

Supplemental Information

Elevated Calprotectin and Abnormal Myeloid Cell

Subsets Discriminate Severe from Mild COVID-19

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Supplemental Tables

Table S1 related to all Figures: Main characteristics of the patients enrolled in the study. A total number of 158 patients were included. Samples collected from a given patients have been used in several experiments.

	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild	SARS-CoV-2 positive Moderate	SARS-CoV-2 positive Severe
Number (%)	158	72 (46)	27 (17)	16 (10)	43 (27)
Age, median (IQR)	53 (37-63)	50 (31-58)	42 (29-56)	64 (53-72)	62 (50-69)
Age > 60 year-old, n (%)	48 (30)	12 (17)	3 (11)	11 (69)	22 (51)
Male, n (%)	69 (44)	27 (38)	8 (30)	5 (31)	29 (67)
Comorbidities, n (%)					
Overweight	78 (49)	33 (46)	9 (33)	5 (31)	31 (72)
Cardiovascular	55 (35)	20 (28)	5 (19)	10 (62)	20 (47)
Diabetes	29 (18)	9 (13)	1 (4)	6 (38)	13 (30)
Respiratory	31 (20)	17 (24)	1 (4)	3 (19)	10 (23)
Cancer	34 (22)	13 (18)	5 (19)	7 (44)	9 (21)
Initial symptoms, n (%)					
Fever	56 (35)	10 (14)	4 (15)	11 (69)	31 (72)
Cough	86 (54)	31 (43)	16 (59)	10 (62)	29 (67)
Dyspnea	46 (29)	3 (4)	2 (7)	7 (44)	34 (79)
Myalgia	49 (31)	27 (38)	11 (41)	1 (6)	10 (23)
Diarrhea	35 (22)	14 (19)	6 (22)	5 (31)	10 (23)
Anosmia/Ageusia	30 (19)	11 (15)	10 (37)	2 (13)	7 (16)
Laboratory findings, median (IQR)					
Leukocytes (G/L)	7.1 (5.6-10.3)	6.7 (5.6-8.5)	5.6 (4.3-6.8)	5.7 (4.7-8.9)	10.4 (7.9-14.6)
Neutrophils (G/L)	4.4 (3.0-7.4)	3.7 (2.9-5.2)	2.8 (2.3-3.5)	4.6 (3.4-6.1)	7.8 (6.4-11.2)
Lymphocytes (G/L)	1.6 (1.0-2.1)	1.9 (1.5-2.3)	1.6 (1.0-2.1)	1.0 (0.7-1.3)	1.1 (0.7-1.7)
Monocytes (G/L)	0.5 (0.4-0.8)	0.5 (0.4-0.6)	0.5 (0.4-0.7)	0.4 (0.2-0.7)	0.8 (0.4-1.1)
Hemoglobin (g/dL)	12.6 (9.9-13.9)	13.7 (12.8-14.7)	13.0 (11.3-13.6)	10.5 (9.6-13.0)	9.8 (8.1-11.9)
Platelets (G/L)	255 (205-320)	257 (227-303)	210 (171-296)	191 (123-323)	273 (210-407)
Fibrinogen (g/L)	5.0 (3.1-6.7)	3.1 (2.5-4.0)	3.4 (3.0-4.5)	5.4 (5.0-6.3)	7.5 (5.5-8.0)
D-dimers (ng/mL)	590 (241-2122)	245 (160-524)	309 (200-594)	1089 (666-1954)	2145 (1285-5331)
IL-6 (ng/L)	1.7 (1.4-39.6)	1.4 (1.4-2.2)	1.4 (1.4-2.9)	36.0 (15.4-48.5)	89.3 (48.8-157.6)
CRP (mg/L)				50.5 (30.6-98.0)	142.8 (91.1-194.5)
Ferritin (µg/L)				858 (598-858)	959 (454-1828)
LDH (U/L)				240 (203-310)	400 (328-460)
Chest CT findings, n (%)					
NA	94 (59)	68 (94)	22 (81)	1 (6)	3 (7)
<10%	3 (4)	0 (0)	2 (7)	1 (6)	0 (0)
10-25%	12 (8)	2 (3)	0 (0)	6 (38)	4 (2)
25-50%	29 (18)	1 (1)	3 (11)	7 (44)	18 (42)
>50%	20 (13)	1 (0)	0 (0)	1 (6)	18 (42)
Anti-inflammatory drugs, n					
Dexamethasone	6	0	0	2	4
anti-IL-1 (anakinra)	3	0	0	1	3
anti-IL-6 (sari, toci)	9	0	0	2	7
Severity criteria					
PE, n (%)	11 (7)	0 (0)	0 (0)	3 (19)	8 (19)
Maximal O ₂ (L/min), median (range)				2 (0-8)	15 (6-50), n=12
Mechanical ventilation, n					30
PaO ₂ /FiO ₂ , median (range)*					157 (75-453)
SOFA, median (range)*					5.5 (2-12)
SOFA ≥ 8, n (%)*					10 (33)
Death, n (%)			1 (4)	0 (0)	9 (21)
Sampling, n (%)					
Delay since 1 st day in hospital ≤ 10 days	150 (95)	71 (99)	27 (100)	16 (100)	36 (84)

IQR, interquartile range; CRP, C reactive protein; LDH, Lactate dehydrogenase; CT, computed tomography; NA, not available; sari, sarilumab; toci, tocilizumab; PE, pulmonary embolism; PaO₂/FiO₂ (mmHg) at sampling; SOFA, Sequential Organ Failure Assessment score; *Parameters calculated for patients under mechanical ventilation; “Delay since the 1st day in hospital ≤ 10 days” indicates the number of patients included in the study within the first 10 days after admission to the hospital.

Table S2 related to Figure 1; Figure S1: Characteristics of patients of the learning cohort analyzed by spectral cytometry (results shown on Figure 1 and supplemental Figure 1).

	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild / Moderate	SARS-CoV-2 positive Severe
Number (%)	25	12 (48)	5 (20)	8 (32)
Age, median (IQR)	54 (31-73)	48 (30-63)	35 (28-56)	73 (45-74)
Age > 60, n (%)	8 (32)	3 (25)	0 (0)	5 (38)
Male, n (%)	13 (52)	7 (58)	0 (0)	6 (25)
Comorbidities, n (%)				
Overweight	12 (48)	3 (25)	1 (20)	8 (100)
Cardiovascular	7 (28)	3 (25)	0 (0)	4 (50)
Diabetes	5 (20)	1 (8)	0 (0)	4 (50)
Respiratory	6 (24)	3 (25)	1 (20)	2 (25)
Cancer	1 (4)	0 (0)	0 (0)	1 (13)
Initial symptoms, n (%)				
Fever	9 (36)	1 (8)	0 (0)	8 (100)
Cough	13 (52)	5 (42)	3 (60)	5 (63)
Dyspnea	6 (24)	0 (0)	0 (0)	6 (75)
Myalgia	13 (52)	6 (50)	3 (60)	4 (50)
Diarrhea	4 (16)	0 (0)	4 (80)	0 (0)
Anosmia / Ageusia	3 (12)	0 (0)	2 (40)	1 (13)
Laboratory findings, median (IQR)				
Leukocytes (G/L)	6.4 (5.0-10.0)	5.8 (4.8-6.6)	6.0 (4.4-7.1)	13.3 (9.6-18.1)
Neutrophils (G/L)	3.7 (2.9-6.8)	3.3 (2.8-3.5)	2.9 (2.8-4.0)	10.9 (7.2-14.0)
Lymphocytes (G/L)	1.8 (1.6-2.3)	1.8 (1.6-2.5)	2.3 (1.7-2.3)	1.8 (0.9-2.0)
Monocytes (G/L)	0.5 (0.4-0.6)	0.4 (0.3-0.5)	0.6 (0.5-0.7)	0.6 (0.5-1.3)
Hemoglobin (g/dL)	12.9 (11.7-14.4)	14.5 (13.0-15.5)	13.1 (12.8-13.1)	11.1 (8.9-12.0)
Platelet count (G/L)	248 (204-304)	235 (202-261)	206 (204-246)	393 (268-522)
Fibrinogen (g/L)	3.0 (2.6-6.3)	2.5 (2.3-2.9)	2.8 (2.8-3.4)	7.8 (6.3-8.8)
D-dimers (ng/mL)	339 (184-568)	184 (85-204)	339 (249-568)	3738 (836-6489)
IL-6 (ng/L)	1.4 (1.4-54.0)	1.4 (1.4-1.4)	1.4 (1.4-2.3)	189.0 (59.2-677.0)
CRP (mg/L)				116.0 (102.5-241.7)
Ferritin (µg/L)				1133 (972-1633)
LDH (U/L)				418 (352-446)
Chest CT findings, n (%)				
NA	17 (68)	11 (92)	5 (100)	1 (13)
<10%	0 (0)	0 (0)	0 (0)	0 (0)
10-25%	3 (12)	1 (8)	0 (0)	2 (25)
25-50%	3 (12)	0 (0)	0 (0)	3 (38)
>50%	2 (8)	0 (0)	0 (0)	2 (25)
Anti-inflammatory drugs, n				
Dexamethasone	0	0	0	0
anti-IL-1 (anakinra)	2	0	1	1
anti-IL-6 (sari, toci)	2	0	1	1
Severity criteria				
PE, n (%)	3 (12)	0 (0)	0 (0)	3 (38)
Mechanical ventilation, n (%)				8 (100)
PaO ₂ /FiO ₂ , median (range)*				138 (95-177)
SOFA, median (range)*				8 (3-14)
SOFA ≥ 8, n (%)*				4 (50)
Death, n (%)			0 (0)	4 (50)
Sampling, n (%)				
Delay since 1 st day in hospital ≤ 10 days	24 (96)	12 (100)	5 (100)	7 (88)

IQR, interquartile range; CRP, C reactive protein; LDH, Lactate deshydrogenase; NA, not available; CT, computed tomography; Sari, sarilumab; toci, tocilizumab; PE, pulmonary embolism; PaO₂/FiO₂ (mmHg) at sampling; SOFA, Sequential Organ Failure Assessment score; *Parameters calculated for patients under mechanical ventilation; "Delay since the 1st day in hospital ≤ 10 days" indicates the number of patients included in the study within the first 10 days after admission to the hospital.

Table S3 related to Figures 2-4; Figures S2-S4: Characteristics of patients analyzed by single cell RNA sequencing (results shown on Figure 2, 3 and 4 and supplemental Figure 2, 3 and 4). M, male; F, female; PE, pulmonary embolism; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment score.

	SARS-CoV2 pos Severe # 1	SARS-CoV2 pos Severe # 2	SARS-CoV2 pos Mild	Control # 1	Control # 2	Control # 3			
Age	69	26	21	54	27	58			
Sex	M	F	F	F	F	F			
SARS-CoV2 RT-PCR	positive	positive	positive	negative	negative	negative			
Comorbidities									
Overweight	Yes	Yes	No	Yes	No	Yes			
Cardiovascular	No	No	No	Yes	No	No			
Diabetes	Yes	Yes	No	No	No	Yes			
Respiratory	No	No	No	No	No	No			
Cancer	No	No	No	No	No	No			
Initial symptoms									
Fever	Yes	No	No	No	No	No			
Cough	Yes	No	Yes	Yes	Yes	No			
Dyspnea	Yes	Yes	No	No	No	No			
Myalgia	No	Yes	Yes	No	Yes	No			
Diarrhea	Yes	Yes	No	No	No	No			
Anosmia / Ageusia	No	No	Yes	No	Yes	No			
Sampling									
	Sample 1 (day 0)	Sample 2 (day 10)	Sample 1 (day 0)	Sample 2 (day 10)	Sample 1 (day 0)	Sample 2 (day 10)	Sample 1	Sample 1	Sample 1
Delay from 1st day at hospital (days)	14	24	10	20	0	0	0	0	0
Laboratory and chest CT findings									
Leukocytes (G/L)	10.2	10.9	11.4	7.4	4.9	6.6	5.7	6.7	7.1
Neutrophils (G/L)	6.9	8.3	7.7	4.9	2.2	3.4	3.4	4.0	4.2
Lymphocytes (G/L)	1.8		2.5		2.3		1.7	1.9	2.2
Monocytes (G/L)	0.7		0.68		0.27		0.48	0.48	0.43
Hemoglobin (g/dL)	9.8	10.5	6.7	6.8	10.4	10.6	12.6	12.4	12.8
Platelets (G/L)	186	136	282	287	281	348	302	236	230
IL-6 (ng/L)	11.1		67.3		< 1.5		3.5	< 1.5	< 1.5
CRP (mg/L)	16.7		193		1.1		< 1.5	< 1.0	4.4
CT damage (%)	50		25-50						
Severity criteria									
PE	No		Yes		No		No	No	No
Maximal O ₂ (L/min)	MV	1	MV	MV	0	0	0	0	0
PaO ₂ /FiO ₂ (mmHg)	124	273	225	233					
SOFA at sampling	7	6	6	3					
Death, n (%)	No		No		No		No	No	No

Samples were collected from four patients examined at Hôtel-Dieu COVID-19 screening unit for cough without or with fever. Only one of these patients was SARS-CoV2 RT-PCR-positive on nasopharyngeal swab. Given her mild symptoms, this 21-year old nurse was not hospitalized. She recovered at home and was seen 10 days later for a second blood screen.

Patient “Severe #1” is a 69-year old man with type 2 diabetes mellitus (body mass index, 26.2) who was hospitalized on April 4, 2020 because of fever, dyspnea, diarrhea and poor general condition. SARS-CoV2 RT-PCR on buccal swab was positive. He was rapidly transferred to Cochin hospital ICU and mechanically ventilated (MV), starting on April 5 (SOFA: 12, PaO₂/FiO₂: 182 at admission). The sample used for scRNAseq was collected on April 20, 2020 (SOFA: 7; PaO₂/FiO₂: 124). He progressively recovered, was released from mechanical ventilation on April 29 and transferred to a medical unit on April 30 (PaO₂/FiO₂: 273), when the sample used for the second scRNAseq analysis was collected. On May 5, the patient was recovering with mild oxygenotherapy (1L/min) in Cochin hospital pneumology care unit.

Patient “Severe #2” is a 26-year old woman with insulin-dependent type 1 diabetes mellitus and obesity (body mass index, 30.6) who was hospitalized on April 3, 2020 because of fever, dyspnea and diarrhea. On April 8, SARS-CoV2 RT-PCR on pharyngeal swab was positive. On April 10, she was hospitalized in Cochin hospital emergency unit with acido-cetosis after she had interrupted her daily insulin therapy. She required oxygenotherapy and was transferred to ICU on April 12 (SOFA score 3). The sample used for scRNAseq was collected on April 20, 2020 (SOFA: 6; PaO₂/FiO₂: 225). She developed a bacterial infection (*P. aeruginosa*, *S. aureus* in bronchoalveolar aspirate) on April 20, partially recovered and was transferred in Cochin hospital pneumology care unit on April 25, then returned to ICU on April 28 with degraded pulmonary condition due to *K. pneumonia* pneumonia pneumopathy and pulmonary embolism. The sample used for the second scRNAseq analysis was collected on April 30th (SOFA 3; PaO₂/FiO₂: 232.8). On May 4, she was still in ICU with progressive recovery of severity parameters (SOFA:1; PaO₂/FiO₂: 312).

Table S4 related to Figures 2-4; Figures S2-S4: Excel sheet providing the detailed results of scRNA seq experiments shown on Figure 2 to 4, including metadata, cell population numbers, cell population differentially expressed genes (DEGs), monocyte DEGs and neutrophils DEGs.

Table S5 related to Figures 3,4; Figures S3,S5: Characteristics of patients whose peripheral blood cells were analyzed by mass cytometry (left) or by RT-PCR (right).

	<i>Cohort of patients whose cells were analyzed by mass cytometry (results shown on Figure 3-4 and supplemental Figure 3-4)</i>				<i>Cohort of patients whose buffy coat was analyzed by RT-qPCR. (results shown on supplemental Figure 5)</i>			
	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild / Moderate	SARS-CoV-2 positive Severe	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild / Moderate	SARS-CoV-2 positive Severe
Number (%)	12 (100)	4 (33)	4 (33)	4 (33)	32	8 (25)	16 (50)	8 (25)
Age, median (IQR)	59 (47-62)	58 (46-62)	42 (27-58)	65 (61-69)	46 (31-61)	30 (26-44)	49 (36-61)	64 (47-69)
Age > 60 year-old, n (%)	5 (42)	2 (50)	0 (0)	3 (75)	9 (28)	0 (0)	5 (31)	4 (50)
Male, n (%)	6 (50)	2 (50)	1 (25)	3 (75)	12 (38)	2 (25)	5 (31)	5 (50)
Comorbidities, n (%)								
Overweight	5 (42)	1 (25)	0 (0)	4 (100)	18 (56)	3 (38)	8 (50)	7 (88)
Cardiovascular	1 (8)	0 (0)	0 (0)	1 (25)	9 (28)	1 (18)	5 (31)	3 (38)
Diabetes	0 (0)	0 (0)	0 (0)	0 (0)	7 (22)	0 (0)	3 (19)	4 (50)
Respiratory	2 (17)	1 (25)	1 (25)	0 (0)	4 (13)	2 (25)	1 (6)	1 (13)
Cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Initial symptoms, n (%)								
Fever	4 (33)	0 (0)	1 (25)	3 (75)	13 (41)	0 (0)	6 (38)	7 (88)
Cough	9 (75)	2 (50)	4 (100)	3 (75)	21 (67)	4 (50)	12 (75)	5 (63)
Dyspnea	5 (42)	0 (0)	1 (25)	4 (100)	13 (41)	1 (13)	4 (25)	8 (100)
Myalgia	4 (33)	2 (50)	2 (50)	0 (0)	11 (34)	3 (38)	4 (25)	4 (50)
Diarrhea	5 (42)	2 (50)	3 (75)	0 (0)	12 (38)	4 (50)	6 (38)	2 (25)
Anosmia / Ageusia	3 (25)	2 (50)	1 (25)	0 (0)	9 (28)	0 (0)	7 (44)	2 (25)
Laboratory findings, median (IQR)								
Leukocytes (G/L)	6.9 (5.7-9.7)	6.7 (5.9-8.0)	6.4 (4.0-8.9)	8.9 (6.4-12.1)	6.6 (1.9-23.4)	7.4 (6.2-9.8)	5.8 (4.0-6.3)	10.7 (9.4-12.7)
Neutrophils (G/L)	4.8 (3.2-6.0)	4.0 (3.0-6.6)	3.7 (2.5-5.3)	6.9 (5.3-8.8)	4.6 (3.4-7.5)	4.3 (3.6-5.1)	3.4 (1.5-4.6)	7.6 (7.2-10.1)
Lymphocytes (G/L)	1.6 (1.0-2.1)	1.8 (1.7-2.0)	1.7 (0.9-2.5)	1.2 (0.7-1.7)	1.6 (0.5-3.9)	2.8 (2.0-3.1)	1.0 (0.8-1.3)	1.5 (1.3-1.7)
Monocytes (G/L)	0.5 (0.5-0.7)	0.5 (0.4-0.7)	0.5 (0.5-0.6)	0.7 (0.5-1.0)	0.5 (0.1-1.7)	0.5 (0.4-0.6)	0.3 (0.2-0.5)	0.6 (0.5-0.9)
Hemoglobin (g/dL)	12.6 (11.4-14.8)	14.2 (12.7-15.5)	13.8 (11.8-16.3)	10.4 (9.3-11.2)	12.6 (10.8-13.5)	13.0 (13.6-14.4)	12.6 (11.6-13.3)	8.5 (7.3-9.8)
Platelets (G/L)	202 (177-271)	217 (190-267)	186 (170-197)	323 (210-442)	261 (86-526)	285 (252-324)	232 (173-394)	224 (131-300)
Fibrinogen (g/L)	3.2 (2.8-5.4)	3.0 (2.6-3.7)	3.0 (2.7-3.5)	7.2 (6.2-7.6)			4.4 (3.1-6.2)	7.5 (6.7-9.9)
D-dimers (ng/mL)	329 (239-1587)	313 (210-410)	244 (219-254)	91.2 (48.8-176.6)			726 (227-1326)	3721 (2134-5544)
IL-6 (ng/L)	2.9 (1.4-37.0)	1.4 (1.4-8.5)	2.1 (1.4-8.7)	113.2 (58.4-186.1)	1.4 (1.4-51.8)	1.4 (1.4-1.4)	1.4 (1.4-36.7)	109.6 (74.5-127.5)
CRP (mg/L)				177 (146-306)			10.0 (0.9-104.0)	169 (128-232)
Ferritin (µg/L)				1888 (1423-2343)			643 (504-856)	1252 (1175-1455)
LDH (U/L)				405 (355-412)			240 (240-293)	462 (370-681)
Chest CT findings, n (%)								
NA	8 (67)	4 (100)	4 (100)	0 (0)	18 (56)	8 (100)	8 (50)	2 (25)
<10%	0 (0)			0 (0)	1 (3)		1 (6)	0 (0)
10-25%	0 (0)			0 (0)	2 (6)		0 (0)	2 (25)
25-50%	4 (33)			4 (100)	6 (17)		5 (31)	1 (13)
>50%	0 (0)			0 (0)	5 (14)		2 (13)	3 (38)
Anti-inflammatory drugs, n								
Dexamethasone	0	0	0	0	2	0	1	1
anti-IL-1 (anakinra)	0	0	0	0	2	0	0	2
anti-IL-6 (sari, toci)	0	0	0	0	2	0	1	1
Severity criteria								
PE, n (%)	2 (17)	0 (0)	0 (0)	2 (50)	3 (9)	0 (0)	1 (6)	2 (25)
Maximal O ₂ (L/min), median (range)				MV (n = 4)			7 (1-10)*	MV (n = 8)
PaO ₂ /FiO ₂ , median (range)**				157 (95-232)				146 (99-249)
SOFA, median (range)**				3 (2-8)				9 (4-12)
SOFA ≥ 8, n (%)**				1 (25)				5 (63)
Death, n (%)	1 (8)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)
Sampling, n (%)								
Delay since 1 st day hospital ≤ 10 days	12 (100)	4 (100)	4 (100)	4 (100)	30 (94)	8 (100)	15 (94)	7 (88)

IQR, interquartile range; LDH, Lactate dehydrogenase; CT, computed tomography; NA: not available; Sari, sarilumab ; toci, tocilizumab; PE, pulmonary embolism; MV, mechanical ventilation; *Maximal O₂ calculated for 8 pts with moderate disease; PaO₂/FiO₂ (mmHg) at sampling; **Parameters calculated for patients under MV; SOFA, Sequential Organ Failure Assessment score; “Delay since the 1st day in hospital ≤ 10 days” indicates the number of patients included in the study within the first 10 days after admission to the hospital.

Table S6 related to Figures 5-7; Figures S5-S7: Characteristics of patients of the validation cohorts, with circulating protein measurements and spectral flow cytometry analyses.

	Cohort of patients with circulating protein level measurements (results shown on Figure 5 and supplemental Figure 5)				Cohort of patients analyzed by spectral flow cytometry (CYTEK) (results shown on Figure 6-7 and supplemental Figure 6)			
	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild / Moderate	SARS-CoV-2 positive Severe	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild / Moderate	SARS-CoV-2 positive Severe
Number (%)	84 (100)	40 (48)	19 (23)	25 (30)	90	48 (53)	16 (18)	26 (29)
Age, median (IQR)	53 (40-62)	52 (36-58)	49 (28-58)	66 (59-73)	49 (31-59)	42 (30-52)	45 (28-58)	62 (47-72)
Age > 60 year-old, n (%)	25 (30)	6 (15)	3 (16)	16 (64)	20 (22)	3 (12)	3 (19)	14 (54)
Male, n (%)	35 (42)	14 (35)	3 (16)	18 (72)	37 (41)	15 (31)	4 (25)	18 (69)
Comorbidities, n (%)								
Overweight	45 (54)	18 (45)	6 (32)	21 (84)	48 (53)	20 (42)	4 (25)	24 (92)
Cardiovascular	29 (35)	13 (22)	4 (21)	12 (48)	25 (28)	11 (23)	4 (25)	10 (38)
Diabetes	16 (19)	3 (8)	3 (16)	10 (40)	11 (12)	1 (2)	3 (19)	7 (27)
Respiratory	15 (18)	9 (23)	1 (5)	5 (20)	17 (19)	9 (19)	1 (8)	7 (27)
Cancer	4 (5)	2 (5)	1 (5)	1 (4)	6 (7)	2 (4)	2 (13)	2 (8)
Initial symptoms, n (%)								
Fever	30 (36)	7 (18)	4 (21)	19 (76)	27 (30)	6 (12)	4 (25)	23 (88)
Cough	46 (55)	17 (43)	12 (63)	17 (65)	49 (54)	24 (50)	10 (63)	18 (69)
Dyspnea	24 (29)	0 (0)	3 (16)	21 (84)	21 (23)	1 (2)	3 (19)	23 (88)
Myalgia	31 (37)	18 (45)	6 (32)	7 (28)	32 (36)	20 (42)	6 (38)	10 (38)
Diarrhea	20 (24)	6 (15)	7 (37)	7 (28)	21 (23)	12 (25)	6 (38)	6 (23)
Anosmia / Ageusia	18 (45)	8 (20)	5 (26)	5 (20)	15 (17)	8 (17)	3 (19)	5 (19)
Laboratory findings, median (IQR)								
Leucocytes (G/L)	7.1 (5.6-10.3)	6.7 (5.6-8.5)	5.6 (4.3-6.8)	5.7 (4.7-8.9)	7.6 (5.6-9.9)	6.5 (5.6-8.1)	5.1 (4.0-6.2)	11.1 (8.8-14.5)
Neutrophils (G/L)	4.4 (3.0-7.4)	3.7 (2.9-5.2)	2.8 (2.3-3.5)	4.6 (3.4-6.1)	4.4 (2.9-7.0)	3.4 (2.9-4.8)	3.5 (2.9-4.9)	8.4 (6.4-12.1)
Lymphocytes (G/L)	1.6 (1.0-2.1)	1.9 (1.5-2.3)	1.6 (1.0-2.1)	1.0 (0.7-1.3)	1.8 (1.3-2.3)	2.0 (1.7-2.5)	1.5 (1.0-2.1)	1.5 (0.8-1.9)
Monocytes (G/L)	0.5 (0.4-0.8)	0.5 (0.4-0.6)	0.5 (0.4-0.7)	0.4 (0.2-0.7)	0.5 (0.4-0.7)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.7 (0.5-0.9)
Hemoglobin (g/dL)	12.6 (9.9-13.9)	13.7 (12.8-14.7)	13.0 (11.3-13.6)	10.5 (9.6-13.0)	13.1 (11.2-14.3)	14.0 (13.2-14.8)	13.0 (11.3-13.9)	9.8 (8.3-11.3)
Platelets (G/L)	255 (205-320)	257 (227-303)	210 (171-296)	191 (123-323)	256 (210-320)	254 (225-303)	186 (132-293)	292 (233-394)
Fibrinogen (g/L)	3.8 (2.9-5.9)	2.9 (2.5-3.1)	3.5 (2.9-4.9)	6.7 (5.4-8.2)	4.1 (2.9-7.0)	2.9 (2.5-3.1)	3.5 (2.9-4.9)	7.7 (5.8-9.1)
D-dimers (ng/mL)	483 (194-1581)	204 (144-292)	384 (217-1081)	2270 (1285-5944)	435 (209-2135)	200 (144-274)	476 (254-1085)	2330 (1632-5790)
IL-6 (ng/L)	3.1 (1.4-45.8)	1.4 (1.4-3.6)	2.3 (1.4-5.8)	91.2 (48.8-176.6)	2.3 (1.4-2762.0)	1.4 (1.4-2.6)	1.4 (2.3-8.0)	83.7 (54.5-172.8)
CRP (mg/L)				50.5 (30.6-98.0)				165.5 (104.0-245.0)
Ferritin (µg/L)				781 (416-1472)				994 (627-1633)
LDH (U/L)				418 (350-464)				424 (339-452)
Chest CT findings, n (%)								
NA	54 (64)	40 (100)	12 (63)	2 (8)	63 (70)	48 (100)	12 (100)	3 (12)
<10%	0 (0)		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)
10-25%	6 (7)		1 (5)	4 (16)	5 (6)		2 (13)	3 (12)
25-50%	7 (8)		3 (16)	4 (16)	14 (16)		2 (13)	12 (46)
>50%	18 (21)		3 (16)	15 (60)	8 (9)		0 (0)	8 (31)
Anti-inflammatory drugs, n								
Dexamethasone	2	0	0	2	1	0	0	1
anti-IL-1 (anakinra)	1	0	0	1	2	0	0	2
anti-IL-6 (sari, toci)	2	0	1	1	13	0	1	2
Severity criteria								
PE, n (%)	9 (11)	0 (0)	2 (11)	7 (28)	8 (9)	0 (0)	2 (13)	6 (23)
Maximal O ₂ (L/min)			2 (1-9)*	15 (9-50) or MV (n=20)			2 (2-4)**	12 (n=1) or MV (n=25)
PaO ₂ /FiO ₂ , median (range)***				164 (75-404)				159 (75-404)
SOFA, median (range)***				7 (2-14)				4 (2-14)
SOFA ≥ 8, n (%)***				10 (50)				5 (19)
Death, n (%)				6 (24)				7 (27)
Sampling, n (%)								
Delay since 1 st day hospital ≤ 10 days	78 (93)	40 (100)	19 (100)	19 (76)	86 (95)	48 (100)	16 (100)	21 (81)

IQR: interquartile range; LDH, lactate dehydrogenase; CT: computed tomography; NA, not available; Sari, sarilumab; toci, tocilizumab; PE, pulmonary embolism; *Maximal O₂ for 6 patients with moderate disease; **Maximal O₂ for 3 patients with moderate disease; MV, mechanical ventilation; PaO₂/FiO₂ (mmHg) at sampling; SOFA: Sequential Organ Failure Assessment score; ***Parameters calculated for patients under MV. “Delay since the 1st day in hospital ≤ 10 days” indicates the number of patients included in the study within the first 10 days after admission to the hospital.

Table S7 related to Figure 7; Figure S7: Characteristics of patients tested by conventional flow cytometry for non-classical monocyte fraction measurement (results shown on Figure 7 and supplemental Figure 7).

	<i>Learning cohort</i>					<i>Validation cohort</i>				
	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild	SARS-CoV-2 positive Moderate	SARS-CoV-2 positive Severe	All patients	SARS-CoV-2 negative Controls	SARS-CoV-2 positive Mild	SARS-CoV-2 positive Moderate	SARS-CoV-2 positive Severe
Number (%)	98	56 (57)	16 (16)	10 (10)	16 (16)	24	10 (42)	3 (13)	4 (17)	7 (29)
Age, median (IQR)	50 (20-89)	46 (31-54)	37 (26-58)	57 (46-74)	68 (49-75)	60 (54 - 68)	63 (57 - 68)	56 (52 - 68)	69 (65 - 74)	46 (43 - 58)
Age > 60 y, n (%)	23 (23)	6 (11)	2 (13)	5 (50)	10 (62)	12 (50)	7 (70)	1 (33)	4 (100)	0 (0)
Male, n (%)	39 (40)	19 (34)	5 (31)	3 (30)	12 (75)	12 (50)	6 (60)	1 (33)	1 (25)	4 (57)
Comorbidities, n (%)										
Overweight	45 (46)	24 (43)	4 (25)	5 (50)	12 (75)	7 (29)	3 (30)	1 (33)	1 (25)	2 (29)
Cardiovascular	33 (34)	15 (27)	2 (13)	6 (60)	9 (56)	10 (42)	4 (40)	2 (67)	3 (75)	1 (14)
Diabetes	16 (16)	4 (7)	1 (6)	4 (40)	7 (44)	8 (33)	5 (50)	0 (0)	2 (50)	1 (14)
Respiratory	19 (19)	12 (21)	2 (13)	2 (20)	3 (19)	8 (33)	5 (50)	0 (0)	1 (25)	3 (43)
Cancer	10 (10)	3 (5)	2 (13)	3 (30)	2 (12)	21 (87)	10 (100)	3 (100)	4 (100)	4 (57)
Initial symptoms, n (%)										
Fever	50 (51)	25 (45)	10 (63)	5 (50)	10 (62)	9 (37)	1 (10)	1 (33)	1 (25)	6 (86)
Cough	19 (19)	1 (2)	0 (0)	5 (50)	13 (81)	10 (42)	2 (20)	1 (33)	3 (75)	4 (57)
Dyspnea	38 (39)	23 (41)	8 (50)	1 (10)	6 (38)	1 (4)	0 (0)	0 (0)	1 (25)	0 (0)
Myalgia	24 (24)	12 (21)	5 (31)	4 (40)	3 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	23 (23)	11 (20)	7 (44)	1 (10)	4 (25)	1 (4)	0 (0)	0 (0)	0 (0)	1 (14)
Anosmia / Ageusia	25 (26)	8 (14)	1 (6)	5 (50)	11 (69)	12 (50)	2 (20)	1 (33)	4 (100)	5 (71)
Laboratory findings, median (IQR)										
Leucocytes (G/L)	6.4 (1.9-22.9)	6.5 (5.6-8.2)	4.9 (4.3-6.0)	5.0 (3.6-6.9)	10.5 (9.0-16.4)	10.5 (6.8 - 12.1)	8.8 (5.6 - 12.1)	11.2 (7.9 - 13.0)	10.4 (6.2 - 11.9)	10.6 (6.8 - 15.2)
Neutrophils (G/L)	3.5 (1.1-19.1)	3.4 (2.8-4.6)	2.8 (2.4-3.3)	3.4 (2.8-5.5)	7.7 (6.5-12.4)	7.2 (3.9 - 9.1)	7.2 (3.7 - 9.6)	8.5 (3.4 - 9.0)	7.1 (3.9 - 8.6)	7.9 (4.0 - 12.5)
Lymphocytes (G/L)	1.8 (0.2-3.9)	2.0 (1.7-2.4)	1.7 (1.3-2.2)	1.0 (0.5-1.3)	0.9 (0.6-1.6)	1.0 (0.8 - 1.7)	1.0 (0.6 - 1.5)	1.6 (0.3 - 3.5)	1.7 (0.6 - 2.6)	1.4 (0.8 - 2.3)
Monocytes (G/L)	0.5 (0.0-9.3)	0.5 (0.4-0.6)	0.5 (0.4-0.7)	0.2 (0.2-0.6)	0.8 (0.4-1.1)	0.9 (0.6 - 1.2)	0.8 (0.4 - 1.1)	1.0 (0.6 - 1.7)	1.1 (0.7 - 1.1)	1.2 (0.5 - 1.3)
Hemoglobin (g/dL)	13.2 (11.6-14.1)	13.7 (13.1-14.7)	13.1 (11.4-13.7)	11.5 (9.8-13.3)	9.8 (8.1-12.0)	10.1 (8.9 - 12.8)	12.6 (9.7 - 15.2)	9.1 (8.9 - 11.9)	9.4 (8.6 - 10.1)	8.7 (8.2 - 11.1)
Platelets (G/L)	247 (43.0-737.0)	255 (225-302)	231 (159-317)	140 (106-233)	246 (203-339)	298 (200 - 494)	272 (212 - 433)	456 (155 - 507)	445 (186 - 613)	264 (153 - 444)
Fibrinogen (g/L)				5.1 (3.9-7.2)	6.9 (5.6-9.2)				5.5 (4.9 - 7.2)	8.0 (4.9 - 8.5)
D-dimers (ng/mL)				1052 (409-2292)	3172 (1209-5301)				1630 (860 - 7360)	2490 (605 - 5073)
CRP (mg/L)				44.2 (30.6-79.7)	123.0 (86.0-179.0)				37.0 (5.1 - 266.5)	155.1 (52.9 - 248.9)
IL-6 (ng/L)				20.2 (5.4-74.5)	73.3 (55.9-111.1)					
Ferritin (µg/L)				724 (412-1371)	972 (694-1419)				1376 (327-5100)	1730 (1144-3060)
LDH (U/L)				254 (204-382)	435 (341-455)				256 (200-318)	338 (312-1022)
Chest CT findings, n (%)										
NA	71 (72)	54 (96)	14 (88)	1 (10)	2 (12)	7 (29)	7 (70)	0 (0)	0 (0)	0 (0)
<10%	4 (4)	1 (2)	2 (13)	1 (10)	0 (0)	3 (13)	1 (10)	1 (33)	1 (25)	0 (0)
10-25%	9 (9)	1 (2)	0 (0)	5 (50)	3 (19)	2 (8)	1 (10)	0 (0)	2 (50)	0 (0)
25-50%	5 (5)	0 (0)	0 (0)	2 (20)	3 (19)	7 (29)	0 (0)	2 (67)	1 (25)	5 (71)
>50%	8 (8)	0 (0)	0 (0)	0 (0)	8 (50)	3 (13)	1 (10)	0 (0)	0 (0)	2 (29)
Anti-inflammatory drugs, n										
Dexamethasone	6	0	0	2	4	0	0	0	0	0
anti-IL-1 (anakinra)	4	0	0	1	3	0	0	0	0	0
anti-IL-6 (sari, toci)	3	0	0	2	1	3	0	0	0	3
Severity criteria										
PE, n (%)	7 (7)	1 (2)	0 (0)	2 (20)	4 (25)	1 (4)	0 (0)	0 (0)	1 (25)	0 (0)
PaO ₂ /FiO ₂ , median (range)					140 (75-226)*					169 (112-453)**
SOFA, median (range)					11 (2-14)*					3 (0 - 6)**
Death, n (%)	4 (4)	0 (0)	0 (0)	0 (0)	4 (25)	1 (4)	0 (0)	0 (0)	0 (0)	1 (14)
Sampling, n (%)										
Delay since 1 st day hospital ≤ 10 days	96 (98)	55 (98)	16 (100)	11 (100)	15 (94)	24 (100)	10 (100)	3 (100)	4 (100)	7 (100)

y, year-old; LDH, lactate deshydrogenase; IQR, interquartile range; CT, computed tomography; NA, not available; Sari, sarilumab ; toci, tocilizumab; PE, pulmonary embolism; PaO₂/FiO₂ (mmHg) at sampling; SOFA, Sequential Organ Failure Assessment score; *Parameters calculated for 13 patients under mechanical ventilation; **Parameters calculated for 3 patients under mechanical ventilation; “Delay since the 1st day in hospital ≤ 10 days” indicates the number of patients included in the study within the first 10 days after admission to the hospital.