Supplemental Online Content

Tripathi S, Nadiger M, McGarvey JS, et al; Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group. Association of early steroid administration with outcomes of children hospitalized for COVID-19 without multisystem inflammatory syndrome in children. *JAMA Pediatr*. Published online October 3, 2022. doi:10.1001/jamapediatrics.2022.3611

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

eMethods: Other measured variables and confounders

Race and ethnicity were self-reported separately. These were later categorized as composite index as non-Hispanic Asian, non-Hispanic black, non-Hispanic White, non-Hispanic others, and Hispanic as per the current CDC reporting on race/ethnicity disparities pertaining to COVID-19[1]. Race was included in the regression models as a proxy variable for socioeconomic disparities. However, due to some categories occurring infrequently, and in order to reduce the total number of parameters that would need to be estimated by the model with a limited sample size, race and ethnicity were collapsed into 2 categories (non-Hispanic white vs other). Inotrope/vasopressor included patients who received any predefined inotrope/vasopressor on any hospital day from day 0 to 14. Pediatric Risk of Mortality (PRISM III) [2] was determined using the online calculator if the summative score was not already entered by the individual site [3]. Patients' temperature was entered into the REDCap database on days 0-3, 7, 14, and 21. We defined fever as a temperature > 38°C. Besides steroids, other medication use assessed for this study included hydroxychloroquine, azithromycin, therapeutic anticoagulation, vitamin C, vitamin D, zinc, aspirin, convalescent plasma, IVIG, and biological agents. For descriptive analysis, medication was counted as administered if entered as given on any day of the hospitalization (days 0-14, day 21, and day 28). Only remdesivir administration on or prior to day 2 of admission was included as a confounder in the regression model.

The VIRUS database allows daily lab entries for days 0-3, 7, 14, and 21. For this analysis, the following inflammatory and other laboratory parameters were assessed: White cell count, platelet count, C-reactive protein, procalcitonin, ferritin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum albumin,

interleukin-6, brain natriuretic peptide (BNP), Pro-BNP, fibrinogen, D-dimer and lactate dehydrogenase (LDH). Maximum serum creatinine on days 1, 2, 3, 7, 14, and 21 were also obtained. They were then categorized as normal and abnormal based on standard cutoff levels.[4] Estimated GFR (eGFR) was calculated based on the bedside Schwartz equation.[5] Patients who required invasive respiratory or hemodynamic support during hospitalization were classified as having a critical illness.[6]

eReferences

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eAppendix: Propensity Score Matched analysis

2.1 Propensity Score Matching

A nearest neighbor based propensity score matching algorithm was used to match steroid treated and control patients on number of abnormal inflammatory mediators, remdesivir treatment, treatment outside the US, WHO ordinal score of ≥ 4 or ICU admission ≤2 days, Bacterial or viral coinfection on admission, comorbidity or obesity, ethnicity and age resulting in 184 patients per group. A threshold of 0.1 was used to judge balance using the standardized mean difference for continuous variables and the difference in proportions for binary variables. All matching variables fell under this threshold except Remdesivir treatment so it was included as a covariate with steroid treatment within 2 days in a mixed linear regression on log transformed hospital LOS with site included as a random intercept. The results found no significant effect for steroid treatment (exp coef = 1.04, 95% CI = 0.88, 1.24, p = 0.627). Steroid treated patients had an expected geometric mean hospital LOS of 4.41 days (95% CI = 3.44, 5.59) compared to 4.19 days (95% CI = 3.30, 5.27) in the control group. Remdesivir treatment was significantly associated with longer LOS (exp coef = 1.89, 95% CI = 1.53, 2.32, p < 0.001).

2.2 Inverse Probability Treatment Weights

Average treatment effect among the treated (ATT) inverse probability treatment weights (IPTW) were calculated based on the propensity score for treatment using the same predictors used for propensity score matching. Weights were trimmed at the 1st and 99th percentile, meaning weights below the 1st percentile were replaced with the 1st percentile and weights above the 99th percentile were set at the 99th percentile. The weights were incorporated into a linear mixed effects model using the log transformed hospital LOS as the outcome and steroid treatment as the

predictor with a random intercept for site. The results found no significant effect for steroid treatment (exp coef = 1.06, 95% CI = 0.96, 1.18, p = 0.24). Steroid treated patients had an expected geometric mean hospital LOS of 5.77 days (95% CI = 4.55, 7.25) compared to 5.37 days (95% CI = 4.24, 6.74) in the control group.

eTable 1: Inflammatory mediators and other laboratory parameters on admission

	Category	Unit/Normal value cutoffs	Total Cohort	No steroids	Yes Steroids	*P* value
	Continuous					
1	White cell count	X 10^9 cells/L	8.5 (5.4, 12.6) n = 473	8.5 (5.4, 12.6) n = 368	8.2 (5.4, 13.4) n = 105	0.74
2	Platelet count	X 10^9cells/L	260 (193.5, 345.7) n = 512	269 (206, 363) n = 397	209 (157, 291) n= 115	<0.001
3	CRP	mg/L	5.1 (1.5, 25.3) n = 318	4.5 (1.5, 21.6) n= 236	4.5 (2.0, 40.1) n= 82	0.03
4	Pro-calcitonin	ng/mL	0.14 (0.07, 0.45) n = 200	0.14 (0.07, 0.53) n = 150	0.11 (0.05, 0.35) n = 50	0.13
5	Ferritin	mcg/L	135.5 (51.4, 349.7) n = 156	130.5 (50.9, 328.7) n = 102	147.5 (55.0, 449.7) n = 54	0.41
6	AST	U/L	38 (26.2, 56.7) n = 421	38 (28, 56) n = 315	35.5 (24.5, 60) n= 106	0.29
7	ALT	U/L	26 (17, 44) n = 424	26 (17, 42) n= 316	27 (16.2, 55.5) n= 108	0.72
8	Serum albumin	g/dL	4 (3.5, 4.4) n = 415	4 (3.5, 4.4) n= 309	3.8 (3.2, 4.2) n = 106	0.02
9	IL-6	pg/mL	6.4 (3.9, 15) n = 28	5.4 (3.6, 15) n= 19	7 (4.5, 54.8) n= 9	0.47
10	BNP	pg/mL	20.7 (10, 85) n = 58	32.5 (10.7, 93.5) n = 34	15.5 (10, 46) n = 24	0.16
11	NT Pro BNP	pg/mL	173.5 (32.5, 949.2) n = 48	224 (38, 776) n = 30	93.6 (14.3, 1007.2) n = 18	0.44
12	Fibrinogen	mg/dL	324 (254, 471) n = 114	310 (243, 447) n = 73	388 (271.5, 535.5) n= 41	0.07
13	D-dimer	mcg/mL	0.56 (0.29, 1.38) n = 177	0.60 (0.30, 1.61) n = 107	0.52 (0.27, 0.94) n = 70	0.33
14	LDH	U/L	346.5 (244.5, 595.7) n = 126	330 (238.7, 627) n= 86	359 (257.5, 544.7) n = 40	0.81
15	eGFR	mL/min/1.73m^2	93.4 (76.9, 120.6) n = 436	94.6 (76.6, 122.2) n = 338	91.8 (79.3, 113.1) n = 98	0.58
	Categorical (Percentage abnormal)					
1	White cell count	Age-based*	222/473 (46.9%)	176/368 (47.8%)	46/105 (43.8%)	0.47
2	Platelet count	Age-based*	151/512 (29.4%)	115/397 (28.9%)	36/115 (31.3%)	0.62
3	CRP	≤ 8 mg/L	139/318 (43.7%)	94/236 (39.8%)	45/82 (54.8%)	0.01
4	Pro-calcitonin	≤ 0.15	94/200 (47.0%)	73/151 (48.3%)	21/52 (40.04%)	0.32
5	Ferritin	< 336	40/156 (25.6%)	24/102 (23.5%)	16/54 (29.6%)	0.40
6	AST	Age-based*	115/421 (27.3%)	84/315 (26.6%)	31/106 (29.3%)	0.60
7	ALT	Age-based*	116/424 (27.3%)	82/316 (25.9%)	34/108 (31.4%)	0.26
8	Serum albumin	≥3.5 g/dL	102/415 (24.5%)	65/309 (21.0%)	37/106 (34.9%)	0.004
9	IL-6	≤ 1.8 pg/mL	27/28 (96.4%)	19/19 (100%)	8/9 (88.9%)	0.32
10	BNP	<100 pg/mL**	11/58 (18.9%)	7/34 (20.6%)	4/24 (16.7%)	>0.99
11	NT Pro BNP	< 140 pg/mL*	25/48 (52.0%)	18/30 (60.0%)	7/18 (38.9%)	0.15

	Category	Unit/Normal value cutoffs	Total Cohort	No steroids	Yes Steroids	*P* value
	Continuous					
12	Fibrinogen	200-393*	53/114 (46.5%)	32/73 (43.8%)	21/41 (51.2%)	0.44
13	D-dimer	<0.25	142/177 (80.2%)	86/107 (80.3%)	56/70 (80.0%)	0.95
14	LDH	Age-based*	69/126 (54.7%)	45/86 (52.3%)	24/40 (60.0%)	0.44

Missing/not done Leukocyte count 690 (59.3%), Missing/not done platelets 651 (56.0%), Missing/not done CRP 845 (72.7%), Missing/not done pro calcitonin 963 (82.8%), Missing/not done ferritin 1007 (86.6%), Missing/not done AST 742 (63.8%), Missing/not done ALT 739 (63.5%), Missing/not done serum albumin 748 (64.3%), Missing/not done interleukin 6 1135 (97.6%), Missing/not done BNP 1105 (95.0%), Missing/not done NT BNP 1115 (95.9%), Missing/not done fibrinogen 1049 (90.2%), Missing/not done d-dimer 986 (84.8%), Missing/not done LDH 1037 (89.2%).

Values represent median (interquartile range) or frequency (percentage) as appropriate.

*Reference: https://www.mayocliniclabs.com/test-catalog. Date accessed 09/22/2021.

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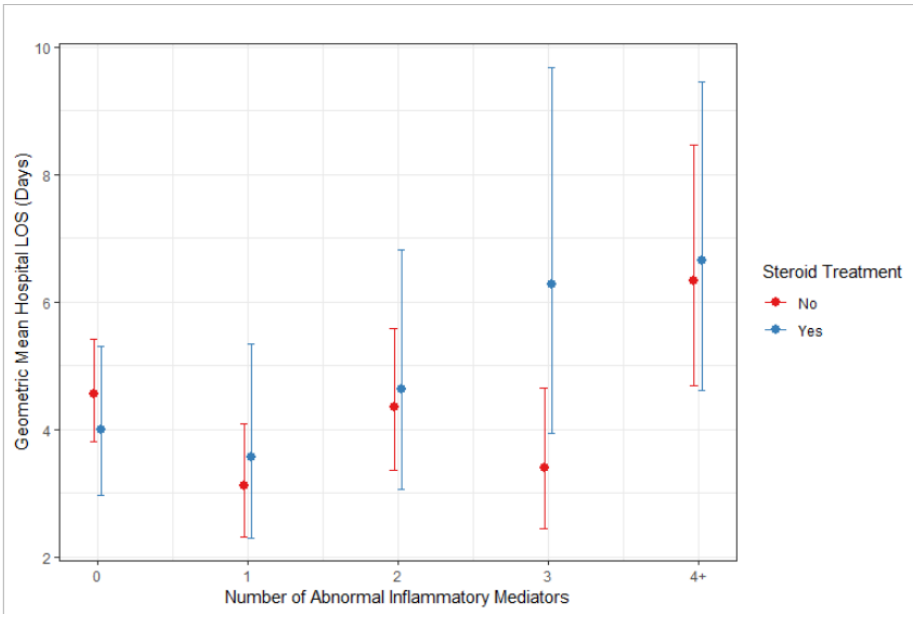
eTable 2: Supplemental multiple regression analysis of hospital length of stay

Variable	Exp coef	95% C.I	*P* value	R
Only including patients with LOS ≥ 2 days[a] (N=729)				
Steroid treatment ≤2 days	0.93	0.78, 1.11	0.414	0.030
Number of abnormal inflammatory mediators	1.05	1.00, 1.09	0.042	0.081
Non-US site	1.75	1.35, 2.26	< 0.001	0.230
Remdesivir treatment ≤ 2 days	1.06	0.88, 1.28	0.515	0.024
Bacterial or viral coinfection at admission	1.20	1.03, 1.41	0.022	0.083
WHO ordinal scale ≥ 4 or ICU admission within ≤ 2 days	1.24	1.10, 1.38	< 0.001	0.138
Obesity or comorbidity	1.14	1.02, 1.28	0.025	0.085
Not White non-Hispanic race	0.96	0.86, 1.06	0.408	0.030
Age	1.01	1.00, 1.02	0.012	0.091
Steroid treatment ≤ 2 days *number of abnormal inflammatory mediators	1.07	1.00, 1.15	0.036[d]	0.077
Only Including patients with WHO Ordinal Score ≥ 4 on admission (respiratory support on admission)[b] (N=286)				
Steroid treatment ≤2 days	1.16	0.91, 1.47	0.237	0.067
Number of abnormal inflammatory mediators	1.20	1.11, 1.29	< 0.001	0.277
Non-US site	1.89	1.15, 3.10	0.013	0.202
Remdesivir treatment ≤ 2 days	1.26	1.00, 1.59	0.051	0.109
Bacterial or viral coinfection at admission	1.19	0.92, 1.53	0.189	0.074
ICU admission within ≤ 2 days	1.26	1.04, 1.51	0.018	0.132
Obesity or comorbidity	1.01	0.81, 1.26	0.936	0.004
Not White non-Hispanic race	1.02	0.84, 1.25	0.827	0.012
Age	1.01	0.99, 1.02	0.222	0.066
Steroid treatment ≤ 2 days *number of abnormal inflammatory mediators	0.96	0.88, 1.05	0.381	0.049
Patients with Missing MIS-C Diagnosis Excluded (N = 1003)[c]				
Steroid treatment ≤2 days	0.95	0.82, 1.11	0.513	0.020
Number of abnormal inflammatory mediators	1.10	1.06, 1.15	< 0.001	0.152
Non-US site	2.20	1.62, 3.00	< 0.001	0.272
Remdesivir treatment ≤ 2 days	1.26	1.05, 1.52	0.013	0.075
Bacterial or viral coinfection at admission	1.20	1.04, 1.38	0.011	0.077
WHO ordinal scale ≥ 4 or ICU admission within ≤ 2 days	1.47	1.33, 1.62	< 0.001	0.224
Obesity or comorbidity	1.21	1.09, 1.34	< 0.001	0.110
Not White non-Hispanic race	0.98	0.89, 1.08	0.699	0.012
Age	1.01	1.00, 1.02	0.002	0.093
Steroid treatment ≤ 2 days *number of abnormal inflammatory mediators	1.04	0.97, 1.11	0.259	0.034

[a] R^2 15.4%, [b] R^2 24.8%, [c] R^2 25.1

[d]The significant positive interaction between steroids and the number of inflammatory mediators in patients with length of stay ≥ 2 days suggest that as the number of inflammatory mediators increase, the difference in length of stay between steroid and control patients would increase, with the steroid treated patients having a longer length of stay. To further analyze this association, a stratified analysis based on the number of abnormal inflammatory mediators (categorized as 0, 1, 2, 3 and 4+) was performed with inclusion of the categorized

number of abnormal inflammatory mediators instead of the numeric variable in the regression analysis. The results found a significant interaction **only** between steroid treatment and three abnormal inflammatory mediators (exp coefficient 1.83, 95% CI 1.18, 2.85, p= 0.008). Suggesting that the difference in length of stay between steroid and control patients is significantly greater when they have three abnormal inflammatory mediators compared to when they have zero abnormal inflammatory mediators; but not with any other number of abnormal inflammatory mediators. (Figure)



The impact was specific to three abnormal inflammatory mediators, which seems to be driving the overall interaction. It is possible that this association is due to presence of another variable which is not controlled in our analysis.

eTable 3: Logistic Regression analysis for select secondary variables

Variable	aOdds ratio	95% CI	*P* value
Fever Defervescence by day 3			
Steroid treatment ≤2 days	1.02	0.86, 1.21	0.830
Number of abnormal inflammatory mediators	1.04	1.01, 1.08	0.015
Non-US site	0.79	0.64, 0.97	0.028
Remdesivir treatment ≤ 2 days	0.97	0.81, 1.16	0.746
Bacterial or viral coinfection at admission	1.07	0.93, 1.22	0.337
WHO ordinal scale ≥ 4 or ICU admission within ≤ 2 days	1.00	0.89, 1.12	0.972
Obesity or comorbidity	1.06	0.95, 1.19	0.285
Not White non-Hispanic race	1.00	0.90, 1.12	0.952
Age	0.98	0.98, 0.99	< 0.001
Steroid treatment ≤ 2 days *number of abnormal inflammatory mediators	1.00	0.94, 1.06	0.905
Normalization of Inflammatory Mediators by day 3			
Steroid treatment ≤2 days	1.03	0.84, 1.26	0.759
Number of abnormal inflammatory mediators	1.09	1.05, 1.13	< 0.001
Non-US site	1.05	0.87, 1.27	0.620
Remdesivir treatment ≤ 2 days	1.05	0.91, 1.21	0.531
Bacterial or viral coinfection at admission	1.06	0.95, 1.19	0.297
WHO ordinal scale ≥ 4 or ICU admission within ≤ 2 days	1.05	0.95, 1.17	0.332
Obesity or comorbidity	1.15	1.04, 1.28	0.009
Not White non-Hispanic race	0.95	0.86, 1.05	0.309
Age	1.01	1.00, 1.02	0.063
Steroid treatment ≤ 2 days *number of abnormal inflammatory mediators	1.00	0.94, 1.06	0.878

eTable 4: Simple bivariate comparison of rare secondary outcome of Interest.

Variable	Steroid treatment		*P* value
	No (n= 979)	Yes (n= 184)	
Hospital mortality	6 (0.61%)	5 (2.7%)	0.02
Nosocomial bacterial infection[a]	7 (0.72%)	2 (1.09%)	0.64
Inotropes needed after D1[b]	5 (0.51%)	5 (2.7%)	0.01
Hyperglycemia complication[c]	11 (1.12%)	8 (4.3%)	0.005
Noninvasive or invasive mechanical ventilation ≥ day 1[d]	10 (1.02%)	8 (4.3%)	0.004

[a] positive blood/urine, or respiratory culture ≥Day 2; [b] no inotropes requirement at admission day +1; [c] excluding patients with DKA; [d] no invasive or noninvasive ventilator requirement on admission day +1.