APPENDIX

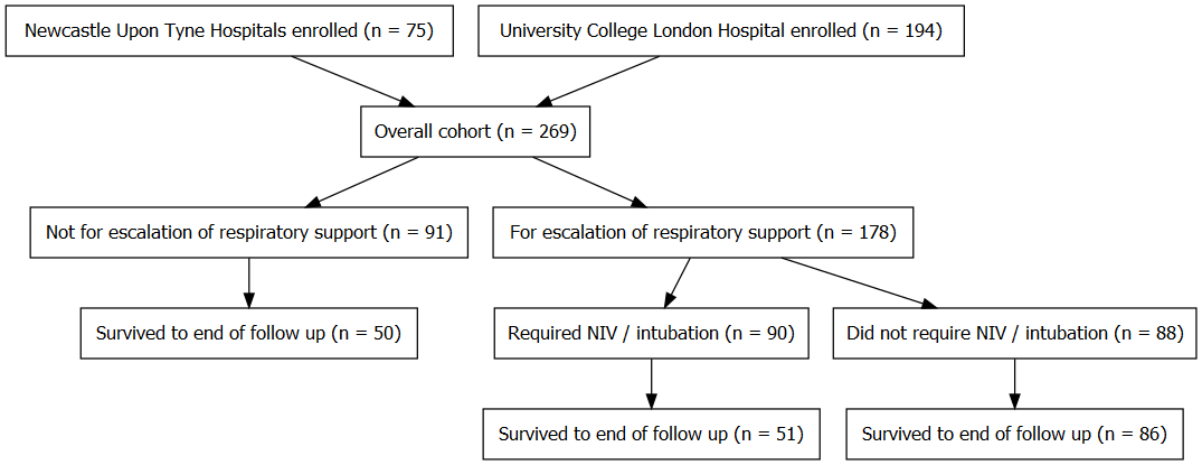
Supplementary Table 1: Cohort demographics and characteristics on admission.

Characteristics by centre with admission observations:	Newcastle upon Tyne Hospitals	University College London Hospitals	Total
Number of patients	75	194	269
Age (years): median (IQR)	76 (63.50, 83.5)	68 (54.0, 80.0)	71 (57.0, 82.8)
Sex: male, n (%)	44 (58.7%)	122 (63.4%)	167 (62.1%)
Ethnicity			
Asian	-	23 (11.9%)	-
Black	-	25 (12.9%)	-
White	71 (94.7%)	99 (51.0%)	170 (63.2%)
Minority ethnic	2 (2.7%)	19 (9.8%)	-
Missing/Not stated	2 (2.7%)	28 (14.4%)	
Alive to end of follow up: died, n (%)	24 (32.0%)	58 (29.9%)	82 (30.5%)
Resuscitation Status			
DNACPR & not for escalation of respiratory support	33 (44.0%)	58 (29.9%)	91 (33.8%)
Charlson Score: Median (IQR)	2 (1, 3)	1 (0, 3)	2 (0, 3
Highest Respiratory Support			
NIV	12 (16.0%)	38 (19.6%)	50 (18.6%)
Intubated	14 (18.7%)	26 (13.4%)	40 (14.9%)
CXR Infiltrates present, n (%)	59 (78.7%)	155 (79.9%)	214 (79.6%)
Corticosteroids or Immunosuppressive medications on admission, n (%)	17 (22.7%)	28 (14.4%)	45 (16.7%)

Supplementary Table 1: Cohort demographics and characteristics on admission. Baseline variables for patients recruited from Newcastle upon Tyne Hospitals and University College London Hospitals. Eligibility for escalation to higher level of respiratory support (defined from as NIV (non-invasive ventilation) or intubated/invasive ventilation), and survival to end of admission.

CXR, chest X-ray; DNACPR, do not attempt cardio-pulmonary resuscitation.

Supplementary Figure 1. Summary of enrolment, escalation of respiratory support and outcome of patients recruited to the study.



Supplementary Table 2: Characteristics by eligibility for escalation	Not for escalation	For escalation
Age (years): median (IQR)	84 (77, 88)	62 (50, 73)
Sex: Male, n (%)	47 (53%)	114 (66%)
Ethnicity		
Asian	5 (6%)	19 (11%)
Black	5 (6%)	20 (12%)
White	66 (74%)	96 (56%)
Minority ethnic	6 (7%)	14 (8%)
Missing / Not stated	7 (8%)	23 (13%)
Alive to end of follow up: died, n (%)	40 (45%)	39 (23%)
Resuscitation Status: DNACPR & not for escalation of respiratory support, n (%)	89 (100%)	0 (0%)
Charlson Score: Median (IQR)	3 (2, 4)	1 (0, 2)
Highest Respiratory Support: n, (%)		
NIV	0 (0%)	50 (29%)
Intubated	0 (0%)	39 (23%)
CXR Infiltrates present: n (%)	65 (73%)	144 (84%)
Corticosteroids or Immunosuppressive medications on admission: n (%)	18 (20%)	26 (15%)

Supplementary Table 2: Cohort demographics and characteristics on admission. Baseline variables for patients separated by whether or not they were eligible for full escalation of care. Eligibility for escalation to higher level of respiratory support (defined from as NIV (non-invasive ventilation) or intubated/invasive ventilation), and survival to end of admission.

CXR, chest X-ray; DNACPR, do not attempt cardio-pulmonary resuscitation.

Supplementary table 3: Baseline laboratory results grouped by survival.

	Patients not for escalation		Patients for full escalation:	
	Died	**Alive**	**Died**	**Alive**
Number of patients	41	50	41	137
Haemoglobin (g/L) NR:130-170 (males); 115-155 (females)	*40*; 129 (111, 139)	*47*; 119 (109, 133)	*40*; 131 (107, 144)	*127*; 132 (117, 146)
Neutrophils (10^9/L) NR: 2.0 – 7.5	40; 7.5 (4.9, 10.9)	47; 4.5 (3.5, 6.4)	40; 5.6 (3.1, 11.0)	*127*; 5.6 (3.6, 7.5)
Lymphocytes (10^9/L) NR: 1.2 – 3.65	*40*; 0.8 (0.5, 1.3)	*47*; 0.8 (0.5, 1.0)	*40;* 0.7 (0.5, 0.9)	*127*; 0.9 (0.7, 1.3)
Platelets (10^9/L) NR: 150 – 400	*39*; 205 (177, 279)	*46*; 224 (164, 299)	*38;* 194 (135.50, 295.75)	*125*; 220 (159, 270)
Creatinine (umol/L) NR: 49 - 92	*35*; 91 (77, 134)	*46*; 94 (78, 114)	*35*; 104 (82, 124)	*119*; 86 (71, 111)
CRP (mg/L) NR: 0 – 5.0	*38*; 103 (56, 227)	*46*; 57 (28, 110)	*37*; 142 (66, 239)	*120*; 71 (42, 174)
Ferritin (ug/L) NR: 30–400 (males); 13–150 (females)	*5*; 1,255 (476, 1,579)	*10*; 327 (171, 810)	*13*; 1,673 (1,004, 2,847)	*42*; 1,296 (489, 2,032)
Monocytes (x10^9/L) NR: 0.2 – 1.0	*40*; 0.6 (0.4, 0.8)	*47*; 0.5 (0.4, 0.7)	*40*; 0.4 (0.3, 0.6)	*126*; 0.4 (0.3, 0.6)
D-dimer (ug/L) NR: 0 – 550	-	-	*6*; 1,585 (804, 1,820)	*11*; 420 (217, 845)
Fibrinogen (g/L) NR: 1.5 – 4.0	*10*; 7.0 (6.0, 8.4)	*12*; 6.8 (5.8, 7.8)	*7*; 8.4 (6.2, 9.2)	*31*; 7.7 (5.5, 8.4)
LDH (IU/L) NR: 135 – 225		*5*; 259 (242, 362)	*6*; 458 (404, 542)	*30*; 356 (292, 446)
ALT (IU/L) NR: 10 - 50	*32*; 22.5 (15.2, 36.2)	*35*; 21.0 (16.0, 27.0)	*36*; 30.5 (23.0, 43.2)	*107*; 39.0 (26.0, 58.5)
Triglycerides (mmol/L) NR: 0.4 – 2.3	-	-	*7*; 1.5 (1.0, 1.8)	*11*; 1.3 (1.1, 1.5)
Urea (mmol/L) NR: 1.7 – 8.3	*13*; 9.8 (7.5, 15.0)	*23*; 8.3 (6.8, 12.9)	*12*; 7.1 (5.7, 9.1)	*36*; 6.4 (4.2, 8.1)
Troponin (ng/L) NR: 0 - 14	*4*; 35.0 (22.8, 88.0)	*4*; 42.0 (33.5, 169.8)	*9*; 14.0 (11.0, 54.0)	*34*; 11.5 (6.0, 25.0)

Supplementary Table 3: Baseline clinical laboratory assessments tests: Baseline clinical laboratory blood tests. Results from the day of COVID-19 positive test or day of admission. Data reported as number; median (Interquartile range (IQR). Numbers <5 not shown. The proportion of missing data reported in Supplementary Table 4. NR = normal ranges.

Supplementary Table 4: Proportion of patients with blood tests results available

	On admission	Overall
Haemoglobin*	254 (94.4%)	269 (100.0%)
Neutrophils*	254 (94.4%)	269 (100.0%)
Lymphocytes*	254 (94.4%)	269 (100.0%)
Monocytes*	253 (94.1%)	269 (100.0%)
Platelets*	248 (92.2%)	268 (99.6%)
CRP	241 (89.6%)	268 (99.6%)
Urea	84 (31.2%)	146 (54.3%)
Creatinine	235 (87.4%)	266 (98.9%)
ALT*	210 (78.1%)	260 (96.7%)
Ferritin*	70 (26.0%)	195 (72.5%)
Triglycerides*	22 (8.2%)	74 (27.5%)
Fibrinogen*	60 (22.3%)	112 (41.6%)
D-Dimer	22 (8.2%)	123 (45.7%)
LDH	44 (16.4%)	29 (10.8%)
Troponin	51 (19.0%)	162 (60.2%)

Supplementary Table 4: Proportion of patients with blood tests results available.
Number (%) of blood test results ever reported. *composite of H-score.

Supplementary Table 5a: Number of patients contributing each day in figure one stratified by their final outcome

Day from symptoms:	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Highest level of respiratory support:																															
Not required escalation	8	13	21	23	24	32	35	37	39	44	45	44	37	32	31	26	23	20	14	11	8	8	7	7	5	5	-	-	-	-	-
NIV	6	7	13	16	19	18	21	26	27	31	36	36	38	37	37	35	34	33	26	25	22	18	17	17	14	13	11	10	8	7	6
Intubated	-	-	6	6	10	12	16	22	24	27	30	31	32	34	35	34	34	33	33	33	34	32	31	30	31	31	30	28	26	23	21

Supplementary Table 5a: Number of patients contributing each day in figure one stratified by their final outcome: In the latter two weeks the number of patients who would not require escalation reduced steadily as people recovered without needing the higher levels of escalation. There is no sudden loss to follow up from large numbers of deaths in these groups, with 1-2 daily deaths. Therefore, although some contribution of survivor bias is inevitable, the most noticeable trends that are observed in the intubated group are more likely to be due to changes in the mean measurements per patients rather than survivor bias. Small numbers <5 suppressed.

Supplementary Table 5b: Number of patients contributing each day in figure two stratified by their final outcome

	Days From Escalation of Respiratory Support																													
	-6	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Final outcome:																											
Died	6	8	11	15	20	23	39	39	37	34	33	28	21	19	18	16	16	16	16	15	15	13	10	8	8	8	7
Alive	6	7	13	19	24	30	51	50	50	50	50	49	47	45	42	41	40	38	35	32	31	31	28	28	26	24	23

Supplementary Table 5b: Number of patients contributing each day in figure two stratified by their final outcome (small numbers <5 suppressed). The numbers in each strata were stable for the 5 days after escalation when there is the most deviation in the curves, but subsequently the inevitable loss from death in the strata whose final outcome is death (and discharge from the strata whose final outcome is alive) was gradual with an increasing contribution of survivor bias in the latter days. However, as the most noticeable trends are observed in the first 10 days, these changes are more likely to reflect changes in the mean measurements per patients rather than due to survivor bias. Small numbers <5 suppressed.

Supplementary table 6 Overall H score laboratory results by end of the admission stratified by survival,

	Patients not for escalation: Died	Patients not for escalation: Alive	Patients for full escalation: Died	Patients for full escalation: Alive
Number of patients	**41**	**50**	**41**	**137**
Ferritin (ug/L)	**17; 665.0 (476.0, 1,282.0)**	**32; 425.5 (245.0, 842.0)**	**36; 1,563.0 (532.3, 2,932.3)**	**110; 713.0 (311.8, 1,548.0)**
ALT (IU/L)	**38; 24.0 (14.5, 39.5)**	**49; 22.0 (15.0, 28.0)**	**32.0 (24.0, 64.0)**	**132; 40.0 (26.0, 71.3)**
Fibrinogen (g/L)	**12; 6.30 (5.50, 7.73)**	**20; 6.70 (4.96, 7.69)**	**24; 5.62 (4.92, 7.38)**	**56; 6.46 (5.37, 8.03)**
Triglycerides (mmol/L)	**-**	**8; 1.35 (1.08, 1.88)**	**20; 1.70 (1.37, 2.28)**	**46; 1.95 (1.30, 2.58)**
H Score	**-**	**-**	**16; 96.0 (81.3, 143.0)**	**31; 84.0 (74.0, 102.0)**

Supplementary table 6 Overall H score laboratory results by end of the admission stratified by survival: mean daily worse values on observed days. number; median (IQR). Small numbers <5 suppressed.

Supplementary Table 7: Characteristics by admission hyperinflammatory criteria

	Not meeting hyperinflammatory criteria	Meeting hyperinflammatory criteria
Total patients: n (%)	179 (66%)	90 (33%)
Age (years): median (IQR)	71 (56, 83)	66 (57, 80)
Sex: Male. N (%)	105 (59%)	62 (69%)
Ethnicity		
Asian	16 (9%)	8 (9%)
Black	15 (8%)	10 (11%)
White	116 (65%)	54 (60%)
Minority ethnic	14 (8%)	6 (7%)
Missing/Not stated	18 (10%)	12 (13%)
Alive to end of follow up: died, n (%)	46 (26%)	36 (40%)
Resuscitation Status: DNACPR & not for escalation of respiratory support, n (%)	66 (37%)	25 (28%)
Charlson Score: Median (IQR)	2 (0, 3)	1 (0, 2)
Highest Respiratory Support: n (%)		
NIV	28 (16%)	22 (24%)
Intubated	17 (9%)	23 (26%)
CXR Infiltrates present: n(%)	128 (72%)	86 (96%)
Corticosteroids or Immunosuppressive medications on admission: N (%)	27 (15%)	18 (20%)

Supplementary table 8: Number of patients meeting COV-HI definition by each criterion initial 3 days included to allow for CRP doubling)

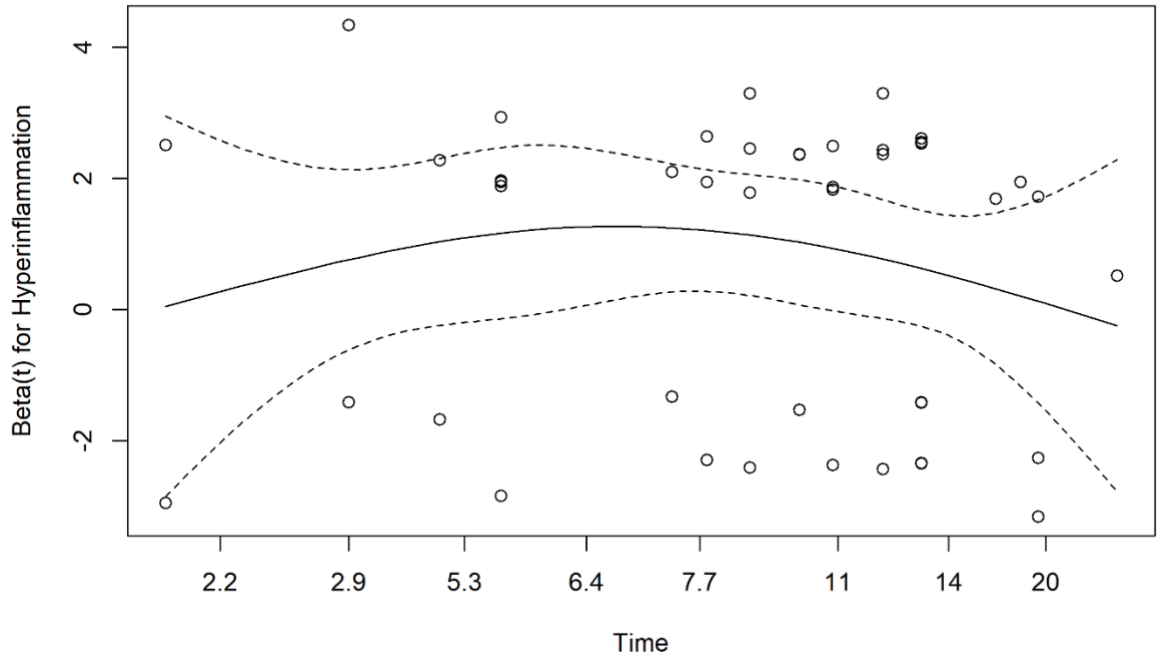
Day of admission	Ferritin > 1500	CRP >50 and doubled	CRP > 150	Total meeting hyperinflammation criteria	Additional patients identified by Ferritin
0	29	0	74	90	16
1	38	1	81	102	21
2	48	2	93	119	26

Supplementary Table 9:	Age and Sex	Co-morbidity	Admission steroids/ immunosuppression	Lymphocytes	Neutrophils	Creatinine	O2 saturation
Hyperinflammatory Criteria	2.22 (1.60-2.839)	2.22 (1.59-2.84)	2.24 (1.62-2.87)	1.78 (1.12-2.43)	2.09 (1.44-2.73)	1.78 (1.12-2.44)	1.806 (1.160-2.451)
Age (years)	1.040 (1.017-1.062)	1.040 (1.017-1.064)	1.040 (1.016-1.063)	1.038 (1.016-1.061)	1.039 (1.016-1.061)	1.038 (1.015-1.061)	1.030 (1.007-1.054)
Gender (Male)	2.54 (1.80-3.28)	2.41 (1.64-3.18)	2.48 (1.67-3.26)	2.31 (1.56-3.07)	2.55 (1.81-3.29)	2.26 (1.48-3.04)	1.835 (1.081-2.588)
Charlson index: (Single Co-morbidity)		0.89 (0.021-1.75)	0.93 (0.044-1.81)				
Charlson index: (Multiple or Severe Co-morbidity)		1.07 (0.37-1.77)	1.13 (0.39-1.88)				
Steroids or Immunosuppressant on admission			0.83 (0.032-1.63)				
Log lymphocytes				0.55 (0.064-1.04)		0.56 (0.064-1.05)	
Log neutrophils					1.22 (0.64-1.80)		
Creatinine						1.001 (0.994-1.008)	
O2 saturation: <94%							4.18 (3.46-4.90)
Observations (patients n =127)	683	683	683	683	683	683	683
Akaike Inf. Crit.	315.35	319.15	320.93	311.77	316.90	313.73	299.34

Supplementary Table 9: Time varying multivariable proportional hazards analysis of factors associated with next day escalation of support or death from daily measurements among patients eligible for escalation of respiratory support who had either ferritin or CRP measured at study enrolment as well as complete data of other included measurements (n=127). Covariate for hyperinflammatory criteria is based on evidence to support hyperinflammation criteria at admission (CRP >150mg/ml or Ferritin >1500ug/L). Refer to Table 2.

Supplementary Figure 2.A-2.F

2.A



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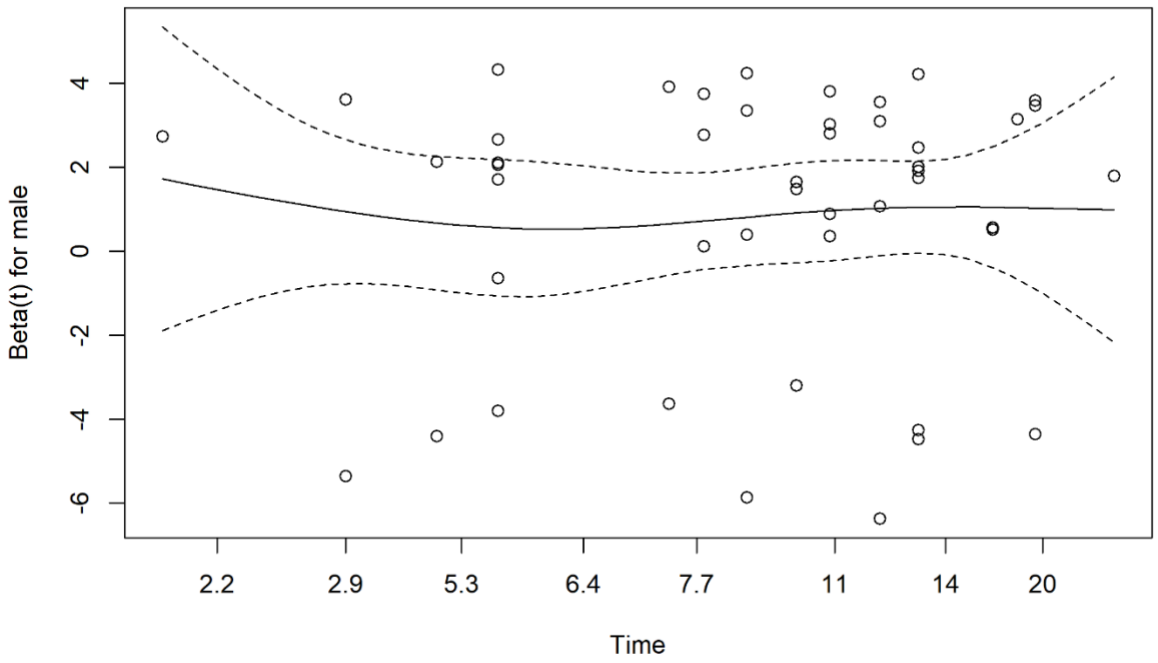
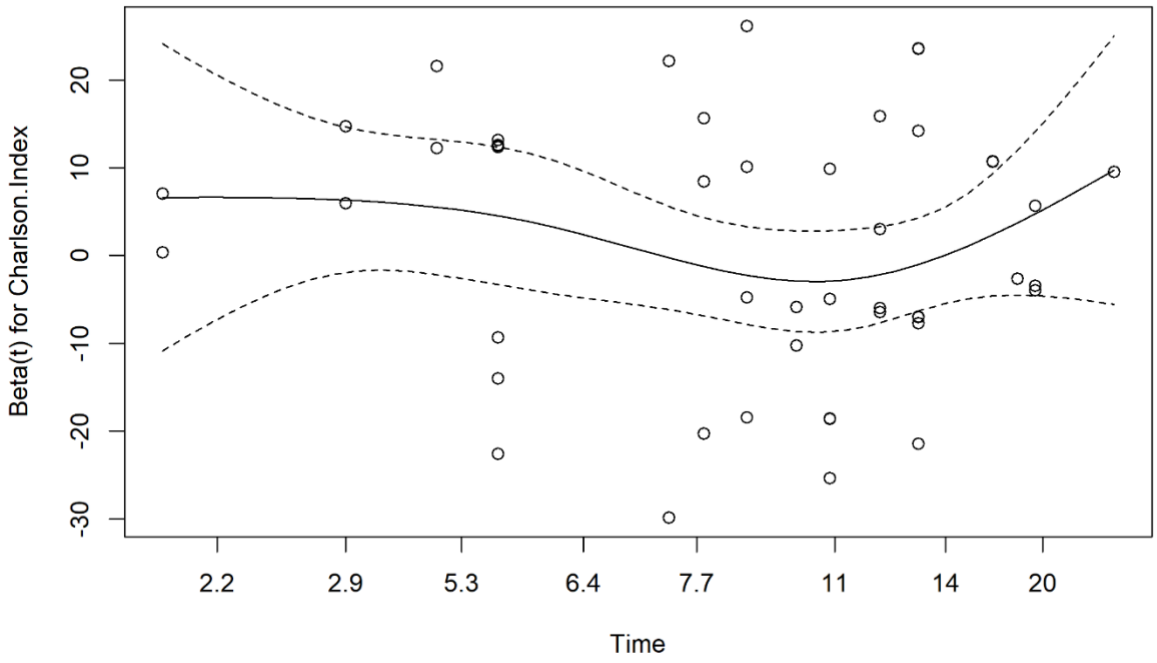
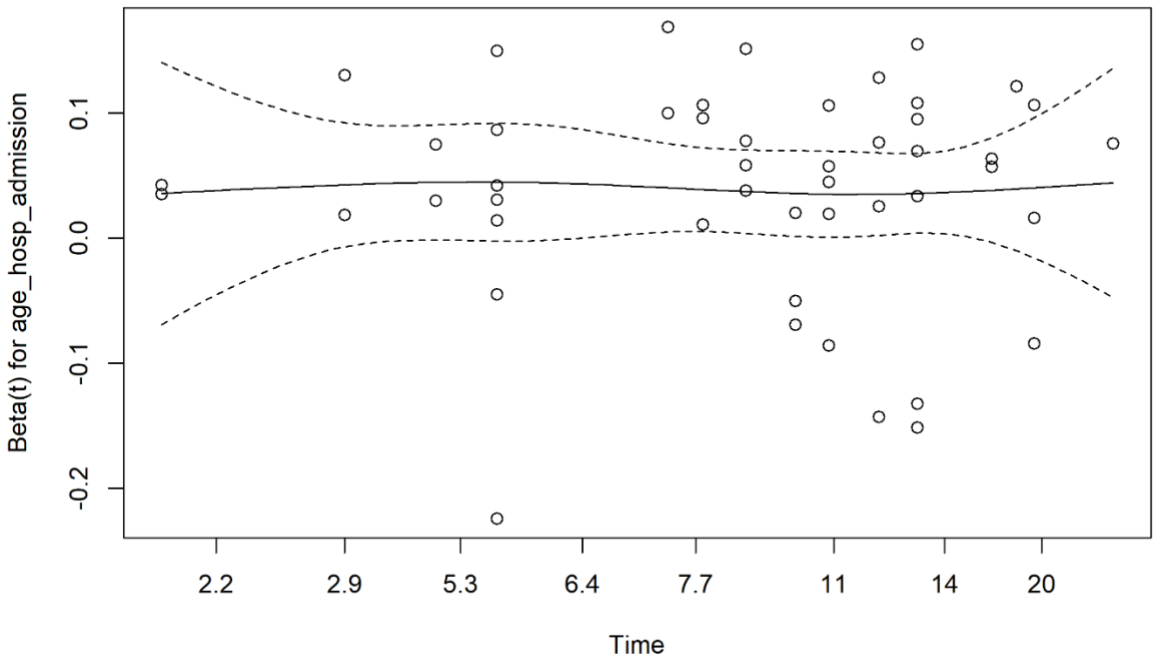


2.C


Beta(t) for Charlson.Index
20
10
0
-10
-20
-30
2.2
2.9
5.3
6.4
7.7
11
14
20
Time

2.D


Beta(t) for age_hosp_admission
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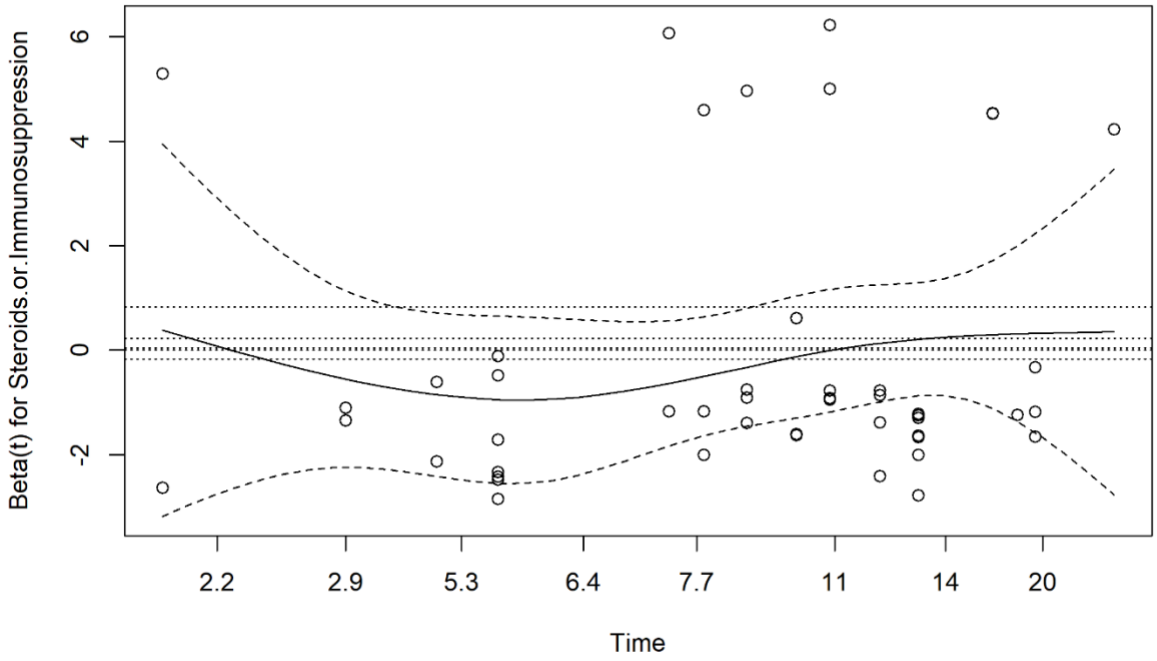
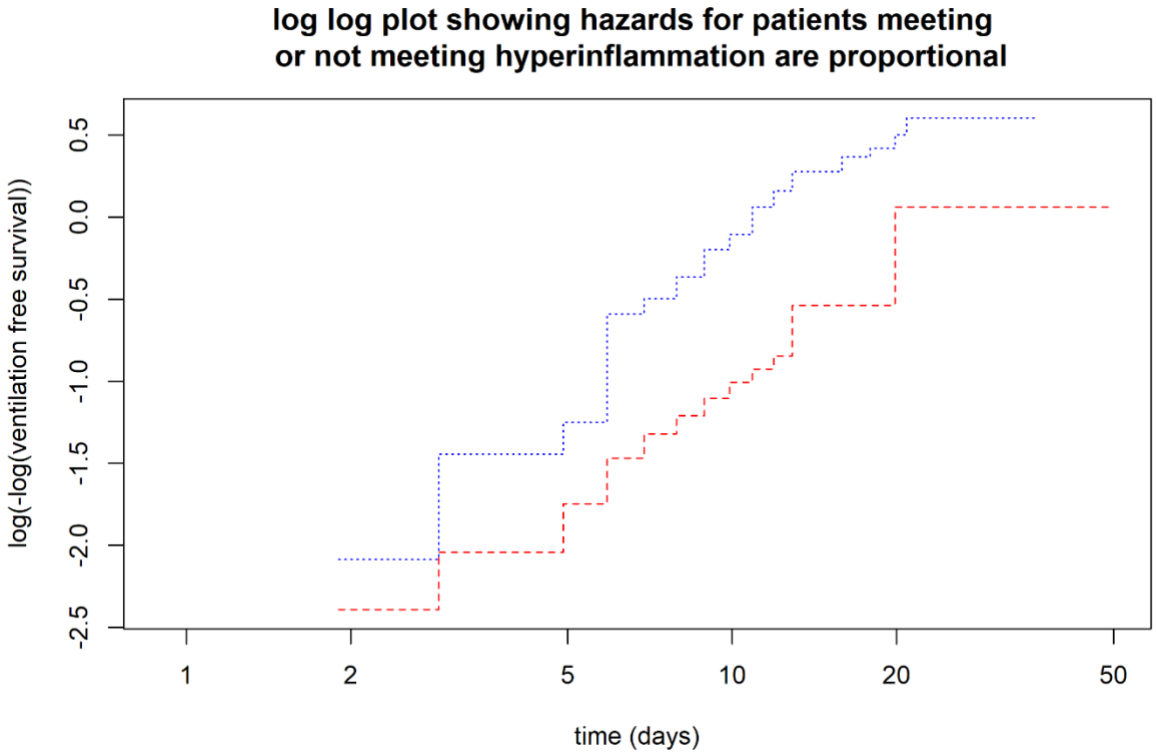
2.2
2.9
5.3
6.4
7.7
11
14
20
Time

2.E



2.F



Supplementary Figure 2.A-2.F: The residual plots for main model covariates:. There was no clear systematic pattern in the residuals for the key predictors, and a fitted line was approximately horizontal, so given the number of data points the proportional hazard assumption was appropriate (Schoenfeld residual plots (A-E) and log(-log) plots (F) are

shown). Low numbers for steroids or immunosuppression medications on admission mean related plots showed a less good fit, but their effect on the main predictor of hyperinflammation was minimal compared to other models in supplementary table 9:

References

1. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48**(2): 124-31.
2. La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019; **133**(23): 2465-77.
3. DAVÌ S, CONSOLARO A, GUSEINOVA D, et al. An International Consensus Survey of Diagnostic Criteria for Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis. *The Journal of Rheumatology* 2011; **38**(4): 764-8.
4. Fardet L, Galicier L, Lambotte O, et al. Development and Validation of the HScore, a Score for the Diagnosis of Reactive Hemophagocytic Syndrome. *Arthritis & Rheumatology* 2014; **66**(9): 2613-2