Supplementary Appendix

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

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Son M.B.F., Murray N, Friedman K et al. "Multisystem Inflammatory Syndrome in Children- Initial Therapy and Outcomes."

Table of Contents:

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SUPPLEMENTARY METHODS:

We first evaluated the need for propensity score adjustment by comparing 1) the difference in mean linear propensity scores for the two groups, 2) the ratio of the variances of the two linear propensity scores, and 3) the ratios of the variances of the residuals from each covariate. We also looked at standardized differences of means in continuous and binary variables to see the effects of matching and ensured balance.

For the continuous covariates in the propensity score model, we assume they are linear on the logit scale. We use continuous data where available except in cases of higher levels of unknown lab values like CRP, where we dichotomize the variable.

The ICU length of stay outcome is assessed after propensity score matching using Wilcoxon signed rank test to compare distributions.

While propensity score methods do a good job of accounting for measured confounding, unmeasured confounding may still be present. A sensitivity analysis can be performed to evaluate the strength required of a potential unmeasured confounder to change the association. VanderWeele and Ding (DOI: 10.7326/M16-2607, 2017) propose a value to measure the "evidence of causality" called the E-value. We calculate E-values for our primary and secondary outcomes to assess the potential of unmeasured confounders to influence our results.

Figure S1: Balance of Baseline Variables for the Propensity Score-matched Analysis

Absolute Standardized Difference Plot
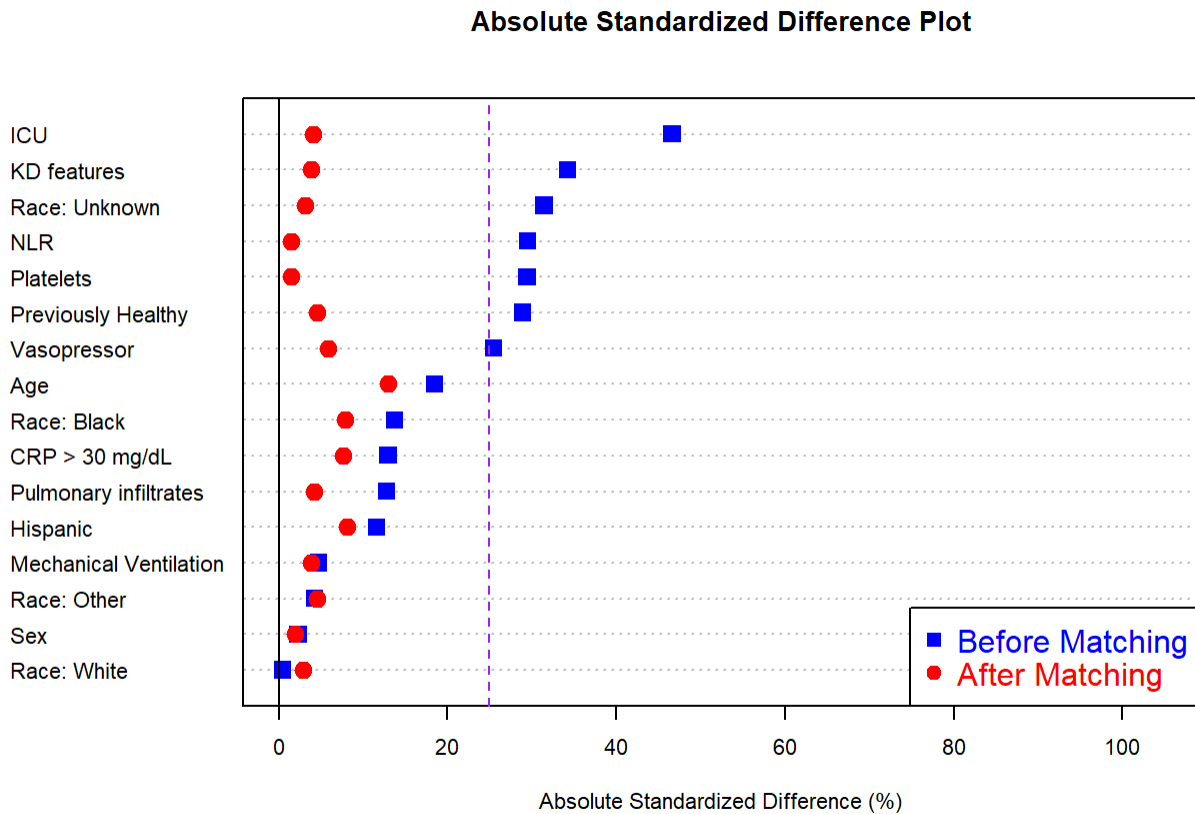
Variables denoted on y-axis include: demographics (age, race/ethnicity, absence of pre-existing conditions or "previously healthy", and sex); commonly measured laboratory markers of inflammation on day of admission (neutrophil to lymphocyte ratio [NLR], C-reactive protein [CRP], platelet count); and clinical observations or interventions (intensive care unit admission [ICU], Kawasaki disease-like features without severe cardiovascular or respiratory involvement at admission [KD features], vasopressor use, mechanical ventilation use; pulmonary infiltrates)

Figure S2: Propensity Score Distribution Comparison Post-Matching by Treatment
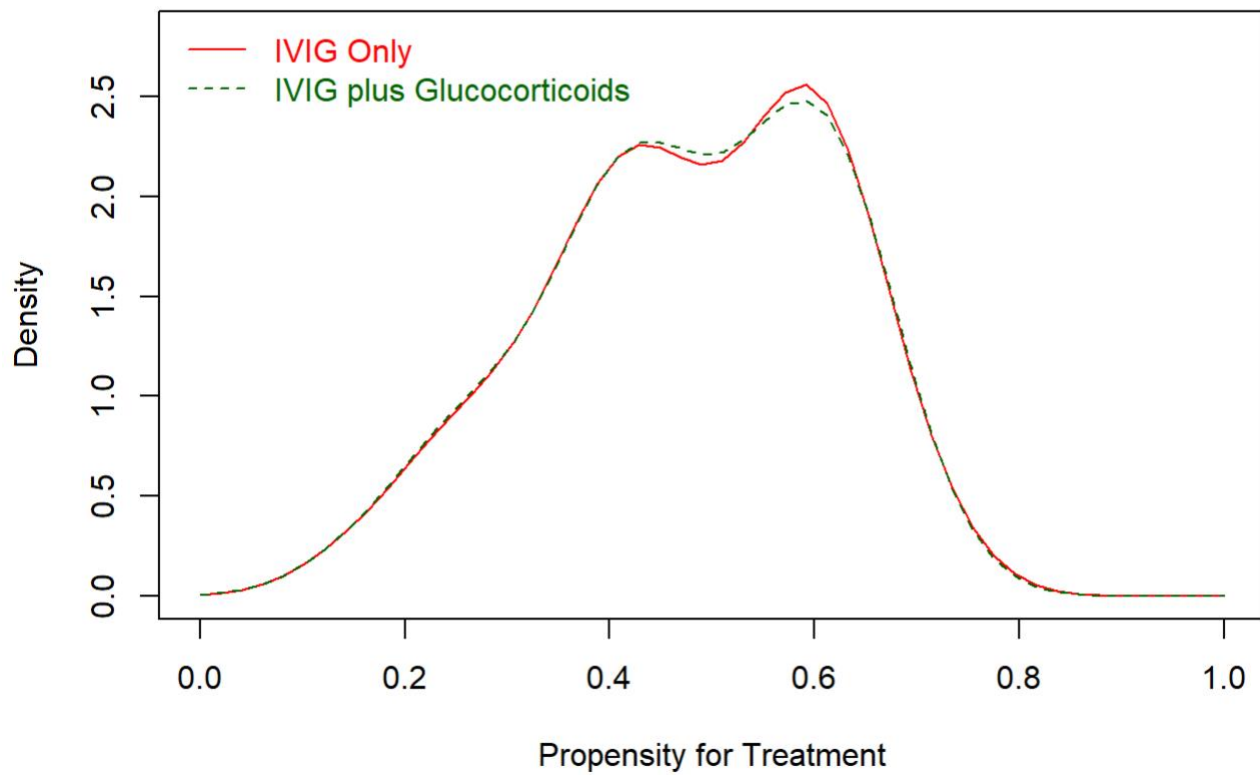
Distribution of propensity scores after matching Multisystem Inflammatory Syndrome in Children (MIS-C) patients with Index Treatment of IVIG plus Glucocorticoids (green, dashed line) versus IVIG alone (red, solid line)

Figure S3: Inverse Probability of Treatment Weights Distributions by Treatment
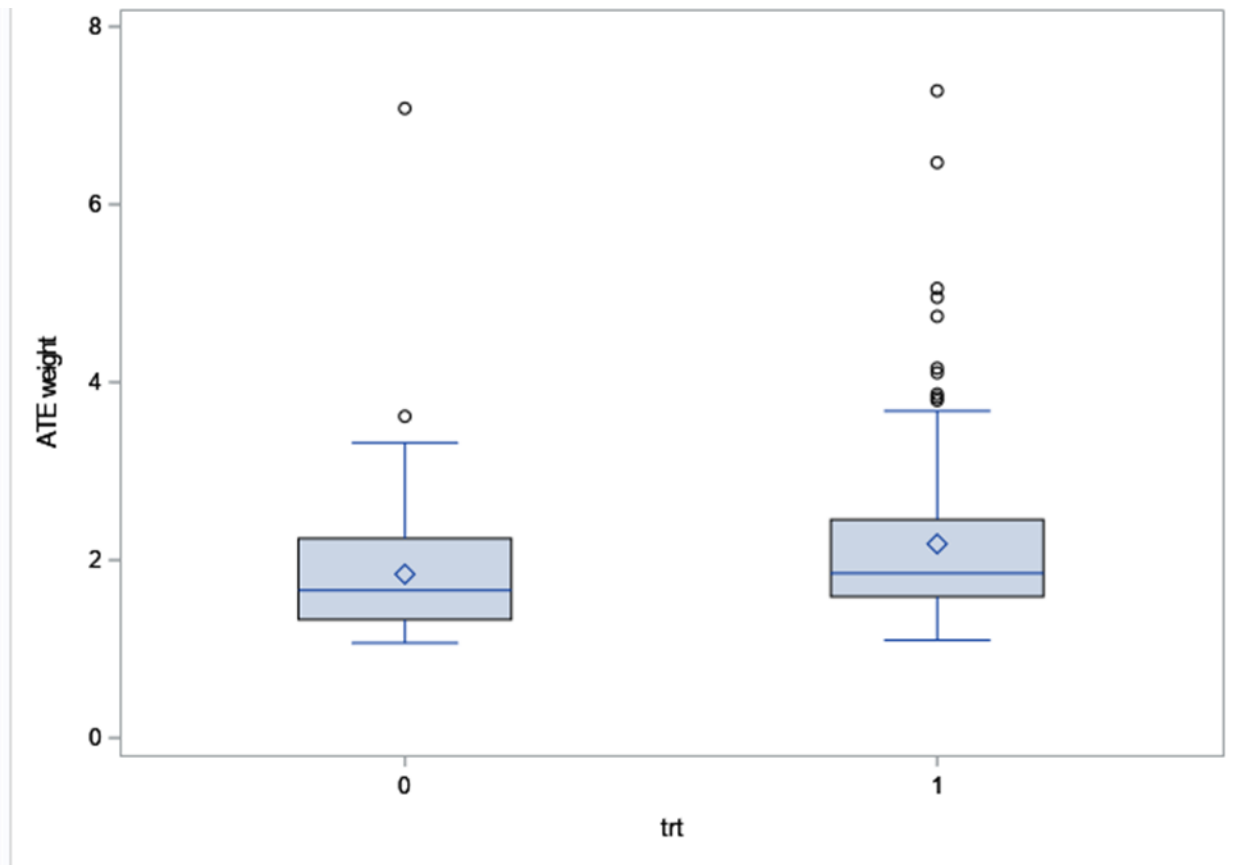
Distribution of inverse probability of treatment weights (ATE weight) for Multisystem Inflammatory Syndrome in Children (MIS-C) patients with Index Treatment of IVIG plus Glucocorticoids (shown as trt=1; median, 1.85; IQR, 1.59 to 2.46; minimum, 1.10; maximum, 7.28) versus IVIG alone (shown as trt=0; median, 1.66; IQR, 1.33 to 2.24; minimum, 1.07; maximum, 7.08).

Table S1: Clinical Characteristics of 9 Hospitalized Patients Aged <21 years that Died

	Age category (yrs)	Sex	Race/ethnicity	Obes-ity	Clinically documented underlying conditions	Treat-ment Strategy	ECMO	Primary listed cause of death
Patient 1	5-9	Male	Unknown	No	None	Other Treatment	Yes	Brain death/ severe brain injury
Patient 2	1-4	Female	White	No	Oncologic (neuroblastoma)	Other Treatment	Yes	Other
Patient 3	5-9	Male	White	Yes	Oncologic (leukemia), systemic hypertension, adrenal insufficiency	IVIG, Glucocor-ticoids, Biologic	No	Primary respiratory
Patient 4	10-14	Female	Hispanic or Latino	Yes	Severe congenital neurological disorder	Other Treatment	No	Multiorgan failure
Patient 5	10-14	Male	Black or African American	Yes	Asthma, chronic kidney disease, adrenal insufficiency	Other Treatment	No	Primary respiratory
Patient 6	15-21	Female	Hispanic or Latino	No	Oncologic (CNS tumor), spastic quadriplegia, seizure disorder, neuromuscular scoliosis	IVIG, Glucocor-ticoids, Biologic	Yes	Primary respiratory
Patient 7	15-21	Female	Black or African American	No	None	IVIG Only	Yes	Primary cardiac
Patient 8	15-21	Male	Black or African American	Yes	None	Other Treatment	Yes	Primary cardiac
Patient 9	5-9	Female	Hispanic or Latino	No	None	IVIG, Glucocor-ticoids, Biologic	No	Brain death/ severe brain injury

Table S2: Use of Immunomodulatory Medications: Day of Hospitalization and Dosing

Medication, number of patients	Median day of Hospitalization (IQR)	Median dose (IQR)
IVIG – First Dose, n = 466	1 (0, 2)	2 g/kg (1.7, 2)
IVIG – Second Dose, n = 125	2 (2, 3)	2 g/kg (1, 2)
IV Methylprednisolone, n = 353 • 2 mg/kg/day (n=284) • ≥10 and <20mg/kg/day (n=38) • ≥20 and < 30 mg/kg/day (n=13) • ≥30 mg/kg/day (n=18)	1 (0, 2)	2 mg/kg/day (1.5, 2.67)
IV Dexamethasone, n = 44	2 (0, 3.5)	0.3 mg/kg/day (0.15, 2)
Oral Prednisolone, n = 18	2 (0, 2.8)	2 mg/kg/day (1, 2.1)
Anakinra, n = 102	2 (1, 3.8)	4 mg/kg/day (2.2, 5.9)
Infliximab, n = 16	3 (2, 5)	10 mg/kg (9, 10)
Tocilizumab, n = 18	Not Available	Not Available

Abbreviations: IQR = interquartile range; IVIG = intravenous immunoglobulin; IV = intravenous

Table S3: Adjunctive Treatments on Day 1 or later after Initial Treatment with IVIG Plus Glucocorticoids or IVIG Alone on Day 0, by Pre and Post Propensity Score Matching

Adjunctive Treatments ≥Day 1 after Initial Treatment	Initial treatment			
	Pre-propensity score matching		Post-propensity score matching	
	IVIG Plus Glucocorticoids (N=157)	IVIG Alone (N=192)	IVIG Plus Glucocorticoids (N=103)	IVIG Alone (N=103)
Adjunctive Treatments (alone or combination)	65 (41%)	121 (63%)	36 (35%)	74 (72%)
Adjunctive Treatment - alone				
Glucocorticoids alone	0	63 (33%)	0	40 (39%)
Second Dose IVIG alone	35 (22%)	15 (8%)	25 (24%)	8 (8%)
Biologic alone	16 (10%)	8 (4%)	6 (6%)	5 (5%)
Adjunctive Treatment - combination				
Glucocorticoids and Second Dose IVIG	0	19 (10%)	0	13 (13%)
Glucocorticoids, Second Dose IVIG and Biologic	0	14 (7%)	0	7 (7%)
Second Dose IVIG and Biologic	14 (9%)	2 (1%)	5 (5%)	1 (1%)
Adjunctive Treatment – any [a]				
Glucocorticoids (any) [a]	0	96 (50%)	0	60 (58%)
Second Dose IVIG (any) [a]	49 (31%)	50 (26%)	30 (29%)	29 (28%)

Biologic (any) [a]	30 (19%)	24 (13%)	11 (11%)	13 (13%)

a: Treatments were not mutually exclusive - patients may have received these treatments alone or in combination with other adjunctive treatments

Table S4: Regression Details for the Propensity Score Model

	Coefficient Estimate	Standard Error Estimate
Intercept	-1.51	1.27
Male	0.11	0.26
Age	0.01	0.03
Race/Ethnicity		
White, non-Hispanic	0.07	1.16
Black, non-Hispanic	0.28	1.16
Other race, non-Hispanic	0.1	1.1
Unknown	-0.5	1.22
Hispanic or Latino ethnicity	0.39	1.19
Previously healthy	0.73	0.31
Pulmonary infiltrates on chest x-ray	0.11	0.3
Kawasaki disease signs without cardiorespiratory involvement	-0.69	0.49
Neutrophil-to-lymphocyte ratio	0.01	0.01
Platelets	-0.0007	0.001
C-reactive protein > 30 (mg/dL)	0.37	0.49
Intensive care unit admission	0.72	0.3
Vasopressor treatment	-0.09	0.31
Mechanical ventilation	-0.09	0.54

Model results from logistic regression with treatment as the outcome and listed covariates as linear predictors.

Model has a deviance of 368.6 and an Akaike Information Criterion value of 402.57.

Table S5: E-values to Assess Unmeasured Confounding in the Primary and Secondary Outcomes

	Statistic	
	E-value*	E-value Upper Limit**
Outcome		
Persistent cardiovascular dysfunction	2.970223	1.324414
Left ventricular dysfunction	3.771406	1
Vasopressor requirement	3.107839	1
Adjunctive immunomodulatory therapy	3.498251	2.448628
Persistent/recurrent fever	1.883387	1

*E-value interpretations: For the primary outcome, persistent cardiovascular dysfunction, the reported risk ratio could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 2.97-fold each. Similarly, for adjunctive immunomodulatory therapy, the reported risk ratio could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 3.50-fold each.

**E-value upper limit interpretations: For the primary outcome, persistent cardiovascular dysfunction, the reported risk ratio upper limit indicating statistical significance could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 1.32-fold each. Similarly, for adjunctive immunomodulatory therapy, the reported risk ratio

upper limit indicating statistical significance could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 2.45-fold each. Our propensity score models adjust for demographics, multiple markers of inflammation, and clinical observations of patients, making our study relatively robust to unmeasured confounding since the unmeasured confounder would need to be in causal pathways independent of our many included covariates' pathways to the treatment and outcome.

Note: secondary outcomes with reported risk ratio confidence intervals including 1 generally do not indicate evidence of association and thus will always have an E-value upper limit of 1. Therefore, we do not interpret these E-values individually.