

**Online supplement table S1:** Sub-analysis of coagulation factor levels in patients with stable COPD and control subjects, after excluding patients with diabetes mellitus type 2

Coagulation factors levels	Control group (n=34)	COPD (n=84)	p-value <sup>a</sup>
Fibrinogen, mg/dL	337 ±57	397 ±83	0.001
FII, %	110 ±19	123 ±22	0.008
FV, %	121 ±21	131 ±24	0.044
FVII, %	109 ±18	116 ±21	0.081
FVIII, %	122 ±19	144 ±32	<0.001
FIX, %	111 (103-123)	117 (108-126)	0.096
FX, %	98 (87-108)	114 (94-135)	0.001
D-dimers, ng/mL	230 (175-395)	375 (232-590)	0.001
INR	1.01 (0.95-1.02)	1.00 (0.92-1.05)	0.971
PT, sec	14.1 (13.2-14.2)	13.6 (12.8-14.4)	0.278
aPTT, sec	29.8 ±2.7	29.0 ±3.5	0.220
Free Protein S Antigen, %	114 (97-124)	96 (87-106)	0.007
Protein C, %	115.1±16.2	110.5±16.4	0.169
Antithrombin, %	104.5±14.7	92.5±14.6	0.001

All values are presented as means ± SD or median (interquartile range). SD = standard deviation. N = 118; <sup>a</sup>Mann–Whitney *U* test

**Online supplement table S2:** Correlations of fibrinogen, FII, FV, FVII, FVIII, FIX, FX with demographic, respiratory and inflammatory parameters in patients with stable COPD

Variables	Factor I		Factor II		Factor V		Factor VII		Factor VIII		Factor IX		Factor X	
	r <sup>a</sup>	p	r	p	r	p	r	p	r	p	r	p	r	p
Age	.002	0.981	-.301	0.002	-.140	0.160	-.239	0.015	.021	0.834	-.155	0.199	-.227	0.021
BMI	-.027	0.784	.047	0.533	.047	0.640	.162	0.102	-.050	0.613	.338	0.001	-.014	0.889
PY	.051	0.606	-.500	0.613	.097	0.332	.131	0.186	-.003	0.979	-.047	0.741	.050	0.613
FEV1	.038	0.701	-.352	<0.001	-.311	0.001	-.286	0.003	-.132	0.182	-.283	0.004	-.311	0.001
CAT	-.055	0.582	.247	0.012	.187	0.039	.154	0.121	.077	0.442	.120	0.229	.172	0.083
EXC	-.079	0.429	.293	0.003	.221	0.129	.196	0.095	.168	0.090	.180	0.069	.289	0.030
TLC	-.059	0.559	.066	0.507	.027	0.785	.098	0.327	-.014	0.891	.090	0.368	.115	0.119
DLCOSB	-.129	0.192	-.142	0.152	-.136	0.172	.086	0.388	-.155	0.118	-.002	0.982	-.023	0.817
NEU	.205	0.037	.213	0.031	.042	0.674	-.026	0.791	.224	0.023	.200	0.042	.200	0.063
ESR	.578	<0.001	.003	0.978	.054	0.585	-.272	0.005	.219	0.027	.001	0.993	-.108	0.276
CRP	.388	<0.001	.133	0.181	-.035	0.728	-.040	0.690	.062	0.533	.235	0.118	-.014	0.887
LDL	.119	0.231	.220	0.020	.078	0.436	-.014	0.890	.211	0.033	.252	0.010	.383	<0.001
HOMA-IR	-.007	0.942	-.081	0.418	.096	0.334	-.104	0.297	-.065	0.512	-.050	0.615	-.165	0.096
HbA1c %	-.001	0.991	-.111	0.265	.087	0.384	-.034	0.732	.056	0.573	-.074	0.459	-.138	0.165

r<sup>a</sup> = Spearman correlation coefficient

BMI = Body Mass Index; PY = pack years; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide; NEU = neutrophils; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment for insulin resistance.

**Online supplement table S3:** Correlations of D-dimers, INR, PT, APTT, protein S, protein C, AT with demographic, respiratory and inflammatory parameters in patients with stable COPD

Variables	D-dimers		INR		PT		APTT		Protein S		Protein C		AT	
	r <sup>a</sup>	p	r	p	r	p	r	p	r	p	r	p	r	p
Age	.183	0.100	.319	0.001	.303	0.002	.210	0.033	-.375	<0.001	-.109	0.271	-.328	0.001
BMI	-.073	0.461	-.027	0.784	.009	0.925	-.168	0.090	.043	0.666	-.041	0.684	.106	0.287
PY	.219	0.026	-.089	0.369	-.085	0.393	.060	0.550	.602	0.052	.009	0.929	-.023	0.820
FEV1	-.076	0.448	.255	0.009	.245	0.013	.242	0.014	.079	0.430	-.171	0.084	-.031	0.759
CAT	.159	0.110	-.055	0.582	-.022	0.827	-.019	0.846	-.229	0.020	.121	0.222	.015	0.877
EXC	.056	0.572	-.142	0.152	-.244	0.013	-.246	0.017	-.018	0.857	.018	0.858	-.040	0.685
TLC	-.113	0.254	.016	0.872	.020	0.840	-.006	0.952	.052	0.559	-.123	0.215	.097	0.328
DLCOSB	-.199	0.044	.026	0.796	-.067	0.500	-.079	0.430	.154	0.121	-.147	0.137	-.019	0.846
NEU	-.102	0.307	.144	0.146	.059	0.557	-.175	0.077	.078	0.436	.205	0.037	-.472	0.006
ESR	.242	0.014	-.061	0.539	.152	0.125	.139	0.160	.078	0.431	-.093	0.352	-.054	0.588
CRP	.052	0.599	.164	0.097	.149	0.132	.054	0.591	.219	0.026	.072	0.469	-.219	0.026
LDL	.005	0.960	-.102	0.305	-.148	0.137	-.266	0.007	.180	0.069	.086	0.388	.138	0.163
HOMA-IR	-.030	0.767	.187	0.059	.150	0.130	.031	0.752	-.152	0.126	-.164	0.098	-.045	0.653
HbA1c %	-.077	0.442	.096	0.333	.071	0.474	.010	0.916	-.003	0.973	-.030	0.764	-.023	0.816

r<sup>a</sup> = Spearman correlation coefficient

BMI = Body Mass Index; PY = pack years; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide; NEU = neutrophils; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment for insulin resistance.

**Online supplement table S4:** Associations of demographic and clinical variables with levels of fibrinogen in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	0.027	-2.195, 2.249	0.981	0.262	-1.921, 2.445	0.812
BMI	-0.487	-4.007, 3.032	0.784	-0.602	-3.939, 2.734	0.721
Current smoking	-6.909	-39.505, 25.687	0.675	-12.675	-43.953, 18.604	0.423
PY	0.248	-0.651, 1.148	0.585	-0.100	-0.986, 0.786	0.830
NEU	0.008	0.000, 0.015	0.037	0.004	-0.003, 0.012	0.256
CRP	6.982	3.705, 10.259	<0.001	6.667	3.174, 10.159	<0.001
LDL	0.253	-0.164, 0.671	0.231	0.193	-0.221, 0.608	0.357
FEV1	0.186	-0.773, 1.144	0.701			
CAT	-1.210	-4.265, 1.145	0.582			
EXC	-4.480	-11.230, 8.270	0.597			
DLCOSB	-0.528	-1.281, 0.225	0.167			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables). <sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol.

**Online supplement table S5:** Associations of demographic and clinical variables with levels of FII in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	-0.929	-1.510, -0.348	0.002	-0.751	-1.313, -0.188	0.009
BMI	0.304	-0.660, 1.267	0.533	0.554	-0.311, 1.420	0.206
Current smoking	-4.448	-13.346, 4.449	0.324	-4.344	-12.384, 3.697	0.286
PY	-0.040	-0.287, 0.207	0.748	-0.167	-0.408, 0.065	0.137
NEU	0.002	0.001, 0.004	0.031	0.000	-0.002, 0.002	0.868
CRP	0.656	-0.309, 1.622	0.181	0.686	-0.208, 1.579	0.131
LDL	0.134	0.021, 0.246	0.020	0.115	0.008, 0.222	0.035
FEV1	-0.469	-0.715, -0.233	<0.001	-0.394	-0.694, -0.094	0.011
CAT	4.880	1.155, 8.915	0.012			
EXC	6.497	2.082, 10.911	0.0041	2.998	-2.091, 8.090	0.245
DLCOSB	-0.144	-0.351, 0.062	0.169			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables).

<sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol, forced expiratory volume in 1 second, and history of exacerbations.

**Online supplement table S6:** Associations of demographic and clinical variables with levels of FV in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	-0.477	-1.145, 0.191	0.160	-0.446	-1.131, 0.239	0.199
BMI	0.252	-0.816, 1.320	0.640	0.559	-0.493, 1.612	0.294
Current smoking	1.962	-7.936, 11.860	0.695	2.552	-0.493, 1.612	0.608
PY	0.146	-0.126, 0.418	0.290	0.091	-0.193, 0.375	0.527
NEU	0.001	-0.002, 0.003	0.674	0.000	-0.003, 0.002	0.715
CRP	-0.190	-1.268, 0.889	0.728	-0.309	-1.404, 0.787	0.577
LDL	0.050	-0.077, 0.177	0.436	0.034	-0.097, 0.164	0.611
FEV1	-0.459	-0.736, -0.182	0.001	-0.466	-0.765, -0.167	0.003
CAT	3.593	1.429, 6.243	0.039			
EXC	3.880	-1.155, 8.915	0.129			
DLCOSB	-0.162	-0.390, 0.067	0.164			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>b</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables). <sup>c</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol and forced expiratory volume in 1 second.

**Online supplement table S7:** Associations of demographic and clinical variables with levels of FVIII in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	0.052	-0.804, 0.909	0.904	0.445	-0.429, 1.319	0.315
BMI	-0.315	-1.671, 1.042	0.646	-0.259	-1.595, 1.077	0.701
Current smoking	-5.053	-17.593, 7.487	0.426	-3.760	-16.287, 8.768	0.553
PY	0.110	-0.237, 0.457	0.531	0.026	-0.329, 0.380	0.886
NEU	0.004	0.001, 0.007	0.008	0.004	0.001, 0.007	0.015
CRP	0.390	-0.979, 1.758	0.573	-0.068	-1.466, 1.331	0.924
LDL	0.172	0.014, 0.331	0.033	0.161	-0.005, 0.327	0.058
FEV1	-0.289	-0.655, 0.176	0.119			
CAT	2.537	-2.443, 4.518	0.280			
EXC	4.510	-1.896, 10.916	0.166			
DLCOSB	-0.255	-0.544, 0.034	0.083			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables). <sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol.

**Online supplement table S8:** Associations of demographic and clinical variables with levels of FX in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	-0.708	-1.307, -0.110	0.021	-0.403	-0.973, 0.167	0.164
BMI	-0.069	-1.043, 0.905	0.889	0.241	-0.635, 1.117	0.586
Current smoking	1.987	-7.032, 11.005	0.663	3.271	-4.923, 11.465	0.430
PY	0.102	-0.147, 0.350	0.418	-0.025	-0.261, 0.212	0.837
NEU	0.002	-0.001, 0.004	0.063	0.001	-0.001, 0.003	0.326
CRP	-0.071	-1.054, 0.913	0.887	-0.347	-1.258, 0.565	0.452
LDL	0.226	0.118, 0.333	<0.001	0.210	0.102, 0.319	<0.001
FEV1	-0.418	-0.670, -0.165	0.001	-0.394	-0.643, -0.145	0.002
CAT	4.038	-0.480, 6.627	0.083			
EXC	5.034	0.500, 9.567	0.030			
DLCOSB	-0.016	-0.226, 0.195	0.882			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables).

<sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol, and forced expiratory volume in 1 second.

**Online supplement table S9:** Associations of demographic and clinical variables with levels of D-dimers in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	0.006	-0.003, 0.015	0.198	0.004	-0.005, 0.013	0.387
BMI	-0.006	-0.021, 0.008	0.377	-0.003	-0.018, 0.011	0.642
Current smoking	0.023	-0.112, 0.157	0.739	0.018	-0.116, 0.153	0.786
PY	0.006	0.002, 0.009	0.002	0.006	0.002, 0.009	0.004
NEU	-0.001	0.000, 0.000	0.497	-0.001	0.000, 0.000	0.680
CRP	0.004	-0.011, 0.019	0.598	0.001	-0.014, 0.016	0.896
LDL	0.001	-0.002, 0.002	0.928	0.000	-0.002, 0.001	0.743
FEV1	-0.001	-0.005, 0.003	0.514			
CAT	0.003	-0.008, 0.013	0.639			
EXC	-0.006	-0.075, 0.063	0.864			
DLCOSB	-0.004	-0.007, 0.001	0.015			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide. D-Dimers were entered as log10 in univariate and multivariate analysis.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables).

<sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol.

**Online supplement table S10:** Associations of demographic and clinical variables with levels of Protein S in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	-0.965	-1.437, -0.494	<0.001	-1.021	-1.507, -0.535	<0.001
BMI	0.176	-0.629, 0.981	0.666	0.247	-0.496, 0.990	0.511
Current smoking	2.688	-4.758, 10.133	0.476	3.464	-3.499, 10.426	0.326
PY	0.060	-0.145, 0.266	0.562	0.051	-0.146, 0.248	0.609
NEU	0.001	-0.001, 0.002	0.436	0.000	-0.002, 0.001	0.704
CRP	0.902	0.108, 1.695	0.026	0.960	0.183, 1.737	0.016
LDL	0.088	-0.007, 0.182	0.069	0.042	-0.050, 0.134	0.371
FEV1	0.087	-0.131, 0.306	0.430			
CAT	-1.893	-3.257, -1.532	0.020			
EXC	-0.593	-4.429, 3.243	0.760			
DLCOSB	0.134	-0.036, 0.303	0.121			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables).

<sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol.

**Online supplement table S11:** Associations of demographic and clinical variables with levels of AT in patients with stable COPD

Variables	Univariate			Multivariate <sup>b</sup>		
	$\beta$	95% CI	p-value <sup>a</sup>	$\beta$	95% CI	p-value
Age	-0.522	-0.818, -0.225	0.001	-0.499	-0.792, -0.206	0.001
BMI	0.267	-0.228, 0.761	0.287	0.251	-0.197, 0.699	0.269
Current smoking	0.098	-4.800, 4.997	0.968	1.639	-2.561, 5.840	0.440
PY	-0.058	-0.193, 0.777	0.398	-0.046	-0.165, 0.073	0.445
NEU	-0.001	-0.002, -0.001	0.003	-0.002	-0.003, -0.001	<0.001
CRP	-0.593	-1.114, -0.072	0.026	-0.429	-0.898, -0.040	0.038
LDL	0.042	-0.017, 0.100	0.163	0.014	-0.041, 0.070	0.611
FEV1	-0.021	-0.156, 0.114	0.759			
CAT	0.328	-2.789, 4.375	0.877			
EXC	0.468	-1.899, 2.835	0.696			
DLCOSB	-0.010	-0.116, 0.095	0.846			

BMI = Body Mass Index; PY = pack years; NEU = neutrophils; CRP = C-reactive protein; LDL = low-density lipoprotein cholesterol; FEV1 = Forced expiratory volume in 1 second; CAT = COPD assessment test; EXC = exacerbations; DLCOSB = diffusing capacity of lung for carbon monoxide.

<sup>a</sup>Bonferroni correction was adopted for multiple analyses, and Bonferroni corrected P value was 0.0045 (0.05/11 variables).

<sup>b</sup>Multivariate analysis was adjusted for age, body mass index, current smoking, pack years, neutrophils, C-reactive protein and low-density lipoprotein cholesterol.

## **Figure legends**

### FIGURE 1

Selection flow chart for patients with stable COPD and non-COPD control subjects.

### FIGURE 2

Levels of fibrinogen FII, FV, FVIII, FX, and D-dimers in control subjects (n = 42) and patients with stable COPD (n = 103). Boxplots display median with interquartile range and whiskers show minimum and maximum values (\**P* < 0.05, \*\**P* < 0.001, Mann-Whitney test).

### FIGURE 3

Levels of coagulation inhibitors AT and protein S in control subjects (n = 42) and patients with stable COPD (n = 103). Boxplots display median with interquartile range and whiskers show minimum and maximum values (\**P* < 0.05, \*\**P* < 0.001, Mann-Whitney test).

### FIGURE 4

Levels of coagulation factors II, V, VIII, and X in control subjects (n = 42) and Groups A-D of patients with stable COPD (n = 103), classified according to GOLD COPD 2021 guidelines (\**P* < 0.05, Kruskal-Wallis test). Group A, n = 28; Group B, n = 27; Group C, n = 15; Group D, n = 33.

### ONLINE SUPPLEMENTARY FIGURE S1

Levels of coagulation factors II, V, and X in patients with stable COPD according to exacerbation history. Boxplots display median with interquartile range and whiskers show minimum and maximum values (\**P* < 0.05, Mann-Whitney test). Exacerbations <2, n = 78; Exacerbations ≥ 2, n = 25.

### ONLINE SUPPLEMENTARY FIGURE S2

Levels of FX and Protein S in patients with stable COPD according to CAT score. Boxplots display median with interquartile range and whiskers show minimum and maximum values (\**P* < 0.05, Mann-Whitney test). CAT < 10, n = 43; CAT ≥ 10, n = 60.

### ONLINE SUPPLEMENTARY FIGURE S3

Levels of coagulation factors II, V, and X in patients with stable COPD according to FEV1% predicted. Boxplots display median with interquartile range and whiskers show minimum and maximum values (\**P* < 0.05, Mann-Whitney test). FEV1 ≥ 50%, n = 62; FEV1 <50%, n = 41.