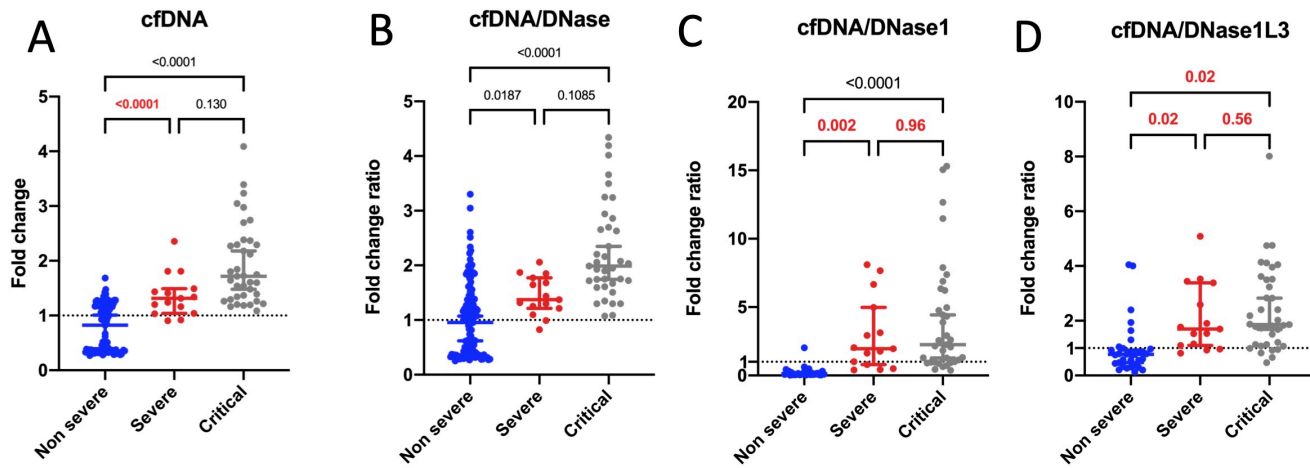
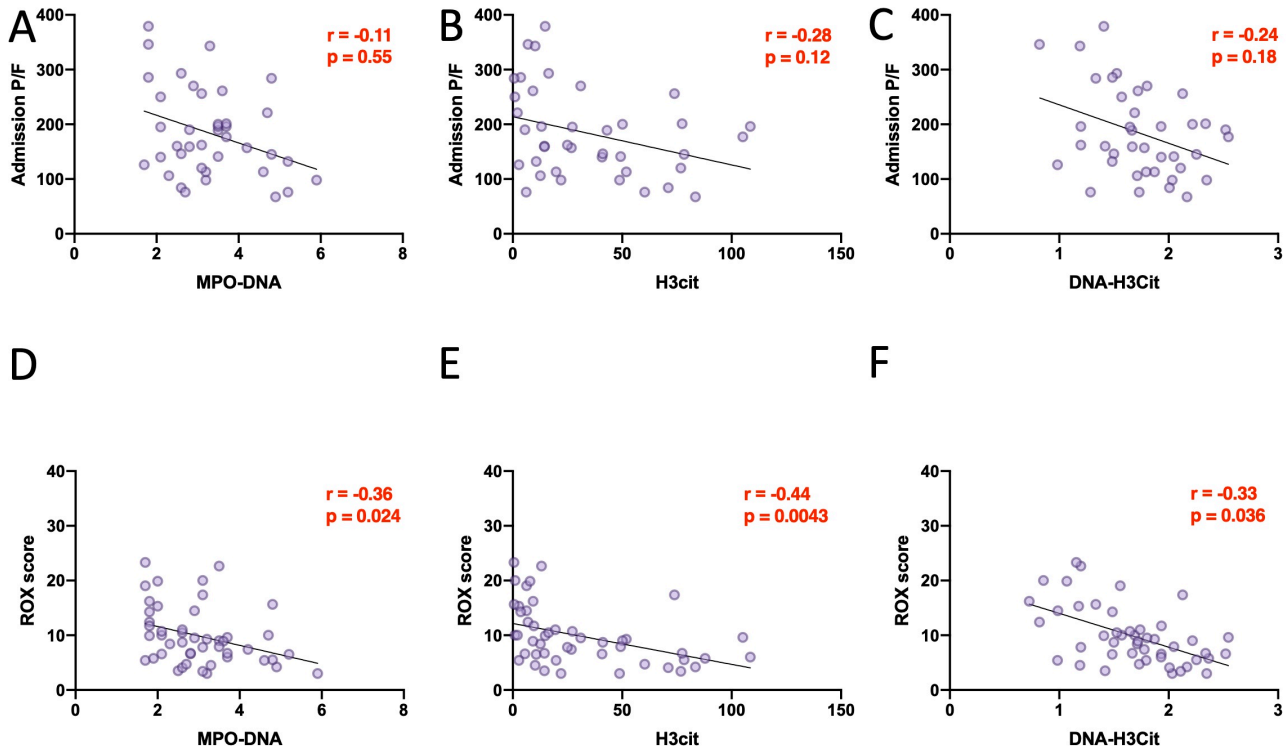


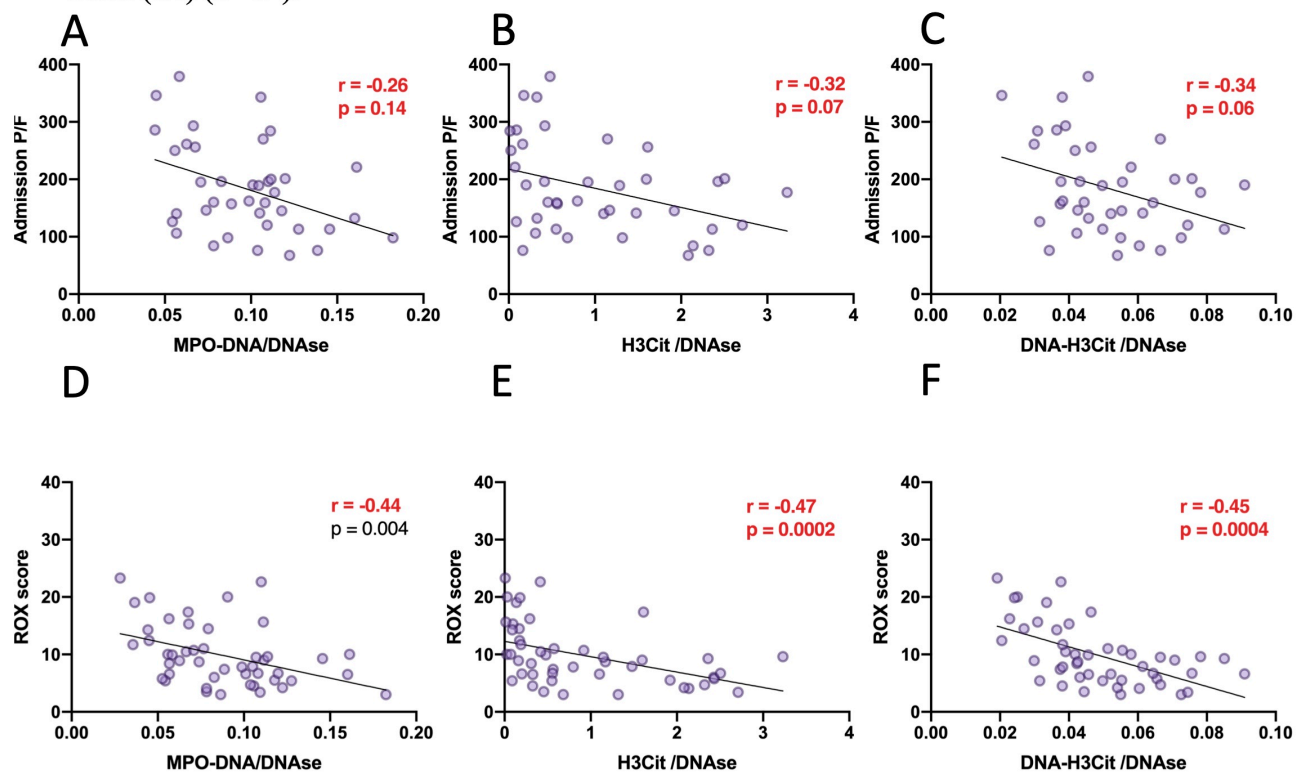
Supplementary Figure 1 –cfDNA according to COVID 19 clinical severity (a); ratios between cfDNA and functional DNase (b), DNase1 protein (c) and DNase1L3 protein (d). Results expressed in fold change and fold change ratio between non-severe (n = 32), severe (n = 15) and critical COVID-19 patients (n = 37) and healthy donors (n = 7). Comparisons between groups were performed using a Compound Poisson-Gamma model adjusted for age, sex and BMI.



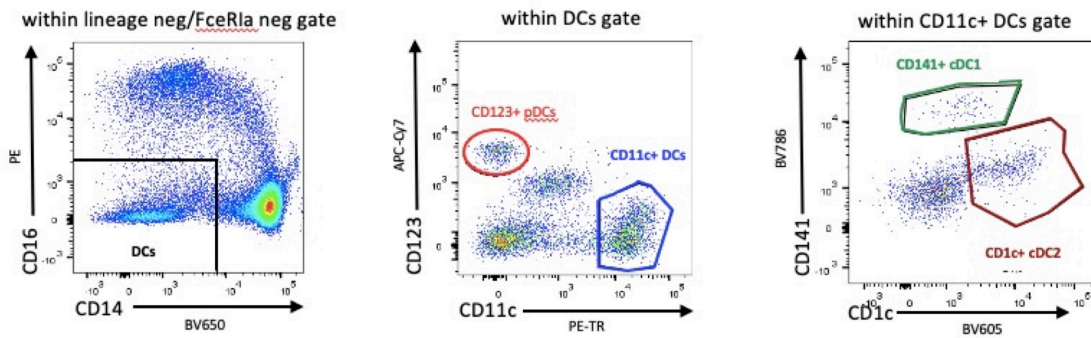
Supplementary Figure 2 – Spearman correlation **adjusted for age, sex and BMI** between three NET biomarkers, MPO-DNA (a, d), H3cit (b, e), and H3cit-DNA (c, f) and two markers of disease severity, *i.e.* the PaO₂/FiO₂ ratio (a-c) and the ROX index (d-f) (n =52).



Supplementary Figure 3 – Spearman correlation **adjusted for age, sex and BMI** between the ratios of three NET biomarkers, MPO-DNA (a, d), H3cit (b, e), and H3cit-DNA complexes (c, f) over functional DNase and two markers of disease severity, *i.e.* the PaO₂/FiO₂ ratio (a-c) and the ROX index (d-f) (n =52).



Supplementary Figure 4 – Gating strategy for dendritic cells (cDC1 and cDC2) and plasmacytoid dendritic cells (pDCs) analysis. DC were selected from living Lin⁻ cells after basophil exclusion, as CD14⁻ and CD16⁻. Among DCs, pDC were defined as CD123⁺CD11c⁻ cells and cDC as CD123⁻CD11c⁺ cells. cDC1 and cDC2 subpopulations were discriminated by their expression of CD141 and CD1c.



Supplemental Table 1 – Primers used for DNASE1 genotyping

DNASE1						
Accession NG_009285 Transcript ID NM_005223.3						
ID		Sequence (5'→3')	Length	Tm	GC%	Product length
DNASE1_5UTR	F	TCCTGACTTTCGACCTTGGC	20	59.97	55.00	650
	R	ACCCCGCCACTCATTCTTG	20	60.61	55.00	
DNASE1_EX1a	F	CTTCAGACGTCCAGTCTCCG	20	59.83	60.00	872
	R	CCAGGCCTCAGGTCCAGTAA	20	60.91	60.00	
DNASE1_EX1b	F	CCAAGAAATTACTGGACCTGAGGC	24	61.40	50.00	522
	R	AAAATGTCTGATAACAAGGCCAAAG	25	58.54	36.00	
DNASE1_EX1c	F	ACGGGATAGGAACCTTTGGC	20	59.74	55.00	614
	R	TCCTACAACGTCCAGAAAGCC	21	60.00	52.38	
DNASE1_EX2	F	GTTTGGCTTTCTGGACGTTGT	21	59.60	47.62	656
	R	ATGTCATAGCGGCTCAGGATCT	22	61.09	50.00	
DNASE1_EX3-4	F	CTTTGTGGCGCTGTAGGGT	19	60.30	57.89	482
	R	TAGGACAAACTACTTCCCTGCTC	23	59.49	47.83	
DNASE1_EX5-6	F	CTCCTGGGAAGCAGGAGTG	19	60.9	63.2	674
	R	CTGGGAGGGTCTCACATAGC	20	59.7	60	
DNASE1_EX7-8	F	ATGTCCAAGAGAAATGGGGCT	21	59.36	47.62	799
	R	GTCTGGGCTGAGCCTACCTG	20	61.97	65.00	
DNASE1_EX9	F	GTATGTGTCCTCCCTGCACA	21	60.00	52.38	364
	R	CATGGTGGGCCGCTTGAAT	19	61.05	57.89	

Supplemental Table 2 – Primers used for DNASE1L3 genotyping

DNASE1L3						
Accession NG_032070 Transcript ID NM_004944.4						
ID		Sequence (5'->3')	Length	Tm	GC%	Product length
DNASE1L3_EX1	F	TCCTCAGAGAACTGAAAGTTGC	22	58.27	45.45	415
	R	CAAGCCAGCTTCTACATTCCC	21	58.98	52.38	
DNASE1L3_EX2	F	CACTCAGTGCAATACTTAAAAACAG	25	57.16	36.00	311
	R	CAACACTGGCTGTGTGAACTG	21	59.94	52.38	
DNASE1L3_EX3	F	GCGTATGGAGGCAGATTGGA	20	59.89	55.00	325
	R	AGGCCCTAGTTTTGACAGC	20	59.96	55.00	
DNASE1L3_EX4	F	AGAAAGCCATGGGAACCTACA	21	59,01	47,62	353
	R	CACTGAACTGCATCGTCTACATTG	24	60,2	45,83	
DNASE1L3_EX5	F	CTGGTTTCCCTCCAGCAGTGT	21	62.27	57.14	337
	R	GCTGAAGAAAGGCCTTAAAGAATGC	25	61.13	44.00	
DNASE1L3_EX6	F	TCAGCCCATAACAGACCCTG	20	59.09	55.00	695
	R	ACATTTAATTGACTCAGCTCTGC	23	57.44	39.13	
DNASE1L3_EX7	F	GAACCATGGCAGGGACTGAT	20	59.74	55.00	633
	R	AGGGTCAAGGTCTAGTGCCC	20	60.91	60.00	
DNASE1L3_EX8	F	CCTCCCTGGTCCTAAATTTGC	21	58.62	52.38	768
	R	GATGACACTGATGCTTCCTGG	21	58.71	52.38	

Supplemental Table 3 – Antibodies used for Flow Cytometry experiments

Fluorochrome	Marker	Company	Clone	Dilution	Purpose
BV510	CD3	BD Bioscience	UCHT1/563109	1:100	T cells
VioGreen	CD8	Miltenyi	REA734	1:100	T cells
VioGreen	CD19	Miltenyi	REA675	1:100	B cells
BV510	CD56	Biologend	HCD56	1:100	NK cells
405/520	Viability	Miltenyi	-	1:1000	Viability
PerCP-700	FCeRIa	Miltenyi	REA758	1:100	Basophils
BV650	CD14	Biologend	M5E2	3:100	Monocytes
PE	CD16	Beckman Coulter	A07766	1:25	Monocytes
APC-Vio 770	CD123	Miltenyi	REA918	1:100	pDCs
PE-Vio 615	CD11c	Miltenyi	REA618	1:100	DCs
BV785	CD141	Biologend	M80	1:100	cDC1s
BV605	CD1c	BD	F10/21A3	1:100	cDC2s
VioBlue	HLA-DR	Miltenyi	REA805	1:20	

Supplemental Table 4 – List of DNASE1L3 polymorphisms identified in hospitalized patients

rsID	Genomic position (GRCh38)	Alleles ¹	Amino Acid position	Localization
rs2292677	58210912	c.-6G>A		5'UTR
rs34252389	58210856	c.51C>T		Exon 1
rs3732631	58208324	c.142-18G>T		Intron 1
rs74350392	58205547	c.244G>C	p.Gly82Arg	Exon 3
rs2070117	58205539	c.252G>A	p.Thr84=	Exon 3
rs17058970	58205515	c.276G>C	p.Arg92=	Exon 3
rs3772985	58200992	c.546+5G>T		Intron 5
rs35677470	58197909	c.616C>T	p.Arg206Cys	Exon 6
rs113844064	58197694	c.704+127G>T		Intron 6
rs1210058558 ²	58193474	c.705-35G>A		Intron 6
rs3732630	58193301	c.801+42A>G	p.Lys281=	Intron 7
rs144058112	58193270	c.801+73T>C		Intron 7
rs3732629	58193139	c.801+204G>A		Intron 7
rs34882513	58192419	c.*268delC		3' UTR

¹ : Nomenclature according to NM_004944.4 reference.

² : This variant is present in less than 3 individuals in our cohort

Supplemental Table 5 – List of DNASE1 polymorphisms identified in hospitalized patients

rsID	Genomic position (GRCh38)	Alleles ¹	Amino Acid position	Localization
NA ²	3653234	c.-1812C>T	NA	Upstream transcript
rs45564535	3653249	c.-1797A>C	NA	Upstream transcript
rs45606645	3653474	c.-1572T>C	NA	Upstream transcript
rs45626736	3653508	c.-1538G>A	NA	Upstream transcript
rs111733271 ²	3653575	c.-1471G>A	NA	Upstream transcript
NA ²	3653620	c.-1426A>T	NA	Upstream transcript
NA ²	3653653	c.-1393A>T	NA	Upstream transcript
rs960348066 ²	3653835	c.-1211A>C	NA	Upstream transcript
rs865833716	3653840	c.-1206A>C	NA	Upstream transcript
rs867920095	3653841	c.-1205A>G	NA	Upstream transcript
rs77563984	3653879	c.-1167C>T	NA	Upstream transcript
rs79356805	3653880	c.-1166C>G	NA	Upstream transcript
rs45522434 ²	3654385	c.-661C>A	NA	Upstream transcript
rs17136471	3654596	c.-450G>A	NA	Upstream transcript
rs45479597 ²	3654737	c.-309G>A	NA	5UTR
NA	3654725_3654729	c.-317_-313del	NA	5UTR
rs769858733 ²	3655050	c.-2+6C>T		Intron 1
rs117176134	3655097	c.-2+54G>C		Intron 1
NA ²	3655333_3655336	c.-1-40_-1-38del		Intron 1
rs8176922	3655358	c.-1-15C>T		Intron 1
rs34907394 ²	3655478	c.105G>C	p.Glu35Asp	Exon 2
rs146417970	3655625	c.147+105T>C		Intron 2
rs181314680	3655818	c.148-31C>G		Intron 2
rs143058517 ²	3656648	c.331G>A	p.Val111Met	Exon 5
rs34923865 ²	3656667	c.350A>C	p.Tyr117Ser	Exon 5
NA ²	3656722	c.405A>G	p.(Pro135=)	Exon 5
rs8176938 ²	3657090	c.528C>G	p.Val176=	Exon 6
NA ²	3657115	c.556A>T	p.(Met186Leu)	Exon 7
rs1452101461 ²	3657326	c.689A>G	p.His230Arg	Exon 7
rs1799892	3657408	c.704+67G>C		Intron 7
rs1053874	3657746	c.731G>A	p.(Arg244Gln)	Exon 8
NA ²	3657788	c.773A>T	p.(Gln258Leu)	Exon 8

¹ : Nomenclature according to NM_005223.4 reference

² : This variant is present in less than 3 individuals in our cohort