

Supplementary data – Collagen and elastin degradation markers

SUPPLEMENTARY DATA

Supplementary figures

Figure S1: Boxplots showing the distribution of each biomarker in the exacerbation phase group (baseline) and the stable patient group (1 month). There were 299 and 200 patients with C5M, C6M, and ELP-3 measurements in the exacerbation phase group and stable phase group, respectively. 297 and 197 had measurements available for CPa9-HNE in the exacerbation phase group and stable phase group, respectively.

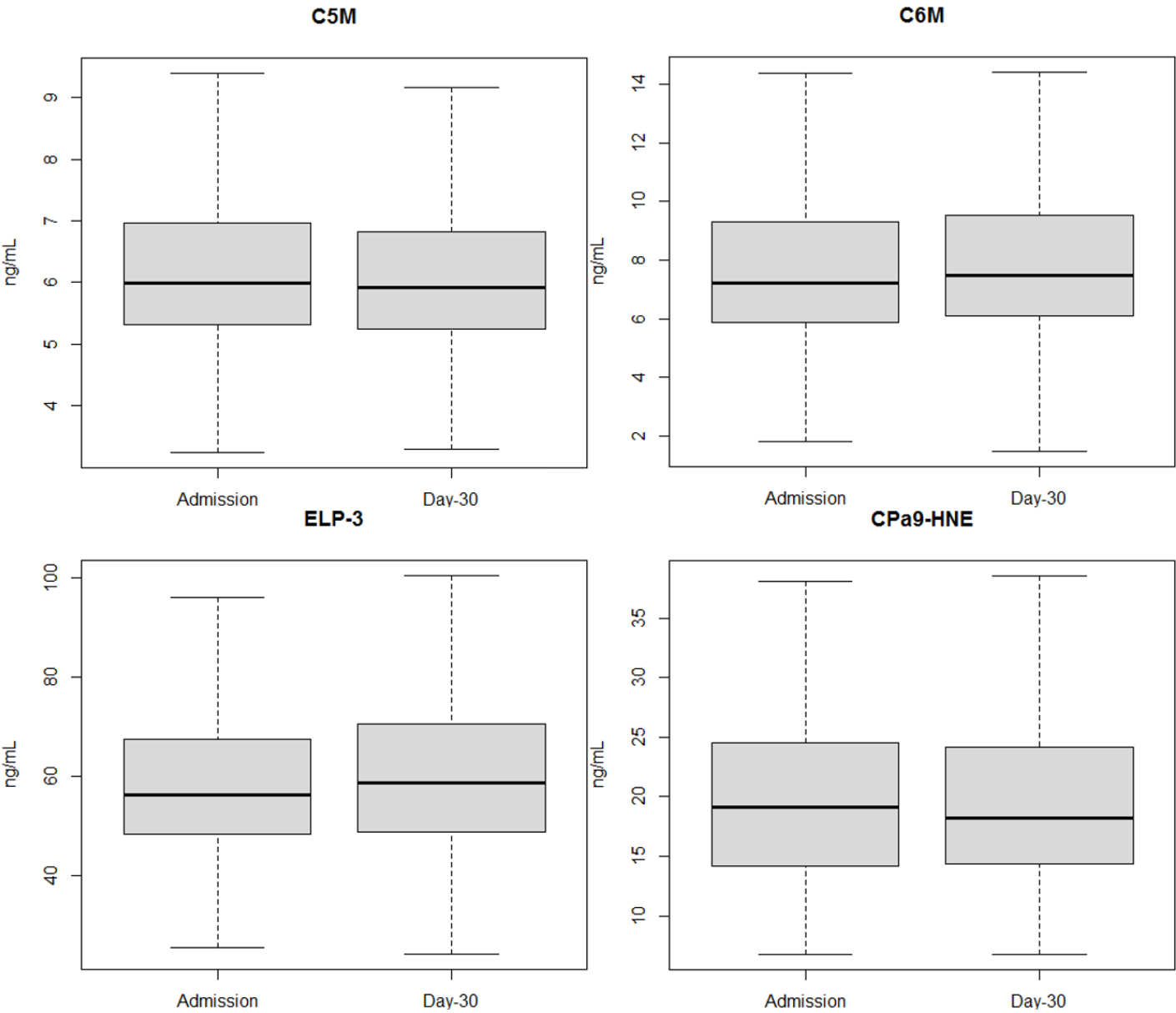


Figure S2: Graphs with paired biomarker values, showing the trajectories from admission to day-30.

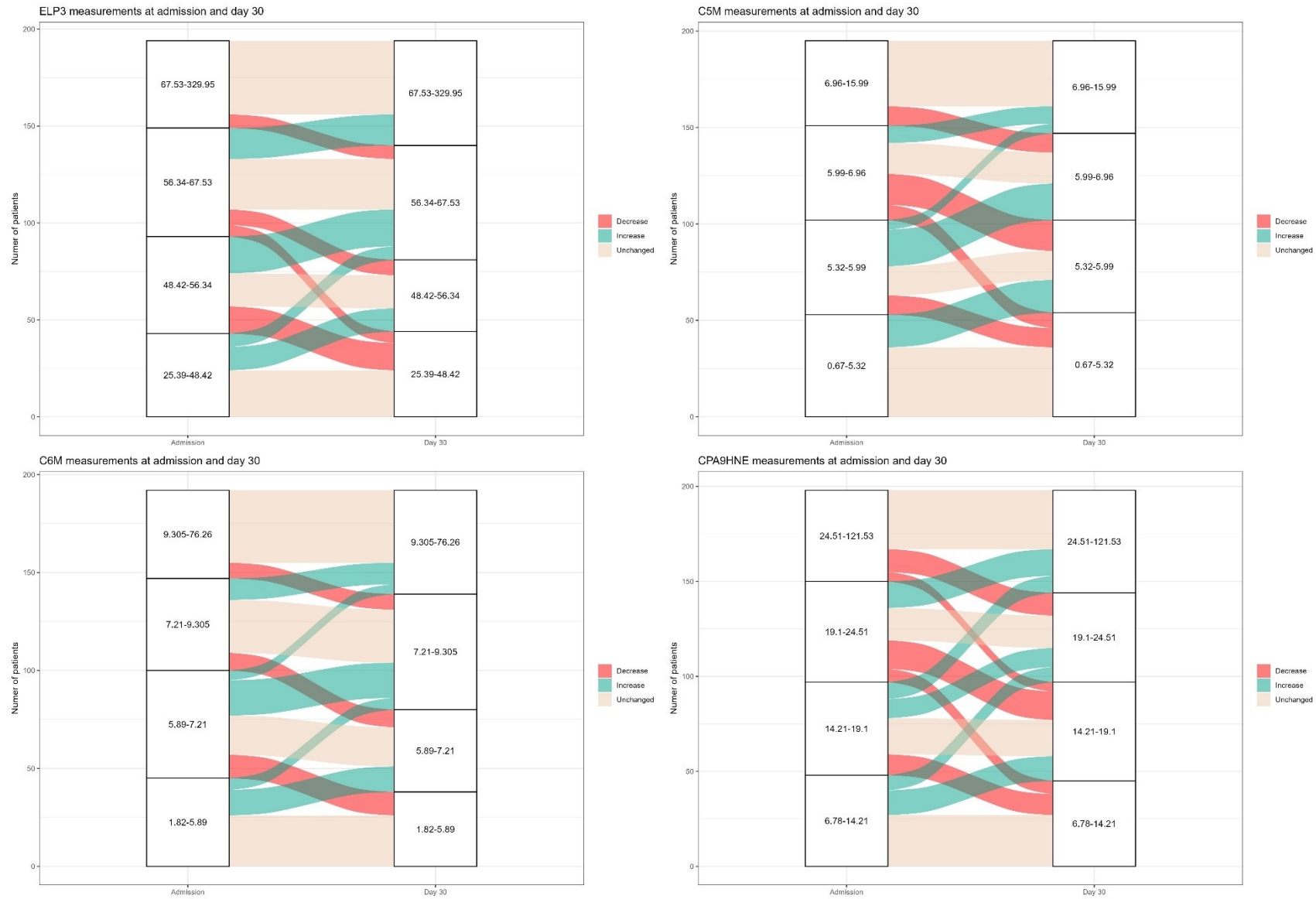


Figure S3: Kaplan-Meier curves showing the AECOPD-free survival in the exacerbation phase group for C5M (a), C6M (b), ELP-3 (c), and CPa9-HNE (d)

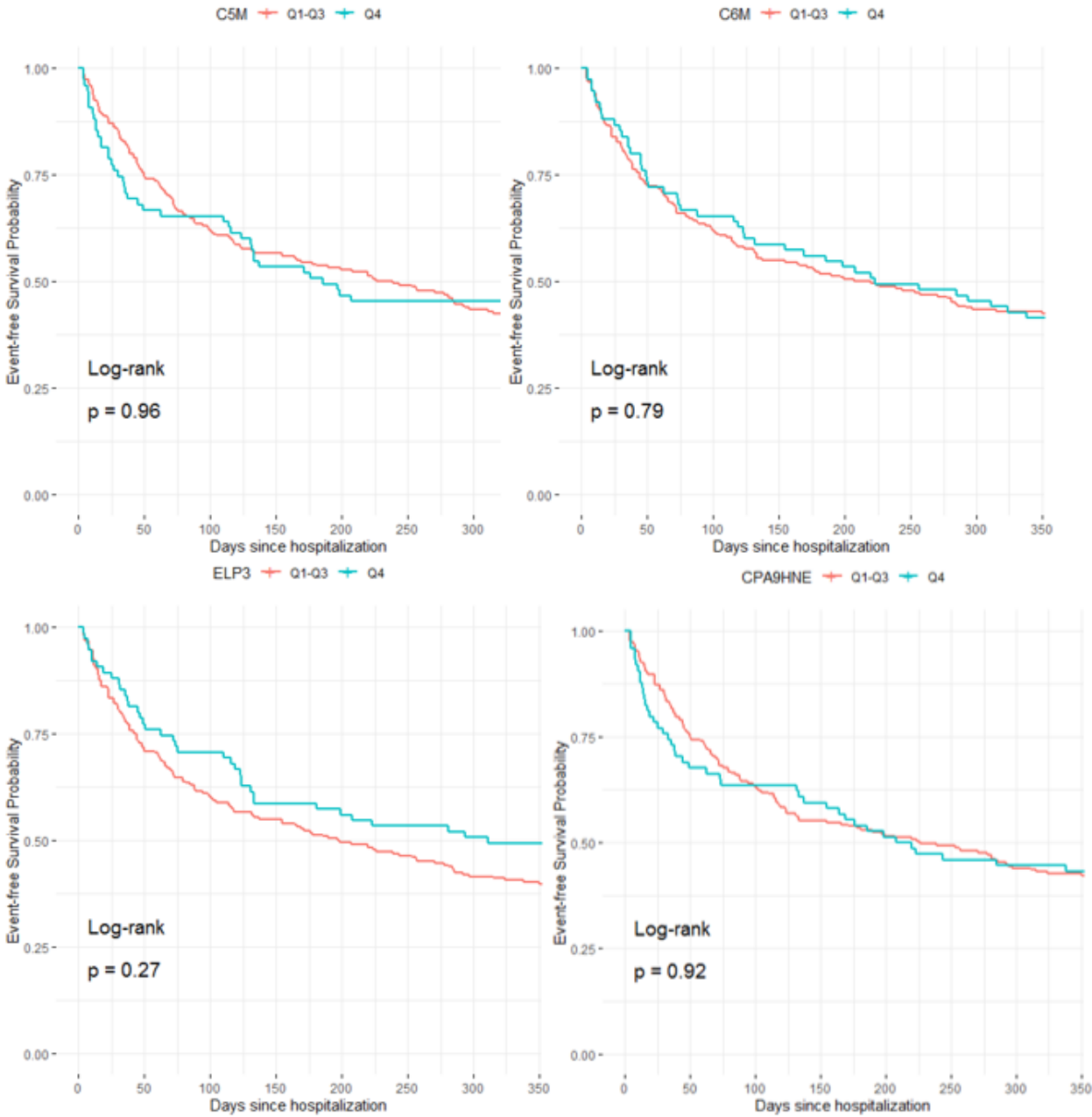


Figure S4: Kaplan-Meier curves showing the AECOPD-free survival in the stable phase group for C5M (a), C6M (b), ELP-3 (c), and CPa9-HNE (d)

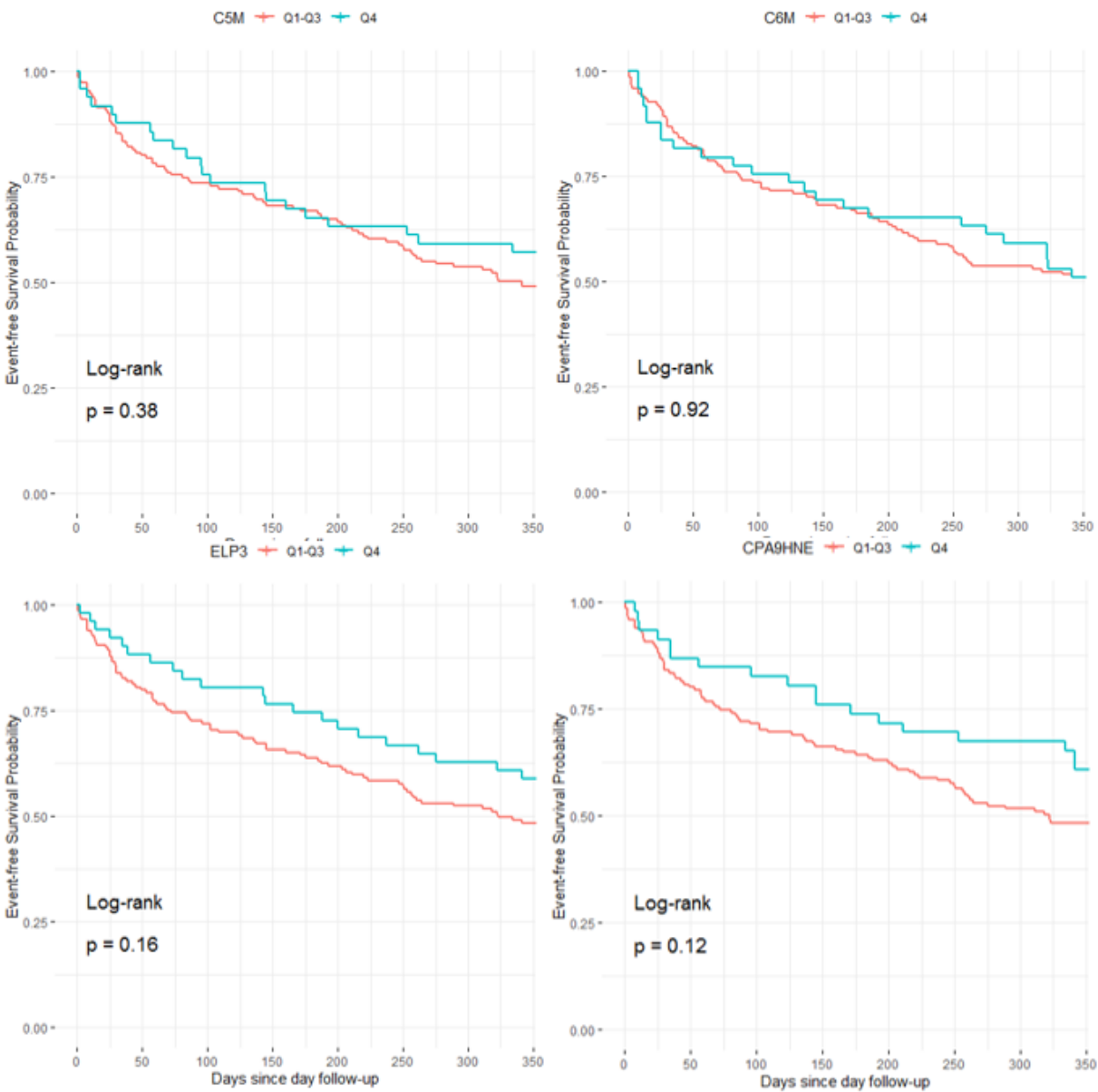


Figure S5: Receiver operating characteristics curves showing each biomarkers AUC for predicting time to readmission with AECOPD or mortality from baseline.

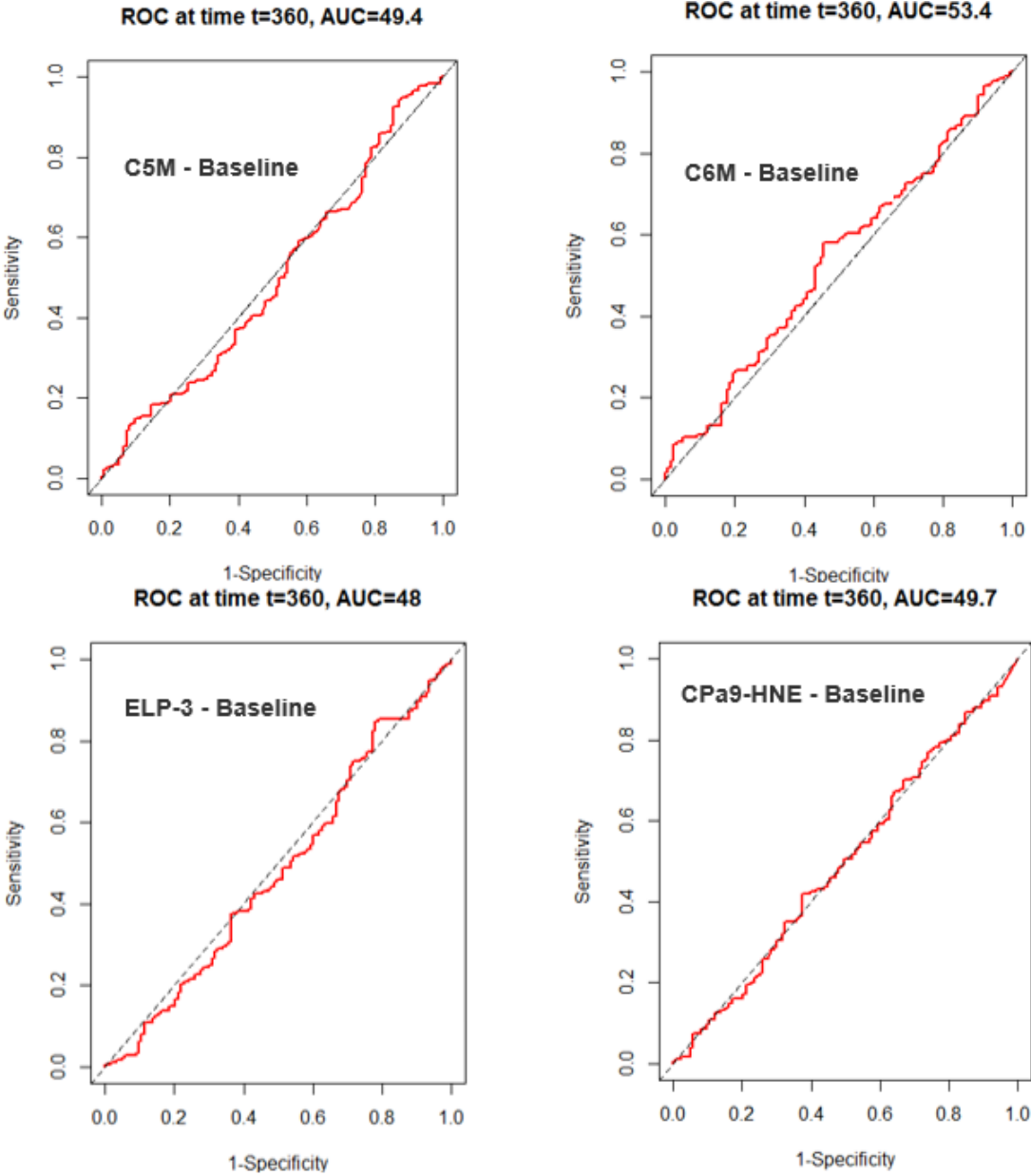
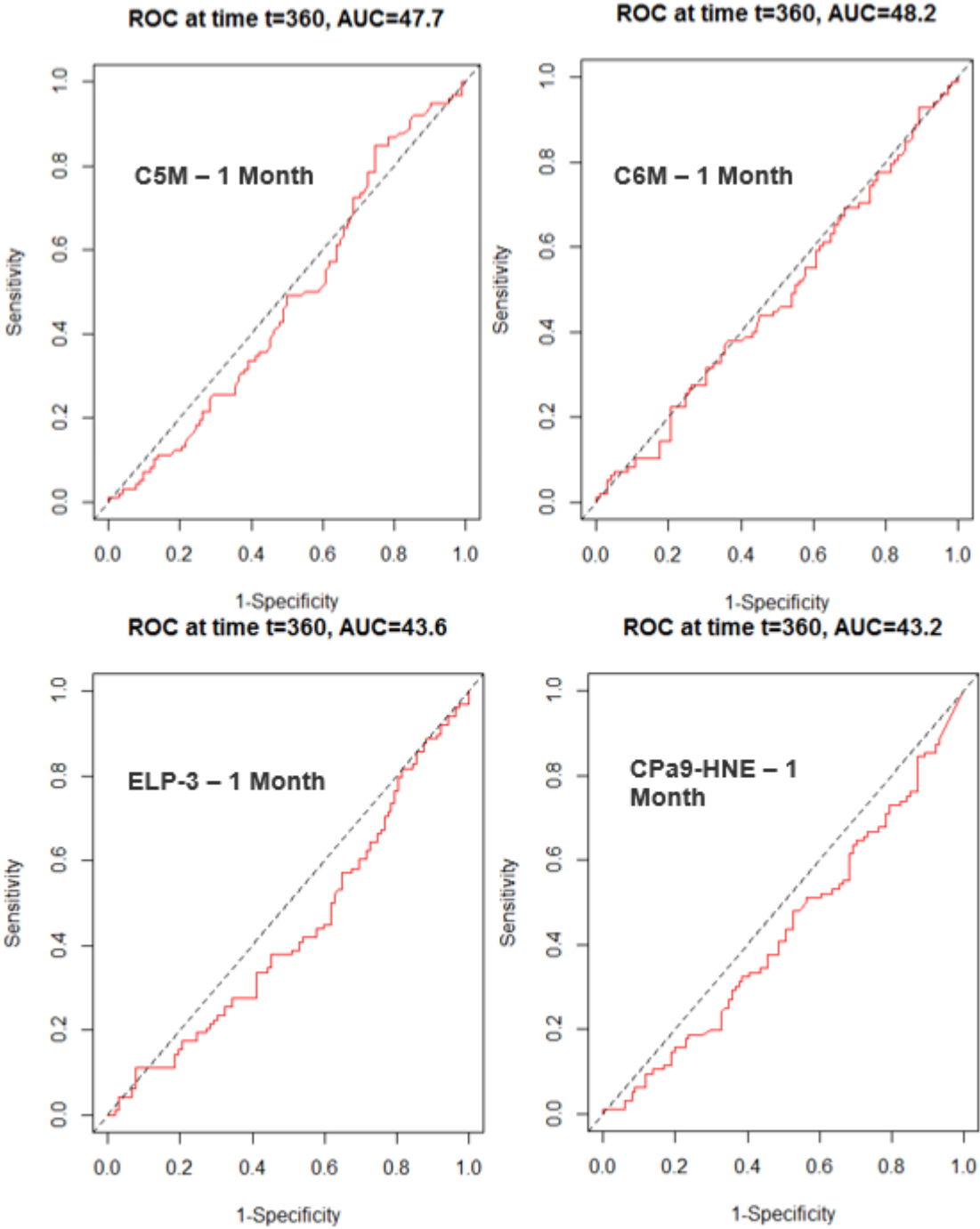


Figure S6: Receiver operating characteristics curves showing each biomarkers AUC for predicting time to readmission with AECOPD or mortality from 1 month.



Supplementary tables

Patient demographics of paired data for each biomarker in each phase:

C5M				
	Exacerbation phase		Stable phase	
	Low (Q1-Q3)	High (Q4)	Low (Q1-Q3)	High (Q4)
<i>n</i>	224	75	151	49
<i>Age (mean (SD))</i>	74.9 (9.5)	75.4 (8.2)	74.7 (9.1)	73.9 (7.6)
<i>Male (%)</i>	100 (44.6)	35 (46.7)	73 (48.3)	23 (46.9)
<i>Pack years (mean (SD))</i>	45.3 (20.0)	48.6 (17.4)	44.8 (19.6)	49.3 (18.5)
<i>FEV1% (mean (SD))</i>	42.3 (17.1)	38.5 (16.5)	41.2 (17.6)	41.0 (15.9)
<i>C5M (median (IQR))</i>	5.64 (1.08)	8.09 (1.88)	5.59 (1.03)	8.11 (3.04)
<i>CCI (mean)</i>	0.371	0.32	0.404	0.327
<i>Events</i>	134	43	77	21
<i>Time to event (mean)</i>	210	203	243	256

Table S1 - Demographics on paired data for patients in high and low biomarker groups of C5M in exacerbation phase and stable phase.

C6M				
	Exacerbation phase		Stable phase	
	Low (Q1-Q3)	High (Q4)	Low (Q1-Q3)	High (Q4)
<i>n</i>	224	75	151	49
<i>Age (mean (SD))</i>	74.8 (9.5)	75.8 (8.1)	74.1 (8.9)	75.8 (8.3)
<i>Male (%)</i>	104 (46.4)	31 (41.3)	76 (50.3)	20 (40.8)
<i>Pack years (mean (SD))</i>	45.9 (19.0)	46.8 (20.7)	44.8 (17.9)	49.6 (23.1)
<i>FEV1% (mean (SD))</i>	40.9 (17.2)	42.8 (16.4)	40.4 (17.5)	43.6 (16.1)
<i>C6M (median (IQR))</i>	6.56 (2.25)	11.3 (2.55)	6.92 (2.26)	12.0 (3.49)
<i>CCI (mean)</i>	0.34	0.4	0.318	0.592
<i>Events</i>	130	47	74	24
<i>Time to event (mean)</i>	207	213	244	253

Table S2 - Demographics on paired data for patients in high and low biomarker groups of C6M in exacerbation phase and stable phase.

ELP-3

	<i>n</i>	Exacerbation phase		Stable phase	
		Low (Q1-Q3)	High (Q4)	Low (Q1-Q3)	High (Q4)
		224	75	149	51
Age (mean (SD))		75.8 (9.1)	72.8 (9.2)	74.6 (8.4)	74.2 (9.7)
Male (%)		98 (43.8)	37 (49.3)	75 (50.3)	21 (41.2)
Pack years (mean (SD))		45.1 (19.5)	49.4 (19.1)	46.4 (19.6)	44.4 (18.8)
FEV1% (mean (SD))		40.6 (16.7)	43.7 (17.8)	39.6 (16.2)	45.8 (19.1)
ELP-3 (median (IQR))		52.5 (13.0)	81.3 (22.1)	55.5 (14.0)	86.8 (29.2)
CCI (mean)		0.384	0.28	0.376	0.412
Events		136	41	77	21
Time to event (mean)		202	227	237	272

Table S3 - Demographics on paired data for patients in high and low biomarker groups of ELP-3 in exacerbation phase and stable phase.

CPa9-HNE

	<i>n</i>	Exacerbation phase		Stable phase	
		Low (Q1-Q3)	High (Q4)	Low (Q1-Q3)	High (Q4)
		223	74	151	46
Age (mean (SD))		75.0 (9.4)	75.3 (8.3)	74.5 (8.9)	74.2 (8.3)
Male (%)		106 (47.5)	28 (37.8)	72 (47.7)	21 (45.7)
Pack years (mean (SD))		45.9 (19.7)	45.9 (17.9)	45.1 (18.9)	48.6 (20.6)
FEV1% (mean (SD))		41.7 (17.0)	40.7 (16.8)	41.6 (17.6)	39.5 (16.3)
CPa9-HNE (median (IQR))		16.7 (7.3)	28.9 (7.4)	16.6 (7.08)	28.3 (8.45)
CCI (mean)		0.381	0.284	0.424	0.283
Events		132 (59.1%)	43 (58.1%)	78 (51.7%)	18 (39.1%)
Time to event (mean)		210	207	237	277

Table S4 - Demographics on paired data for patients in high and low biomarker groups of CPa9-HNE in exacerbation phase and stable phase.

Biomarker	0%	25%	50%	75%	100%
C5M (ng/mL)	0.67	5.32	5.99	6.96	15.99
C6M (ng/mL)	1.82	5.89	7.21	9.31	76.3
ELP-3 (ng/mL)	25.4	48.4	56.3	67.5	330
CPa9-HNE (ng/mL)	6.8	14.2	19.1	24.5	122
Age	47	69	75	82	96
Pack years	5	30	47	57	124

Table S5 – Exacerbation phase cut-points for biomarkers, age and pack-years in the exacerbation phase cohort. Q1-Q3 corresponds to 0%-75% and Q4 corresponds to 75%-100%.

Biomarker	0%	25%	50%	75%	100%
C5M (ng/mL)	1.33	5.27	5.94	6.83	15.23
C6M (ng/mL)	1.48	6.22	7.76	9.61	99.69
ELP-3 (ng/mL)	24.24	48.86	58.49	70.20	285.84
CPa9-HNE (ng/mL)	6.78	14.63	19.32	24.69	54.30
Age	47	68.75	75	80.25	96
Pack years	5	30	48	57	124

Table S6 – Stable phase cut-points for biomarkers, age and pack-years in the stable-phase cohort. Q1-Q3 corresponds to 0%-75% and Q4 corresponds to 75%-100%.

Cox regressions from admission to readmission with exacerbation or death:

C5M baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C5M lower quartiles</i> <i>C5M upper quartile</i>	Ref 1.08	Ref (0.76-1.55)	Ref 0.668
<i>Age Q1</i> <i>Age Q2</i> <i>Age Q3</i> <i>Age Q4</i>	Ref 0.8 1.1 1.23	Ref (0.51-1.25) (0.72-1.69) (0.8-1.89)	Ref 0,33 0,652 0,34
<i>Female</i> <i>Male</i>	Ref 0.96	Ref (0.70-1.31)	Ref 0.805
<i>Pack years Q1</i> <i>Pack years Q2</i> <i>Pack years Q3</i> <i>Pack years Q4</i>	Ref 1.28 1.36 1.16	Ref (0.82-2.0) (0.88-2.11) (0.75-1.79)	Ref 0.274 0.169 0.502
<i>CCI (per unit)</i>	1.24	(1.06-1.44)	0.006*
<i>Standard therapy</i> <i>Eosinophil guided</i>	Ref 0.84	Ref (0.62-1.14)	Ref 0.258

Table S7 – full cox regression model output for C5M in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

C6M baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C6M lower quartiles</i> <i>C6M upper quartile</i>	Ref 1.04	Ref (0.74-1.47)	Ref 0.81
<i>Age Q1</i> <i>Age Q2</i> <i>Age Q3</i> <i>Age Q4</i>	Ref 0.81 1.11 1.24	Ref (0.52-1.26) (0.72-1.7) (0.8-1.9)	Ref 0.347 0.645 0.334
<i>Female</i> <i>Male</i>	Ref 0.97	Ref (0.71-1.32)	Ref 0.827
<i>Pack years Q1</i> <i>Pack years Q2</i> <i>Pack years Q3</i> <i>Pack years Q4</i>	Ref 1.28 1.36 1.17	Ref (0.82-1.99) (0.88-2.11) (0.76-1.8)	Ref 0.276 0.17 0.475

<i>CCI (per unit)</i>	1.23	(1.06-1.44)	0.007*
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.83	(0.61-1.13)	0.235

Table S8 – full cox regression model output for C6M in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

ELP-3 baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>ELP-3 lower quartiles</i>	Ref	Ref	Ref
<i>ELP-3 upper quartile</i>	0.91	(0.63-1.31)	0.609
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.79	(0.51-1.25)	0.318
<i>Age Q3</i>	1.08	(0.7-1.67)	0.724
<i>Age Q4</i>	1.23	(0.8-1.89)	0.351
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	0.96	(0.71-1.31)	0.812
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.27	(0.82-1.99)	0.283
<i>Pack years Q3</i>	1.35	(0.87-2.1)	0.18
<i>Pack years Q4</i>	1.19	(0.77-1.83)	0.444
<i>CCI (per unit)</i>	1.23	(1.06-1.43)	0.007*
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.83	(0.62-1.13)	0.24

Table S9 – full cox regression model output for ELP-3 in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

CPa9-HNE baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>CPa9-HNE lower quartiles</i>	Ref	Ref	Ref
<i>CPa-9HNE upper quartile</i>	1.05	(0.74-1.51)	0.771
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.82	(0.53-1.29)	0.394

<i>Age Q3</i>	1.1	(0.72-1.7)	0.654
<i>Age Q4</i>	1.26	(0.82-1.94)	0.284
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	0.97	(0.71-1.33)	0.859
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.28	(0.82-2.0)	0.282
<i>Pack years Q3</i>	1.34	(0.86-2.08)	0.197
<i>Pack years Q4</i>	1.15	(0.75-1.78)	0.518
<i>CCI (per unit)</i>	1.24	(1.06-1.44)	0.006*
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.81	(0.6-1.1)	0.181

Table S10 – full cox regression model output for CPa9-HNE in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

Cox regressions from stable phase to exacerbation or death:

C5M stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C5M lower quartiles</i> <i>C5M upper quartile</i>	Ref 0.77	Ref (0.47-1.27)	Ref 0.311
<i>Age Q1</i> <i>Age Q2</i> <i>Age Q3</i> <i>Age Q4</i>	Ref 0.77 1.04 0.77	Ref (0.44-1.36) (0.61-1.79) (0.42-1.40)	Ref 0.373 0.881 0.392
<i>Female</i> <i>Male</i>	Ref 1.04	Ref (0.70-1.61)	Ref 0.78
<i>Pack years Q1</i> <i>Pack years Q2</i> <i>Pack years Q3</i> <i>Pack years Q4</i>	Ref 1.04 1.12 1.39	Ref (0.56-1.91) (0.62-2.03) (0.79-2.45)	Ref 0.912 0.699 0.257
<i>CCI</i>	1.31	(1.09-1.57)	0.004**
<i>Standard therapy</i> <i>Eosinophil guided</i>	Ref 1.02	Ref 0.68-1.53	Ref 0.924

Table S11 – full cox regression model output for C5M in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

C6M stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C6M lower quartiles</i> <i>C6M upper quartile</i>	Ref 0.92	Ref (0.56-1.52)	Ref 0.757
<i>Age Q1</i> <i>Age Q2</i> <i>Age Q3</i> <i>Age Q4</i>	Ref 0.76 1.05 0.78	Ref (0.43-1.33) (0.61-1.80) (0.43-1.43)	Ref 0.328 0.871 0.422
<i>Female</i> <i>Male</i>	Ref 1.06	Ref (0.70-1.61)	Ref 0.796
<i>Pack years Q1</i> <i>Pack years Q2</i> <i>Pack years Q3</i> <i>Pack years Q4</i>	Ref 1.05 1.14 1.35	Ref (0.57-1.93) (0.63-2.06) (0.77-2.38)	Ref 0.885 0.676 0.295
<i>CCI</i>	1.32	(1.10-1.58)	0.003**
<i>Standard therapy</i> <i>Eosinophil guided</i>	Ref 1.01	Ref (0.67-1.52)	Ref 0.968

Table S12 – full cox regression model output for C6M in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

ELP-3 stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>ELP-3 lower quartiles</i>	Ref	Ref	Ref
<i>ELP-3 upper quartile</i>	0.75	(0.45-1.24)	0.257
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.75	(0.43-1.32)	0.319
<i>Age Q3</i>	1.01	(0.59-1.75)	0.964
<i>Age Q4</i>	0.76	(0.42-1.39)	0.377
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.05	(0.69-1.58)	0.834
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.0	(0.54-1.85)	0.997
<i>Pack years Q3</i>	1.08	(0.60-1.97)	0.795
<i>Pack years Q4</i>	1.3	(0.74-2.3)	0.364
<i>CCI</i>	1.32	(1.10-1.58)	0.003**
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	1.02	(0.68-1.53)	0.926

Table S13 – full cox regression model output for ELP-3 in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

CPa9-HNE stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>CPa9-HNE lower quartiles</i>	Ref	Ref	Ref
<i>CPa-9HNE upper quartile</i>	0.68	(0.40-1.17)	0.163
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.78	(0.45-1.38)	0.396
<i>Age Q3</i>	1.06	(0.61-1.83)	0.842
<i>Age Q4</i>	0.75	(0.41-1.38)	0.352

<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.03	(0.68-1.57)	0.888
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.04	(0.56-1.93)	0.913
<i>Pack years Q3</i>	1.11	(0.61-2.02)	0.722
<i>Pack years Q4</i>	1.31	(0.74-2.32)	0.347
<i>CCI</i>	1,31	(1.09-1.57)	0.004**
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	1.1	(0.66-1.51)	0.988

Table S14 – full cox regression model output for CPa9-HNE in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to exacerbation or death as outcome.

Cox regressions from baseline to all-cause mortality

C5M baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C5M lower quartiles</i>	Ref	Ref	Ref
<i>C5M upper quartile</i>	0.86	(0.48-1.54)	0.617
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	1.11	(0.5-2.48)	0.797
<i>Age Q3</i>	1.75	(0.85-3.62)	0.129
<i>Age Q4</i>	3.41	(1.68-6.93)	0.001**
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.1	(0.67-1.79)	0.71
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.18	(0.59-2.36)	0.644
<i>Pack years Q3</i>	1.79	(0.92-3.48)	0.088
<i>Pack years Q4</i>	0.74	(0.36-1.56)	0.435
<i>CCI</i>	1.19	(0.94-1.49)	0.149
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.68	(0.42-1.11)	0.125

Table S15 – full cox regression model output for C5M in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

C6M baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C6M lower quartiles</i>	Ref	Ref	Ref
<i>C6M upper quartile</i>	0.75	(0.42-1.33)	0.324

<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	1.14	(0.51-2.55)	0.745
<i>Age Q3</i>	1.73	(0.84-3.58)	0.137
<i>Age Q4</i>	3.54	(1.74-7.23)	0.001***
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.09	(0.67-1.79)	0.719
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.2	(0.6-2.4)	0.613
<i>Pack years Q3</i>	1.82	(0.93-3.54)	0.079
<i>Pack years Q4</i>	0.73	(0.35-1.53)	0.406
<i>CCI</i>	1.21	(0.95-1.53)	0.119
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.7	(0.43-14)	0.15

Table S16 – full cox regression model output for C6M in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

ELP-3 baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>ELP-3 lower quartiles</i>	Ref	Ref	Ref
<i>ELP-3 upper quartile</i>	0.94	(0.52-1.69)	0.831
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	1.09	(0.49-2.43)	0.841
<i>Age Q3</i>	1.73	(0.83-3.62)	0.144
<i>Age Q4</i>	3.36	(1.65-6.82)	0.001**
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.1	(0.67-1.8)	0.701
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.18	(0.59-2.37)	0.632
<i>Pack years Q3</i>	1.78	(0.92-3.47)	0.088
<i>Pack years Q4</i>	0.73	(0.35-1.53)	0.409
<i>CCI</i>	1.19	(0.94-1.5)	0.154
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.69	(0.42-1.12)	0.131

Table S17 – full cox regression model output for ELP-3 in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

CPa9-HNE baseline cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>CPa9-HNE lower quartiles</i>	Ref	Ref	Ref
<i>CPa-9HNE upper quartile</i>	0.98	(0.55-1.73)	0.939
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	1.1	(0.49-2.46)	0.815
<i>Age Q3</i>	1.66	(0.8-3.47)	0.175
<i>Age Q4</i>	3.37	(1.66-6.83)	0.001**
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.13	(0.69-1.86)	0.616
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	1.19	(0.59-2.41)	0.62
<i>Pack years Q3</i>	1.73	(0.88-3.39)	0.111
<i>Pack years Q4</i>	0.74	(0.35-1.54)	0.414
<i>CCI</i>	1.18	(0.93-1.49)	0.174
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.66	(0.4-1.08)	0.099

Table S18 – full cox regression model output for CPa9-HNE in the exacerbation phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

Cox regressions from stable phase to all-cause mortality

C5M stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C5M lower quartiles</i>	Ref	Ref	Ref
<i>C5M upper quartile</i>	1.18	(0.52-2.68)	0.698
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.88	(0.29-2.65)	0.816
<i>Age Q3</i>	1.73	(0.64-4.64)	0.28
<i>Age Q4</i>	2.33	(0.80-6.77)	0.12
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.24	(0.6-2.59)	0.561
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	0.65	(0.19-2.28)	0.502
<i>Pack years Q3</i>	2.34	(0.86-6.37)	0.097
<i>Pack years Q4</i>	1.15	(0.40-3.29)	0.796
<i>CCI</i>	1.24	(0.93-1.65)	0.138

<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	1.08	(0.53-2.2)	0.825

Table S19 – full cox regression model output for C5M in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

C6M stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>C6M lower quartiles</i>	Ref	Ref	Ref
<i>C6M upper quartile</i>	0.55	(0.21-1.45)	0.226
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.92	(0.30-2.79)	0.882
<i>Age Q3</i>	1.59	(0.59-4.27)	0.359
<i>Age Q4</i>	2.46	(0.85-7.17)	0.099
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.16	(0.56-2.43)	0.686
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	0.67	(0.19-2.33)	0.527
<i>Pack years Q3</i>	2.52	(0.92-6.87)	0.071
<i>Pack years Q4</i>	1.19	(0.42-3.44)	0.742
<i>CCI</i>	1.32	(0.97-1.8)	0.075
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	1.02	(0.5-2.08)	0.963

Table S20 – full cox regression model output for C6M in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

ELP-3 stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>ELP-3 lower quartiles</i>	Ref	Ref	Ref
<i>ELP-3 upper quartile</i>	0.91	(0.38-2.16)	0.832
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.87	(0.29-2.65)	0.81
<i>Age Q3</i>	1.66	(0.61-4.52)	0.317
<i>Age Q4</i>	2.29	(0.79-6.63)	0.127
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.22	(0.59-2.54)	0.59

<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	0.63	(0.18-2.21)	0.472
<i>Pack years Q3</i>	2.28	(0.84-6.2)	0.105
<i>Pack years Q4</i>	1.14	(0.40-3.28)	0.803
<i>CCI</i>	1.24	(0.93-1.65)	0.142
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	1.07	(0.52-2.18)	0.854

Table S21 – full cox regression model output for ELP-3 in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

CPa9-HNE stable phase cox regression	Hazard Ratio	95% Confidence interval	p-value
<i>CPa9-HNE lower quartiles</i>	Ref	Ref	Ref
<i>CPa9-HNE upper quartile</i>	1.08	(0.46-2.53)	0.863
<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.88	(0.29-2.67)	0.825
<i>Age Q3</i>	1.75	(0.65-4.68)	0.267
<i>Age Q4</i>	2.41	(0.84-6.94)	0.103
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.29	(0.62-2.7)	0.491
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	0.62	(0.18-2.19)	0.461
<i>Pack years Q3</i>	2.21	(0.81-5.98)	0.12
<i>Pack years Q4</i>	1.14	(0.40-3.24)	0.81
<i>CCI</i>	1.22	(0.92-1.62)	0.17
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	1.05	(0.52-2.14)	0.891

Table S22 – full cox regression model output for CPa9-HNE in the stable phase group, adjusted for age, sex, pack years, CCI, and intervention status with time to death as outcome.

CPa9-HNE change cox regression	Hazard Ratio	Confidence interval	p-value
<i>upper quartiles</i>	Ref	Ref	Ref
<i>lowest quartile</i>	1.88	(1.18-3.01)	0.008*

<i>Age Q1</i>	Ref	Ref	Ref
<i>Age Q2</i>	0.80	(0.44-1.43)	0.445
<i>Age Q3</i>	1.22	(0.69-2.15)	0.49
<i>Age Q4</i>	0.79	(0.43-1.48)	0.466
<i>Female</i>	Ref	Ref	Ref
<i>Male</i>	1.07	(0.70-1.65)	0.749
<i>Pack years Q1</i>	Ref	Ref	Ref
<i>Pack years Q2</i>	0.98	(0.52-1.86)	0.952
<i>Pack years Q3</i>	1.08	(0.58-1.99)	0.812
<i>Pack years Q4</i>	1.26	(0.71-2.25)	0.435
<i>CCI (per unit)</i>	1.38	(1.15-1.67)	0.001**
<i>Standard therapy</i>	Ref	Ref	Ref
<i>Eosinophil guided</i>	0.99	(0.65-1.51)	0.963

Table S23 – full cox regression model output for within-patient CPa9-HNE change from baseline to stable state. Model was adjusted for age, sex, pack years, CCI, and intervention status with time to readmission with AECOPD or death as a composite outcome.

<i>Biomarker</i>	0%	25%	50%	75%	100%
CPa9-HNE change (ng/mL)	-67.23	-3.7875	0	3.54	22.73

Table S24 – Cut-points for CPa9-HNE change.

Demographics by quartile of plasma CPa9-HNE change			
	Low change (Q1)	High change (Q2-Q4)	P-value
<i>n</i>	47	141	
<i>Age (mean (SD))</i>	74.0 (8.24)	74.6 (8.96)	0.68
<i>Male (%)</i>	22 (46.8)	67 (47.5)	1.00
<i>Pack years (mean (SD))</i>	44.9 (18.3)	46.7 (19.9)	0.56
<i>FEV1% (mean (SD))</i>	41.1 (19.2)	41.5 (16.8)	0.91
<i>CCI (mean)</i>	0.319	0.426	0.62
<i>Events</i>	29 (61,7%)	63 (44,7%)	
<i>Time to event (mean)</i>	209	259	
<i>Admission CPa9-HNE (median (IQR))</i>	23.8 (10.5)	17.5 (9.21)	3.59*10 ⁻⁷
<i>30-day CPa9-HNE (median (IQR))</i>	16.5 (9.22)	19.8 (9.86)	0.008
<i>CPa9-HNE change (median (IQR))</i>	-7.67 (4.49)	0.98 (5.36)	

Table S25 - Demographics on paired data for patients in high and low biomarker groups of CPa9-HNE change from the exacerbation phase to the stable phase. Patients in Q1 (low

change) had the biggest decrease in plasma CPa9-HNE. Statistical significance was determined using t-test (age, pack years, FEV1), chi-squared test (sex), or Wilcoxon rank-sum test (CCI, CPa9-HNE).