

A HISTORICALLY CONTROLLED COMPARISON OF GLUCOCORTICOID WITH- OR WITHOUT TOCILIZUMAB vs. SUPPORTIVE CARE ONLY IN PATIENTS WITH COVID-19-ASSOCIATED CYTOKINE STORM SYNDROME

Results of the CHIC-study

Supplementary material

Supplementary Table S1. Age and gender distribution of the treated and control groups

Age category	Treated group		Control group		
	Females	Males	Females	Males	
<50	0	6	0	6	12
50-60	4	13	4	13	34
60-70	5	19	5	19	48
70-80	6	22	6	22	56
≥80	3	8	3	8	22
Total	86		86		172

Supplementary Table S2. Effect of treatment (vs control) on outcomes, from multivariable analysis stratified for low/high ferritin[‡]

	Effect of treatment vs control in low ferritin Multivariable analysis* HR or coefficient (95% CI)	Effect of treatment vs control in high ferritin Multivariable analysis* HR or coefficient (95% CI)
<i>Primary outcome</i>		
Clinical improvement (2 points) in WHO score[§]	1.59 (0.72; 3.52)	2.72 (1.35; 5.48)
<i>Key secondary outcomes</i>		
In-hospital mortality[§]	0.17 (0.06; 0.54)	0.07 (0.01; 0.40)
Mechanical ventilation[§]	0.44 (0.12; 1.63)	0.24 (0.05; 1.31)
<i>Other secondary outcomes</i>		
Clinical improvement (1 point) in WHO score[§]	1.73 (0.79; 3.78)	2.62 (1.34; 5.12)
Independence from oxygen therapy[§]	1.50 (0.64; 3.54)	2.76 (1.35; 5.64)
Duration of mechanical ventilation in survivors[±]	‡	‡
Duration of hospitalization in survivors[±]	-4.05 (-9.29; 1.19)	-5.31 (-12.02; 1.39)

[‡] Stratified at 1419µg/L, median of ferritin at baseline

*Adjusted for age, gender, body mass index, smoking status, hypertension, diabetes, cardiovascular disease and arrhythmia

[§] Results from Cox regression models

[±] Results from linear regression models

[‡] Not possible to run due to low number of patients in each stratum

HR, hazard ratio; CI, confidence interval, WHO, World Health Organization

Supplementary Table S3. Outcomes from the sensitivity analyses

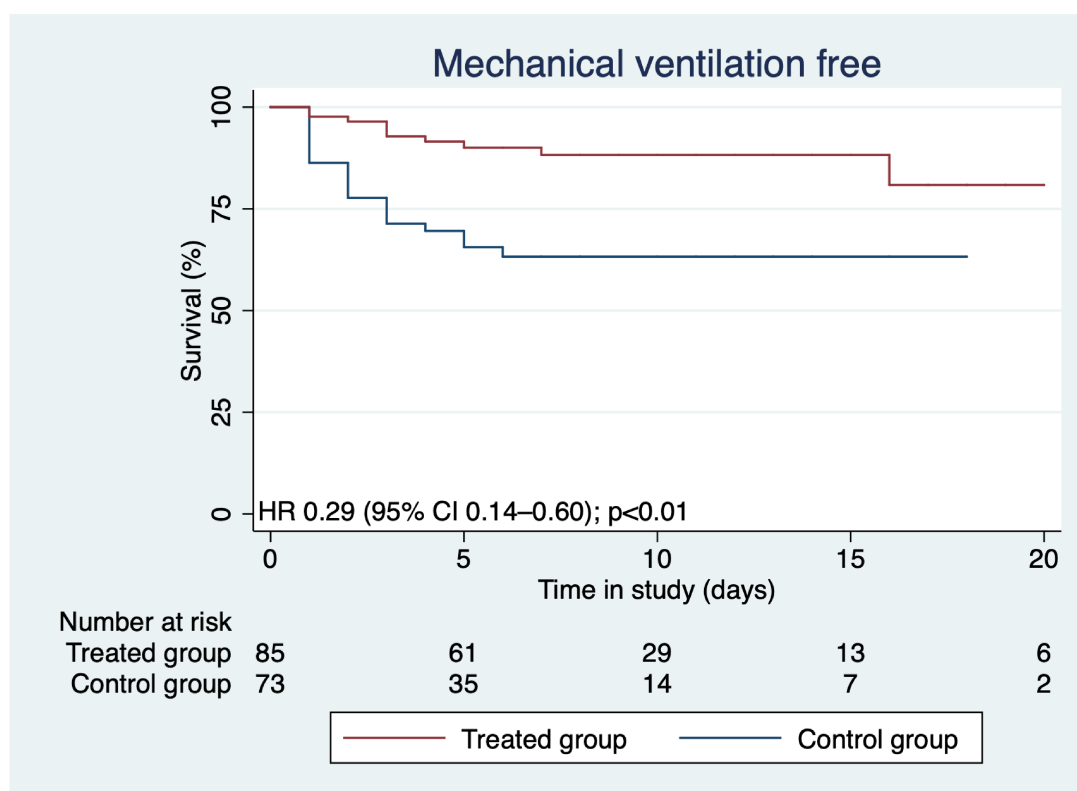
	Treated group N = 86	Control group N = 86	p-value*
Primary outcome			
Clinical improvement (2 points) in WHO score			
<i>Excluding ventilated patients at baseline</i>			
- Number of improvements	63	38	0.0154
- Daily incidence rate (95% CI)	7.0% (5.5; 9.0)	4.4% (3.2; 6.0)	
- 25% Survival time (days)	6	7	
- 50% Survival time (days)	10	16	
<i>Excluding patients receiving TCZ</i>			
- Number of improvements	39	44	<0.0001
- Daily incidence rate (95% CI)	9.1% (6.7; 12.5)	4.0% (3.0; 5.4)	
- 25% Survival time (days)	6	8	
- 50% Survival time (days)	8	18	
<i>Excluding extreme age groups</i>			
- Number of improvements	53	36	0.0014
- Daily incidence rate (95% CI)	6.9% (5.2; 9.0)	3.7% (2.7; 5.2)	
- 25% Survival time (days)	6	10	
- 50% Survival time (days)	10	19	
Key secondary outcomes			
Hospital mortality			
<i>Excluding ventilated patients at baseline</i>			
- Number of deaths	14	34	0.003
- Daily incidence rate (95% CI)	1.5% (0.9; 2.6)	3.9% (2.8; 5.4)	
- 25% Survival time (days)	16	5	
- 50% Survival time (days)	--	17	
<i>Excluding patients receiving TCZ</i>			
- Number of deaths	7	41	0.0089
- Daily incidence rate (95% CI)	1.6% (0.8; 3.4)	3.5% (2.6; 4.7)	
- 25% Survival time (days)	16	5	
- 50% Survival time (days)	--	18	
<i>Excluding extreme age groups</i>			
- Number of deaths	9	32	0.0012
- Daily incidence rate (95% CI)	1.1% (0.6; 2.2)	3.0% (2.1; 4.3)	
- 25% Survival time (days)	19	7	
- 50% Survival time (days)	--	18	
Mechanical ventilation			
<i>Excluding patients receiving TCZ</i>			
- Number of mechanical ventilation	2	24	0.0001
- Daily incidence rate (95% CI)	0.6% (1.4; 2.3)	5.4% (3.6; 8.0)	
- 25% Survival time (days)	--	3	
- 50% Survival time (days)	--	--	
<i>Excluding extreme age groups</i>			
- Number of mechanical ventilation	10	22	0.0010
- Daily incidence rate (95% CI)	1.6% (0.9; 3.1)	6.0% (3.9; 9.1)	
- 25% Survival time (days)	--	3	
- 50% Survival time (days)	--	--	
Other secondary outcomes			
Clinical improvement (1 point) in WHO score			
<i>Excluding ventilated patients at baseline</i>			
- Number of improvements	68	39	0.0033
- Daily incidence rate (95% CI)	8.8% (6.9; 11.1)	5.0 (3.7; 6.9%)	
- 25% Survival time (days)	5	6	
- 50% Survival time (days)	9	14	
<i>Excluding patients receiving TCZ</i>			
- Number of improvements	42	45	<0.0001
- Daily incidence rate (95% CI)	12% (8.9; 16.3)	4.6% (3.4; 6.2)	
- 25% Survival time (days)	4	7	
- 50% Survival time (days)	6	16	
<i>Excluding extreme age groups</i>			
- Number of improvements	55	37	0.0006
- Daily incidence rate (95% CI)	8.2% (6.3; 10.7)	4.2% (3.1; 5.9)	
- 25% Survival time (days)	5	8	
- 50% Survival time (days)	9	18	
Independence from oxygen therapy			
<i>Excluding ventilated patients at baseline</i>			
- Number of patients free of oxygen	60	37	0.0475
- Daily incidence rate (95% CI)	6.0% (4.7; 7.8)	4.0% (2.9; 5.5)	
- 25% Survival time (days)	6	8	
- 50% Survival time (days)	10	17	

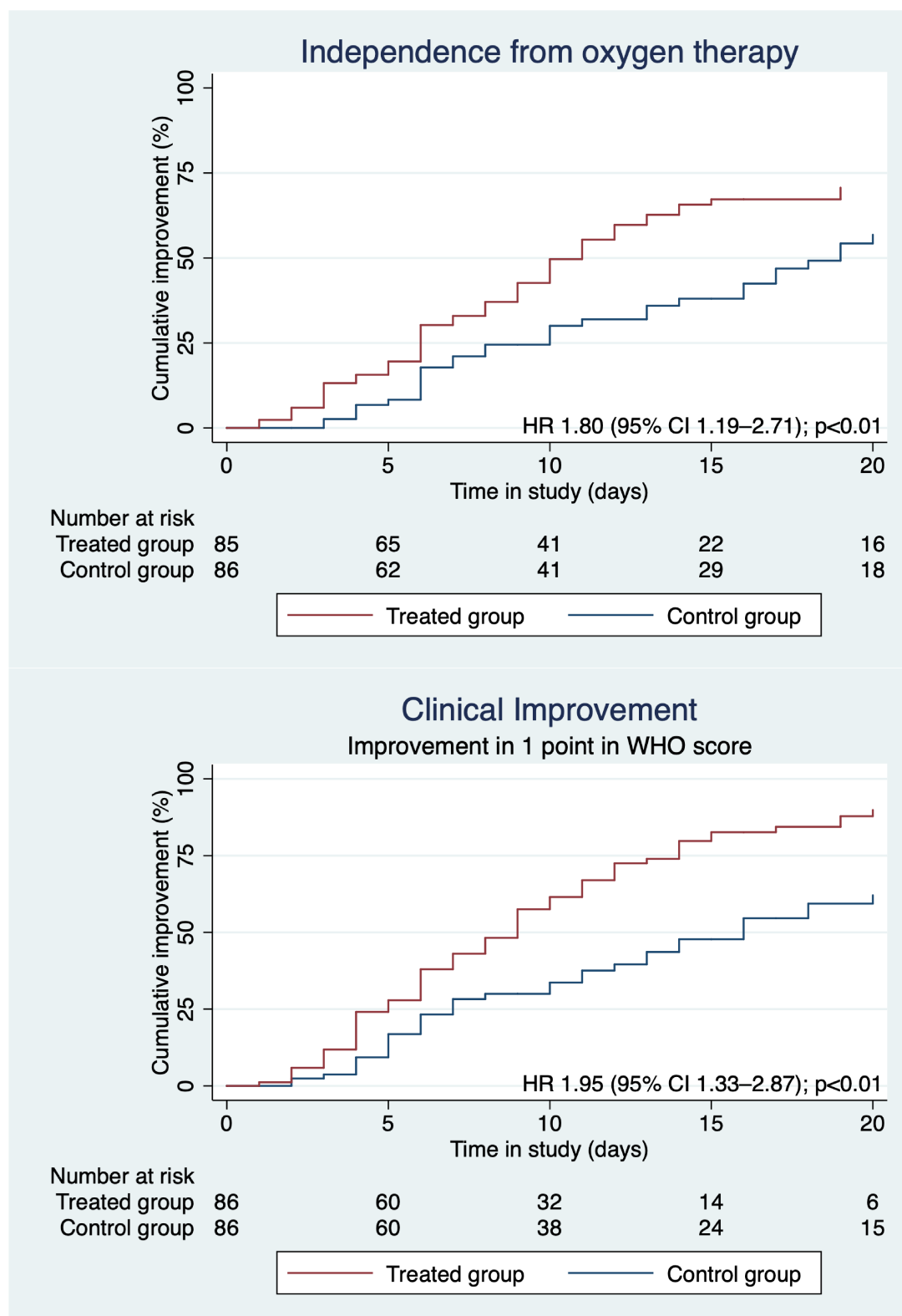
<i>Excluding patients receiving TCZ</i>			
- Number of patients free of oxygen	38	40	0.0001
- Daily incidence rate (95% CI)	7.7% (5.6; 10.6)	3.3% (2.4; 4.4)	
- 25% Survival time (days)	10	4	
- 50% Survival time (days)	19	8	
<i>Excluding extreme age groups</i>			
- Number of patients free of oxygen	51	32	0.0016
- Daily incidence rate (95% CI)	5.8% (4.4; 7.6)	2.9% (2.0; 4.1)	
- 25% Survival time (days)	6	10	
- 50% Survival time (days)	11	20	
Duration of mechanical ventilation in survivors (days)			
<i>Excluding ventilated patients at baseline</i>	14.3 (11.3)	18.0 (10.3)	0.4840
<i>Excluding patients receiving TCZ</i>	22.0 (11.3)	18.8 (10.2)	0.6835
<i>Excluding extreme age groups</i>	16.3 (11.9)	20.5 (10.4)	0.3899
Duration of hospitalization in survivors and discharged (days)			
<i>Excluding ventilated patients at baseline</i>	10.3 (5.7)	15.8 (13.0)	0.0163
<i>Excluding patients receiving TCZ</i>	9.3 (7.5)	15.9 (12.7)	0.0058
<i>Excluding extreme age groups</i>	11.0 (7.2)	16.8 (13.4)	0.0273

Data are number of cases, n (%), incidence rate with 95% confidence interval, number of days or mean (standard deviation), as indicated

*Calculated with t-test, Chi-square or log-rank test, as appropriate

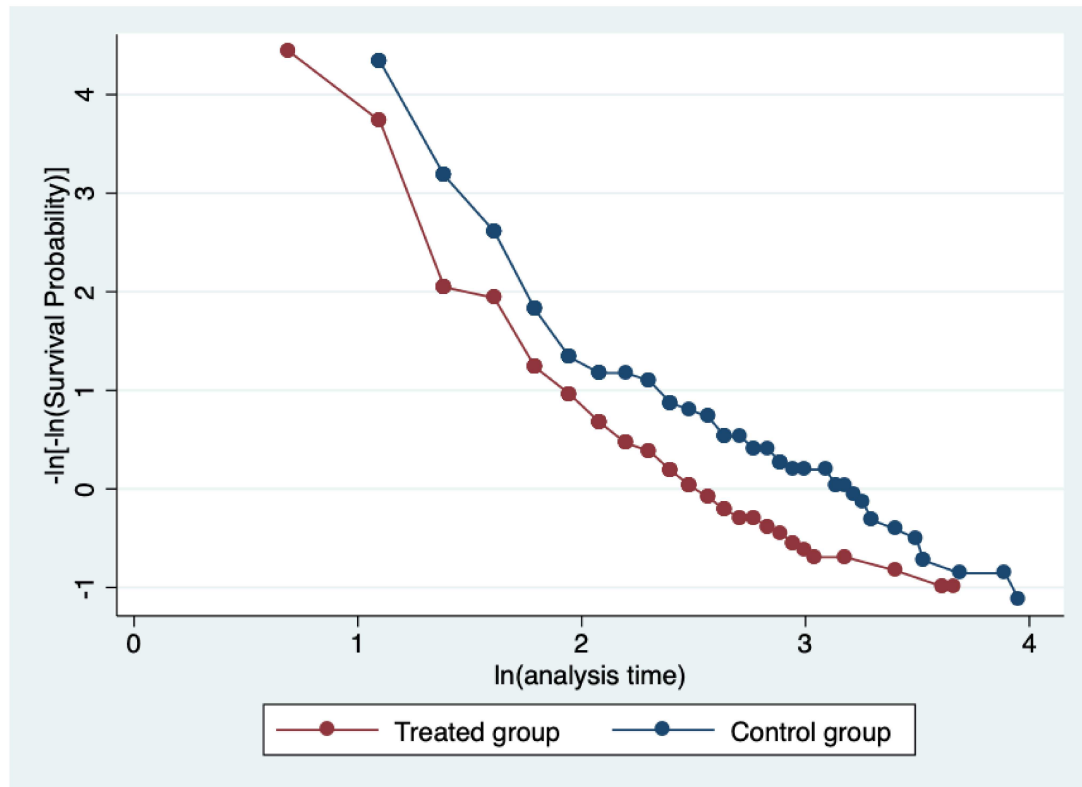
WHO, World Health Organization; CI, confidence interval; TCZ, tocilizumab

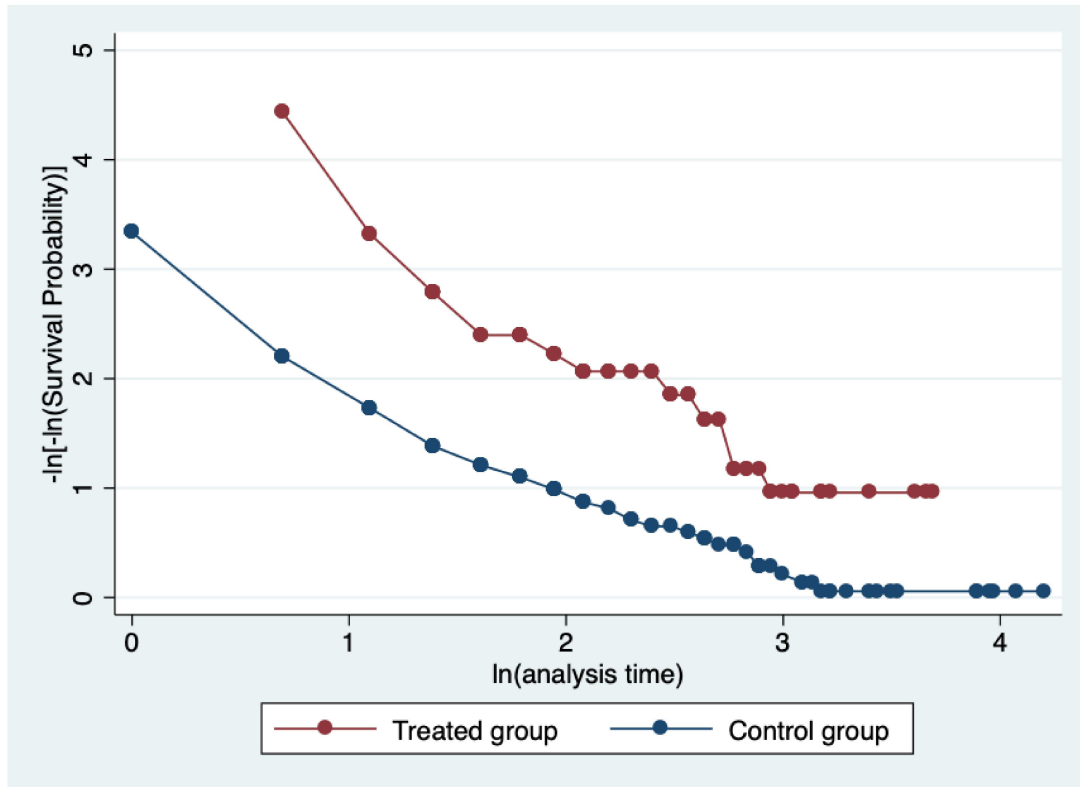
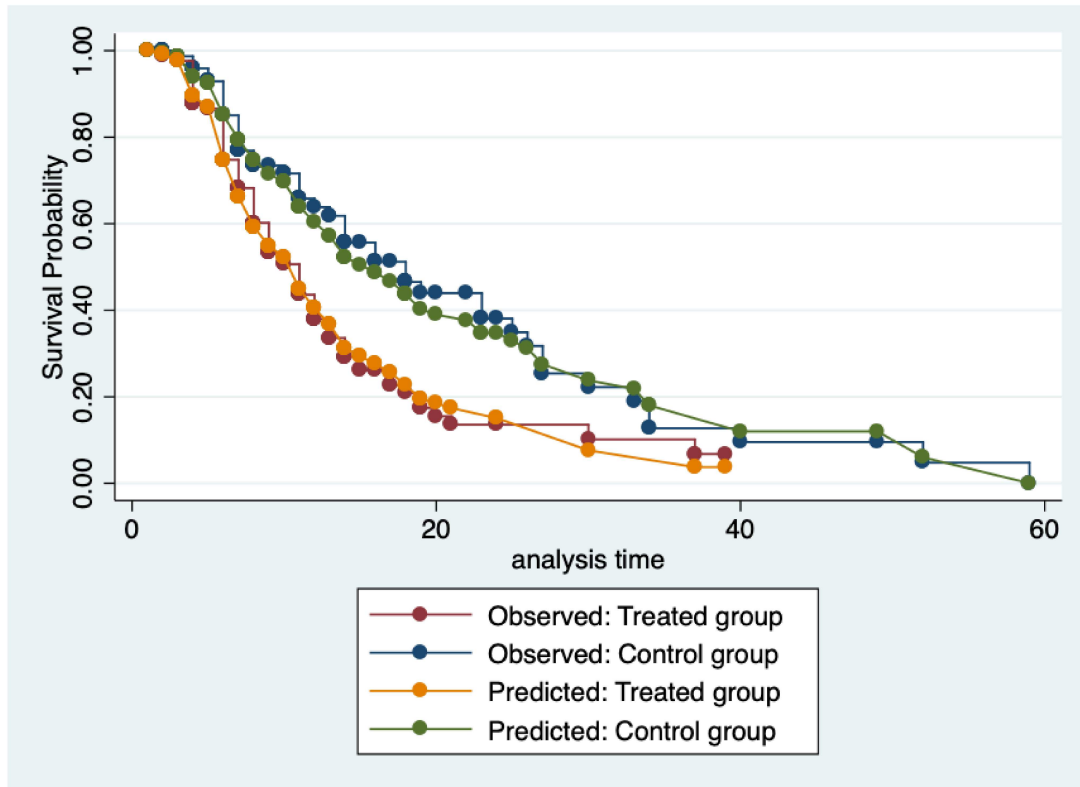


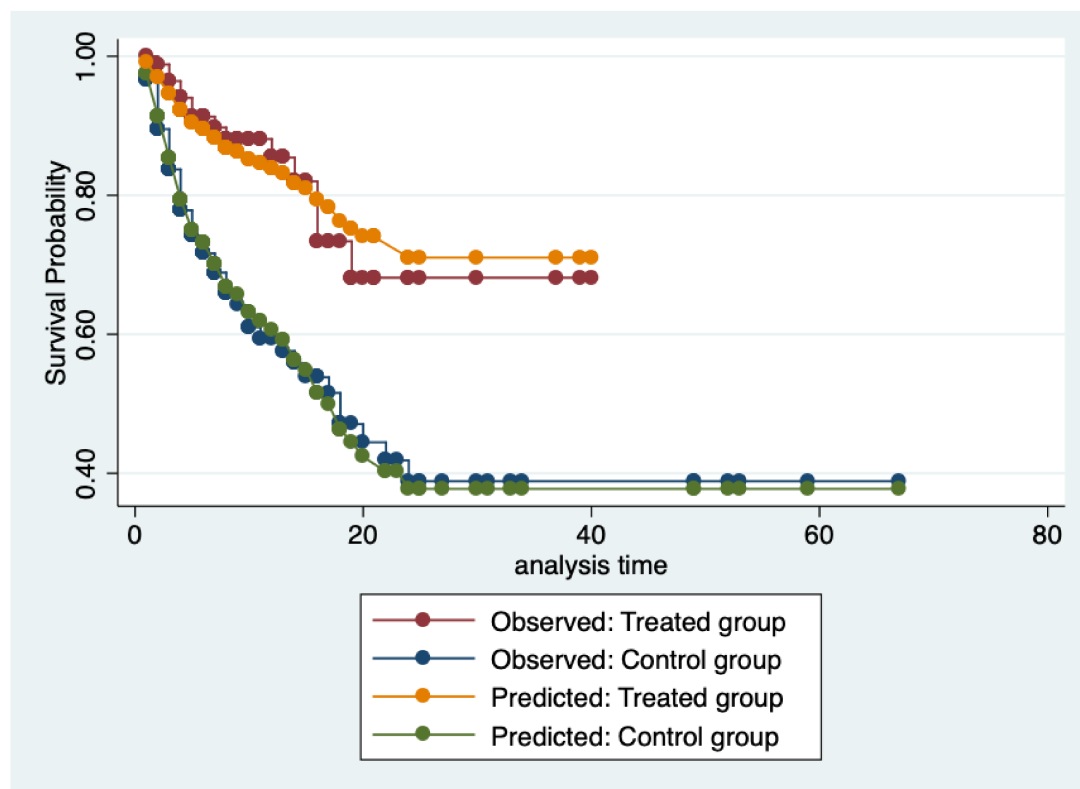


Supplementary Figure S1. Mechanical ventilation free, independence from oxygen therapy and clinical improvement.

Plots show mechanical ventilation free (A), independence from oxygen therapy (B) and clinical improvement (C) defined as a 1-point improvement in the 7-point WHO score, in patients with COVID-19 associated cytokine-release syndrome stratified for treatment (treated vs control group).
HR, hazard ratio; CI, confidence interval







Supplementary Figure S2. Proportional-hazards assumption graphs for the 2 main outcomes.

Plots show log-log plot of survival for the WHO 2-point clinical improvement (A), Kaplan-Meier and predicted survival plot for the WHO 2-point clinical improvement (B), log-log plot of survival for hospital mortality (C), Kaplan-Meier and predicted survival plot for hospital mortality (D). A and C display lines that are parallel, implying that the proportional-hazards assumption for treatment (vs control) has not been violated. This is confirmed in figures B and D, where the observed values and predicted values are close together.