Supplemental Methods:

Cohort of patients with COVID-19-associated nephropathy

We conducted an immunofluorescence study on anonymized kidney biopsies from a multicenter, retrospective case series of patients with COVID-19 who developed acute kidney injury (AKI) and/or proteinuria and underwent a kidney biopsy in Paris and its metropolitan area. All clinical investigations have been conducted in accordance with the principles of the Declaration of Helsinki.

Thirty-one adult patients who tested positive for SARS-CoV-2 by polymerase chain reaction on a nasopharyngeal swab or a pulmonary sample were hospitalized in five Nephrology departments in the Paris metropolitan area from March 2020 to June 2021, and were eligible. Patients with a history of end-stage kidney disease were excluded. This study was conducted in compliance with the Helsinki Declaration and approved by the local institutional review board as minimal-risk research, utilizing retrospective data collected for routine clinical practice. Due to the study's observational nature, patient consent was waived per French law.

Immunofluorescence staining

Kidney biopsy specimens with sufficient tissue for immunohistochemical evaluation, following completion of the diagnostic workup, were included. Dual KIM-1/ACE2 and LCN2/KIM-1 immunostaining could be performed in 37 and 17 COVID-19 kidney samples, respectively, and in 8 and 5 non-COVID-19 controls. For immunofluorescence, paraffin-embedded sections were stained with the following primary antibodies: rabbit anti-ACE2 (Bio-techne &D systems NBP2-67692, 1:150), goat anti-KIM-1 (Bio-techne &D systems AF1750, 1:200), rabbit anti-LCN2 (Atlas antibodies HPA002695, 1:500). The following secondary antibodies were used: Donkey Anti-Rabbit IgG (H+L) cya3 (Jackson Immunoresearch 711-165-152, 1:250, Donkey Anti-Goat IgG (H+L) Alexa Fluor® 647 (Jackson Immunoresearch 705-605-147, 1:250). The nuclei were stained with Hoechst (33342). Whole images

were taken with an Olympus SLIDEVIEW VS200 slide scanner. Quantification was done using the HALO® image analysis software (Indica Labs, Albuquerque, USA).

RNA expression analyses in tissues from deceased patients with critical COVID-19

For the liver, n = 7 controls (non-COVID autopsy) and n = 11 COVID cases (patients with PCR-positive results in the lung) were selected. For the kidney, n = 10 controls and n = 20 COVID cases were selected. Data from some of the liver specimens have already been reported (1). RNA was extracted using QIAGEN RNeasy® Micro kit according to the manufacturer's instructions, followed by Agilent Bioanalyzer sample quality control, library preparation with Lexogen Corall Total RNA, and rRNA depletion. Single-end RNA sequencing was performed on a 75-bp NextSeq v2.5, yielding more than 30 million reads. Raw reads were trimmed using TrimGalore! V0.4.3 (http://www.bioinformatics.babraham.ac.uk/projects/trim_galore/) and aligned using RNA STAR (2). Mapped reads were counted with HTSeq (3). Normalized read counts were obtained using DESeq2-normalized counts (4). For every graph, the ROUT outlier detection algorithm with Q = 1% was run using GraphPad Prism 9, which removed 0-2 samples per dataset. U Mann-Whitney tests were performed within individual comparisons for each gene and organ, respectively. Only statistically significant differences are shown in the graph.

Single-nuclei RNA sequencing (snRNA-seq) data analysis

To delineate the cellular origin of markers of interest, the study was complemented with data mining from a single-cell atlas of an autopsy cohort comprising 20 male and 12 female donors of various ages (ranging from 30 to 89 years), as previously published (5). A biobank was created with a subset of 17 donors. We collected tissue from the lungs, kidneys, hearts, and livers of most donors, preserving specimens for single-cell and spatial analysis as previously reported (5). Data were obtained from the Single Cell Portal (SCP) (5, 6). Dot plots for kidney samples were generated in Python v3.9.6using

scanpy v1.9.3 [Ref https://genomebiology.biomedcentral.com/articles/10.1186/s13059-017-1382-0]. Dot plots for lung samples were generated in R version 4.2.1 using Seurat version 4.3.0 (7).

Patient recruitment in trials

Training cohort: To test these hypotheses, we performed a multiplexed immunoassay-based study on 196 patients enrolled in two multicenter, open-label, randomized, Phase 2/3 clinical trials nested within the CORIMUNO-19 cohort (Cohort of Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients), NCT04324047. These two trials were conducted in March and April 2020. First, we used data from the CORIMUNO-SARI multicenter, adaptive, open-label study, which enrolled patients with COVID-19 from six French hospitals in randomized controlled trials of different therapeutic regimens (the CORIMUNO-19 cohort). Patients with moderate-to-severe pneumonia were enrolled in the CORIMUNO-SARI-1 trial (8). These analyzed patients were 18 years or older, hospitalized with COVID-19 in 6 French centers, requiring at least 3L/min of oxygen either without ventilation assistance and a WHO Clinical Progression Scale [CPS] score of 5 or with high-flow or with mechanical ventilation assistance (CPS $\geq$ 6) (9). This completed trial is closed to new participants and is registered on ClinicalTrials.gov under NCT04324073.

Measurements of the 42 biological parameters were available in 91 subjects. Their clinical characteristics are summarized in Tables 1 and 3.

Validation cohort: Next, we replicated these measurements for external validation using an independent study population of 105 subjects enrolled in the CORIMUNO-TOCI trial, a multicenter randomized clinical trial involving 9 hospitals, with the same inclusion criteria as previously described (10, 11). This completed trial is now closed to new participants and is registered with ClinicalTrials.gov under the identifier NCT04331808. The clinical characteristics of patients are summarized in Tables 2 and 3.

Bead-based multianalyte Luminex multiplex assay

The serum concentrations of inflammatory mediators (the interleukin-6 system (soluble Interleukin 6 RA (sIL6RA), soluble gp130), the interleukin-1 system (interleukin 1 alpha (IL1α), interleukin 1 beta (IL1β)), interleukin 17A (IL17A), interferon-gamma (IFNγ), C-X-C motif chemokine ligand 10 (CXCL10)/Interferon gamma-induced protein 10 (IP-10), granzyme A and granzyme B), were complemented by molecules involved in endothelial maintenance (Vascular Endothelial Growth Factor A (VEGFA), soluble VEGF Receptor 1 (sVEGFR1), Platelet-derived Growth Factor AA (PDGF-AA), PDGF-BB, soluble endoglin (sEng), Placental Growth Factor (PlGF), Basic Fibroblast Growth Factor (bFGF)), and of vascular injury (soluble E-selectin, soluble P-selectin, soluble L-selectin, soluble urokinase plasminogen activator (sUPAR), soluble InterCellular Adhesion Molecule 1 (sICAM-1), soluble Vascular Cell Adhesion Molecule 1 (sVCAM-1), soluble von Willebrand Factor (vWF), Clusterin). We combined the above-cited analytes with markers of kidney dysfunction (estimated glomerular filtration rate (eGFR) and injury: serum concentrations of Cystatin C, Retinol Binding protein 4 (RBP4), Lipocalin 2 (LCN2) (also named as neutrophil gelatinase-associated lipocalin (NGAL)), Osteopontin, and Trefoil Factor 3 (TFF3). These molecules were measured using Biotechne Luminex High-Performance assay kits according to manufacturer recommendations. Serum samples were thawed and centrifuged at 16,000 g for 4 min immediately before use. Reads and calculations of results were done on a Bio-Rad Bio-Plex station. Three persons carried out all these measurements, centralized at the Paris Cardiovascular Center (PARCC), Inserm, Paris.

Microfluidic cartridge-based immunoassay platform

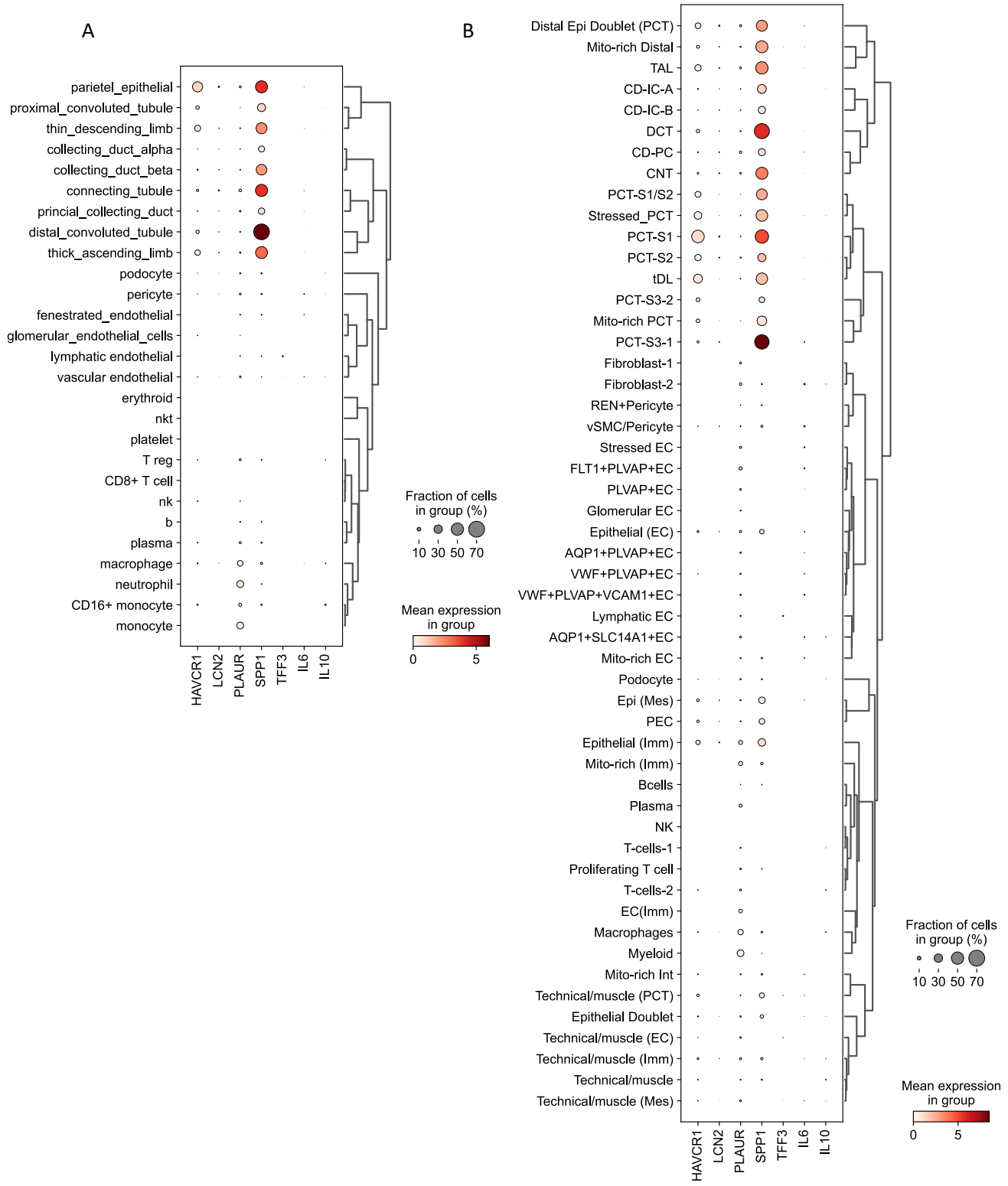
We assessed serum concentration of IL-6 (using 2nd generation kits), IL-8, IL-10, CCL2/monocyte chemoattractant protein-1 (MCP-1), interleukin 1 RA (IL1RA), tumor necrosis factor-alpha (TNFα), and kidney injury molecule-1 (KIM-1)/HAVCR, in a centralized manner using an Ella® platform

(ProteinSimple & Biotechne) which is routinely and widely used for the quantification of soluble biomarkers at the Immunology and Histocompatibility Laboratory, Saint-Louis hospital, AP-HP, Paris.

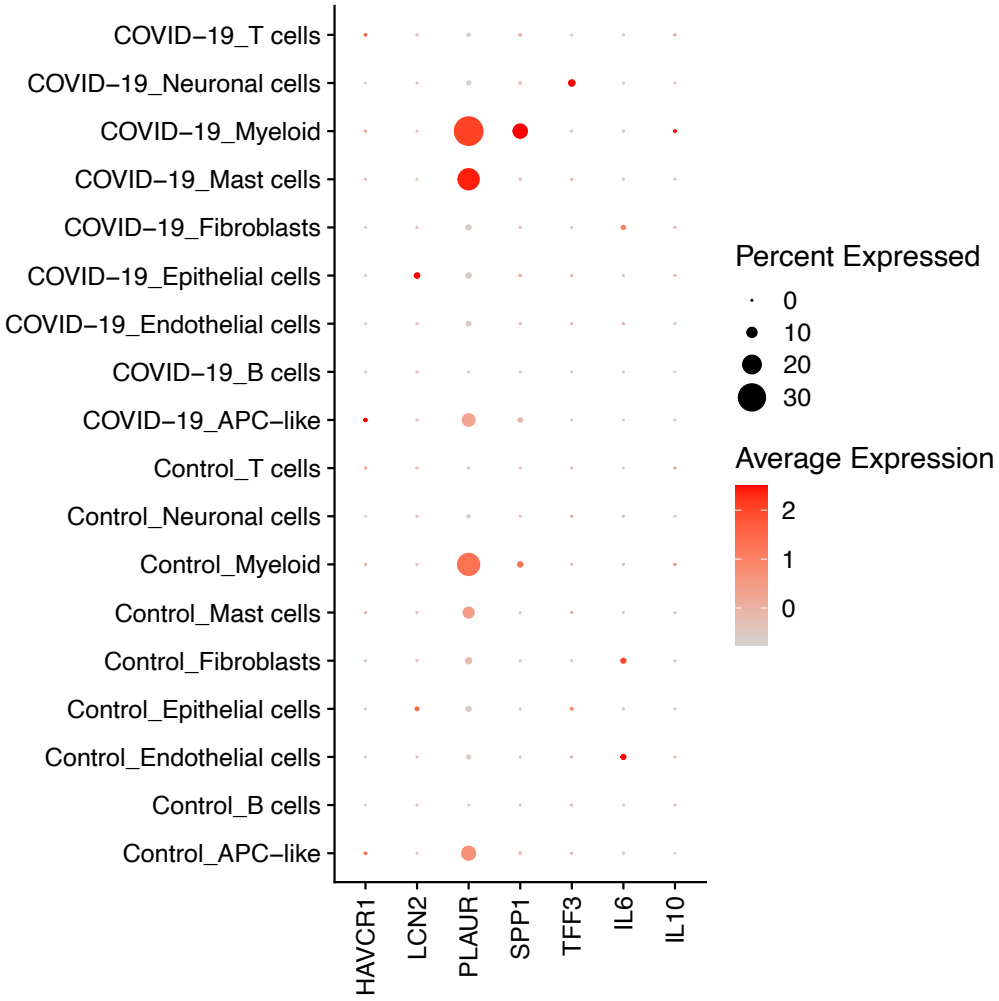
Supplemental references:

1. Wanner N, Andrieux G, Badia IMP, Edler C, Pfefferle S, Lindenmeyer MT, et al. Molecular consequences of SARS-CoV-2 liver tropism. *Nat Metab.* 2022;4(3):310–9.
2. Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, et al. STAR: ultrafast universal RNA-seq aligner. *Bioinformatics.* 2013;29(1):15–21.
3. Anders S, Pyl PT, and Huber W. HTSeq--a Python framework to work with high-throughput sequencing data. *Bioinformatics.* 2015;31(2):166–9.
4. Love MI, Huber W, and Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome biology.* 2014;15(12):550.
5. Delorey TM, Ziegler CGK, Heimberg G, Normand R, Yang Y, Segerstolpe A, et al. COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. *Nature.* 2021;595(7865):107–13.
6. Melms JC, Biermann J, Huang H, Wang Y, Nair A, Tagore S, et al. A molecular single-cell lung atlas of lethal COVID-19. *Nature.* 2021;595(7865):114–9.
7. Hao Y, Hao S, Andersen-Nissen E, Mauck WM, 3rd, Zheng S, Butler A, et al. Integrated analysis of multimodal single-cell data. *Cell.* 2021;184(13):3573–87 e29.
8. group C-C. Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial. *Lancet Rheumatol.* 2022;4(1):e24–e32.
9. Characterisation WHOWGotC, and Management of C-i. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis.* 2020;20(8):e192–e7.
10. Mariette X, Hermine O, Tharaux PL, Resche-Rigon M, Steg PG, Porcher R, et al. Effectiveness of Tocilizumab in Patients Hospitalized With COVID-19: A Follow-up of the CORIMUNO-TOCI-1 Randomized Clinical Trial. *JAMA internal medicine.* 2021;181(9):1241–3.

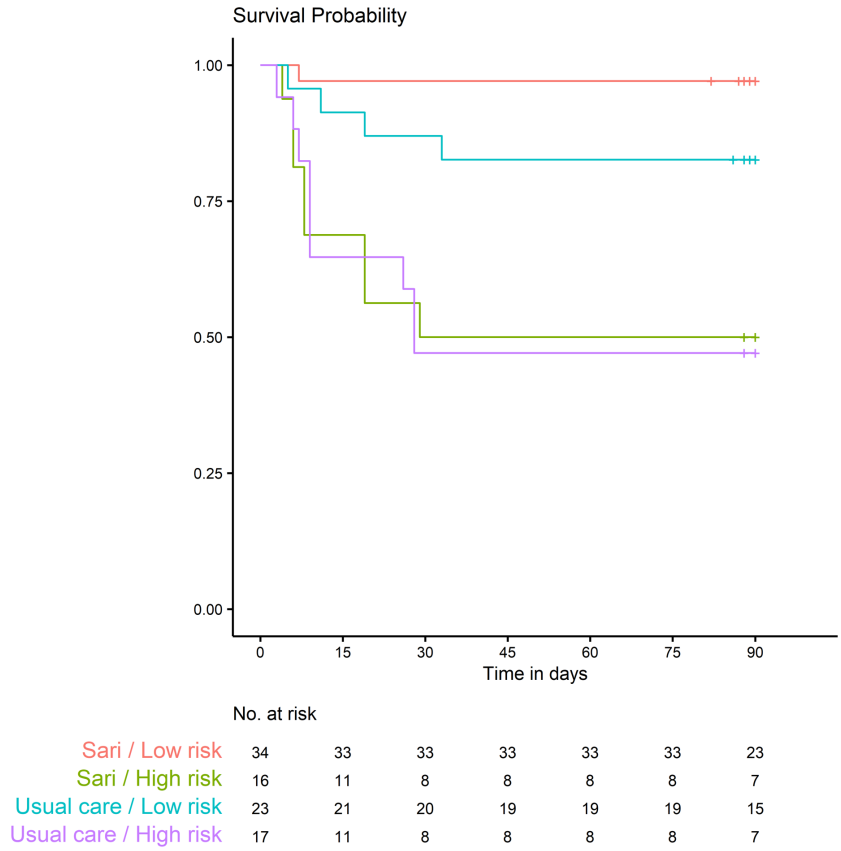
11. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA internal medicine.* 2021;181(1):32–40.



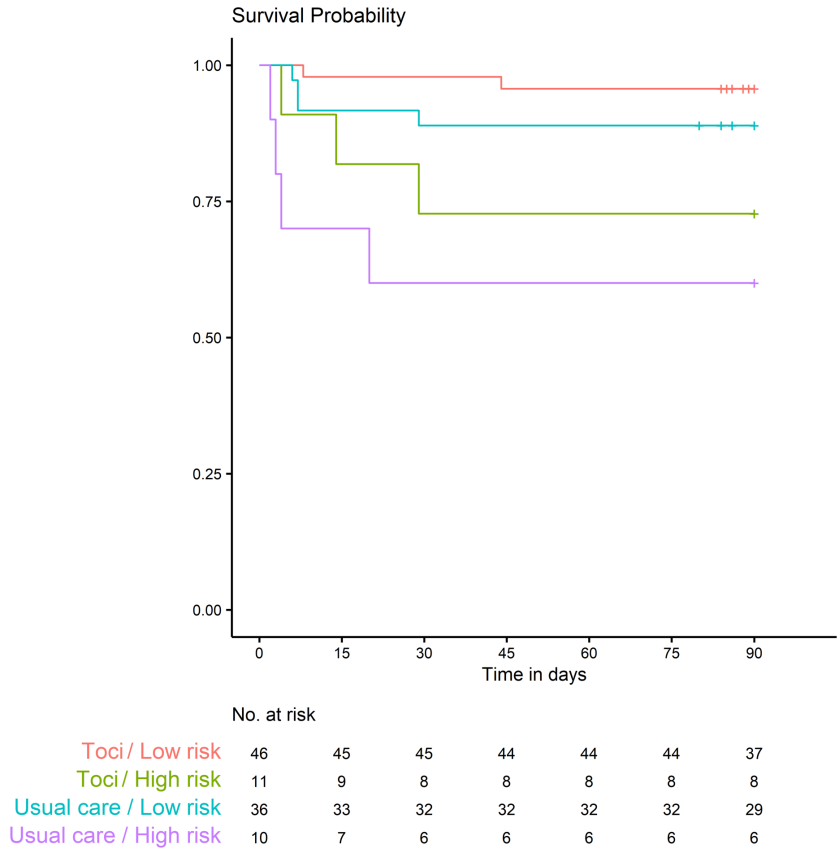
Supplemental Figure 1: **A**. Relative abundance of HAVCR1, LCN2, PLAUR, SPP1, TFF3, IL6 and IL10 mRNA in kidney cell types. Pooled results from single-cell COVID-19 atlas from 16 post-mortem patients deceased from COVID-19 critical pneumonia. **B**. Relative abundance of HAVCR1, LCN2, PLAUR, SPP1, TFF3, IL6 and IL10 mRNA in detailed subsets of kidney cells. CD: collecting duct; IC: intercalated cells; DCT: distal convoluted tubules; EC: endothelial cells; Mes: mesangial cells; PEC: parietal epithelial cells; PCT: proximal convoluted tubules; PCT-S1: proximal convoluted tubules segment 1; PCT-S2: proximal convoluted tubules segment 2; TAL: thick ascending limb; tDL: thin descending limb; NK: natural killer cells; NKT: natural killer T cells; T reg: regulatory T lymphocytes; T cell: T ymphocytes; B: B lymphocytes; plasma: plasma cells; vSMC: vascular smooth muscle cells.



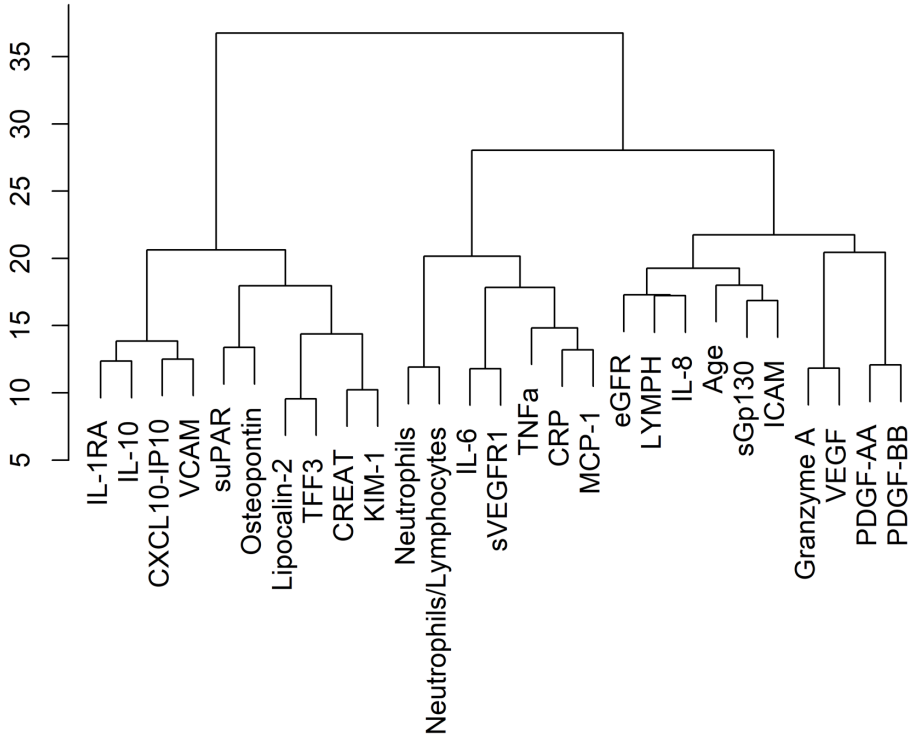
Supplemental Figure 2: Relative abundance of HAVCR1, LCN2, PLAUR, SPP1, TFF3, IL6 and IL10 mRNA in lung cell types. Pooled results from single-cell COVID-19 atlas from16 post-mortem patients deceased from COVID-19 critical pneumonia.



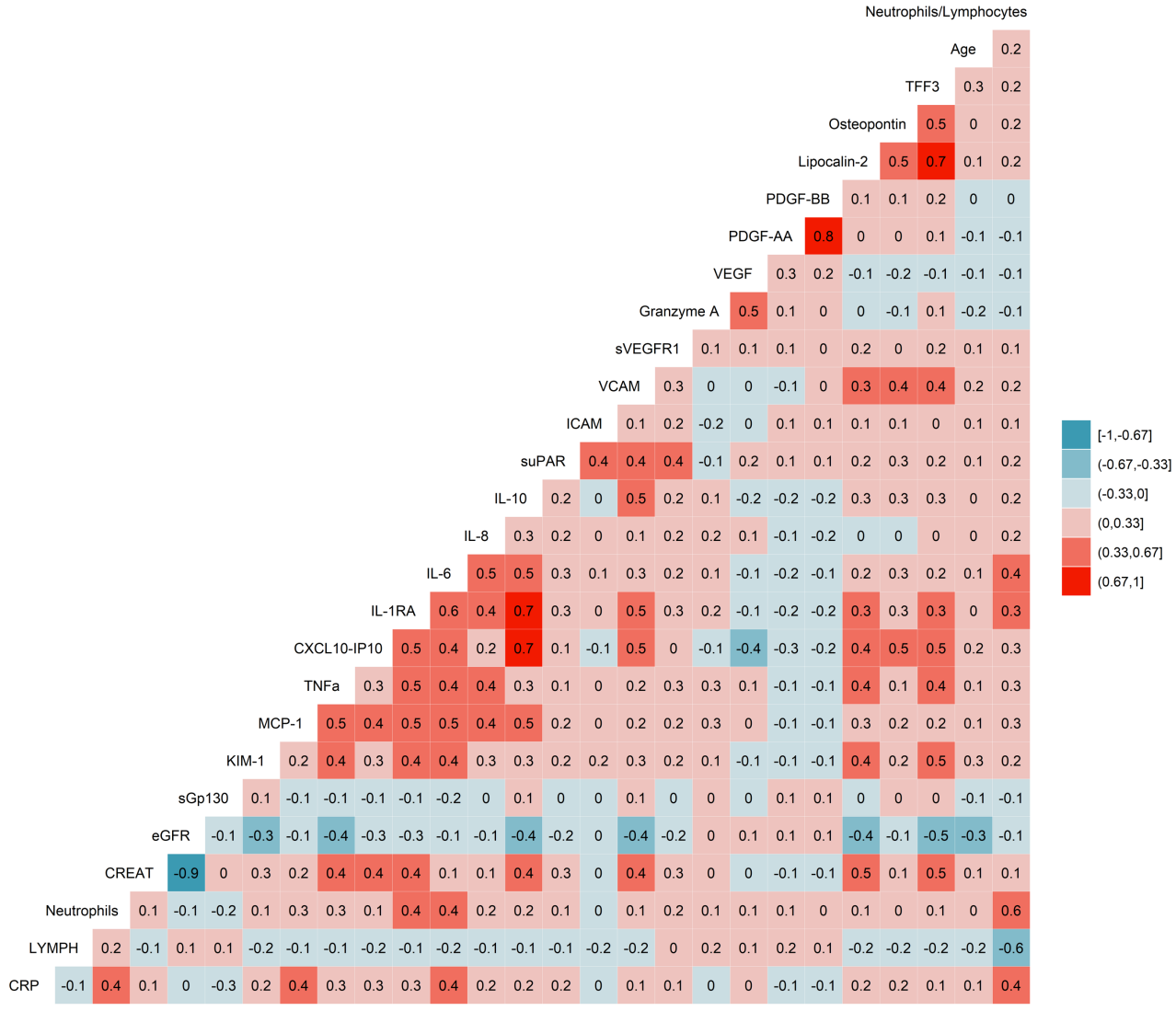
Supplemental Figure 3: Kaplan-Meier survival curves for COVID-19 patients stratified by risk group (high/low) and treatment arm (Sarilumab/Usual Care) in the training cohort.



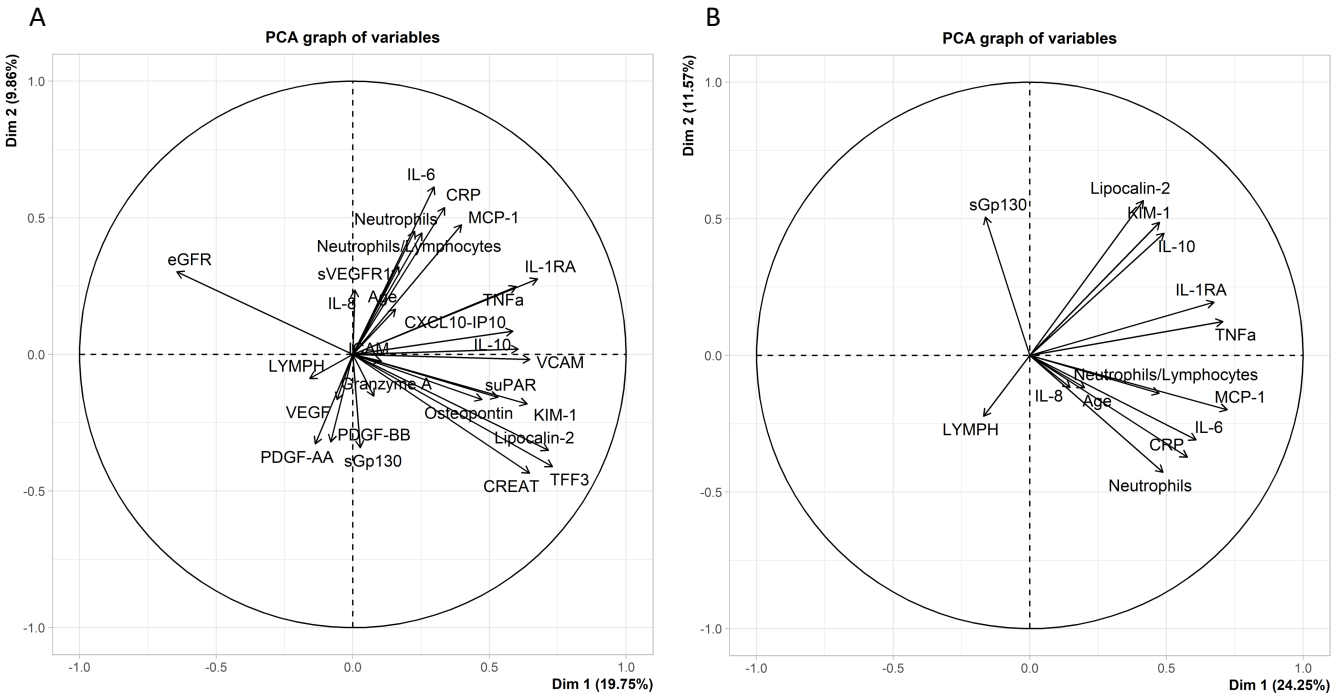
Supplemental Figure 4: Kaplan-Meier survival curves for COVID-19 patients stratified by risk group (high/low) and treatment arm (Tocilizumab/Usual Care) in the validation cohort.



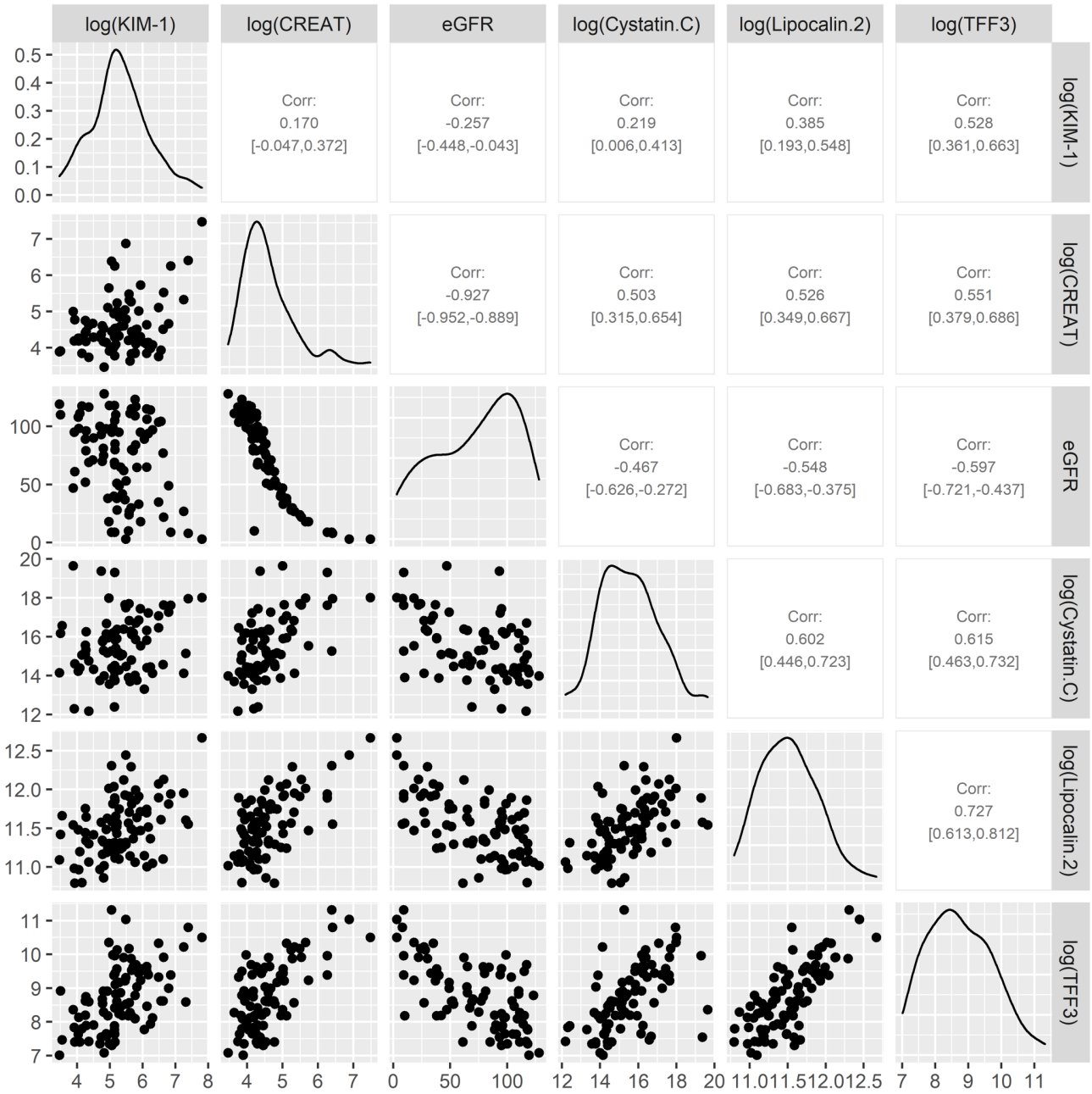
Supplemental Figure 5: Cluster dendrogram of biomarker concentrations in the pooled cohorts. The serum biomarker concentrations were analyzed by unsupervised clustering to determine how similar the values were to each other. The unsupervised clustering resulted in groupings similar to functional groupings for some of the biomarkers. For instance, many of the proteins in the group associated with soluble forms of the interleukin-6 (IL-6) and VEGF receptor 1 (VEGFR1) were clustered in the same group that was distinct from the group containing anti-inflammatory IL-10 and IL-1 receptor antagonist (IL-1Ra). Lipocalin-2 (LCN2), TFF3 and kidney injury molecule-1 (KIM-1) were clustered in the same group. Although C-reactive protein (CRP) levels were classically correlated with IL-6 and MCP-1 levels as well as neutrophils count (NEUTRO), they were less discriminating the group of non-survivors from the group of survivors.



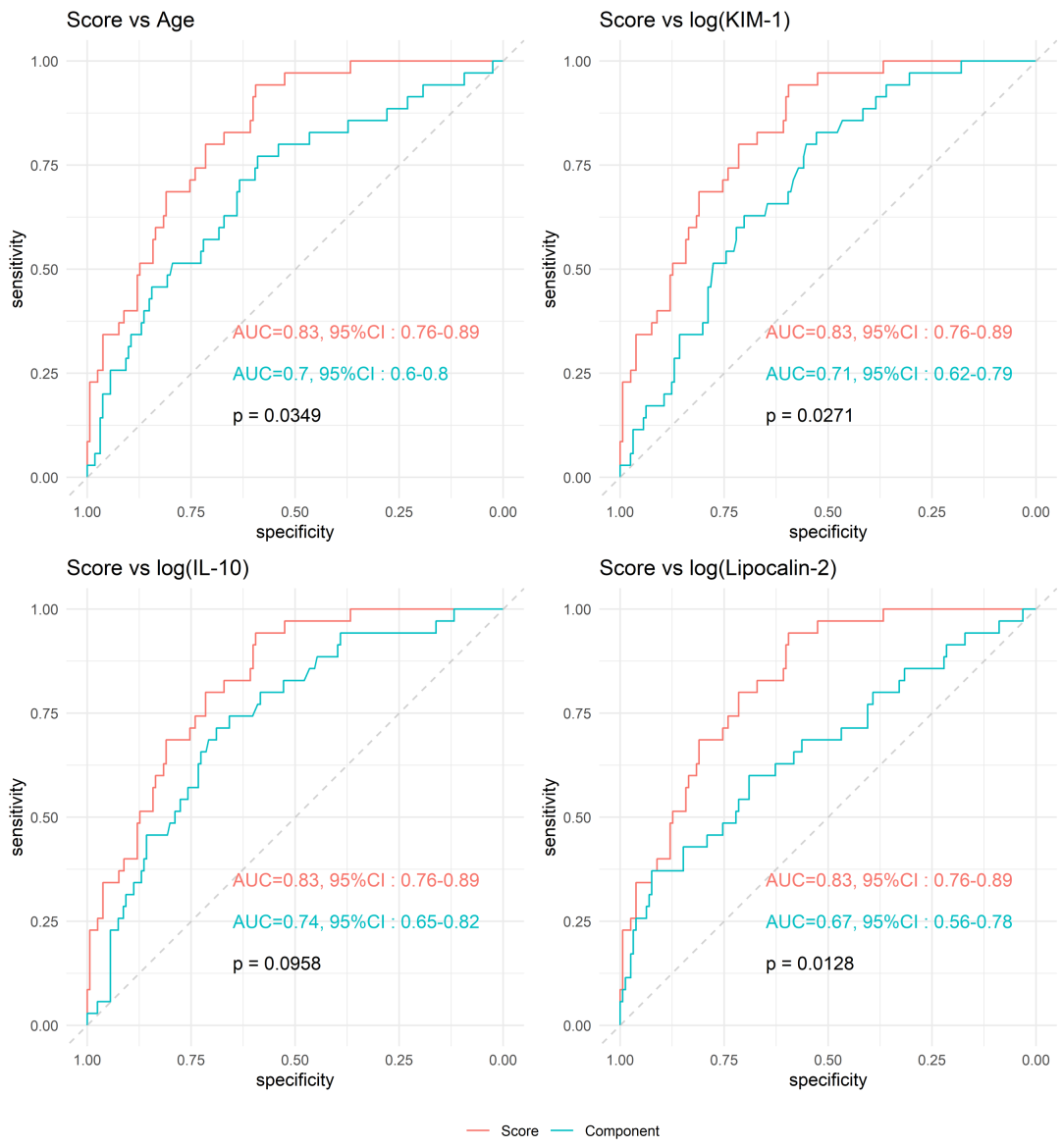
Supplemental Figure 6: Correlation matrix table showing correlation coefficients between variables that are associated with risk of death with 6 classes of color-coding of the values according to the correlation statistics.



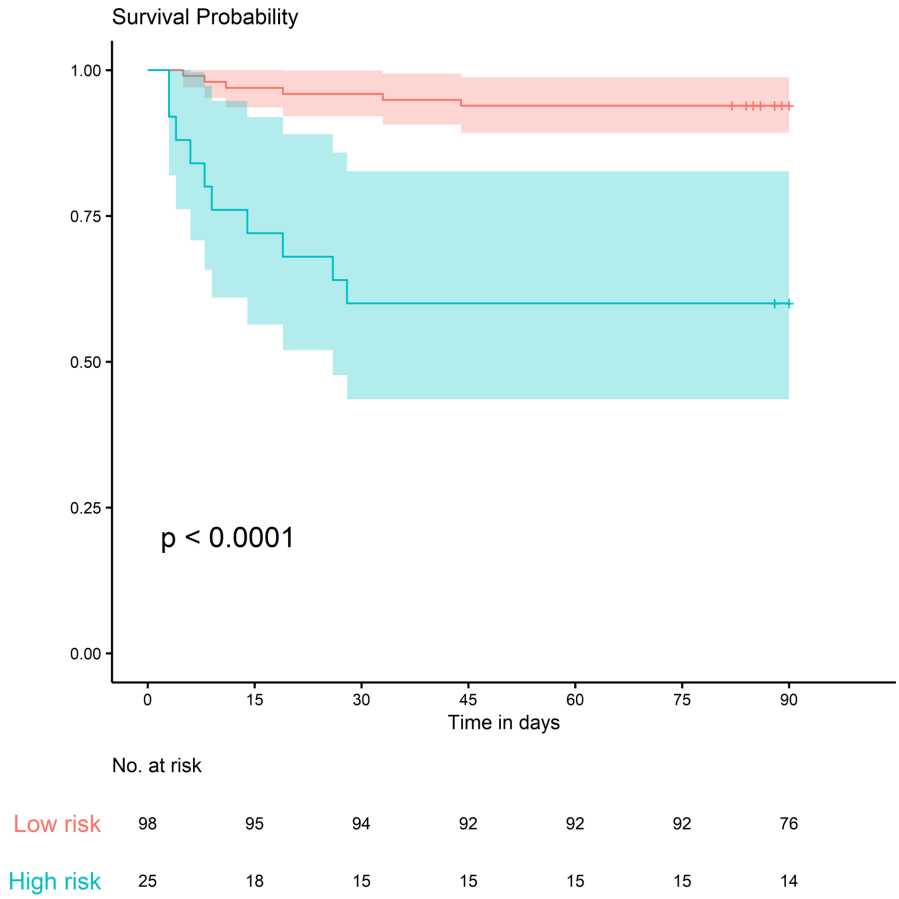
Supplemental Figure 7: **A**. PCA score plot of the first two PCs of data set about profiles of biomarkers independently associated with death in patients with some missing measurements (n=157 subjects, 29 (18.47%) dead by day 90). The figure below displays the relationships between all 26 variables simultaneously (assuming creatinine (CREAT) and eGFR represent the same thing). The first component explains 19.76 % of the variation, and the second component 10.32 %. The further away from the plot origin a variable lies, the stronger the impact that variable has on the model.
B. PCA score plot of the first two PCs of data set about biomarkers independently associated with death in 183 patients (34 (18.58%) dead by day 90).



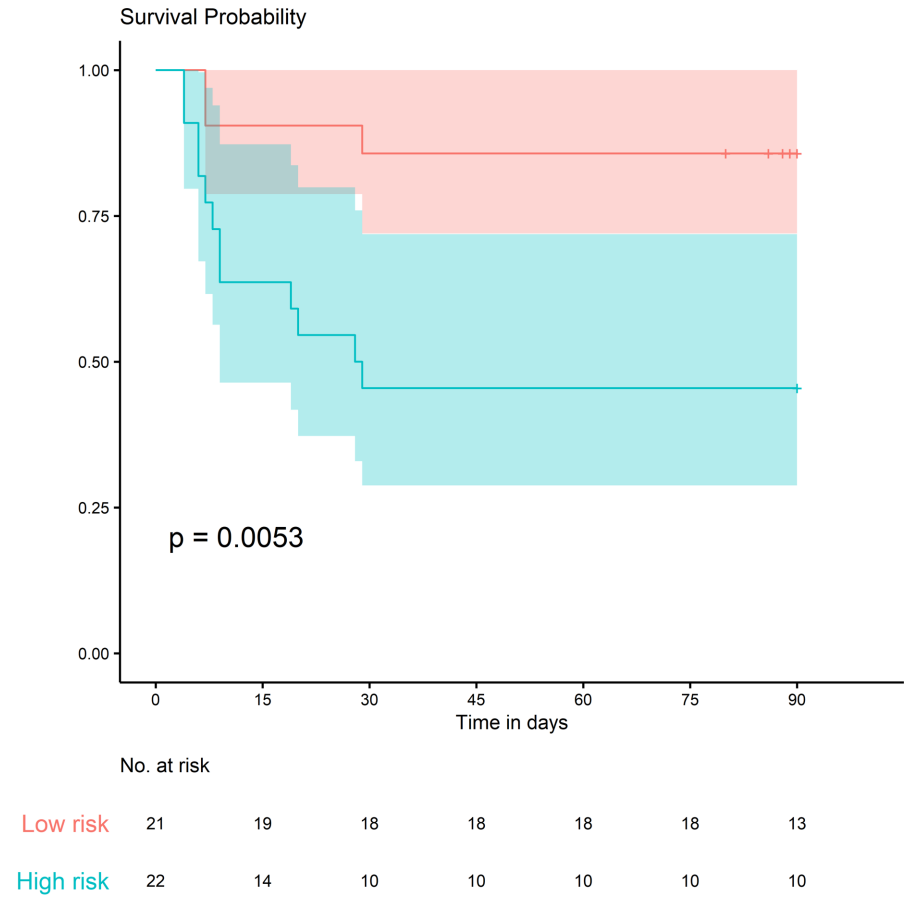
Supplemental Figure 8: distribution curves and correlation coefficient for the variables linked to kidney injury (KIM-1 log, Creatininemia log, eGFR, Cystatin c log, LCN2 log and TFF3 log). Data are presented as Spearman correlation coefficient (r) with 95% CI.



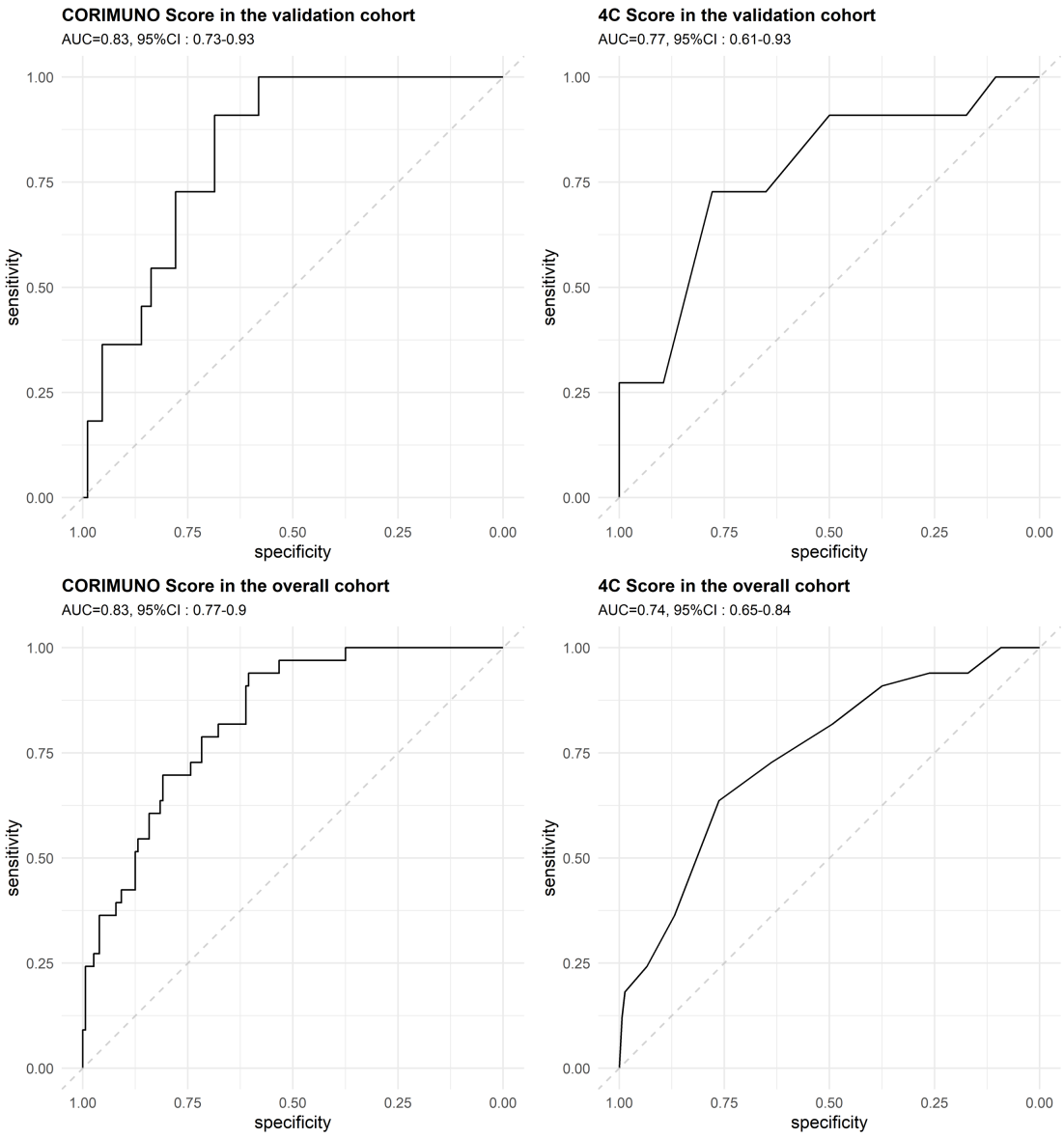
Supplemental Figure 9: Comparison of the respective ROC curves and AUC for each variable component of the global CORIMUNO SCORE (age, KIM-1, IL-10, LCN2)(cyan curve), along with the overall score itself (magenta curve).



Supplemental Figure 10: Kaplan-Meier survival curves with 95% CIs for high- and low-risk groups in the group of patients with eGFR ≥ 60 mL/min/1.73 m2 at inclusion.



Supplemental Figure 11: Kaplan-Meier survival curves with 95% CIs for high- and low-risk groups in the group of patients with eGFR < 60 mL/min/1.73 m2 at inclusion.



Supplemental Figure 12: respective ROC curves and AUC for the CORIMUNO-SCORE and the ISARI-4C score in the independent validation cohort (upper panels) and in the overall cohort (lower panels).

Supplemental Table 1: Serum concentration of immune mediators, cytokines, and markers of kidney and endothelial injury in the CORIMUNO cohort. Data are expressed as median and interquartile range.

Parameters	Values	N	Statistics
		196	
CRP		194	155 [99.2;232.2]
D-dimers		128	1185 [777.5;2007]
Lymphocytes		188	0.9 [0.6;1.2]
Neutrophils		190	6 [4.5;7.9]
Neutrophils/Lymphocytess		187	6.9 [4.5;10.2]
CREAT		167	74 [56.5;102.5]
eGFR		169	87 [57;104.9]
KIM-1		196	166 [99.8;281.5]
Cystatine-c		176	4116800 [1746175;11857500]
RBP4		193	64025000 [22839000;179070000]
Lipocalin-2		193	93864.1 [73069.2;121517.1]
Osteopontin		190	82092.3 [43875.2;190789.9]
TFF3		193	5117.9 [2539.8;11585.2]
IL-6		196	89 [36.5;170]
IL-6R		196	36894.5 [29284.8;47013.5]
sGp130		196	320.6 [263.4;364.9]
Granzyme B		196	35.5 [21;54]
IFNg		196	6.1 [2.3;18.7]
MCP-1		196	973.5 [561.2;1516.5]
TNFα		196	22.6 [17.4;29.4]
CXCL10-IP10		193	580.7 [237.3;1313.4]
IL-1a		196	0 [0;0]
IL-1b		196	0.4 [0;0.8]
IL-1RA		195	2548 [1301.5;4705.5]
IL-8		196	50.4 [30.5;80.4]
IL-10		196	16.2 [10.3;30.5]
IL-17A	< 2.1	179	91.33 %
	≥ 2.1	17	8.67 %
suPAR		192	4263.8 [1603.6;6241.1]
Granzyme A		192	64.9 [36.5;91.7]
Endoglin		192	1927.1 [1347.3;2873.2]

Parameters	Values	N	Statistics
PLGF		192	34.2 [21.9;74.7]
bFGF		192	21.6 [11.6;37.9]
ICAM-1		192	526674.6 [379449.7;730821.4]
VCAM-1		192	4118150 [2277950;5783775]
L-Selectin		190	550725.5 [411730.2;739683.8]
E-Selectin		192	30883.6 [22805.5;40457.2]
P-Selectin		192	52680.5 [36341.2;84014.2]
VEGF		192	198.3 [111.3;360.6]
sVEGFR1		192	270.8 [204.3;379]
vWF		191	55697.1 [25904.3;92225.8]
PDGF-AA		191	4635 [2867.7;7647.5]
PDGF-BB		191	7928.9 [4179.4;15180.8]
Clusterin		177	640740000 [362910000;1021900000]

Supplemental Table 2: Univariate comparison of values measured on day 1 in groups of patients with or without worsening of the WHO clinical progression score by day 14. Data are expressed as median and interquartile range.

Parameters	N	Statistics	N	Statistics	p-value
	140	**No WHO score worsening**	47	**WHO score worsening**	
CRP	138	142 [91.8;221.8]	47	174 [128.5;245]	0.048
D-dimers	89	1190 [780;1880]	33	1450 [730;2770]	0.35
Lymphocytes	134	0.9 [0.6;1.2]	45	0.8 [0.6;1]	0.014
Neutrophils	136	5.7 [4.4;7.8]	45	6.6 [5.3;9.9]	0.062
Neutrophils/Lymphocytes	133	6.2 [4.4;9.4]	45	8.3 [5.9;17.2]	0.0007
CREAT	117	70 [54;94]	43	93 [68.5;141]	0.001
eGFR	119	92 [68.5;105.5]	43	74 [41;92.5]	0.004
KIM-1	140	145.5 [96.6;244.2]	47	226 [120.5;336.5]	0.022
Cystatine-c	124	3609000 [1711000;10300000]	43	10260000 [2662000;16050000]	0.021
RBP4	138	64350000 [23870000;173200000]	46	62570000 [22710000;184500000]	0.60
Lipocalin-2	138	92880 [70700;118900]	46	96470 [80010;145500]	0.15
Osteopontin	137	79260 [43800;162900]	44	119200 [55060;226700]	0.10
TFF3	138	4688 [2392;10770]	46	6098 [3374;12740]	0.040
IL-6	140	73.9 [25.8;142.5]	47	142 [86.9;272.5]	<0.0001
IL-6R	140	37550 [29450;47700]	47	36880 [24630;44510]	0.23
sGp130	140	324.2 [268.2;369.1]	47	304.3 [256.3;347.6]	0.063
Granzyme B	140	34.1 [20.9;50.4]	47	37.3 [22.1;57.8]	0.62
IFNg	140	6.1 [2.3;19.3]	47	6.7 [2.3;17.6]	0.94
MCP-1	140	854.5 [531.8;1370]	47	1238 [932;1807]	0.001
TNFα	140	22.7 [17.4;29]	47	23.3 [17.4;32.2]	0.71
CXCL10-IP10	138	507.6 [172.6;1022]	46	991.4 [484.1;2273]	0.0006
IL-1a	140	0 [0;0]	47	0 [0;0]	0.32
IL-1b	140	0.4 [0;0.7]	47	0.5 [0;0.9]	0.058

Parameters		N	Statistics	N	Statistics	p-value
IL-1RA		139	2225 [1204;4044]	47	3995 [2300;6904]	<0.0001
IL-8		140	47 [26.6;73.6]	47	58.3 [38.5;107]	0.020
IL-10		140	13.2 [9.4;21.6]	47	29.8 [18.4;41.8]	<0.0001
IL-17A	< 2.1	126	90 %	45	95.74 %	0.37
	≥ 2.1	14	10 %	2	4.26 %	
suPAR		138	4144 [1603;5997]	45	5321 [2313;7159]	0.077
Granzyme A		138	67.5 [39.4;93.2]	45	57.1 [8.4;81.2]	0.033
Endoglin		138	1986 [1350;2846]	45	2246 [1341;3093]	0.46
PLGF		138	34.3 [21.6;72.9]	45	34.8 [25.6;81]	0.35
bFGF		138	22 [12.2;39.5]	45	24.8 [9.8;39.9]	0.97
ICAM-1		138	525000 [409600;706500]	45	587900 [359100;858100]	0.61
VCAM-1		138	3704000 [2084000;5435000]	45	5432000 [4034000;7567000]	0.001
L-Selectin		138	573200 [416800;802400]	43	521500 [364200;657700]	0.055
E-Selectin		138	30780 [22620;41180]	45	34340 [24050;44030]	0.33
P-Selectin		138	53180 [37430;87260]	45	57480 [36260;75390]	0.43
VEGF		138	220.2 [123.4;381.8]	45	170.9 [91.1;300.1]	0.11
sVEGFR1		138	267.2 [204.2;351.5]	45	310.9 [210.1;438.2]	0.17
vWF		138	52220 [26360;86120]	44	68540 [40380;137300]	0.055
PDGF-AA		138	5233 [3231;8764]	44	3803 [2313;5041]	0.015
PDGF-BB		138	9257 [4872;17710]	44	7218 [2892;10660]	0.026
Clusterin		125	532800000 [356900000;959600000]	43	924200000 [472300000;1.129e+09]	0.023

Supplemental Table 3: Univariate comparison of values measured on day 1 in groups of patients who subsequently survived or died within the next 90 days. Data are expressed as median and interquartile range.

Parameters		N	Statistics	N	Statistics	p-value
		161	**Death at D90: No**	35	**Death at D90: Yes**	
CRP		159	145 [93;220.5]	35	183 [135;255.5]	0.037
D-dimers		105	1044 [770;1830]	23	1830 [1086;2880]	0.025
Lymphocytes		154	0.9 [0.6;1.2]	34	0.7 [0.6;0.9]	0.013
Neutrophils		156	5.8 [4.3;7.8]	34	6.7 [5.5;9.2]	0.096
Neutrophils/Lymphocytes		153	6.4 [4.4;9.4]	34	8.8 [5.6;16.6]	0.003
CREAT		136	71 [55;94]	31	100 [75;175]	0.0009
eGFR		138	91.4 [69.2;105.8]	31	62 [31.5;86]	0.0004
KIM-1		161	140 [91.8;251]	35	269 [170;356]	0.0001
Cystatine-c		143	3756000 [1744000;10650000]	33	6765000 [1943000;20180000]	0.17
RBP4		158	67730000 [23550000;187300000]	35	55380000 [21390000;161600000]	0.80
Lipocalin-2		158	91140 [70700;114400]	35	113400 [84690;161400]	0.002
Osteopontin		157	79260 [38690;166800]	33	139100 [53160;264200]	0.076
TFF3		158	4522 [2369;9503]	35	10220 [4452;13750]	0.002
IL-6		161	78.3 [28.7;147]	35	142 [82;393.5]	0.0002
IL-6R		161	36900 [29600;47780]	35	36880 [24630;43220]	0.19
sGp130		161	324.1 [269.3;367.5]	35	302.9 [231.7;350.3]	0.051
Granzyme B		161	35.6 [21.5;54.5]	35	35.2 [20.9;47.4]	0.58
IFNg		161	6.1 [2.4;18.5]	35	5.1 [2.2;20.6]	0.80
MCP-1		161	896 [536;1415]	35	1217 [908.5;2336]	0.005
TNFα		161	22.2 [17.3;28.1]	35	26.3 [19.2;36.9]	0.10
CXCL10-IP10		158	521.2 [192.3;1120]	35	1005 [456;2550]	0.005
IL-1a		161	0 [0;0]	35	0 [0;0]	0.71
IL-1b		161	0.4 [0;0.7]	35	0.5 [0;0.9]	0.22
IL-1RA		160	2410 [1212;4270]	35	3995 [2354;6904]	0.0006
IL-8		161	45.9 [28.4;76.9]	35	58.6 [43.1;99.7]	0.031
IL-10		161	14.2 [9.6;24.5]	35	29.8 [18.2;41.8]	<0.0001
IL-17A	< 2.1	147	91.3 %	32	91.43 %	1

Parameters		N	Statistics	N	Statistics	p-value
	≥ 2.1	14	8.7 %	3	8.57 %	
suPAR		157	4038 [1545;5941]	35	5436 [2883;7198]	0.039
Granzyme A		157	67.5 [39.5;99.1]	35	37.5 [11.3;78.3]	0.002
Endoglin		157	1910 [1350;2873]	35	2138 [1332;2793]	0.88
PLGF		157	33.8 [21.5;73.2]	35	38.4 [25.6;77.8]	0.27
bFGF		157	21.6 [11.7;37.5]	35	20.3 [11;37.5]	0.87
ICAM-1		157	516200 [374600;704500]	35	664000 [452700;960700]	0.077
VCAM-1		157	3922000 [2200000;5640000]	35	4925000 [3685000;7492000]	0.027
L-Selectin		156	573200 [423800;769200]	34	456000 [307900;613600]	0.005
E-Selectin		157	30310 [22020;39900]	35	34340 [25210;46950]	0.17
P-Selectin		157	52450 [36260;85550]	35	53520 [38260;79920]	0.83
VEGF		157	219.1 [122.8;381.2]	35	123 [75.1;247.6]	0.005
sVEGFR1		157	265.6 [203.7;347.9]	35	311.8 [224.4;449.7]	0.060
vWF		157	53840 [25740;90150]	34	68500 [26090;119600]	0.22
PDGF-AA		157	5045 [3068;8437]	34	3803 [2255;5256]	0.049
PDGF-BB		157	8123 [4515;17010]	34	7457 [3341;10550]	0.11
Clusterin		144	595800000 [363800000;994500000]	33	737600000 [360200000;1.095e+09]	0.52

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Cohort Multiple randomized controlled trials, open-label of immune modulatory drugs and other treatments in COVID-19 patients

Statistical analysis plan

Specific version of the General Statistical Analysis Plan for MONICOR

Biomonitoring and complex analyses in support of the open-label randomized controlled trial cohort of immunomodulatory products and other treatments for patients with COVID-19.

1. Administrative information

A. General

ACRONYM :	CORIMUNO-19
REGISTRATION NUMBER	Sponsor code: APHP200375 EudraCT: ClinicalTrials.gov: NCT04324047
SAP VERSION & DATE	1.0, 09/05/2020
PROTOCOL VERSION:	Version 6.0 of 04/05/2020

B. Roles and responsibilities

TRIAL CHIEF INVESTIGATOR	Dr THARAUX Pierre-Louis
METHODOLOGIST	Pr RESCHE-RIGON Matthieu
TRIAL STATISTICIAN	WALTER-PETRICH Anouk
SAP AUTHOR	
DATA-MANAGER	
OTHER CONTRIBUTORS	

C. SAP revision history

Version	Date	Author	Description of changes
1.0	09/05/2020		Creation of SAP

2. Introduction

A. Rationale of the study/Hypothesis of the research

A significant challenge to meta-analyzing the various and numerous clinical trials in the field of COVID-19 is to confidently delineate the population enrolled in clinical trials, as they differ markedly in terms of mortality, despite efforts to standardize the assessment of clinical progression scores by the World Health Organisation and empiric comparisons of routine inflammatory markers and comorbidities. Thus, given the uncertainty about stratifying patients with COVID-19, considerable interest exists in risk stratification scores to support frontline clinical decision-making. Available risk stratification tools have a high risk of bias, a small sample size resulting in uncertainty, poor reporting, and a lack of formal validation.

To develop a tool to address these challenges, we will conduct multiparameter molecular analyses in a well-defined patient cohort and replicate them in an independent cohort. Such molecular analyses encompassed markers of acute kidney injury (AKI), systemic inflammation, and endothelial alterations.

We will evaluate whether an early measurement of a panel of inflammation, endothelial, and AKI serum markers is associated with the risk of critical COVID-19 pneumonia and death.

The exploratory set of markers aims at evaluating three groups of biological variables that may reflect the mechanisms or consequences of organ injury and/or represent therapeutic targets:

1- **Inflammatory mediators**: the interleukin-6 system (serum concentration of IL-6, soluble Interleukin 6 RA (sIL6RA), soluble gp130), the interleukin-1 system (interleukin 1 alpha (IL1a), interleukin 1 beta (IL1B)), interleukin 17A (IL17A), interferon-gamma (IFNg), C-X-C motif chemokine ligand 10 (CXCL10)/Interferon gamma-induced protein 10 (IP-10), granzyme A and granzyme B, IL-8, IL-10, CCL2/ monocyte chemoattractant protein-1 (MCP-1), interleukin 1 RA (IL1RA), tumor necrosis factor-alpha (TNFα), myeloperoxydase (MPO).

2- **Markers of endothelial injury or of an inflammatory vascular phenotype**:

Proteins involved in endothelial maintenance: Vascular Endothelial Growth Factor A (VEGFA), soluble VEGF Receptor 1 (sVEGFR1), Platelet-derived Growth Factor AA (PDGF-AA), PDGF-BB, soluble endoglin (sEng), Placental Growth Factor (PlGF), Basic Fibroblast Growth Factor (bFGF),

and of vascular injury: soluble E-selectin, soluble P-selectin, soluble L-selectin, soluble urokinase plasminogen activator (sUPAR), soluble InterCellular Adhesion Molecule 1 (sICAM-1), soluble Vascular Cell Adhesion Molecule 1 (sVCAM-1), soluble von Willebrand Factor (vWF), endothelin-1 (ET-1), Clusterin.

3- We will combine the above-cited analytes with **markers of kidney dysfunction (estimated glomerular filtration rate (eGFR) and injury**: serum concentrations of Cystatin C, Retinol Binding protein 4 (RBP4), Lipocalin 2 (LCN2)/neutrophil

gelatinase-associated lipocalin (NGAL), Osteopontin, and Trefoil Factor 3 (TFF3) and kidney injury molecule-1 (KIM-1)/HAVCR.

We hypothesize that severe and critical forms of COVID-19 pneumonia may be associated with uncontrolled activation of the immune system, microvascular injury and AKI, the latter condition being a known risk factor for high morbidity and mortality in a wide array of conditions, including sepsis.

B. Objectives

I. Primary Objective

To identify and validate a composite score based on biomarkers measured at baseline that predicts 90-day mortality, allowing classification of patients into distinct risk categories (e.g., high-risk vs. low-risk of death).

II. Secondary Objectives

To identify biomarkers associated with an increase of more than one point in the WHO Clinical Progression Scale [CPS] within 14 days after randomization.

III. Exploratory Objectives

- To identify specific markers associated with 90-day mortality.
- To assess the predictive value and discriminative ability of the composite score for survival within each treatment arm (Tocilizumab, Sarilumab, or Usual care)
- To identify biological clusters of patients at Day 1

3. Study methods

A. Study design & framework

This is an exploratory, retrospective analysis combining individual participant data from two randomized controlled trials evaluating Tocilizumab and Sarilumab in patients with COVID-19 (CORIMUNO-TOCI and CORIMUNO-SARI) and biomarker measurements.

B. Randomization

Randomization procedures were conducted within each parent trial according to their original protocols. In this analysis, treatment allocation and trial identifiers will be retained for subgroup analyses. No new randomization or reassignment will occur, and the original allocation structure will be respected for all treatment-related analyses.

C. Sample size justification

Given the exploratory nature of the MONICOR study, it is not possible to infer a minimum number of subjects required. Nonetheless, 1/ several biomarkers that we will test have shown significant association with critical forms of CORIMUNO-19 (sUPAR, IL-6, vWF, sICAM-1) in smaller studies. 2/ The CORIMUNO-TOCI trial suggests that tocilizumab administration to

the studied population may have reduced the risk of non-invasive ventilation, mechanical ventilation, or death by day 14. This may reflect a differential biological profile.

3/ We will use samples collected in the CORIMUNO-SARI trial (NCT04324073) as a training cohort. We will next use an independent external dataset (CORIMUNO-TOCI trial (NCT04331808) to improve the generalisability of our study.

D. Statistical interim analyses and stopping guidance

No interim analyses or stopping rules are planned. Both parent trials have completed data collection and primary analyses. This exploratory work will be performed on finalized, locked datasets, with no sequential testing or alpha adjustment.

E. Timing of final analysis

All outcomes will be analyzed collectively after data harmonization and integration of all biomarker datasets. Assessments will be conducted at predefined time points: Day 1 (baseline), Day 14, and Day 90. All analyses will use the finalized dataset; any subsequent reanalyses will be considered post-hoc and documented separately.

4. Statistical principles

A. Confidence intervals and P-values

Associations with binary outcomes will be quantified using Odds Ratios (ORs), with Wald confidence intervals computed on the natural logarithm of the OR. The area under the ROC curve (AUC) will be estimated, and a confidence interval will be calculated using the DeLong method. Time-to-event outcomes will be evaluated by comparing survival curves, and statistical significance will be assessed using the log-rank test.

A bilateral type I error rate of 5% without multiplicity adjustment will be applied to the analyses.

B. Analysis populations

All analyses will be performed in complete cases: all eligible participants with available biomarker and outcome data.

5. Trial population

A. Eligibility

Inclusion Criteria for the CORIMUNO-19 cohort:

1. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen and/or CT Scan before randomization (Following typical radiological findings (ground glass abnormalities,

and absence of lymphadenopathy, pleural effusion, pulmonary nodules, lung cavitation)

2. Hospitalized patients
3. Illness of any duration and severity (mild, moderate, severe, critical, see annexe 1), with symptoms (fever, cough, respiratory difficulties, shortness of breath), and at least one of the following:
    a. Radiographic infiltrates by imaging (CT scan)
    b. Clinical assessment (evidence of rales/crackles on exam or respiratory rate >25/min) AND SpO2≤94% on room air
    c. SpO2≤97 % with O2 > 5L/min or Respiratory rate>=30/min
    d. Requiring mechanical ventilation
    e. With any comorbidities (TBD such as acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high blood pressure, diabetes, chronic kidney diseases, haematological diseases, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected, etc.)
4. Male or female adult ≥ 18 years of age at time of enrolment
5. Patients must be able and willing to comply with study visits and procedures.
6. Patient agrees to the collection of oropharyngeal and nasal swabs and venous blood per protocol
7. Written informed consent provided by the patient or, alternatively, by the next-of-kin before any protocol-specific procedures.

Exclusion Criteria for the CORIMUNO-19 cohort:

Participation in another clinical trial is not an exclusion criterion, depending on the medication. ***Patients included in the antiviral REACTING trial are not excluded, as well as patients from COVIDICUS trial.***

Severe cardiovascular disease, including acute myocardial infarction, unstable angina pectoris, coronary revascularisation procedure, congestive heart failure of NYHA Class III or IV, stroke, including a transient ischemic attack, oedema of cardiac origin and left ventricular ejection fraction ≤ 50% are not excluded and should be discussed in each therapeutic arm.

- Patients with any condition that the physician judges could be detrimental to the patient's participation in this study, including any clinically important deviations from normal clinical laboratory values or concurrent medical conditions (active infections, such as severe bacterial infections, aspergillosis, or tuberculosis, depending on the tested medication).
- Absence of Health Insurance
- Subject protected by law under guardianship or curatorship

Inclusion Criteria for the CORIMUNO-TOCI trial:

1. Patients included in the CORIMUNO-19 cohort
2. Patients belonging to one of the 2 following groups:

*- Group 1: patients **not requiring ICU** at admission with moderate and severe pneumopathy according to the WHO **Criteria of severity of COVID pneumopathy.***

Moderate cases

Cases meeting all of the following criteria:

- Showing fever and respiratory symptoms with radiological findings of pneumonia.
- Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97%

Severe cases

Cases meeting any of the following criteria:

- Respiratory distress (≧30 breaths/ min);
- Oxygen saturation ≤93% at rest in ambient air, or Oxygen saturation ≤97 % with O2 > 5L/min.
- PaO2/FiO2≦300mmHg

*- Group 2: patients **requiring ICU** based on **Criteria of severity of COVID pneumopathy.***

- Respiratory failure and requiring mechanical ventilation
- No do-not-resuscitate order (DNR order)

Exclusion Criteria for the CORIMUNO-TOCI trial:

- Patients with exclusion criteria to the CORIMUNO-19 cohort.
- Known hypersensitivity to Tocilizumab or to any of their excipients.
- Pregnancy
- Current documented bacterial infection
- Patient with any of the following laboratory results out of the ranges detailed below at screening should be discussed, depending on the medication:
    - Absolute neutrophil count (ANC) ≤ 1.0 x 109/L
    - Haemoglobin level: no limitation
    - Platelets (PLT) < 50 G /L

SGOT or SGPT > 5N

Inclusion Criteria for the CORIMUNO-SARI trial:

1. Patients included in the CORIMUNO-19 cohort

2. Patients belonging to one of the 2 following groups:

*- Group 1: patients **not requiring ICU** at admission with moderate and severe pneumopathy according to the WHO **Criteria of severity of COVID pneumopathy.***

Moderate cases

Cases meeting all of the following criteria:

- Showing fever and respiratory symptoms with radiological findings of pneumonia.
- Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97%

Severe cases

Cases meeting any of the following criteria:

- Respiratory distress (≧30 breaths/ min);
- Oxygen saturation≤93% at rest in ambient air, or Oxygen saturation ≤97 % with O2 > 5L/min.
- PaO2/FiO2≦300mmHg

*- Group 2: patients **requiring ICU** based on **Criteria of severity of COVID pneumopathy.***

- Respiratory failure requiring mechanical ventilation
- No do-not-resuscitate order (DNR order)

Exclusion Criteria for the CORIMUNO-SARI trial:

1. Patients with exclusion criteria from the CORIMUNO-19 cohort.
2. Known hypersensitivity to Sarilumab or to any of their excipients.
3. Pregnancy
4. Current documented bacterial infection
5. Patient with any of the following laboratory results out of the ranges detailed below at screening should be discussed, depending on the medication:
    a. Absolute neutrophil count (ANC) ≤ 1.0 x 109/L
    b. Haemoglobin level: no limitation
    c. Platelets (PLT) < 50 G /L

SGOT or SGPT > 5N

C. Recruitment

Participants for this analysis will be recruited from two completed randomized controlled trials evaluating Tocilizumab and Sarilumab in patients with COVID-19 (TOCI and SARI trials).

Only patients who were randomized in either trial, have a biomarker measurement at Day 1, and have sufficient follow-up to assess the primary endpoint (90-day mortality) will be included.

No new patient recruitment will occur, as this is a retrospective secondary analysis based on existing trial data.

D. Withdrawal/follow-up

Participant withdrawal and follow-up information will be based on data recorded in the two randomized controlled trials.

No additional follow-up will be performed for this secondary analysis.

E. Baseline patient characteristics

Variable	Computation (if done)	Type of variable	Measurement unit
Baseline characteristics			
Age	(Randomization date – Birth date) / 365.25 For birth date, imputation of day by 01	Continuous	Years
Sex	-	Binary (Male/Female)	-
Weight	-	Continuous	Kg
BMI	-	Continuous	Kg/m^2
WHO score	-	Binary (≥ 6/<6)	
RT-PCR-confirmed SARS-CoV-2 infection	-	Binary (Yes/No)	
Temperature	-	Continuous	C
Respiratory rate (bpm)	-	Continuous	Bpm
O2 Flow (L/min)	-	Continuous	L/min
SpO2 (%)	-	Continuous	%
Time from symptoms onset to randomization (days)	(Randomization date – Symptom onset date)	Continuous	Days
Time from hospital admission to randomization (days)	(Randomization date – hospital admission date)	Continuous	Days
Chronic cardiac disease	-	Binary (Yes/No)	-
Diabetes	-	Binary (Yes/No)	-
Chronic kidney disease (stage 1 to 3)	-	Binary (Yes/No)	-
Asthma	-	Binary (Yes/No)	-
Chronic pulmonary disease (not asthma)	-	Binary (Yes/No)	-
Active malignant neoplasm	-	Binary (Yes/No)	-
Smoking	-	Binary (Yes/No)	-
Measurements			
Platelets	-	Continuous	$10^9/L$
CRP	-	Continuous	mg/L
DDimers	-	Continuous	ng/mL
Lymphocytes	-	Continuous	$10^9/L$
Neutrophils	-	Continuous	$10^9/L$
Neutrophils / Lymphocytes	Neutrophils / Lymphocytes	Continuous	
Creatinine	-	Continuous	micromol/L
eGFR	-	Continuous	mL/min/1,73m2
KIM-1	-	Continuous	pg/mL
Cystatine C	-	Continuous	pg/mL
RBP4	-	Continuous	pg/mL
Lipocalin-2	-	Continuous	pg/mL
Osteopontin/OPN	-	Continuous	pg/mL
TFF3	-	Continuous	pg/mL
Gp130 soluble	-	Continuous	pg/mL
IL-6	-	Continuous	pg/mL
IL-6 receptor	-	Continuous	pg/mL
Granzyme A	-	Continuous	pg/mL
Granzyme B	-	Continuous	pg/mL
IFNg	-	Continuous	pg/mL
MCP-1	-	Continuous	pg/mL

TNF alpha	-	Continuous	pg/mL
IL-1a	-	Continuous	pg/mL
IL-1b	-	Continuous	pg/mL
IL1-RA	-	Continuous	pg/mL
IL-8	-	Continuous	pg/mL
IL-10	-	Continuous	pg/mL
IL-17A	-	Continuous	pg/mL
uPAR	-	Continuous	pg/mL
Endoglin	-	Continuous	pg/mL
PLGF	-	Continuous	pg/mL
L-Selectin	-	Continuous	pg/mL
E-Selectin	-	Continuous	pg/mL
P-Selectin	-	Continuous	pg/mL
bFGF	-	Continuous	pg/mL
ICAM-1	-	Continuous	pg/mL
VEGFA	-	Continuous	pg/mL
PDGF-AA	-	Continuous	pg/mL
PDGF-BB	-	Continuous	pg/mL
vWF	-	Continuous	pg/mL
Clusterin	-	Continuous	pg/mL
CXCL10-IP10	-	Continuous	pg/mL
ET1	-	Continuous	pg/mL
MPO	-	Continuous	ng/mL

6. Analysis

A. Outcome definitions

Objective	Endpoint	Time of measurement	Computation (if done)	Analysis method
Primary outcome				
To identify and validate a composite score based on biomarkers measured at baseline that predicts 90-day mortality, allowing classification of patients into distinct risk categories (e.g., high-risk vs. low-risk of death).	All-cause mortality by Day 90.	Day 90	Composite biomarker-based risk score predicting 90-day mortality.	Biomarkers will be analyzed in the SARI cohort (training set) using Wilcoxon rank-sum tests to identify candidates associated with 90-day mortality. Selected biomarkers will then be combined in a LASSO logistic regression model to derive a composite risk score. The optimal cut-off will be determined using the Youden index from the ROC curve to classify patients as high-risk or low-risk. Survival between risk groups will be compared by Kaplan–Meier curves and log-rank tests in both the SARI (training) and TOCI (validation) cohorts.
Secondary outcome				
To identify biomarkers associated with an increase of more than one point in the WHO Clinical Progression Scale [CPS] within 14 days after randomization.	Clinical worsening defined as an increase of >1 point on the WHO Clinical Progression Scale (CPS) compared with baseline.	Day 14	ΔCPS = CPS_D14 – CPS_D0; dichotomized as >1 vs ≤1	Biomarker concentrations will be compared between patients with and without clinical worsening (ΔCPS > 1 vs ≤ 1) using Wilcoxon rank-sum tests in the pooled cohort combining the SARI and TOCI trials.
Exploratory outcomes				
To identify specific markers associated with 90-day mortality.	All-cause mortality by Day 90 in the pooled cohort	Day 90		Biomarker concentrations will be compared between survivors and non-survivors at Day 90 using Wilcoxon rank-sum tests in the pooled cohort combining the SARI and TOCI trials.
To assess the predictive value and discriminative ability of the composite score for survival within each treatment arm (Tocilizumab, Sarilumab, or Usual care)	Overall survival up to Day 90 according to biomarker-based risk groups (high-risk vs low-risk) defined by the composite score cut-off.	D1 to Day 90	Time from randomization to death from any cause; survivors censored at last follow-up.	Patients will be classified into high- and low-risk groups according to the biomarker-based score. Survival curves will be generated using the Kaplan–Meier method, and differences between groups will be compared using log-rank tests within each treatment arm (Tocilizumab, Sarilumab, and Usual care).
To identify biological clusters of patients at Day 1	Identification of biological clusters of patients at day 1	D1		Unsupervised multivariate analysis; visualization by dendrogram; correlation matrices used to explore relationships among biomarkers.

B. Analysis methods

Quantitative data will be described using median, range and interquartile range [IQR]. Qualitative data will be presented as frequencies and percentages (based on the non-missing sample size).

Comparisons will be performed using the Wilcoxon rank-sum test for quantitative data and the Fisher's exact test for qualitative data. We will next use regularization to control model complexity. To overcome the risk of overfitting, we will consider a multivariable model using penalized logistic regression (Least Absolute Shrinkage and Selection Operator (LASSO)) to predict death at 90 days. All variables with a P-value below 0.05 in the univariate analyses will be included in the model. The penalization parameter (lambda) will be assessed by cross-validation. Final associations will be estimated using Odds Ratios and their 95% Confidence Intervals (95% CI). Receiver operating characteristic (ROC) curves will then be generated from the linear predictor of the previous model, and the areas under the curves (AUCs) will be calculated to evaluate the model's performance on the training, validation, and combined cohorts. AUC 95% CIs will be generated using the DeLong method. The risk threshold will be determined with Youden's index. Survival and their 95% Confidence Intervals will be estimated using the Kaplan-Meier estimator and compared using log-rank tests. All tests will be two-sided at the 0.05 level.

Exploratory analyses of biomarker relationships:
Hierarchical clustering of standardized biomarker concentrations will be performed using Euclidean distance and Ward's minimum variance method to explore similarities among biomarkers, and relationships between biomarkers will be assessed using Spearman correlation coefficients.

C. Missing data

Analyses will be performed on complete cases only; missing data will not be imputed.

D. Statistical software

Analyses will be made using R version 4.1.0.