Supplemental material

Supplemental material index

admission to transfusion (N=1939). Simple slope analyses were conducted for the decomposition of the significant interaction two separate ways: to examine the impact of high serology versus low serology across number of days from admission to transfusion, and to examine the impact of 0-3 days to transfusions versus 4+ days to transfusion across level of serology.

Supplemental Table 8. Medication list by categories. Description of medications that were included into each medication category.

Supplemental Table 9. Calendar epoch intervals. Definitions of six calendar epochs used to account for changes in HCA treatment recommendations for patients hospitalized with COVID-19 over time in 2020.

Supplemental Table 10. WHO progression score (WHO PS) categories. List defining the modified 6-point WHO progression score categories (WHO PS) used to match for baseline disease severity.

Supplemental methods

Patient encounters. For patients that had multiple hospital admissions within the date range of the data pull, we identified the longest encounter that was within the determined window of the first positive SARS-CoV-2 test and proceeded to link encounters, before and/or after, that were within 36 hours of that longest encounter's admission and discharge times to create a continuum of care to adequately evaluate the disease course. For the CP group, the anchoring encounter included the first transfusion date of CP and before and after encounters within 36 hours were linked as already described.

Comparison group pseudo-baseline assignment. The day of the first CP transfusion was considered baseline (day 0) for the CP group. The comparison group was automatically assigned a pseudo-baseline prior to matching that reflected equal distribution of the time interval from admission to transfusion as the CP group. Since the distribution of baseline dates was randomly assigned, there was a potential to assign a pseudo-baseline after a patient's discharge date. To minimize this issue, we stratified the sample into different treatment epoch intervals before assigning the pseudo-baseline to the comparison group (Table S5). We removed any comparison patients that were discharged prior to their assigned pseudo-baseline (Figure 1)

Epoch intervals for evolving treatment recommendations. The time interval from admission to CP transfusion decreased over time when investigating calendar dates. To account for this shift, we created date ranges that aligned with updates in HCA treatment recommendations which resulted in six epoch intervals which including March 2 to April 2, April 3 to April 29, April 30 to May 19, May 20 to July 5, July 6 to August 23, and August 24 to September 28. For an in-depth description of these clinico-demographic shifts, see Table S2. Additionally, we used epoch interval as a matching variable in our analyses. Since there were still major shifts in treatment approaches and hotspots for COVID19 cases within each epoch interval, we also included a covariate of a numerated calendar date for patient admission.

Matching and covariates. A variety of patient characteristics were captured at baseline that were considered for matching criteria. Demographic characteristics included age, sex, and race/ethnicity. Age ranges were grouped 18-44, 45-64, 65-74, 75-84, and over 84 (1). Baseline severity was matched on either the 6-point WHO PS, where only 2 to 5 were possible at baseline, or baseline RTRM probabilities in increments of 0.10. Additional clinical characteristics were included in matching such as preadmission comorbidities (as detailed below), admission epoch interval, and intubation during hospitalization. Due to missingness of smoking status (~20%), we provided these data descriptively but excluded them from inferential analyses. Body mass index was found to be unreliably reported, especially for non-ambulatory patients, so it was excluded from all evaluations.

Covariates for models were considered for patient data that were related to the hospital stay. Treatment characteristics included pharmacy data: in-hospital administration of other medications inclusive of anticoagulants, statins/ACEi, steroids, other immunomodulators, antivirals, antibiotics, remdesivir, hydroxychloroquine (HCQ), tocilizumab, and azithromycin (Table S4), where ACEi is Angiotensin converting enzyme inhibitors. Azithromycin was considered a separate medication grouping from antibiotics because it was often used in conjunction with HCQ and/or for its additional anti-inflammatory properties. SARS-CoV-2 monoclonal antibodies were not authorized (EUA) for use in hospitalized patients prior to our data pull so no instances of monoclonal infusion occurred in our cohort (2). Medications were computed as indicators of usage over the length of hospitalization. Secondary infections were considered such as bacterial pneumonia, sepsis, and severe sepsis but were included in the RTRM calculations and, thus, were not included in the RTRM-matched models. However, secondary infections were included as covariates in the WHO PS-matched models. Although epoch intervals were included in the matching criteria, we included numerated calendar date as a covariate to account for the fluctuations within the epoch intervals. Finally, since all inferential analyses started with day 0 at transfusion date/pseudo-baseline, the number of days from admission to baseline was also included in the models as a covariate.

Comorbidities included in the RTRM were based on the Charlson Comorbidity Index and included diabetes with chronic complications, diabetes without chronic complications, all-inclusive diabetes, hypertension, chronic ischemic heart disease, congestive heart failure, renal disease (mild or moderate), renal disease (severe), asthma or reactive airway disease, chronic pulmonary disease (excluding asthma), HIV infection, cancer (including solid tumors and blood cancers but excluding non-melanoma skin cancer), and recently diagnosed cancer within two years of admission date (3, 4). For the current analyses, we also accounted for both organ-specific and systemic autoimmune diseases (5).

Analytic Software. All analyses were performed using R v3.6.3 with the following packages: “cem”, “survival”, "coxme", "lme4" (6). The pseudo-baseline assignment was conducted using an automated macro in SAS 9.4 (SAS Inc., Cary NC) (7).

Supplemental references

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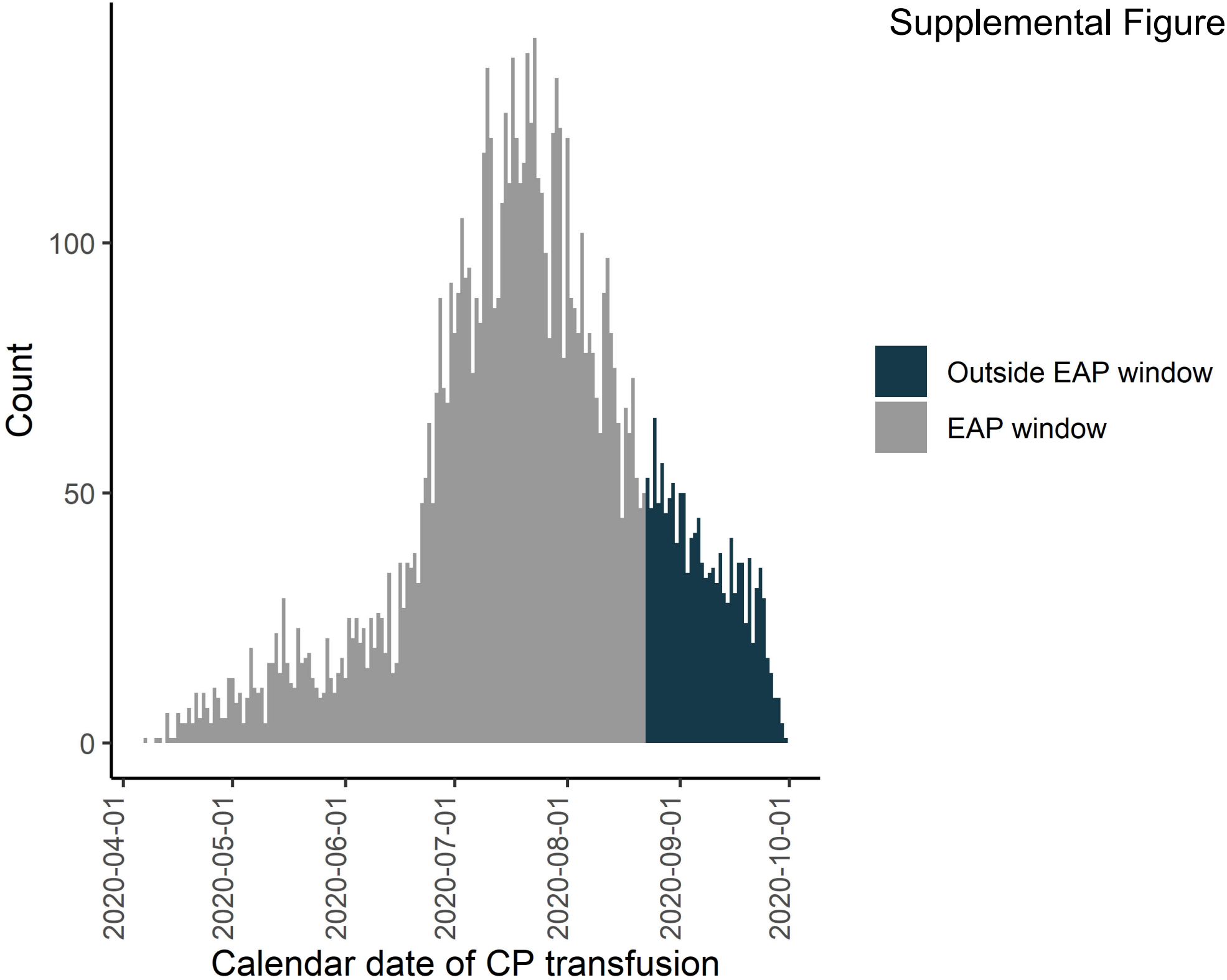
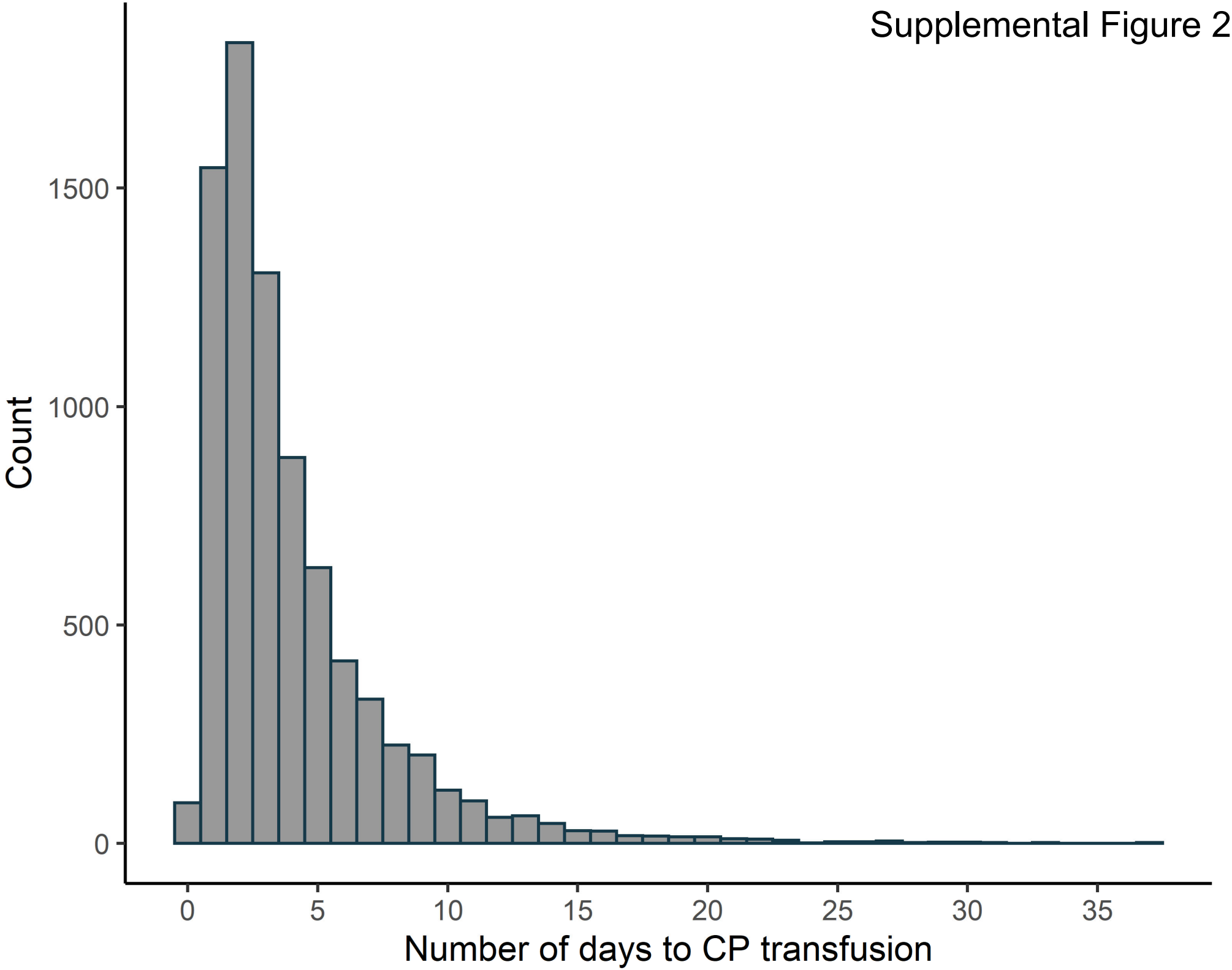
Supplemental Figure 1



Supplemental Figure 2



Supplemental tables

Supplemental Table 1. Demographics for WHO PS-matched model

	Pre-match CP	Pre-match comparison	Post-match CP	Post-match comparison
Total number of patients, N	7419	22234	4337	8708
Age groupings[M]				
18-44	955 (12.9%)	3544 (15.9%)	680 (15.7%)	1365 (15.7%)
45-64	2866 (38.6%)	7262 (32.7%)	1900 (43.8%)	3815 (43.8%)
65-74	1720 (23.2%)	4457 (20.0%)	857 (19.8%)	1721 (19.8%)
75-84	1323 (17.8%)	3999 (18.0%)	615 (14.2%)	1235 (14.2%)
85+	555 (7.5%)	2972 (13.4%)	285 (6.6%)	572 (6.6%)
Race/ethnicity[M]				
Hispanic	3260 (43.9%)	7242 (32.6%)	2153 (49.6%)	4323 (49.6%)
Non-Hispanic black	1156 (15.6%)	5069 (22.8%)	560 (12.9%)	1124 (12.9%)
Non-Hispanic other[#]	462 (6.2%)	1242 (5.6%)	215 (5.0%)	432 (5.0%)
Non-Hispanic white	2541 (34.2%)	8681 (39.0%)	1409 (32.5%)	2829 (32.5%)
Sex[M]				
Female	3093 (41.7%)	10986 (49.4%)	1733 (40.0%)	3480 (40.0%)
Male	4326 (58.3%)	11248 (50.6%)	2604 (60.0%)	5228 (60.0%)
Smoking status				
Current smoker	263 (3.5%)	1297 (5.8%)	134 (3.1%)	370 (4.2%)
Former smoker	1455 (19.6%)	3888 (17.5%)	746 (17.2%)	1372 (15.8%)
Never smoker	4827 (65.1%)	13277 (59.7%)	3002 (69.2%)	5706 (65.5%)
Missing	868 (11.7%)	3772 (17.0%)	455 (10.5%)	1260 (14.5%)
Pre-admission comorbidities				
Asthma or reactive airway disease	711 (9.6%)	2255 (10.1%)	308 (7.1%)	604 (6.9%)
COPD (excluding asthma) [M]	1430 (19.3%)	4699 (21.1%)	428 (9.9%)	859 (9.9%)
Autoimmune disorders	885 (11.9%)	2785 (12.5%)	104 (2.4%)	209 (2.4%)
Organ-related autoimmune disorders[M]	440 (5.9%)	1764 (7.9%)	53 (1.2%)	106 (1.2%)
Systemic autoimmune disorders[M]	510 (6.9%)	1275 (5.7%)	53 (1.2%)	106 (1.2%)
Cancer	425 (5.7%)	1431 (6.4%)	52 (1.2%)	104 (1.2%)
Cancer (diagnosed in the last 2 years)	230 (3.1%)	785 (3.5%)	28 (0.6%)	51 (0.6%)
Chronic ischemic heart disease[M]	1556 (21.0%)	5166 (23.2%)	518 (11.9%)	1040 (11.9%)
Congestive heart failure[M]	1358 (18.3%)	4589 (20.6%)	400 (9.2%)	803 (9.2%)

Diabetes	3233 (43.6%)	9128 (41.1%)	1394 (32.1%)	2783 (32%)
Diabetes with chronic complications	1412 (19.0%)	4278 (19.2%)	453 (10.4%)	893 (10.3%)
Diabetes without chronic complications[M]	1821 (24.5%)	4850 (21.8%)	941 (21.7%)	1889 (21.7%)
HIV infection	33 (0.4%)	125 (0.6%)	12 (0.3%)	26 (0.3%)
Hypertension	4704 (63.4%)	14733 (66.3%)	2215 (51.1%)	4447 (51.1%)
Renal disease (mild or moderate) [M]	1156 (15.6%)	3888 (17.5%)	388 (8.9%)	779 (8.9%)
Renal disease (severe)	495 (6.7%)	1372 (6.2%)	95 (2.2%)	191 (2.2%)

Categorical data are N (%) and continuous variables are presented as median [IQR]. IQR=interquartile range;
CP=Convalescent Plasma; COPD=Chronic obstructive pulmonary disease
[M] indicates variables used for CEM matching
[#] other is defined as 60% recorded in the medical record as "other" race where the remaining 40% includes reported race of American Indian/Alaska Native, Asian, Asian Indian, Native Hawaiian/Other Pacific Islander, or multiracial.

Supplemental Table 2. Clinical characteristics for WHO PS-matched model

	Pre-match CP	**Pre-match comparison**	**Post-match CP**	**Post-match comparison**
Total number of patients, N	7419	22234	4337	8708
Medications				
Anticoagulants	7257 (97.8%)	19482 (87.6%)	4235 (97.6%)	8259 (94.8%)
Azithromycin	5462 (73.6%)	14061 (63.2%)	3180 (73.3%)	6424 (73.8%)
Antibiotics – other	6731 (90.7%)	18453 (83.0%)	3823 (88.1%)	7677 (88.2%)
Antivirals	165 (2.2%)	475 (2.1%)	68 (1.6%)	133 (1.5%)
Hydroxychloroquine	434 (5.8%)	2586 (11.2%)	188 (4.3%)	316 (3.6%)
Remdesivir	4563 (61.5%)	3171 (14.3%)	2597 (59.9%)	2946 (33.8%)
Tocilizumab	788 (10.6%)	561 (2.5%)	347 (8%)	475 (5.5%)
Statins	2970 (40.0%)	8276 (37.2%)	1487 (34.3%)	2636 (30.3%)
Systemic corticosteroids	7017 (94.6%)	12951 (58.2%)	4115 (94.9%)	7307 (83.9%)
Immunomodulators – other	12 (0.2%)	22 (0.1%)	2 (0.0%)	4 (0.0%)
Clinical variables				
Intubation[M]	1302 (17.5%)	827 (3.7%)	222 (5.1%)	446 (5.1%)
All-cause death	1543 (20.8%)	1526 (6.9%)	505 (11.6%)	852 (9.8%)
Baseline RTRM score	0.14 [0.04, 0.45]	0.05 [0.02, 0.13]	0.08 [0.02, 0.25]	0.07 [0.02, 0.20]
Admission WHO PS				
WHO PS 2	867 (11.7%)	7968 (35.8%)	476 (11%)	1181 (13.6%)
WHO PS 3	3834 (51.7%)	11416 (51.3%)	2466 (56.9%)	4521 (51.9%)

WHO PS 4	2539 (34.2%)	2298 (10.3%)	1349 (31.1%)	2807 (32.2%)
WHO PS 5	148 (2.0%)	278 (1.3%)	31 (0.7%)	99 (1.1%)
Missing	35 (0.5%)	274 (1.2%)	15 (0.3%)	99 (1.1%)
Baseline WHO PS[M]				
WHO PS 2	247 (3.3%)	7366 (33.1%)	165 (3.8%)	331 (3.8%)
WHO PS 3	2510 (33.8%)	11358 (51.1%)	1910 (44%)	3835 (44%)
WHO PS 4	4011 (54.1%)	2949 (13.3%)	2182 (50.3%)	4381 (50.3%)
WHO PS 5	651 (8.8%)	561 (2.5%)	80 (1.8%)	161 (1.8%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Secondary infections				
Bacteremia	45 (0.6%)	154 (0.7%)	20 (0.5%)	52 (0.6%)
Bacterial pneumonia	434 (5.8%)	672 (3.0%)	167 (3.9%)	316 (3.6%)
Sepsis	2030 (27.4%)	4954 (22.3%)	1323 (30.5%)	2269 (26.1%)
Severe sepsis	1891 (25.5%)	2642 (11.9%)	766 (17.7%)	1367 (15.7%)

Categorical data are N (%) and continuous variables are presented as median [IQR]. IQR=interquartile range; RTRM=Real-time Risk Model; CP=Convalescent Plasma; WHO PS=World Health Organization Progression Score

[M] indicates variables used for CEM matching

Supplemental Table 3. Admission and baseline biomarkers for WHO PS-matched model

	Pre-match CP	**Pre-match comparison**	**Post-match CP**	**Post-match comparison**
Total number of patients, N	7419	22234	4337	8708
Admission biomarkers				
Absolute lymphocyte count x10^3/uL	1.0 [0.7, 1.5]	1.0 [0.7, 1.5]	0.9 [0.6, 1.2]	1.0 [0.7, 1.3]
Absolute neutrophil count x10^3/uL	5.1 [3.4, 7.6]	5.1 [3.4, 7.6]	6.1 [4.1, 8.8]	6.2 [4.2, 8.9]
Alanine aminotransferase units/L	31 [21, 51]	31 [21, 51]	39 [26, 62]	38 [26, 61]
Aspartate aminotransferase units/L	38 [26, 59]	38 [26, 59]	48 [34, 70]	45 [32, 66]
C reactive protein mg/dL	7.1 [3.2, 13.2]	7.1 [3.3, 13.3]	11.0 [6.0, 17.7]	10.0 [5.3, 16.8]
D-dimer ng/mL DDU	485 [298, 881]	485 [298, 883]	458 [297, 788]	483 [302, 800]
Ferritin ng/mL	385 [172, 808]	389 [174, 815]	572 [288, 1020]	532 [260, 1009]
Hemoglobin A1c	6.8 [6.0, 9.0]	6.9 [6.0, 9.0]	7.0 [6.1, 9.3]	7.0 [6.1, 8.9]
Interleukin-6 pg/mL	37.2 [14.0, 89.0]	37.4 [14.1, 90.2]	40.5 [16.9, 98.0]	49.2 [17.0, 122.5]
Lactic acid blood mmol/L	1.4 [1.0, 1.9]	1.4 [1.1, 1.9]	1.5 [1.2, 1.9]	1.5 [1.2, 1.9]
Lactate dehydrogenase – Serum/Plasma U/L	299 [225, 408]	300 [225, 411]	374 [287, 504]	365 [276, 488]

Procalcitonin ng/mL	0.17 [0.09, 0.49]	0.17 [0.09, 0.50]	0.20 [0.10, 0.50]	0.2 [0.10, 0.53]
Serum creatinine mg/dL	1.00 [0.78, 1.40]	1.0 [0.78, 1.40]	0.97 [0.78, 1.24]	0.95 [0.75, 1.24]
Total bilirubin mg/dL	0.5 [0.4, 0.8]	0.5 [0.4, 0.8]	0.6 [0.4, 0.8]	0.6 [0.4, 0.8]
Troponin I ng/mL	0.03 [0.02, 0.09]	0.04 [0.02, 0.09]	0.03 [0.01, 0.07]	0.03 [0.01, 0.09]
White blood cell count x10^3/uL	7.0 [5.1, 9.7]	6.9 [5.1, 9.7]	7.5 [5.5, 10.3]	7.8 [5.7, 10.8]
Baseline biomarkers				
Absolute lymphocyte count x10^3/uL	1.0 [0.7, 1.5]	1.0 [0.7, 1.5]	0.9 [0.6, 1.2]	1.0 [0.6, 1.4]
Absolute neutrophil count x10^3/uL	5.4 [3.5, 8.5]	5.4 [3.5, 8.5]	7.9 [5.3, 10.9]	7.3 [4.7, 10.4]
Alanine aminotransferase units/L	34 [21, 59]	34 [22, 59]	43 [28, 70]	42 [28, 70]
Aspartate aminotransferase units/L	37 [25, 59]	37 [26, 59]	42 [29, 62]	40 [28, 61]
C reactive protein mg/dL	5.1 [2.3, 9.9]	5.1 [2.3, 10.0]	5.9 [3.0, 11.2]	5.4 [2.4, 10.9]
D-dimer ng/mL DDU	500 [298, 915]	500 [298, 915]	484 [290, 931]	478 [300, 895]
Ferritin ng/mL	421 [195, 823]	424 [198, 828]	589 [324, 995]	530.84 [259, 959]
Hemoglobin A1c	6.9 [6.0, 8.9]	6.9 [6.0, 9.0]	6.8 [6.2, 8.5]	7.1 [6.2, 8.8]
Interleukin-6 pg/mL	33.3 [10.8, 85.6]	33.2 [11.0, 85.6]	19.6 [7.0, 63.4]	46.4 [15.4, 179.9]
Lactic acid blood mmol/L	1.4 [1.0, 2.0]	1.4 [1.0, 2.0]	1.6 [1.2, 2.2]	1.7 [1.2, 2.3]
Lactate dehydrogenase – serum/plasma U/L	293 [224, 403]	294 [224, 405]	369 [282, 518]	341 [259, 478]
Procalcitonin ng/mL	0.21 [0.09, 0.76]	0.21 [0.10, 0.77]	0.17 [0.08, 0.40]	0.20 [0.09, 0.54]
Serum creatinine mg/dL	0.87 [0.69, 1.20]	0.88 [0.70, 1.20]	0.80 [0.67, 1.01]	0.80 [0.65, 1.07]
Total bilirubin mg/dL	0.5 [0.3, 0.7]	0.5 [0.3, 0.7]	0.5 [0.4, 0.7]	0.5 [0.4, 0.6]
Troponin I ng/mL	0.08 [0.03, 0.27]	0.08 [0.03, 0.27]	0.08 [0.03, 0.49]	0.11 [0.03, 0.33]
White blood cell count x10^3/uL	7.2 [5.1, 10.1]	7.2 [5.1, 10.1]	9.0 [6.4, 12.2]	8.6 [6.1, 12.0]
Admission oxygenation measures				
Arterial blood partial pressure CO2	34.2 [30.0, 38.6]	34.6 [30.3, 39.2]	34.0 [30.4, 37.8]	33.9 [30.0, 38.4]
Arterial blood partial pressure O2	68.6 [59.0, 84.2]	73.6 [62.0, 93.5]	68.6 [59.0, 83.5]	69.4 [60.0, 86.3]
Blood pH	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]
PaO2/FiO2 ratio	110.0 [71.0, 207.1]	232.0 [121.7, 319.0]	121.9 [74.3, 226.3]	141.5 [77.0, 250.9]
Tidal volume mL	480 [43, 550]	480 [420, 500]	471 [425, 552]	500 [433, 559]
Baseline oxygenation measures				
Arterial blood partial pressure CO2	37.0 [32.4, 42.6]	36.1 [31.2, 41.9]	36.5 [32.3, 40.8]	36.1 [31.2, 41.7]
Arterial blood partial pressure O2	69.6 [58.9, 87.5]	73.0 [61.2, 94.0]	69.0 [58.1, 83.2]	71.0 [60.72, 86.91]
Blood pH	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]
PaO2/FiO2 ratio	89.6 [65.3, 141.9]	150.9 [86.3, 250.0]	88.8 [65.4, 137.7]	94.9 [70.2, 161.2]
Tidal volume mL	450 [420, 500]	450 [400, 500]	450 [400, 500]	500 [450, 504]

Categorical data are N (%) and continuous variables are presented as median [IQR]. IQR=interquartile range; RTRM=Real-time Risk Model;

CP=Convalescent Plasma

Supplemental Table 4. Demographic description of epoch intervals.

	All eligible patients	Epoch 1	Epoch 2	Epoch 3	Epoch 4	Epoch 5	Epoch 6
Total number of patients, N	33987	1380	2668	1585	8527	15753	4074
Number of CP patients, N	8034	10	158	260	2173	4281	1152
Age groupings							
18-44	5734 (16.9%)	215 (15.6%)	370 (13.9%)	277 (17.5%)	1821 (21.4%)	2435 (15.5%)	616 (15.1%)
45-64	11481 (33.8%)	523 (37.9%)	878 (32.9%)	526 (33.2%)	3141 (36.8%)	5143 (32.6%)	1270 (31.2%)
65-74	6942 (20.4%)	298 (21.6%)	545 (20.4%)	292 (18.4%)	1551 (18.2%)	3378 (21.4%)	878 (21.6%)
75-84	5961 (17.5%)	208 (15.1%)	477 (17.9%)	272 (17.2%)	1229 (14.4%)	2956 (18.8%)	819 (20.1%)
85+	3862 (11.4%)	135 (9.8%)	398 (14.9%)	217 (13.7%)	783 (9.2%)	1838 (11.7%)	491 (12.1%)
Race/ethnicity							
Hispanic	11040 (32.5%)	290 (21%)	664 (24.9%)	483 (30.5%)	3510 (41.2%)	5121 (32.5%)	972 (23.9%)
Non-Hispanic black	6479 (19.1%)	389 (28.2%)	600 (22.5%)	324 (20.4%)	1522 (17.8%)	2985 (18.9%)	659 (16.2%)
Non-Hispanic other	1810 (5.3%)	97 (7%)	200 (7.5%)	101 (6.4%)	463 (5.4%)	763 (4.8%)	186 (4.6%)
Non-Hispanic white	11823 (34.8%)	481 (34.9%)	1011 (37.9%)	534 (33.7%)	2375 (27.9%)	5585 (35.5%)	1837 (45.1%)
Sex							
Female	16430 (48.3%)	645 (46.7%)	1298 (48.7%)	755 (47.6%)	4052 (47.5%)	7635 (48.5%)	2045 (50.2%)
Male	17547 (51.6%)	734 (53.2%)	1370 (51.3%)	829 (52.3%)	4473 (52.5%)	8113 (51.5%)	2028 (49.8%)
Unknown	3 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)	1 (0%)
Pre-admission comorbidities							
Asthma or reactive airway disease	3251 (9.6%)	165 (12%)	283 (10.6%)	139 (8.8%)	802 (9.4%)	1468 (9.3%)	394 (9.7%)
COPD (excluding asthma)	6615 (19.5%)	260 (18.8%)	542 (20.3%)	325 (20.5%)	1410 (16.5%)	3240 (20.6%)	838 (20.6%)
Autoimmune disorders total	4008 (11.8%)	154 (11.2%)	363 (13.6%)	204 (12.9%)	905 (10.6%)	1865 (11.8%)	517 (12.7%)
Organ-related autoimmune disorders	2390 (7%)	91 (6.6%)	207 (7.8%)	131 (8.3%)	516 (6.1%)	1156 (7.3%)	289 (7.1%)
Systemic autoimmune disorders	1956 (5.8%)	78 (5.7%)	182 (6.8%)	95 (6.0%)	469 (5.5%)	865 (5.5%)	267 (6.6%)
Cancer	2021 (5.9%)	83 (6.0%)	182 (6.8%)	76 (4.8%)	441 (5.2%)	969 (6.2%)	270 (6.6%)
Cancer (diagnosed in the last 2 years)	1132 (3.3%)	43 (3.1%)	106 (4%)	41 (2.6%)	254 (3.0%)	538 (3.4%)	150 (3.7%)

Chronic ischemic heart disease	7257 (21.4%)	269 (19.5%)	599 (22.5%)	354 (22.3%)	1512 (17.7%)	3572 (22.7%)	951 (23.3%)
Congestive heart failure	6481 (19.1%)	245 (17.8%)	616 (23.1%)	309 (19.5%)	1367 (16%)	3101 (19.7%)	843 (20.7%)
Diabetes total	13545 (39.9%)	539 (39.1%)	1128 (42.3%)	608 (38.4%)	3235 (37.9%)	6507 (41.3%)	1528 (37.5%)
Diabetes with chronic complications	6154 (18.1%)	232 (16.8%)	517 (19.4%)	300 (18.9%)	1312 (15.4%)	3056 (19.4%)	737 (18.1%)
Diabetes without chronic complications	7391 (21.7%)	307 (22.2%)	611 (22.9%)	308 (19.4%)	1923 (22.6%)	3451 (21.9%)	791 (19.4%)
HIV infection	171 (0.5%)	8 (0.6%)	16 (0.6%)	11 (0.7%)	56 (0.7%)	73 (0.5%)	7 (0.2%)
Hypertension	21368 (62.9%)	951 (68.9%)	1825 (68.4%)	996 (62.8%)	4977 (58.4%)	10059 (63.9%)	2560 (62.8%)
Renal disease (mild or moderate)	5497 (16.2%)	230 (16.7%)	486 (18.2%)	271 (17.1%)	1147 (13.5%)	2666 (16.9%)	697 (17.1%)
Renal disease (severe)	2021 (5.9%)	77 (5.6%)	187 (7%)	117 (7.4%)	440 (5.2%)	991 (6.3%)	209 (5.1%)

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Supplemental Table 5. Clinical description of epoch intervals.

	All eligible patients	**EPOCH 1**	**EPOCH 2**	**EPOCH 3**	**EPOCH 4**	**EPOCH 5**	**EPOCH 6**
Total number of patients, N	33987	1380	2668	1585	8527	15753	4074
Number of CP patients, N	8034	10	158	260	2173	4281	1152
Medications							
Anticoagulants	29233 (86.0%)	1020 (73.9%)	2161 (81%)	1357 (85.6%)	7569 (88.8%)	13835 (87.8%)	3291 (80.8%)
Azithromycin	21167 (62.3%)	1140 (82.6%)	1846 (69.2%)	976 (61.6%)	5475 (64.2%)	9584 (60.8%)	2146 (52.7%)
Antibiotics – other	27507 (80.9%)	1196 (86.7%)	2185 (81.9%)	1301 (82.1%)	7100 (83.3%)	12703 (80.6%)	3022 (74.2%)
Antivirals	697 (2.1%)	134 (9.7%)	91 (3.4%)	39 (2.5%)	152 (1.8%)	241 (1.5%)	40 (1.0%)
Hydroxychloroquine	3282 (9.7%)	793 (57.5%)	1435 (53.8%)	413 (26.1%)	342 (4.0%)	265 (1.7%)	34 (0.8%)
Remdesivir	8303 (24.4%)	11 (0.8%)	41 (1.5%)	136 (8.6%)	2510 (29.4%)	4389 (27.9%)	1216 (29.8%)
Tocilizumab	1466 (4.3%)	26 (1.9%)	179 (6.7%)	131 (8.3%)	574 (6.7%)	549 (3.5%)	7 (0.2%)
Statins/ACE inhibitors (ACEi)	12100 (35.6%)	476 (34.5%)	1033 (38.7%)	576 (36.3%)	2746 (32.2%)	5771 (36.6%)	1498 (36.8%)
Steroids	21690 (63.8%)	290 (21.0%)	699 (26.2%)	482 (30.4%)	5437 (63.8%)	11967 (76.0%)	2815 (69.1%)
Immunomodulators – other	37 (0.1%)	2 (0.1%)	4 (0.1%)	2 (0.1%)	12 (0.1%)	13 (0.1%)	4 (0.1%)
Clinical variables							

Days to transfusion (CP only), *M (SD)*	4.0 (3.7)	20.9 (4.9)	8.8 (6.4)	4.4 (3.4)	4.4 (4.0)	4.0 (3.4)	2.4 (2.1)
Length of stay, *M (SD)*	9.5 (9.2)	10.6 (11.7)	11.4 (11.9)	11.3 (10.5)	10.2 (10.2)	9.3 (8.4)	6.8 (5.2)
Intubation	2277 (6.7%)	156 (11.3%)	203 (7.6%)	104 (6.6%)	608 (7.1%)	1053 (6.7%)	153 (3.8%)
All cause death	3431 (10.1%)	158 (11.4%)	310 (11.6%)	134 (8.5%)	827 (9.7%)	1692 (10.7%)	310 (7.6%)
Admission WHO PS							
WHO PS 2	9572 (28.2%)	413 (29.9%)	741 (27.8%)	479 (30.2%)	2482 (29.1%)	4262 (27.1%)	1195 (29.3%)
WHO PS 3	16489 (48.5%)	762 (55.2%)	1454 (54.5%)	796 (50.2%)	4106 (48.2%)	7498 (47.6%)	1873 (46%)
WHO PS 4	5237 (15.4%)	87 (6.3%)	288 (10.8%)	191 (12.1%)	1318 (15.5%)	2787 (17.7%)	566 (13.9%)
WHO PS 5	539 (1.6%)	57 (4.1%)	56 (2.1%)	21 (1.3%)	127 (1.5%)	228 (1.4%)	50 (1.2%)
Missing	2150 (6.3%)	61 (4.4%)	129 (4.8%)	98 (6.2%)	494 (5.8%)	978 (6.2%)	390 (9.6%)
Baseline WHO PS							
WHO PS 2	8108 (23.9%)	288 (20.9%)	669 (25.1%)	403 (25.4%)	2046 (24%)	3596 (22.8%)	1106 (27.1%)
WHO PS 3	14853 (43.7%)	695 (50.4%)	1288 (48.3%)	712 (44.9%)	3637 (42.7%)	6772 (43%)	1749 (42.9%)
WHO PS 4	7489 (22%)	148 (10.7%)	390 (14.6%)	302 (19.1%)	2032 (23.8%)	3862 (24.5%)	755 (18.5%)
WHO PS 5	1331 (3.9%)	172 (12.5%)	177 (6.6%)	57 (3.6%)	320 (3.8%)	540 (3.4%)	65 (1.6%)
Missing	2206 (6.5%)	77 (5.6%)	144 (5.4%)	111 (7.0%)	492 (5.8%)	983 (6.2%)	399 (9.8%)
Secondary infections							
Bacteremia	221 (0.7%)	7 (0.5%)	15 (0.6%)	12 (0.8%)	44 (0.5%)	115 (0.7%)	28 (0.7%)
Bacterial pneumonia	1218 (3.6%)	87 (6.3%)	115 (4.3%)	61 (3.8%)	294 (3.4%)	538 (3.4%)	123 (3.0%)
Sepsis	7756 (22.8%)	321 (23.3%)	637 (23.9%)	393 (24.8%)	2041 (23.9%)	3515 (22.3%)	849 (20.8%)
Severe sepsis	5045 (14.8%)	255 (18.5%)	501 (18.8%)	243 (15.3%)	1226 (14.4%)	2288 (14.5%)	532 (13.1%)

Data are N (%) unless otherwise indicated. Epochs were all in 2020 and were defined as follows based on changes in treatment recommendations: Epoch 1, March 1 to April 2; Epoch 2, April 3 to April 29; Epoch 3, April 30 to May 19; Epoch 4, May 20 to July 5; Epoch 5, July 6 to August 23; Epoch 6, August 24 to September 28. CP=Convalescent Plasma; WHO PS=World Health Organization Progression Score

Supplemental Table 6. Transfusion related adverse events.

	All CP	Verified FFP	Non-CP, Non-FFP
Total number of patients, N	8034	572	25953
Transfusion-related acute lung injury (TRALI) [T] ICD10 J95.84	5 (0.06%)	1 (0.17%)	0 (0.00%)
Transfusion-associated circulatory overload (TACO) ICD10 E87.71	0 (0.00%)	0 (0.00%)	1 (0.004%)
Transfusion related infection ICD10 T80.21, T80.22, T80.29, T80.29X	7 (0.09%)	2 (0.35%)	20 (0.08%)
Thromboembolic/thrombotic event ICD10 T80.1, T81.72, T82.90	2 (0.02%)	0 (0.00%)	3 (0.01%)
Severe allergic transfusion reaction ICD10 T80.69	0 (0.00%)	0 (0.00%)	0 (0.00%)
Severe hemolytic transfusion reaction ICD10 T80.310, T80.311, T80.319, T80.410, T80.411, T80.419, T80.A10, T80.A11, T80.A19	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transfusion related severe anaphylaxis ICD10 T80.51	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transfusion related adverse event - unspecified ICD10 T80.89, T80.92	5 (0.06%)	2 (0.35%)	5 (0.02%)
Total transfusion related adverse events	19 (0.23%)	5 (0.87%)	29 (0.11%)

Adverse events related to transfusion are reported for three subgroups including eligible patients transfused with CP, patients transfused with verified fresh frozen plasma (FFP), or eligible patients who received neither CP nor FFP. All CP=CP transfusion within the eligible patient pool of 33,987. Verified FFP=fresh frozen plasma transfusion defined by either having no detectable SARS-CoV-2 antibodies (S/Co≤1) or was designated an FFP blood product by suppliers and donated prior to January 1, 2020. Non-CP, Non-FFP=patients who did not receive a transfusion blood product of either CP or FFP, yet other blood product transfusions cannot be ruled out (representative of the comparison cohort). Transfusion related adverse events are obtained by passive reporting and not manually validated; thus, reported rates may systematically underestimate the actual incidence across all groups. [T], TRALI rates may be an overestimate because the imputability of reported TRALI events is unknown.

Supplemental Table 7. Effects and interactions of donor serology in the CP cohort.

	HR	LLCI	ULCI	p-value
Continuous S/Co levels				
Donor serology	0.999	0.999	1.000	0.084
Categorical S/Co levels				
Low (below 20th percentile)^{R}	--	--	--	--
Medium (20th – 80th percentile)	0.864	0.657	1.137	0.297
High (above 80th percentile)	0.777	0.548	1.101	0.155
S/ColLevels by days to transfusion				
Donor serology	0.998	0.997	0.999	**0.013**
Days to transfusion	1.036	1.002	1.071	**0.037**
Donor serology * days to transfusion	1.0002	1.0000	1.0004	**0.044**
Effects from simple slopes by serology				
Low donor serology: days to transfusion	1.043	1.014	1.073	**0.003**
High donor serology: days to transfusion	1.097	1.056	1.139	**<0.001**
Effects from simple slopes by days				
0-3 days: donor serology	0.998	0.997	0.999	**0.029**
4+ days: donor serology	1.000	0.999	1.001	0.736

For cases where patients received more than one CP transfusion within 1 week of their first CP transfusion, the serologic levels were averaged to create one serologic level per patient.

HR=hazard ratio, LLCI=lower limit confidence interval, ULCI=upper limit confidence interval

^{R} represents the reference variable for the categorical S/Co serology levels. N=1944

Five patients with erroneous admission dates removed for all results that included Days to Transfusion. N=1939

Simple slope analyses were conducted for the decomposition of the significant interaction; the transformed scores were centered by mean±SD (178.21±138.49, N=1939) to examine the impact of high serology versus low serology across number of days from admission to transfusion as separate models.

Supplemental Table 8. Medication list by categories

Medication categories	List of included medications
Anticoagulants	anticoagulant, acd, argatroban, arixtra, coumadin, eliquis, enoxaparin, heparin, lovenox, fondaparinux, warfarin, apixaban
Tocilizumab	actemra, tocilizumab
Azithromycin	azithromycin, zithromax, zmax
Statins/ACE inhibitors (ACEi)	Statins: statin, crestor, lipitor, pravachol, pravastatin, rosuvastatin, zocor, atorvastatin, simvastatin ACEi: ACE, ramipril, capoten, prinivil, vasotec, zestril, captopril, lisinopril, enalapril
Steroids	steroid, corticosteroid, cortef, hydrocortisone, decadron, dexamethasone, deltasone, prednisone, deltisone, solu-cortef, hydrocortisone, solu-medrol, methylprednisolone
Other immunomodulators	imuran, myfortic, azathioprine, mycophenolic
Hydroxychloroquine	plaquenil, hydroxychloroquine
Remdesivir	remdesivir, veklury
Antivirals	antiviral, acyclovir, zovirax, abacavir, kivexa, ziagen, epzicom, trizivir, triumeq, tamiflu, oseltamivir, nrti, epivir, lamivudine
Other antibiotics	amoxicillin, amoxil, augmentin, moxatag, ampicillin, principen, unasyn, oxacillin, penicillin, pfizerpen, bicillin, ancef, cefazolin, cefepime, maxipime, ceftin, cefuroxime, cefdinir, omnicef, fortaz, ceftazidime, keflex, cephalexin, kefzol, rocephin, ceftriaxone, zerbaxa, ceftolozane, cephalosporin, azactam, aztreona, monobactam, bactrim, trimethoprim, sulfonamide, cipro, ciprofloxacin, levaquin, levofloxacin, fluoroquinolone, cleocin, clindamycin, lincosamide, cubicin, daptomycin, flagyl, metronidazole, invanz, ertapenem, merrem, meropenem, carbapenem, macrobid, nitrofurantoin, macrodantin, nebcin, aminoglycoside, sulfamethoxazole, gantanol, sulfatrim, zotrim, vancocin, vancomycin, firvanq, xifaxan, rifaximin, rifamycin, rimactane, aemcolo, zosyn, piperacillin, zyvox, linezolid

Supplemental Table 9. Calendar epoch intervals

Epoch	Calendar definitions	Summary of treatment recommendations
Epoch 1	March 2 – April 2, 2020	• Consider only hydroxychloroquine without azithromycin • Consider remdesivir • Avoid steroids
Epoch 2	April 3 – April 29, 2020	• Consider hydroxychloroquine with azithromycin • Consider tocilizumab • Consider convalescent plasma
Epoch 3	April 30 – May 19, 2020	• Consider only hydroxychloroquine, no azithromycin • Consider low-dose, short-course steroids in later pulmonary phase
Epoch 4	May 20 – July 5, 2020	• Do not consider hydroxychloroquine
Epoch 5	July 6 – August 23, 2020	• Steroids recommended for all patients requiring oxygen supplementation
Epoch 6	August 24 – September 28, 2020	• Consider convalescent plasma for patients with lesser severity illness[#]

#Shift in treatment recommendation for convalescent plasma from patient with more severe disease to patients with less severe disease based on the shift from the expanded access program (EAP) requirements to the emergency use authorization (EUA) (4).

Supplemental Table 10. WHO progression score (WHO PS) categories.

WHO PS	Description
1	Discharged alive
2	Hospitalized with no supplemental oxygen
3	Hospitalized on low-flow supplemental oxygen
4	Hospitalized on non-invasive or high-flow oxygen including continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BIPAP)
5	Hospitalized on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
6	Expired

The WHO PS is a modified 6-point scale, adapted from the WHO R&D Blueprint group to assess disease severity and measure clinical improvement in hospitalized patients. Patients were assigned a daily WHO PS based on their most severe status that day, except at discharge which was assigned 1 (4).