Figure S1 Flowchart, exclusion/inclusion criteria for the present study.
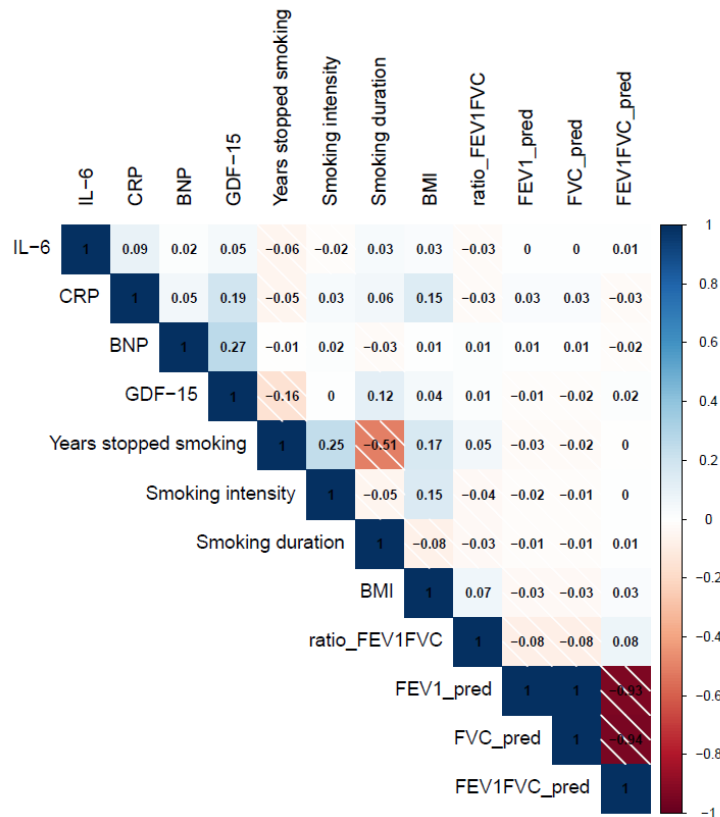

Figure S2 Spearman's partial correlations adjusted by age and sex among plasma levels of interleukin 6 (IL-6), growth/differentiation factor-15 (GDF-15), N-terminal pro-brain natriuretic protein (NT-proBNP) and C-reactive protein (CRP), sociodemographic covariates and smoking history. The calculations were made within the subcohort (n=1,678).

Table S1 Odds Ratios for moderate-severe COPD [stages 2-4] (n=258) and PRISm (n=295) across quartiles of biomarkers from the LUSI cohort [CT screening arm]

Biomarkers		Unadjusted			Adjusted[1]		
		OR	95%CI	P_{trend}	OR	95%CI	P_{trend}
COPD (stages 2-4)							
Quartile 1 GDF-15 ref	n=48						
Quartile 2 GDF-15	n=62	1.34	0.90–2.00		1.12	0.74–1.69	
Quartile 3 GDF-15	n=68	1.49	1.01–2.22		1.09	0.72–1.65	
Quartile 4 GDF-15	n=80	1.81	1.24–2.67	0.002	1.11	0.73–1.70	0.686
Quartile 1 IL-6 ref	n=37						
Quartile 2 IL-6	n=52	1.46	0.94–2.28		1.38	0.88–2.18	
Quartile 3 IL-6	n=81	2.44	1.63–3.73		2.24	1.47–3.47	
Quartile 4 IL-6	n=88	2.71	1.82–4.12	<0.001	2.49	1.63–3.86	<0.001
Quartile 1 CRP ref	n=50						
Quartile 2 CRP	n=60	1.32	0.88–1.98		1.31	0.87–1.99	
Quartile 3 CRP	n=61	1.35	0.91–2.03		1.29	0.85–1.96	
Quartile 4 CRP	n=87	2.06	1.41–3.03	<0.001	1.97	1.33–2.96	0.001
Quartile 1 BNP ref	n=53						
Quartile 2 BNP	n=60	1.20	0.81–1.80		1.05	0.70–1.58	
Quartile 3 BNP	n=64	1.30	0.88–1.93		1.06	0.71–1.59	
Quartile 4 BNP	n=81	1.72	1.18–2.55	0.005	1.19	0.80–1.80	0.419
PRISm							
Quartile 1 GDF-15 ref	n=49						
Quartile 2 GDF-15	n=60	1.26	0.84–1.88		1.23	0.82–1.85	
Quartile 3 GDF-15	n=79	1.76	1.19–2.56		1.69	1.14–2.51	
Quartile 4 GDF-15	n=107	2.50	1.77–3.69	<0.001	2.32	1.58–3.45	<0.001
Quartile 1 IL-6 ref	n=49						
Quartile 2 IL-6	n=63	1.33	0.90–1.99		1.25	0.84–1.87	
Quartile 3 IL-6	n=81	1.79	1.23–2.64		1.54	1.04–2.30	
Quartile 4 IL-6	n=102	2.40	1.67–3.49	<0.001	2.02	1.38–3.00	<0.001
Quartile 1 CRP ref	n=69						
Quartile 2 CRP	n=66	1.10	0.75–1.59		1.00	0.68–1.46	
Quartile 3 CRP	n=69	1.16	0.80–1.68		0.99	0.68–1.46	
Quartile 4 CRP	n=91	1.61	1.14–2.31	0.007	1.32	0.91–1.91	0.146
Quartile 1 NT-proBNP ref	n=74						
Quartile 2 NT-proBNP	n=63	0.89	0.62–1.28		0.89	0.60–1.27	
Quartile 3 NT-proBNP	n=69	0.95	0.66–1.37		0.98	0.68–1.41	
Quartile 4 NT-proBNP	n=89	1.32	0.94–1.86	0.085	1.33	0.92–1.91	0.102

[1], logistic regression models adjusted by age, sex body mass index and smoking history; GDF-15, growth/differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic protein.

Table S2 Risk of lung cancer by quartiles of biomarker measurements in the screening arm (n=52), control arm (n=13) and in both arms combined (n=65) for those early stage lung cancer cases

Biomarkers	CT screening arm[1]				Control arm[1]				CT screening arm + control arm[1]			
	$N_{cases}/N_{non-cases}$	OR	95% CI	P_{trend}	$N_{cases}/N_{non-cases}$	OR	95% CI	P_{trend}	$N_{cases}/N_{non-cases}$	OR	95% CI	P_{trend}
Lung cancer cases												
Quartile 1 GDF-15 ref	n=7/564				n=4/308				n=11/872			
Quartile 2 GDF-15	n=14/460	2.04	0.83–5.49		n=2/407	0.31	0.04–1.65		n=16/867	1.20	0.55–2.70	
Quartile 3 GDF-15	n=14/420	2.00	0.80–5.42		n=2/446	0.24	0.03–1.34		n=16/866	1.04	0.47–2.36	
Quartile 4 GDF-15	n=17/377	2.36	0.96–6.42	0.108	n=5/483	0.52	0.12–2.44	0.531	n=22/860	1.25	0.58–2.81	0.67
Quartile 1 IL-6 ref	n=6/463				n=2/415				n=8/878			
Quartile 2 IL-6	n=10/458	1.59	0.58–4.75		n=5/407	2.29	0.48–16.35		n=15/865	1.78	0.76–4.48	
Quartile 3 IL-6	n=16/452	2.51	0.99–7.21		n=3/412	1.44	0.23–11.37		n=19/864	2.22	0.98–5.51	
Quartile 4 IL-6	n=20/448	3.09	1.25–8.79	0.010	n=3/410	1.40	0.21–11.25	0.971	n=23/858	2.64	1.18–6.53	0.022

[1], Cox regression models adjusted by age, sex, Body Mass Index and smoking history. GDF-15, growth/differentiation factor-15; IL-6, interleukin 6.

Table S3 Risk of lung cancer by quartiles of biomarker measurements in the screening arm (n=88) additionally adjusted by lung function impairment (COPD or PRISm)

Biomarkers	$N_{cases}/N_{non-cases}$	CT screening arm[1]		
		OR	95% CI	P_{trend}
Lung cancer cases (n=88)				
Quartile 1 GDF-15 ref	n=11/560			
Quartile 2 GDF-15	n=19/455	1.79	0.84–3.97	
Quartile 3 GDF-15	n=25/409	2.19	1.06–4.79	
Quartile 4 GDF-15	n=33/361	2.84	1.40–6.17	0.001
Quartile 1 IL-6 ref	n=12/457			
Quartile 2 IL-6	n=17/451	1.34	0.63–2.95	
Quartile 3 IL-6	n=28/440	2.03	1.01–4.33	
Quartile 4 IL-6	n=31/437	1.98	0.97–4.25	0.042
Quartile 1 CRP ref	n=19/502			
Quartile 2 CRP	n=15/467	0.80	0.39–1.61	
Quartile 3 CRP	n=29/433	1.72	0.93–3.23	
Quartile 4 CRP	n=25/383	1.42	0.75–2.75	0.022
Quartile 1 NT-proBNP ref	n=24/488			
Quartile 2 NT-proBNP	n=25/480	0.83	0.45–1.51	
Quartile 3 NT-proBNP	n=13/420	0.43	0.21–0.87	
Quartile 4 NT-proBNP	n=26/397	0.70	0.37–1.31	0.121

[1], logistic regression models additionally adjusted by lung function impairment (COPD or PRISm). GDF-15, growth/differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic protein.

Table S4 Hazard Ratios for all-cause mortality in the screening arm (n=221) by quartiles of biomarker measurements

Biomarkers	$N_{cases}/N_{non-cases}$	CT screening arm[1]			CT screening arm[2]		
		HR	95% CI	P_{trend}	HR	95% CI	P_{trend}
All-cause mortality							
Quartile 1 GDF-15 ref	n=31/540						
Quartile 2 GDF-15	n=39/435	1.35	0.82–2.24		1.24	0.75–2.07	
Quartile 3 GDF-15	n=60/374	2.14	1.34–3.47		1.82	1.13–2.97	
Quartile 4 GDF-15	n=91/303	3.75	2.39–6.02	<0.001	3.08	1.94–4.96	<0.001
Quartile 1 IL-6 ref	n=26/443						
Quartile 2 IL-6	n=43/425	1.55	0.93–2.63		1.42	0.85–2.42	
Quartile 3 IL-6	n=62/406	2.13	1.31–3.57		1.71	1.03–2.88	
Quartile 4 IL-6	n=90/378	3.44	2.14–5.67	<0.001	2.60	1.60–4.34	<0.001
Quartile 1 CRP ref	n=49/472						
Quartile 2 CRP	n=44/438	0.92	0.59–1.43		0.89	0.56–1.35	
Quartile 3 CRP	n=61/401	1.47	0.97–2.24		1.37	0.90–2.17	
Quartile 4 CRP	n=67/341	1.81	1.19–2.76	0.001	1.51	0.99–2.33	0.015
Quartile 1 NT-proBNP ref	n=51/461						
Quartile 2 NT-proBNP	n=44/461	0.70	0.45–1.09		0.70	0.44–1.09	
Quartile 3 NT-proBNP	n=42/391	0.71	0.45–1.11		0.70	0.44–1.10	
Quartile 4 NT-proBNP	n=84/339	1.35	0.90–2.05	0.301	1.31	0.86–2.01	0.091

[1], Cox regression models adjusted by age, sex, body mass index and smoking history; [2], Cox regression models adjusted by age, sex, body mass index, smoking history, and spirometry (COPD and PRISm. Abbreviations: GDF-15, growth/differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic protein.