

Key factors of the deranged antiviral response in elderly patients with COVID-19: a machine-learning analysis

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Baseline characteristics (Validation Cohort: ICU patients). Elderly group.				
Clinical characteristics and outcomes	Elderly group	90-day Survivors	90-day mortality	P value
Demographics and underlying conditions				
No. (%)	119	71 (59.6)	48 (40.3)	-
Age [median years (IQR)]	75.0 (5.00)	75.0 (5.00)	75.0 (5.75)	0.696
Male [n (%)]	79 (66.4)	46 (64.8)	33 (68.8)	0.654
Smoking [n (%)]	3 (2.50)	0 (0.00)	3 (6.30)	0.033
Comorbidities				
Hypertension [n (%)]	74 (62.2)	40 (56.3)	34 (70.8)	0.110
Diabetes [n (%)]	44 (37.0)	20 (28.2)	24 (50.0)	0.016
Obesity [n (%)]	32 (26.9)	23 (32.4)	9 (18.8)	0.100
Chronic cardiovascular disease [n (%)]	23 (19.3)	14 (19.7)	9 (18.8)	0.896
Chronic neurological disease [n (%)]	12 (10.1)	6 (8.50)	6 (12.5)	0.472
Chronic renal disease [n (%)]	13 (10.9)	8 (11.3)	5 (10.4)	0.884
Chronic pulmonary disease [n (%)]	9 (7.60)	6 (8.50)	3 (6.30)	0.656
Cancer [n (%)]	6 (5.00)	5 (7.00)	1 (2.10)	0.225
Admission status and scores				
Day since symptoms onset to hospital admission [median years (IQR)]	6.00 (5.00)	7.00 (6.00)	6.00 (4.00)	0.108
SOFA score [median (IQR)]	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	0.352
PaO ₂ /FIO ₂ (< 400) [n (%)] *102	102 (100)	60 (100)	42 (100)	-
MAP (< 70 mmHg) [n (%)]	6 (5.00)	3 (4.20)	3 (6.30)	0.620
Charlson SCORE [median (IQR)]	4.00 (2.00)	4.00 (2.00)	4 (1.75)	0.351
Laboratory parameters at hospital admission				
Hyperglycemia (Glucose > 126 mg/dl) [n (%)] *112	90 (80.4)	49 (75.4)	41 (87.2)	0.119
Creatinine ≥ 1.2 mg/dL [n (%)] *115	10 (8.7)	6 (8.80)	4 (8.50)	0.953
Bilirubin ≥ 1 mg/dL [n (%)] *95	6 (6.30)	4 (7.00)	2 (5.30)	0.731
Hypertransaminasemia (ALT > 40 UI/L) [n (%)] *107	40 (37.4)	26 (40.6)	14 (32.6)	0.398
Hyperuremia (> 50 mg/dL) [n (%)] *106	61 (57.5)	35 (53.8)	26 (63.4)	0.332
Hypernatremia (Na > 145 mmol/L) [n (%)] *116	5 (4.30)	2 (2.90)	3 (6.40)	0.364
LDH >280 UI/L [n (%)] *102	94 (92.2)	54 (90.0)	40 (95.2)	0.333
Lactate > 2 mmol/L [n (%)] *69	22 (31.9)	14 (31.8)	8 (32.0)	0.988
Hemoglobin < 12 g/dL [n (%)] *112	35 (31.3)	22 (32.4)	13 (29.5)	0.754
Thrombocytopenia (Platelets < 150 cell x 10 ³ / μl) [n (%)] *115	9 (7.80)	4 (5.90)	5 (10.6)	0.351
C-reactive protein > 100 mg/L [n (%)] *111	62 (55.9)	36 (55.4)	26 (56.5)	0.905
Lymphopenia (< 1000 cells/mm ³) [n (%)] *111	97 (87.4)	54 (83.1)	43 (93.5)	0.104
Neutrophilia (>7500 cells/mm ³) [n (%)] *110	70 (63.3)	34 (53.1)	36 (78.3)	0.007
Monocytopenia (< 200 cells/mm ³) [n (%)] *109	31 (28.4)	18 (28.1)	13 (28.9)	0.931
Treatments				
Remdesivir [n (%)]	25 (21.0)	20 (28.2)	5 (10.4)	0.020
Heparin [n (%)] *118	114 (96.6)	69 (98.6)	45 (93.8)	0.155
Corticoids [n (%)] *118	116 (98.3)	69 (98.6)	47 (97.9)	0.787
Tocilizumab [n (%)]	22 (18.5)	11 (15.5)	11 (22.9)	0.306
Antibiotics [n (%)]	114 (95.8)	66 (93.0)	48 (100)	0.060
Non invasive mechanical ventilation [n (%)] *118	41 (34.7)	22 (31.0)	19 (40.4)	0.292
Invasive mechanical ventilation [n (%)]	93 (78.2)	48 (67.6)	45 (93.8)	0.001
Complications				
ARDS [n (%)]	95 (79.8)	53 (74.6)	42 (87.5)	0.085
Acute cardiac failure [n (%)]	2 (1.70)	0 (0.00)	2 (4.20)	0.083
Acute renal failure [n (%)]	43 (36.1)	20 (28.2)	23 (47.9)	0.028
Nosocomial infection [n (%)] *118	64 (54.2)	31 (43.7)	33 (70.2)	0.005
Length of hospital stay [median days (IQR)]	26.0 (24.0)	29.0 (36.0)	24.0 (11.3)	0.048
ARDS [n (%)]	95 (79.8)	53 (74.6)	42 (87.5)	0.085
Data are presented as No. (%) or median [IQR]. P values are calculated by χ^2 or Fisher's test when appropriate.				
Abbreviations: SOFA, Sequential Organ Failure Assessment. MAP, Mean Arterial Pressure.				

Supplementary Table 16. Clinical characteristics for Intensive Care Unit (ICU) hospitalized patients. Elderly group. Statistics: Continuous variables are represented as [median (interquartile range)] and categorical variables as absolute count [(n, (%)). P-values were assessed by using the Mann-Whitney test for continuous variables, and Chi-squared test for categorical variables. SOFA, Sequential Organ Failure Assessment. MAP, Mean Arterial Pressure.

<i>Biomarkers' profile (Validation Cohort: ICU patients). Elderly group.</i>				
Clinical characteristics and outcomes	Elderly group	90-day Survivors	90-day mortality	P value
Demographics and underlying conditions				
No. (%)	119	71 (59.6)	48 (40.3)	-
Age [median years (IQR)]	75.0 (5.00)	75.0 (5.00)	75.0 (5.75)	0.696
Male [n (%)]	79 (66.4)	46 (64.8)	33 (68.8)	0.654
Smoking [n (%)]	3 (2.50)	0 (0.00)	3 (6.30)	0.033
Virological and serological status				
RNAemia (YES), [n (%)]	92 (77.3)	50 (70.4)	42 (87.5)	0.029
Viral RNA load in plasma (copies N1/mL) [median (IQR)]	1361 (6848)	683 (17583)	5856 (16375)	<0.001
Anti-SARS-CoV-2 S1 antibodies (AU/mL) [median (IQR)]	212 (903)	305 (928)	120 (843)	0.189
Protein biomarkers' profile				
IL-2 (pg/mL) [median (IQR)] *116	0.294 (0.589)	0.301 (0.711)	0.282 (0.535)	0.646
GMCSF (pg/mL) [median (IQR)] *116	1.09 (1.09)	1.12 (1.14)	1.05 (1.17)	0.803
CCL2 (pg/mL) [median (IQR)] *116	425.5 (457)	363 (313)	575 (674)	0.006
Granzyme A (pg/mL) [median (IQR)] *115	66.5 (44.9)	67.2 (39.9)	66.5 (47.3)	0.439
IFN- γ (pg/mL) [median (IQR)] *116	1.87 (3.58)	1.85 (3.86)	1.97 (4.37)	0.298
IL-4 (pg/mL) [median (IQR)] *116	0.140 (0.238)	0.164 (0.247)	0.110 (0.243)	0.306
TNF α (pg/mL) [median (IQR)] *116	12.0 (6.17)	11.4 (6.17)	12.8 (5.85)	0.154
B7H1 (PD-L1) (pg/mL) [median (IQR)] *116	206 (88.3)	203 (72.8)	217 (133)	0.115
Endothelin-1 (pg/mL) [median (IQR)] *115	2.51 (2.11)	2.38 (2.19)	2.90 (2.40)	0.039
IFN- α (pg/mL) [median (IQR)] *115	0.971 (2.16)	0.932 (1.55)	1.19 (4.68)	0.188
IL-10 (pg/mL) [median (IQR)] *116	13.1 (13.9)	8.89 (13.7)	15.8 (14.2)	0.004
IL-7 (pg/mL) [median (IQR)] *116	6.71 (6.31)	7.09 (6.14)	6.50 (8.42)	0.931
IL-15 (pg/mL) [median (IQR)] *116	6.38 (3.73)	6.38 (3.13)	6.55 (5.09)	0.517
CXCL10 (pg/mL) [median (IQR)] *115	1498 (1334)	1371 (1308)	1758 (1426)	0.045
IL-6 (pg/mL) [median (IQR)] *116	53.4 (160)	27.4 (86.4)	89.1 (290)	<0.001
D-Dimer (pg/mL) [median (IQR)] *116	2282017 (3232829)	2168157 (2697148)	2561084 (3621950)	0.891
RANTES/CCL5 (pg/mL) [median (IQR)] *114	21844 (27285)	22374 (23650)	18388 (37682)	0.219
Pentraxin-3 (pg/mL) [median (IQR)] *115	31436 (49723)	17074 (34120)	43228 (64024)	0.002
Lipocalin-2 (pg/mL) [median (IQR)] *116	101401 (52840)	99630 (48352)	101804 (68291)	0.707
Data are presented as No. (%) or median [IQR]. P values are calculated by χ^2 or Fisher's test when appropriate.				
Abbreviations: SOFA, Sequential Organ Failure Assessment.				

Supplementary Table 17. Biomarkers' profile for Intensive Care Unit (ICU) hospitalized patients. Elderly group. Statistics: Continuous variables are represented as [median (interquartile range)] and categorical variables as absolute count [(n, (%))]. P-values were assessed by using the Mann-Whitney test for continuous variables, and Chi-squared test for categorical variables.

Baseline characteristics (Validation Cohort: ICU patients). Adult group.				
Clinical characteristics and outcomes	Adult group	90-day Survivors	90-day mortality	P value
Demographics and underlying conditions				
No. (%)	125	111 (88.8)	14 (1.12)	-
Age [median years (IQR)]	55.0 (18.0)	54.0 (17.0)	61.5 (18.0)	0.034
Male [n (%)]	80 (64.0)	71 (64.0)	9 (64.3)	0.981
Smoking [n (%)]	11 (8.80)	11 (9.90)	0 (0.00)	0.217
Comorbidities				
Hypertension [n (%)]	44 (35.2)	38 (34.2)	6 (42.9)	0.524
Diabetes [n (%)]	18 (14.4)	16 (14.4)	2 (14.3)	0.990
Obesity [n (%)]	54 (43.2)	51 (45.9)	3 (21.4)	0.081
Chronic cardiovascular disease [n (%)]	13 (10.4)	11 (9.90)	2 (14.3)	0.613
Chronic neurological disease [n (%)]	3 (2.40)	1 (0.900)	2 (14.3)	0.002
Chronic renal disease [n (%)]	2 (1.60)	1 (0.900)	1 (7.10)	0.079
Chronic Pulmonary disease [n (%)]	11 (8.80)	9 (8.10)	2 (14.3)	0.442
Cancer [n (%)]	4 (4.00)	5 (4.50)	0 (0.00)	0.418
Admission status and scores				
Day since symptoms onset to hospital admission [median years (IQR)]	7.00 (4.00)	7.00 (4.00)	6.50 (4.50)	0.531
SOFA score [median (IQR)]	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	0.117
PaO ₂ /FIO ₂ (< 400) [n (%)] *107	106 (99.1)	96 (99.0)	10 (100)	0.747
MAP (< 70 mmHg) [n (%)]	4 (3.20)	4 (3.60)	0 (0.00)	0.470
Charlson SCORE [median (IQR)]	1.00 (2.00)	1.00 (2.00)	2.00 (1.25)	0.015
Laboratory parameters at hospital admission				
Hyperglycemia (Glucose > 126 mg/dl) [n (%)] *121	83 (68.6)	73 (68.2)	10 (71.4)	0.808
Creatinine ≥ 1.2 mg/dL [n (%)]	4 (3.20)	2 (1.80)	2 (14.3)	0.012
Bilirubin ≥ 1 mg/dL [n (%)] *104	2 (1.90)	2 (2.20)	11 (100)	0.623
Hypertransaminasemia (ALT > 40 UI/L) [n (%)] *112	63 (56.3)	53 (53.0)	10 (83.3)	0.045
Hyperuremia (> 50 mg/dL) [n (%)] *120	46 (38.3)	41 (38.3)	5 (38.5)	0.992
Hypernatremia (Na > 145 mmol/L) [n (%)]	2 (1.60)	1 (0.900)	1 (7.10)	0.079
LDH >280 UI/L [n (%)] *110	87 (79.1)	76 (77.6)	11 (91.7)	0.256
Lactate > 2 mmol/L [n (%)] *87	16 (18.4)	14 (17.9)	2 (22.2)	0.754
Hemoglobin < 12 g/dL [n (%)]	21 (16.8)	19 (17.1)	2 (14.3)	0.789
Thrombocytopenia (Platelets < 150 cell x 103/ μl) [n (%)]	4 (3.20)	4 (3.60)	0 (0.00)	0.470
C-reactive protein > 100 mg/L [n (%)] *120	50 (41.7)	46 (42.6)	4 (33.3)	0.537
Lymphopenia (< 1000 cells/mm3) [n (%)] *124	85 (68.5)	76 (69.1)	9 (64.3)	0.715
Neutrophilia (>7500 cells/mm3) [n (%)] *121	66 (54.5)	58 (53.7)	8 (61.5)	0.592
Monocytopenia (< 200 cells/mm3) [n (%)] *121	23 (19.0)	19 (17.6)	4 (30.8)	0.253
Treatments				
Remdesivir [n (%)]	30 (24.0)	29 (26.1)	1 (7.10)	0.117
Heparin [n (%)]	123 (98.4)	109 (98.2)	14 (100)	0.613
Corticoids [n (%)]	121 (96.8)	107 (96.4)	14 (100)	0.470
Tocilizumab [n (%)]	35 (28.0)	30 (27.0)	5 (35.7)	0.495
Antibiotics [n (%)]	111 (88.8)	97 (87.4)	14 (100)	0.159
Non invasive mechanical ventilation [n (%)]	29 (23.2)	22 (19.8)	7 (50.0)	0.012
Invasive mechanical ventilation [n (%)]	64 (51.2)	50 (45.0)	14 (100)	< 0.001
Complications				
ARDS [n (%)]	86 (68.8)	73 (65.8)	13 (92.9)	0.039
Acute cardiac failure [n (%)]	3 (2.40)	0 (0.00)	3 (21.4)	0.005
Acute renal failure [n (%)]	19 (15.2)	14 (12.6)	5 (35.7)	< 0.001
Nosocomial infection [n (%)] *124	46 (37.1)	36 (32.7)	10 (71.4)	0.023
Length of hospital stay [median days (IQR)]	18.0 (15.0)	17.0 (15.0)	19.5 (8.75)	0.226
ARDS [n (%)]	86 (68.8)	73 (65.8)	13 (92.9)	0.039
Data are presented as No. (%) or median [IQR]. P values are calculated by χ^2 or Fisher's test when appropriate.				
Abbreviations: SOFA, Sequential Organ Failure Assessment. MAP, Mean Arterial Pressure.				

Supplementary Table 18. Clinical characteristics for Intensive Care Unit (ICU) hospitalized patients. Adult group. Statistics: Continuous variables are represented as [median (interquartile range)] and categorical variables as absolute count [(n, (%)). P-values were assessed by using the Mann-Whitney test for continuous variables, and Chi-squared test for categorical variables. SOFA, Sequential Organ Failure Assessment. MAP, Mean Arterial Pressure.

<i>Biomarkers' profile (Validation Cohort: ICU patients). Adult group.</i>				
Clinical characteristics and outcomes	Adult group	90-day Survivors	90-day mortality	P value
Demographics and underlying conditions				
No. (%)	125	111 (88.8)	14 (1.12)	-
Age [median years (IQR)]	55.0 (18.0)	54.0 (17.0)	61.5 (18.0)	0.034
Male [n (%)]	80 (64.0)	71 (64.0)	9 (64.3)	0.981
Smoking [n (%)]	11 (8.80)	11 (9.90)	0 (0.00)	0.217
Virological and serological status				
RNAemia (YES), [n (%)]	78 (62.4)	67 (60.4)	11 (78.6)	0.002
Viral RNA load in plasma (copies N1/mL) [median (IQR)]	314 (1230)	286 (1244)	379 (926)	< 0.001
Anti-SARS-CoV-2 S1 antibodies (AU/mL) [median (IQR)]	183 (780)	170 (670)	917 (3023)	0.746
Protein biomarkers' profile				
IL-2 (pg/mL) [median (IQR)] *123	0.123 (0.339)	0.115 (0.308)	0.284 (0.735)	0.164
GMCSF (pg/mL) [median (IQR)] *124	1.02 (0.859)	0.990 (0.802)	1.25 (1.89)	0.053
CCL2 (pg/mL) [median (IQR)] *123	307 (378)	300 (338)	697 (1563)	0.012
Granzyme A (pg/mL) [median (IQR)] *121	75.3 (39.3)	75.0 (39.4)	76.8 (31.0)	0.833
IFN- γ (pg/mL) [median (IQR)] *123	1.66 (4.48)	1.57 (4.12)	1.80 (7.99)	0.091
IL-4 (pg/mL) [median (IQR)] *123	0.141 (0.235)	0.153 (0.231)	0.074 (0.152)	0.201
TNF α (pg/mL) [median (IQR)] *123	10.2 (5.93)	10.2 (5.72)	11.2 (8.37)	0.275
B7-H1 (PD-L1) (pg/mL) [median (IQR)] *124	196 (113)	188 (98.5)	240 (87.3)	0.037
Endothelin-1 (pg/mL) [median (IQR)] *121	2.01 (1.39)	1.84 (1.35)	2.53 (0.975)	0.103
IFN- α (pg/mL) [median (IQR)] *121	1.39 (5.20)	1.37 (5.24)	1.74 (5.17)	0.481
IL-10 (pg/mL) [median (IQR)] *124	9.78 (13.9)	9.00 (13.3)	17.3 (21.9)	0.013
IL-7 (pg/mL) [median (IQR)] *124	6.645 (6.48)	6.66 (6.34)	6.09 (7.94)	0.776
IL-15 (pg/mL) [median (IQR)] *123	5.54 (3.17)	5.32 (2.94)	7.62 (4.74)	0.004
CXCL10 (pg/mL) [median (IQR)] *124	1347 (1439)	1256 (1313)	2145 (2450)	0.016
IL-6 (pg/mL) [median (IQR)] *124	27.0 (119)	22.1 (99.3)	99.6 (702)	0.013
D-Dimer (pg/mL) [median (IQR)] *124	1343230 (2211967)	1189592 (2132450)	2746747 (7613719)	0.016
RANTES/CCL5 (pg/mL) [median (IQR)] *123	24020 (30843)	24020 (31025)	20978 (22318)	0.286
Pentraxin-3 (pg/mL) [median (IQR)] *123	19085 (27441)	18992 (27634)	24615 (27604)	0.535
Lipocalin-2 (pg/mL) [median (IQR)] *124	86031 (47544)	81359 (44969)	107583 (39001)	0.036
Data are presented as No. (%) or median [IQR]. P values are calculated by χ^2 or Fisher's test when appropriate.				
Abbreviations: SOFA, Sequential Organ Failure Assessment.				

Supplementary Table 19. Biomarkers' profile for Intensive Care Unit (ICU) hospitalized patients. Adult group. Statistics: Continuous variables are represented as [median (interquartile range)] and categorical variables as absolute count [(n, (%))]. P-values were assessed by using the Mann-Whitney test for continuous variables, and Chi-squared test for categorical variables.

Variables	Multivariable				Multivariable				Multivariable				Multivariable			
	HR	CI95%		p	HR	CI95%		p	HR	CI95%		p	HR	CI95%		p
Age	1.04	0.919	1.19	0.507	1.03	0.91	1.17	0.608	1.04	0.912	1.18	0.573	1.04	0.916	1.18	0.543
Sex	1.41	0.609	3.25	0.423	1.28	0.5607	2.93	0.557	15.6	0.676	3.58	0.298	1.15	0.496	2.64	0.751
SOFA score	1.18	0.590	2.35	0.642	1.29	0.659	2.56	0.451	1.10	0.541	2.23	0.794	1.26	0.637	2.50	0.506
CCL2 (pg/mL)	1.95	1.16	3.29	0.012												
B7-H1 (PD-L1) (pg/mL)					2.447	1.01	5.93	0.047								
Endothelin-1 (pg/mL)									2.04	1.03	4.05	0.041				
IL-10 (pg/mL)													1.79	1.12	2.86	0.014

Supplementary Table S20 (Part 1). Logistic regression analysis performed to predict 90-day mortality in the validation (ICU) cohort. Elderly group. Statistically significant differences are shown in bold.

Variables	Multivariable				Multivariable				Multivariable				Multivariable			
	HR	CI95%		p	HR	CI95%		p	HR	CI95%		p	HR	CI95%		p
Age	1.04	0.915	1.18	0.542	1.02	0.897	1.17	0.729	1.09	0.957	1.25	0.189	1.03	0.917	1.16	0.608
Sex	1.09	0.470	2.54	0.838	1.15	0.490	2.69	0.749	1.46	0.616	3.44	0.392	1.18	0.513	2.72	0.696
SOFA score	1.26	0.638	2.50	0.502	15.0	0.740	3.04	0.261	1.43	0.707	2.902	0.319	1.51	0.772	2.97	0.227
CXCL10 (pg/mL)	1.72	1.03	2.85	0.037												
IL-6 (pg/mL)					1.589	1.21	2.09	0.001								
Pentraxin-3 (pg/mL)									1.91	1.28	2.85	0.002				
Viral RNA load in plasma													1.13	1.04	1.23	0.003

Supplementary Table S20 (Part 2). Logistic regression analysis performed to predict 90-day mortality in the validation (ICU) cohort. Elderly group. Statistically significant differences are shown in bold.

Variables	Univariable			
	OR	CI95%		<i>p</i>
IL-2 (pg/mL)	0.988	0.907	1.08	0.788
GM-CSF (pg/mL)	1.09	0.791	1.51	0.593
CCL2 (pg/mL)	1.96	1.18	3.27	0.010
Granzyme A (pg/mL)	1.38	0.658	2.90	0.393
IFN- γ (pg/mL)	1.17	0.899	1.53	0.239
IL-4 (pg/mL)	0.951	0.851	1.06	0.380
TNF α (pg/mL)	1.75	0.761	4.04	0.187
B7-H1 (PD-L1) (pg/mL)	2.52	1.06	6.04	0.037
Endothelin-1 (pg/mL)	1.99	1.01	3.92	0.048
IFN- α (pg/mL)	1.08	0.97	1.20	0.171
IL-10 (pg/mL)	1.83	1.15	2.89	0.010
IL-7 (pg/mL)	1.17	0.689	1.98	0.566
IL-15 (pg/mL)	1.39	0.619	3.12	0.425
CXCL10 (pg/mL)	1.76	1.07	2.90	0.027
IL-6 (pg/mL)	1.57	1.21	2.06	0.001
D-Dimer (pg/mL)	0.938	0.708	1.24	0.657
CCL5 (pg/mL)	0.807	0.55	1.19	0.280
Pentraxin-3 (pg/mL)	1.78	1.22	2.61	0.003
Lipocalin-2 (pg/mL)	1.63	0.708	3.74	0.252
Anti-SARS-CoV-2 S IgG (AUC)	0.970	0.92	1.03	0.300
Viral RNA load in plasma (copies/mL plasma)	1.13	1.04	1.23	0.004

Supplementary Table S20 (Part 3). Logistic regression analysis performed to predict 90-day mortality in the validation (ICU) cohort. Elderly group. Statistically significant differences are shown in bold.

Variables	Multivariable				Multivariable				Multivariable			
	HR	CI95%		<i>p</i>	HR	CI95%		<i>p</i>	HR	CI95%		<i>p</i>
Age	1.05	0.988	1.12	0.113	1.05	0.983	1.12	0.154	1.05	0.992	1.12	0.088
Sex	1.06	0.301	3.72	0.928	0.929	0.260	3.32	0.910	0.670	0.187	2.39	0.537
SOFA score	124064702	0	-	0.998	141820996	0	-	0.998	90115413	0	-	0.998
GM-CSF (pg/mL)	3.07	1.21	7.82	0.018								
CCL2 (pg/mL)					2.599	1.303	5.18	0.007				
IL-10 (pg/mL)									2.01	1	4.04	0.049

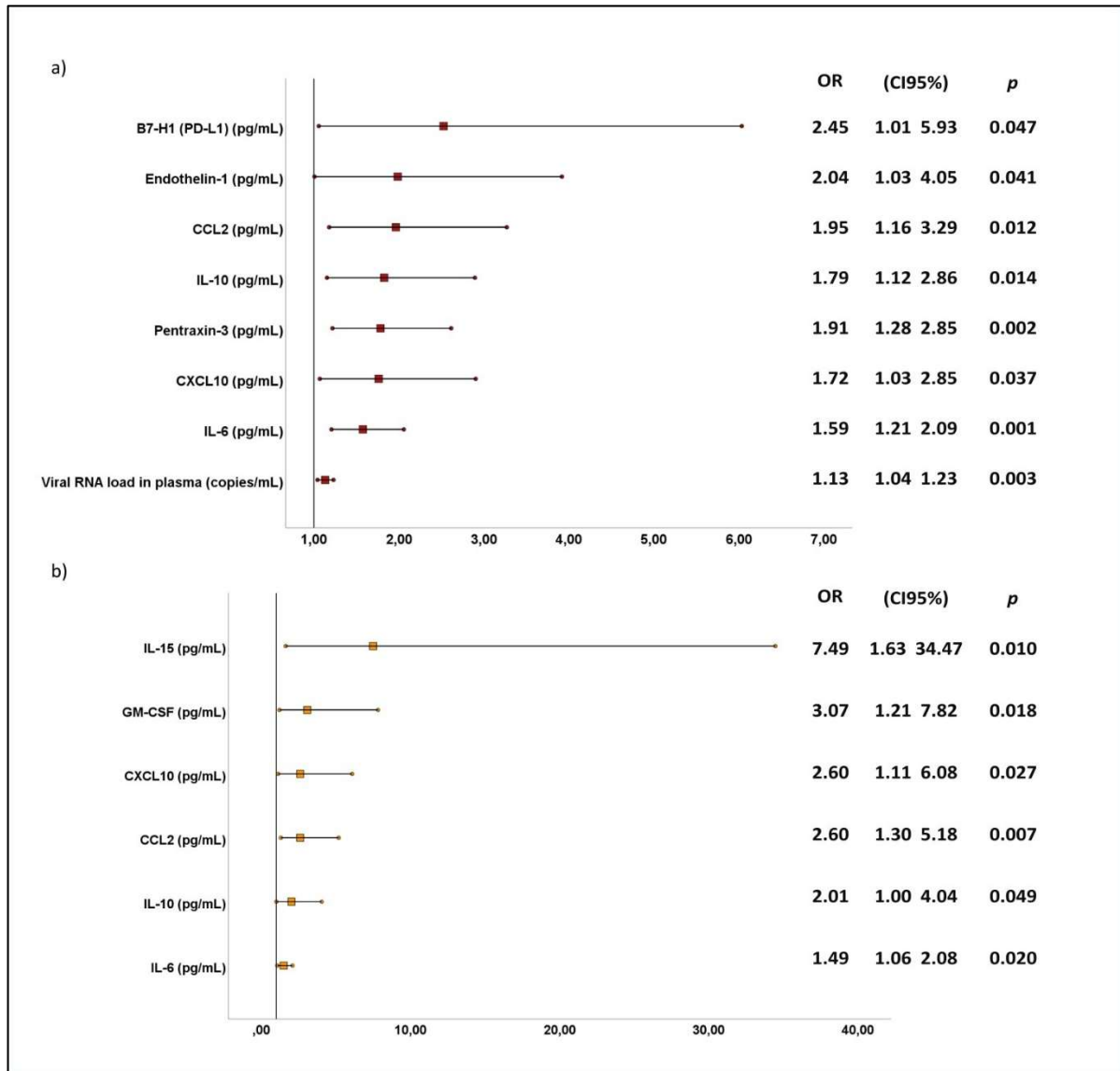
Supplementary Table S21 (Part 1). Logistic regression analysis performed to predict 90-day mortality in the validation (ICU) cohort. Adult group. Statistically significant differences are shown in bold.

Variables	Multivariable				Multivariable				Multivariable			
	HR	CI95%		<i>p</i>	HR	CI95%		<i>p</i>	HR	CI95%		<i>p</i>
Age	1.04	0.975	1.11	0.240	1.04	0.981	1.11	0.173	1.04	0.979	1.11	0.199
Sex	0.463	0.116	1.84	0.274	0.604	0.167	2.19	0.442	0.9402	0.272	3.25	0.922
SOFA score	119914320	0	-	0.998	110147097	0	-	0.998	96138776	0	-	0.998
IL-15 (pg/mL)	7.49	1.63	34.5	0.010								
CXCL10 (pg/mL)					2.60	1.11	6.08	0.027				
IL-6 (pg/mL)									1.49	1.06	2.08	0.020

Supplementary Table S21 (Part 2). Logistic regression analysis performed to predict 90-day mortality in the validation (ICU) cohort. Adult group. Statistically significant differences are shown in bold.

Variables	Univariable			
	OR	CI95%		<i>p</i>
IL-2 (pg/mL)	1.05	0.92	1.20	0.466
GM-CSF (pg/mL)	2.78	1.27	6.11	0.011
CCL2 (pg/mL)	2.67	1.38	5.13	0.003
Granzyme A (pg/mL)	1.02	0.24	4.31	0.982
IFN- γ (pg/mL)	1.38	0.92	2.07	0.121
IL-4 (pg/mL)	0.970	0.81	1.16	0.758
TNF α (pg/mL)	2.30	0.59	8.96	0.232
B7-H1 (PD-L1)(pg/mL)	1.50	0.52	4.38	0.456
Endothelin-1 (pg/mL)	1.95	0.72	5.24	0.188
IFN- α (pg/mL)	1.09	0.87	1.37	0.440
IL-10 (pg/mL)	2.01	1.06	3.80	0.033
IL-7 (pg/mL)	1.02	0.462	2.33	0.930
IL-15 (pg/mL)	6.72	1.74	26.0	0.006
CXCL10 (pg/mL)	2.82	1.21	6.56	0.016
IL-6 (pg/mL)	1.58	1.14	2.18	0.006
D-Dimer (pg/mL)	1.42	0.99	2.04	0.058
CCL5 (pg/mL)	0.74	0.37	1.51	0.414
Pentraxin-3 (pg/mL)	1.19	0.73	1.94	0.479
Lipocalin-2 (pg/mL)	2.00	0.69	5.76	0.200
Anti-SARS-CoV-2 S IgG (AUC)	1.04	0.92	1.19	0.533
Viral RNA load in plasma (copies/mL plasma)	1.01	0.95	1.08	0.697

Supplementary Table S21 (Part 3). Logistic regression analysis performed to predict 90-day mortality in the validation (ICU) cohort. Adult group. Statistically significant differences are shown in bold.



Supplementary Figure S10. Forest plot of multivariable logistic regression analysis performed in the validation cohort for factors associated with 90-day mortality in each group of patients: a) elderly group and b) adult group.

