Immunoglobulin, Glucocorticoid, or combination therapy for Multisystem Inflammatory Syndrome in Children: A propensity weighted cohort study

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ABSTRACT

Background

SARS-CoV-2 associated Multisystem Inflammatory Syndrome in Children (MIS-C) has emerged as a serious illness in children world-wide. Immunoglobulin and/or glucocorticoids are currently recommended treatments.

Methods

The “Best Available Treatment Study” evaluated immunomodulatory treatments for MIS-C in an international observational cohort. Analysis of the first 614 patients was previously reported. Clinical and outcome data were collected onto a web-based database. Inverse probability weighting was used to compare primary treatments with intravenous immunoglobulin (IVIG), IVIG plus glucocorticoids (IVIG+G), or glucocorticoids alone, using IVIG as the reference treatment. Primary outcomes were: a composite of inotropic or ventilator support from the second day after treatment initiation, or death; and time-to-improvement on an ordinal clinical severity scale. Secondary outcomes included treatment escalation, clinical deterioration, fever, and coronary artery aneurysm occurrence and resolution.

Findings

After exclusions, 2009 children with clinically diagnosed MIS-C from 39 countries were enrolled between May 2020 and April 2022. 680 received primary treatment with IVIG; 698 IVIG+G; 487 glucocorticoids alone; 59 other combinations including biologics, and 85 no immunomodulator.

There were no significant differences between treatments for primary outcomes for the 1586 patients considered for primary analysis: adjusted odds ratios relative to IVIG for ventilation, inotropic support or death were 1·09 (95% confidence interval [CI] 0·75-1·58) and 0·93 (95% CI: 0·58-1·47) for IVIG+G and glucocorticoids alone respectively. Adjusted average hazard ratios for time-to-improvement were 1·04 (95% CI: 0·91-1·20) and 0·84 (95% CI: 0·70-1·00) for the same

comparisons. Treatment escalation was less frequent for IVIG+G and glucocorticoids alone vs IVIG. Persistent fever was less common with IVIG+G compared with either IVIG or glucocorticoids alone. Coronary artery aneurysm occurrence and resolution did not differ significantly between treatment groups.

Interpretation

Recovery rates, including occurrence and resolution of coronary artery aneurysms, were similar for primary treatment with IVIG when compared to glucocorticoids or combination IVIG+G. Initial treatment with glucocorticoids appears to be a safe alternative to immunoglobulin or combined therapy, and may be advantageous in view of the cost and limited availability of IVIG in many countries.

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The funders and sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the final manuscript.

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Contributors

ML, AJM, OV, AC, EW, JH, MK, HP, PS, CW, RN, TD, and CH conceived the original study. OV, SCW, CB, ES, HP, GS and IK undertook data checks and quality control. OV, SCW and ML accessed and verified the underlying data reported in the manuscript. SCW, OB, AJM and ML conceived the current statistical analysis plan, which was reviewed by all co-authors prior to publication. SCW, ES, EP, and HP undertook the current analysis. SCW and ML prepared the manuscript. All authors had full access to all the data in the study. All authors read and approved the final manuscript and had final responsibility for the decision to submit for publication.

Conflict of Interest Statements/Declaration of interests

AT has provided unpaid consultancy work for Janssen Pharmaceuticals. DM has received grant support from the British Embassy in Moscow ('StopCOVID Cohort: Clinical Characterisation of

Russian Patients') and holds the following unpaid positions: Co-Chair of International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Global Paediatric Long COVID Working Group, Member of ISARIC working group on long-term follow-up in adults, Co-lead of the PC-COS project aiming to define the Core Outcome Set for Long-COVID, in collaboration with the WHO. MJC reports a personal fee from BioTest for speaking at the BioTest Immunology Forum 2022, Royal Society (www.biotest.com). EW holds the following unpaid positions: member of the paediatric steering committee for the RECOVERY trial; paediatric representative for NHS England working on the National paediatric virtual advisory network and expert advisory group for COVID treatment, Independent advisory group for COVID monoclonal antibodies, and co-lead for the pan-London Post-COVID service for children. All other authors declare no competing interests.

Ethics Committee approval

Please see "oversight" section in main text for relevant details.

RESEARCH IN CONTEXT

Evidence before this study

In the first wave of the COVID-19 pandemic paediatricians around the world rapidly identified and described a new inflammatory disorder, causing shock and multi-system failure in children approximately 4-6 weeks after SARS-CoV-2 infection. Faced with this new life-threatening disorder, termed multisystem inflammatory syndrome in children (MIS-C), with unknown pathophysiological mechanisms, paediatricians, national, and international paediatric bodies rapidly adopted treatments which are of benefit in other inflammatory disorders.

Based on the similarity in clinical features of MIS-C to Kawasaki Disease (KD), intravenous immunoglobulin (IVIG), the recognised treatment for KD, was adopted as the most widely used initial treatment, often combined with glucocorticoids and a range of biological agents. In the absence of data from randomised controlled trials (RCT), national and international organisations, including the World Health Organisation (WHO), American College of Rheumatology, and UK Royal College of Paediatrics and Child Health (RCPCH) produced treatment guidelines recommending IVIG as initial treatment, combined with glucocorticoids or biological agents for the most seriously ill or unresponsive patients.

We searched for publications on treatment of MIS-C (and the alternative name Paediatric Multisystem Inflammatory Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS)) since April 2020 when the disorder was first recognised, until November 2022. In the extensive literature now published on MIS-C, there are many hundreds of observational studies, treatment recommendations and guidelines based on expert opinion, and reports of outcome after treatment. However, we found no RCTs, and only four propensity matched comparisons reporting outcomes after specific treatments, only two of which included comparison of glucocorticoids alone and IVIG, and all were based on relatively small patient cohorts.

Added value of this study

The Best Available Treatment Study (BATS) allowed us to compare treatment of MIS-C with IVIG alone, glucocorticoids alone, and combined glucocorticoids plus IVIG (combined therapy), in over 2000 patients from 39 different countries. This is the largest study to date of immunomodulator treatment options in MIS-C, including the largest cohort of patients treated initially with glucocorticoid monotherapy. After correcting for known confounders using propensity score weighting, initial treatment with glucocorticoid monotherapy or combined therapy demonstrated no significant difference to treatment with IVIG monotherapy in either time-to-improvement measured on an ordinal clinical severity scale, or in a composite outcome of inotropic support or ventilator support (invasive or non-invasive) from the second day after starting treatment or later, or death. Comparison of glucocorticoid monotherapy with combined therapy suggested a small benefit from combined therapy in time-to-improvement, but this appeared to be restricted to those who did not require inotropic and/or ventilatory support at baseline. Combined therapy was associated with faster fever resolution and less escalation of treatment, but with no other differences in secondary outcomes. Occurrence and resolution of coronary artery aneurysms was similar in all treatment groups, with the large majority of aneurysms resolving during follow up.

Implications of all the available evidence

Our study increases confidence that initial treatment of MIS-C with glucocorticoids is associated with similar outcomes to treatment with IVIG or combined therapy. In the context of all current observational data, there is, at best, only a small benefit in initial therapy combining IVIG and glucocorticoids compared to monotherapy with IVIG or glucocorticoids alone. Given the high cost and limited availability of IVIG in many countries this evidence supports initial glucocorticoid monotherapy as an acceptable alternative.

BACKGROUND

Since recognition in April 2020, Multi-system Inflammatory Syndrome in Children (MIS-C), temporally associated with SARS-CoV-2 infection,[1–4] has emerged as a rare but serious post-infectious illness.[5–8] In the absence of evidence from randomised controlled trials (RCT), treatment recommendations for the new disease were developed by clinical consensus in many countries. Based on similarity of MIS-C to Kawasaki disease (KD), for which Intravenous immunoglobulin (IVIG) is the established treatment,[9] national and international guidance has recommended IVIG as initial treatment, with addition of glucocorticoids and/or other immunomodulatory agents for patients with severe illness.[10,11]

While there have been no RCTs comparing treatments for MIS-C published to date, several observational studies using propensity score methods have suggested that combination treatment with IVIG and glucocorticoids was associated with improved cardiac outcomes.[12–14]

The Best Available Treatment Study (BATS) was initiated in the early months after first recognition of MIS-C and aimed to provide evidence for treatment recommendations by systematic data collection, and analysis of outcomes of treatments chosen by individual paediatricians responsible for patient care. In view of the urgent need for evidence to support treatment recommendations, analysis of the first 614 patients enrolled in BATS was reported in July 2021.[15] No significant differences in outcome were observed between patients treated with IVIG alone, glucocorticoids alone, or combination of IVIG and glucocorticoids (IVIG+G), although this may have been due to limited sample size. In this report, we compare the initial treatments for MIS-C in a much larger cohort of children, and also describe the outcomes of cardiac complications.

METHODS

Study Design

Details of the BATS propensity-weighted observational cohort study were described in the initial report.[15] Minor modifications of the data collection procedure and analysis plan were undertaken which are described below and in the published analysis plan and supplementary appendix. Briefly, paediatricians world-wide were invited to join BATS and upload data from patients with suspected MIS-C onto a web-based Research Electronic Data Capture database,[16] from June 2020 through to April 2022. As the spectrum of post-SARS-CoV-2 inflammatory disease was unknown when BATS was initiated,[3,5,17–19] and the reliability of the published criteria for MIS-C was unknown we invited recruitment of children with severe inflammatory illness after SARS-CoV-2 infection in addition to those meeting the USA Centre for Disease Control (CDC), WHO or UK case definitions.[20–22] De-identified longitudinal data were collected on presenting features, demography, laboratory findings, immunomodulatory (IVIG, glucocorticoids or biologicals) and supportive treatments. Treatments and daily data were collected by calendar day. Duration of admission, organ support required, and health status on discharge were recorded.

The original BATS case report form recorded no data on coronary artery aneurysms (CAA) after hospital discharge, and we therefore added an additional follow up questionnaire regarding CAA resolution (appendix p68).

Treatments and endpoints

The first calendar day of immunomodulatory treatment was defined as “day 0”, and subsequent treatment and outcomes defined relative to this. Primary treatment was defined as the immunomodulatory agent(s) initiated on day 0. Three primary treatment groups were large enough for weighted comparison according to our predefined sample-size estimations (appendix p69): IVIG alone, glucocorticoids alone, or IVIG+G. Two other groups were pre-

defined for additional analyses: those receiving other immunomodulator treatments (including in combination with IVIG and/or glucocorticoids), or no immunomodulator treatments.

Primary outcomes were modified from the previous analysis. The first primary outcome remained a composite of inotropic support or ventilator support (invasive or non-invasive) on day 2 or later, or death. However, the second primary outcome was altered from improvement on the ordinal severity scale by day 2, to time to improvement of at least one level on the ordinal clinical severity scale (ventilated and on inotropic support; ventilated; on inotropic support; receiving oxygen; no supportive therapy stratified by CRP level; and discharged – appendix p14). This modification was justified by the greater clinical relevance and additional statistical power of the time to event analysis.

Secondary outcomes included: immunomodulator escalation (any additional immunomodulator, a second dose of IVIG if primary treatment included IVIG, and if primary treatment included glucocorticoids, an increment of 5 mg/kg equivalent daily-dose of prednisolone)[23]; fever from day 2 onwards; individual components of the first primary outcome (death, or inotropic or ventilator support from day 2); CAA occurrence and resolution following treatment (coronary artery Z-score ≥2·5 or aneurysm documented)[24]; left ventricular (LV) dysfunction on echocardiography from day 2 onwards; no improvement in clinical severity scale at day 2; any increase in cardiorespiratory supportive therapy after day 0; therapeutic complications; and temporal dynamics of blood markers of inflammation and organ damage.

Analysis and Statistics

We applied inverse probability of treatment weighting (IPTW) using covariate-balancing propensity scores[25] to account for baseline differences between the three primary treatment groups. Confounding covariates were selected by expert consensus prior to analysis and were used in both covariate balancing and treatment effect estimation to produce doubly-robust estimates (appendix p18-20). As specified in the analysis plan, IVIG alone was the reference

treatment group. Weighted quasibinomial logistic-regression was used for dichotomous outcomes and weighted Cox-regression for time-to-event analyses. Outcomes were reported as adjusted odds ratios or average hazard ratios with 95% confidence intervals and p-values. P-value correction for multiple hypothesis testing was performed for the two primary outcomes and two treatment-group comparisons with the Bonferroni-Holm procedure (appendix p20).

All clinician-diagnosed MIS-C cases were included in analysis, with those meeting more restrictive definitions evaluated in subgroup or sensitivity analyses: restricting to patients meeting the WHO MIS-C criteria,[22] those meeting KD criteria; subgroups by age category and baseline inflammation; analysis by propensity score matching; and defining primary treatments as those received on days 0 and 1. Extensive additional subgroup and sensitivity analyses were performed as planned (appendix p21-22).

Inflammatory markers were plotted as percentages of each patient's peak value by admission day relative to treatment initiation. Smoothed curves with confidence intervals were weighted by the same approach and fitted using the generalized additive model method (appendix p18).

Oversight

BATS was designed by the study team at Imperial College London (members and roles in appendix p3). Patient data were collected by local investigators (consortium members in appendix p3-11). The updated statistical analysis plan was developed by the study management team and international advisory board, and analysis undertaken by the statistical group (appendix p3). The study was approved by the UK REC (20/HRA/2957) and registered with the international trial registry (ISRCTN69546370). Participating centers obtained ethical approval based on requirements in each country. The initial manuscript was drafted by the first and last authors and developed by all listed authors. The corresponding author, data management group, and analysis group had access to all data, vouching for the completeness and accuracy of data, and for fidelity to the protocol and analysis plan.

RESULTS

From 20th June 2020 to 25th April 2022, data from 2101 MIS-C patients from 39 countries and 121 sites were uploaded to BATS (appendix p48-51). 92 records were excluded, including four neonates and those with incomplete data, duplicate entries, or admission after the recruitment deadline (Fig1A). Of 2009 patients included for analysis, 680 received primary treatment with IVIG, 487 with glucocorticoids, 698 with combination IVIG+G, 59 received other immunomodulator combinations, and 85 received no immunomodulators (Fig1A). In the three main primary treatment groups, 579/1865 (31·0%) received additional immunomodulators by day 2, with 953/1865 (51.1%) receiving secondary agents in total. Treatment trajectories are described in detail (Fig1B, appendix p23).

Clinical and laboratory findings

Baseline clinical and laboratory findings showed some differences between primary treatment groups (Table 1, appendix p24,52). Patients in the no therapy group had significantly less derangement in laboratory markers of inflammation and organ dysfunction, while those in the combined IVIG+G and other treatments groups had the highest level of derangement overall. The combined IVIG+G and other immunomodulator groups had a higher proportion of patients receiving inotropes or ventilation on day 0 (appendix p55). Considering treatment received by day 2, a higher proportion of those on both IVIG+G or in whom biological agents were added were receiving inotropes or ventilated at baseline (appendix p55), but there were no major differences seen in blood markers between these groups (appendix p53).

1602/2009 (80·0%) patients met WHO MIS-C criteria (appendix p26). The most common missing criterion was evidence of SARS-CoV-2 exposure (appendix p56). SARS-CoV-2 antibody measurements were not tested in 406/2009 (20·4%), and negative in 259/2009 (13·0%). Bacteria were cultured in the blood of a small proportion of patients (appendix p26).

629/2009 (31·3%) overall, and 544/1602 (34·0%) of those meeting WHO MIS-C criteria also met the American Heart Association (AHA) definitions for complete KD (appendix p28,57).

Primary outcomes

Of 1865 patients in the three main treatment groups, 166 patients (9·0%) received immunomodulators prior to transfer to the reporting hospital and an additional 113 patients (6.1%) were missing baseline covariates, with a total of 1586 patients considered for our primary weighted analyses (Fig1A). Acceptable covariate balance was achieved for all IPTW outcome analyses (appendix p60-61,66). For the first primary outcome, receipt of inotropic support or ventilation on day 2 or later, or death, the adjusted odds ratios (OR) for patients receiving primary treatment with IVIG+G, or glucocorticoids alone as compared with IVIG were 1·09 (95% CI: 0·75-1·58, adjusted p-value 1·00) and 0·93 (95% CI: 0·58-1·47, adjusted p-value 1·00) respectively (Fig2A & 2C, appendix p29).

For the second primary outcome, time to improvement on the ordinal clinical severity scale, the adjusted average hazard ratio (AHR) for patients receiving IVIG+G vs IVIG was 1·04 (95% CI: 0·91-1·20, adjusted p-value 1·00) and for glucocorticoids alone vs IVIG was 0·84 (95% CI: 0·70-1·00, adjusted p-value 0·22, Fig2B, 2D & 3A, appendix p29), suggesting slower improvement in the glucocorticoid group. Subgroup analyses of time to improvement in severely ill children (requiring ventilatory or inotropic support at baseline), and those not requiring intensive support showed the suggested slower improvement in those receiving glucocorticoids vs combined treatment was confined to the less severely ill patients (AHR 1·06 (95% CI: 0·75-1·49) in the severe group vs 0·83 (95% CI: 0·62-1·11) in the milder group, Fig2B, 2D & 3B-C, appendix p34).

All sensitivity and subgroup analyses, including restricting to patients meeting WHO MIS-C criteria, showed no significant difference in the first primary outcome for the comparisons of IVIG+G or glucocorticoids alone with IVIG (Fig2A & 2C, appendix p32). For the second primary

outcome, in the subgroup of patients without significant comorbidities, the time-to-improvement was slower in the glucocorticoid group vs IVIG alone (AHR 0·82 (95% CI: 0·69-0·99), Fig2B & 2D, appendix p34) and the two-point time-to-improvement was slower in the IVIG+G group vs IVIG alone (AHR 0·87 (95% CI: 0·75-1·00)). All other planned sensitivity and subgroup analyses showed no significant difference in time-to-improvement for the comparisons of IVIG+G or glucocorticoids alone with IVIG alone.

Secondary outcomes

Escalation of immunomodulator treatment was less common in the IVIG+G and glucocorticoid groups compared to the IVIG group (OR 0·15 (95% CI: 0·11-0·20) & 0·68 (95% CI: 0·50-0·93) respectively, appendix p58). Persistent fever from day 2 was less common in patients receiving IVIG+G vs IVIG alone (OR 0·50 (95% CI: 0·38-0·67)), with no difference between the glucocorticoid or IVIG groups. In a post-hoc sensitivity analysis, there was no difference in persistent fever from day 3 between the IVIG+G and IVIG groups. Individual components of the composite outcome showed no differences between treatments (Fig2A & 2C, appendix p30). Of 1918 with reported echocardiograms, 236 (12·3%) had CAA at any time (13·6% in IVIG recipients, 8·9% glucocorticoid, and 12·9% IVIG+G (appendix p36)), with the largest disparity in aneurysm detection before starting immunomodulatory treatment (appendix p36). In the 705 patients with inpatient echocardiograms before and after treatment initiation (appendix p30) 50 (7.1%) had CAA present on the final echocardiogram before discharge, with no statistically significant difference apparent between groups after IPTW analysis, including for post-hoc analyses restricted to patients who did and did not meet complete KD criteria (appendix p58). Follow-up echocardiogram data were available in 196/236 (83·1%) patients with CAA during admission. Most CAA resolved during follow-up (92·9% total), with similar rates amongst primary treatment groups (appendix p36). Similar rates of resolution were seen when restricted to patients with follow-up by 6- and 12-weeks (appendix p37).

To establish if patients who did not receive IVIG were at greater risk of CAA, or had different rates of resolution, we explored CAA incidence in the glucocorticoid alone primary treatment group. 17/239 (7·1%) of those never receiving IVIG had CAA detected at any time during admission, compared with 24/221 (10·9%) who received IVIG later during admission. CAA were present at discharge in 5/239 (2·1%) of those without later IVIG and 9/221 (4·1%) of those receiving later IVIG treatment, with over 93% of CAA resolving in both groups on reported follow-up (appendix p38). No difference was seen between treatment groups in severity of CAA as judged by the distribution of z-scores (appendix p39). Larger z-scores were seen in younger patients (appendix p39).

Left ventricular dysfunction was reported in 202/1512 (13·4%) of patients with echocardiograms from day 2 onwards, with no difference between groups (appendix p30,58). There were no differences between IVIG+G or glucocorticoids vs IVIG for the secondary outcomes of no improvement by day 2 or increase in level of support after initiation of primary treatment. Death occurred in 8 (1·2% unadjusted), 10 (2·1%) and 5 (0·8%) patients in the complete IVIG+G, glucocorticoid and IVIG groups respectively.

Drug complications were reported in 59/1623 (3·6%) of patients receiving any glucocorticoids and 25/1658 (1·5%) patients receiving IVIG. Glucocorticoid complications were predominantly hypertension and hyperglycemia (appendix p40).

IVIG+G vs Glucocorticoids alone

A planned secondary analysis comparing glucocorticoids alone and combined IVIG+G demonstrated no difference in the first primary outcome, but a faster time-to-improvement for the IVIG+G group (AHR 1·25 (95% CI: 1·05-1·48), appendix p59). This was predominantly seen in the later days following treatment, and in those patients not requiring intensive support at baseline (Fig3A-C). Secondary outcomes for this comparison showed that escalation of primary

therapy and persistence of fever from day 2 were more common in the glucocorticoid alone group (appendix p30,59).

Effect of Immunomodulation on blood markers.

CRP declined more rapidly in patients receiving immunomodulators than in untreated patients (Fig4A). Comparison of primary treatment groups showed more rapid decline of CRP in the glucocorticoid and IVIG+G groups than in the IVIG treated patients (Fig4B). There was a suggestion of more rapid decline in troponin and ferritin in the glucocorticoid and combined treatment groups with a similar trend when restricting to those not receiving additional treatment between days 0 and 2 (Fig4C). Time course plots of other blood markers showed similar dynamics of blood markers between groups (appendix p62).

To investigate whether inadvertent inclusion of children with KD within BATS enrolment might have influenced treatment responses, we explored changes in blood markers separately in children most resembling KD. As KD is generally a disease in children aged 5-years and below, and MIS-C is often reported in older children, we compared those meeting AHA criteria for KD, and all children under 6 years (“KD-like”), with the remaining MIS-C patients.

The rate of decline in CRP was similar between the younger and older children and those fulfilling KD criteria treated with IVIG, with a suggestion of a more rapid decline in CRP in the non-KD-like patients receiving glucocorticoids alone (appendix p63).

DISCUSSION

Our comparison of treatment outcomes in an international cohort of 2009 children with MIS-C shows that treatment with glucocorticoids alone, or IVIG+G are not associated with significant differences in primary outcomes (requirements for inotropic support, ventilation on day two or beyond, or death; or rate of improvement on the ordinal severity scale) in comparison with IVIG alone. The findings are consistent with our preliminary report of 614 children.[15] However, the larger number of patients in each treatment group, increases the confidence in our findings. There was a non-significant trend towards a slower rate of improvement in patients treated with glucocorticoids alone in comparison with IVIG, but this comparison was confined to those with less severe illness at presentation. Reassuringly, we found no difference in CAA outcomes between primary treatment groups, with resolution seen in the vast majority of patients.

Our planned secondary analysis comparing glucocorticoids alone with combined IVIG+G demonstrated no difference in the first primary outcome, but a faster time-to-improvement for the IVIG+G group. This comparison was not adjusted for multiple hypothesis testing and the effect appears confined to those patients not requiring intensive support at baseline. Other Secondary endpoints, and thus also not corrected for multiple hypothesis testing, showed lower rates of treatment escalation and lower rates of fever on day 2 in the IVIG+G group.

A key question for clinicians is whether the potential incremental benefits of IVIG+G to reduce severity of illness and hasten resolution of fever are sufficient to justify the use of both agents. We note that the primary outcomes (progression or recovery from organ support) were chosen to select the most clinically important outcomes, whereas the secondary outcomes may detect less clinically important findings. Furthermore, we suggest that the finding of more common escalation of treatment for those on single agents, which was also observed in earlier studies,[12,13] may be biased by greater clinician readiness to add other treatments in seriously ill patients who do not

rapidly improve on monotherapy, whereas options to escalate treatment are fewer in patients treated with primary combination IVIG+G.

This question of whether combined IVIG+G is beneficial as compared to Glucocorticoids alone is relevant to both resource rich countries where IVIG is readily available and countries where IVIG has limited availability or cost imposes limitations in its use. For resource limited settings, our data suggests that primary treatment with glucocorticoids alone, is a safe alternative to IVIG or combined treatment, with IVIG being reserved for patients who fail to improve on glucocorticoids alone. For countries where IVIG cost is less prohibitive, the limited supply of IVIG and potential for combined treatments to have more side effects than single agents would argue for initial treatment with a single agent, and addition of second agents only in those who do not improve.

A higher proportion of patients receiving IVIG+G as primary treatment were receiving inotropes or ventilation at day 0, and had more deranged blood markers, suggesting more severely ill patients may have received IVIG+G. Importantly, key differences between treatment groups were adjusted for in the propensity score analysis. Children treated with IVIG+G had more rapid resolution of fever than children treated with IVIG or glucocorticoids alone. However no other clinically significant findings were more frequent in the IVIG+G group in comparison with either of the single agent treatment groups.

Patients who were initially treated with glucocorticoids or IVIG alone and then received additional treatment by day 2 were more likely to be receiving inotrope or ventilatory support at baseline. However, patients who received additional treatment did not differ substantially from patients who did not receive additional treatment across multiple biomarkers, suggesting that treatment with inotrope or ventilatory support influenced the clinical decision for administration of additional treatment. We have included adjustment for both baseline inotrope and ventilatory support in our IPTW analysis.

The use of IVIG as treatment for MIS-C has largely been driven by the similarity of MIS-C to KD, for which IVIG is the established treatment to reduce risk of CAA.[9] As coronary artery aneurysms

are observed in 10-20% of MIS-C cases,[13,15,26] there has been concern that failure to include IVIG in initial treatment would be associated with increased risk of CAA. We found that the incidence of CAA in patients receiving glucocorticoids as initial treatment was similar to the incidence of CAA in IVIG recipients (either IVIG or IVIG+G). Furthermore, the severity of CAA (as measured by z-score) and the proportion of patients undergoing complete resolution of CAA by time of discharge, or on follow up was similar in the glucocorticoid alone group to the IVIG and IVIG+G groups, including post-hoc analysis restricting to patients who never received IVIG. Our study thus provides reassurance that initial therapy with single agent glucocorticoids is not associated with increased risk of long-term coronary artery damage in MIS-C.

The American College of Rheumatologists currently recommends combined treatment with IVIG and glucocorticoids for MIS-C,[11] based on limited evidence of benefit from the USA and French propensity matched studies,[12,13] which showed lower rates of treatment escalation and improved cardiac function detected by echocardiogram with combined therapy. Neither of these studies included a glucocorticoid only group, and both were smaller than our current analysis.

We observed a more rapid decline in CRP in all three treatment groups as compared to patients not receiving immunomodulators. Although the curves for each treatment were overlapping, there was a non-significant trend to a more rapid decline in CRP, ferritin and troponin in the glucocorticoid containing groups.

Our study has several limitations. A key concern is the extent to which a retrospective comparison of outcomes following non-randomised choice of treatment can be used to guide clinical practice. We applied two different propensity score methods (weighting and matching), to remove bias caused by differences in severity, demography, or resource setting. We achieved good covariate balance between comparator groups using both approaches. However, other unmeasured differences might influence the results, and a large RCT would be the preferred approach to provide definitive answers. In addition, there is a risk of bias from the voluntary nature of data collection, as not all cases of MIS-C from each site were necessarily included in the study.

A second potential limitation is our use of the broad inclusion criteria of clinician diagnosed MIS-C. At the time BATS was initiated the accuracy of the published diagnostic criteria was unknown, and there were differences between the WHO, CDC and RCPCH criteria. Furthermore, availability of antibody testing for SARS-CoV-2 was limited in many countries. We therefore chose to include patients whose responsible clinicians considered them to have MIS-C, and in whom alternative diagnoses had been excluded. As we expected, our data confirms that the most commonly "missed" criteria to meet the WHO or CDC definitions of MIS-C was the presence of evidence of SARS-CoV-2 exposure. It is noteworthy that as the pandemic has evolved, and a high proportion of children have become SARS-CoV-2 antibody positive through natural infection or vaccination, the value of antibody against SARS-CoV-2 as evidence of recent infection has reduced. In view of the high rates of SARS-CoV-2 infection in schools, and the high proportion of asymptomatic childhood infection, a history of exposure to infection is of little value in diagnosis of MIS-C, and the WHO and CDC criteria may need to be re-evaluated. Despite these concerns, the large majority of patients in BATS did meet the WHO criteria, with only small differences in the proportions from each of the primary treatment groups. Our subgroup and sensitivity analyses did not find any difference in outcome when restricted to those meeting the WHO criteria, or the group with features overlapping KD.

An additional concern may be that the nature, severity, and epidemiology of MIS-C has changed over time, and with successive SARS-CoV-2 waves and introduction of childhood vaccinations against COVID-19. The disorder appears to have become less common in many countries as a high proportion of children have previous infection, and both natural infection and vaccination may reduce the incidence of MIS-C.[27] However, with SARS-CoV-2 now increasing in the previously unexposed population of China, there is likely to be a new wave of MIS-C and the findings reported here may be of considerable help to the clinicians experiencing this disease for the first time.

Other limitations include the wide variety of steroid dosing regimens used, and the large number of patients in whom additional treatments were added after the primary treatment. Although we have attempted to compare those remaining on a single agent, this group may have been less severely ill and therefore not representative of the treatment group overall. Additionally, after excluding patients with incomplete baseline covariates from the IPTW analysis, the final numbers of patients used for primary analyses were marginally below those stated in our sample-size calculations. However, the suggested effect sizes in these calculations are relatively arbitrary. More important is the final width of confidence intervals for treatment effects, which were generally small for our primary analyses. An additional limitation is the use of a composite primary outcome. This was necessitated by the relatively small numbers of patients with individual outcomes, and our aim to capture effects of treatment in patients across a wide spectrum of severity. As mitigation we evaluated the individual components of the composite score as secondary analyses. The time-to-improvement outcome also incurs the possibility of "built-in selection bias"[28] although we have attempted to isolate known factors that could incur such bias through extensive subgroup analyses. This limitation is relevant to all survival analysis, and would not be avoidable even for RCTs using the same outcome. Finally, we are not able to detect rare or longer-term effects of either IVIG or glucocorticoid administration.

The absence of significant differences between treatment groups poses several questions on the mechanisms underlying MIS-C. As IVIG and glucocorticoids have different possible modes of action in MIS-C,[29,30] the lack of difference between them, and the fact that dual therapy was not superior to single agent therapy is puzzling. One possible explanation might be different underlying disease processes in MIS-C, some of which respond to IVIG and some to glucocorticoids. If so, we would have expected that combination treatment would be superior to each treatment individually. Alternatively, glucocorticoids and IVIG may act at different points in the same causal pathway and with equal efficacy. This would explain the similar outcomes and lack of additive effect. A final possibility is that neither treatment has a significant effect on the

disease process. As the number of patients receiving no immunomodulator treatment was small and phenotypically distinct from those receiving immunomodulator treatment, we did not have an adequate “No treatment group” to evaluate this possibility. However, the more rapid decline in CRP in the treated vs untreated groups supports a beneficial effect of all three treatment regimes. In addition to IVIG and glucocorticoids, several other immunomodulatory agents were administered, including anti-IL1, anti-IL6 and anti-TNF agents. The numbers of patients receiving these agents were too low to enable IPTW comparison between them, or with IVIG, glucocorticoids and IVIG+G. Biologicals tended to be administered in combination with IVIG and glucocorticoids, and to more unwell patients.

The key question in interpreting clinical significance of this analysis is whether the findings are sufficiently robust to enable glucocorticoids to replace IVIG as primary treatment of MIS-C. The lack of significant difference in outcomes between patients treated with glucocorticoids as primary treatment, and those receiving IVIG or IVIG+G, and in particular the lack of difference in CAA severity, frequency, or resolution, suggests that initial treatment with glucocorticoids is a safe alternative to IVIG. A concern in adopting this approach is the difficulty in distinguishing MIS-C from KD, particularly in younger patients, and the possibility that IVIG will be withheld from children with KD because they are thought to have MIS-C. This concern highlights the need for a rapid diagnostic test to distinguish MIS-C from KD, as well as the need for urgent cardiology assessment in patients presenting with a suspected diagnosis of either disease. It also suggests that where clinical features closely resemble KD, particularly in younger children, retaining IVIG as a component of initial therapy is prudent.

MIS-C has emerged as an important childhood problem in low- and middle-income countries.[26,31] As IVIG is costly[32] and has limited availability in many countries, its use in preference to cheaper anti-inflammatory agents such as glucocorticoids should be supported by sound evidence. We did not find significant differences in outcome between treatment with glucocorticoids or IVIG as single agents or between the single and dual agent primary

treatments. Our findings suggest that glucocorticoids are not inferior to IVIG or combination IVIG+G as primary treatment of MIS-C, and their wide availability and lower cost would support their choice as initial treatment for MIS-C.

Figures and Tables

Figure 1A | Study flowchart

The study flow chart gives an overview of the total number of patients enrolled, excluded, and included for the analyses. Patients meeting the inclusion criteria are categorized by treatment groups (IVIG, Glucocorticoids, IVIG & Glucocorticoids, Other immunomodulator treatments [this includes: anti-tumor necrosis factor, anti-interleukin 1, anti-interleukin 6] and no immunomodulator treatments) and subdivided by our data-drive classification according to the WHO MIS-C criteria.

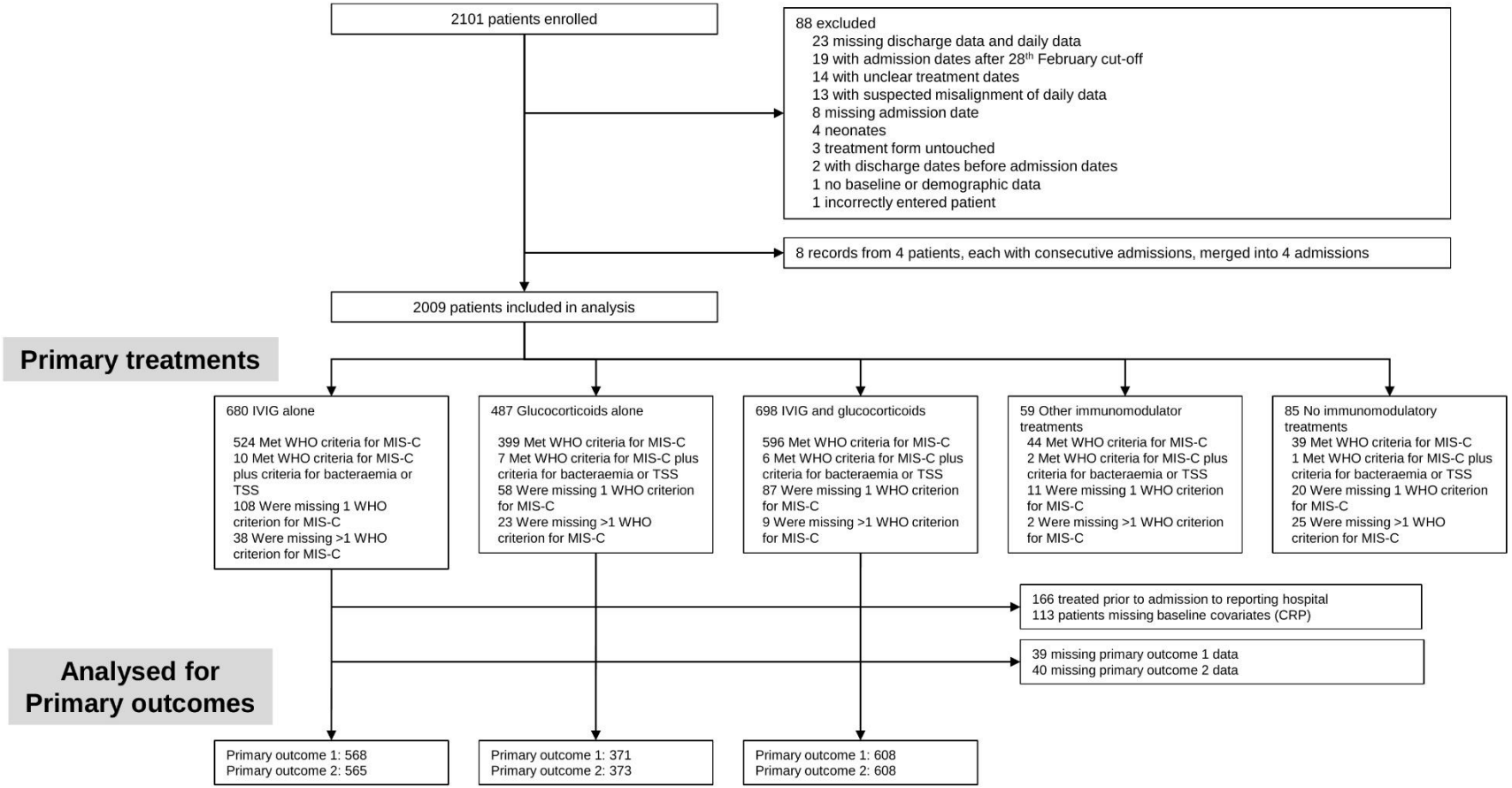

Figure 1B | Treatments received by patients over time following initiation of immunomodulator treatment

The Sankey diagram demonstrates the number of patients receiving cumulative therapies from days following initiation of immunomodulator treatment. Each vertical stack represents a different day in the patients' admission relative to starting immunomodulatory treatment (days 0 to 5), with day 0 representing the first day of immunomodulator treatment. The grey bands represent movement of patients between treatment groups from relative day 0 to 1, day 1 to 2, day 2 to 3, day 3 to 4 and day 4 to 5. The width of the grey bands is proportional to the number of patients (flow). The flow of patients is independent between time intervals; there is no continuous correspondence across days 1 to 5. The treatment groups are as stated. Of note, "Glucocorticoids" include intravenous and oral glucocorticoids (appendix p41). "Other" includes one or more other immunomodulatory treatment(s) given alone or in combination with Glucocorticoids and/or IVIG. Other immunomodulatory treatments include: anti-interleukin1, anti-interleukin 6, anti-tumour necrosis factor, cytokine adsorber (CytoSorb), granulocyte colony stimulating factor, colchicine, mesenchymal stem cells, convalescent plasma, cyclophosphamide, plasmapheresis and hydroxychloroquine

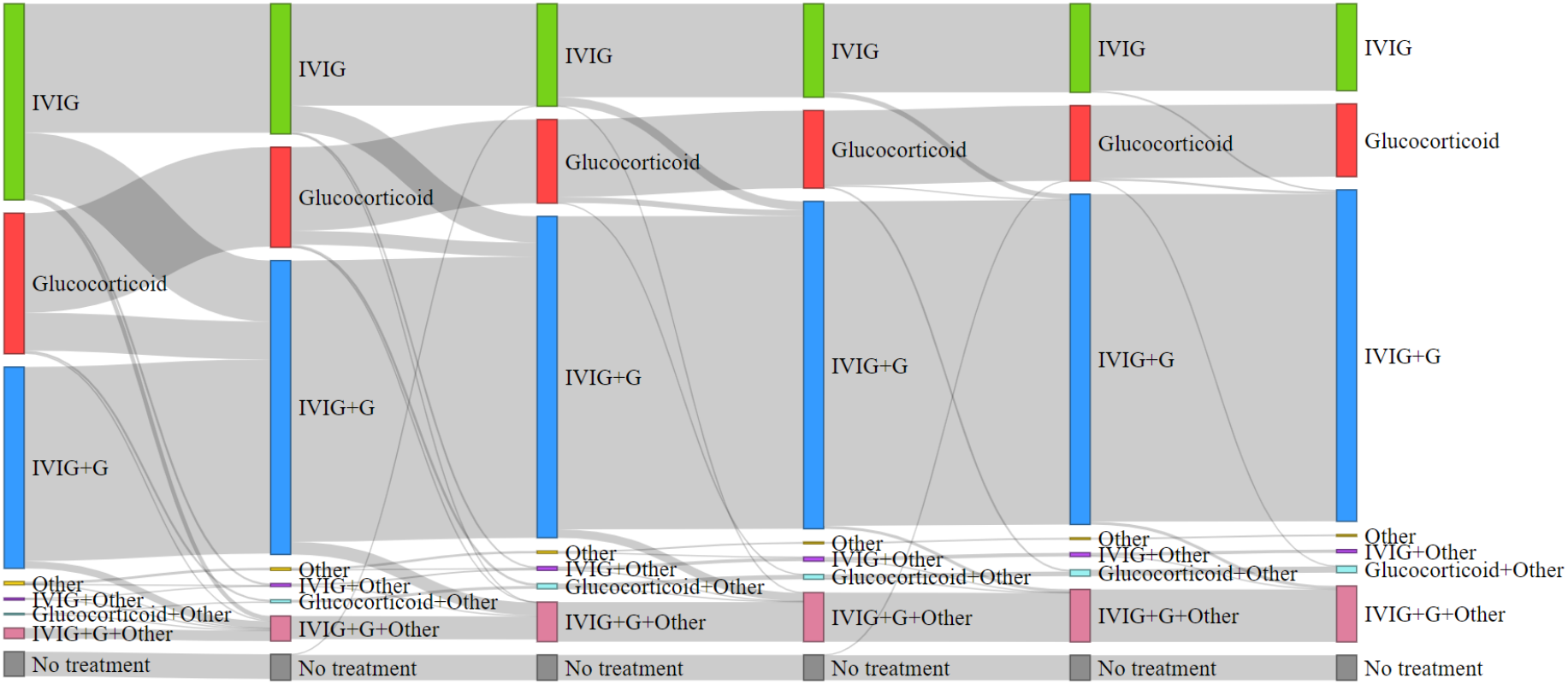

Figure 2 | Forest plots summarizing point estimates and 95% confidence intervals for primary analyses, including all subgroup and sensitivity analyses.

*Shown are outcomes for patients with suspected MIS-C who received IVIG plus glucocorticoids (Panels A & B) or glucocorticoids alone (Panels C & D) as compared with those who received IVIG alone (reference group, indicated by an odds ratio or average hazard ratio of 1·00). Displayed values are adjusted odds ratios or average hazard ratios (indicated on the x-axis). Panels A & C show the first primary outcome analyses, risk of inotropes, ventilation or death, and values to the right of the dotted line indicate superiority of IVIG alone. Panels B & D show the second primary outcome analyses, time to improvement in ordinal clinical severity score, with values to the left indicating superiority of IVIG alone. *indicates p-values corrected for multiple hypothesis testing using the Bonferroni-Holm procedure, observed p-value x4. Absolute numbers of patients included in each analysis can be found in appendix p29-32.*

Abbreviations: CRP: C-reactive protein; KD: Kawasaki Disease; WHO: World Health Organisation.

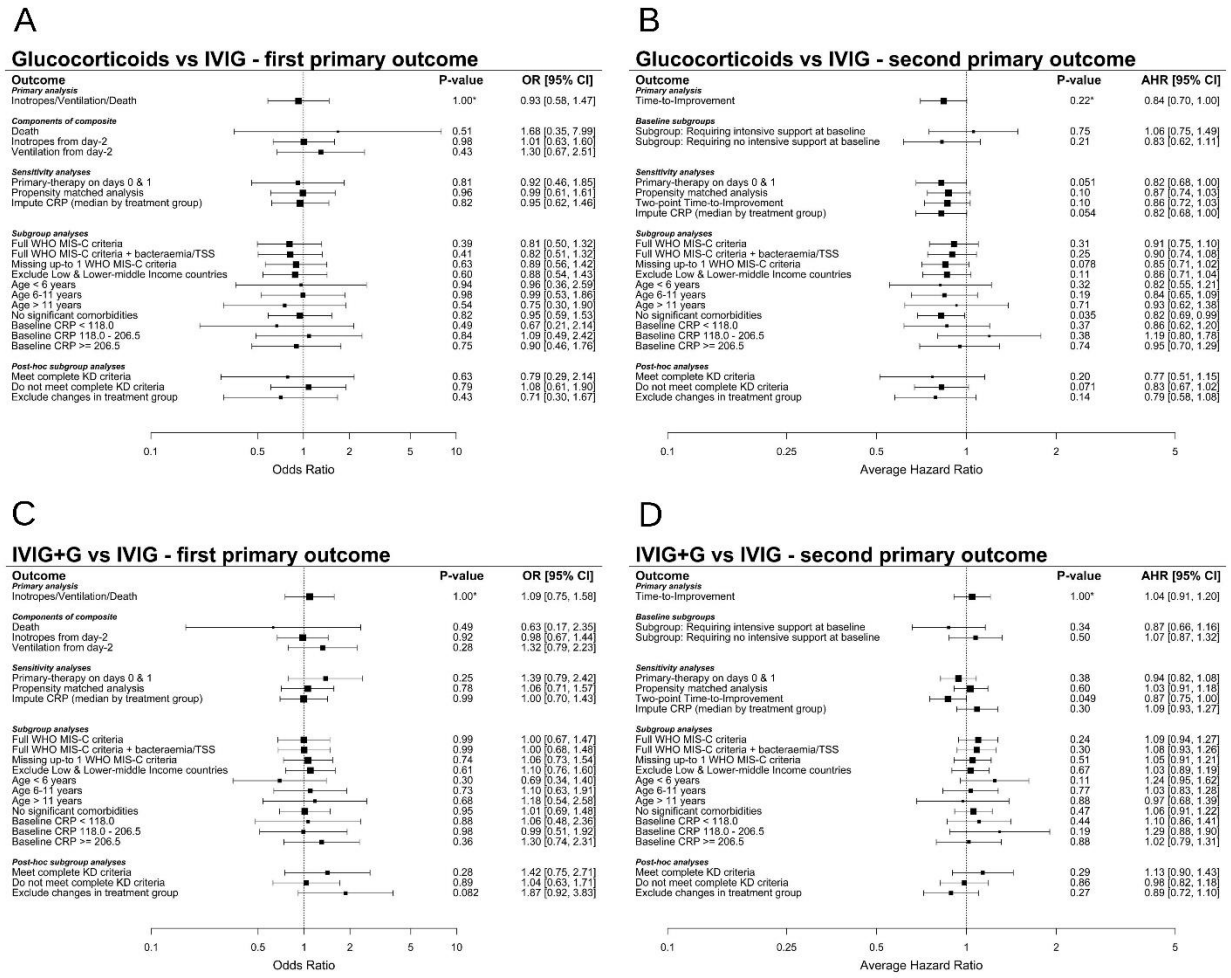

Figure 3 | Weighted clinical improvement over time

Panels A-C: Kaplan-Meier curves for the three main primary treatment groups showing time to one-point improvement in clinical severity on ordinal scale weighted by inverse probability of treatment, for (A) all patients, (B) subgroup of patients needing at least one of inotropes or ventilation at baseline, (C) subgroup of patients not requiring inotropes or ventilation at baseline. Tables below the Kaplan-Meier curves show the numbers at risk at the start of each day, and the number censored at this specific time point. Panel D: Clinical severity on ordinal scale, shown as proportional column charts from two days before treatment to 10 days after treatment, separated by primary treatment group, and weighted by inverse probability of treatment. Additional groups have been added for graphical purposes.

Abbreviations: CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation.

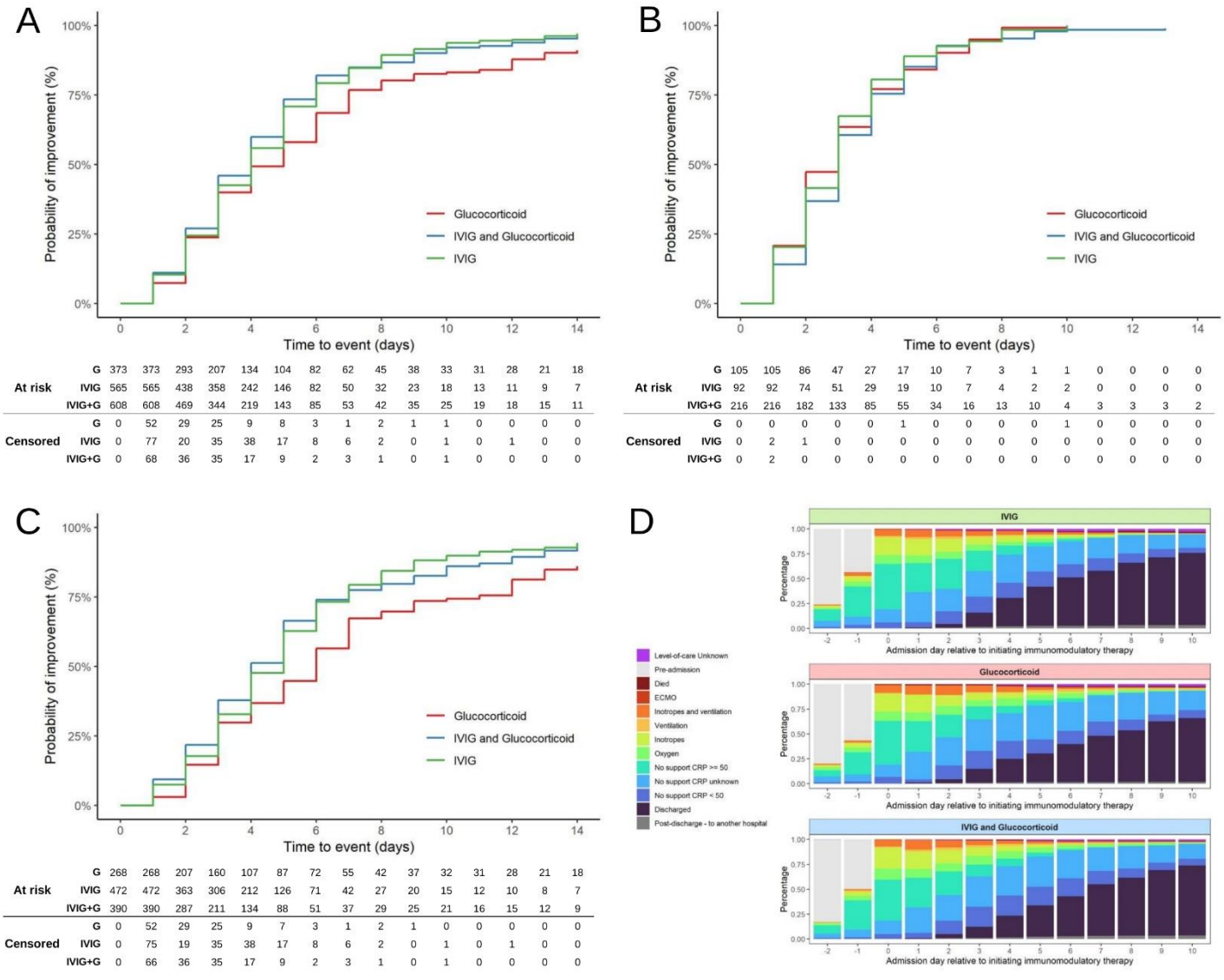

Figure 4 | Change in C-reactive protein (CRP), troponin and ferritin over time

Each of three key markers of inflammation (C-reactive protein, troponin, and ferritin) is plotted as a line and weighted by the covariate balancing propensity score. The levels are shown as a percentage of each patient's peak value, plotted by day relative to starting treatment. A generalized additive model was used to fit the curves. 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, troponin ≥ 14 ng/L, and ferritin ≥ 50 microgram/L). Panel A shows the fitted curves for the three measures in patients who received any immunomodulators, as compared with those who did not receive immunomodulators, using day of admission as relative admission day for patients not receiving immunomodulator treatment (NOTE: Curves for troponin in panel A were fitted using a loess model due to small sample numbers). Panel B shows the fitted curves for patients who received IVIG alone, IVIG plus glucocorticoids, and glucocorticoids alone as their primary treatment. Panel C shows the fitted curves for the three treatments combined in the patients whose primary treatment did not change between treatment initiation (day 0) and day 2.

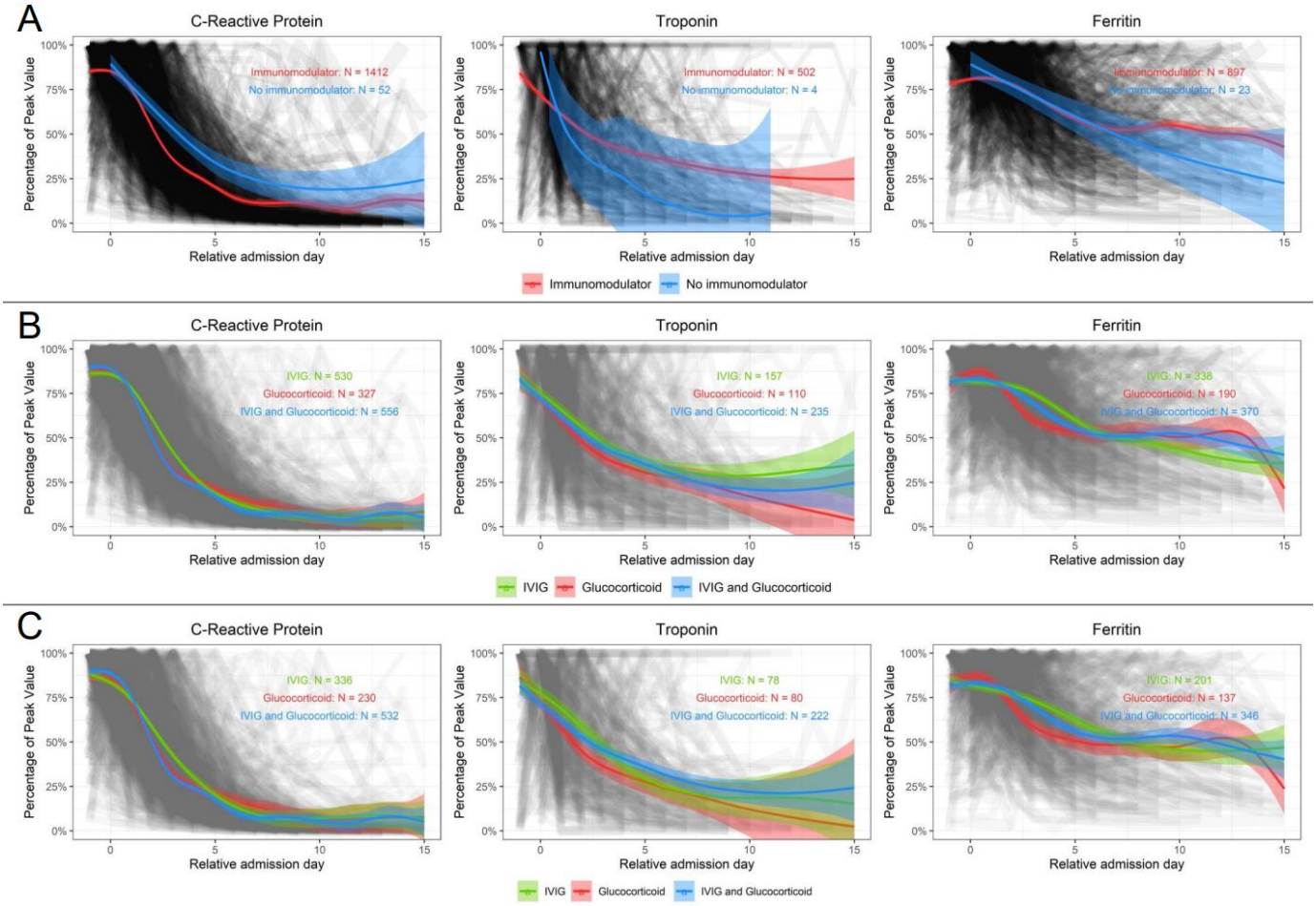

Table 1 | Clinical and demographic features in all treatment groups

Descriptive table of demographic features, clinical features and blood markers on admission, and proportion of patients meeting Kawasaki Disease criteria according to American Heart Association criteria. Patients with coronary artery aneurysms met the definition of Kawasaki Disease with less than 4 Kawasaki Disease clinical features. Patients were divided by treatment arm on day 0 (IVIG alone, glucocorticoid alone, IVIG+G, no treatment, and other (any other treatment combination including biologicals)). SARS-CoV-2 PCR data refer to test taken during admission. Organ support refers to receipt of ventilation, inotropes or ECMO on admission. Missing data (where applicable) are available in a full unabridged version in appendix p24.

Abbreviations: Ab: Antibody; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; PCR: polymerase chain reaction. ^Clinical and demographic features given as number and (%). +Numerical values given as median values and [interquartile ranges].

	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%)
^Proportion female	818 (40·7%)	264 (38·8%)	199 (40·9%)	288 (41·3%)	15 (25·4%)	52 (61·2%)
^Weight (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%)
^SARS-CoV-2 PCR positive	415 (20·8%)	131 (19·4%)	97 (20·0%)	148 (21·4%)	13 (22·0%)	26 (31·7%)
^SARS-CoV-2 Ab positive	1321 (66·5%)	412 (61·2%)	344 (71·4%)	492 (71·6%)	43 (72·9%)	30 (35·3%)
^Baseline requirement for ventilation/inotropes/ECMO	535 (26·6%)	117 (17·2%)	127 (26·1%)	252 (36·1%)	29 (49·2%)	10 (11·8%)
^Clinical features during 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%)
Diarrhoea	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%)
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%)
^Proportion meeting Kawasaki Disease criteria	629 (31·3%)	265 (39·0%)	119 (24·4%)	225 (32·2%)	12 (20·3%)	8 (9·41%)
+Bloods on admission						
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]
Troponin (ng/L)	25 [6·1 - 80]	13 [5·0 - 43]	31 [9·8 - 100]	40 [10 - 110]	48 [10 - 270]	10 [2·0 - 38]
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]
Albumin (g/L)	32 [28 - 37]	34 [28 - 39]	32 [27 - 36]	32 [27 - 36]	32 [27 - 36]	35 [30 - 41]

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DATA SHARING STATEMENT

Question	Response
Will individual participant data be available (including data dictionaries)?	Yes
Rationale for data sharing statement	BATS has collected de-identified data from multiple institutions in many countries. Each institution has signed an agreement with Imperial College on data security. We will need to assess requests for data on a case-by-case basis to ensure that the data that are provided fall within the existing agreements within the consortium.
What data in particular will be shared?	De-identified clinical and laboratory findings and response to treatment for the cohort included in this study. Any data provided will be de-identified and will conform to the agreements within the consortium for data sharing.
What other documents will be available?	The study handbook and statistical analysis plans are available at the ISRCTN registry at the following link: https://doi.org/10.1186/ISRCTN69546370
When will data availability start?	On publication of the manuscript. However, as approval for all data will have to be obtained from the consortium and partner institutions, approximately 3 months may be required before the data is provided.
When will data availability end?	Two years after publication
To whom will data be available?	Legitimate researchers and clinicians from medical and academic institutions.
For what types of analyses?	Only for academic and clinical research.
By what mechanism will data be made available?	On request to the corresponding author.
	Data requestors will need to sign a data access agreement