SUPPLEMENTARY MATERIAL

Appendix 1. Institutional Review Boards and Ethics Committees

Comitato Etico dell'IRCCS San Matteo di Pavia	Comitato Etico dell'IRCCS San Matteo di Pavia, IRCCS Policlinico San Matteo, Viale Golgi, 19, 27100, Pavia, Lombardia, Italy	Italy
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
CPP Sud Ouest et Outre Mer I	CPP Sud Ouest et Outre Mer I, 10 Chemin du Raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
CPP Sud Ouest et Outre Mer I	CPP Sud Ouest et Outre Mer I, 10 Chemin du Raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
CEIC Área 5: Hospital Universitario la Paz	CEIC Área 5: Hospital Universitario la Paz, Paseo de la Castellana, 261, 28036, Madrid, Spain	Spain
CEIC Área 5: Hospital Universitario la Paz	CEIC Área 5: Hospital Universitario la Paz, Paseo de la Castellana, 261, 28036, Madrid, Spain	Spain
CEIC Área 5: Hospital Universitario la Paz	CEIC Área 5: Hospital Universitario la Paz, Paseo de la Castellana, 261, 28036, Madrid, Spain	Spain
CEIC Área 5: Hospital Universitario la Paz	CEIC Área 5: Hospital Universitario la Paz, Paseo de la Castellana, 261, 28036, Madrid, Spain	Spain
Comité d'Éthique de la Recherche	Comité d'Éthique de la recherche, CHUM, Pavillion R, 900 Rue St-Denis, 3rd Floor, H2X 0A9, Montreal, Quebec, Canada	Canada
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO)	Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO), Dr. Nassaulaan 10, 9401 HK, Assen, Netherlands	Netherlands

Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO)	Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO), Dr. Nassaulaan 10, 9401 HK, Assen, Netherlands	Netherlands
West Midlands: Coventry & Warwickshire Research Ethics Committee	West Midlands: Coventry & Warwickshire Research Ethics Committee, The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom	United Kingdom
Ethikkommission der Medizinischen Fakultät Universität zu Köln	Ethikkommission der Medizinischen Fakultät Universität zu Köln, Kerpener Str. 62, Gebäude 5, 50937, Köln, Germany	Germany
Ethikkommission der Medizinischen Fakultät Universität zu Köln	Ethikkommission der Medizinischen Fakultät Universität zu Köln, Kerpener Str. 62, Gebäude 5, 50937, Köln, Germany	Germany
Ethikkommission der Medizinischen Fakultät Universität zu Köln	Ethikkommission der Medizinischen Fakultät Universität zu Köln, Kerpener Str. 62, Gebäude 5, 50937, Köln, Germany	Germany
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
University Health Network Research Ethics Board	University Health Network Research Ethics Board, 700 Bay Street, 17th Floor, Suite 1700, M5G 1Z6, Toronto, Ontario, Canada	Canada
CPP Sud Ouest Et Outre Mer I	CPP Sud Ouest Et Outre Mer I, 10 Chemin du Raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
CPP Sud Ouest Et Outre Mer I	CPP Sud Ouest Et Outre Mer I, 10 Chemin du Raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
CPP Sud Ouest Et Outre Mer I	CPP Sud Ouest Et Outre Mer I, 10 Chemin du Raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
CPP Sud Ouest Et Outre Mer I	CPP Sud Ouest Et Outre Mer I, 10 Chemin du Raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
Videnskabsetiske Komité Region Midt	Videnskabsetiske Komité Region Midt, Sundhedssekr., Skottenborg 26, Postboks 21, 8800, Viborg, Denmark	Denmark
Videnskabsetiske Komité Region Midt	Videnskabsetiske Komité Region Midt, Sundhedssekr., Skottenborg	Denmark

	26, Postboks 21, 8800, Viborg, Denmark	
Videnskabsetiske Komité Region Midt	Videnskabsetiske Komité Region Midt, Sundhedssekr., Skottenborg 26, Postboks 21, 8800, Viborg, Denmark	Denmark
Videnskabsetiske Komité Region Midt	Videnskabsetiske Komité Region Midt, Sundhedssekr., Skottenborg 26, Postboks 21, 8800, Viborg, Denmark	Denmark
CPP Sud Ouest Et Outre Mer	CPP Sud Ouest Et Outre Mer I, 10 chemin du raisin, ARS Midi-Pyrénées, Bureau 1028, 31050, Toulouse cedex 9, France	France
Comitato Etico Brianza	Comitato Etico Brianza, Via Pergolesi, 33, 20900, Monza, Lombardia, Italy	Italy
Hamilton Integrated Research Ethics Board	Hamilton Integrated Research Ethics Board, 293 Wellington St. North, Suite 102, L8L 8E7, Hamilton, Ontario, Canada	Canada
Hamilton Integrated Research Ethics Board	Hamilton Integrated Research Ethics Board, 293 Wellington St. North, Suite 102, L8L 8E7, Hamilton, Ontario, Canada	Canada
Comitato Etico della Seconda Università di Napoli; Az. Osp. Univ. S.U.N., A.O.R.N. "Ospedali"	Comitato Etico della Seconda Università di Napoli, Az. Osp. Univ. S.U.N., A.O.R.N. "Ospedali," Via Costantinopoli, 104, 80138, Napoli, Italy	Italy
Comitato Etico Ist. Naz. Mal. Inf. L. Spallanzani	Comitato Etico Ist. Naz. Mal. Inf. L. Spallanzani, Via Portuense, 292, 149, Roma, Italy	Italy
Comitato Etico Della Provincia di Bergamo	Comitato Etico della Provincia di Bergamo, Piazza OMS-Organizzazione Mondiale della Sanità, 1, 24127, Bergamo, Italy	Italy
Comitato Etico Milano Area 1, c/o ASST FBF Sacco, P.O. L. Sacco	Comitato Etico Milano Area 1, c/o ASST FBF Sacco, P.O. L. Sacco, Via G.B. Grassi, 74, 20157, Milano, Italy	Italy
Hamilton Integrated Research Ethics Board	Hamilton Integrated Research Ethics Board, 293 Wellington St. North, Suite 102, L8L 8E7, Hamilton, Canada	Canada
Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO)	Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO), Dr.	Netherlands

	Nassaulaan 10, 9401 HK, Assen, Netherlands	
Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO)	Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO), Dr. Nassaulaan 10, 9401 HK, Assen, Netherlands	Netherlands
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CEIC Área 5: Hospital Universitario la Paz	CEIC Área 5: Hospital Universitario la Paz, Paseo de la Castellana, 261, 28036, Madrid, Spain	Spain
West Midlands: Coventry & Warwickshire Research Ethics Committee	West Midlands: Coventry & Warwickshire Research Ethics Committee, The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom	United Kingdom
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Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
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Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Sharp HealthCare	Sharp HealthCare, IRB, 7930 Frost Street, Suite 300, San Diego, CA, 92123, United States	United States
Rush University Medical Center	Rush University Medical Center Institutional Review Board, 1653 West Congress Parkway, Jelke Building Room 1591, Chicago, IL, 60612, United States	United States
Cleveland Clinic	Cleveland Clinic, Institutional Review Board, 10681 Carnegie Ave, OS-1, Cleveland, OH, 44195, United States	United States
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Providence St. Joseph Health IRB	Providence St. Joseph Health IRB, 1801 Lind Ave SW, Renton, WA, 98057, United States	United States
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Duke University	Duke University; DUHS Institutional Review Board, Hock Plaza, 2424 Erwin Rd, Durham, NC, United States	United States

Bronx VAMC IRB	Bronx VAMC IRB, 130 West Kingsbridge Road, 2Fo1 Research & Development, Bronx, NY, 10468, United States	United States
Advarra	Advarra, 6940 Columbia Gateway Drive, Columbia, MD, 21046, United States	United States
Univ. of Chicago	Univ of Chicago, Institutional Review Board, 5841 S. Maryland Ave., MC7132, I-625, Chicago, IL, 60637, United States	United States

Appendix 2. Propensity Score Matching Methods

Data from the tocilizumab 8-mg/kg arm of MARIPOSA were analyzed and compared with data from the placebo arm of COVACTA, followed by sensitivity analysis including pooled data from the tocilizumab 8-mg/kg and 4-mg/kg arms of MARIPOSA. Inclusion criteria were matched, and the subset of patients with severe disease in MARIPOSA (similar to the COVACTA population) was included but patients with moderate disease were excluded. Propensity scores were calculated based on the following covariates, which could impact treatment assignment or outcome: ordinal baseline score (captures mechanical ventilation status), age, sex, antiviral use (yes/no), and corticosteroid use (yes/no). Overlapping support was checked for the propensity score distributions. Matching was performed using the MatchIt (version 3.0.2) algorithm, which matched the treatment groups from MARIPOSA and the control group from COVACTA using propensity scores with the nearest neighbor algorithm. Weighting was performed using inverse probability weighting according to the ATT estimand (1). Success of weighting and matching was assessed using Love plots, which chart the standardized differences of variables (standardized mean difference [SMD] = x_treatment – x_control)/(pooled standard deviation), where SMD <0.1 or SMD <0.25 was considered acceptable (2, 3), and histograms (for categorical variables) or density plots (for continuous variables) before and after weighting were used for visual comparison. Several methods were used to estimate the treatment difference for subgroup analysis and the interaction term between the continuous predictive biomarker and treatment: ATT estimand via propensity score weighting (primary analysis method), propensity score regression, naive, propensity score matching.

Table S1. Baseline Characteristics of Patients in MARIPOSA (severe disease subset) and COVACTA

	COVACTA ***N* = 437**	**MARIPOSA** ***N* = 77**
Mechanical ventilation, *n* (%)		
No	270 (61.8)	65 (84.4)
Yes	167 (38.2)	12 (15.6)
Ordinal scale category, *n* (%)		
2	15 (3.4)	2 (2.6)
3	122 (27.9)	22 (28.6)
4	133 (30.4)	41 (53.2)
5	60 (13.7)	9 (11.7)
6	107 (24.5)	3 (3.9)
Sex, *n* (%)		
Female	136 (30.2)	29 (37.7)
Male	315 (69.8)	48 (62.3)
Age		
Mean (SD)	61.0 (14.3)	59.1 (14.4)
Median	63	60
Q1–Q3	53–71	50–70
Min–Max	22–96	27–91
Antiviral use, *n* (%)		
No	336 (74.5)	41 (53.2)
Yes	115 (25.5)	36 (46.8)
Steroid use, *n* (%)		
No	353 (78.3)	57 (74.0)
Yes	98 (21.7)	20 (26.0)

One patient who had an ordinal scale score of 7 at baseline (death) was excluded from the analysis. Q = quarter.

Table S2. Combinations of Predictive Biomarkers

Biomarker Combination	Estimate	*p* Value	2.5%	97.5%
Combined ferritin, IL-6, and CRP (*n* = 257)				
Ferritin	0.20	0.04	0.04	0.87
IL-6	0.89	0.88	0.18	3.97
CRP	0.48	0.42	0.06	2.51
Ferritin and IL-6	0.62	0.52	0.14	2.69
Ferritin and CRP	0.41	0.23	0.09	1.73
IL-6 and CRP	0.79	0.75	0.18	3.32
Ferritin or IL-6	0.48	0.16	0.16	1.30
Ferritin or CRP	0.40	0.09	0.12	1.08
IL-6 or CRP	0.82	0.68	0.29	2.09
Combined ferritin, LDH, and D-dimer (*n* = 165)				
Ferritin	0.19	0.05	0.03	0.99
D-dimer	1.16	0.86	0.22	6.09
LDH	1.68	0.56	0.29	9.61
Ferritin and D-dimer	0.54	0.49	0.09	3.13
Ferritin and LDH	0.32	0.20	0.05	1.83
D-dimer and LDH	1.97	0.44	0.36	11.46
Ferritin or D-dimer	0.51	0.25	0.16	1.56
Ferritin or LDH	0.47	0.22	0.14	1.51
D-dimer or LDH	1.30	0.66	0.40	4.07
LDH and D-dimer and ferritin	0.50	0.50	0.06	3.93

A median cutoff value was used for each biomarker.

CRP = C-reactive protein; IL-6 = interleukin-6; LDH = lactate dehydrogenase.

Table S3. Ferritin Levels According to Baseline Ordinal Scale

Baseline Ordinal Scale Category	Mean	Median	25%	75%	Standard Deviation	*n*
2	1135.88	640.17	201.78	2071.73	1036.74	12
3	2126.42	1677.39	870.15	2798.08	1634.71	104
4	3978.09	2422.27	1256.07	4458.50	7849.37	103
5	4315.15	3148.05	1659.09	5207.03	3860.48	54
6	3619.02	2464.96	1297.69	4392.89	4132.11	91

Ferritin levels are shown as pmol/L.

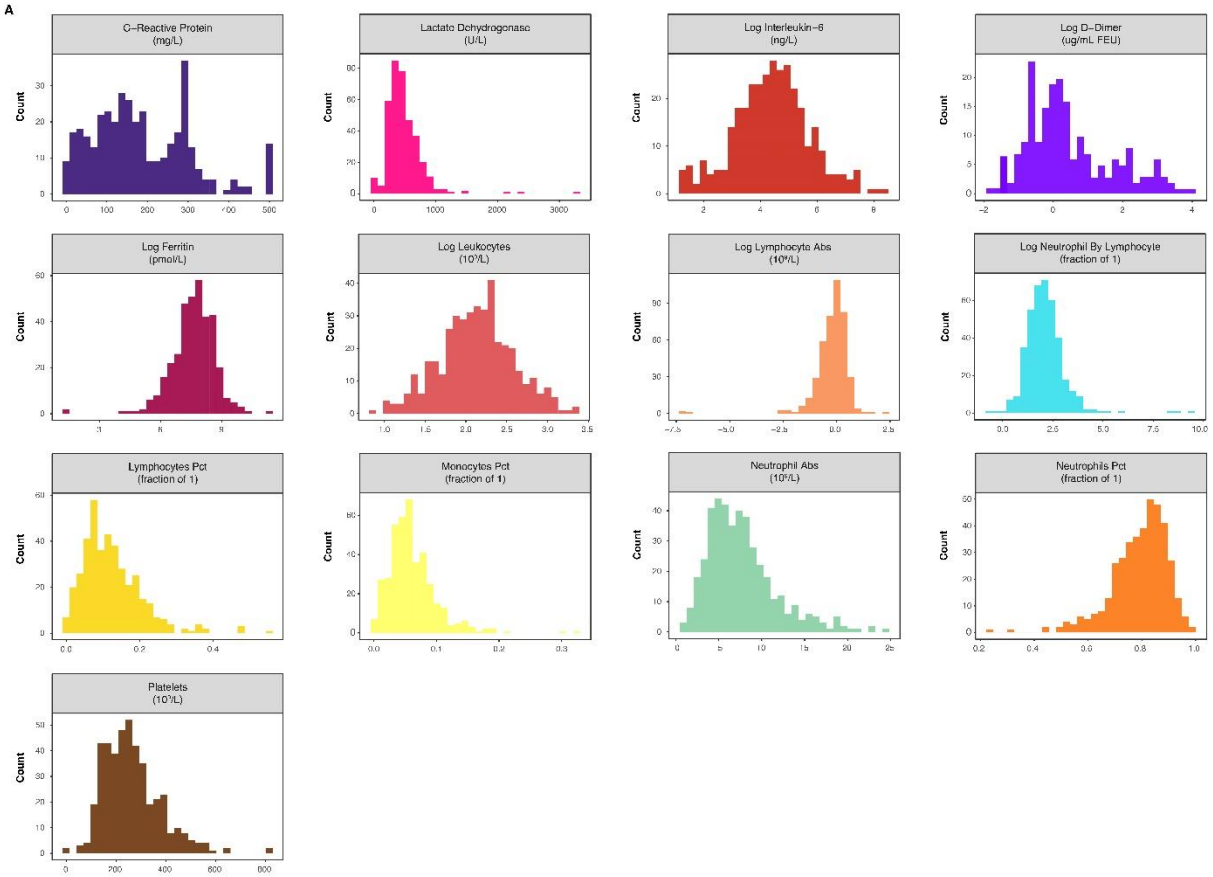
Table S4. D-Dimer Levels Among Survivors and Nonsurvivors in COVACTA and Published Studies

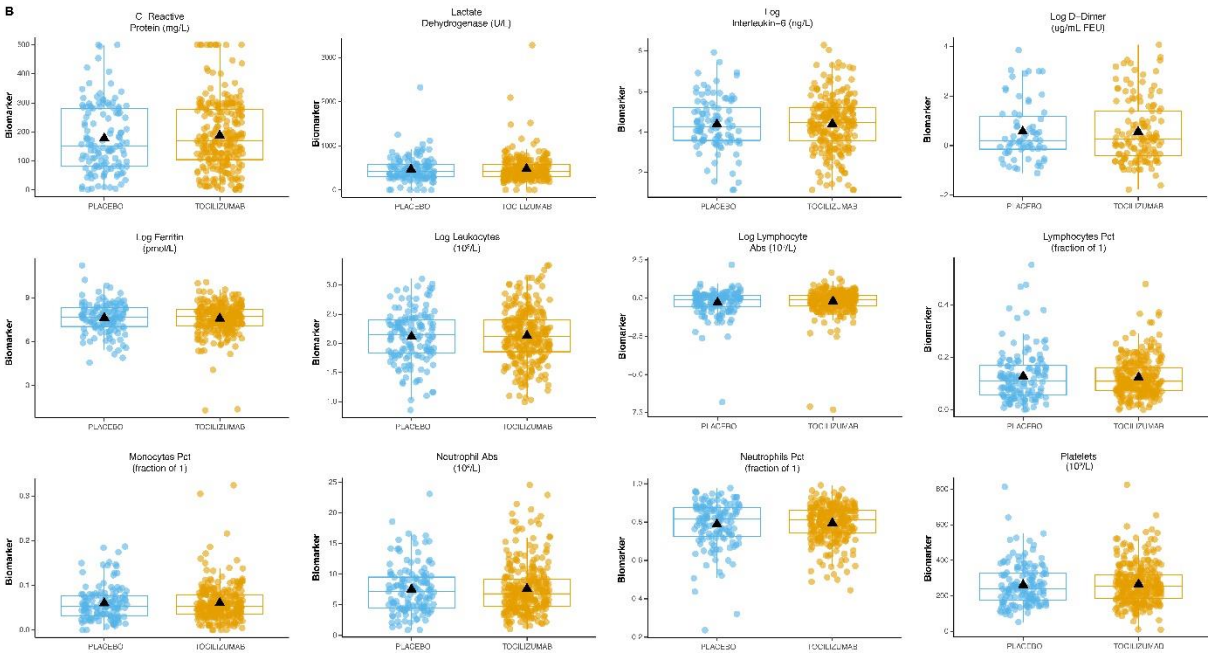
	Nonsurvivors		**Survivors**	
D-dimer, μg/mL*	***N***	**Mean (IQR) [median]**	***N***	**Mean (IQR) [median]**
COVACTA	47	7.16 (1.02–8.37) [2.68]	150	3.58 (0.63–2.32) [1.13]
Zhou F et al (4)	54	5.2 (1.5–21.1) [NR]	137	0.6 (0.3–1.0) [NR]
Tang N et al (5)	21	2.12 (0.77–5.27) [NR]	162	0.61 (0.35–1.29) [NR]

*Reported as fibrinogen equivalent units for COVACTA, though published studies do not state whether D-dimer was reported as fibrinogen equivalent units or D-dimer units.

IQR = interquartile range; NR = not reported.

Figure S1. Baseline biomarker levels. (A) Overall and (B) by treatment arm. (C) Correlation between baseline biomarkers. Ferritin, neutrophil-to-lymphocyte ratio, IL-6, D-dimer, absolute lymphocyte, and absolute leukocyte values are log transformed. IL-6 = interleukin-6.





c

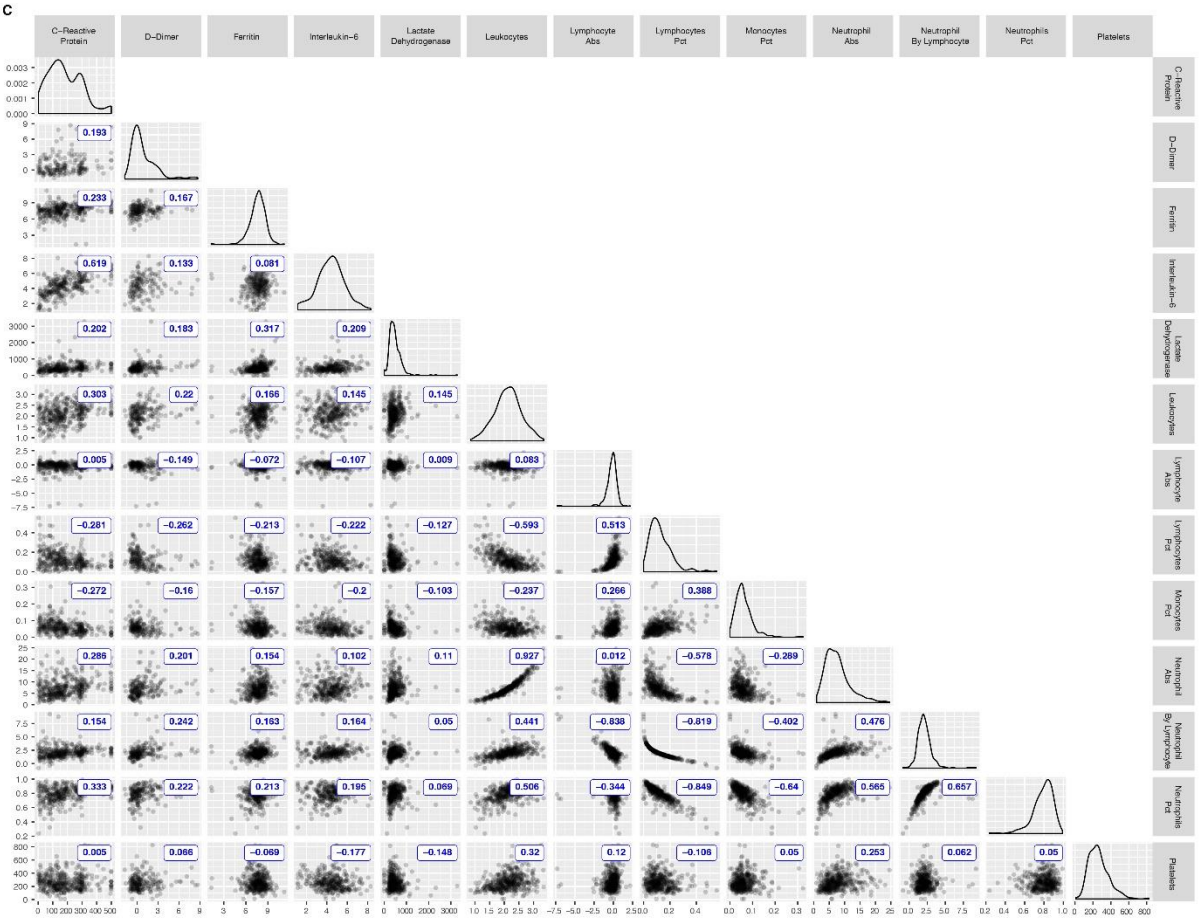
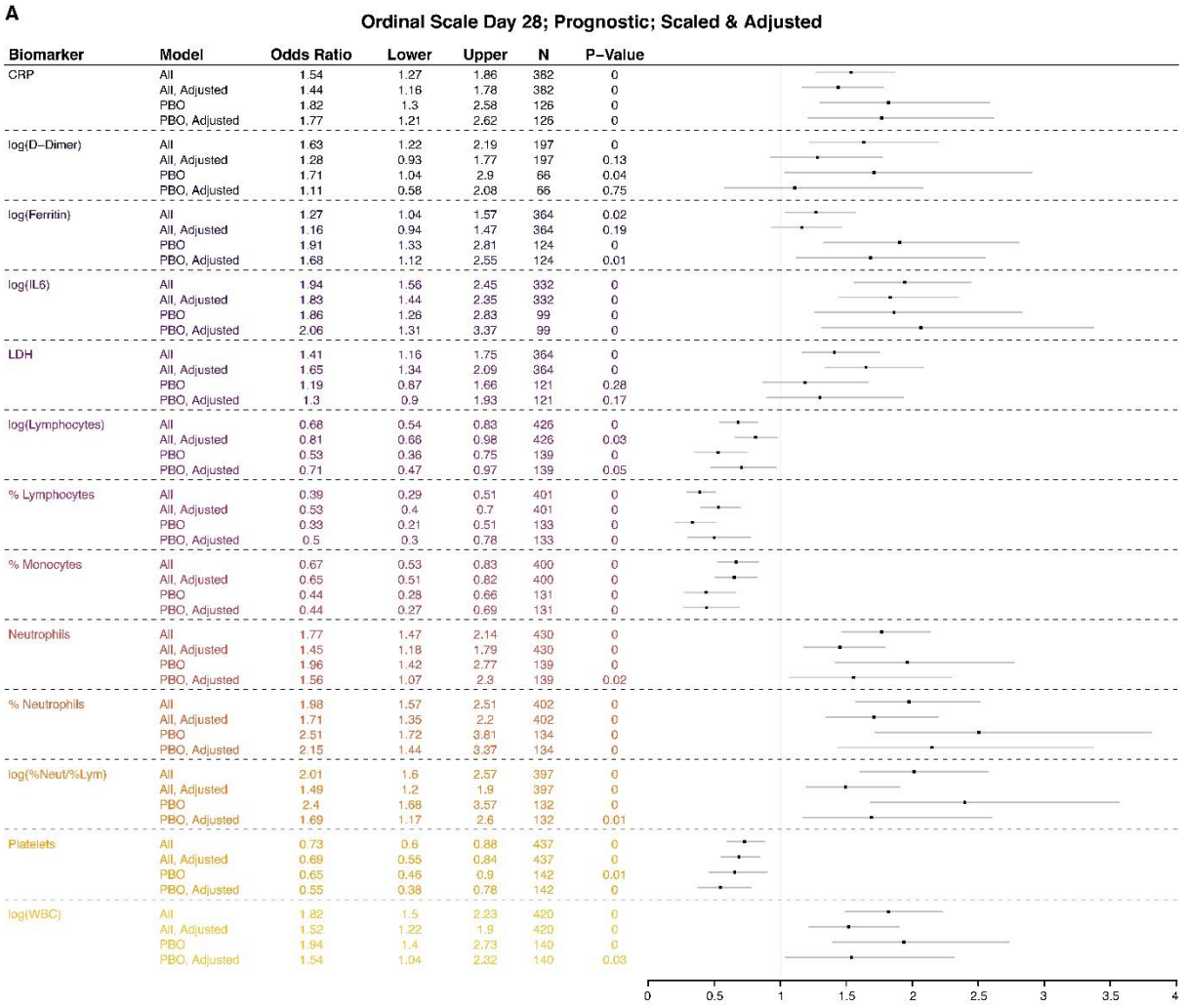

C-Reactive Protein
D-Dimer
Ferritin
Interleukin-6
Lactate Dehydrogenase
Leukocytes
Lymphocyte Abs
Lymphocytes Pct
Monocytes Pct
Neutrophil Abs
Neutrophil By Lymphocyte
Neutrophils Pct
Platelets

Figure S2. Prognostic forest plots. (A) Ordinal scale and (B) time to hospital discharge.

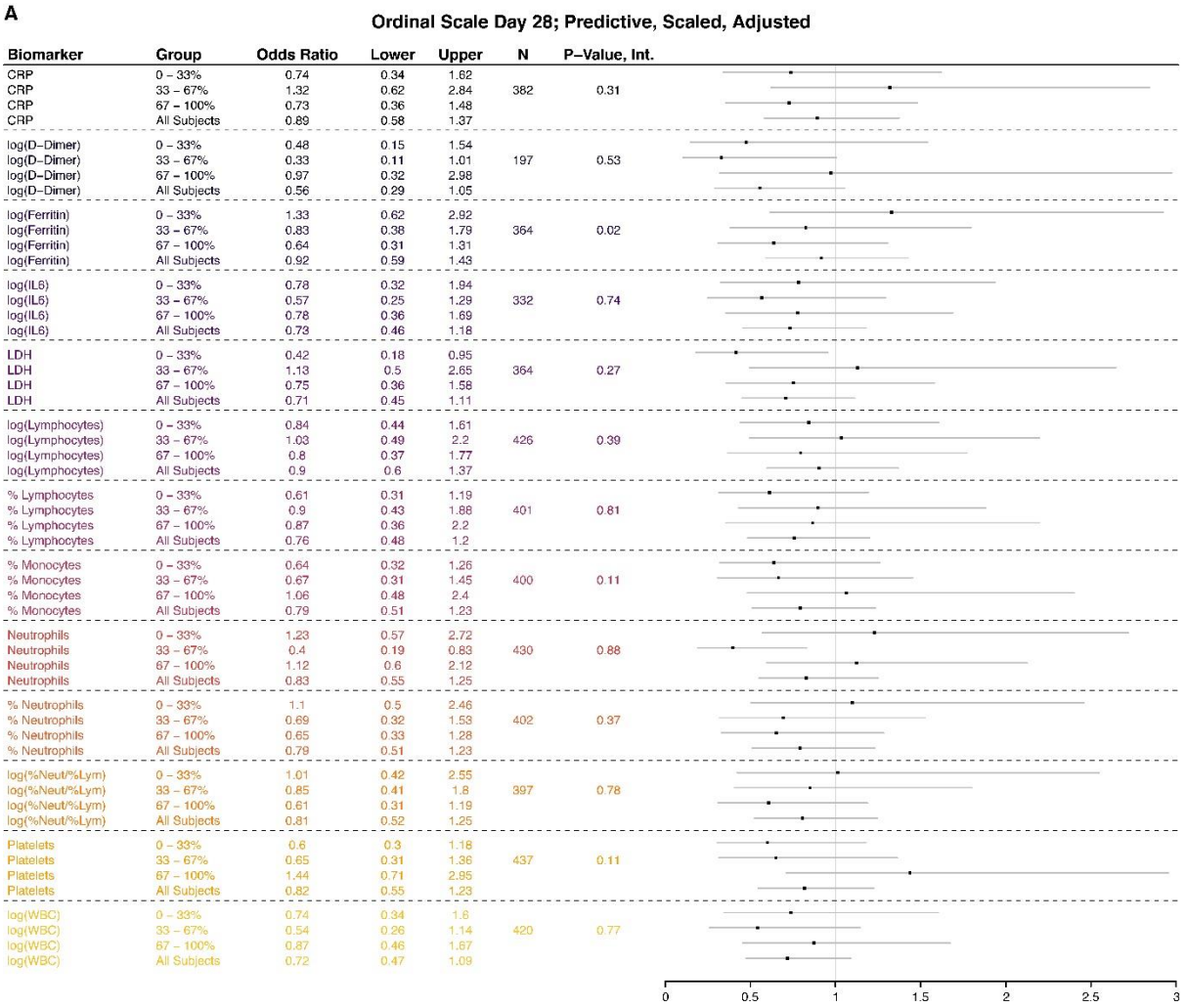


B

Time to Hospital Discharge (Fine–Gray); Prognostic; Scaled & Adjusted

Biomarker	Model	Hazard Ratio	Lower	Upper	N	P–Value
CRP	All	0.68	0.6	0.78	382	0
	All, Adjusted	0.73	0.63	0.85	382	0
	PBO	0.58	0.44	0.75	126	0
	PBO, Adjusted	0.61	0.47	0.8	126	0
log(D–Dimer)	All	0.67	0.54	0.84	197	0
	All, Adjusted	0.83	0.68	1.02	197	0.08
	PBO	0.68	0.44	1.06	66	0.09
	PBO, Adjusted	0.84	0.57	1.25	66	0.4
log(Ferritin)	All	0.83	0.72	0.96	364	0.02
	All, Adjusted	0.84	0.73	0.97	364	0.02
	PBO	0.65	0.53	0.81	124	0
	PBO, Adjusted	0.74	0.58	0.93	124	0.01
log(IL6)	All	0.64	0.56	0.74	332	0
	All, Adjusted	0.56	0.47	0.68	332	0
	PBO	0.6	0.43	0.83	99	0
	PBO, Adjusted	0.47	0.3	0.73	99	0
LDH	All	0.71	0.59	0.85	364	0
	All, Adjusted	0.6	0.48	0.75	364	0
	PBO	0.85	0.65	1.12	121	0.25
	PBO, Adjusted	0.81	0.58	1.13	121	0.21
log(Lymphocytes)	All	1.44	1.16	1.8	426	0
	All, Adjusted	1.4	1.08	1.83	426	0.01
	PBO	2.14	1.66	2.76	139	0
	PBO, Adjusted	1.73	1.32	2.28	139	0
% Lymphocytes	All	1.63	1.45	1.82	401	0
	All, Adjusted	1.46	1.32	1.63	401	0
	PBO	1.69	1.4	2.05	133	0
	PBO, Adjusted	1.49	1.26	1.77	133	0
% Monocytes	All	1.19	1.04	1.36	400	0.01
	All, Adjusted	1.19	1	1.41	400	0.05
	PBO	1.64	1.31	2.05	131	0
	PBO, Adjusted	1.69	1.36	2.1	131	0
Neutrophils	All	0.59	0.49	0.69	430	0
	All, Adjusted	0.73	0.61	0.87	430	0
	PBO	0.42	0.3	0.59	139	0
	PBO, Adjusted	0.54	0.37	0.77	139	0
% Neutrophils	All	0.66	0.58	0.74	402	0
	All, Adjusted	0.68	0.6	0.76	402	0
	PBO	0.6	0.49	0.74	134	0
	PBO, Adjusted	0.64	0.53	0.76	134	0
log(%Neut/%Lym)	All	0.5	0.41	0.61	397	0
	All, Adjusted	0.6	0.48	0.75	397	0
	PBO	0.41	0.31	0.55	132	0
	PBO, Adjusted	0.51	0.39	0.67	132	0
Platelets	All	1.14	1.01	1.27	437	0.03
	All, Adjusted	1.16	1.04	1.29	437	0.01
	PBO	1.2	1	1.45	142	0.05
	PBO, Adjusted	1.2	1	1.44	142	0.05
log(WBC)	All	0.65	0.58	0.74	420	0
	All, Adjusted	0.78	0.68	0.9	420	0
	PBO	0.55	0.44	0.69	140	0
	PBO, Adjusted	0.69	0.54	0.89	140	0

Figure S3. Predictive forest (tertiles and continuous analysis) plots. (A) Ordinal scale and (B) time to hospital discharge.



B

Time to Hospital Discharge; Fine Gray; Predictive, Scaled, Adjusted

Biomarker	Group	Hazard Ratio	Lower	Upper	N	P–Value, Int.
CRP	0 – 33%	1.13	0.72	1.76		
CRP	33 – 67%	1.11	0.64	1.94	382	0.08
CRP	67 – 100%	1.8	1.01	3.21		
CRP	All Subjects	1.34	0.99	1.82		
log(D–Dimer)	0 – 33%	2.1	0.99	4.45		
log(D–Dimer)	33 – 67%	1.38	0.71	2.69	197	0.67
log(D–Dimer)	67 – 100%	1.19	0.58	2.44		
log(D–Dimer)	All Subjects	1.49	1	2.22		
log(Ferritin)	0 – 33%	1.33	0.82	2.18		
log(Ferritin)	33 – 67%	1.33	0.81	2.18	364	0.09
log(Ferritin)	67 – 100%	1.78	0.97	3.26		
log(Ferritin)	All Subjects	1.5	1.1	2.05		
log(IL6)	0 – 33%	1.17	0.72	1.9		
log(IL6)	33 – 67%	2.74	1.49	5.03	332	0.9
log(IL6)	67 – 100%	1.93	0.86	4.35		
log(IL6)	All Subjects	1.68	1.17	2.42		
LDH	0 – 33%	2.29	1.46	3.6		
LDH	33 – 67%	1.03	0.64	1.64	364	0.09
LDH	67 – 100%	1.32	0.69	2.53		
LDH	All Subjects	1.47	1.08	2.01		
log(Lymphocytes)	0 – 33%	1.34	0.76	2.38		
log(Lymphocytes)	33 – 67%	1.02	0.67	1.56	426	0.2
log(Lymphocytes)	67 – 100%	1.75	1.1	2.8		
log(Lymphocytes)	All Subjects	1.4	1.04	1.88		
% Lymphocytes	0 – 33%	2.23	1.15	4.31		
% Lymphocytes	33 – 67%	1.44	0.84	2.48	401	0.79
% Lymphocytes	67 – 100%	1.29	0.86	1.94		
% Lymphocytes	All Subjects	1.59	1.17	2.15		
% Monocytes	0 – 33%	2.11	1.06	4.18		
% Monocytes	33 – 67%	1.63	1.02	2.6	400	0
% Monocytes	67 – 100%	1.24	0.79	1.94		
% Monocytes	All Subjects	1.56	1.15	2.1		
Neutrophils	0 – 33%	1.02	0.68	1.55		
Neutrophils	33 – 67%	1.86	1.08	3.2	430	0.07
Neutrophils	67 – 100%	1.57	0.86	2.86		
Neutrophils	All Subjects	1.51	1.09	2.08		
% Neutrophils	0 – 33%	1.24	0.82	1.9		
% Neutrophils	33 – 67%	1.52	0.89	2.61	402	0.57
% Neutrophils	67 – 100%	1.97	1.06	3.66		
% Neutrophils	All Subjects	1.58	1.17	2.13		
log(%Neut/%Lym)	0 – 33%	1.26	0.85	1.93		
log(%Neut/%Lym)	33 – 67%	1.47	0.83	2.62	397	0.26
log(%Neut/%Lym)	67 – 100%	2.16	1.14	4.09		
log(%Neut/%Lym)	All Subjects	1.61	1.16	2.24		
Platelets	0 – 33%	1.87	1.05	3.33		
Platelets	33 – 67%	1.39	0.88	2.2	437	0.48
Platelets	67 – 100%	1.05	0.67	1.62		
Platelets	All Subjects	1.4	1.05	1.85		
log(WBC)	0 – 33%	1.26	0.85	1.94		
log(WBC)	33 – 67%	1.65	0.98	2.77	420	0.18
log(WBC)	67 – 100%	1.88	1	3.55		
log(WBC)	All Subjects	1.58	1.17	2.15		

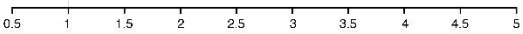
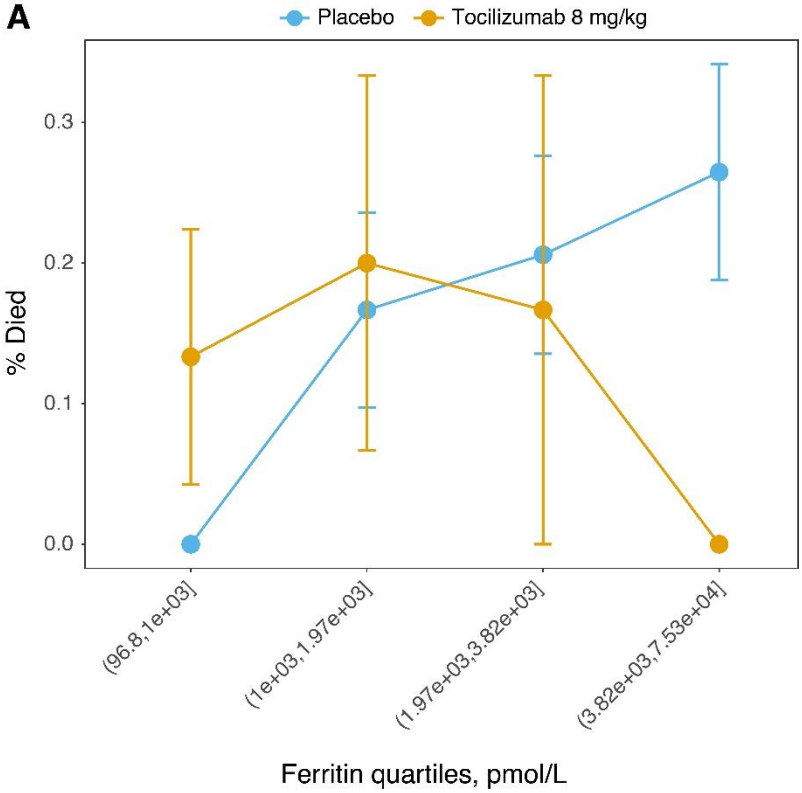
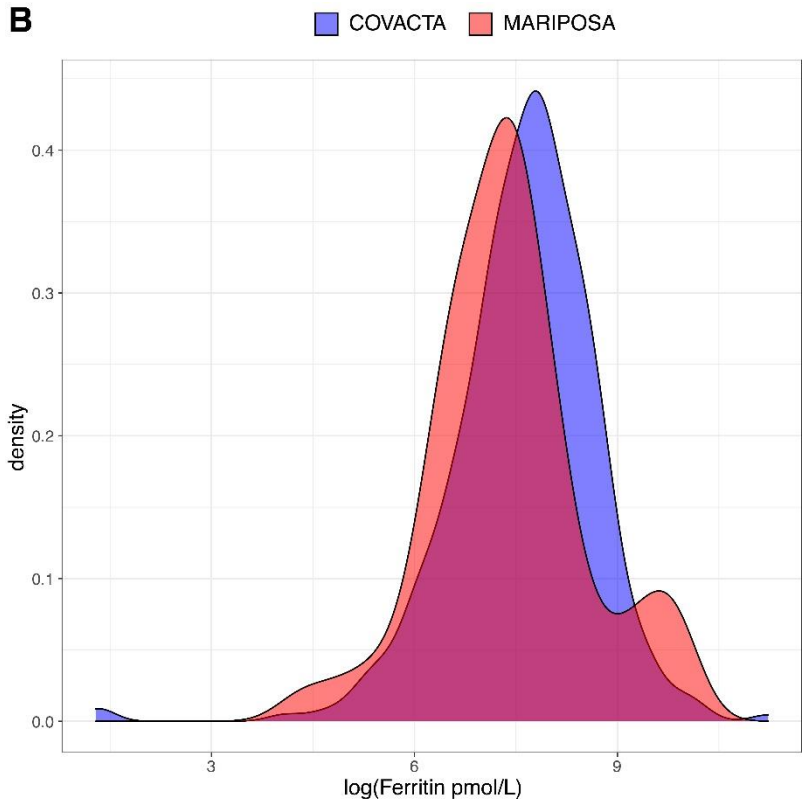
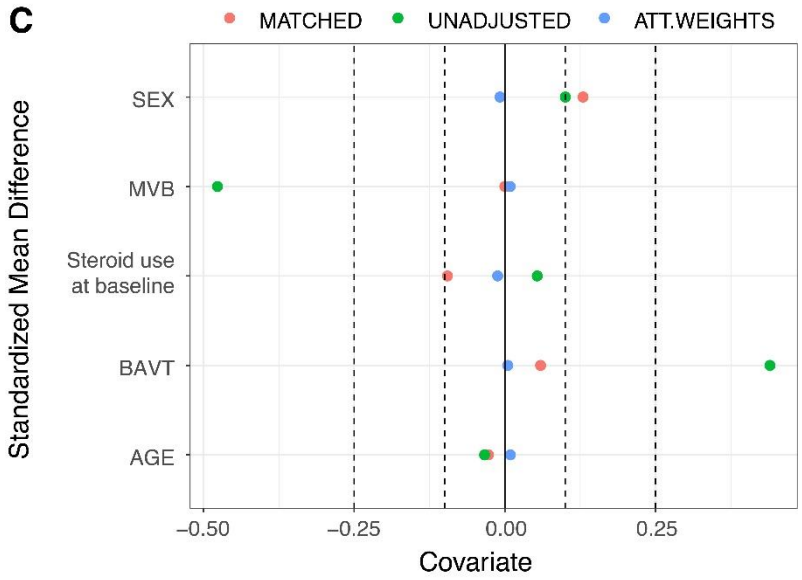


Figure S4. (A) Ferritin as a predictive biomarker for death by day 28 in combined analysis of COVACTA and MARIPOSA. (B) Baseline ferritin levels in MARIPOSA and COVACTA. (C) Love plot showing the standardized mean difference using matched subjects, unadjusted, and ATT weights. (D) Descriptive plot of subgroups of patients receiving or not receiving mechanical ventilation in MARIPOSA and COVACTA. (A, D) Data are shown as mean ± standard error based on 124 patients from the placebo arm of COVACTA and 67 patients from the tocilizumab 4-mg/kg and 8-mg/kg arms of MARIPOSA. BAVT = baseline antiviral treatment; MVB = mechanical ventilation at baseline; PBO = placebo.




B
COVACTA
MARIPOSA
density
0.4
0.3
0.2
0.1
0.0
3
6
9
log(Ferritin pmol/L)


C
MATCHED
UNADJUSTED
ATT.WEIGHTS
Standardized Mean Difference
SEX
MVB
Steroid use at baseline
BAVT
AGE
−0.50
−0.25
0.00
0.25
Covariate

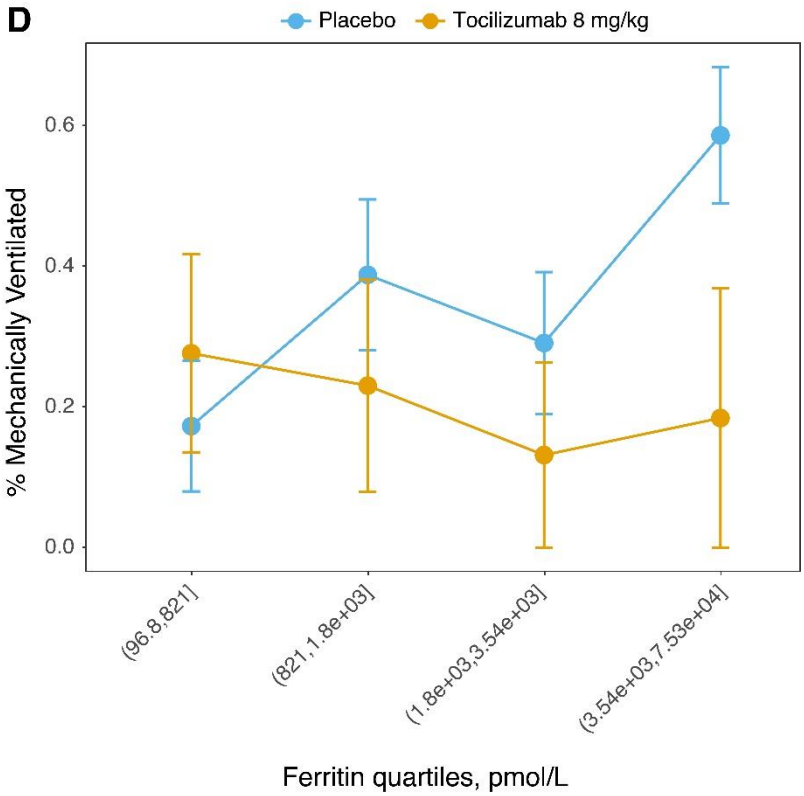

D
Placebo
Tocilizumab 8 mg/kg
% Mechanically Ventilated
0.0
0.2
0.4
0.6
(96.8,821]
(821,1.8e+03]
(1.8e+03,3.54e+03]
(3.54e+03,7.53e+04]
Ferritin quartiles, pmol/L

Figure S5. Day 28 outcomes by baseline IL-6 tertiles (mITT population). (A) Ordinal scale category and (B) death. Seven-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death. IL-6 values are log-transformed. ICU = intensive care unit; IL-6 = interleukin-6.

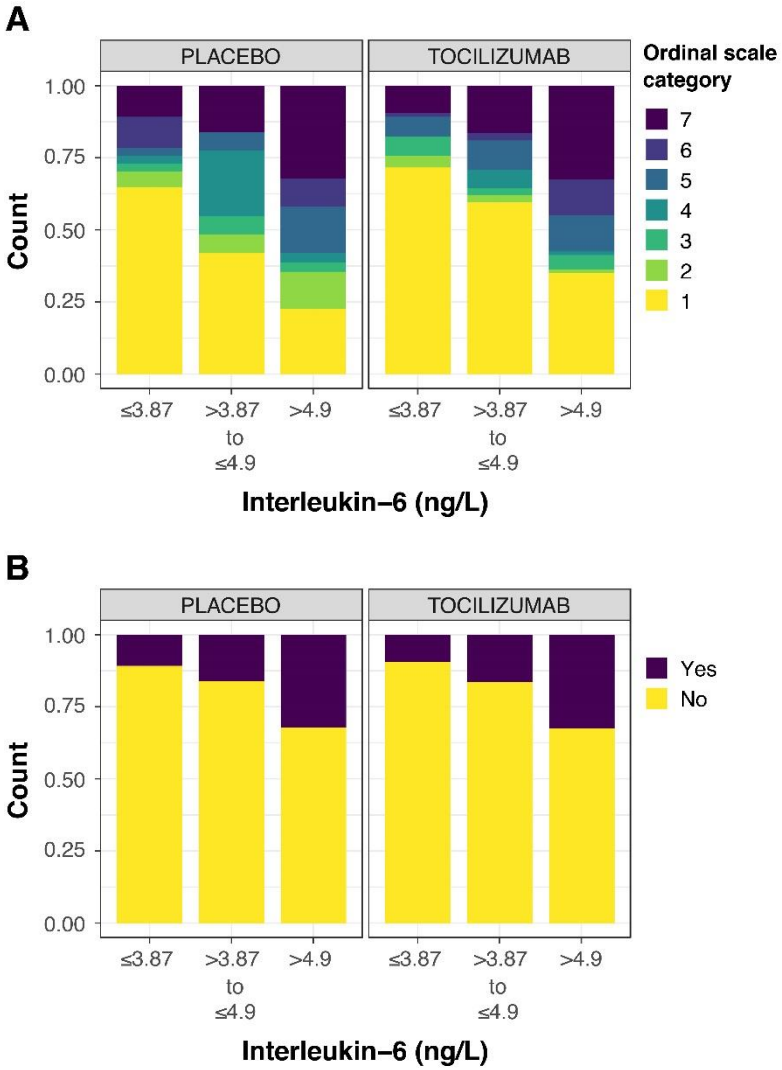
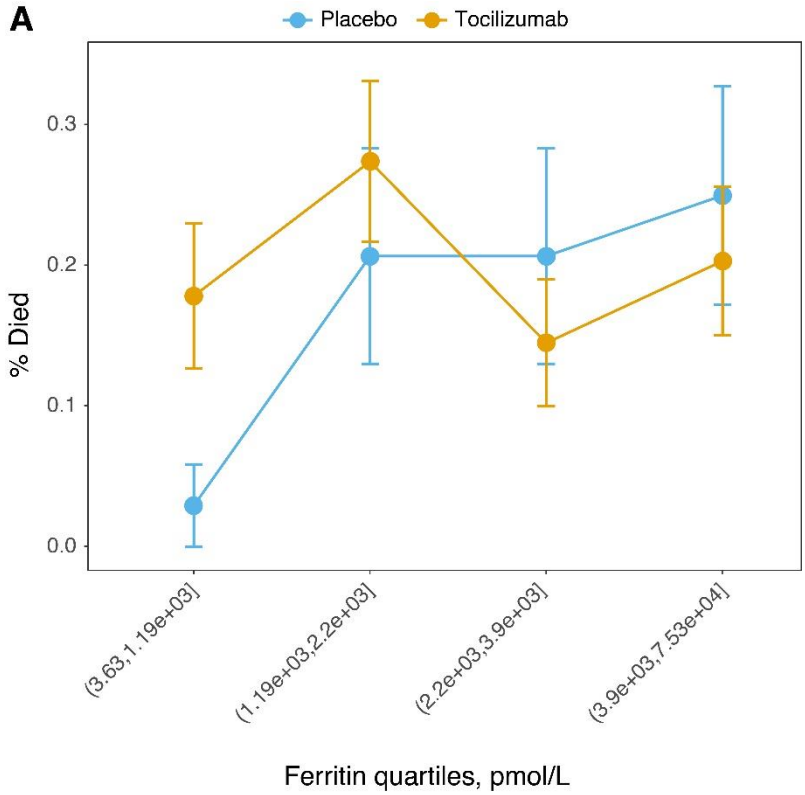
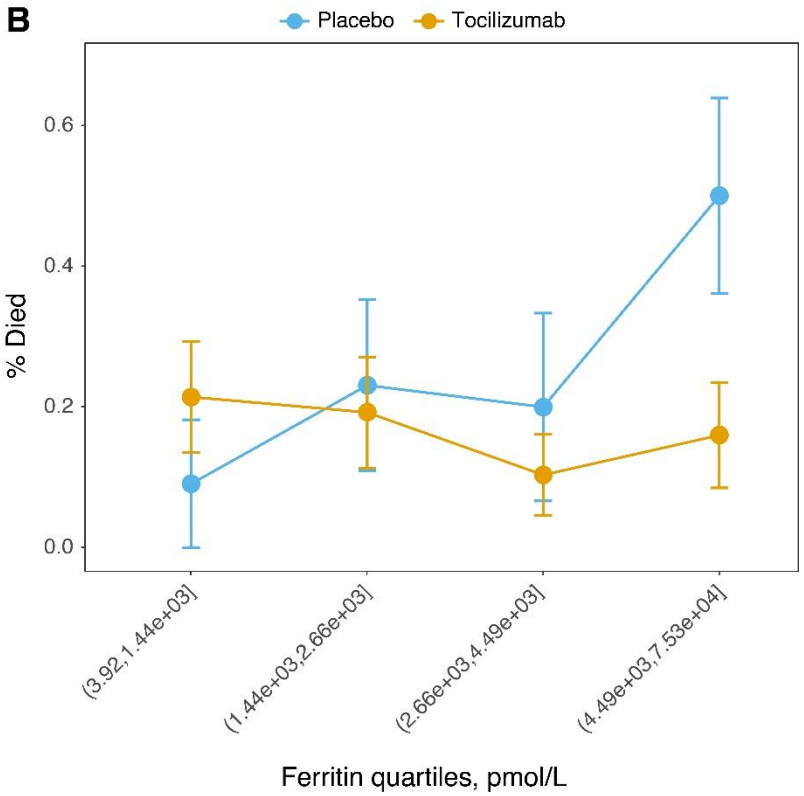


Figure S6. Unmodeled data by ferritin quartiles (A) in all-comers (*N* = 437) and (B) in the subgroup of patients requiring positive pressure or mechanical ventilation at baseline (ordinal scale categories 4 and 5) (*n* = 157). (C) Baseline ordinal scale versus baseline ferritin levels. (A, B) Data are shown as descriptive mean ± SE. (C) The blue line shows Loess smoothing. SE = standard error.




B
Placebo
Tocilizumab
% Died
0.6
0.4
0.2
0.0
(3.92,1.44e+03]
(1.44e+03,2.66e+03]
(2.66e+03,4.49e+03]
(4.49e+03,7.53e+04]
Ferritin quartiles, pmol/L

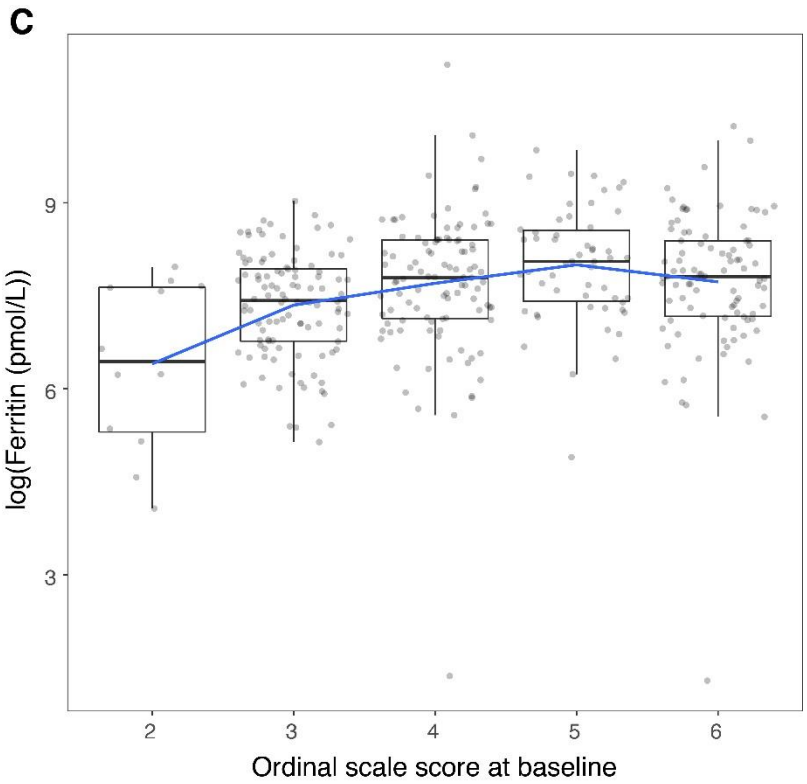
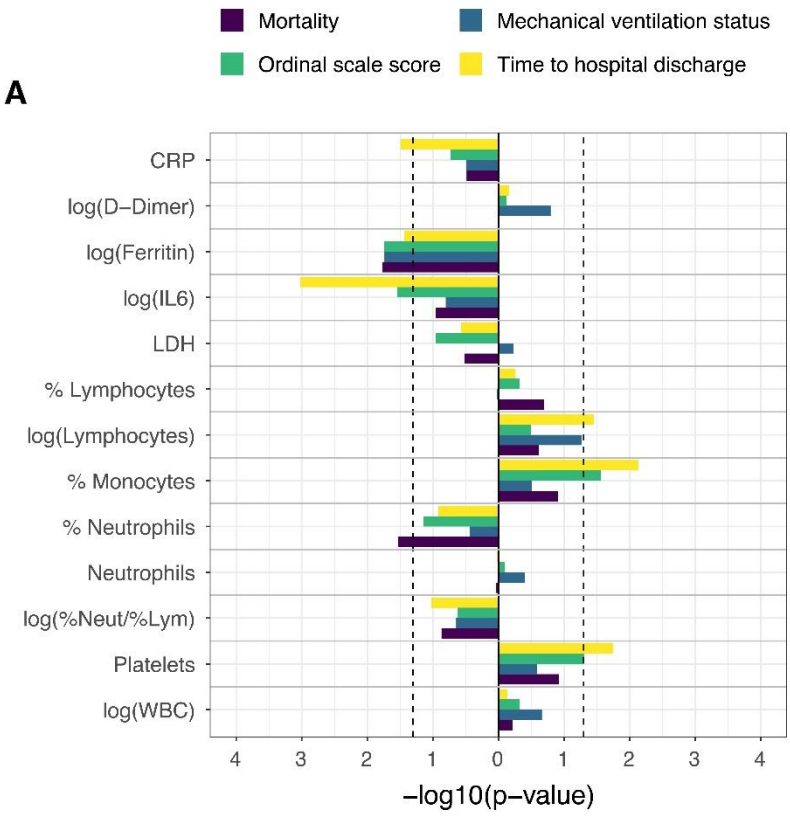
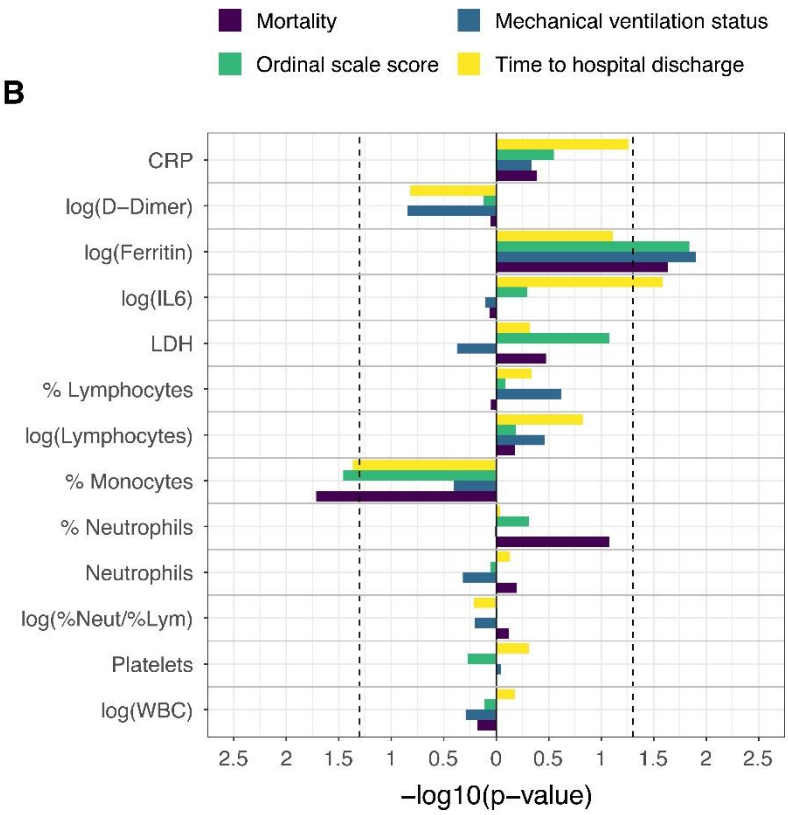

C
log(Ferritin (pmol/L))
9
6
3
2
3
4
5
6
Ordinal scale score at baseline

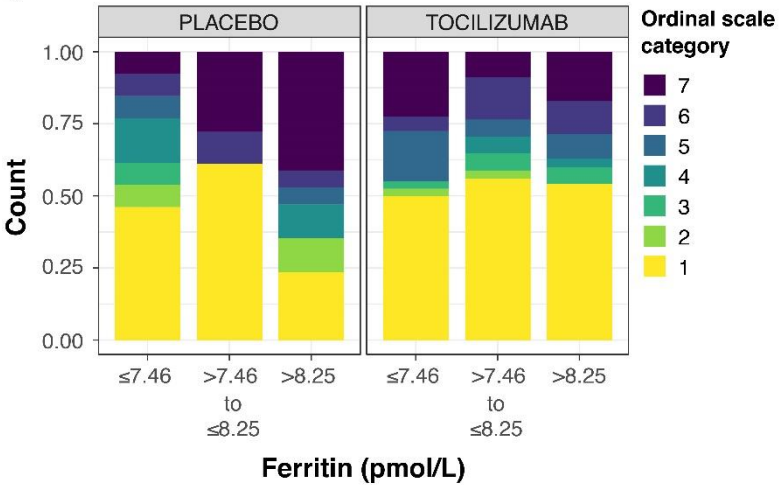
Figure S7. (A) Prognostic models and (B) predictive models for clinical outcomes by biomarkers and by ferritin tertiles (C, ordinal scale score; D, mechanical ventilation status; E, mortality; F, hospital discharge) in the subgroup of patients requiring positive pressure or mechanical ventilation at baseline (ordinal scale categories 4 and 5) (*n* = 157). Seven-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death. ICU = intensive care unit.



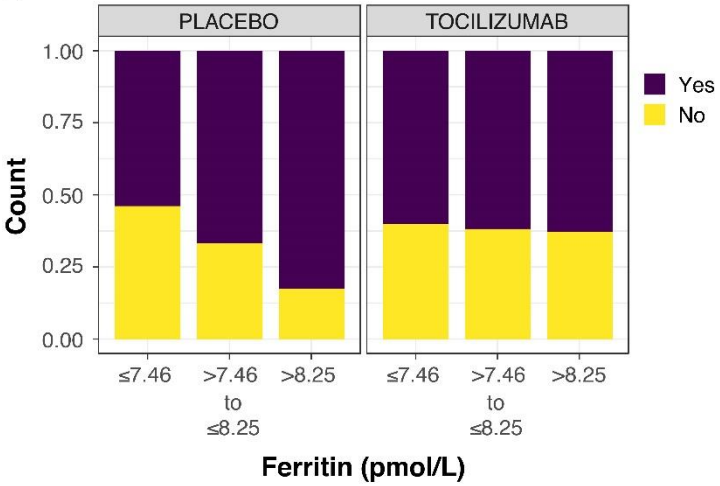
B


Mortality
Mechanical ventilation status
Ordinal scale score
Time to hospital discharge
CRP
log(D−Dimer)
log(Ferritin)
log(IL6)
LDH
% Lymphocytes
log(Lymphocytes)
% Monocytes
% Neutrophils
Neutrophils
log(%Neut/%Lym)
Platelets
log(WBC)
2.5 2 1.5 1 0.5 0 0.5 1 1.5 2 2.5
−log10(p−value)

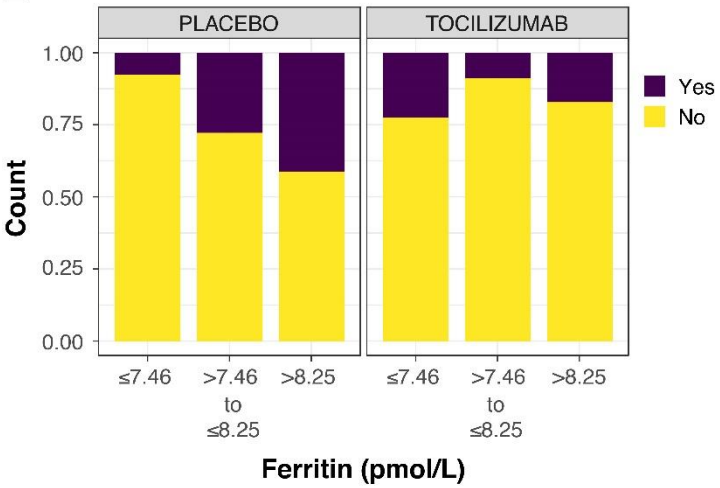
C


PLACEBO
TOCILIZUMAB
Ordinal scale category
7
6
5
4
3
2
1
Count
1.00
0.75
0.50
0.25
0.00
≤7.46
>7.46 to ≤8.25
>8.25
Ferritin (pmol/L)

D


PLACEBO
TOCILIZUMAB
1.00
0.75
0.50
0.25
0.00
Count
Yes
No
≤7.46
>7.46 to ≤8.25
>8.25
Ferritin (pmol/L)

E


PLACEBO
TOCILIZUMAB
1.00
0.75
0.50
0.25
0.00
Count
Yes
No
≤7.46
>7.46 to ≤8.25
>8.25
Ferritin (pmol/L)

F

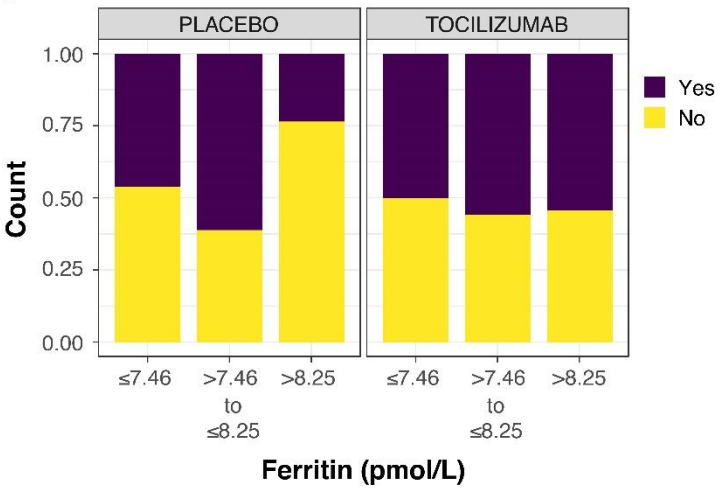
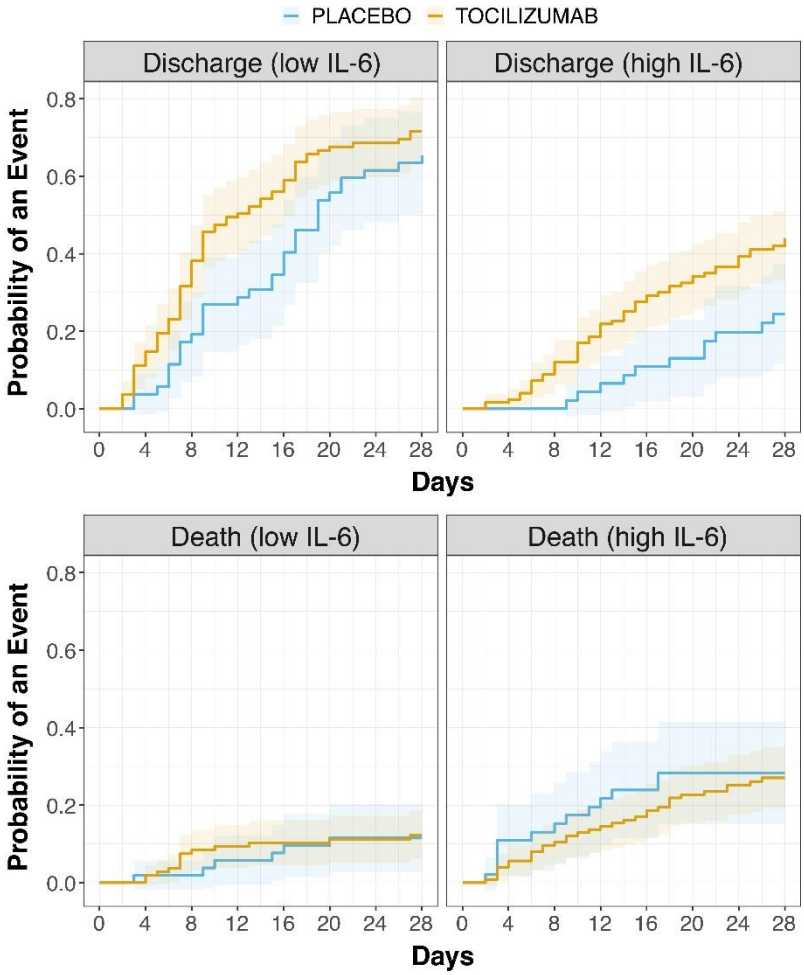

PLACEBO
TOCILIZUMAB
1.00
0.75
0.50
0.25
0.00
Count
Yes
No
≤7.46
>7.46 to ≤8.25
>8.25
Ferritin (pmol/L)

Figure S8. Cumulative probability of time to discharge and death by day 28 according to baseline IL-6 concentration in patients requiring positive pressure or mechanical ventilation at baseline (ordinal scale categories 4 and 5) (*n* = 157). IL-6 values are log transformed. A cutoff IL-6 value of 80 ng/L was chosen for visualization purposes only (C) based on the median (IQR) value of 85.8 (35.6–188.0) ng/mL. IL-6 = interleukin-6; IQR = interquartile range.



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5. 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; 18:844–847.