SUPPLEMENTAL MATERIAL

to

Growth differentiation factor-15 provides prognostic information superior to established cardiovascular and inflammatory biomarkers in unselected patients hospitalized with COVID-19

Suppl. Table I. Baseline characteristics stratified by quartiles of growth differentiation factor 15 (GDF-15) concentration at baseline

	GDF-15 Q1	**GDF-15 Q2**	**GDF-15 Q3**	**GDF-15 Q4**	
	n=31	**n=31**	**n=31**	**n=30**	**P-value for trend**
GDF-15	*1170 [996, 1454]*	*2273 [1942, 2514]*	*3673 [3167, 4066]*	*7447 [5247, 9984]*	
Age, years	48.6 ± 14.6	60.4 ± 12.8	62.5 ± 12.8	67.3 ± 14.3	<0.001
Male sex	14 (45.2%)	18 (58.1%)	16 (51.6%)	23 (76.7%)	0.029
White race	14 (45.2%)	18 (58.1%)	18 (58.1%)	18 (60.0%)	0.27
Body mass index, kg/m^2	27.0 ± 4.1	28.9 ± 4.1	29.9 ± 7.9	27.4 ± 4.4	0.56
Obesity	5 (17.2%)	11 (35.5%)	10 (32.3%)	6 (20.7%)	0.85
Diabetes Mellitus	1 (3.2%)	1 (3.2%)	6 (19.4%)	13 (43.3%)	<0.001
Hypertension	3 (10.0%)	8 (25.8%)	12 (40.0%)	16 (53.3%)	<0.001
Cardiovascular disease	1 (3.2%)	2 (6.5%)	7 (22.6%)	8 (22.6%)	0.002
Chronic pulmonary disease	0 (0.0%)	1 (3.2%)	4 (12.9%)	1 (3.3%)	0.25
Chronic kidney disease	1 (3.2%)	0 (0.0%)	0 (0.0%)	8 (26.7%)	<0.001
Smoking	1 (3.2%)	3 (9.7%)	1 (3.2%)	1 (3.3%)	0.73
Baseline Parameters					
Days of symptoms	9.3 ± 5.4	10.3 ± 4.3	9.0 ± 4.0	8.6 ± 4.5	0.39
Oxygen saturation, %	95.6 ± 2.1	93.6 ± 2.7	91.4 ± 4.1	90.6 ± 9.4	<0.001
Temperature, °C	38.0 ± 0.8	38.3 ± 0.9	38.3 ± 1.0	37.8 ± 0.8	0.31
Heart rate, /min	89.7 ± 16.5	87.4 ± 13.5	91.4 ± 15.3	92.0 ± 21.0	0.43
Respiratory rate, /min	25.5 ± 8.9	25.1 ± 6.6	28.1 ± 10.6	28.6 ± 7.8	0.08
Systolic blood pressure, mmHg	134.9 ± 17.7	132.7 ± 16.5	127.1 ± 15.3	133.5 ± 23.9	0.51
Baseline Laboratory Values					
Hemoglobin, g/dL	14.5 [13.2, 15.2]	14.1 [13.1, 15.0]	13.8 [12.4, 14.7]	13.1 [11.3, 14.0]	0.002
White blood cell count, x 10^9 /L	5.2 [4.4, 6.2]	5.3 [3.8, 7.9]	6.6 [5.5, 9.5]	7.9 [5.1, 10.8]	<0.001
Lymphocyte count, x 10^9 /L	1.3 [1.0, 1.9]	0.8 [0.7, 1.1]	1.0 [0.9, 1.3]	0.8 [0.7, 1.0]	0.002
Thrombocyte count, x 10^9 /L	182 [144, 236]	179 [134, 245]	186 [148, 233]	190 [161, 262]	0.23
Sodium, mmol/L	137 [136, 138]	136 [134, 138]	136 [135, 138]	135 [133, 138]	0.10

Potassium, mmol/L	4.1 [3.7, 4.2]	4.1 [3.7, 4.2]	4.1 [3.8, 4.4]	4.2 [3.9, 4.6]	0.037
eGFR, ml/min/$m^{1,73}$	100 [87, 114]	89 [80, 106]	86 [67, 98]	65 [30, 90]	<0.001
Alanine transaminase, IU/L	32 [25, 42]	29 [20, 40]	38 [26, 53]	33 [25, 58]	0.28
Bilirubin, umol/L	12 [8, 14]	10.5 [9, 14]	14 [11, 19]	11.5 [10, 15]	0.16
Lactate dehydrogenase, U/L	235 [210, 290]	280 [230, 370]	360 [300, 510]	360 [260, 480]	<0.001
Lactate, mmol/L	0.9 [0.7, 1.0]	0.9 [0.8, 1.1]	1.0 [0.8, 1.3]	1.0 [0.7, 1.3]	0.12
Interleukin-6, pg/mL	14.7 [6.8, 24.7]	37.0 [19.6, 61.7]	59.2 [41.5, 102.0]	71.5 [29.1, 133.0]	<0.001
C-reactive protein, mg/L	25 [6, 45]	60 [32, 130]	90 [60, 190]	110 [60, 200]	<0.001
Procalcitonin, ug/L	0.6 [0.4, 0.8]	1.0 [0.6, 1.7]	1.8 [1.3, 3.7]	2.8 [1.6, 6.0]	<0.001
Ferritin, ug/L	231 [132, 384]	444 [244, 901]	710 [466, 1471]	691 [412, 1763]	<0.001
D-dimer, mg/L	0.3 [0.3, 0.4]	0.5 [0.4, 0.7]	0.6 [0.4, 1.0]	1.0 [0.6, 2.0]	<0.001
Cardiac Troponin T, ng/L	5 [4, 7]	10 [5, 15]	12 [7, 15]	21 [9, 38]	<0.001
NT-proBNP, ng/L	30 [17, 60]	109 [42, 253]	121 [57, 265]	316.5 [143, 788]	<0.001

Abbreviations: RAS = Renin-Angiotensin-System; NEWS = National Early Warning Score; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide

Suppl. Table II. Spearman correlation between baseline concentrations of biomarkers

	GDF-15	IL-6	CRP	PCT	Ferritin	D-Dimer	cTnT	NT-proBNP
IL-6	0.50							
CRP	0.53	0.62						
PCT	0.64	0.69	0.65					
Ferritin	0.45	0.49	0.54	0.67				
D-Dimer	0.46	0.29	0.47	0.37	0.36			
cTnT	0.52	0.40	0.31	0.43	0.25	0.32		
NT-proBNP	0.49	0.50	0.42	0.51	0.34	0.41	0.68	

All correlations were significant ($p<0.05$)

Abbreviations: IL-6= interleukin 6; CRP = C-reactive protein; PCT = procalcitonin; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; GDF-15= growth differentiation factor 15

Suppl. Table III. Multivariable regression of baseline log_2-transformed concentrations of growth differentiation factor 15

	Coef. (95% CI)	**P-value**
Age, years	0.019 (0.004 to 0.034)	0.015
Male sex		0.62
White race	-0.42 (-0.77 to -0.08)	0.016
Body mass index, kg/m^2		0.94
Cardiovascular disease		0.74
$_{log}$ eGFR, $ml/min/m^{1.73}$	-0.53 (-0.99 to -0.07)	0.025
$_{log}$ Interleukin-6, pg/mL		0.49
$_{log}$ C-reactive protein, mg/L	0.17 (0.003 to 0.35)	0.046
$_{log}$ Procalcitonin, ug/L	0.25 (0.02 to 0.46)	0.030
$_{log}$ Ferritin, ug/L		0.98
$_{log}$ D-dimer, mg/L	0.33 (0.14 to 0.52)	0.001
$_{log}$ TnT, ng/L		0.68
$_{log}$ NT-proBNP, ng/L		0.54

Abbreviations: eGFR = estimated glomerular filtration rate; IL-6= interleukin 6; CRP = C-reactive protein; PCT = procalcitonin; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide

Suppl. Table IV. Multivariable logistic regression of severe acute respiratory syndrome coronavirus 2 viremia at baseline, with all variables listed in the model.

		OR (95% CI)	P-value
IL-6	(pg/mL)	1.63 (0.97-2.74)	0.07
CRP	(mg/L)	1.61 (0.90-2.88)	0.29
PCT	(ug/L)	0.72 (0.39-1.31)	0.11
Ferritin	(ug/L)	1.58 (0.93-2.68)	0.09
D-dimer	(mg/L)	0.60 (0.34-1.06)	0.08
cTnT	(ng/L)	1.35 (0.74-2.44)	0.32
NT-proBNP	(ng/L)	0.73 (0.48-1.13)	0.16
GDF-15	(pg/mL)	1.96 (0.14-3.35)	0.014

All biomarker values were log-2 transformed in the adjusted regression model.

Abbreviations: IL-6= interleukin 6; CRP = C-reactive protein; PCT = procalcitonin; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; GDF-15= growth differentiation factor 1

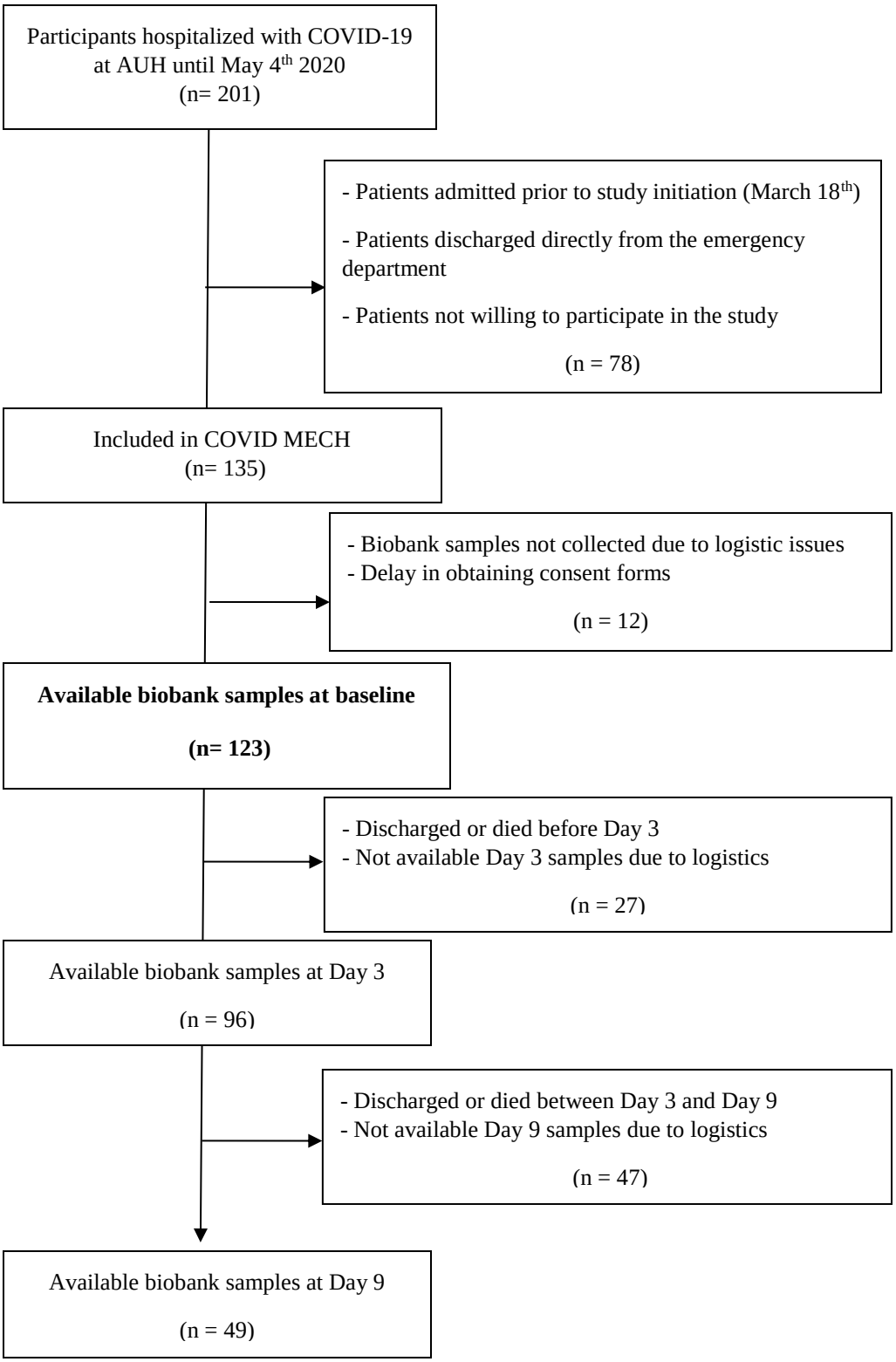
Suppl. Table V. Concentrations of baseline cardiovascular and inflammatory biomarkers and the association with all cause death among patients hospitalized with COVID-19 (n=123)

	Survivor (n=115)	**Non-survivor (n=8)**	**P-value unadjusted**	**ROC AUC (95% CI)**	**P-value adj. Model 1**
IL-6 (pg/mL)	38.3 [17.5, 63.4]	108.5 [32.5, 186]	0.037	0.72 (0.53-0.91)	0.67
CRP (mg/L)	60 [30, 130]	115 [75, 200]	0.11	0.67 (0.48-0.86)	0.58
PCT (ug/L)	1.3 [0.6, 2.3]	1.9 [1.4, 7.4]	0.06	0.70 (0.54-0.86)	0.95
Ferritin (ug/L)	469 [231, 919]	1142 [434, 1852.5]	0.07	0.69 (0.50-0.88)	0.67
D-dimer (mg/L)	0.5 [0.3, 0.9]	1.1 [0.9, 2.4]	0.009	0.78 (0.63-0.92)	0.25
cTnT (ng/L)	8 [5, 14]	24.5 [18, 30]	0.001	0.84 (0.75-0.92)	0.40
NT-proBNP (ng/L)	97 [35, 242]	359 [192, 1431]	0.021	0.74 (0.57-0.92)	0.73
GDF-15 (pg/mL)	2583 [1512, 4225]	7790 [4716, 9317]	<0.001	0.87 (0.79-0.94)	0.027

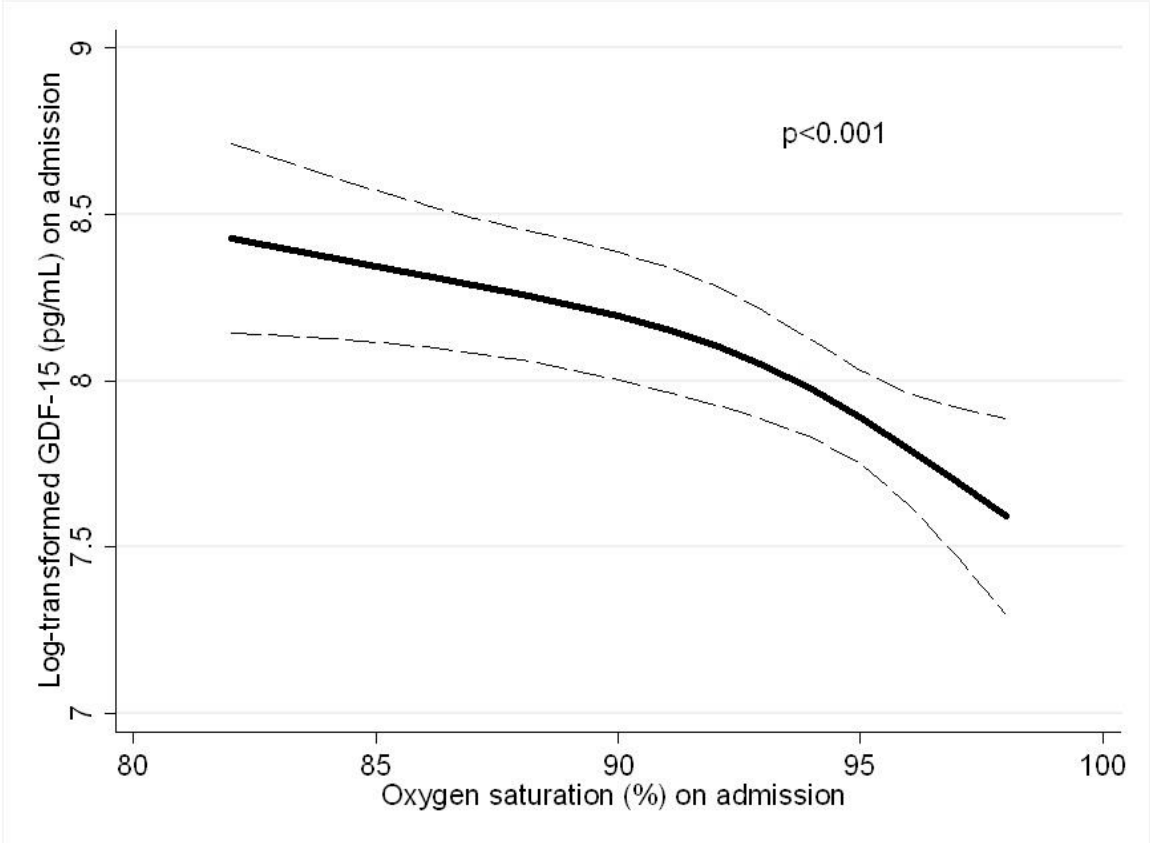
Model 1: Adjusted for age, sex, race, body mass index, cardiovascular disease and estimated glomerular filtration rate
Concentrations are reported as median (Q1, Q3). All biomarker values were log transformed in the adjusted regression model.

Abbreviations: IL-6= interleukin 6; CRP = C-reactive protein; PCT = procalcitonin; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; GDF-15= growth differentiation factor 15; ROC AUC = area under the receiver operating curves

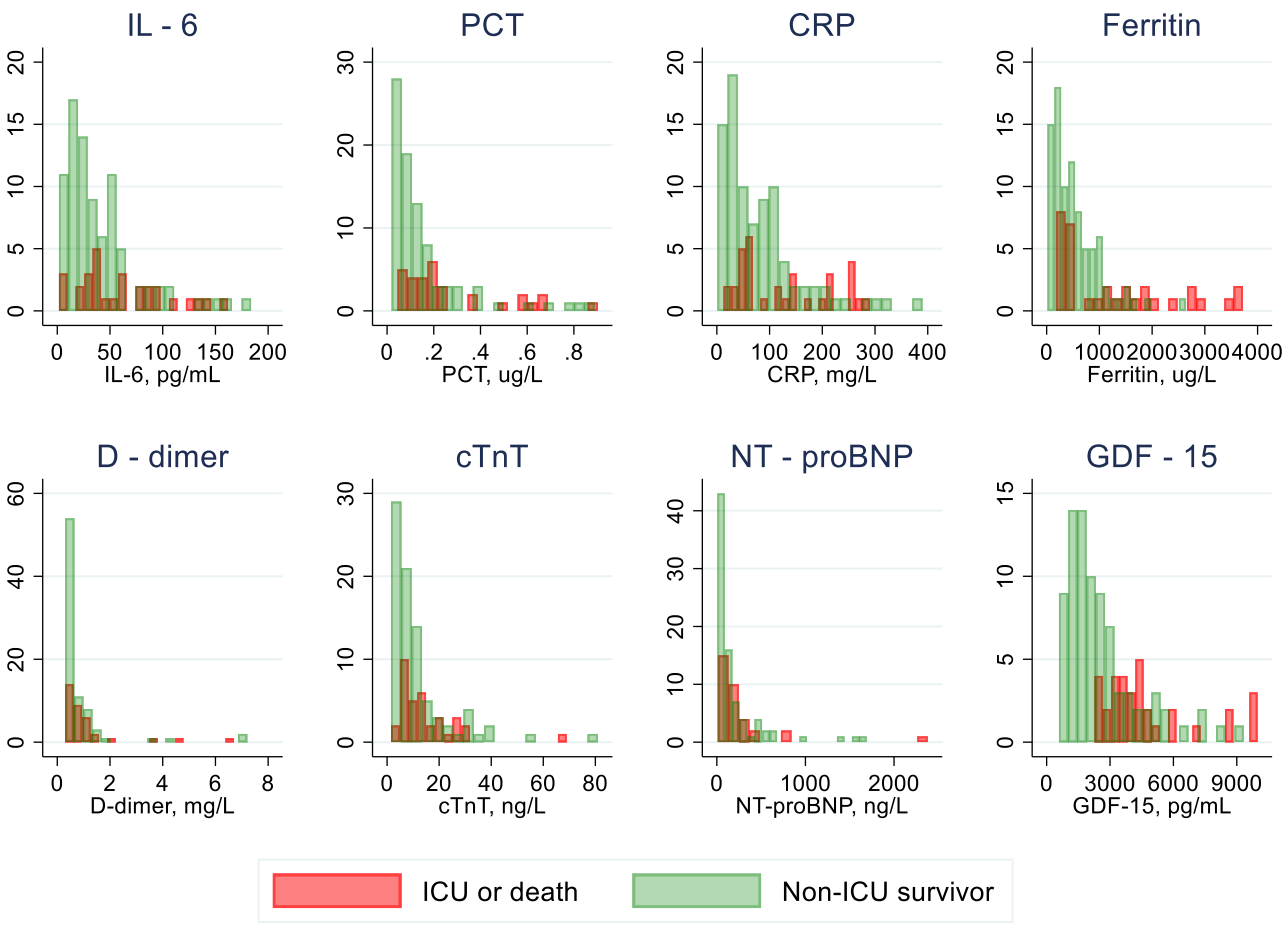
Suppl. Figure I. Flow diagram of patients in the COVID MECH study



Suppl. Figure II. Association between oxygen saturation and log transformed growth differentiation factor 15 at baseline

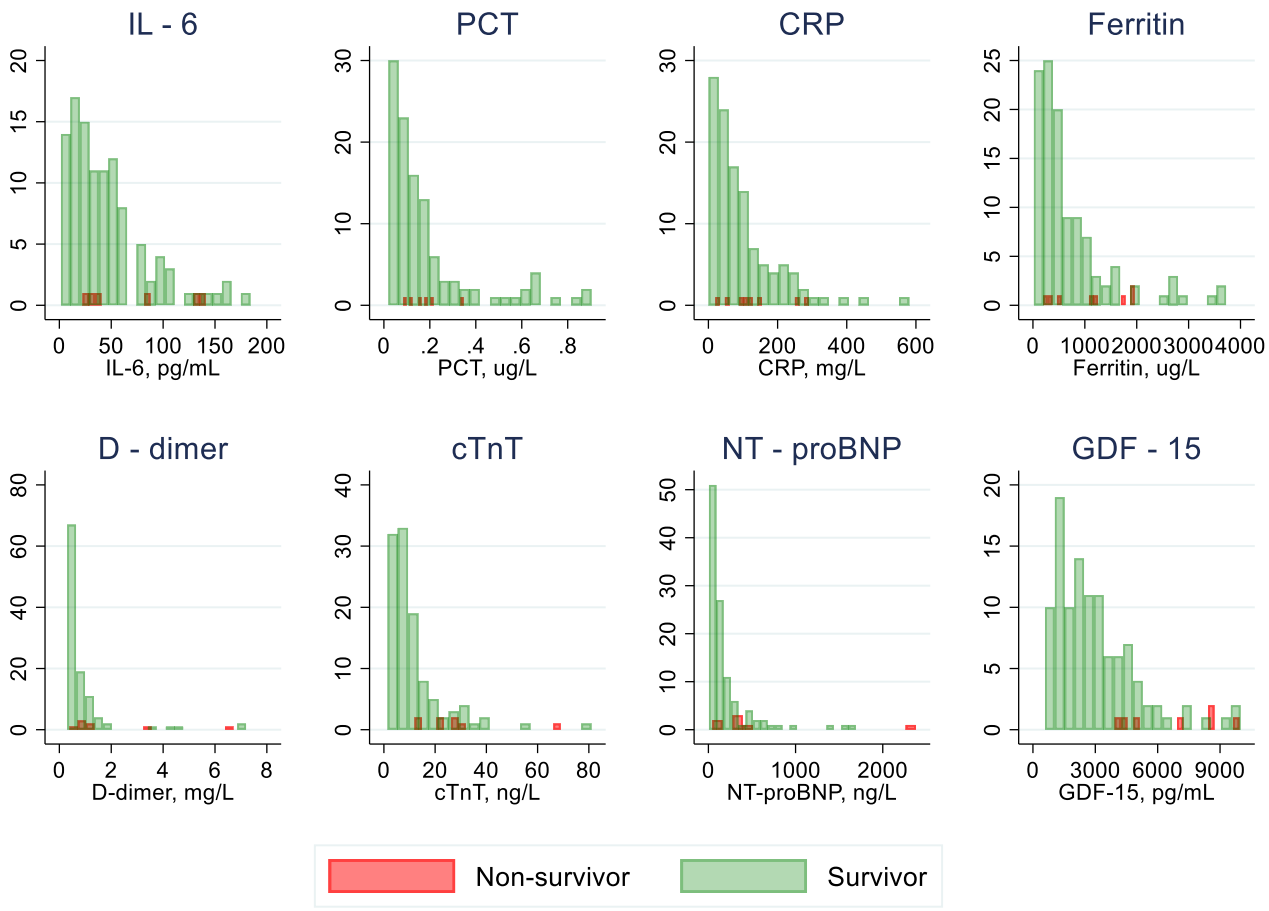


Suppl. Figure III. Distributions of the cardiovascular and inflammatory biomarkers by the *primary endpoint.*



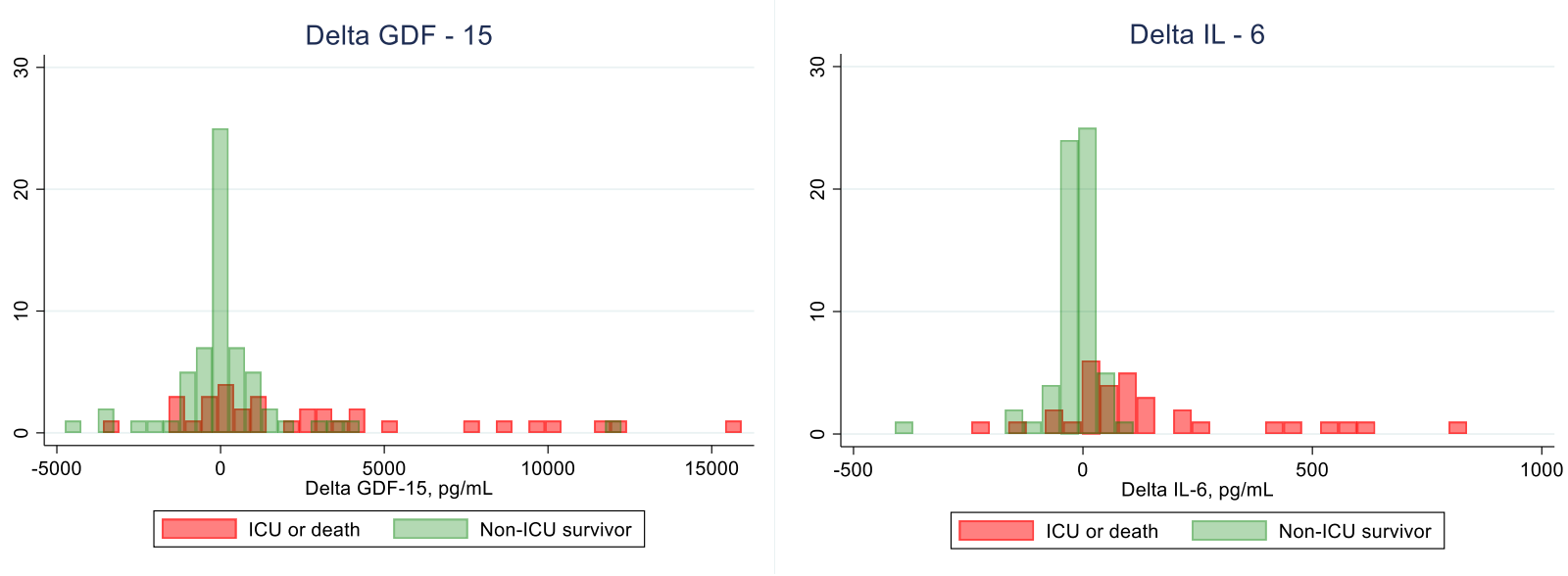
Outliers are excluded from the histograms for visual presentation purposes: n=8 with IL-6 >200 pg/mL; n=6 with PCT>1.0 ug/L; n=2 with CRP>400 mg/L; n=2 with ferritin>5000 ug/L; n=3 with D-dimer>10 mg/L; n=4 with cTnT>100 ng/L; n=6 with NT-proBNP>2500 ng/L and n=7 with GDF-15 >10 000 pg/mL

Suppl. Figure IV. Distributions of the cardiovascular and inflammatory biomarkers by *all-cause death*



Outliers are excluded from the histograms for visual presentation purposes: n=8 with IL-6 >200 pg/mL; n=6 with PCT>1.0 ug/L; n=2 with CRP>400 mg/L; n=2 with ferritin>5000 ug/L; n=3 with D-dimer>10 mg/L; n=4 with cTnT>100 ng/L; n=6 with NT-proBNP>2500 ng/L and n=7 with GDF-15 >10 000 pg/mL

Suppl. Figure V. Distributions of changes in GDF-15 and IL-6 from baseline to day 3 by the primary endpoint



Outliers are excluded from the histograms for visual presentation purposes: n=1 with delta GDF-15 < -10000 and n=1 with delta IL-6 >2000 pg/m