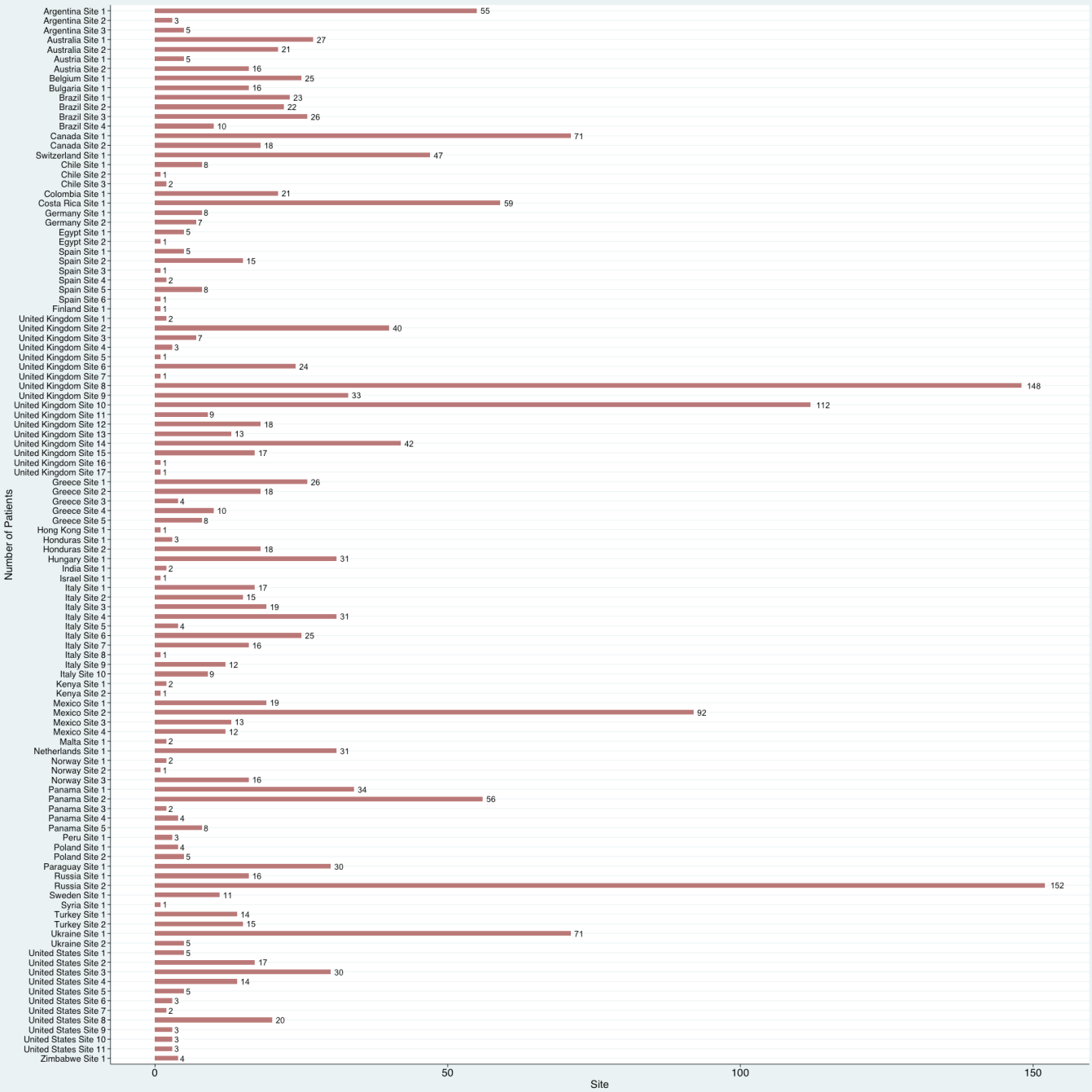


Figure S3: BATS registrations by month between May 2020 and April 2022

Data used in this figure is following exclusions, and shows total number of registrations by month

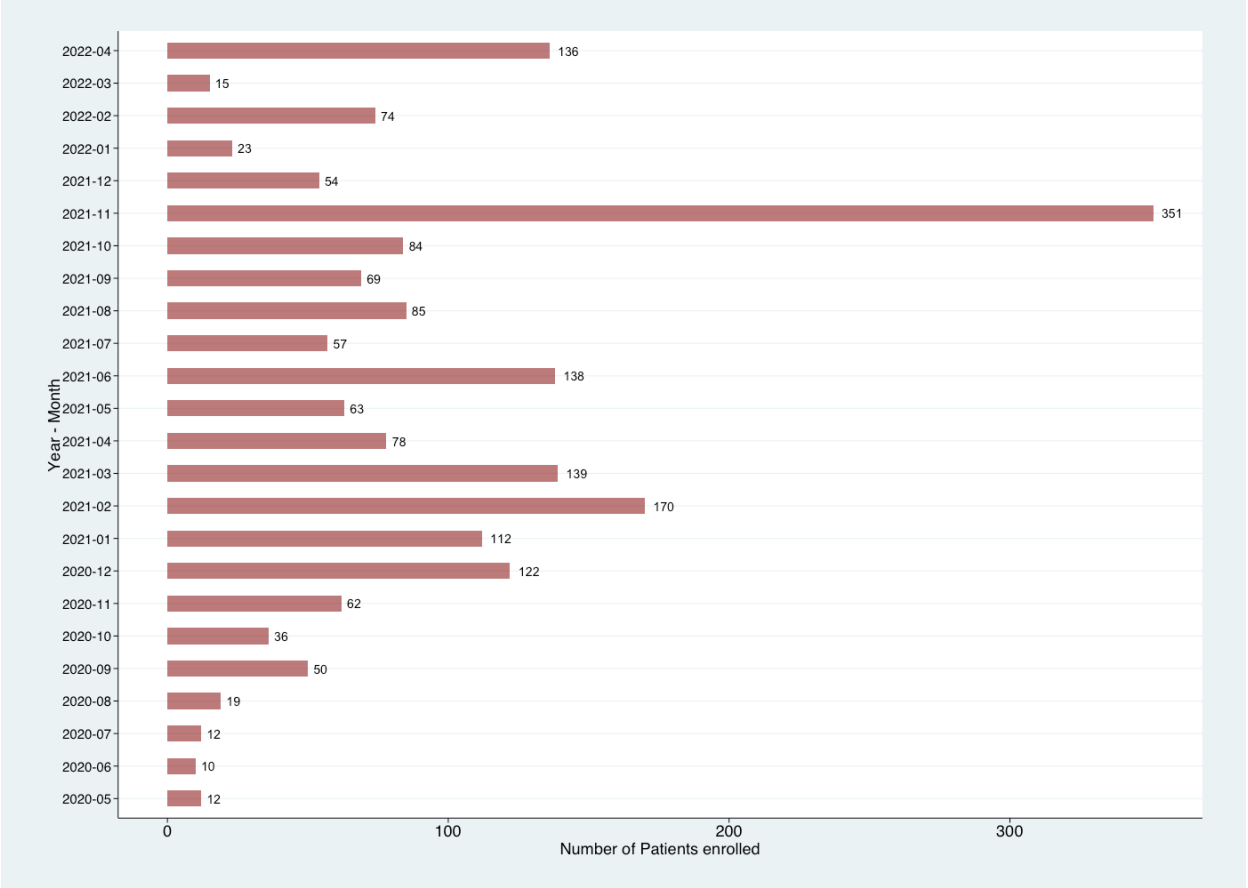


Figure S4: Comparison of blood results across treatment groups at day 0 (baseline)

*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. Specific blood results were log-transformed prior to comparisons if they appeared significantly skewed and have been plotted on this scale (reported on y-axes). For each blood test we have adjusted p-values for the 10 pairwise comparisons performed using the Bonferroni-Holm procedure. Comparisons are only shown if significant at alpha level 0.05 after adjustment for multiple testing within each blood test. Outliers are defined as any points beyond the whiskers, which are drawn up to 1.5*IQR away from the upper and lower quartiles.*

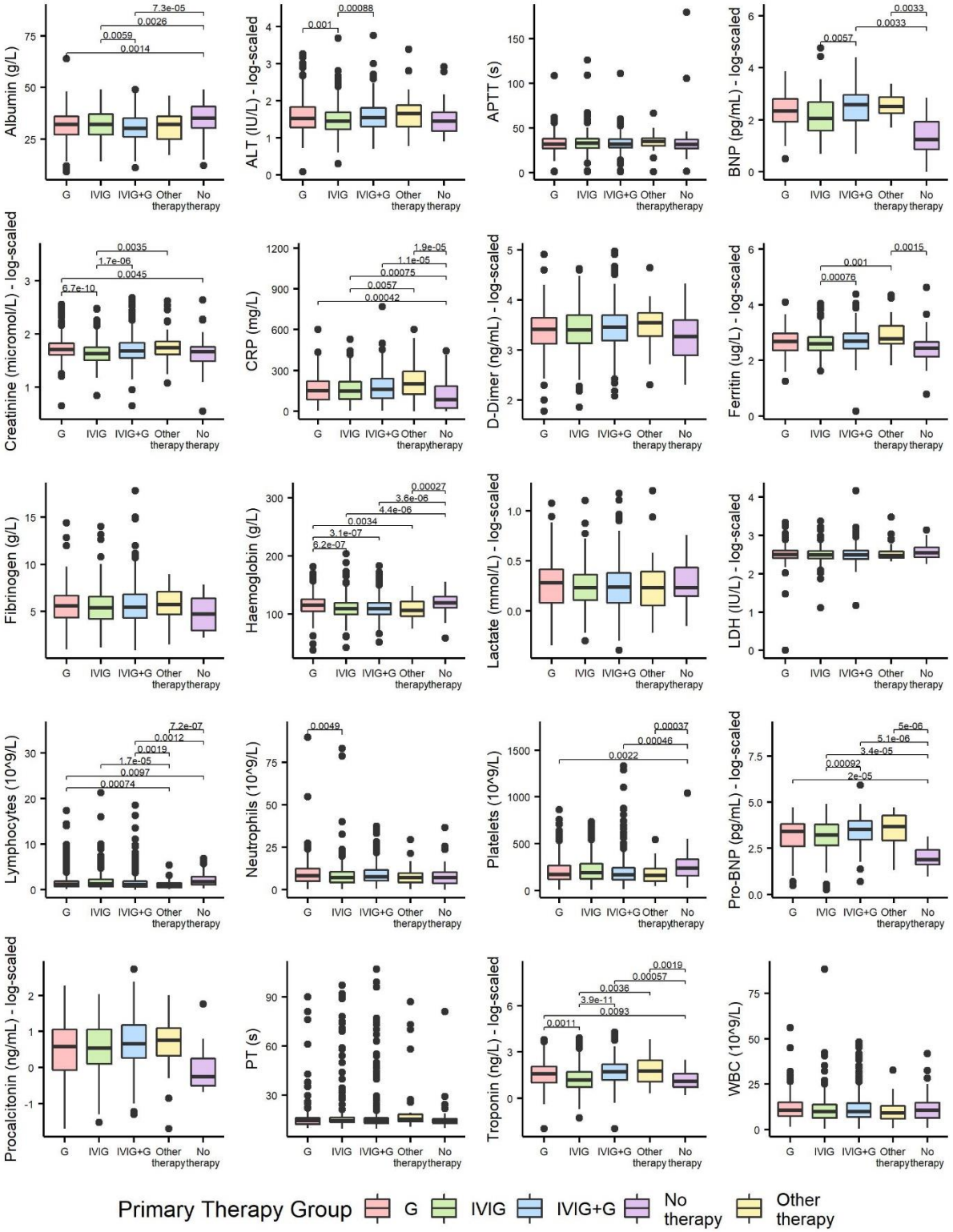
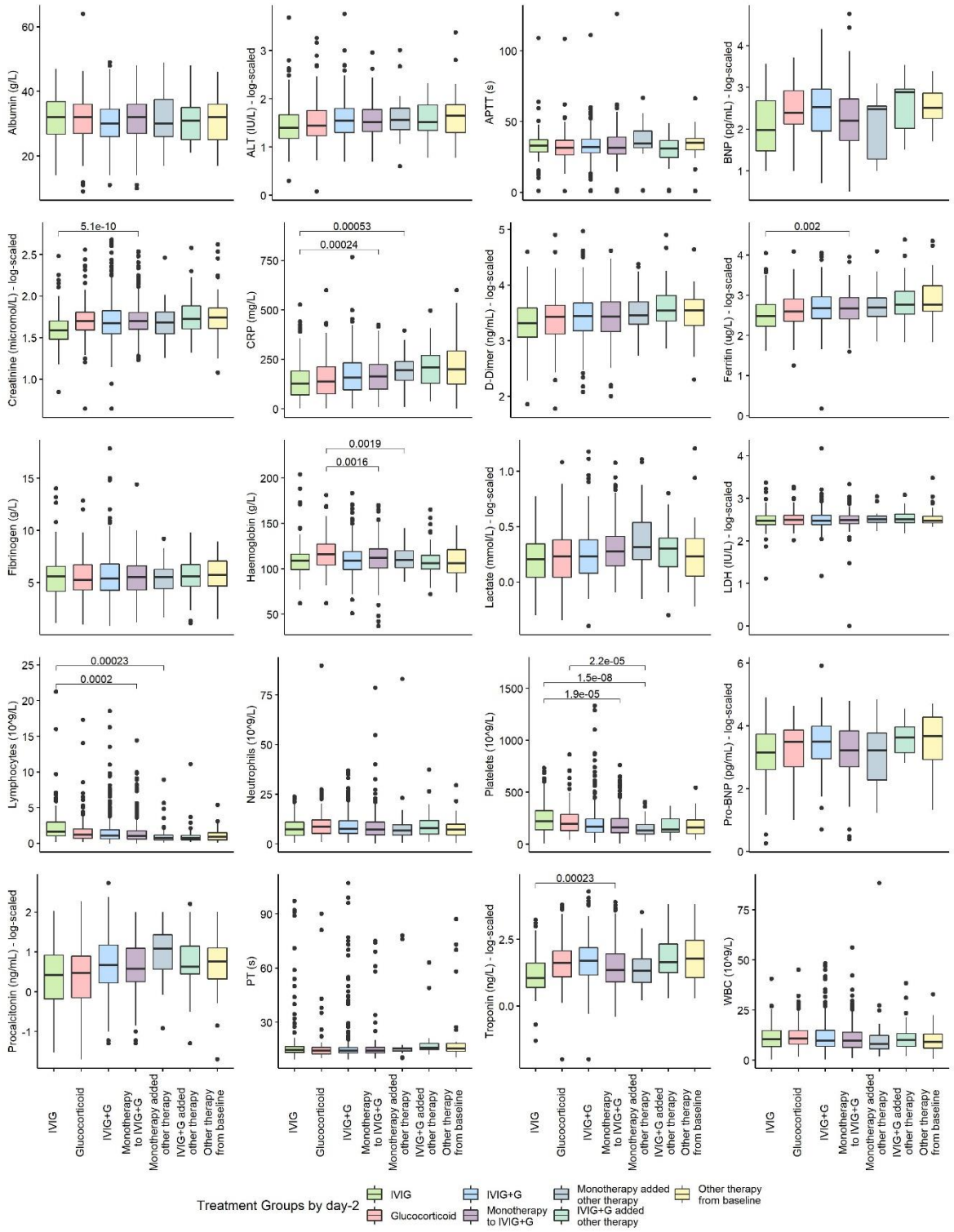


Figure S5: Comparison of baseline blood results across treatment groups between day 0 and day 2



Comparison of baseline blood results (day 0) 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 on monotherapy (with IVIG or Glucocorticoids alone) who have received additional treatments by day 2 have been labelled either "monotherapy to IVIG+G" or "monotherapy added other therapy" depending on if they had received IVIG+G only, or other immunomodulator treatments. Patients on IVIG+G at baseline who have escalated to other therapies by day 2 are labelled "IVIG+G added other therapy". Patients who were on other treatments or combinations

*at baseline are labelled "Other therapy from baseline". For each blood result we have used a two-sided t-test to compare each monotherapy arm with the two relevant escalation arms, and also the IVIG+G arm to the IVIG+G escalation group (5 comparisons for each blood test). We have adjusted the 5 obtained p-values using the Bonferroni-Holm procedure. Comparisons are only plotted when significant at alpha level 0.05 after adjustment for multiple testing within each blood test. Outliers are defined as any points beyond the whiskers, which are drawn up to 1.5*IQR away from the upper and lower quartiles.*

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

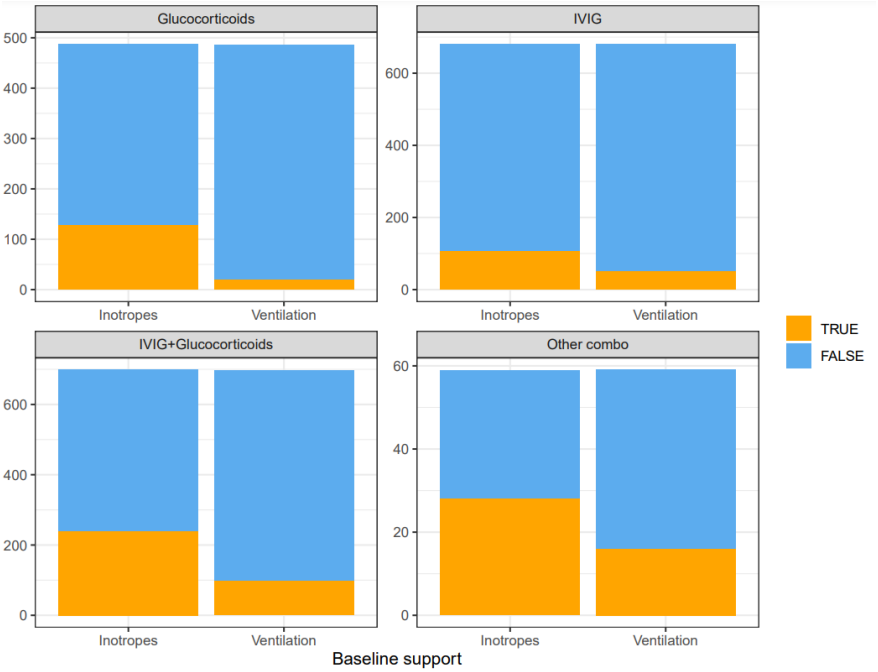


Figure S6B: Proportion of patients on inotropes or ventilated at baseline across treatment groups between day 0 and day 2

Comparison of baseline (day 0) requirement for inotropes or ventilation 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 on monotherapy (with IVIG or Glucocorticoids alone) who have received additional treatments by day 2 have been labelled either "switched Rx arm" or "Switched to biologicals" depending on if they had received IVIG+G only, or other immunomodulator treatments. Patients on IVIG+G at baseline who have escalated to other therapies by day 2 are labelled "Switched to biologicals". Patients who were on other treatments or combinations at baseline are labelled "Started on biological".

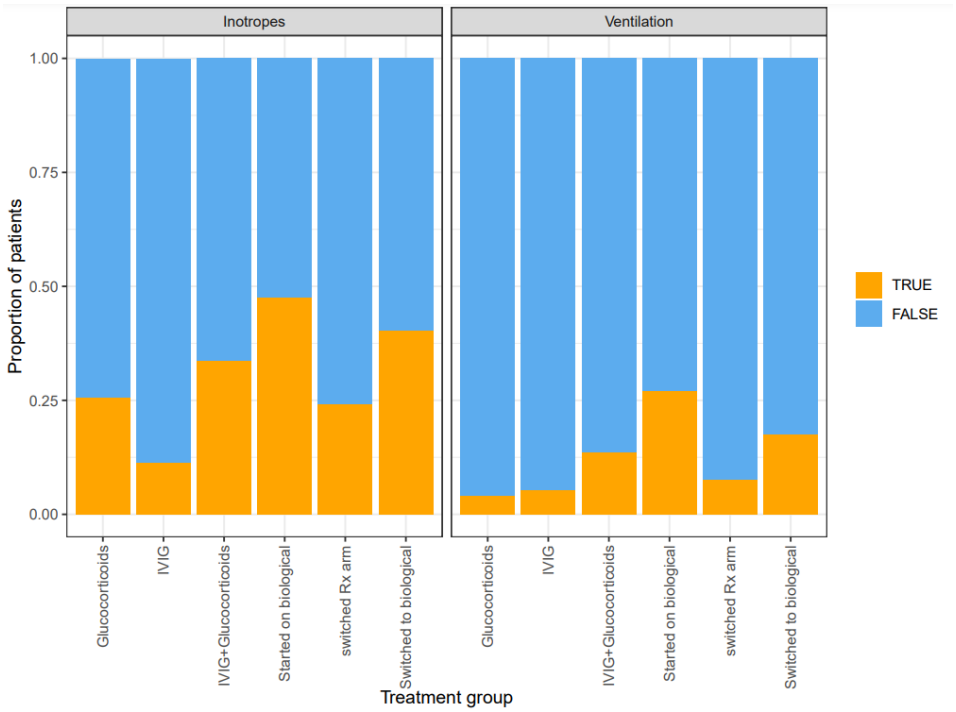


Figure S7: Missing components in patients with all but one component of the WHO MIS-C criteria

The 284 patients not meeting the full WHO MIS-C criteria but only missing one criterion were classified by the mandatory WHO-PIMS 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.

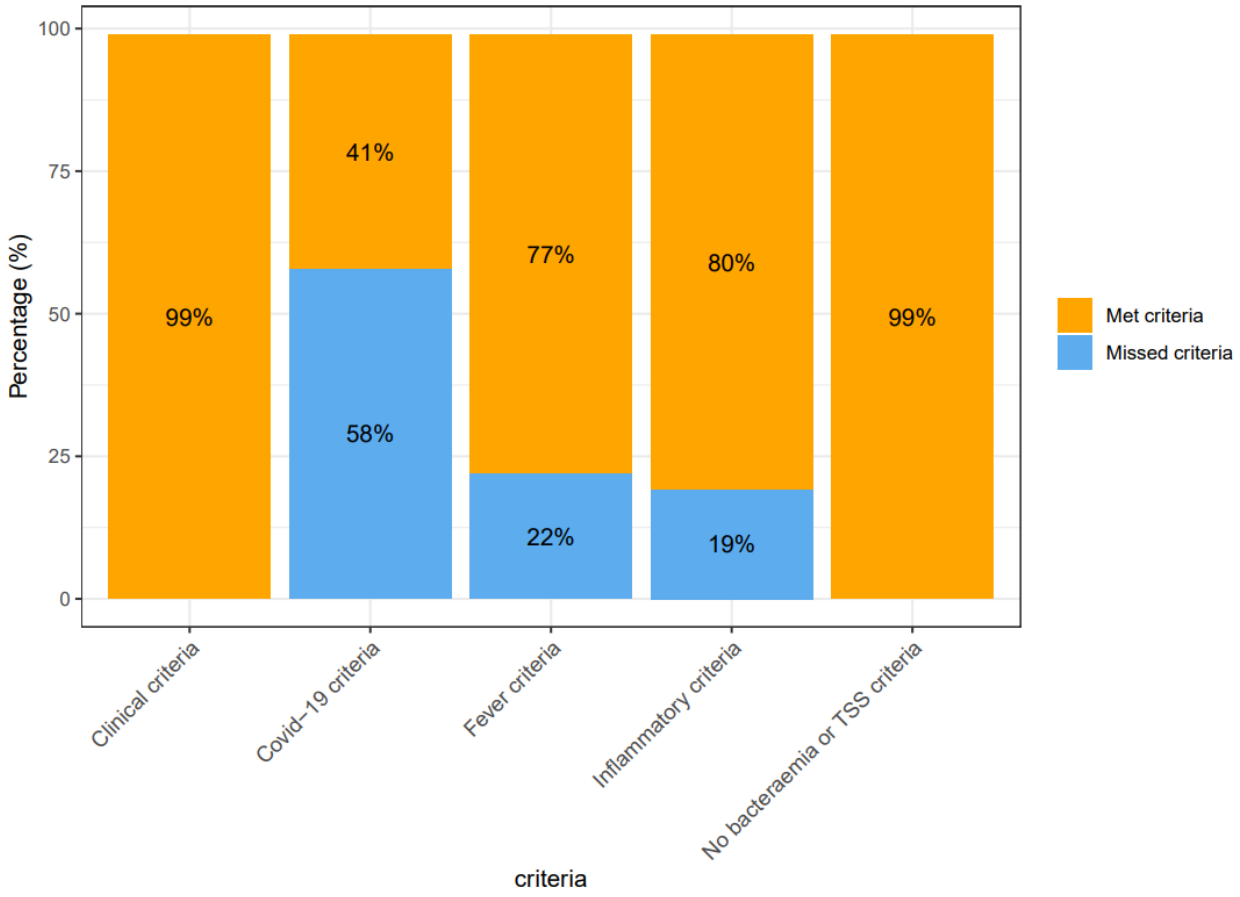


Figure S8: Proportion of patients with clinical features of Kawasaki disease across primary treatment groups up to treatment initiation

Proportion of patients with clinical features of Kawasaki disease and those that met the AHA criteria for complete Kawasaki Disease across primary treatment groups up to treatment initiation.

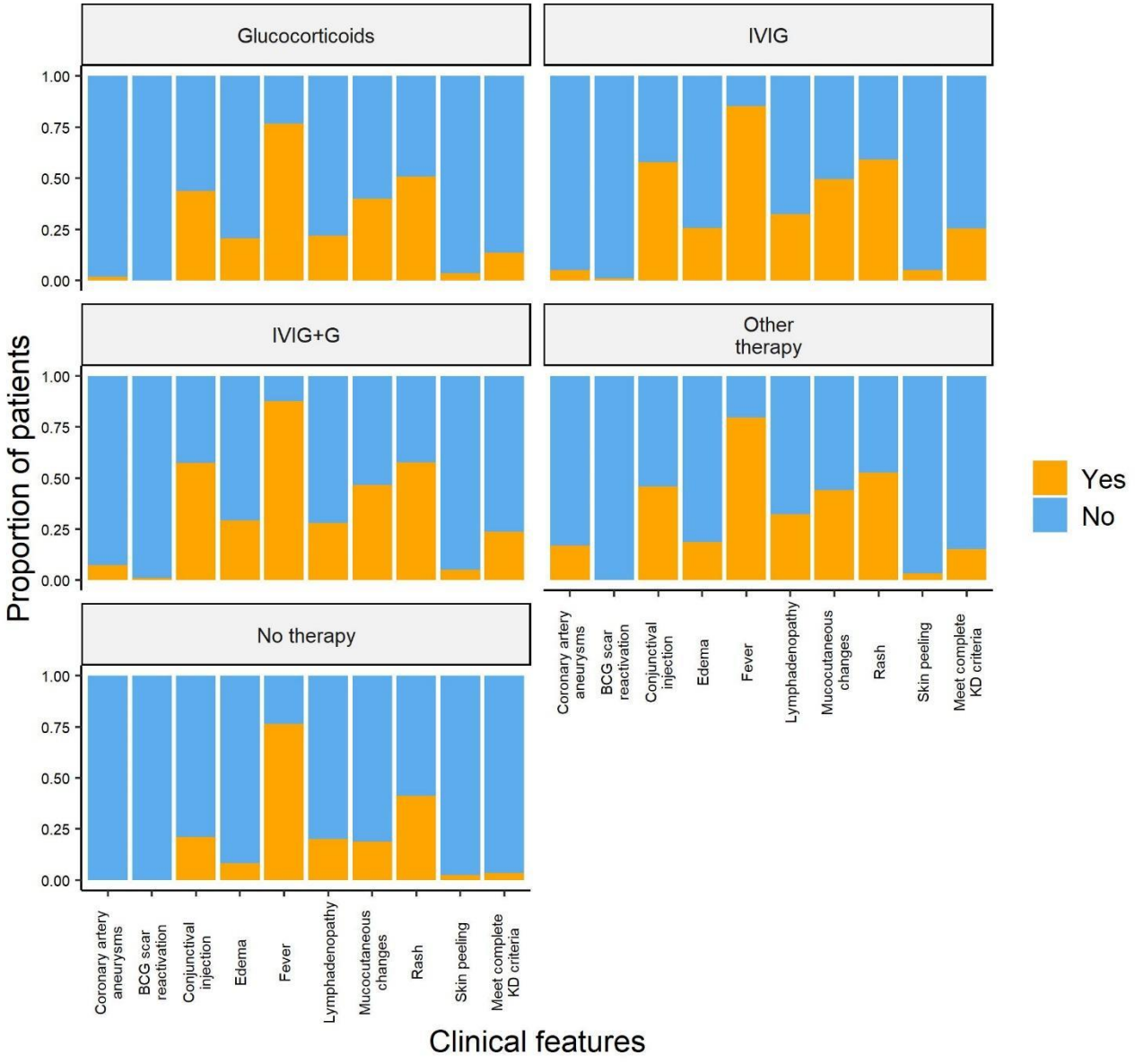
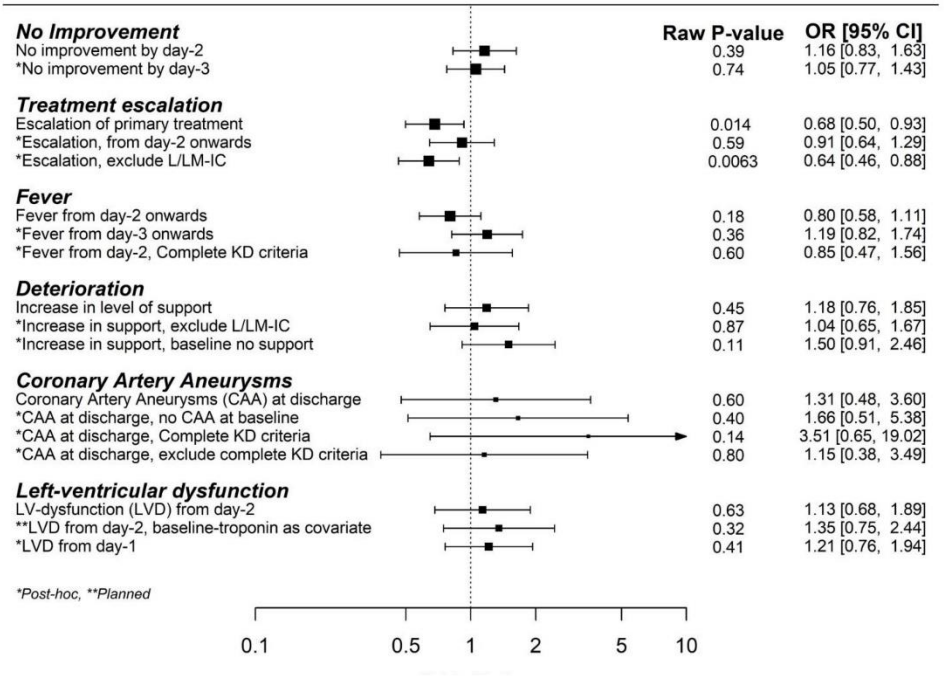


Figure S9: Forest plots summarizing point estimates and 95% confidence intervals for secondary outcomes, including planned and post-hoc additional analyses

*Displayed values are odds ratios and p-values without correction for multiple hypothesis testing. (A) Glucocorticoids vs IVIG, (B) IVIG+G vs IVIG. Values to the right of the dashed vertical lines indicate the superiority of IVIG alone. *indicates post-hoc analysis, ** indicates planned analysis*

A



B

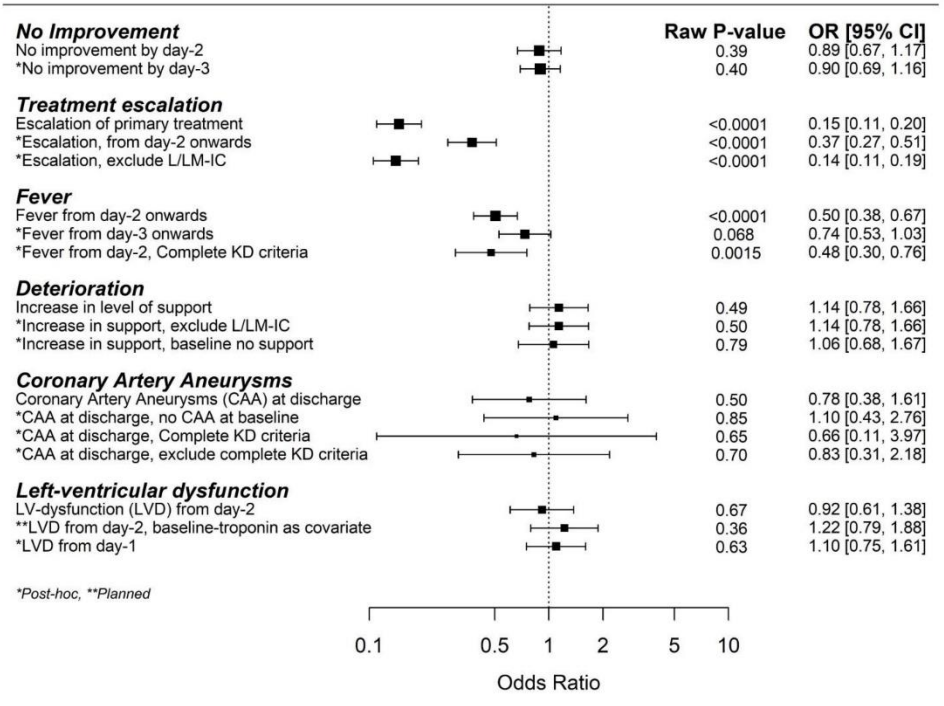


Figure S10: Forest plot summarizing point estimates and 95% confidence intervals for primary and secondary outcomes for planned secondary analysis of IVIG+G versus glucocorticoids alone

*Displayed values are odds ratios or average hazard ratios (indicated by *) for all primary and secondary outcomes for the planned secondary analysis of IVIG+G with glucocorticoids alone. Values to the right of the dashed vertical line indicate the superiority of glucocorticoids alone, except Time-to-improvement primary outcome (indicated by blue arrows), for which values to the left indicate the superiority of glucocorticoids alone. **indicates post-hoc analysis.*

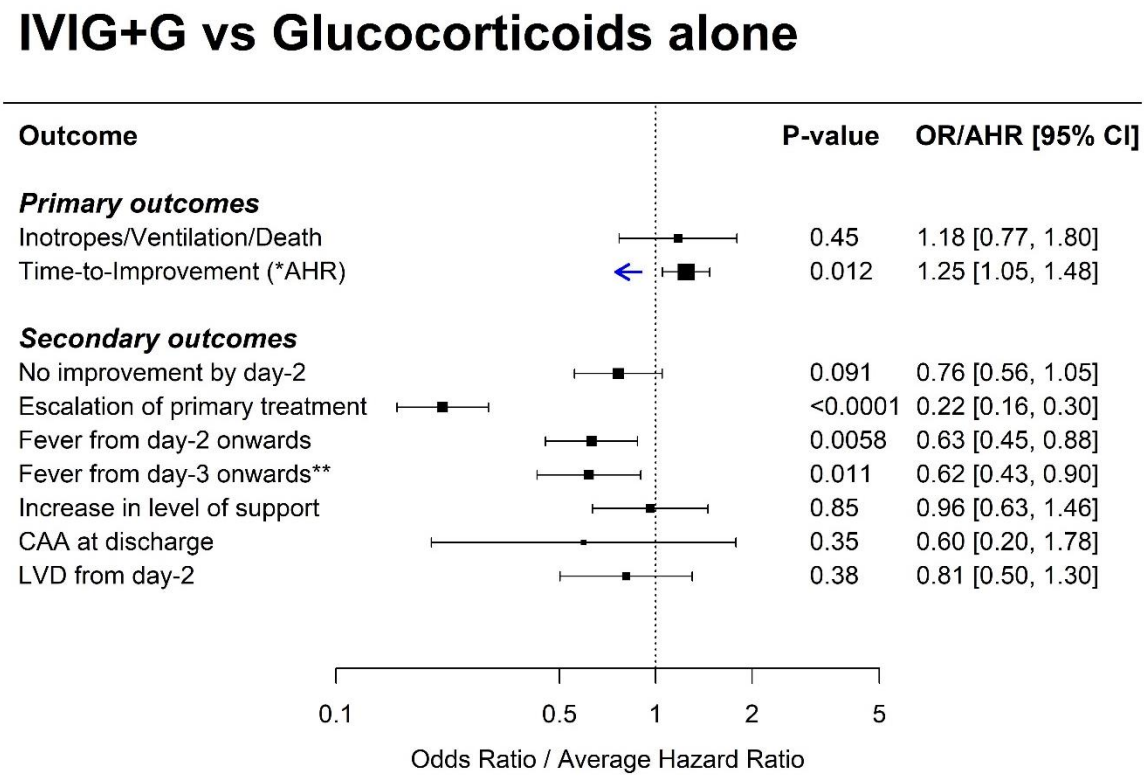


Figure S11: Inverse probability weight distributions and covariate balance plots for first primary outcome: Inotropes/ventilation from day 2 onwards or death

Panel A: covariate balance plots. Red coloured line shows unadjusted absolute standardized mean differences and Kolmogorov-Smirnov statistics; blue coloured line reflects absolute standardized mean differences and Kolmogorov-Smirnov statistics following covariate-balancing propensity score weighting. Panel B: inverse probability of treatment weight (IPTW) distributions for the three treatment groups derived from the covariate-balancing propensity score models, after stabilisation and truncation of large weights at the upper 99th quantile. Panels C & D: Distributions of unadjusted (left) and adjusted by IPTW (right) covariates for dichotomous and continuous variables respectively, for samples in the main three primary therapy groups after exclusions and removal of patients with missing baseline covariates.

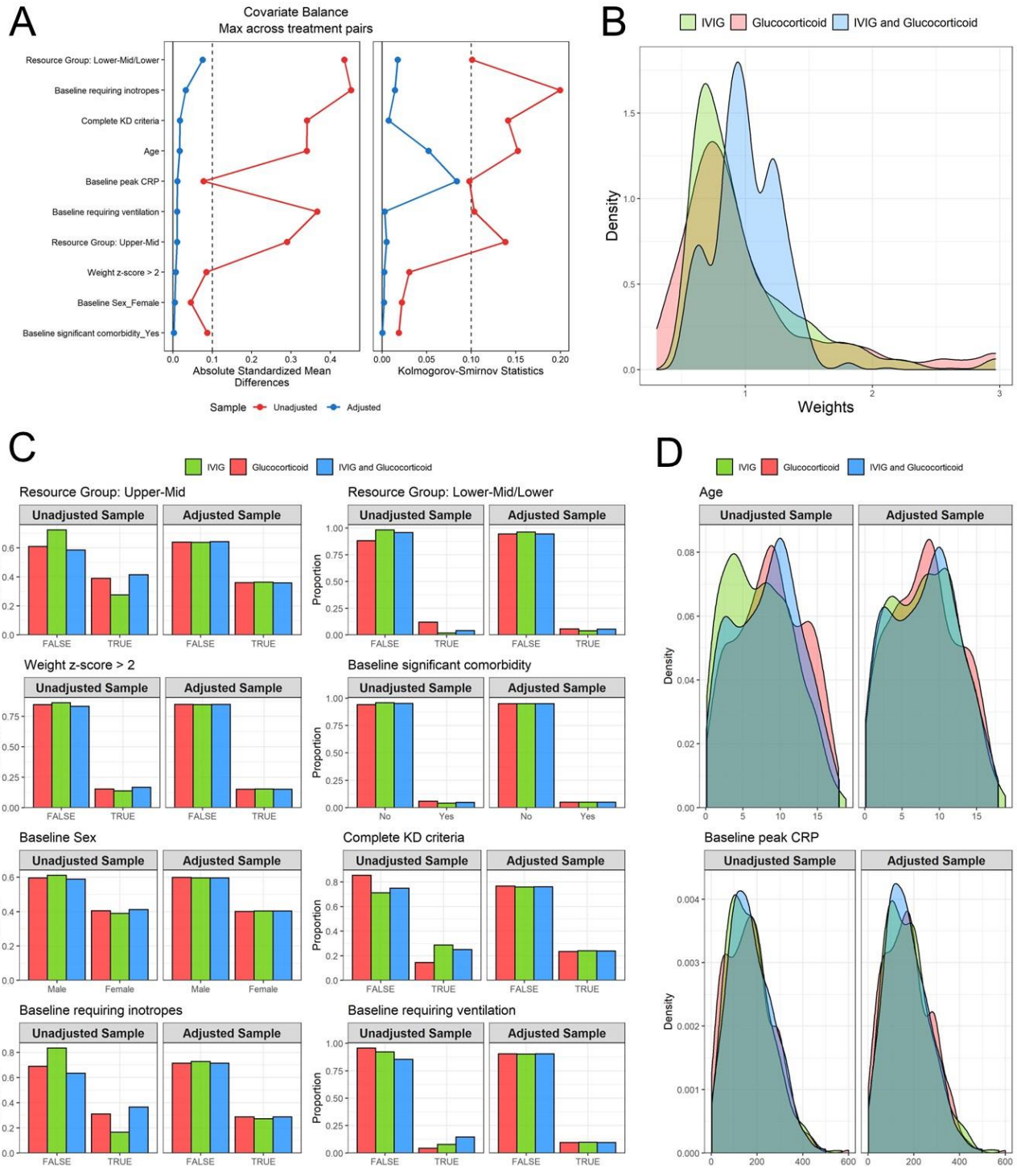


Figure S12: Inverse probability weight distributions and covariate balance plots, second primary outcome: Time-to-improvement of ordinal scale of clinical severity

Panel A: covariate balance plots. Red coloured lines show unadjusted absolute standardized mean differences and Kolmogorov-Smirnov statistics; blue coloured line reflects absolute standardized mean differences and Kolmogorov-Smirnov statistics following covariate-balancing propensity score weighting. Panel B: inverse probability of treatment weight (IPTW) distributions for the three treatment groups derived from the covariate-balancing propensity score models, after stabilisation and truncation of large weights at the upper 99th quantile.

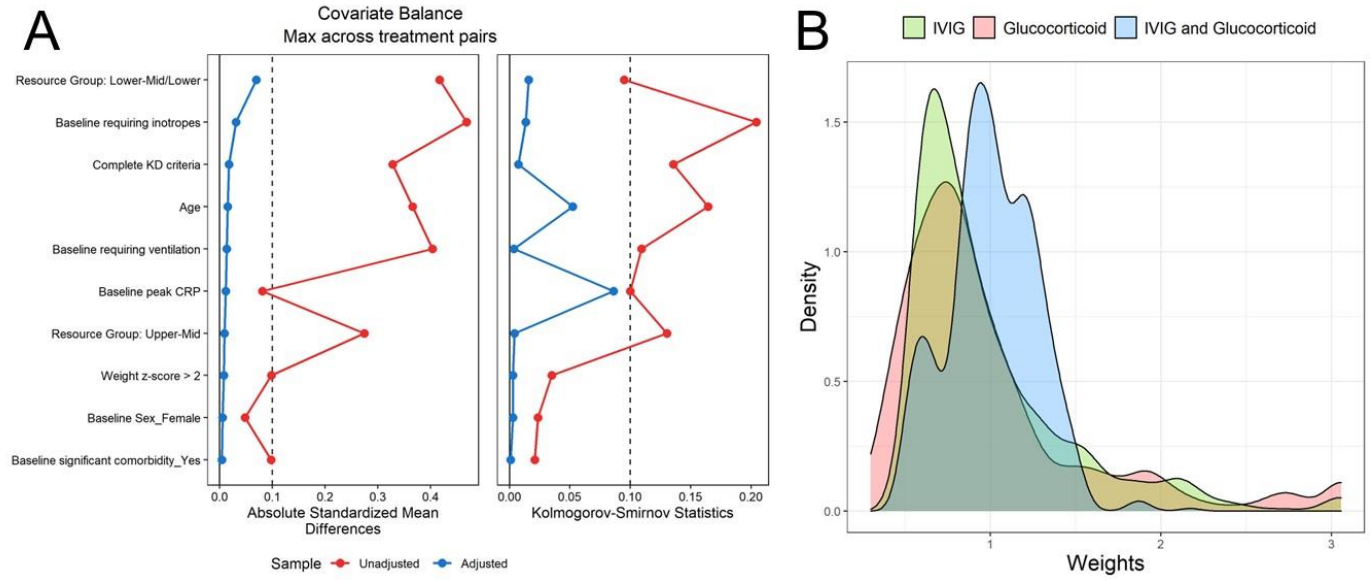


Figure S13: Change in other blood results over time from treatment initiation

Time course plots of additional blood results are plotted as a line and weighted by IPTW as described in supplementary methods. Each blood marker is shown as a percentage of each patient's peak value. For each plot patients are only included if they had blood results available both before and after treatment initiation, and only if their last value up to treatment initiation was abnormal (Abnormal levels defined as: albumin ≤ 34g/L; NLT ≥ 3.53; no cut-off used for hemoglobin; platelets ≥ 450x10^9/L; ALT ≥ 45 IU/L; fibrinogen ≥ 4.5g/L; proBNP ≥ 400ng/L; D-dimer ≥ 530ng/mL; creatinine ≥ 40 micromol/L; LDH ≥ 170 U/L; lymphocytes ≤ 1.5x10^9/L; neutrophils ≥ 7x10^9/L). Fitted curves are plotted for patients who received IVIG alone, IVIG plus glucocorticoids, and glucocorticoids alone as their primary treatment, using a generalized additive model to fit the curves.

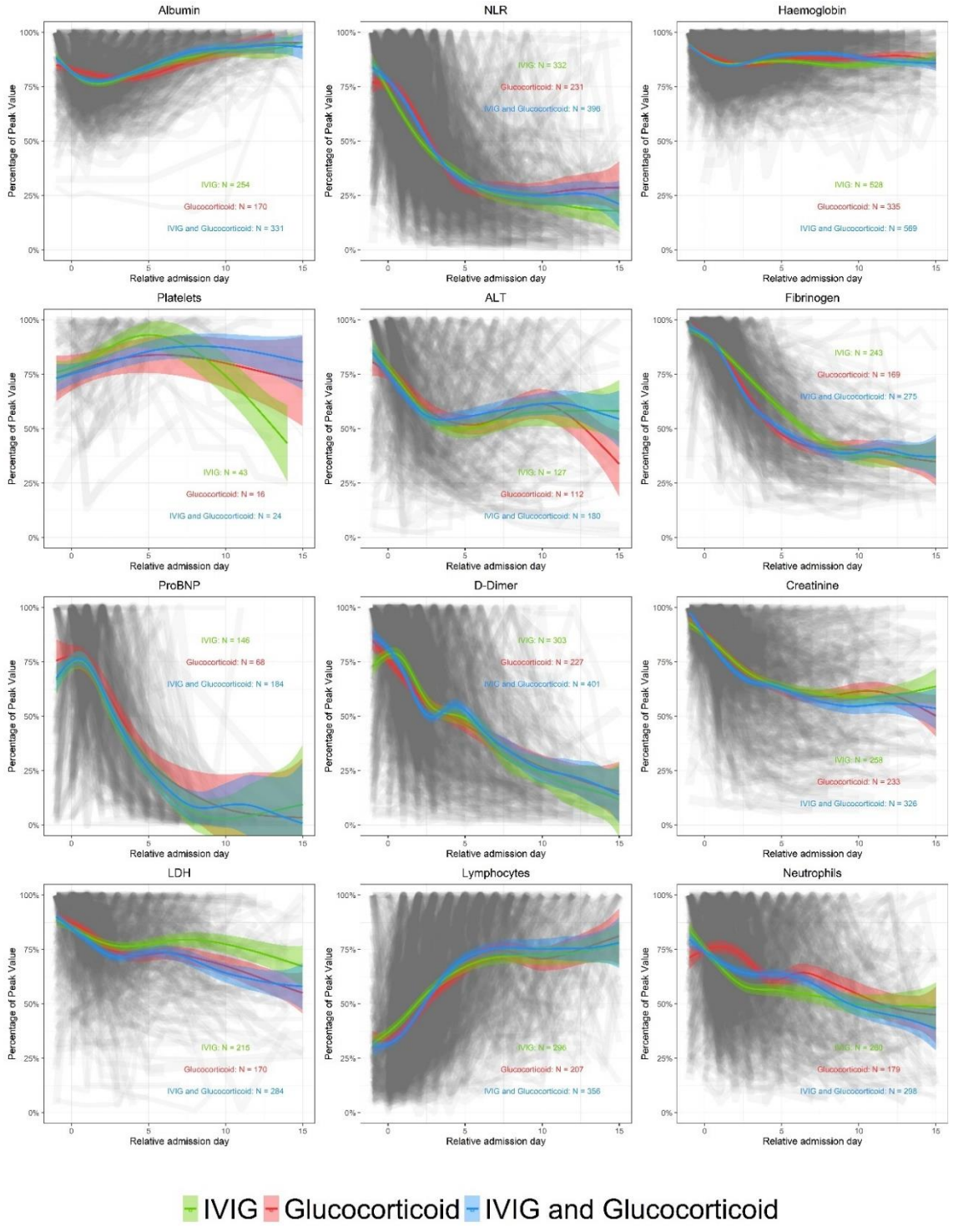


Figure S14: Percentage of the CRP peak value by admission day relative to treatment initiation for three main primary treatments

Percentage of the CRP peak value by admission day relative to treatment initiation 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 curves plotted for each group using a generalized additive model. For each plot patients are only included if they had blood results available both before and after treatment initiation, and only if their last value up to treatment initiation was abnormal (CRP ≥ 8mg/L). Panel A shows the fitted curves for CRP of children receiving primary treatment with IVIG, glucocorticoid or IVIG+Glucocorticoid, younger versus older than 6 years old. Panel B shows the fitted curves for CRP of children receiving primary treatment with IVIG, glucocorticoid or IVIG and glucocorticoid combined. 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 receiving primary treatment with IVIG, glucocorticoid or IVIG and glucocorticoid combined, and whose treatment remained the same between treatment initiation (day 0) and day 2. 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.

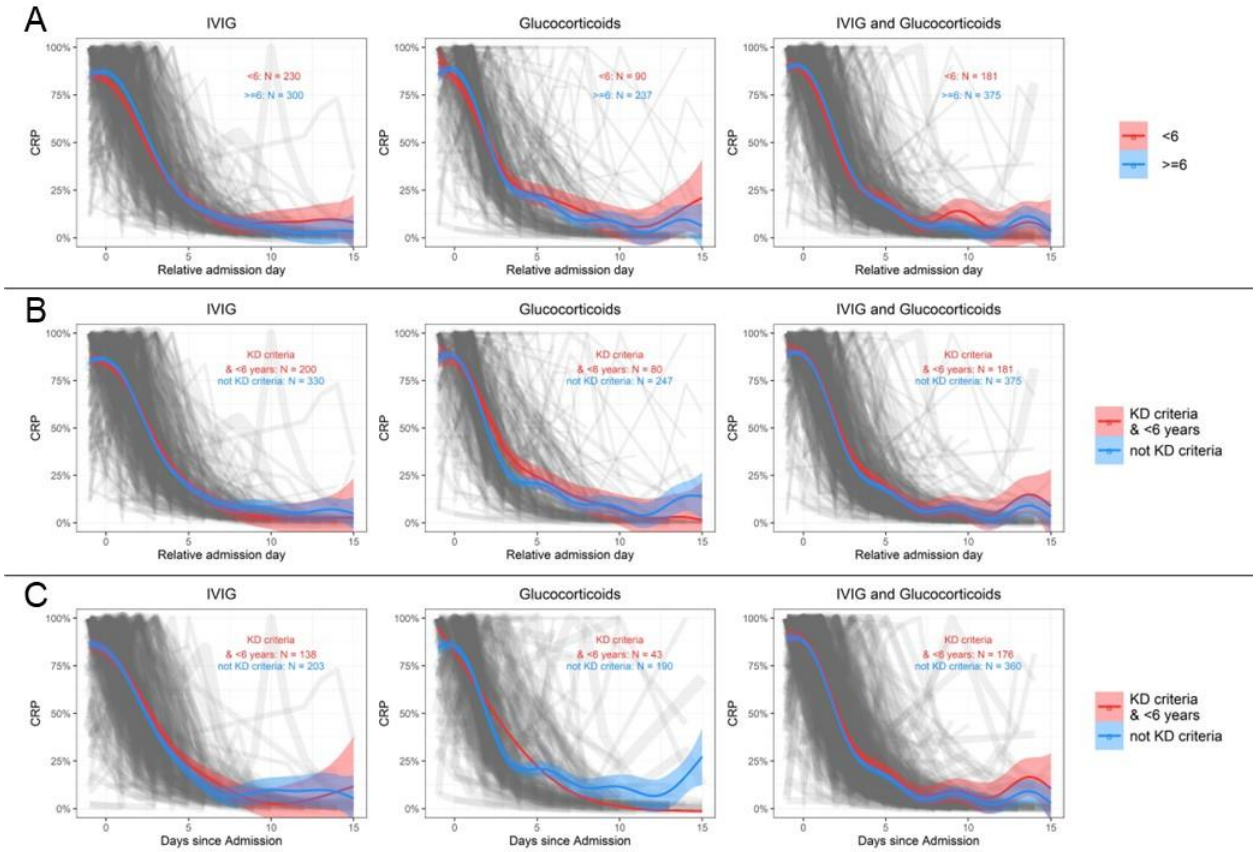


Figure S15A: Forest plots for additional post-hoc sensitivity analyses for first primary outcome (PO1)

Displayed values are odds ratios, 95% confidence intervals and p-values without correction for multiple hypothesis testing. Results for the full analysis using all covariates is presented for comparison, followed by results repeating the IPTW analysis with individual covariates removed.

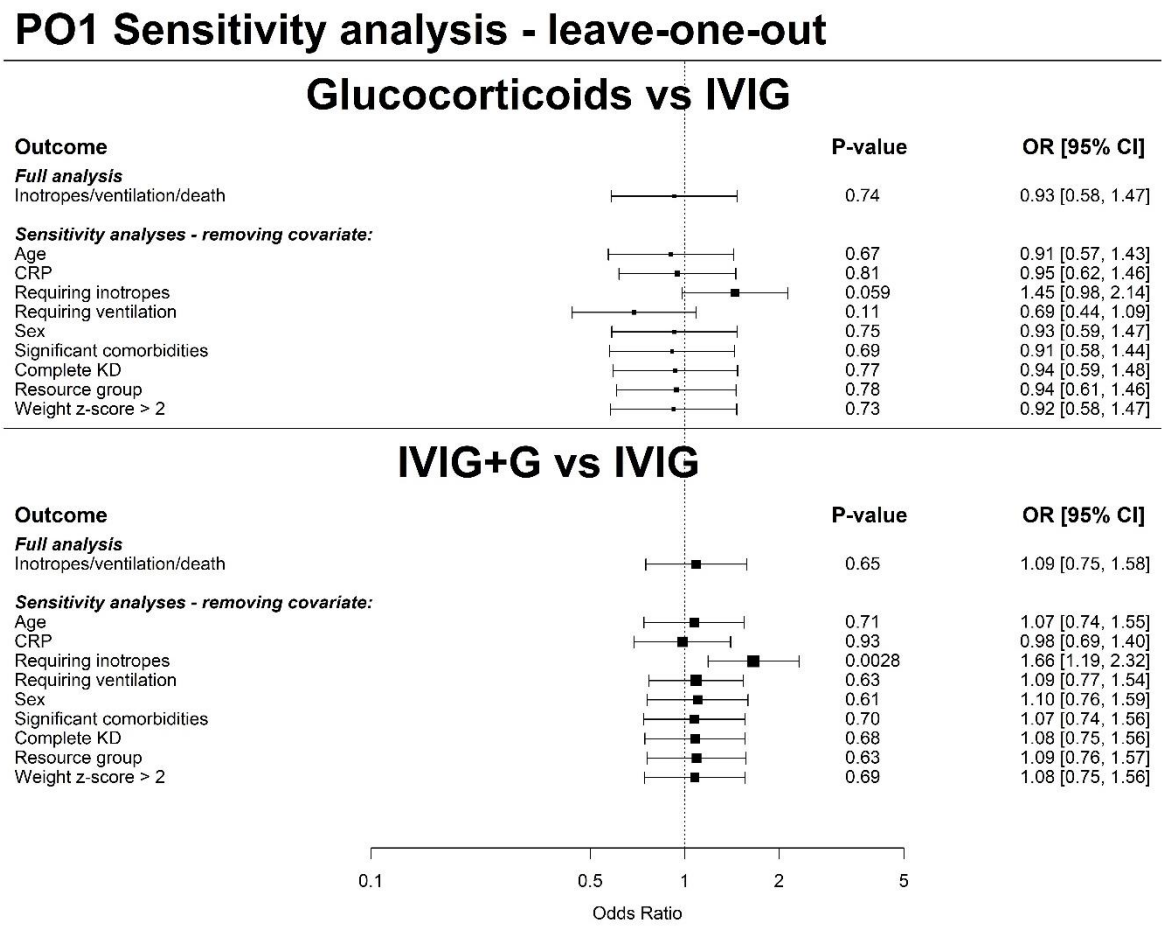


Figure S15B: Forest plots for additional post-hoc sensitivity analyses for second primary outcome (PO2)

Displayed values are average hazard ratios, 95% confidence intervals and p-values without correction for multiple hypothesis testing. Results for the full analysis using all covariates is presented for comparison, followed by results repeating the IPTW analysis with individual covariates removed. We also present results of an additional post-hoc sensitivity analysis exploring the right censoring approach used (page 16).

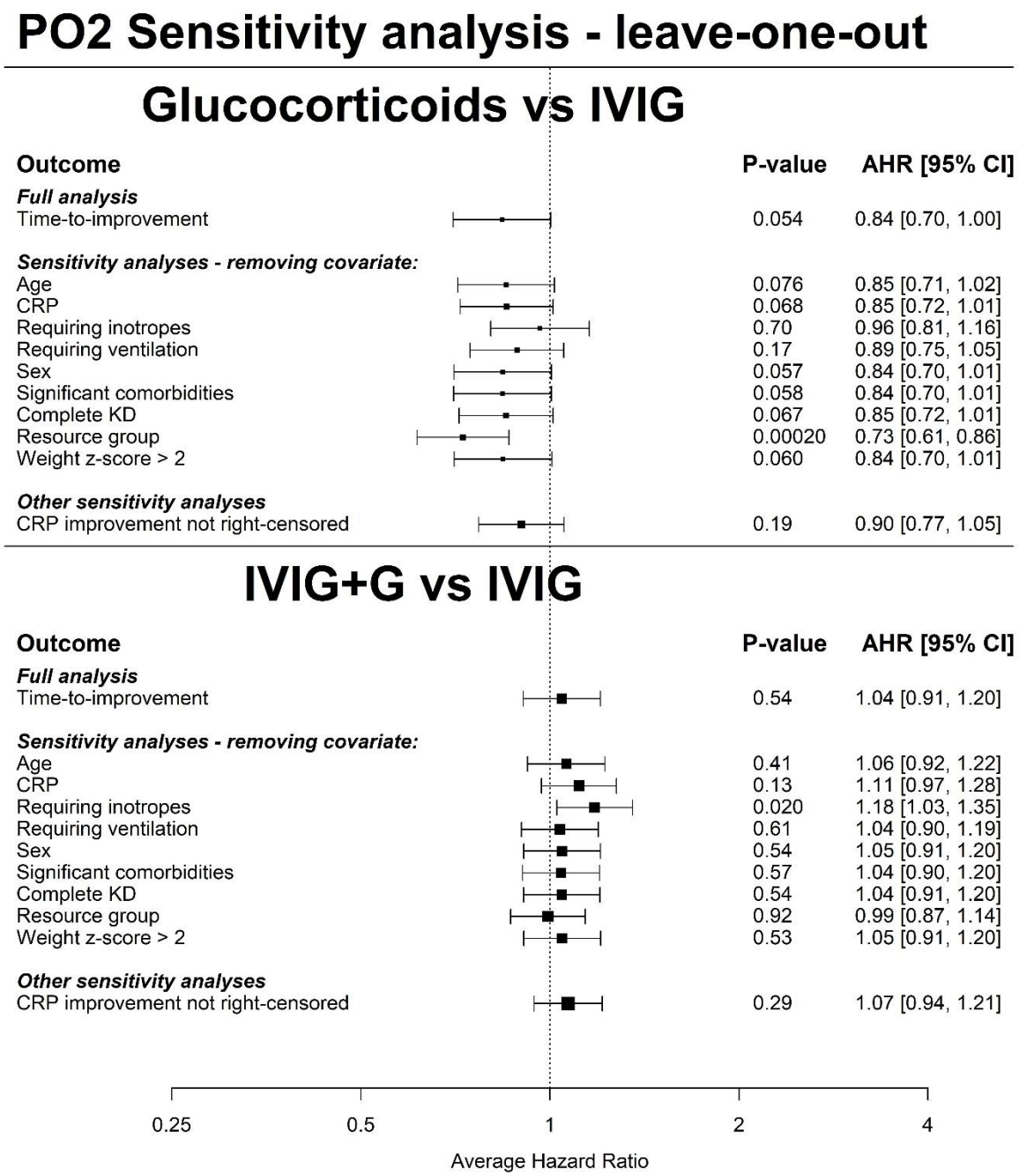


Figure S16: Covariate balance plots for matched analysis of first and second primary outcomes

Covariate balance plots for sensitivity analysis using propensity matched methods to estimate treatment effect on the first and second primary outcomes (full details on page 20). Red coloured lines show unadjusted absolute standardized mean differences; blue coloured lines show absolute standardized mean differences following propensity score matching. Panel A: first primary outcome, Glucocorticoids vs IVIG; panel B: second primary outcome, Glucocorticoids vs IVIG; panel C: first primary outcome, IVIG and Glucocorticoids vs IVIG; panel D: second primary outcome, IVIG and Glucocorticoids vs IVIG

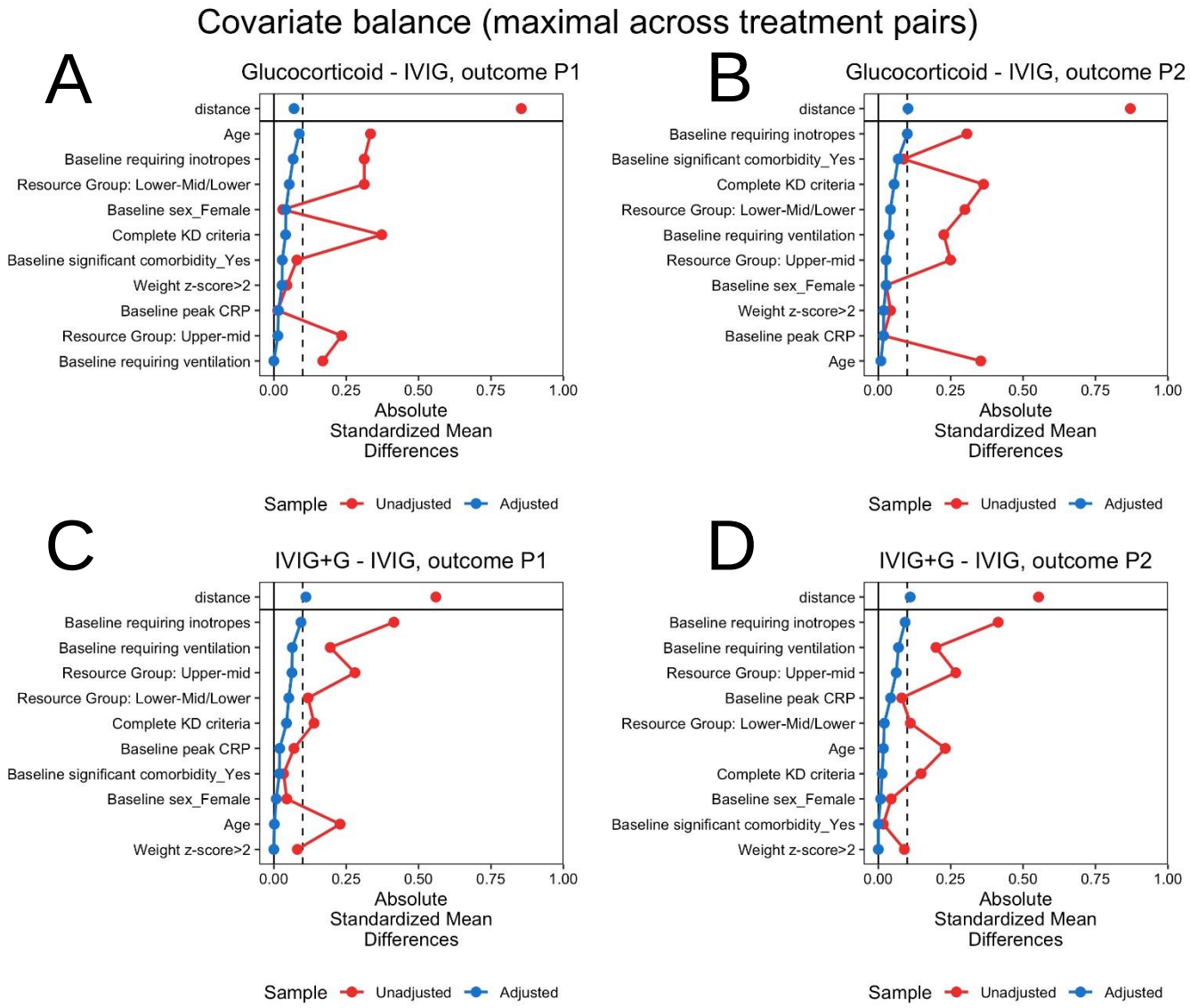
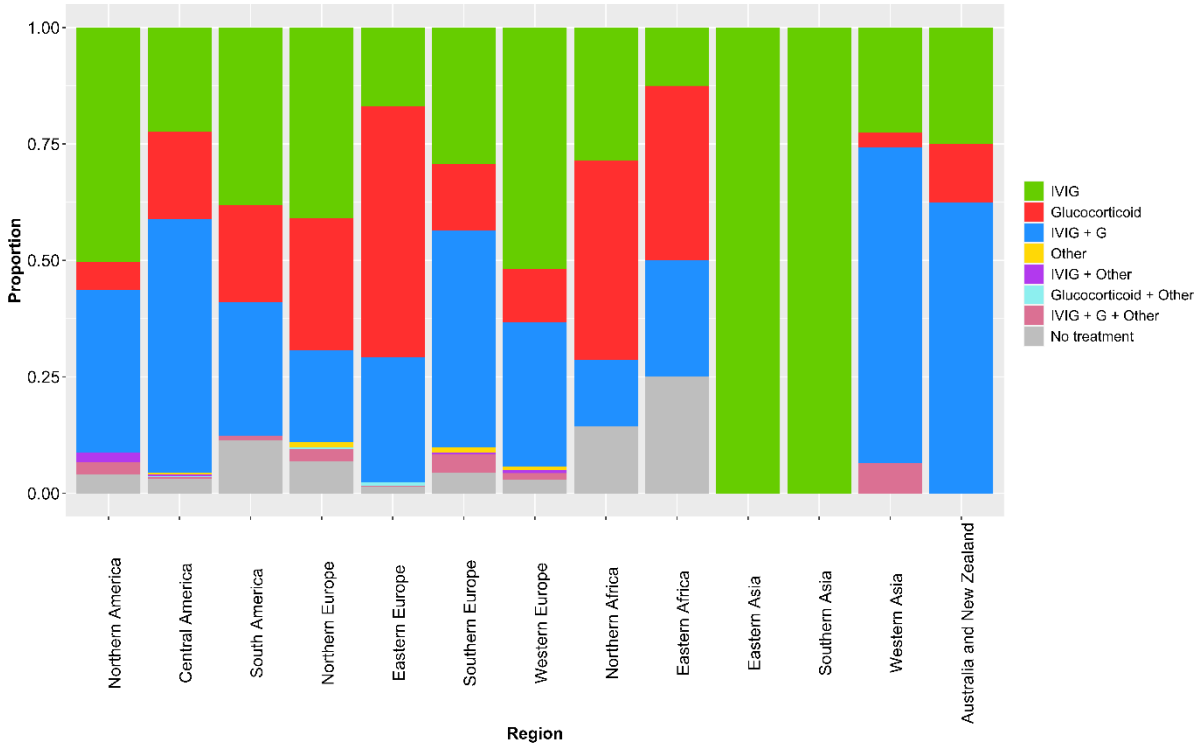


Figure S17: Proportion of patients in each primary treatment group by region



Appendices

Appendix A – Targeted coronary aneurysm questionnaire

To provide minimum required data to determine longer-term coronary artery aneurysm outcomes, the following questionnaire was sent to all recruiting sites for patients who were reported to have coronary artery aneurysms still present on their final echocardiogram entered onto the REDCap database. Recruiting sites were contacted a minimum of three times to minimise loss to follow-up.

1. Did coronary artery aneurysms resolve during follow-up?
2. What was the date of the last follow-up echocardiogram showing Coronary Artery Aneurysm(s), and if recorded what was the maximal z-score during this echocardiogram?
3. What was the date of the first follow-up echocardiogram not showing Coronary Aneurysm(s), and if recorded what was the maximal z-score during this echocardiogram?

Appendix B – Sample-size calculations

Primary outcome 1 - Inotropic support or ventilation or death (dichotomous)

Assumptions:

1. 30% of patients in the control arm will have an outcome (estimated from the weighted numbers seen in previous analysis)
2. Aim to detect a 30% relative decrease in outcomes in the experimental arm (clinically appreciable improvement)
3. Aim for power of 0.8
4. Aim for type-1 error rate of 0.013 – this equates to global type-1 error rate of 0.05 across four comparisons (2 treatment comparisons, 2 primary outcomes)
5. Using a two-sided test
6. Assume equal proportion of patients in each arm

Under these assumptions, we would require **516 patients** in each group. If we assume instead that there are 600 patients in our largest group, we will require 452 **patients** in the smaller group to have the above power to detect the assumed effect size above.

Varying effect size

Below is a table demonstrating how changing effect size (relative decrease) alters the number of patients needed in each arm, when assuming equal proportions.

Relative Decrease	N
20%	1208
25%	758
30%	516
35%	370

Primary outcome 2 - Time to improvement (continuous)

Assumptions:

1. 90% of patients in both arms will have an outcome (estimated from the numbers seen in previous analysis)
2. Aim to detect a postulated hazard ratio of 0.8 between treatment arms (clinically appreciable improvement)
3. Aim for power of 0.8
4. Aim for type-1 error rate of 0.013 – this equates to global type-1 error rate of 0.05 across four comparisons
5. Assume equal proportion of patients in each arm

Under these assumptions, using the Cox Proportional-Hazards Model we would require **498 patients** in each group. If we assume instead that there are 50% more patients in our largest group, we will require **595 patients** in the larger group and **397 patients** in the smaller group to have the above power to detect the assumed effect size above.

Notes: These calculations have been performed using the packages pwr[17] and powerSurvEpi.[18]

Appendix C – List of R packages used for analysis

Packages used for processing, analysis or visualisation are listed below, in no particular order. References are also included.

- ggplot2[9]
- WeightIt[11]
- survey[12]
- EValue[16]
- MatchIt[15]
- CBPS[19]
- cobalt[20]
- coxphw[21]
- jskm[22]
- Hmisc[23]
- vistime[24]
- stringi[25]
- tidyverse[26]
- magrittr[27]
- metafor[28]
- spatstat[29]
- ggpubr[30]
- networkD3[31]
- survival[32]
- viridis[33]

Appendix D – Key fields required for full analysis

Field category	**Fields**
Admission	Admission date; treatments received prior to admission at recruiting hospital
Discharge	Date of discharge or death; place of discharge
Demographics	Age (in years & months); weight; sex-at-birth
Clinical history	Presenting symptoms; presence of comorbidities
Therapy	Start dates of immunomodulator therapies; steroid name, dose, and route
Daily level-of-care & support	Level-of-care; supportive therapies, including oxygen, ventilation, inotropes, renal replacement therapy and Extracorporeal membrane oxygenation
Investigations	CRP & other blood results by day; echocardiogram results, including presence of coronary artery aneurysms

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