Supplementary Figure 1

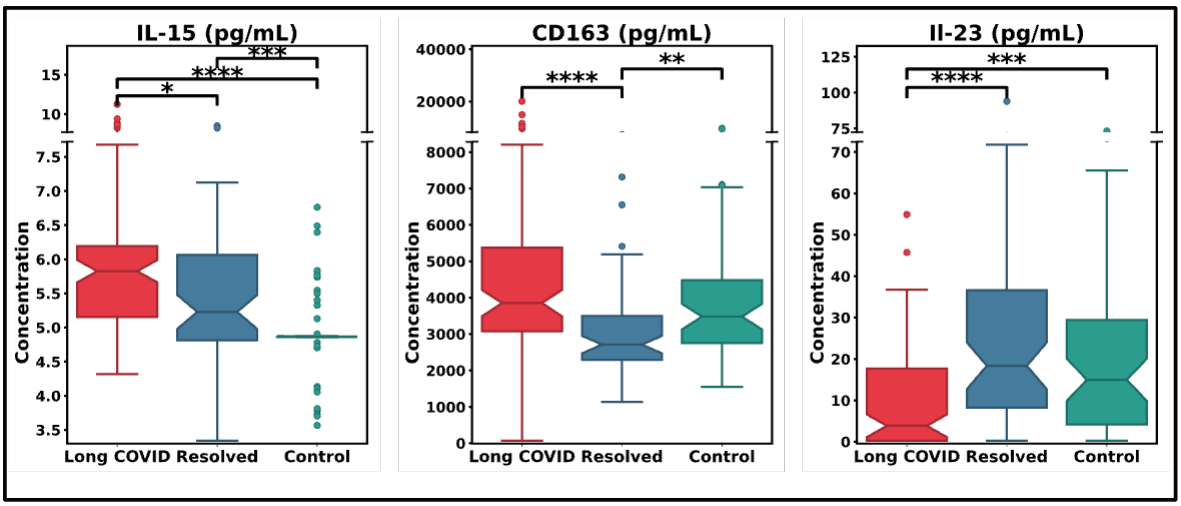


Figure Supp. 1: Distribution of concentrations for the less significant cytokines and activation markers. *The significance of differences between groups was assessed with FDR-adjusted Dunn's post hoc test. Significance levels are indicated as: **** for $p < 0.0001$, *** for $p < 0.001$, ** for $p < 0.01$, and * for $p < 0.05$.*

Supplementary Figure 2

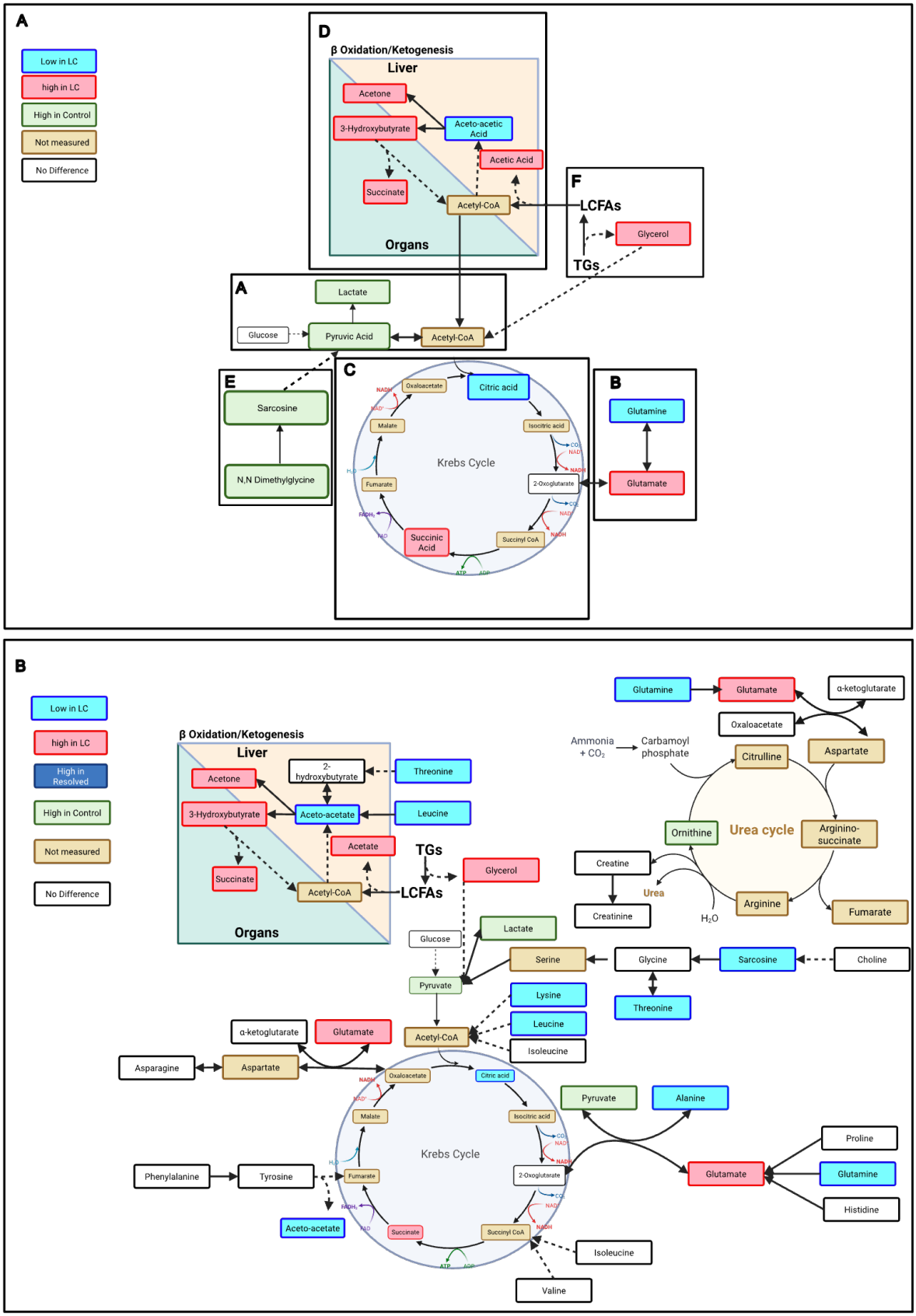


Figure Supp. 2 *Schematic diagram of the metabolic pathways involving the significant variables.*

Supplementary Figure 3

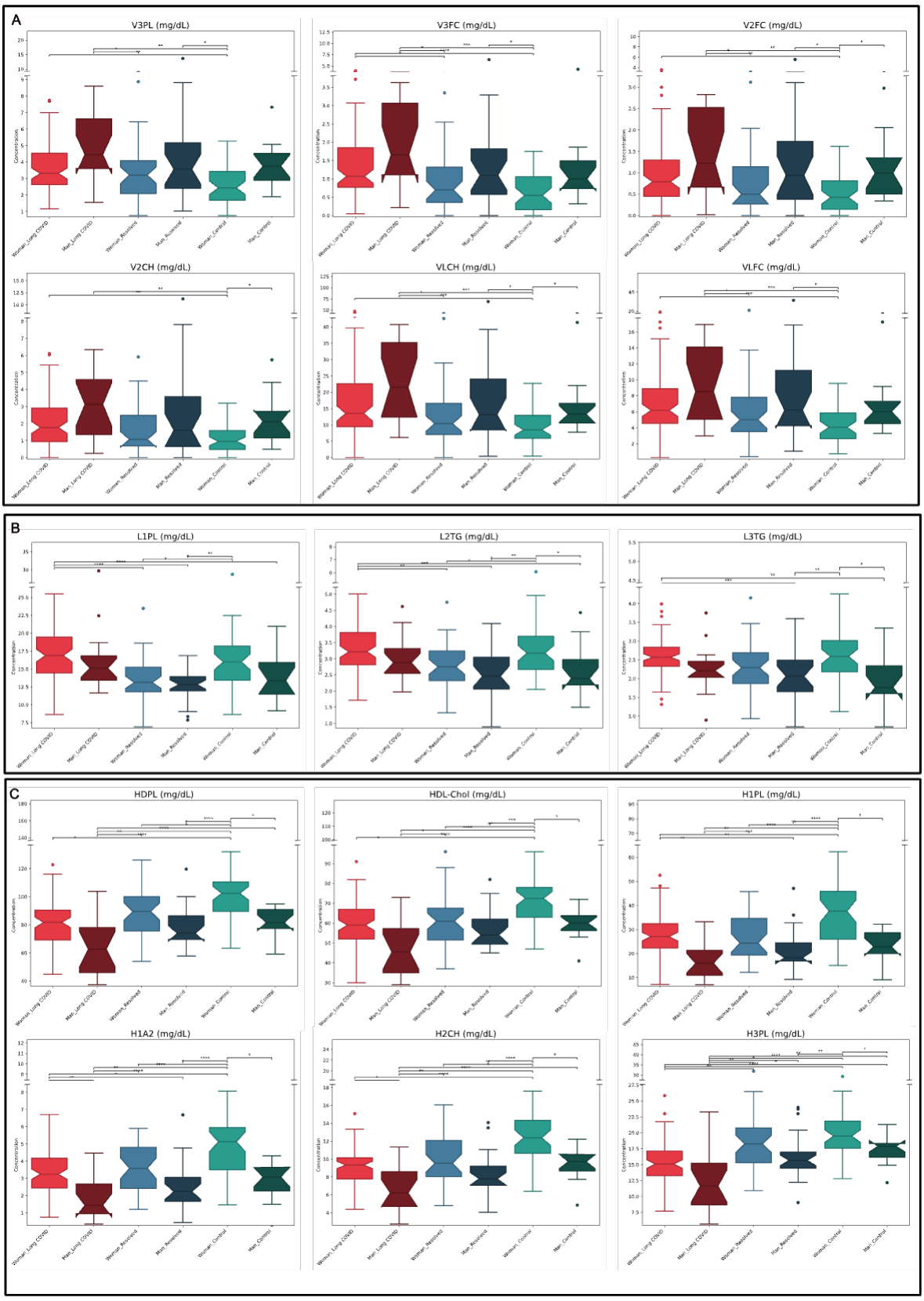


Figure Supp. 3: Distribution of concentrations for lipoprotein subfractions VLDL (A), LDL (B) and HDL (C) between men and women across the three different groups. *The significance of differences between groups was assessed using FDR-adjusted Mann-Whitney tests. Significance levels are indicated as: **** for p < 0.0001, *** for p < 0.001, ** for p < 0.01, and * for p < 0.05.*

Supplementary Figure 4

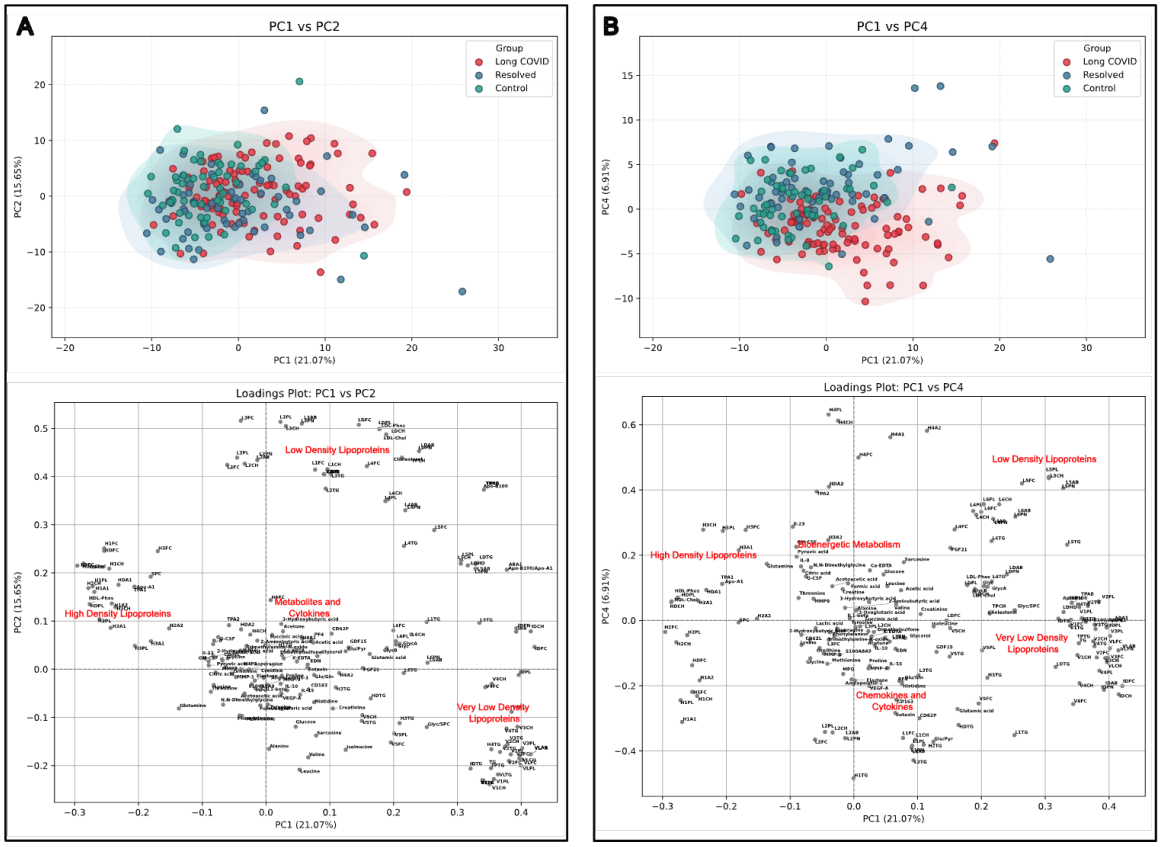
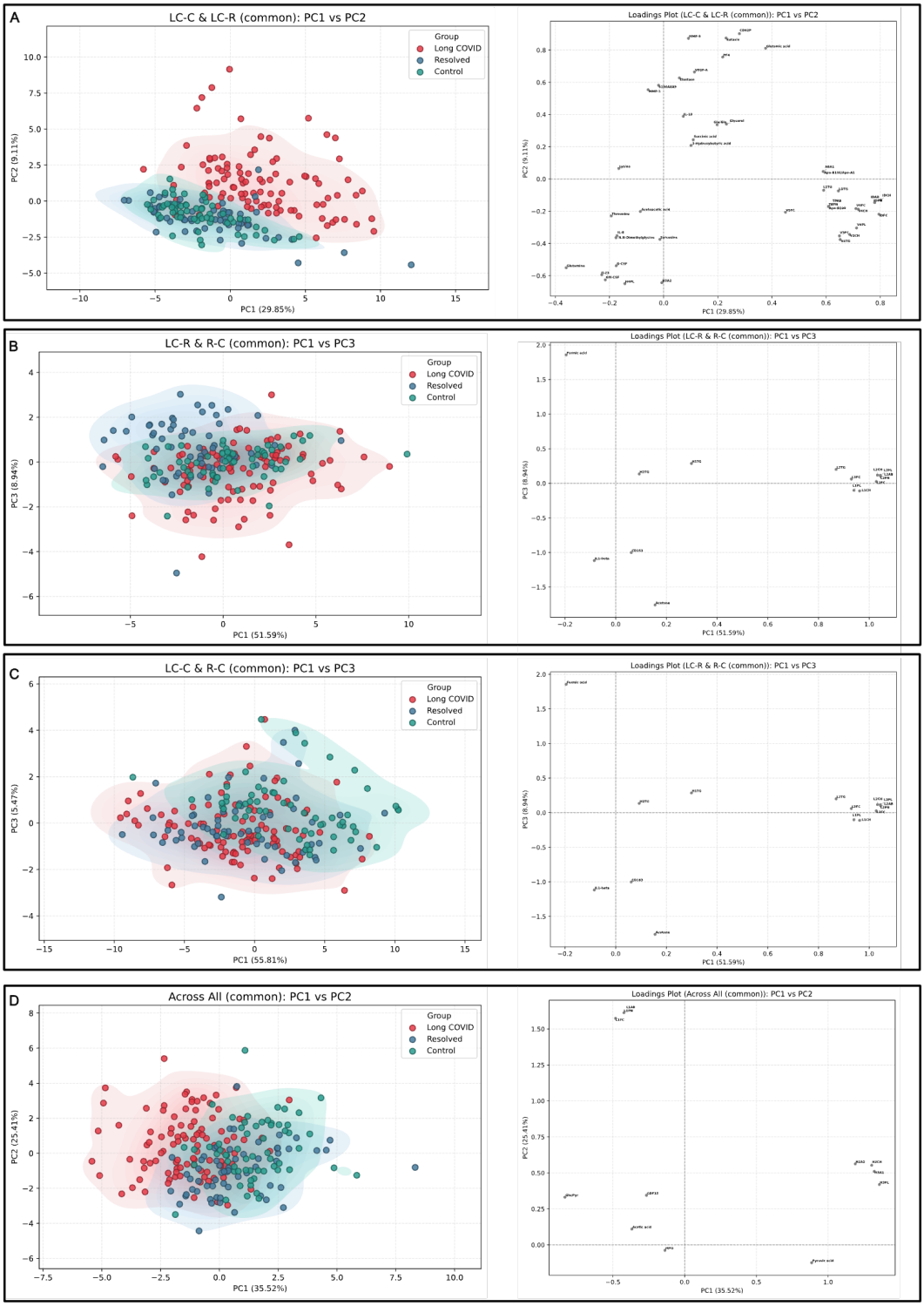


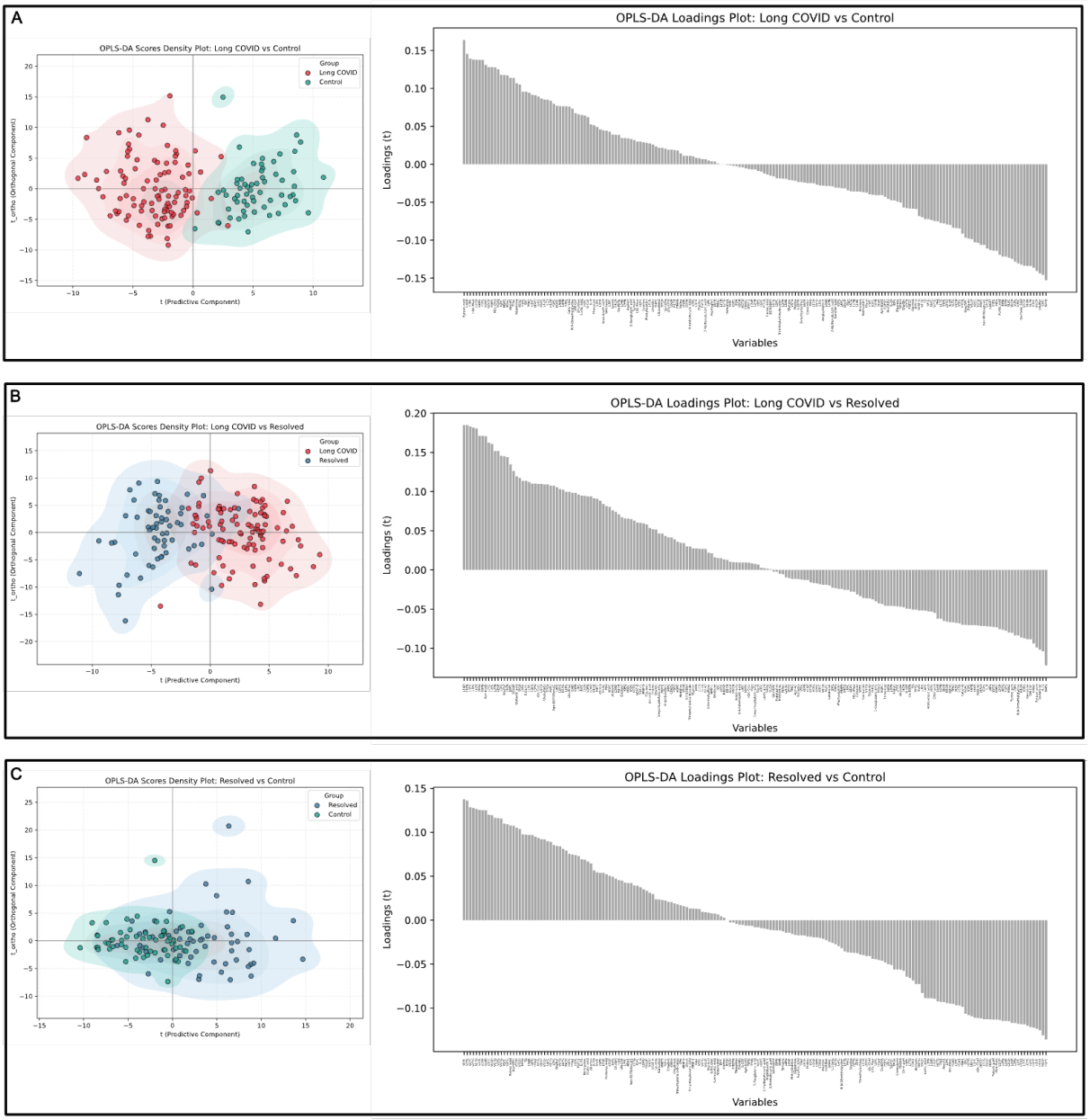
Figure Suppl. 4: Principal component analysis (PCA)*. The upper plot shows the scores plot of PC1 versus PC2 (A) and PC1 versus PC4 (B) vectors showing the distribution of control, resolved COVID, and long COVID cases based on biomolecule levels. Loadings for PC1 and PC2, indicating the principal contributing features. Positive and negative loadings reflect the direction and magnitude of the contribution of each feature to the principal components. The control and resolved COVID samples are partially separated from long COVID cases along the axes corresponding to the first two components. Lipoproteins were among the main drivers of this separation, suggesting that their dysregulation is a key feature of long COVID.*

Supplementary Figure 5



Supplementary Figure 5. Principal component analysis (PCA) of grouped variable fold changes. *The left panels show PCA score plots, illustrating sample clustering after the elimination of noise from variable with minimal or negative contributions to variance. The analysis highlights biologically relevant variance due to variables unique to long COVID (A), resolved COVID (B), or control (C) groups, and those differentially abundant across all three groups (D). The right panels display the corresponding loading plots, indicating the biomolecular variables making the largest contributions to the observed separations. s*

Supplementary Figure 6



Supplementary Figure 6. Pairwise orthogonal partial least squares discriminant analysis (OPLS-DA). *Left panels show the OPLS-DA score plots, illustrating group separation along the predictive (x) axis. Right panels display the corresponding loading plots, indicating variables that covary with each group. (A) OPLS-DA between long COVID and control, (B) between long COVID and resolved COVID, and (C) between resolved COVID and control.*

Supplementary Figure 7

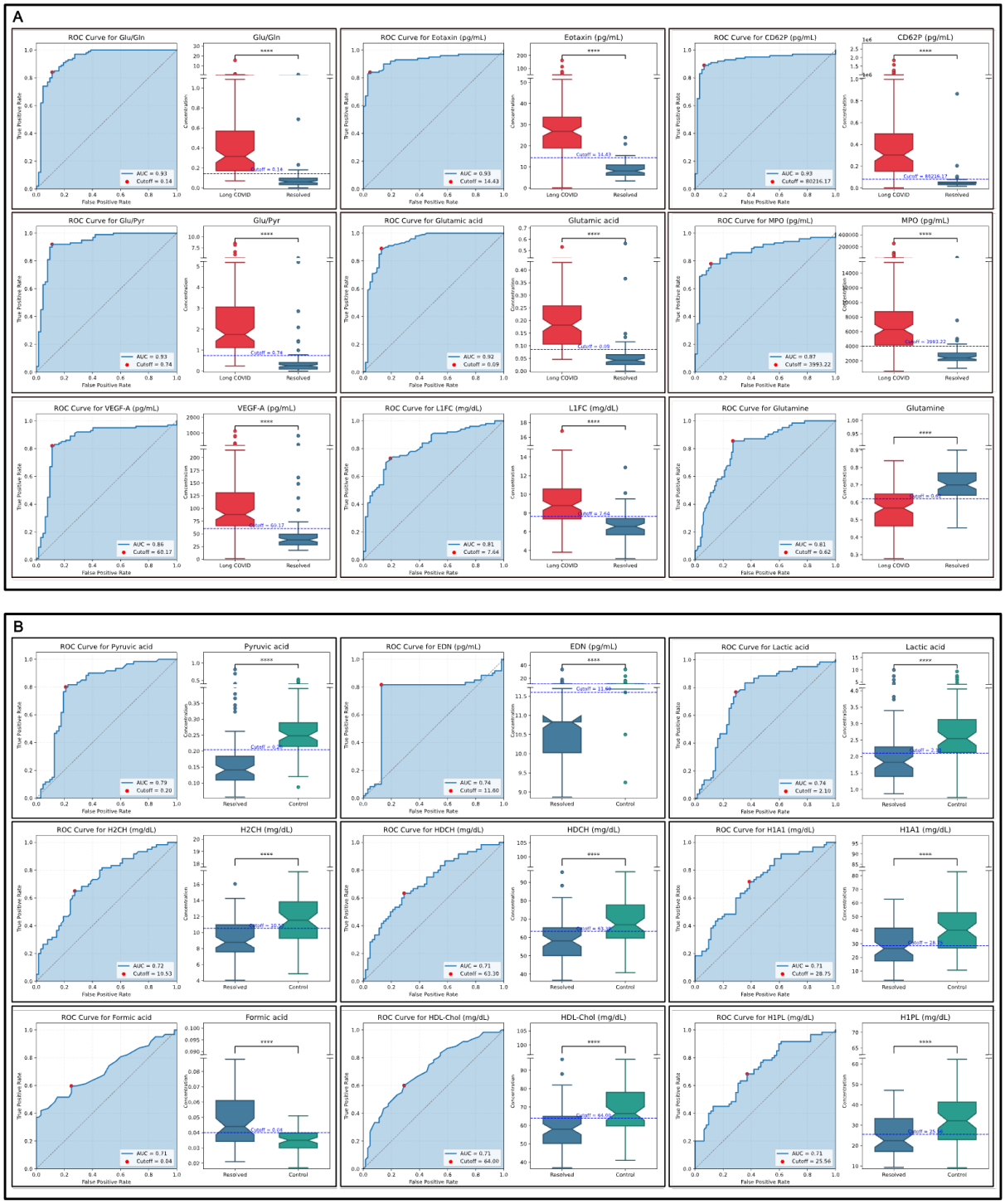


Figure Supp. 7: Receiver-operating characteristic curve (ROC) for the biomolecules with the greatest area under the curve (AUC) for long COVID vs. resolved COVID (A) and resolved COVID vs. control comparisons (B). The figure on the left shows the AUC ROC curve with the cutoff closest to the top left corner, the figure on the right shows the box plot with a Mann Whitney test presenting the optimal cutoff from ROC AUC.

Supplementary Figure 8

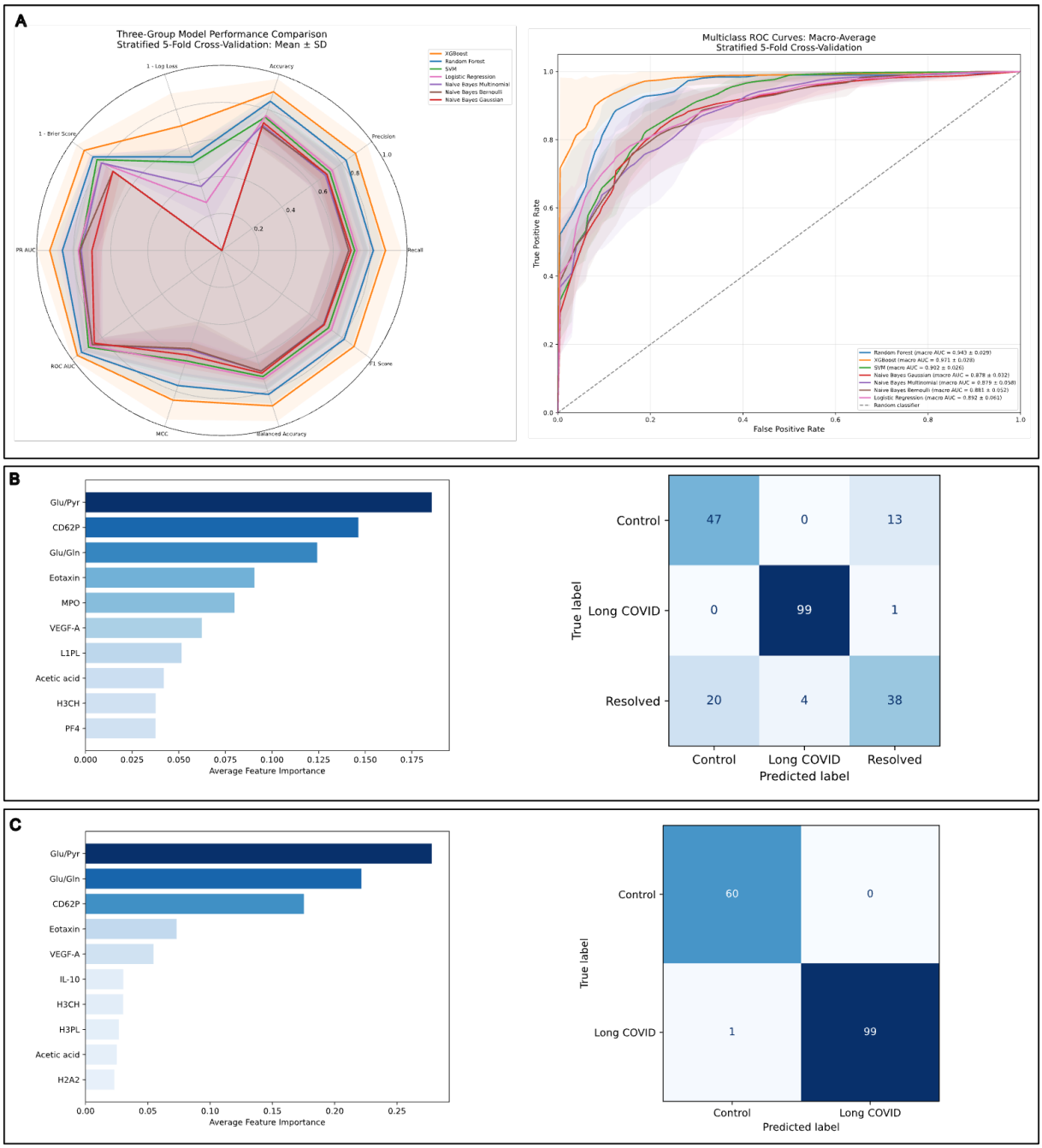


Figure 8. Comparative performance of different machine learning models for the classification of three different groups. *Performance of discriminatory power of machine learning models. Left: Radar plot showing model performance across classification metrics, including accuracy, precision, recall, F1 score, balanced accuracy, Matthews correlation coefficient (MCC), ROC AUC, precision–recall (PR) AUC, Brier score, and log loss. Right: Multiclass receiver operating characteristic (ROC) curves showing macro-averaged performance (A).* ***Random Forest classifier feature importance (left) and confusion matrix (right) for the three groups (B) and for LC and UC (C).***

Table 1. Charactaristics of the Participants

Description	Total	Long COVID	Resolved	Control	P value
Number of samples	**222**	**100**	**62**	**60**	
Median age (year) at sampling date (25–75%)	45.0 (35.5–52.5)	47.0 (39.0–53.0)	36.5 (30.2–47.0)	47.0 (36.0–55.0)	0.0012
Age class (year)					0.0023
≥45	106 (47.7%)	56 (56.0%)	18 (29.0%)	32 (53.3%)	
<45	116 (52.3%)	44 (44.0%)	44 (71.0%)	28 (46.7%)	
Sex					0.0463
Man	53 (23.9%)	16 (16.0%)	23 (37.1%)	14 (23.3%)	
Woman	164 (73.9%)	79 (79.0%)	39 (62.9%)	46 (76.7%)	
Transgender	1 (0.5%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	
Diabetes type 1 or type 2					0.9141
Missing	8 (3.6%)	8 (8.0%)	0 (0.0%)	0 (0.0%)	
Yes	9 (4.1%)	4 (4.0%)	3 (4.8%)	2 (3.3%)	
No	205 (92.3%)	88 (88.0%)	59 (95.2%)	58 (96.7%)	
Obesity					0.2441
Missing	8 (3.6%)	8 (8.0%)	0 (0.0%)	0 (0.0%)	
Yes	7 (3.2%)	2 (2.0%)	4 (6.5%)	1 (1.7%)	
No	207 (93.2%)	90 (90.0%)	58 (93.5%)	59 (98.3%)	
Center (Site)					0
Fournier	122 (55%)	100 (100.0%)	22 (35.5%)	0 (0.0%)	
Bordeaux	100 (45.0%)	0 (0.0%)	40 (64.5%)	60 (100.0%)	

Table 2. Medical Conditions of Long COVID Patients

Characteristics	Sample size	Percentage	95%CI	
Median age at sampling date (IQR 25-75%)	45.0 37.0-51.0			
Health professional				
No	72	75.79	65.92	83.99
Yes	23	24.21	16.01	34.08
Obesity History				
No	93	97,89	92,60	99,74
Yes	2	2,11	0,26	7,40
Diabetes history				
No	91	95.79	89.57	98.84
Yes	4	4.21	1.16	10.43
Arterial hypertension history				
No	91	95.79	89.57	98.84
Yes	4	4.21	1.16	10.43
Asthma history				
No	88	92.63	85.41	96.99
Yes	7	7.37	3.01	14.59
Allergic condition				
No	41	43.16	33.03	53.72
Yes	54	56.84	46.28	66.97
Autoimmune condition				
No	65	68.42	58.08	77.58
Yes	30	31.58	22.42	41.92
Personal autoimmune				
No	79	83.16	74.10	90.06
Yes	16	16.84	9.94	25.90
Familial autoimmune				
No	76	80.00	70.54	87.51
Yes	19	20.00	12.49	29.46
History of anxiety disorders				
No	63	66.32	55.89	75.69
Yes	32	33.68	24.31	44.11
History of antidepressant treatment				
Missing data	3	3.26	0,66	8.95
No	87	94.57	84.08	96.29
Yes	5	5.43	1.73	11.86

Tabacco				
No	68	78.16	61.40	80.36
Stop	9	10.34	4.42	17.22
Yes	10	11.49	5.16	18.51
Sports before COVID				
No	44	47.31	36.02	56.85
Yes	49	52.69	41.10	61.96

Table 3. Description of the first acute COVID episode among the long COVID

Characteristics	Sample size	Percentage	95%CI	
Period of 1st COVID episode				
Missing data	1	1.06	0.03	5.73
2019	2	2.13	0.26	7.40
2020	60	63.83	52.64	72.83
2021	18	19.15	11.63	28.28
2022	14	14.89	8.30	23.49
Types of symptoms at acute COVID				
Number of symptoms (median IQR) 5 (4-7)				
Less than 4 symptoms	20	21.05	13.36	30.62
4 at 5 symptoms	31	32.63	23.36	43.02
6 at 8 Symptoms	34	35.79	26.21	46.28
More than 8 symptoms	10	10.53	5.16	18.51
Asthenia				
No	35	36.84	27.17	47.36
Yes	60	63.16	52.64	72.83
Thermoregulation disorders (Fever. shivering)				
No	34	35.79	26.21	46.28
Yes	61	64.21	53.72	73.79
Smell disorder (Anosmia. dysosmia)				
No	39	41.05	31.06	51.62
Yes	56	58.95	48.38	68.94
Dysgeusia				
No	47	49.47	39.05	59.93
Yes	48	50.53	40.07	60.95
Other ENT symptoms (Rhinorrhoea. Odynophagia)				
No	62	65.26	54.80	74.74
Yes	33	34.74	25.26	45.20
Osteo-muscular symptoms (Arthralgia. Myalgia)				
No	69	72.63	62.52	81.28
Yes	26	27.37	18.72	37.48
Cardiothoracic symptoms (Cough. shortness of breath. chest oppression. tachycardia)				
No	21	22.11	14.23	31.78
Yes	74	77.89	68.22	85.77
Digestive symptoms (diarrhoea. nausea. vomiting)				
No	66	69.47	59.18	78.51
Yes	29	30.53	21.49	40.82
Neurological symptoms				
No	37	38.95	29.11	49.50
Yes	58	61.05	50.50	70.89
Ophthalmic symptoms				
No	89	93.68	86.76	97.65
Yes	6	6.32	2.35	13.24
Cutaneous symptoms				
No	86	90.53	82.78	95.58
Yes	9	9.47	4.42	17.22

Table 4. Description of long COVID severity

	Sample size	Percentage	95%CI	
Symptoms				
Number of symptoms at acute COVID phase (median IQR)	5 (4-7)			
Less than 4 symptoms	20	21.05	13.36	30.62
4 at 5 symptoms	31	32.63	23.36	43.02
6 at 8 Symptoms	34	35.79	26.21	46.28
More than 8 symptoms	10	10.53	5.16	18.51
Number of symptoms at long covid phase (median IQR)	7 (7-9)			
Less than 5 symptoms	18	18,95	11,63	28,28
5 at 6 symptoms	28	29,47	20,56	39,71
7 at 8 Symptoms	24	25,26	16,91	35,22
9 at 10 Symptoms	19	20	12,49	29,46
More than 10 symptoms	6	6,32	2,35	13,24
Scales				
Exercise intolerance				
Missing data	18	18.95	11.63	28.28
Negative (<=23)	20	21.05	13.36	30.62
Positive (> 23)	57	60.00	49.44	69.92
Severity grade				
Missing data	32	33,68	24,31	44,11
No	12	12,63	6,70	21,03
Middle	37	38,95	29,11	49,50
Severe	9	9,47	4,42	17,22
Very severe	5	5,26	1,73	11,86
Scan				
PET scan				
Missing data	54	56,84	46,28	66,97
Hypometabolism	18	18,95	11,63	28,28
Discrete hypometabolism	8	8,42	3,71	15,92
Hypofixation	1	1,05	0,03	5,73
Normal	14	14,74	8,30	23,49
Activities				
Work during long COVID phase				
Missing data	26	27,37	18,72	37,48
Full time	18	18,95	11,63	28,28
No	43	45,26	35,02	55,81
Part time	8	8,42	3,71	15,92
Time off work > 1 year	76	80	70,54286	87,5079
Missing data	22	23.16	15.12	32.94

Full time	9	9.47	4.42	17.22
No	40	42.11	32.04	52.67
Part time	24	25.26	16.91	35.22
Return to work				
Missing data	22	23.16	15.12	32.94
Full time	9	9.47	4.42	17.22
No	40	42.11	32.04	52.67
Part time	24	25.26	16.91	35.22

Table 5. Description of Long COVID patients Vaccination Status

Characteristics	Sample size	Percentage	95%CI	
At least 1 dose of COVID vaccination				
Missing data	11	11,58	5,92	19,77
No	17	17,89	10,78	27,10
Yes	67	70,53	60,29	79,44
Vaccination schemes				
Missing data	15	15,79	9,12	24,70
0	17	17,89	10,78	27,10
1	25	26,32	17,81	36,35
2	19	20,00	12,49	29,46
3	18	18,95	11,63	28,28
4	1	1,05	0,03	5,73
At least one dose of m RNA				
Yes	63	66,32	55,89	75,69
At least one dose of Pfizer				
Yes	58	61,05	50,50	70,89
At least one dose of Moderna				
Yes	11	11,58	5,92	19,77
At least one dose of Astra Zeneca				
Yes	3	3,16	0,66	8,95
COVID vaccination and long COVID phase				
Missing data	40	42,11	32,04	52,67
Vaccination after long covid	27	28,42	19,64	38,60
Vaccination before long covid	28	29,47	20,56	39,71