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Comparative Survival Analysis of Immunomodulatory Therapy for Coronavirus Disease 2019 Cytokine Storm.

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Comparative Survival Analysis of Immunomodulatory Therapy for Coronavirus Disease 2019 Cytokine Storm

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BACKGROUND: Cytokine storm is a marker of coronavirus disease 2019 (COVID-19) illness severity and increased mortality. Immunomodulatory treatments have been repurposed to improve mortality outcomes.

RESEARCH QUESTION: Do immunomodulatory therapies improve survival in patients with COVID-19 cytokine storm (CCS)?

STUDY DESIGN AND METHODS: We conducted a retrospective analysis of electronic health records across the Northwell Health system. COVID-19 patients hospitalized between March 1, 2020, and April 24, 2020, were included. CCS was defined by inflammatory markers: ferritin, > 700 ng/mL; C-reactive protein (CRP), > 30 mg/dL; or lactate dehydrogenase (LDH), > 300 U/L. Patients were subdivided into six groups: no immunomodulatory treatment (standard of care) and five groups that received either corticosteroids, anti-IL-6 antibody (tocilizumab), or anti-IL-1 therapy (anakinra) alone or in combination with corticosteroids. The primary outcome was hospital mortality.

RESULTS: Five thousand seven hundred seventy-six patients met the inclusion criteria. The most common comorbidities were hypertension (44%-59%), diabetes (32%-46%), and cardiovascular disease (5%-14%). Patients most frequently met criteria with high LDH (76.2%) alone or in combination, followed by ferritin (63.2%) and CRP (8.4%). More than 80% of patients showed an elevated D-dimer. Patients treated with corticosteroids and tocilizumab combination showed lower mortality compared with patients receiving standard-of-care (SoC) treatment (hazard ratio [HR], 0.44; 95% CI, 0.35-0.55; $P < .0001$) and with patients treated with corticosteroids alone (HR, 0.66; 95% CI, 0.53-0.83; $P = .004$) or in combination with anakinra (HR, 0.64; 95% CI, 0.50-0.81; $P = .003$). Corticosteroids when administered alone (HR, 0.66; 95% CI, 0.57-0.76; $P < .0001$) or in combination with tocilizumab (HR, 0.43; 95% CI, 0.35-0.55; $P < .0001$) or anakinra (HR, 0.68; 95% CI, 0.57-0.81; $P < .0001$) improved hospital survival compared with SoC treatment.

INTERPRETATION: The combination of corticosteroids with tocilizumab showed superior survival outcome when compared with SoC treatment and treatment with corticosteroids alone or in combination with anakinra. Furthermore, corticosteroid use either alone or in combination with tocilizumab or anakinra was associated with reduced hospital mortality for patients with CCS compared with patients receiving SoC treatment. CHEST 2020; ■(■):■-■

KEY WORDS: anakinra; coronavirus; corticosteroids; infection; SARS-CoV-2; tocilizumab

ABBREVIATIONS: A = anakinra only; CCS = coronavirus disease 2019 cytokine storm; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; HR = hazard ratio; IMV = invasive mechanical ventilation; LDH = lactate dehydrogenase; S = corticosteroids only; SA = corticosteroids and anakinra; SoC = standard-of-care; ST = corticosteroids and tocilizumab; T = tocilizumab only

AFFILIATIONS: From the Division of Rheumatology (S. N., G. M.), Department of Medicine, the Division of Allergy and Immunology (B. K.), Department of Pediatrics, Northwell Health, Great Neck, NY; the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health (S. N., G. M., B. K., P. M., O. B., M. L. L., N. H.), Hempstead, NY;

In March 2020, New York City and its metropolitan area became the epicenter for coronavirus disease 2019 (COVID-19) in the United States, with more than 250,000 cases and more than 17,000 deaths by early May 2020.² Throughout this outbreak, physicians and scientists have struggled to understand the pathogenesis and clinical course of this infection. Early retrospective data from China and Italy showed increased mortality in those with elevated inflammatory markers, such as ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), IL-6, and D-dimer.³ Uncontrolled and unabated cytokine release and a hyperinflammatory response, termed the COVID-19 cytokine storm (CCS), was described as a major determinant of poor survival.⁴

Limited data existed to guide clinical decision-making in the absence of Food and Drug Administration-approved COVID-19-specific therapies. Faced with rapidly increasing rates of infection and hospitalizations, physicians repurposed immunomodulatory treatments in an attempt to curtail morbidity and mortality. Although initial reports discouraged the use of corticosteroids, later publications suggested survival benefits.^{3,5,6} Small retrospective studies reported improved outcomes in CCS by using anti-IL-6 (ie, tocilizumab [Roche]) and anti-IL-1

therapies (ie, anakinra [Sobi])⁷⁻⁹ that are used commonly for inflammatory conditions such as cytokine release syndrome and macrophage-activation syndrome. Further evidence supporting the use of anti-IL-1 was based on previous reports of improved survival in a subgroup of patients with sepsis and hyperferritinemia.¹⁰

Within Northwell Health, the largest private nonprofit health system in New York State, a multidisciplinary committee consisting of pulmonology, infectious disease, immunology, and rheumatology specialists was formed to create COVID-19 treatment protocols. This included the identification of CCS, which we defined as ferritin > 700 ng/mL¹¹ or CRP > 30 mg/dL^{3,12} or LDH > 300 U/L.³ Treatment protocols with corticosteroids, tocilizumab, and anakinra as potential immunomodulatory therapies were based on the available literature at the time.^{3,11,12} Because of the rapidly evolving data and surge of patients in a short period, wide variation in the use of these drugs occurred across the health system. In this retrospective study, we leveraged this natural experiment to compare mortality in patients meeting criteria for CCS who received different combinations of these immunomodulatory

Methods

Study Population

We retrospectively analyzed electronic health record data of patients admitted to the 12 hospitals and EDs within the Northwell Health

the Biostatistics Unit (D. G. S., M. L. L.), the Institute of Health Innovations and Outcomes Research (D. G. S., M. L. L., N. H.), the Institute of Molecular Medicine (O. B., M. L. L.), The Feinstein Institutes for Medical Research, the Division of Pulmonary, Critical Care and Sleep Medicine (A. G. W., N. H.), the Division of Infectious Diseases (P. M.), Department of Medicine (A. L.), Northwell Health, Manhasset, NY; and the Division of Allergy and Infectious Diseases (A. S. C.), Department of Medicine, University of Washington and Center for Immunity and Immunotherapies, Seattle Children's Research Institute, Seattle, WA.

*Collaborators from the Northwell COVID-19 Research Consortium are listed in the Acknowledgments.

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system between March 1, 2020, and April 24, 2020. The institutional review board for the Feinstein Institutes of Medical Research at Northwell Health approved this study as minimal-risk research and waived the requirement for informed consent. Inclusion criteria were: COVID-19 positivity as determined by polymerase chain reaction testing of nasopharyngeal swabs; age older than 18 years; and meeting CCS criteria of ferritin > 700 ng/mL¹¹ or CRP > 30 mg/dL^{3,12} or LDH > 300 U/L³ (e-Fig 1). T₀ was identified as the time at which a patient first met this definition. Patients who received any of the prespecified immunomodulatory drugs before T₀ were excluded from this study.

Group Definition

Six groups were identified based on whether they received any of the predefined immunomodulatory drugs. One group consisted of those who received none of the medications, labeled as the standard-of-care (SoC) group. Five treatment groups received varying combinations of the three immunomodulatory drugs: corticosteroids only (S), corticosteroids and tocilizumab (ST), corticosteroids and anakinra (SA), tocilizumab only (T), and anakinra only (A). In the timeframe of this analysis, hydroxychloroquine, azithromycin, colchicine, and vitamin C, either alone or in combination, were administered to COVID-19 patients as part of institutional protocols (e-Table 1).

Statistical Methods

The primary objective was to compare in-hospital mortality among COVID-19 patients with CCS who received combinations of immunomodulatory treatments vs SoC treatment. Potentially confounding variables (covariates) were included in the multivariate model based on clinical experience and the COVID-19 literature at

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TABLE 1] Patient Demographics

Variable	Missing Data	Standard of Care (N = 3,076)	Steroids Only (n = 1,383)	Steroids plus Tocilizumab (n = 454)	Steroids plus Anakinra (n = 733)	Tocilizumab Only (n = 73)	Anakinra Only (n = 57)	P Value
Demographics								
Age, y		64.6 (53.5-76.4)	66.5 (55.8-76.9)	64.5 (54.9-73.1)	65.7 (56.5-74.7)	62.4 (55.1- 68.7)	66.7 (57.6- 74.6)	.01
Sex								
Female		1,185 (38.5)	489 (35.4)	123 (27.1)	238 (32.5)	21 (28.8)	19 (33.3)	< .0001
Male		1,891 (61.5)	894 (64.6)	331 (72.9)	495 (67.5)	52 (71.2)	38 (66.7)	
Race								
White		1,021 (33.2)	474 (34.3)	163 (35.9)	208 (28.4)	239(39.7)	12 (21.1)	.0013
Black		656 (21.3)	293 (21.2)	68 (15)	139 (19)	8 (11)	17 (29.8)	
Asian		372 (12.1)	161 (11.6)	64 (14.1)	98 (13.4)	8 (11)	1 (1.8)	
Other/multiracial		867 (28.2)	372 (26.9)	132 (29.1)	243 (33.2)	24 (32.9)	23 (40.4)	
Unknown		160 (5.2)	83 (6)	27 (5.9)	45 (6.1)	4 (5.5)	4 (7)	
Ethnicity								
Hispanic or Latino		671 (21.8)	319 (23.1)	119 (26.2)	171 (23.3)	13 (17.8)	12 (21.1)	.41
Non-Hispanic or Latino		2,141 (69.6)	944 (68.3)	295 (65)	513 (70)	55 (75.3)	42 (73.7)	
Other/unknown		264 (8.6)	120 (8.7)	40 (8.8)	49 (6.7)	5 (6.8)	3 (5.3)	
Insurance								
Commercial		916 (29.8)	410 (29.6)	159 (35)	230 (31.4)	35 (47.9)	15 (26.3)	< .0001
Medicare		1,354 (44)	656 (47.4)	178 (39.2)	319 (43.5)	26 (35.6)	27 (47.4)	
Medicaid		634 (20.6)	271 (19.6)	103 (22.7)	162 (22.1)	12 (16.4)	14 (24.6)	
Self-pay		49 (1.6)	30 (2.2)	7 (1.5)	15 (2)	0 (0)	0 (0)	
Other		123 (4)	16 (1.2)	7 (1.5)	7 (1)	0 (0)	1 (1.8)	
Smoking status								
Active		67 (2.2)	22 (1.6)	10 (2.2)	18 (2.5)	1 (1.4)	2 (3.5)	.15
Former		426 (13.8)	212 (15.3)	71 (15.6)	107 (14.6)	13 (17.8)	9 (15.8)	
Never		2,203 (71.6)	971 (70.2)	305 (67.2)	523 (71.4)	54 (74)	41 (71.9)	
Smoker/status unknown		122 (4)	38 (2.7)	17 (3.7)	14 (1.9)	3 (4.1)	2 (3.5)	
Unknown		258 (8.4)	140 (10.1)	51 (11.2)	71 (9.7)	2 (2.7)	3 (5.3)	
Hospital status								

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Variable	Missing Data	Standard of Care (N = 3,076)	Steroids Only (n = 1,383)	Steroids plus Tocilizumab (n = 454)	Steroids plus Anakinra (n = 733)	Tocilizumab Only (n = 73)	Anakinra Only (n = 57)	P Value
Community		1,108 (36)	414 (29.9)	142 (31.3)	169 (23.1)	17 (23.3)	15 (26.3)	< .0001
Tertiary		1,968 (64)	969 (70.1)	312 (68.7)	564 (76.9)	56 (76.7)	42 (73.7)	
Comorbidities								
BMI, kg/m ²	808 (14)							
18.5-24.9		666 (25.9)	270 (22.1)	75 (18.2)	152 (23.2)	23 (37.1)	18 (36.7)	.004
< 18.5		286 (11.1)	139 (11.4)	41 (10)	71 (10.8)	1 (1.6)	5 (10.2)	
25-29.9		821 (31.9)	405 (33.2)	149 (36.3)	215 (32.8)	14 (22.6)	12 (24.5)	
≥ 30		799 (31.1)	405 (33.2)	146 (35.5)	217 (33.1)	24 (38.7)	14 (28.6)	
Charlson comorbidity index	1 (0.02)							
0		333 (10.8)	102 (7.4)	30 (6.6)	48 (6.5)	4 (5.5)	3 (5.3)	< .0001
1-2		683 (22.2)	184 (20.5)	127 (28)	182 (24.8)	14 (19.2)	15 (26.3)	
3-4		710 (23.1)	353 (25.5)	133 (29.3)	221 (30.2)	26 (35.6)	14 (24.6)	
≥ 5		1,349 (43.9)	644 (46.6)	164 (36.1)	282 (38.5)	29 (39.7)	25 (43.9)	
Asthma		134 (4.4)	105 (7.6)	25 (5.5)	48 (6.5)	9 (12.3)	2 (3.5)	.01
COPD		88 (2.9)	67 (4.8)	14 (3.1)	31 (4.2)	1 (1.4)	3 (5.3)	.02
HTN		1454 (47.3)	682 (49.3)	224 (49.3)	379 (51.7)	43 (58.9)	25 (43.9)	.11
DM		980 (31.9)	460 (33.3)	154 (33.9)	241 (32.9)	27 (37)	26 (45.6)	.27
Cardiovascular disease		393 (12.8)	181 (13.1)	59 (13)	88 (12)	10 (13.7)	3 (5.3)	.63
CKD_ESRD	11 (0.2)	356 (11.6)	145 (10.5)	29 (6.4)	55 (7.5)	4 (5.5)	5 (8.8)	.001
Hemodialysis		43 (1.4)	4 (0.3)	1 (0.2)	7 (1)	0 (0)	0 (0)	.01
Cancer		178 (5.8)	86 (6.2)	33 (7.3)	49 (6.7)	8 (11)	5 (8.8)	.35
Chronic liver disease		19 (0.6)	5 (0.4)	4 (0.9)	4 (0.5)	0 (0)	0 (0)	.75
Autoimmune disease		38 (1.2)	31 (2.2)	8 (1.8)	15 (2)	0 (0)	1 (1.8)	.14
Interstitial lung disease		52 (1.7)	64 (4.6)	43 (9.5)	27 (3.7)	7 (9.6)	1 (1.8)	< .0001
Severity of illness surrogates								
Mechanical ventilation		143 (4.6)	82 (5.9)	35 (7.7)	30 (4.1)	7 (9.6)	1 (1.8)	.01
Vasopressor use		89 (2.9)	50 (3.6)	18 (4)	18 (2.5)	3 (4.1)	1 (1.8)	.49

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Laboratory data								
CRP, mg/dL	738 (12.8)							
0-0.5		21 (0.8)	1 (0.1)	1 (0.2)	3 (0.5)	0 (0)	0 (0)	< .0001
> 0.5-2.5		164 (6.3)	32 (2.6)	3 (0.7)	4 (0.6)	0 (0)	0 (0)	
> 2.5		2,405 (92.9)	1211 (97.3)	427 (99.1)	645 (98.9)	68 (100)	53 (100)	
D-dimer, ng/mL DDU	2,026 (35.1)							
< 230		350 (19.1)	112 (12.5)	56 (16)	80 (14.1)	18 (30)	4 (8.3)	.0002
230-1150		1129 (61.8)	582 (65.1)	222 (63.2)	360 (63.3)	31 (51.7)	33 (68.8)	
> 1150		349 (19.1)	200 (22.4)	73 (20.8)	129 (22.7)	11 (18.3)	11 (22.9)	
Serum ferritin, ng/mL	615 (10.7)							
< 30		1 (0)	2 (0.1)	1 (0.2)	1 (0.1)	0 (0)	0 (0)	< .0001
30-400		423 (15.7)	182 (14.5)	28 (6.5)	59 (8.8)	7 (10.9)	4 (7.7)	
> 400-2000		1,783 (66.3)	805 (64.2)	307 (71.6)	457 (68)	49 (76.6)	34 (65.4)	
> 2000		484 (18)	264 (21.2)	93 (21.7)	155 (23.1)	8 (12.5)	14 (26.9)	
LDH, U/L	991 (17.1)							
< 242		106 (4.2)	20 (1.7)	1 (0.3)	5 (0.8)	3 (5.5)	3 (5.6)	< .0001
≥ 242		2413 (95.8)	1170 (98.3)	341 (99.7)	620 (99.2)	52 (94.5)	51 (94.4)	
Hemoglobin, g/dL	121 (2.1)							
< 11.5		767 (25.4)	304 (22.5)	55 (12.4)	117 (16.3)	16 (21.9)	11 (20.8)	< .0001
11.5-15.5		2,025 (67.1)	938 (69.4)	343 (77.6)	546 (76.3)	52 (71.2)	34 (64.2)	
> 15.5		227 (7.5)	110 (8.1)	44 (10)	53 (7.4)	5 (6.8)	8 (15.1)	
Eosinophils, K/ μ L	310 (5.4)							
0-0.5		2,891 (99.6)	1,307 (99.8)	435 (100)	697 (99.9)	69 (100)	52 (100)	.56
> 0.5		12 (0.4)	2 (0.2)	0 (0)	1 (0.1)	0 (0)	0 (0)	
Neutrophil-to-lymphocyte ratio	321 (5.6)							
< 0.75		23 (0.8)	5 (0.4)	2 (0.5)	2 (0.3)	0 (0)	0 (0)	< .0001
0.75-4		823 (28.4)	227 (17.4)	70 (16.1)	93 (13.5)	15 (21.4)	12 (23.5)	
> 4-20		1879 (64.7)	939 (72)	309 (70.9)	518 (75)	48 (68.6)	34 (66.7)	
> 20		177 (6.1)	134 (10.3)	55 (12.6)	78 (11.3)	7 (10)	5 (9.8)	

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Platelets, K/ μ L	129 (2.2)							
< 150		615 (20.4)	271 (20.1)	91 (20.6)	128 (17.9)	15 (20.5)	9 (17)	.42
150-500		2,348 (77.9)	1062 (78.8)	347 (78.5)	572 (80)	58 (79.5)	42 (79.2)	
> 500		53 (1.8)	15 (1.1)	4 (0.9)	15 (2.1)	0 (0)	2 (3.8)	
Serum sodium, mM	53 (0.9)							
< 135		913 (29.9)	440 (32.1)	191 (42.6)	314 (43.3)	25 (34.7)	22 (39.3)	< .0001
135-145		1,921 (62.9)	835 (60.9)	248 (55.4)	380 (52.3)	43 (59.7)	32 (57.1)	
> 145		218 (7.1)	95 (6.9)	9 (2)	32 (4.4)	4 (5.6)	2 (3.6)	
Alanine aminotransferase, IU/ L	153 (2.7)							
< 40		1,667 (55.8)	741 (54.9)	219 (49.5)	371 (51.5)	44 (63.8)	31 (55.4)	.06
40-200		1,235 (41.4)	578 (42.8)	208 (47.1)	338 (46.9)	24 (34.8)	23 (41.1)	
> 200		84 (2.8)	30 (2.2)	15 (3.4)	12 (1.7)	1 (1.4)	2 (3.6)	
Aspartate amino transferase, IU/L	151 (2.6)							
< 40		1,090 (36.5)	360 (26.7)	97 (21.9)	173 (24)	30 (43.5)	13 (23.2)	< .0001
40-200		1,767 (59.1)	946 (70.1)	327 (74)	526 (73)	30 (43.5)	39 (69.6)	
> 200		131 (4.4)	43 (3.2)	18 (4.1)	22 (3.1)	4 (5.8)	4 (7.1)	
eGFR	54 (0.9)							
< 15		313 (10.3)	118 (8.6)	17 (3.8)	49 (6.7)	3 (4.2)	3 (5.4)	< .0001
15-60		839 (27.5)	444 (32.4)	123 (27.5)	228 (31.4)	26 (36.1)	24 (42.9)	
> 60		1,788 (58.6)	761 (55.5)	301 (67.2)	438 (60.3)	41 (56.9)	29 (51.8)	
> 120		110 (3.6)	47 (3.4)	7 (1.6)	11 (1.5)	2 (2.8)	0 (0)	

Data are presented as No. (%) or median (25th-75th percentiles) unless otherwise indicated. CKD_ESRD = ; CRP = C-reactive protein; DDU = ; DM = diabetes mellitus; eGFR = estimate glomerular filtration rate; HTN = hypertension; LDH = lactate dehydrogenase. Chi-square, Fisher exact, or Kruskal-Wallis tests were used to compare statistical significance, between groups, as appropriate. Demographics and comorbidity data were obtained at baseline on admission. Vasopressor and invasive mechanical ventilation use was within 24 h before T₀. Laboratory values included the closest value to T₀ from within 96 h before T₀. CRP, ferritin, LDH, and D-dimer were defined within 96 h before T₀ and up to 12 h after T₀ because of laboratory ordering practices.

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TABLE 2] Hazard Ratios with 95% CIs for Cox Regression Model

Variable	Hazard Ratio (95% Confidence Limits)	P Value
Treatment groups ^a
Standard of care	Reference	...
Steroids only	0.66 (0.57-0.76)	< .0001
Steroids plus tocilizumab	0.44 (0.35-0.55)	< .0001
Steroids plus anakinra	0.68 (0.57-0.81)	< .0001
Tocilizumab only	0.79 (0.47-1.32)	0.36
Anakinra only	0.79 (0.44-1.42)	0.43
Demographics
Age	1.03 (1.02-1.04)	< .0001
Sex
Female	Reference	...
Male	1.13 (0.99-1.29)	.07
Race
White	Reference	...
Asian	0.94 (0.78-1.14)	.53
Black	0.80 (0.68-0.95)	.01
Other/multiracial	0.84 (0.70-1.02)	.08
Unknown	0.91 (0.64-1.30)	.61
Ethnicity
Not Hispanic or Latino	Reference	...
Hispanic or Latino	1.02 (0.83-1.24)	.88
Other/unknown	0.84 (0.61-1.17)	.30
Insurance
Commercial	Reference	...
Medicaid	1.25 (1.01-1.56)	.04
Medicare	1.13 (0.94-1.35)	.20
Other	0.91 (0.49-1.70)	.76
Self-pay	2.28 (1.45-3.56)	.0003
Smoking status
Never	Reference	...
Active	1.43 (0.94-2.21)	.11
Former	0.93 (0.78-1.11)	.42
Smoker (unknown active/former)	1.42 (1.09-1.83)	.01
Unknown	3.02 (2.58-3.56)	< .0001
Disease severity indexes
Mechanical ventilation
No	Reference	...
Yes	1.49 (1.18-1.87)	.0007
On vasopressors
No	Reference	...
Yes	0.97 (0.74-1.27)	.83
Laboratory parameters
Eosinophils, K/uL
0-0.5	Reference	...
> 0.5	1.16 (0.29-4.61)	.84

(Continued) 770

TABLE 2] (Continued)

Variable	Hazard Ratio (95% Confidence Limits)	P Value
Platelets, K/uL
150-500	Reference	...
< 150	1.20 (1.05-1.37)	.01
> 500	1.10 (0.66-1.84)	.71
Hemoglobin, g/dL
11.5-15.5	Reference	...
< 11.5	1.01 (0.88-1.17)	.90
> 15.5	1.05 (0.84-1.31)	.64
eGFR
60-120	Reference	...
< 15	2.30 (1.83-2.89)	< .0001
15-60	1.74 (1.50-2.01)	< .0001
> 120	1.09 (0.59-2.00)	.79
AST, U/L
0-40	Reference	...
> 40	1.35 (1.15-1.58)	.0002
> 200	1.58 (1.13-2.21)	.01
ALT, U/L
0-40	Reference	...
> 40	0.84 (0.72-0.97)	.02
> 200	1.07 (0.71-1.62)	.76
Sodium, mM
135-145	Reference	...
< 135	1.20 (0.96-1.26)	.19
> 145	1.24 (1.03-1.50)	.03
Ferritin, ng/mL
30-400	Reference	...
< 30	2.26 (0.27-18.92)	.45
> 400	1.04 (0.84-1.30)	.73
> 2000	1.21 (0.94-1.56)	.14
CRP, mg/dL
0-0.5	Reference	...
> 0.5	3.12 (0.34-28.33)	.31
> 2.5	4.11 (0.47-35.70)	.20
D-dimer, ng/mL DDU
0-230	Reference	...
> 230	1.34 (1.03-1.75)	.03
> 1150	1.67 (1.24-2.26)	.0008
LDH, U/L
<242	Reference	...
≥ 242	1.59 (0.96-2.63)	.07
NLR
0.75-4	Reference	...
< 0.75	2.10 (1.17-3.77)	.01
> 4	1.22 (1.03-1.46)	.03

(Continued) 880

TABLE 2] (Continued)

Variable	Hazard Ratio (95% Confidence Limits)	P Value
> 20	1.17 (0.92-1.49)	.20
Hospital status
Community	Reference	...
Tertiary	0.64 (0.56-0.73)	< .0001
Comorbidities
Charlson comorbidity index
0	Reference	...
1-2	1.00 (0.62-1.63)	1.00
3-4	1.11 (0.68-1.82)	.69
≥ 5	1.42 (0.84-2.40)	.19
Asthma
No	Reference	...
Yes	1.35 (1.01-1.79)	.04
COPD
No	Reference	...
Yes	1.23 (0.95-1.59)	.12
Chronic liver disorder
No	Reference	...
Yes	0.95 (0.46-1.95)	.89
DM
No	Reference	...
Yes	1.02 (0.89-1.17)	.79
HTN
No	Reference	...
Yes	0.83 (0.73-0.94)	.0045
ILD
No	Reference	...
Yes	2.17 (1.76-2.69)	< .0001
Autoimmune disorder
No	Reference	...
Yes	1.21 (0.74-1.98)	.44
Cardiovascular disease
No	Reference	...
Yes	1.13 (0.96-1.33)	.13
CKD
No	Reference	...
Yes	0.88 (0.72-1.07)	.21
Cancer
No	Reference	...
Yes	1.20 (0.96-1.50)	.10
Hemodialysis
No	Reference	...
Yes	0.99 (0.58-1.69)	.96
BMI, kg/m ²
18.5-24.9	Reference	...

(Continued)

TABLE 2] (Continued)

Variable	Hazard Ratio (95% Confidence Limits)	P Value
< 18.5	1.15 (0.93-1.44)	.20
25-29.9	0.98 (0.83-1.42)	.77
≥ 30	1.07 (0.90-1.27)	.46

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD = ; CRP = C-reactive protein; DDU = ; DM = diabetes mellitus; eGFR = estimate glomerular filtration rate; HTN = hypertension; ILD = interstitial lung disease; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio. Results of the multivariate model of in-hospital mortality for coronavirus disease 2019 patients meeting inclusion criteria with coronavirus disease 2019 cytokine storm. Hazard ratios for treatment groups represent adjustment for covariates in the model, comparing with standard of care treatment as reference. Treatment group hazard ratios are not adjusted for multiple comparisons between treatment groups. Refer to Figure 3 (and e-Table 6) for treatment differences using Tukey's adjustment for multiple comparisons between treatment groups.

the time. These included demographic data such as age, sex, race or ethnicity, smoking history, insurance status, and whether patients were treated in a tertiary vs community medical center. Comorbidities examined included chronic lung disease (ie, asthma, COPD), cardiovascular disease, hypertension, diabetes, renal disease, hemodialysis, liver disease, cancer, autoimmune disease, Charlson comorbidity index, and BMI. Laboratory data included CRP, ferritin, D-dimer, LDH, hemoglobin, platelet count, serum sodium, serum transaminases, and neutrophil-to-lymphocyte ratio. We also included disease severity surrogates, such as use of invasive mechanical ventilation (IMV; at any time before T_0) and vasopressor use (within 24 h of T_0).

Statistical Analyses

Treatment groups were compared using demographic variables, comorbidities, and baseline laboratory values using the χ^2 , Fisher exact, or Kruskal-Wallis tests, as appropriate. Categorical variables were summarized using percentages. Continuous variables were summarized using medians with 25th to 75th percentiles. Laboratories considered clinically important were included in the analysis. Baseline laboratory values in this study were defined as the value closest to T_0 within the 96 h before T_0 . Exceptions

were for CRP, ferritin, and D-dimer, which were defined as within 96 h before T_0 and up to 12 h after T_0 because of laboratory ordering practices. Patient survival was calculated from T_0 to the time of in-hospital death. Data from patients discharged from the hospital or remaining in the hospital on April 24, 2020, were considered censored.

Patient survival was compared between treatment groups using the Cox regression model, adjusting for all covariates outlined above. The proportional hazards assumption was assessed and deemed acceptable. Missing laboratory values were handled using multiple imputation, using 50 imputed datasets. We used the fully conditional method with a discriminant function for the imputation of the laboratory categories (eg, low, normal, or high, as specified in Table 2). PROC MI (SAS version 9.4 software [SAS Institute]), with all variables from Table 1, was used for the multiple imputation. Holm's stepdown procedure for multiple comparisons was used to account for the 15 pairwise tests resulting from the six groups. The final model included all clinically important covariates regardless of their statistical significance (the full model). SAS version 9.4 software was used for the statistical analysis. Results were considered statistically significant if $P < .05$.

Results

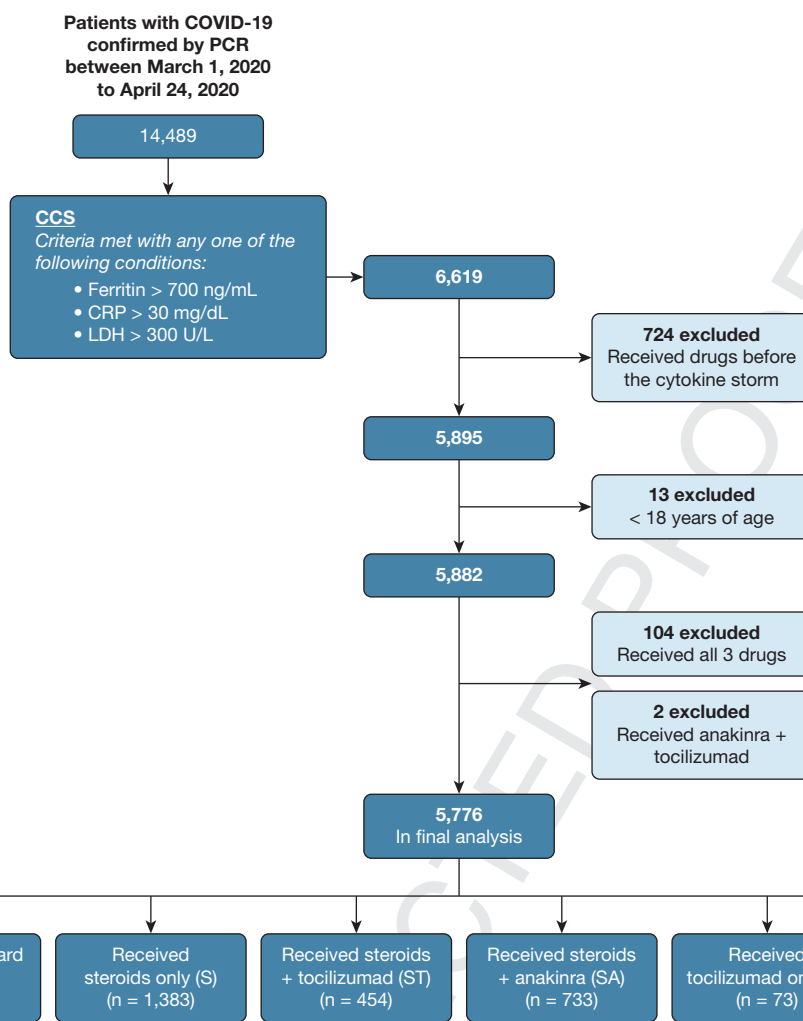
Patient Characteristics

Of the 14,489 patients with COVID-19 seen in EDs or admitted to hospitals within the Northwell Health system during the study period, 6,619 (45.7%) patients met at least one criterion for the definition of CCS. Of these, 5,776 patients were included in the final analysis (Fig 1).

Demographic characteristics and distribution of covariates across groups are reported in Table 1. Men outnumbered women by a ratio of 2:1. A significant difference in the racial distribution across treatment groups was noted, with more Black people in the A group and White people in the T group. A higher proportion of patients identifying as other or multiracial race were noted in the A group. Most of the cohort (> 65%) had never smoked. The most common comorbidities across groups were: hypertension (44%-

59%), diabetes (32%-46%), cardiovascular disease (5%-14%), chronic kidney disease (5%-12%), cancer (5%-11%), and asthma (3%-12%). Less than 2% of patients were receiving hemodialysis before T_0 . Approximately 40% of the patients in the cohort demonstrated a low predicted 10-year survival rate based on Charlson comorbidity index score (≥ 5). More patients had a moderate to high Charlson comorbidity index score (≥ 3) in the T group as compared with other treatment groups. More patients in the S, ST, and T treatment groups were receiving IMV and vasopressors at T_0 .

More than 80% of the patients who met criteria for CCS showed elevated D-dimer levels, of which approximately 20% showed levels more than five times the upper limit of normal. The most common criterion met for CCS definition was high LDH, which was found in 76.2% of patients, either alone or in combination with other criteria, followed by high ferritin (63.2%) and CRP (8.4%). The definition of CCS was met by only one



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Figure 1 – Consort diagram showing selection of patients, inclusion criteria, and exclusion criteria applied to form the final cohort of 3,098 patients. Exclusion criteria included receiving any of the immunomodulatory drugs before the diagnosis of cytokine storm, age younger than 18 years, having received all three study drugs, having received the combination of anakinra and tocilizumab, or missing clinically relevant covariates. Three thousand ninety-eight patients remained in the final analysis. CCS = coronavirus disease 2019 cytokine storm; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; LDH = lactate dehydrogenase; PCR = polymerase chain reaction.

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criterion in 56.0% of patients, by two criteria in 40.2% of patients, and by three criteria in 3.8% of patients. The distribution of CRP, ferritin, and LDH levels is provided in e-Figure 1. A statistically significant difference was found between treatment arms with respect to CRP, ferritin, and LDH levels ($P < .0001$), with the SoC group showing lower median CRP, ferritin, and LDH levels compared with the S, ST, and SA groups.

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Kaplan-Meier (unadjusted) survival estimates for treatment groups are presented in Figure 2. A Cox proportional hazards regression model was used to compare treatment groups, adjusting for clinically important variables. In this model, demographic covariates that were statistically significantly associated with increased mortality were older age, unknown smoking status,

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Medicaid, and self-pay insurance (Table 2). Higher mortality was associated with the presence of asthma, interstitial lung disease, and the need for IMV at T_0 . Higher mortality also was associated with elevated D-dimer level, thrombocytopenia, low glomerular filtration rate, transaminitis, hyponatremia, and abnormal neutrophil-to-lymphocyte ratio. Lower mortality was associated with hypertension and Black race.

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Pairwise comparisons between treatment groups are presented in Figure 3. Patients in the ST, SA, and S groups showed significantly improved survival compared with the SoC group (ST vs SoC: hazard ratio [HR], 0.44; 95% CI, 0.35-0.55; $P < .0001$; SA vs SoC: HR, 0.68; 95% CI, 0.57-0.81; $P < .0001$; S vs SoC: HR, 0.66; 95% CI, 0.57-0.76; $P < .0001$). When comparing

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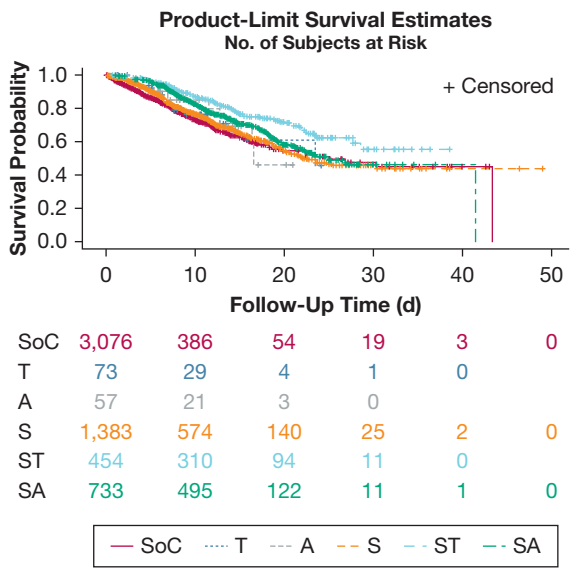


Figure 2 – Model-based Kaplan-Meier plots showing treatment groups (adjusted for covariates). This figure represents the unadjusted Kaplan-Meier plots for treatment groups with number of patients at risk. The treatment groups are as follows: A = anakinra only; S = steroid only; SA = steroids plus anakinra; SoC = standard of care; ST = steroids plus tocilizumab; T = tocilizumab only.

the treatment groups with each other, the ST group showed significantly improved survival compared with SA or S groups (ST vs SA: HR, 0.64; 95% CI, 0.50-0.81; $P = .003$; ST vs S: HR, 0.66; 95% CI, 0.53-0.83; $P = .004$). No significant differences were seen between the other treatment groups.

At T_0 , in patients receiving only one of the three treatments, corticosteroids were started earlier (median, 27.6 h; 25th-75th percentiles, 7.6-77.9 h) than either tocilizumab (median, 54.4 h; 25th-75th percentiles, 25.0-99.2 h) or anakinra (median, 66.3 h; 25th-75th percentiles, 23.9-97.6 h). In both groups that received combination therapy with corticosteroids, on average corticosteroids were started before the second drug and at a similar interval from T_0 (e-Fig 2). The time from T_0 to tocilizumab dosing was comparable when used alone (median, 54.4 h; 25th-75th percentiles, 25.0-99.2 h) or in combination with corticosteroids (median, 58.5 h; 25th-75th percentiles, 23.6-129.7 h). Anakinra alone was begun earlier (median, 66.3 h; 25th-75th percentiles, 23.9-97.6 h) than anakinra in the SA group (median, 77.5 h; 25th-75th percentiles, 36.6-130.7 h). Patients received oral or IV dexamethasone, IV methylprednisolone, or oral prednisone for corticosteroid therapy (e-Table 2). The average number of days of steroids use was approximately 4.5 days, except for methylprednisolone in the ST and SA groups,

in which the average duration was 6.5 days. The average length of steroid use was 12 to 15 mg for dexamethasone, 85 to 89 mg for methylprednisolone, and 29 to 33 mg for prednisone.

Rates of culture-positive bloodstream infections in the treatment groups are reported in e-Table 3. Approximately 5% of patients in the S group demonstrated bacteremia compared with 10% in the SA and ST groups. Similarly, 2% to 3% of patients in the steroid groups S, ST, and SA were noted to have fungemia. In comparison, the rate of bacteremia in the SoC group was 1.6% and the rate of fungemia was 0.4%. No bacteremia or fungemia were reported in the T or A groups.

Discussion

This large retrospective, observational study leveraged natural heterogeneity in practice patterns for CCS patients. We described hospital survival outcomes in patients receiving different combinations of immunomodulatory therapy with careful consideration of potential confounders available in the electronic health records. Our findings suggested that corticosteroids used alone or in combination with tocilizumab or anakinra were associated with lower mortality as compared with SoC treatment. This association remained after controlling for covariates that influence mortality in COVID-19.

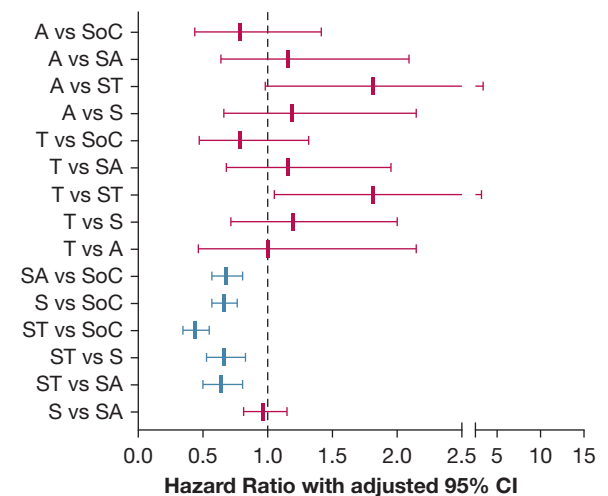


Figure 3 – Graph showing hazard ratios for treatment differences using Tukey's adjustment for multiple comparisons. The figure represents pairwise comparisons for all treatment groups with Tukey's adjustment for multiple comparison. Groups in red are statistically significant. The groups are as follows: A = anakinra only; S = steroid only; SA = steroids plus anakinra; SoC = standard of care; ST = steroids plus tocilizumab; T = tocilizumab only.

Age was associated with increased mortality regardless of treatment group, consistent with other COVID-19 survival analyses. Contradictory to previous reports, Black race was associated with better overall survival compared with White race. Inherent differences may have existed in clinically important covariates in this population that may have contributed to better survival and that could not be analyzed further. Medicaid and self-pay insurance were associated with increased mortality. We speculate that this may be because of factors such as hospital admission later in disease course or socioeconomic disadvantages. For surrogates of illness severity, the need for IMV before T_0 was associated with increased mortality, whereas the need for vasopressors was not.

Prior diagnosis of interstitial lung disease was associated with increased mortality, consistent with existing literature.¹³ Surprisingly, those with comorbid hypertension showed lower mortality, which is contradictory to other reports.^{1,14} One study suggested that use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers via renin-angiotensin pathway modulation may confer a protective effect in the setting of CCS.¹⁵ Our analysis did not include consideration of home medications. Alternatively, adjustments for covariates in our model may have uncovered an association between hypertension and COVID-19 outcomes that could be investigated further. Interestingly, increased mortality was associated with asthma, but not with COPD. Early in the pandemic, chronic lung disease, including asthma, was reported as one of the comorbidities associated with hospital admissions.¹⁶ Later studies failed to demonstrate increased mortality in patients with asthma and COPD,¹⁷ although pre-existent asthma was reported to be associated with prolonged intubation time. Atopic asthma and treatment with inhaled corticosteroids were reported to correlate with lower sputum cell expression of ACE2,¹⁸⁻²⁰ implying decreased susceptibility and morbidity in these patients.

High D-dimer level was associated significantly with in-hospital mortality. This is consistent with known evidence that elevated D-dimer level is associated with worse outcomes²¹ and predicts a higher chance of requiring ICU admission and increased 28-day mortality.^{5,22,23} Thrombocytopenia is associated with severity of SARS-CoV-2 infection.²⁴ We also found thrombocytopenia to be associated with higher

mortality. Both thrombocytopenia and elevated D-dimer level reflect the known coagulopathy in COVID-19.²⁵

IL-6 is an important mediator of inflammation that plays an essential role in host response to viral infection (Chau et al, in press). Higher IL-6 levels were observed in patients with severe COVID-19 compared with those with mild disease.^{3,26} Therefore, tocilizumab was proposed early in the pandemic as a potential treatment for those with CCS.^{27,28} Small retrospective, observational studies of tocilizumab use in COVID-19 have been published with continued controversy.^{7,29} Biran et al³⁰ and Guaraldi et al³¹ published larger reports with 210 and 544 patients, respectively, who received either intravenous or subcutaneous tocilizumab. Per Biran et al, tocilizumab seemed to decrease hospital-related mortality (HR, 0.64; 95% CI, 0.47-0.87; $P = .0040$). Guaraldi et al³¹ reported a reduced requirement of IMV or death (adjusted HR, 0.61; 95% CI, 0.40-0.92; $P = .020$). More recently, Mikulska et al examined the combined effect of steroids and tocilizumab and noted an overall survival benefit as compared with SoC treatment (HR, 0.41; 95% CI, 0.19-0.89; $P = .025$). Supporting this result, our cohort who received ST were more likely to survive compared with those who received SoC treatment. Notably, ST treatment seemed to show an augmented survival effect compared with S treatment alone. Tocilizumab alone did not improve survival.

Although corticosteroids are used in the treatment of hyperinflammatory syndromes and ARDS,³² their use in viral infections is controversial. Although initially not recommended by the World Health Organization³³ for use in COVID-19 pneumonia, corticosteroids have become a widely accepted treatment option after the RECOVERY trial demonstrated improved survival compared with SoC treatment both in patients receiving IMV (29.3% vs 41.4%; rate ratio, 0.64; 95% CI, 0.51-0.81) and in patients without IMV (23.3% vs 26.2%; rate ratio, 0.82; 95% CI, 0.72-0.94).³⁴ More recently, the World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies published a meta-analysis supporting the independent use of corticosteroids in patients with COVID-19. However, the RECOVERY trial contributed 59.1% of patients to this analysis, which favors dexamethasone over hydrocortisone (OR, 0.69; 95% CI, 0.43-1.12; $P = .13$) and methylprednisolone (OR, 0.91; 95% CI, 0.29-2.87; $P = .87$).³⁵ Overall, our study findings support the use of corticosteroids in COVID-19 and may add to the data presented by the RECOVERY trial and the World Health Organization

1431 Rapid Evidence Appraisal for COVID-19 Therapies
 1432 data.
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 1434 Anti-IL-1 therapy has been an attractive choice in the
 1435 treatment of COVID-19 because of its short half-life,
 1436 safety, and tolerability profile. IL-1 β has been implicated
 1437 in lung inflammation, fibrosis,³⁶ and indirectly, with
 1438 activation of the inflammatory cascade.³⁷⁻⁴⁰ A study
 1439 examining cytokine kinetics during COVID-19 showed
 1440 an IL-1 peak before the apex of respiratory distress and
 1441 the surge of other inflammatory cytokines.⁴¹ Anakinra
 1442 also has been shown to improve survival in a subset of
 1443 sepsis patients with hyperferritinemia and hepatobiliary
 1444 dysfunction¹⁰ when compared with placebo.⁴²
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 1446 Small studies report improvement in clinical outcomes
 1447 with use of anakinra in COVID-19.^{8,43,44} Cavalli et al⁸
 1448 evaluated 36 hospitalized non-ICU patients with CCS
 1449 and observed improvements in respiratory function,
 1450 inflammatory markers, and intubation avoidance in
 1451 72% of patients receiving high-dose intravenous
 1452 anakinra as compared with low-dose IV anakinra or SoC
 1453 treatment. Huet et al⁴³ described a prospective study
 1454 with a historical comparison group in which anakinra
 1455 was dosed subcutaneously at 100 mg twice daily for 72 h
 1456 followed by 100 mg daily for 7 days. IMV or death was
 1457 reduced when compared with SoC treatment (HR, 0.22;
 1458 95% CI, 0.11-0.41; $P < .0001$). Most recently, Cauchois
 1459 et al⁴⁴ reported that 12 patients who received
 1460 intravenous anakinra 300 mg for 5 days, tapered to
 1461 200 mg daily for 2 days, and finally 100 mg for 1 day
 1462 showed similar beneficial results.
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 1465 In our study, although patients treated with anakinra in
 1466 combination with corticosteroids showed improved
 1467 survival compared with patients receiving SoC
 1468 treatment, patients receiving anakinra alone did not. The
 1469 dose of anakinra suggested in our health system protocol
 1470 (100 mg subcutaneous four times daily for 3 days,
 1471 followed by a suggested taper) was modest in
 1472 comparison with that used in some of the above studies.
 1473 The lack of benefit with anakinra may have been the
 1474 result of lower doses, delayed time to treatment, and
 1475 subcutaneous administration, leading to decreased drug
 1476 availability, especially in the critically ill.
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 1478 Biological effects of anakinra and tocilizumab are slower
 1479 when compared with steroids. Also with anakinra, we
 1480 observed a delay in drug initiation when combined with
 1481 corticosteroids. This leads us to question whether the
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timing to drug administration and the time to onset of
 action influenced the outcome among our treatment
 groups. Statistical analysis of the variation of drug
 administration across treatment groups was not feasible
 in this study. Further analysis of our data is needed to
 evaluate the effects of immunomodulatory treatments
 on disease progression, including rates of thrombosis.

Given the small sample sizes in the groups receiving
 tocilizumab or anakinra only, we should be cautious in
 interpreting the relative lack of survival advantage in
 these groups. To test the robustness of the model, we
 performed sensitivity analyses by removing groups with
 small sample sizes (either the A or T groups). The results
 remained consistent with those of the full model.

Increased rates of bacteremia and fungemia were found
 in the steroid groups compared with the SoC group (e-
 Table 5). However, despite this increase in the infection^{Q14}
 rate, improved survival remained in these cohorts.

Although we were rigorous in our approach to the
 study design and data analysis, intrinsic limitations
 exist that preclude definitive conclusions in
 retrospective studies. Although the effect of variability
 in systematic practices across the individual hospitals
 in the health system could not be evaluated, we did
 look at differences between tertiary vs community
 hospitals. Despite similar use of immunomodulatory
 therapies in tertiary and community centers, tertiary
 facilities showed a higher survival. Potential
 explanations for this could include a greater number
 of ICU beds, subspecialist availability, or differences in
 patient demographics between hospitals.

To our knowledge, our study is the largest retrospective
 analysis to date reporting on outcomes comparing the^{Q15}
 use of immunomodulatory therapies such as
 corticosteroids, tocilizumab, and anakinra in the
 treatment of COVID-19 CCS. Our findings suggest that
 patients receiving steroids and tocilizumab experienced
 the lowest mortality of all treatment groups.
 Corticosteroid use, either alone or in combination with
 tocilizumab or anakinra, was associated with lower
 hospital mortality compared with SoC treatment. A
 randomized clinical trial with head-to-head comparison
 of tocilizumab plus corticosteroids vs corticosteroids
 alone is warranted. Further investigation into the effect
 of dosing and timing of these drugs also needs to be
 elucidated.

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1549^{Q23} ***Northwell COVID-19 Research**

1550 **Consortium Collaborators:** Stuart L. Cohen, MD (Biostatistics Unit, Northwell Health, Manhasset, NY); the Institute of Health Innovations and Outcomes Research and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Hempstead, New York); Jennifer Cookingham, MHA (Institute of Health Innovations and Outcomes Research, Northwell Health, Manhasset, NY); David A. Hirschwerk, MD (Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Hempstead, New York); Naomi I. Maria, PhD (the Institute of Molecular Medicine, Northwell Health, Manhasset, NY); Sanjaya K Satapathy, MD (Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, and the Feinstein Institute for Medical Research, the Division of Hepatology, Northwell Health, Hempstead, New York); Cristina Sison, PhD; Matthew Taylor, MD (the Institute of Cancer Research and the Division of Critical Care Medicine, Cohen Children's Medical Center of New York, Northwell Health, New Hyde Park, NY); and Michael Qiu, MD, PhD (Department of Medicine, the Department of Information Services, Northwell Health, Manhasset, NY).

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1588^{Q30} **Additional information:** The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

1591 **References**

1592^{Q31} 1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in

the New York City area. *JAMA*. 2020;XX:XX-XX.

2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;XX:XX-XX.
3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;XX:XX-XX.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;XX:XX-XX.
6. Fang X, Mei Q, Yang T, et al. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19. *J Infect*. 2020;XX:XX-XX.
7. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev*. 2020:102568.
8. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;XX:XX-XX.
9. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020. annrheumdis-2020-217706.
10. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Crit Care Med*. 2016;44(2):275-281.
11. Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: differential diagnosis of HLH and sepsis. *Crit Rev Oncol Hematol*. 2017;114:1-12.
12. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5).
13. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*.
14. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;XX:XX-XX.
15. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients

with hypertension. *Emerg Microbes Infect*. 2020;9(1):757-760.

16. Garg S. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 states, March 1–30, 2020. *MMWR Morbid Mortal Wkly Rep*. 2020;69:XX-XX.
17. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. *PLOS One*. 2020;15(8):e0238215.
18. Camiolo MJ, Gauthier M, Kaminski N, Ray A, Wenzel SE. Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype. *J Allergy Clin Immunol*. 2020;XX:XX-XX.
19. Peters MC, Sajuthi S, Deford P, et al. COVID-19 related genes in sputum cells in asthma: relationship to demographic features and corticosteroids. *Am J Respir Crit Care Med*. 2020;(ja).
20. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol*. 2020;XX:XX-XX.
21. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost*. 2020;120(5):876-878.
22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;XX:XX-XX.
23. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
24. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020;506:145-148.
25. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol*. 2020;99(6):1205-1208.
26. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. *Rev Med Virol*. n/a(n/a):e2141.
27. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? *J Transl Med*. 2020;18:164.
28. Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. *Clin Drug Invest*. 2020;40(6):511-518.
29. Colaneri M, Bogliolo L, Valsecchi P, et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms*. 2020;8(5):XX-XX.

- 1651 30. Biran N, Ip A, Ahn J, et al. Tocilizumab
1652 among patients with COVID-19 in the
1653 intensive care unit: a multicentre
1654 observational study. *Lancet Rheumatol.*
2020;XX. XX-XX.
- 1655 31. Guaraldi G, Meschiari M, Cozzi-Lepri A,
1656 et al. Tocilizumab in patients with severe
1657 COVID-19: a retrospective cohort study.
Lancet Rheumatol. 2020;2(8):e474-e484.
- 1658 32. Meduri GU, Bridges L, Shih MC,
1659 Marik PE, Siemieniuk RAC, Kocak M.
1660 Prolonged glucocorticoid treatment is
1661 associated with improved ARDS
1662 outcomes: analysis of individual patients'
1663 data from four randomized trials and
1664 trial-level meta-analysis of the updated
1665 literature. *Intensive Care Med.* 2016;42(5):
1666 829-840.
- 1667 33. World Health Organization. *Clinical
1668 management of COVID-19: an interim
1669 report.* Geneva: World Health
1670 Organization; 2020.
- 1671 34. Dexamethasone in hospitalized patients
1672 with Covid-19—preliminary report.
1673 *N Engl J Med.* 2020;XX. XX-XX.
- 1674 35. WHO Rapid Evidence Appraisal for
1675 COVID-19 Therapies (REACT) Working
1676 Group. Association between
1677 administration of systemic corticosteroids
1678 and mortality among critically ill patients
1679 with COVID-19: a meta-analysis. *JAMA.*
1680 2020;XX. XX-XX.
- 1681 36. Kolb M, Margetts PJ, Anthony DC,
1682 Pitossi F, Gauldie J. Transient expression
1683 of IL-1beta induces acute lung injury and
1684 chronic repair leading to pulmonary
1685 fibrosis. *J Clin Invest.* 2001;107(12):1529-
1686 1536.
- 1687 37. Warnatsch A, Ioannou M, Wang Q,
1688 Papayannopoulos V. Inflammation.
1689 Neutrophil extracellular traps license
1690 macrophages for cytokine production in
1691 atherosclerosis. *Science.* 2015;349(6245):
1692 316-320.
- 1693 38. Meher AK, Spinosa M, Davis JP, et al.
1694 Novel role of IL (interleukin)-1beta in
1695 neutrophil extracellular trap formation
1696 and abdominal aortic aneurysms.
1697 *Arterioscler Thromb Vasc Biol.* 2018;38(4):
1698 843-853.
- 1699 39. Lachowicz-Scroggins ME, Dunican EM,
1700 Charbit AR, et al. Extracellular DNA,
1701 neutrophil extracellular traps, and
1702 inflammasome activation in severe
1703 asthma. *Am J Respir Crit Care Med.*
1704 2019;199(9):1076-1085.
- 1705 40. Guo L, Rondina MT. The era of
thromboinflammation: platelets are
dynamic sensors and effector cells during
infectious diseases. *Front Immunol.*
2019;10:2204.
41. Ong EZ, Chan YFZ, Leong WY,
et al. A dynamic immune response
shapes COVID-19 progression. *Cell
Host Microbe.* 2020;XX. XX-XX.
42. Fisher CJ Jr, Dhainaut JF, Opal SM,
et al. Recombinant human interleukin
1 receptor antagonist in the
treatment of patients with sepsis
syndrome. Results from a
randomized, double-blind, placebo-
controlled trial. Phase III rhIL-1ra
Sepsis Syndrome Study Group. *JAMA.*
1994;271(23):1836-1843.
43. Huet T, Beaussier H, Voisin O, et al.
Anakinra for severe forms of COVID-19:
a cohort study. *Lancet Rheumatol.*
2020;2(7):e393-e400.
44. Cauchois R, Koubi M, Delarbre D,
et al. Early IL-1 receptor blockade in
severe inflammatory respiratory failure
complicating COVID-19. *Proc Natl
Acad Sci U S A.* 2020;117(32):18951-
18953.