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Supplemental information

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A clinical score to predict COVID-19 pneumonia

progression to severe respiratory failure

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SUPPLEMENTARY APPENDIX

Development and validation of SCOPE score: a clinical score to predict progression of COVID-19 pneumonia to severe respiratory failure

Running title: SCOPE score for COVID-19 pneumonia

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Supplementary Table 1. Characteristics of patients participating in both cohorts. Related to Figure 1.

	Discovery cohort (SAVE-MORE study)			**Validation cohort I (SAVE study)**			**Validation cohort II (Dutch)**		
	suPAR <6ng/ml (N=225)	**suPAR ≥6ng/ml (N=390)**	**p-value**	**suPAR <6ng/ml (N=97)**	**suPAR ≥6 ng/ml (N=675)**	**p-value**	**suPAR <6ng/ml (N=25)**	**suPAR ≥6ng/ml (N=147)**	**p-value**
Male gender, n (%)	154 (68.4)	257 (62.1)	0.119[a]	57 (58.8)	420 (62.2)	0.505[a]	19 (76.1)	96 (65.3)	0.363[a]
Age, years, mean (SD)	53.2 (12.2)	60.6 (12.3)	<0.0001[b]	53.4 (10.2)	61.9 (13.6)	<0.0001[b]	64.2 (13.2)	66.8 (12.2)	0.330[b]
BMI, kg/m^2, mean (SD)	29.1 (5.0)	29.5 (5.5)	0.365[b]	na	na		24.9 (4.6)	29.2 (6.2)	0.011[b]
COVID-19 pneumonia severity at enrolment, n (%)									
Moderate	55 (24.4)	56 (13.5)		23 (23.7)	180 (23.3)		12 (48.0)	31 (21.2)	
Severe	170 (75.6)	358 (86.5)	0.0007[a]	74 (76.3)	495 (64.1)	1.00[a]	13 (52.0)	115 (78.8)	0.011[a]
Dexamethasone treatment, n (%)	173 (76.9)	357 (86.2)	0.004[a]	74 (76.3)	495 (64.1)	1.00[a]	13 (52.0)	115 (78.8)	0.011[a]

[a]Fisher's exact test; [b]Student's t-test

Abbreviations BMI: body mass index; na: non-available; SD: standard deviation; suPAR: soluble urokinase-type plasminogen activator receptor; WHO: World Health Organization

Supplementary Table 2 Distribution of the values of the SCOPE score according to the suPAR level in the discovery cohort Related to Figure 3.

SCOPE score	**suPAR ≥6 ng/ml, (n)**	**suPAR <6 ng/ml, (n)**	**Total (n)***
≥ 6	267 Sensitivity: 64.2% (95%CI: 59.4-68.6) PPV: 75.6% (95%CI: 70.9-79.8)	86	353
< 6	149	137 Specificity: 61.4% (95%CI: 54.9-67.5) NPV: 47.9% (95%CI: 42.1-53.9)	286
Total (n)	416	223	639

*The p-value of comparison of this 2 x 2 Table using the Fisher's exact test is <0.0001 demonstrating that patients with suPAR ≥6 ng/ml are distributed towards greatest values of the SCOPE score.

Abbreviations CI: confidence intervals; n: number; NPV: negative predictive value; PPV: positive predictive value

Supplementary Table 3 Distribution of the values of the SCOPE score according to the suPAR level in the validation cohort I Related to Figure 5.

SCOPE score	**suPAR ≥6 ng/ml, (n)**	**suPAR <6 ng/ml, (n)**	**Total (n)***
≥ 6	491 Sensitivity: 72.7% (95%CIs: 69.3-75.9) PPV: 92.3% (95%CIs: 89.7-94.3)	41	532
<6	184	56 Specificity: 57.7% (95%CIs: 47.8-67.1) NPV: 23.3% (95%CIs: 18.4-29.1)	240
Total (n)	675	97	772

*The p-value of comparison of this 2 x 2 Table using the Fisher's exact test is <0.0001 demonstrating that patients with suPAR ≥6 ng/ml are distributed towards greatest values of the SCOPE score.

Abbreviations n: number; NPV: negative predictive value; PPV: positive predictive value

Supplementary Table 4 Distribution of the values of the SCOPE score according to the suPAR level in the validation cohort II Related to Figure 6.

SCOPE score	**suPAR ≥6 ng/ml, (n)**	**suPAR <6 ng/ml, (n)**	**Total (n)***
≥ 6	140 Sensitivity: 95.2% (95%CIs: 90.5-97.7) PPV: 89.2% (95%CIs: 83.3-93.1)	17	157
<6	7	8 Specificity: 32.0% (95%CIs: 17.2-51.6) NPV: 53.3% (95%CIs: 30.1-75.2)	15
Total (n)	147	25	172

*The p-value of comparison of this 2 x 2 Table using the Fisher's exact test is <0.0001 demonstrating that patients with suPAR ≥6 ng/ml are distributed towards greatest values of the SCOPE score.

Abbreviations n: number; NPV: negative predictive value; PPV: positive predictive value

A)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
CRP >50 mg/l	31 Sensitivity: 66.0% PPV: 27.7%	81	112
CRP ≤50 mg/l	16	174 Specificity: 68.2% NPV: 91.6%	190
Total (n)	47	255	302

B)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
D-dimers >1.2 mg/l	8 Sensitivity: 17.0% PPV: 32.3%	29	37
D-dimers ≤1.2 mg/l	39	226 Specificity: 88.6% NPV: 85.3%	265
Total (n)	47	255	302

C)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
Ferritin >700 ng/ml	24 Sensitivity: 51.1% PPV: 30.8%	54	78
Ferritin ≤700 ng/ml	23	201 Specificity: 78.8% NPV: 89.7%	224
Total (n)	47	255	302

D)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
IL-6 >24 pg/ml	30 Sensitivity: 63.8% PPV: 37.0%	51	81
IL-6 ≤24 pg/ml	17	204 Specificity: 80.0% NPV: 92.3%	221
Total (n)	47	255	302

Supplementary Figure 1 Comparative performance of each of the four biomarkers to predict the progression into severe respiratory failure (SRF) or death the first 14 days. Related to Figure 2.

At each of the four panels, the cut-off is coming from the analysis of the Youden index of the co-ordinate points of the receiver operator characteristics curve.

A) C-reactive protein (CRP); B) D-dimers; C) Ferritin; D) interleukin (IL)-6

Abbreviations n: number; NPV: negative predictive value; PPV: positive predictive value

A)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
CRP+ D-dimers + ferritin ≥4	33 Sensitivity: 70.2% PPV: 26.8%	90	123
CRP+ D-dimers + ferritin <4	14	165 Specificity: 64.7% NPV: 92.2%	179
Total (n)	47	255	302

B)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
CRP+ D-dimers + IL-6 ≥4	38 Sensitivity: 80.9% PPV: 28.1%	97	135
CRP+ D-dimers + IL-6 <4	9	158 Specificity: 62.0% NPV: 94.6%	167
Total (n)	47	255	302

C)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
CRP+ ferritin+ IL-6 ≥5	32 Sensitivity: 68.1% PPV: 37.6%	53	85
CRP+ ferritin+ IL-6 <5	15	202 Specificity: 79.2% NPV: 93.1%	217
Total (n)	47	255	302

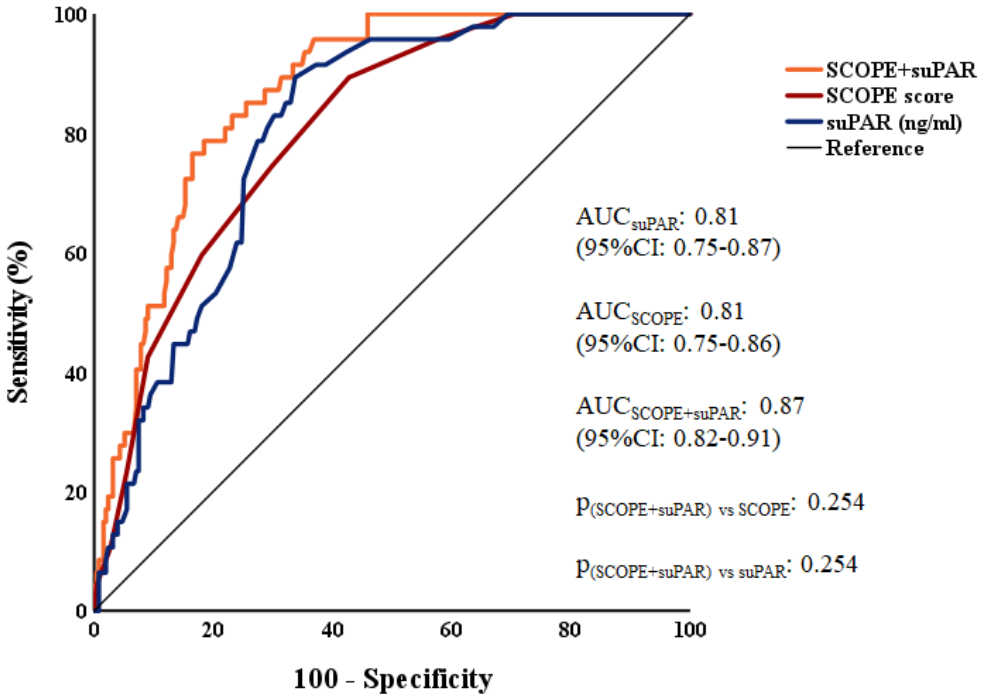
D)

	SRF/death (+) (n)	SRF/death (-) (n)	Total
D-dimers + ferritin+ IL-6 ≥5	33 Sensitivity: 70.2% PPV: 37.1%	56	89
D-dimers + ferritin+ IL-6 <5	14	199 Specificity: 78.0% NPV: 93.4%	213
Total (n)	47	255	302

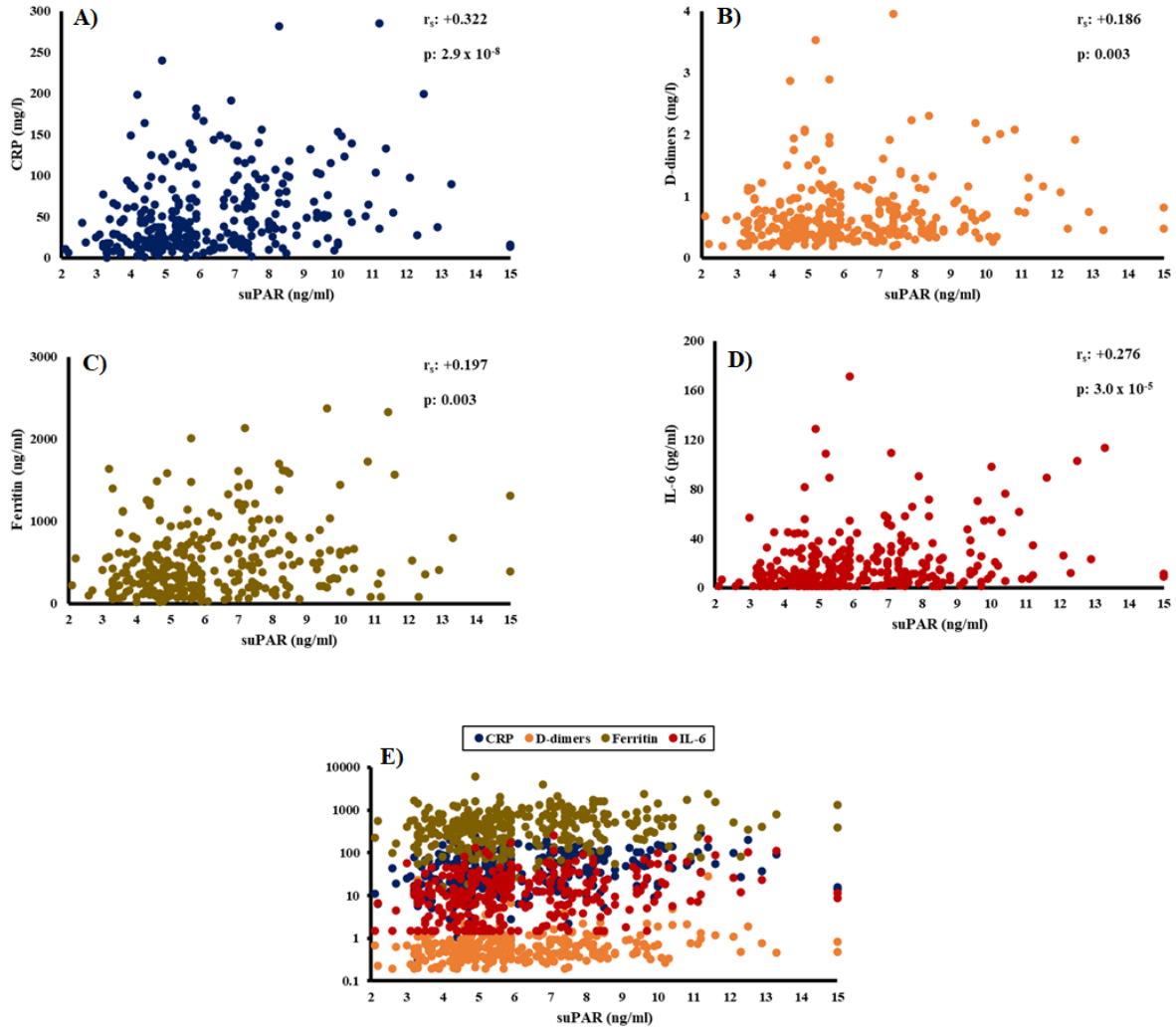
Supplementary Figure 2 N-1 analyses of components of the SCOPE score to predict the progression into severe respiratory failure (SRF) or death the first 14 days in the discovery cohort. Related to Figure 2. The quartiles of the measured concentrations of C-reactive protein, D-dimers, ferritin and interleukin (IL)-6 providing separate points were used to calculate four sub-scores. Sub-scores are (A) adding the points provided by CRP, D-dimers and ferritin; (B) adding the points provided by CRP, D-dimers and IL-6; (C) adding the points provided by CRP, ferritin and IL-6; and (D) adding the points provided by D-dimers, ferritin and IL-6. For each of the four sub-scores, the cut-off is coming from the analysis of the Youden index of the co-ordinate points of the receiver operator characteristics curve.

A) C-reactive protein (CRP); B) D-dimers; C) Ferritin; D) interleukin (IL)-6

Abbreviations n: number; NPV: negative predictive value; PPV: positive predictive value



Supplementary Figure 3 Comparative performance of suPAR, SCOPE score and their interaction for the prediction of progression into severe respiratory failure or death the first 14 days. Related to Figure 2. Receiver Operator Characteristic (ROC) curves of the SCOPE score, of suPAR and of their interaction to predict the progression into SRF or death the first 14 days. The areas under the ROC curves (AUROC) and the 95% confidence intervals of the SCOPE score, of suPAR and of their interaction are provided. The p-values of comparisons of the AUROCs are also provided.



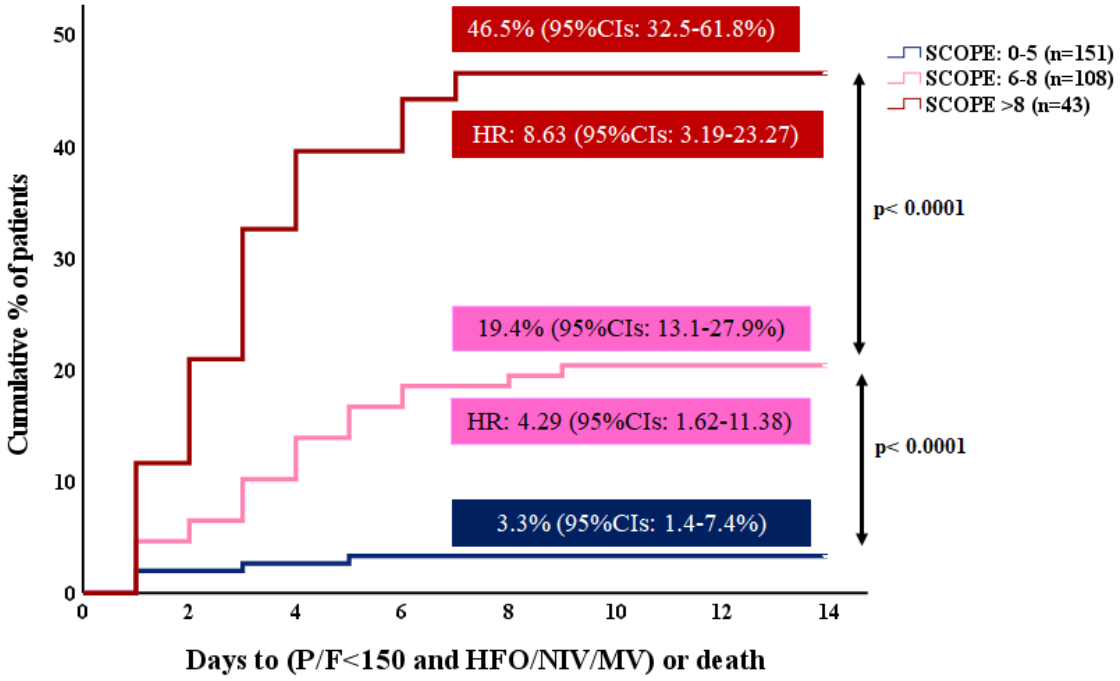
F)

	Univariate analysis		Multivariate analysis	
	OR (95% CIs)	**p**	**OR (95% CIs)**	**p**
CRP quartiles	1.58 (1.29-1.94)	<0.0001	1.35 (1.08-1.69)	0.009
D-dimers quartiles	1.19 (0.97-1.46)	0.088	*	
Ferritin quartiles	1.49 (1.21-1.84)	<0.0001	1.34 (1.07-1.68)	0.011
IL-6 quartiles	1.47 (1.18-1.83)	0.001	1.29 (1.02-1.64)	0.033

Supplementary Figure 4 Lasso regression analysis of the selection of biomarkers for the SCOPE score in the discovery cohort Related to Figure 2.

Correlation of the values of soluble urokinase plasminogen activator receptor (suPAR) with those of A) C-reactive protein (CRP); B) D-dimers; C) ferritin; and D) interleukin (IL)-6. The Spearman (r_s) rank of order correlations and the respective p-values are provided. P-values are corrected for multiple tests. The clustering of correlation between CRP, D-dimers, ferritin and IL-6 with suPAR is provided in panel E. The quartiles of CRP, D-dimers, ferritin and IL-6 have entered univariate and multivariate step-wise forward logistic regression analysis and results are shown in panel F. *did not enter the equation after 3 steps of forward analysis

Abbreviations CI: confidence intervals; OR: odds ratio



Patients at risk (n)

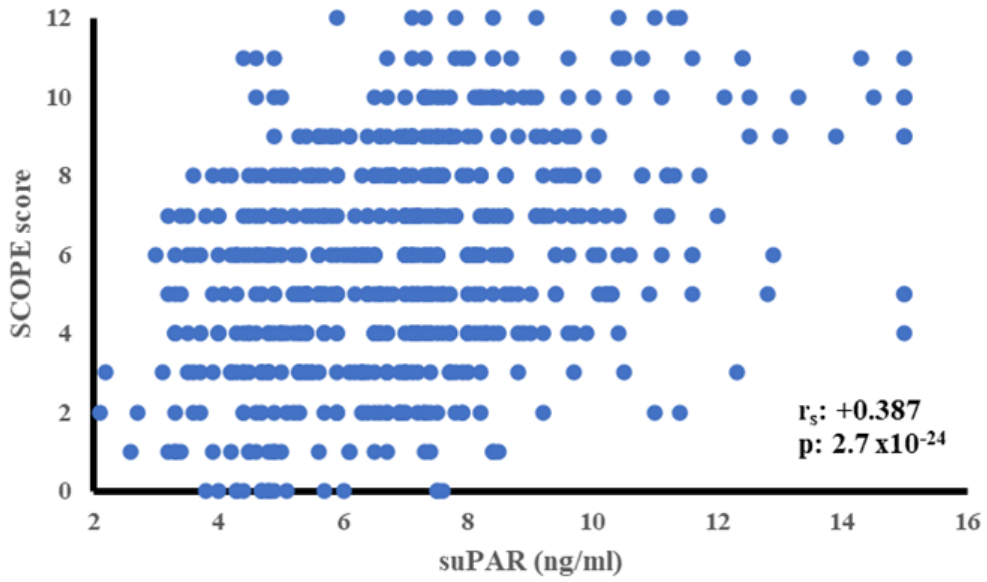
SCOPE >8	43	34	26	24	23	23	23	23
SCOPE 6-8	108	101	93	88	87	86	86	86
SCOPE 0-5	151	148	147	146	146	146	146	146

Supplementary Figure 5 Prognostic performance of different levels of the SCOPE score for severe respiratory failure (SRF) or death after 14 days Related to Figure 3.

Time to progression into SRF or death the first 14 days when the SCORE score is ranging between 0 and 5; between 6 and 8; and more than 8. This analysis includes 302 patients for which the four biomarkers of the SCOPE score were measured and for which clinical information for 14-day outcome was available. The p-values of the indicated comparisons by arrows are provided.

Abbreviations CI: confidence intervals; HFO: high-flow oxygen; HR: hazard ratio; MV: mechanical ventilation; n: number of patients; NIV: non-invasive ventilation

A)



B)

suPAR (ng/ml)	SCOPE score (number of patients, %)						
	6	7	8	9	10	11	12
<2-3.9	5 (6.0)	4 (5.3)	2 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)
4.0-4.9	15 (17.9)	9 (12.0)	6 (9.0)	1 (2.0)	2 (4.9)	3 (12.5)	0 (0)
5.0-5.9	8 (9.5)	9 (12.0)	12 (17.9)	8 (16.0)	1 (2.4)	0 (0)	1 (8.3)
6.0-7.0	16 (19.0)	12 (16.0)	15 (22.4)	10 (20.0)	4 (9.8)	1 (4.2)	0 (0)
7.1-8.0	17 (20.2)	17 (22.7)	12 (17.9)	15 (30.0)	7 (17.1)	5 (20.8)	4 (33.3)
8.1-9.0	11 (13.1)	7 (9.3)	6 (9.0)	4 (8.0)	14 (34.1)	3 (12.5)	1 (8.3)
>9.0	12 (14.3)	17 (22.7)	14 (20.8)	12 (24.0)	13 (31.7)	22 (50.0)	6 (50.0)

r_s: +0.305; p: 4.7 x10^{-9}

C)

<4 ng/ml	4.0-5.9 ng/ml	≥6 ng/ml
3.1%	22.3%	75.6%

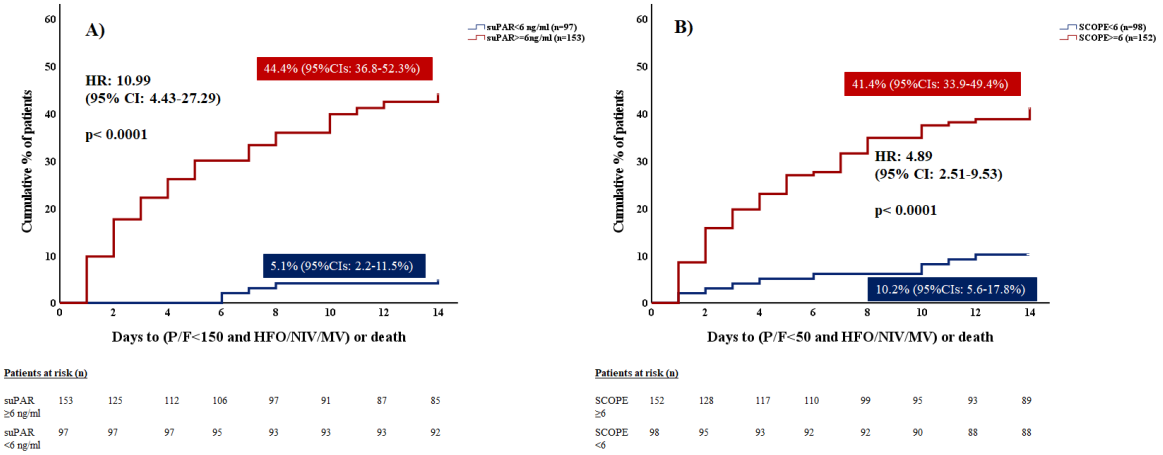
Supplementary Figure 6. Correlation between SCOPE score and suPAR Related to Figure 3.

A) Scatterplot demonstrating the correlation between suPAR and SCOPE score (n=639; all analyzed patients)

B) Heat map of suPAR concentration versus SCOPE score (n=353 patients with SCOPE score ≥6)

(C) and distribution with SCOPE ≥6 (n=353) into three main categories of suPAR (normal [<4.0 ng/ml]; intermediate [4.0–<6.0 ng/ml] and high [≥6.0 ng/ml]).

Abbreviations r_s, Spearman's correlation coefficient; SCOPE, Severe COvid Prediction Estimate; suPAR, suPAR, soluble urokinase-type plasminogen activator receptor.



Supplementary Figure 7 Prognostic performance of suPAR and SCOPE score for progression into severe respiratory failure (SRF) or death the first 14 days in the validation cohort Related to Figure 5.

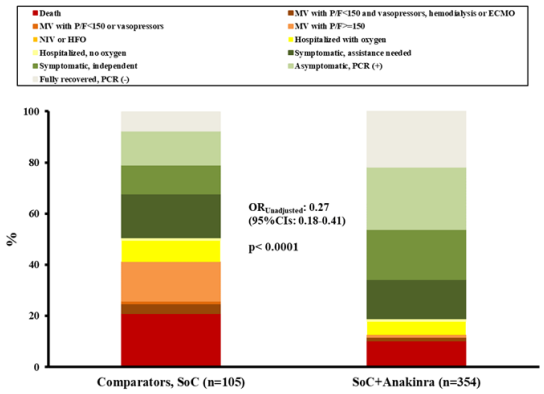
The analysis includes patients screened for eligibility for the SAVE trial. All the patients have similar baseline characteristics to the patients enrolled in the SAVE-MORE trial. More precisely, patients had WHO-CPS 4 or 5 and they received the same SoC treatment.

A) Time to progression into SRF or for death the first 14 days between patients with suPAR 6 ng/ml or more and patients with suPAR less than 6 ng/ml.

B) Time to progression into SRF or for death the first 14 days between patients with SCOPE score 6 or more and patients with SCOPE score less than 6.

Abbreviations CI: confidence intervals; HFO: high-flow oxygen; HR: hazard ratio; MV: mechanical ventilation; n: number of patients; NIV: non-invasive ventilation; suPAR: soluble urokinase plasminogen activator receptor

A)



B)

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CIs)	p-value	OR (95%CIs)	p-value
Group of treatment (anakinra vs placebo)	0.27 (0.18-0.41)	<0.0001	0.29 (0.19-0.43)	<0.0001
Dexamethasone intake (Yes/No)	1.64 (1.10-2.46)	0.015	1.31 (0.87-1.98)	0.189
Severe COVID-19 pneumonia by WHO (Yes/No)	1.64 (1.10-2.46)	0.015	1.31 (0.87-1.98)	0.189

Supplementary Figure 8. Response to anakinra treatment of patients enrolled in the SAVE trial with SCOPE score 6 or more in the validation cohort I Related to Figure 5.

A) Distribution of the World Health Organization (WHO) Clinical Progression Scale (CPS) at day 28 of patients allocated to treatment with standard-of-care (SoC) and placebo and to treatment with SoC and anakinra. The odds ratio (OR) of the unadjusted ordinal regression analysis and the 95% confidence intervals (CIs) are shown.

B) Univariate and multivariate ordinal regression analysis of the WHO-CPS at day 28.

Abbreviations CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HFO: high flow oxygen; MV: mechanical ventilation; NIV: non-invasive ventilation; OR: odds ratio; PCR: polymerase chain reaction; P/F: respiratory failure; SoC; standard-of-care