Online Supplement

Clinical subtype trajectories in sepsis patients admitted to the intensive care unit: a secondary analysis of an observational study

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Supplementary methods

Patients

Within the MARS, information on demographics, daily clinical, laboratory and outcome data and severity indices such as Acute Physiology and Chronic Health Evaluation (APACHE) IV[1] and Sequential Organ Failure Assessment (SOFA) scores[2] were prospectively collected by trained and dedicated ICU researchers. For every patient included in the MARS cohort, the plausibility of an infection was assessed retrospectively using a four-point scale (ascending from none, possible, probable to definite) using the Centers for Disease Control and Prevention[3] and International Sepsis Forum consensus definitions[4] as described[5]. In this secondary analyses all patients fulfilling the Sepsis-3[2], criteria were included defined as any suspected infection for which the clinical team initiated antibiotics, within 48 hours after ICU admission, accompanied by organ failure as indicated by a SOFA score[2] of two or more (central nervous system excluded). When the SOFA score was not available the following variables were used to define organ failure: mechanical ventilation, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) or shock, all on the first day of ICU admission. AKI and ARDS were defined using strict pre-set criteria[6,7]. Shock was defined as the use of noradrenaline for hypotension in a dose of >0.1 µg/kg/min during at least 50% of the day.

Adjudication to clinical subtypes

Since the Elixhauser comorbidity index was not available in either cohort, the Charlson comorbidity index[8] was calculated. When the international normalized ratio (INR) was missing in the MARS cohort, the prothrombin time (PT) value was used to calculate the INR.

Assessment of which variables determine if a patient switches subtypes or stays within the same subtype

To assess which variables determined if a patient switches subtypes or stays within the same subtype, the following analyses were executed: first, for each patient, the difference in Euclidean Distance for various variables between specific time points was calculated. For instance, the Euclidean Distance for heart rate was measured on day 0 and day 2, and the difference between these values was calculated. Next, it was assessed whether these differences were significantly different between patients who remained in the same subtype and those who switched to another subtype. To do this, the effect size using Hedges' G was calculated [9]. For easier interpretation, the effect sizes were categorized based on Cohen's guidelines [10]: less than 0.2 = negligible, between 0.2 and 0.5 = small, between 0.5 and 0.8 = moderate, and greater than 0.8 = large.

Biomarker measurements

Whole blood samples were centrifuged directly (1500 G for 15 min) and frozen at -80°C within 4 hours after blood draw. Interleukin (IL)-6, IL-8, IL-10, soluble intercellular adhesion molecule (ICAM)-1, soluble E-selectin and fractalkine were measured by FlexSet cytometric bead array (BD Biosciences, San Jose, CA) using FACS Calibur (Becton Dickenson, Franklin Lakes, NJ). Matrix metalloproteinase (MMP)-8, angiopoietin-1, angiopoietin-2 and protein C (all R&D systems, Abingdon, UK) and D-dimer (Procartaplex, eBioscience, San Diego, CA) were measured by Luminex multiplex assay using BioPlex 200 (BioRad, Hercules, CA).

Supplementary results

Subtype trajectories

The erythrocyte sedimentation rate (ESR), total number of bands and Glasgow Coma Scale (GCS) were unavailable daily in MARS and thus excluded. No clinical variables exceeded >80% missing on ICU admission (Supplementary Figure 1). In MIMIC-IV, C-reactive protein (CRP) and ESR had >80% missing on baseline and were therefore excluded (Supplementary Figure 3).

Supplementary Table 1. Baseline characteristics and outcomes of patients admitted to the ICU

Cohort	**MARS cohort**	**MIMIC-IV cohort**
Number of patients	**2416**	**10745**
Age (median [IQR])	63 [51, 72]	67 [55, 79]
Sex = male (%)	1484 (61.4)	6201 (57.7)
Race = White (%)	2116 (87.6)	7044 (65.6)
Charlson comorbidity score (median [IQR])	1 [0, 2]	3 [1, 4]
Disease severity on admission		
SOFA (median [IQR])	7 [4, 9]	3 [2, 5]
APACHE III Score (median [IQR])*		53 [39, 75]
APACHE IV Score (median [IQR])**	76 [59, 97]	
Mechanical ventilation (%)	1813 (75.0)	2585 (24.1)
Vital signs and laboratory values on admission		
Respiratory rate (median [IQR])	33 [27, 40]	28 [24, 32]
Heart rate (median [IQR])	128 [113, 146]	106 [92, 121]
Systolic blood pressure (median [IQR])	80 [71, 91]	87 [78, 97]
CRP mg/L (median [IQR])	122 [44, 235]	93 [37, 174]
White cell count *10^9/L (median [IQR])	13.85 [9.10, 19.40]	14.10 [9.88, 19.50]
Platelets *10^9/L (median [IQR])	182 [115, 266]	153 [102, 220]
Creatinine µmol/L(median [IQR])	104 [71, 171]	106 [80, 177]
Outcome		
LOS ICU (median [IQR])	3 [1, 8]	3 [1, 7]
ICU mortality (%)	440 (18.2)	1632 (15.2)
Hospital mortality (%)	681 (28.2)	2208 (20.5)
30-day mortality (%)	619 (26.0)	2174 (20.2)
1-year mortality (%)	1052 (44.9)	2536 (23.6)

*Range: 0-299. **Range: 0-286. Abbreviations: APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; SOFA, sequential organ failure assessment

Supplementary Table 2. Overview of patients remaining in or transitioning to subtype on ICU admission, day 2, 4 and 7 in the MARS cohort

ICU admission – day 2				
Subtype on ICU admission	**Remained in same subtype on day 2**	**Transitioned to different subtype on day 2**	**Discharged alive on day 2**	**Deceased on day 2**
α (n=150)	41 (27%* & 44%†)	52 (35%* & 56%†)	55 (37%)	2 (1%)
β (n=70)	14 (20%* & 29%†)	35 (50%* & 71%†)	21 (30%)	0 (0%)
γ (n=1317)	648 (49%* & 68%†)	302 (23%* & 32%†)	340 (26%)	27 (2%)
δ (n=879)	347 (39%* & 52%†)	320 (36%* & 48%†)	110 (13%)	102 (12%)
Day 2 – day 4				
Subtype on day 2	**Remained in same subtype on day 4**	**Transitioned to different subtype on day 4**	**Discharged alive on day 4**	**Deceased on day 4**
α (n=130)	31 (24%* & 45%†)	38 (29%* & 55%†)	57 (44%)	4 (3%)
β (n=99)	17 (17%* & 35%†)	32 (32%* & 65%†)	47 (47%)	3 (3%)
γ (n=975)	441 (45%* & 69%†)	202 (21%* & 34%†)	302 (31%)	30 (3%)
δ (n=555)	185 (33%* & 50%†)	187 (34%* & 52%†)	124 (22%)	59 (11%)
Day 4 – day 7				
Subtype on day 4	**Remained in same subtype on day 7**	**Transitioned to different subtype on day 7**	**Discharged alive on day 7**	**Deceased on day 7**
α (n=95)	20 (21%* & 39%†)	31 (33%* & 73%†)	41 (43%)	3 (3%)
β (n=82)	16 (20%* & 36%†)	28 (34%* & 61%†)	37 (45%)	1 (1%)
γ (n=645)	275 (43%* & 66%†)	144 (22%* & 35%†)	205 (32%)	21 (3%)
δ (n=311)	95 (31%* & 48%†)	104 (33%* & 57%†)	83 (27%)	29 (9%)
ICU admission – day 4				
Subtype on ICU admission	**Remained in same subtype on day 4**	**Transitioned to different subtype on day 4**	**Discharged alive on day 4**	**Deceased on day 4**
α (n=150)	14 (9%* & 27%†)	38 (25%* & 73%†)	90 (60%)	8 57%)
β (n=70)	9 (13%* & 39%†)	14 (20%* & 61%†)	47 (67%)	0 (0%)
γ (n=1317)	399 (30%* & 65%†)	214 (16%* & 35%†)	646 (49%)	58 (4%)
δ (n=879)	193 (22%* & 43%†)	252 (29%* & 57%†)	273 (31%)	161 (18%)
ICU admission – day 7				
Subtype on ICU admission	**Remained in same subtype on day 7**	**Transitioned to different subtype on day 7**	**Discharged alive on day 7**	**Deceased on day 7**
α (n=150)	15 (10%* & 41%†)	22 (15%* & 59%†)	102 (68%)	11 (7%)
β (n=70)	5 (7%* & 36%†)	9 (13%* & 64%†)	55 (79%)	1 (1%)
γ (n=1317)	226 (17%* & 62%†)	136 (10%* & 38%†)	875 (66%)	80 (6%)
δ (n=879)	112 (13%* & 37%†)	188 (21%* & 63%†)	390 (44%)	189 (22%)

Abbreviations: ICU, intensive care unit, * percentage of all admissions on ICU admission, † percentage of admissions still on the ICU on the corresponding admission day

Supplementary Table 3. Overview of patients remaining in or transitioning to subtype on ICU admission, day 2, 4 and 7 in the MIMIC-IV cohort

ICU admission – day 2				
Subtype on ICU admission	**Remained in same subtype on day 2**	**Transitioned to different subtype on day 2**	**Discharged alive on day 2**	**Deceased on day 2**
α (n=2398)	1100 (46%* & 72%†)	431 (18%* & 28%†)	843 (35%)	24 (1%)
β (n=2365)	1053 (45%* & 67%†)	516 (22%* & 33%†)	745 (32%)	51 (2%)
γ (n=2686)	834 (31%* & 43%†)	1104 (41%* & 57%†)	639 (24%)	109 (4%)
δ (n=3296)	1178 (36%* & 50%†)	1155 (35%* & 50%†)	572 (17%)	391 (12%)
Day 2 – day 4				
Subtype on day 2	**Remained in same subtype on day 4**	**Transitioned to different subtype on day 4**	**Discharged alive on day 4**	**Deceased on day 4**
α (n=2110)	811 (38%* & 68%†)	374 (18%* & 32%†)	904 (43%)	21 (1%)
β (n=1872)	722 (39%* & 67%†)	357 (19%* & 33%†)	741 (40%)	52 (3%)
γ (n=1619)	402 (25%* & 40%†)	597 (37%* & 60%†)	546 (34%)	74 (5%)
δ (n=1770)	612 (35%* & 48%†)	663 (37%* & 52%†)	313 (18%)	182 (10%)
Day 4 – day 7				
Subtype on day 4	**Remained in same subtype on day 7**	**Transitioned to different subtype on day 7**	**Discharged alive on day 7**	**Deceased on day 7**
α (n=1415)	525 (37%* & 64%†)	301 (21%* & 36%†)	557 (39%)	32 (2%)
β (n=1237)	434 (35%* & 64%†)	249 (20%* & 36%†)	491 (40%)	63 (5%)
γ (n=929)	256 (28%* & 43%†)	337 (36%* & 57%†)	275 (30%)	61 (7%)
δ (n=957)	278 (29%* & 43%†)	368 (38%* & 57%†)	196 (20%)	115 (12%)
ICU admission – day 4				
Subtype on ICU admission	**Remained in same subtype on day 4**	**Transitioned to different subtype on day 4**	**Discharged alive on day 4**	**Deceased on day 4**
α (n=2398)	627 (26%* & 70%†)	267 (11%* & 30%†)	1454 (61%)	50 (2%)
β (n=2365)	558 (24%* & 63%†)	322 (14%* & 37%†)	1378 (58%)	107 (7%)
γ (n=2686)	417 (16%* & 35%†)	762 (28%* & 65%†)	1316 (49%)	191 (7%)
δ (n=3296)	604 (18%* & 38%†)	981 (30%* & 62%†)	1155 (35%)	556 (17%)
ICU admission – day 7				
Subtype on ICU admission	**Remained in same subtype on day 7**	**Transitioned to different subtype on day 7**	**Discharged alive on day 7**	**Deceased on day 7**
α (n=2398)	363 (15%* & 66%†)	186 (8%* & 34%†)	1770 (74%)	79 (3%)
β (n=2365)	285 (12%* & 62%†)	178 (8%* & 38%†)	1742 (74%)	160 (7%)
γ (n=2686)	260 (10%* & 67%†)	451 (17%* & 63%†)	1731 (64%)	244 (9%)
δ (n=3296)	317 (10%* & 31%†)	708 (21%* & 69%†)	1579 (48%)	692 (21%)

Abbreviations: ICU, intensive care unit, * percentage of all admissions on ICU admission, † percentage of admissions still on the ICU on the corresponding admission day

Supplementary Table 4. Assessment of which variables determine if a patient switches subtypes or stays within the same subtype

Subtype transitioning	Variable 1	Effect size	Variable 2	Effect size	Variable 3	Effect size	# of variables *
MARS - Day 0-2							
α to other	Albumin	-0.68; Moderate	WBC	-0.51; Moderate	Troponin	-0.49; Small	13
β to other	Heart rate	0.59; Moderate	Troponin	0.53; Moderate	AST	-0.54; Moderate	13
γ to other	ALT	-0.66; Moderate	AST	-0.64; Moderate	Troponin	-0.27; Small	6
δ to other	Troponin	-0.46; Small	ASAT	-0.35; Small	ALT	-0.35; Small	4
MIMIC-IV – Day 0-2							
α to other	Albumin	-0.41; Small	AST	-0.33; Small	ALT	-0.29; Small	5
β to other	AST	-0.52; Moderate	ALT	-0.46; Small	Urea	-0.30; Small	5
γ to other	AST	-0.45; Small	ALT	-0.44; Small	Bands	-0.36; Small	4
δ to other	AST	-0.36; Small	Bilirubin	-0.31; Small	ALT	-0.30; Small	6
MARS - Day 2-4							
α to other	Troponin	-0.54; Moderate	Creatinin	-0.48; Small	Respirato-ry rate	-0.43; Small	9
β to other	Respirato-ry rate	-0.86; Large	ALT	-0.62; Moderate	Lactate	-0.58; Moderate	18
γ to other	AST	-0.58; Moderate	ALT	-0.56; Moderate	Troponin	-0.35; Small	6
δ to other	AST	-0.46; Small	Troponin	-0.40; Small	ALT	-0.40; Small	8
MIMIC-IV – Day 2-4							
α to other	Bands	-0.36; Small	Albumin	-0.36; Small	Respirato-ry rate	-0.27; Small	3
β to other	AST	-0.51; Small	ALT	-0.47; Small	Urea	-0.27; Small	5
γ to other	AST	-0.41; Small	Bands	-0.36; Small	ALT	-0.34; Small	4
δ to other	ALT	-0.49; Small	AST	-0.45; Small	Bilirubin	-0.44; Small	6

* Number of variables that have significant effect sizes, so without the classification 'Negligible'.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cell count.

Supplementary Table 5. Comparing baseline characteristics and outcome in patients with consistent subtype on ICU admission versus those exhibiting a changed subtype by day 2 in the MIMIC-IV cohort

Subtype	γ-γ	γ-δ	*P*-value	δ-δ	δ-γ	*P*-value
Number of patients	**834**	**268**		**1178**	**331**	
Age (median [IQR])	68 [56, 79]	66 [56, 77]	0.217	63 [50, 74]	66 [54, 77]	<0.001
Sex = male (%)	411 (49.3)	149 (55.6)	0.084	732 (62.1)	181 (54.7)	0.017
Race = White (%)	575 (68.9)	181 (67.5)	0.722	706 (59.9)	213 (64.4)	0.164
Charlson comorbidity score (median [IQR])	2.00 [1.00, 3.00]	2.00 [1.00, 4.00]	0.014	3 [2, 5]	2 [1, 4]	<0.001
Disease severity on admission						
APACHE III Score (median [IQR])	53 [42, 71]	67 [50, 90]	<0.001	89 [67, 110]	70 [51, 87]	<0.001
SOFA (median [IQR])	3 [2, 4]	4 [2, 5]	0.001	5 [3, 7]	4 [3, 6]	<0.001
Mechanical ventilation (%)	274 (32.9)	83 (31.0)	0.618	318 (27.0)	86 (26.0)	0.766
Outcome						
LOS ICU (median [IQR])	4 [3, 8]	6 [3, 12]	<0.001	6 [3, 12]	4 [3, 9]	<0.001
ICU mortality (%)	118 (14.1)	53 (19.8)	0.034	357 (30.3)	49 (14.8)	<0.001
Hospital mortality (%)	172 (20.6)	66 (24.6)	0.194	435 (36.9)	71 (21.5)	<0.001
30-day mortality (%)	175 (21.0)	66 (24.6)	0.242	419 (35.6)	68 (20.5)	<0.001
1-year mortality (%)	209 (25.1)	79 (29.5)	0.176	469 (39.8)	85 (25.7)	<0.001

Only patients with the δ and γ subtype were included in this table, since this was also done for the MARS cohort. Abbreviations: ICU, intensive care unit; LOS, length of stay; SOFA, sequential organ failure assessment

Supplementary Table 6. Absolute biomarker concentrations stratified per subtype on ICU admission-day 2 and per day – part I

	δ-δ	δ-γ	γ-δ	γ-γ	*P*-value
Day 0-1					
n	202	147	116	384	
IL-6 (median [IQR])	489.50 [99.79, 4195.53]	150.07 [38.28, 1110.38]	321.57 [59.39, 1853.53]	132.68 [32.12, 576.49]	<0.001
IL-8 (median [IQR])	354.36 [118.91, 1563.83]	126.33 [40.74, 388.54]	229.86 [71.06, 745.60]	79.84 [32.11, 227.55]	<0.001
IL-10 (median [IQR])	48.69 [15.25, 240.01]	14.54 [5.74, 52.26]	23.16 [7.68, 76.64]	8.00 [3.04, 21.43]	<0.001
MMP8 (median [IQR])	5251.62 [1616.86, 13196.17]	2523.78 [698.71, 6871.61]	4525.14 [1113.33, 11164.65]	2240.77 [731.41, 6708.44]	<0.001
D-Dimer (median [IQR]) *	13046.00 [5441.93, 24360.75]	9701.20 [4576.95, 20292.50]	7867.20 [3241.78, 13518.50]	7688.90 [3462.53, 14497.50]	<0.001
Protein C (median [IQR])	109079.55 [86365.36, 140780.30]	117332.81 [90693.10, 170142.94]	116477.39 [89541.41, 159345.67]	117888.20 [86560.78, 159519.59]	0.065
Ang-1 (median [IQR])	1380.20 [656.18, 3486.00]	2227.59 [957.60, 6758.82]	1535.09 [693.23, 4887.58]	2985.38 [986.31, 7338.64]	<0.001
Ang-2 (median [IQR])	12416.80 [5182.49, 23909.17]	6482.24 [2581.20, 14280.36]	8392.02 [4208.86, 20960.35]	5752.30 [3014.58, 10302.76]	<0.001
Ang-2/-ang-1 (median [IQR])	7.78 [2.42, 26.20]	2.47 [0.63, 11.60]	6.17 [1.06, 15.67]	1.71 [0.61, 6.15]	<0.001
E-Selectin (median [IQR])	36.55 [15.22, 92.88]	35.42 [17.07, 69.49]	45.03 [18.72, 89.44]	28.15 [13.74, 67.69]	0.016
Fractalkine (median [IQR])	52.74 [28.19, 110.49]	26.92 [15.80, 62.78]	32.68 [15.33, 64.75]	19.54 [13.08, 38.27]	<0.001
ICAM (median [IQR])	212462.43 [116911.62, 366076.91]	159551.04 [94256.15, 269930.75]	232272.22 [145282.72, 337400.02]	159924.58 [97542.81, 262899.30]	<0.001
Day 2					
n	218	161	121	394	
IL-6 (median [IQR])	138.58 [49.85, 1005.63]	59.62 [20.80, 166.36]	76.75 [29.41, 399.49]	57.90 [20.94, 156.92]	<0.001
IL-8 (median [IQR])	192.24 [76.49, 609.54]	60.56 [25.20, 173.43]	129.12 [42.47, 412.48]	46.61 [23.25, 117.00]	<0.001
IL-10 (median [IQR])	19.19 [7.87, 69.45]	7.58 [2.84, 16.95]	11.39 [3.80, 29.86]	4.47 [2.09, 10.31]	<0.001
MMP8 (median [IQR])	4273.32 [1205.04, 15234.74]	1535.56 [516.39, 6034.57]	2712.16 [852.96, 10062.60]	1796.61 [535.68, 4776.36]	<0.001
D-Dimer (median [IQR]) *	13319.00 [5805.10, 24732.00]	8341.30 [3618.40, 15877.00]	8875.50 [3932.50, 15760.00]	7634.85 [3710.65, 14444.25]	<0.001
Protein C (median [IQR])	106118.10 [79618.55, 136702.69]	120290.20 [94504.16, 159039.47]	114613.73 [93159.49, 145838.58]	131012.66 [97172.38, 169424.87]	<0.001
Ang-1 (median [IQR])	1031.27 [545.71, 2186.14]	1472.00 [672.52, 3270.81]	1315.74 [595.23, 2874.56]	2295.20 [911.70, 5430.81]	<0.001
Ang-2 (median [IQR])	18405.06 [8342.35, 40078.72]	8047.49 [3561.18, 15246.79]	12010.82 [4185.33, 21861.26]	5595.03 [2748.61, 10487.39]	<0.001
Ang-2/-ang-1 (median [IQR])	20.98 [5.44, 50.93]	5.29 [1.49, 16.52]	8.91 [2.08, 31.12]	2.30 [0.67, 9.28]	<0.001
E-Selectin (median [IQR])	37.11 [17.70, 79.08]	33.74 [13.81, 65.24]	37.44 [15.84, 82.03]	28.84 [13.48, 54.71]	0.002
Fractalkine (median [IQR])	58.30 [26.10, 132.28]	27.24 [13.37, 54.39]	37.44 [14.91, 74.17]	17.59 [12.75, 35.11]	<0.001
ICAM (median [IQR])	264604.01 [139960.44, 417702.93]	189431.08 [111981.84, 324731.67]	227402.56 [146374.12, 332676.82]	181294.90 [110650.70, 290225.19]	<0.001

Supplementary Table 6. Absolute biomarker concentrations stratified per subtype on ICU admission-day 2 and per day – part II

	δ-δ	δ-γ	γ-δ	γ-γ	*P*-value
Day 4					
n	146	109	85	275	
IL-6 (median [IQR])	63.94 [23.62, 206.19]	37.54 [15.51, 97.13]	55.25 [18.87, 173.80]	29.94 [11.84, 91.06]	<0.001
IL-8 (median [IQR])	115.73 [61.42, 271.02]	49.33 [20.80, 137.55]	111.74 [43.94, 251.78]	40.10 [16.24, 99.59]	<0.001
IL-10 (median [IQR])	11.18 [4.79, 29.22]	4.78 [2.31, 12.90]	7.41 [3.81, 16.49]	3.75 [1.96, 8.42]	<0.001
MMP8 (median [IQR])	2776.02 [745.41, 7155.01]	1177.99 [540.21, 3640.92]	2049.03 [683.54, 5724.20]	1275.73 [506.97, 3380.81]	<0.001
D-Dimer (median [IQR]) *	13635.00 [5853.43, 23796.75]	9833.90 [5377.20, 17235.00]	8629.00 [4403.70, 16758.00]	9368.00 [5354.75, 16941.00]	0.005
Protein C (median [IQR])	102155.39 [78583.44, 147578.55]	137526.54 [104622.00, 194788.05]	125320.50 [95292.45, 174241.27]	144165.24 [100450.40, 191524.46]	<0.001
Ang-1 (median [IQR])	809.00 [422.97, 1790.07]	1865.10 [815.37, 3136.87]	996.06 [556.51, 2509.87]	2272.12 [747.62, 4914.04]	<0.001
Ang-2 (median [IQR])	12165.87 [6017.92, 22970.81]	5507.53 [2689.95, 10870.70]	7051.79 [2444.12, 14503.13]	4395.15 [2223.28, 8793.63]	<0.001
Ang-2/-ang-1 (median [IQR])	13.35 [4.36, 40.03]	3.73 [1.25, 9.93]	6.15 [1.45, 24.34]	1.99 [0.48, 8.49]	<0.001
E-Selectin (median [IQR])	29.50 [15.09, 59.73]	24.99 [12.81, 44.56]	26.81 [15.61, 43.92]	26.62 [13.78, 51.75]	0.340
Fractalkine (median [IQR])	58.75 [31.10, 148.69]	25.56 [13.95, 56.24]	49.01 [20.64, 125.56]	20.77 [12.75, 41.34]	<0.001
ICAM (median [IQR])	258001.90 [182195.54, 430212.25]	189446.56 [121849.54, 301016.48]	248898.25 [144444.37, 384404.06]	201967.60 [117237.69, 319053.97]	<0.001
Day 6-8					
n	34	21	21	79	
IL-6 (median [IQR])	49.86 [21.37, 165.60]	27.26 [13.42, 69.53]	44.69 [16.73, 96.38]	24.86 [9.13, 52.42]	0.030
IL-8 (median [IQR])	109.06 [45.88, 221.38]	52.01 [29.07, 82.10]	86.24 [39.51, 216.29]	42.11 [21.31, 100.35]	0.008
IL-10 (median [IQR])	9.42 [4.88, 17.33]	3.15 [1.47, 6.68]	5.70 [3.44, 15.13]	3.28 [1.60, 6.41]	<0.001
MMP8 (median [IQR])	2255.35 [951.82, 3861.82]	864.79 [480.69, 3605.29]	1948.60 [645.26, 4068.04]	1330.16 [588.61, 2405.47]	0.222
D-Dimer (median [IQR]) *	17145.00 [9562.30, 20088.00]	10127.00 [7345.70, 13999.00]	18505.00 [8959.40, 24858.00]	11779.00 [5929.90, 21596.50]	0.098
Protein C (median [IQR])	123040.31 [97911.90, 170611.63]	164618.51 [127390.68, 205896.88]	137783.78 [98908.67, 210257.14]	167468.88 [122591.83, 214128.86]	0.016
Ang-1 (median [IQR])	886.78 [534.92, 2073.90]	1192.84 [754.68, 2677.12]	1051.27 [568.08, 2851.31]	2144.34 [666.22, 5458.76]	0.343
Ang-2 (median [IQR])	10094.40 [5622.90, 17420.07]	4445.76 [2164.96, 9123.84]	3326.26 [2453.65, 8508.91]	3737.63 [2756.56, 6627.10]	0.003
Ang-2/-ang-1 (median [IQR])	9.75 [3.29, 31.69]	3.33 [1.33, 6.35]	4.04 [0.29, 14.72]	2.29 [0.69, 8.29]	0.013
E-Selectin (median [IQR])	45.74 [17.21, 66.04]	32.45 [16.82, 69.09]	32.10 [20.65, 64.24]	27.17 [13.89, 61.13]	0.621
Fractalkine (median [IQR])	42.64 [24.16, 99.77]	24.99 [18.63, 48.01]	20.75 [13.37, 94.57]	19.82 [12.75, 39.40]	0.004
ICAM (median [IQR])	309338.27 [242274.10, 456972.28]	261894.49 [113760.93, 418716.02]	258187.17 [206502.44, 414920.22]	185529.72 [130378.30, 338427.07]	0.025

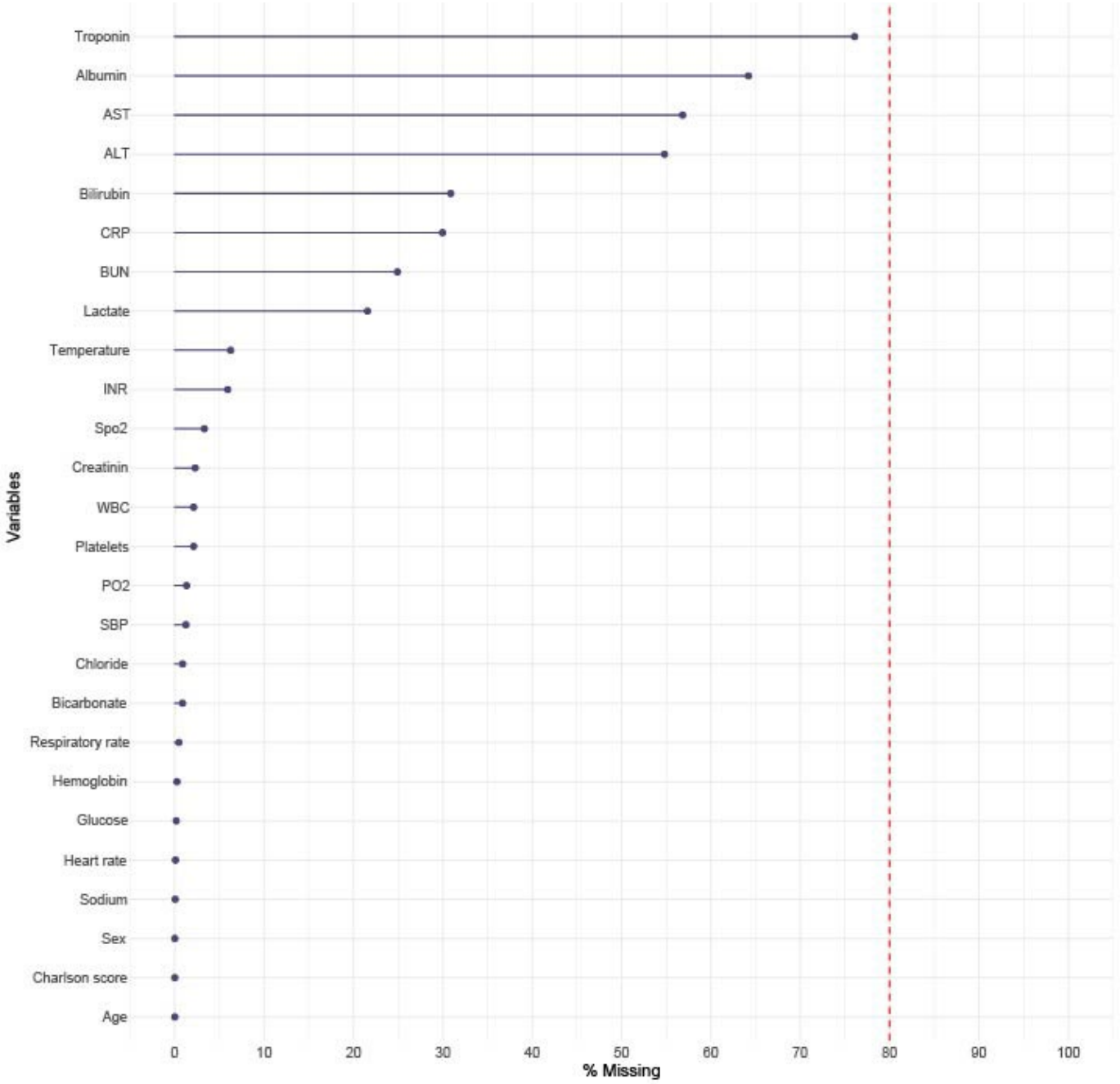
Concentrations are in pg/ml, except for *, these are in ng/ml. Abbreviations: ang, angiopoietin; IL, interleukin; MMP, matrix metalloproteinase; ICAM, intercellular adhesion molecule.

Supplementary Table 7. Longitudinal change in the biomarkers in a linear mixed model compared to δ-δ

Biomarker	Comparator	Estimate	95% CI	Interaction p-value unadjusted*
Biomarkers of inflammation				
IL-6	γ-γ	0.04	0.01-0.07	0.021
	γ-δ	0.02	-0.02-0.06	0.393
	δ-γ	0.02	-0.02-0.06	0.439
IL-8	γ-γ	0.04	0.02-0.06	<0.001**
	γ-δ	0.02	-0.01-0.05	0.112
	δ-γ	0.01	-0.02-0.04	0.434
IL-10	γ-γ	0.06	0.04-0.08	<0.001**
	γ-δ	0.03	0.00-0.07	0.027
	δ-γ	0.03	-0.00-0.06	0.094
MMP8	γ-γ	0.01	-0.02-0.05	0.436
	γ-δ	-0.03	0.08-0.02	0.292
	δ-γ	-0.02	-0.07-0.03	0.434
Biomarkers of coagulation				
D-Dimer	γ-γ	0.01	-0.00-0.03	0.113
	γ-δ	0.02	-0.00-0.04	0.083
	δ-γ	-0.00	-0.02-0.02	0.949
Protein C	γ-γ	0.02	-0.00-0.03	<0.001**
	γ-δ	0.01	0.00-0.02	0.049
	δ-γ	0.01	-0.00-0.02	0.114
Biomarkers of endothelial dysfunction				
Ang-1	γ-γ	0.01	-0.01-0.02	0.600
	γ-δ	0.01	-0.02-0.03	0.651
	δ-γ	-0.01	-0.03-0.02	0.635
Ang-2	γ-γ	0.01	-0.03-0.04	0.635
	γ-δ	-0.05	-0.09-0.00	0.045
	δ-γ	-0.02	-0.06-0.03	0.430
Ang-2/Ang-1	γ-γ	0.00	-0.04-0.04	0.929
	γ-δ	-0.05	-0.11-0.00	0.066
	δ-γ	-0.01	-0.06-0.04	0.645
E-Selectin	γ-γ	0.01	-0.01-0.02	0.450
	γ-δ	-0.01	-0.03-0.01	0.183
	δ-γ	-0.00	-0.02-0.02	0.773
Fractalkine	γ-γ	-0.01	-0.03-0.00	0.043
	γ-δ	0.01	-0.01-0.03	0.164
	δ-γ	-0.02	-0.04-0.00	0.014
ICAM-1	γ-γ	-0.01	-0.02--0.00	0.048
	γ-δ	-0.02	-0.03-0.00	0.032
	δ-γ	-0.01	-0.02-0.01	0.199

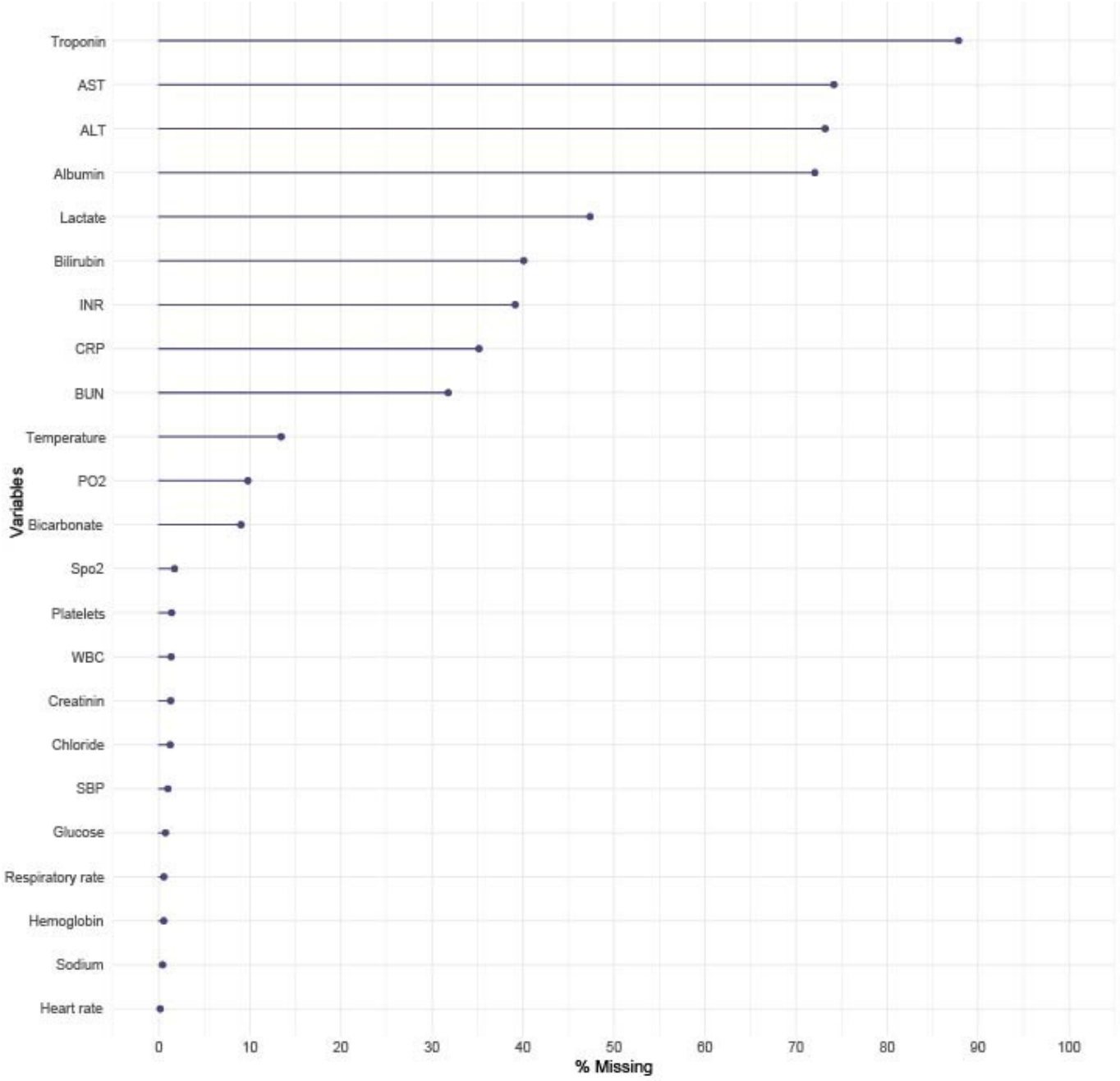
*Unadjusted for multiple comparison. **Significant after adjustment for multiple comparison.
Abbreviations: ang, angiopoietin; IL, interleukin; MMP, matrix metalloproteinase; ICAM, intercellular adhesion molecule.

Supplementary Figure 1. Percentage of the missing variables on ICU admission in the MARS cohort



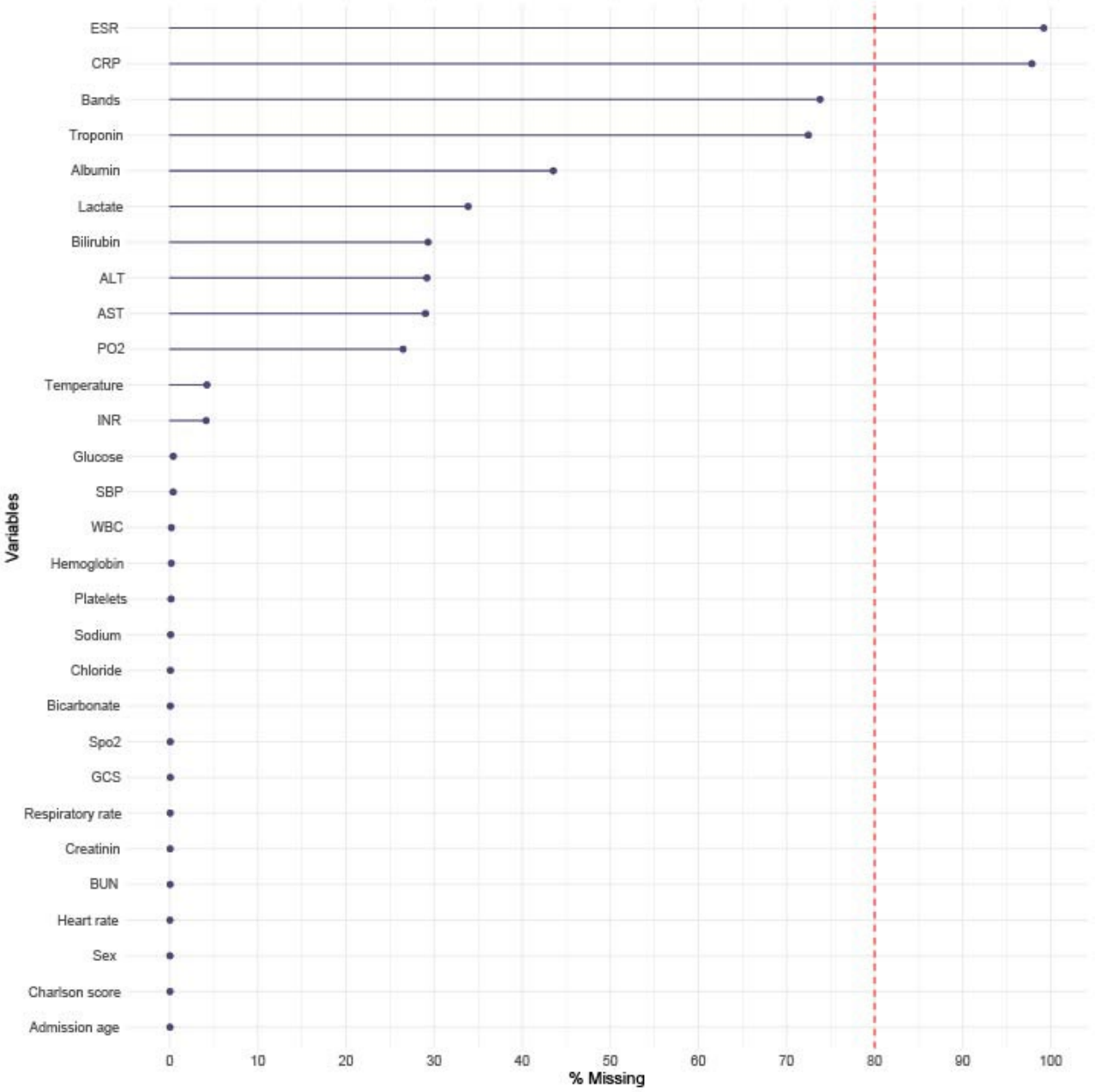
The red dashed line indicates the limit, which was applied to include variables for the subtype adjudication, only variables with <80% missing on ICU admission were used for subtype adjudication. Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; INR, international normalized ratio; Po2, Partial pressure of oxygen; SBP, systolic blood pressure; Spo2, oxygen saturation; WBC, white blood cell count.

Supplementary Figure 2. Percentage of the missing variables on day 2, 4 and 7 in the MARS cohort



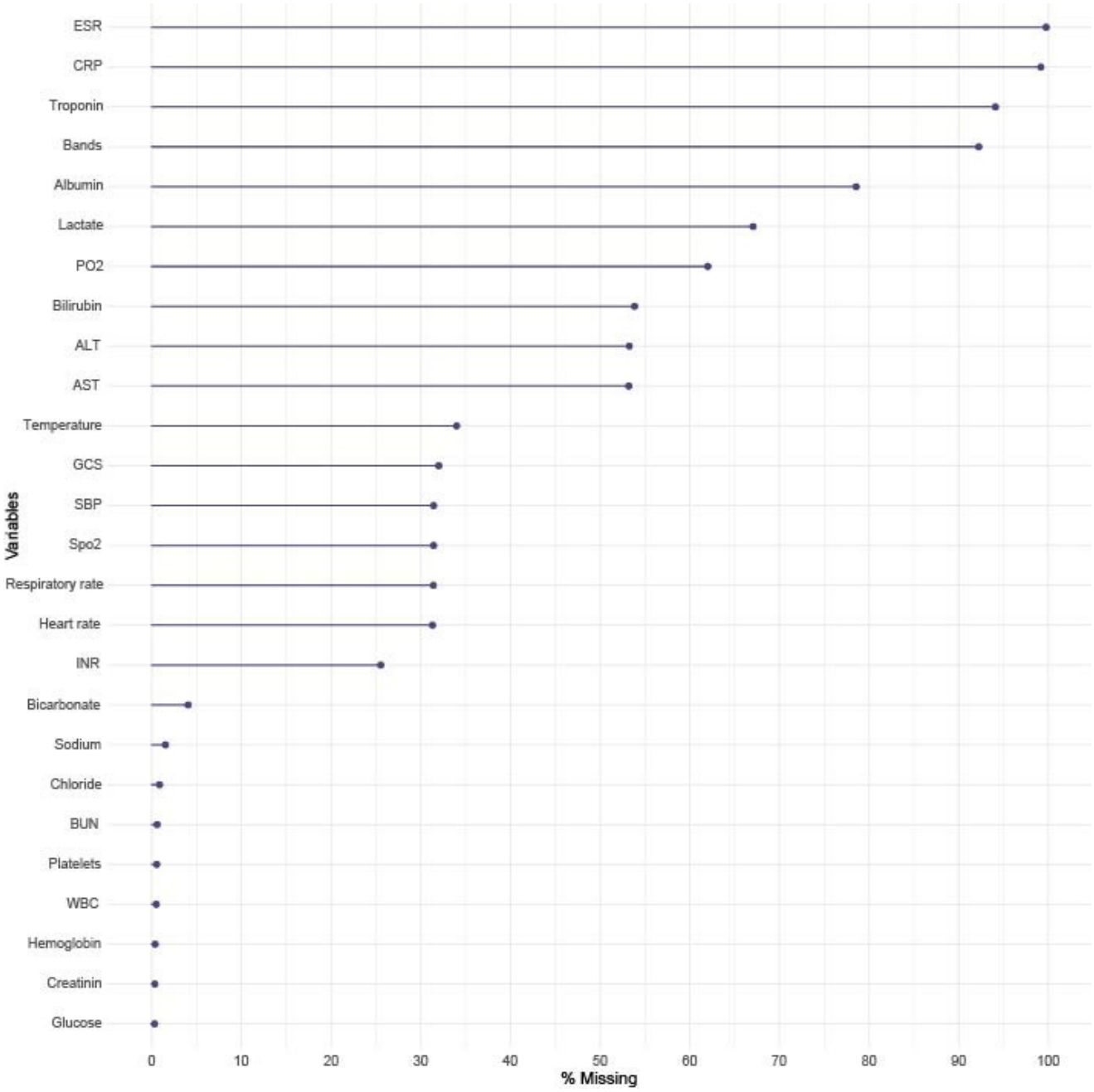
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; INR, international normalized ratio; Po2, Partial pressure of oxygen; SBP, systolic blood pressure; Spo2, oxygen saturation; WBC, white blood cell count.

Supplementary Figure 3. Percentage of the missing variables on ICU admission in the MIMIC-IV cohort



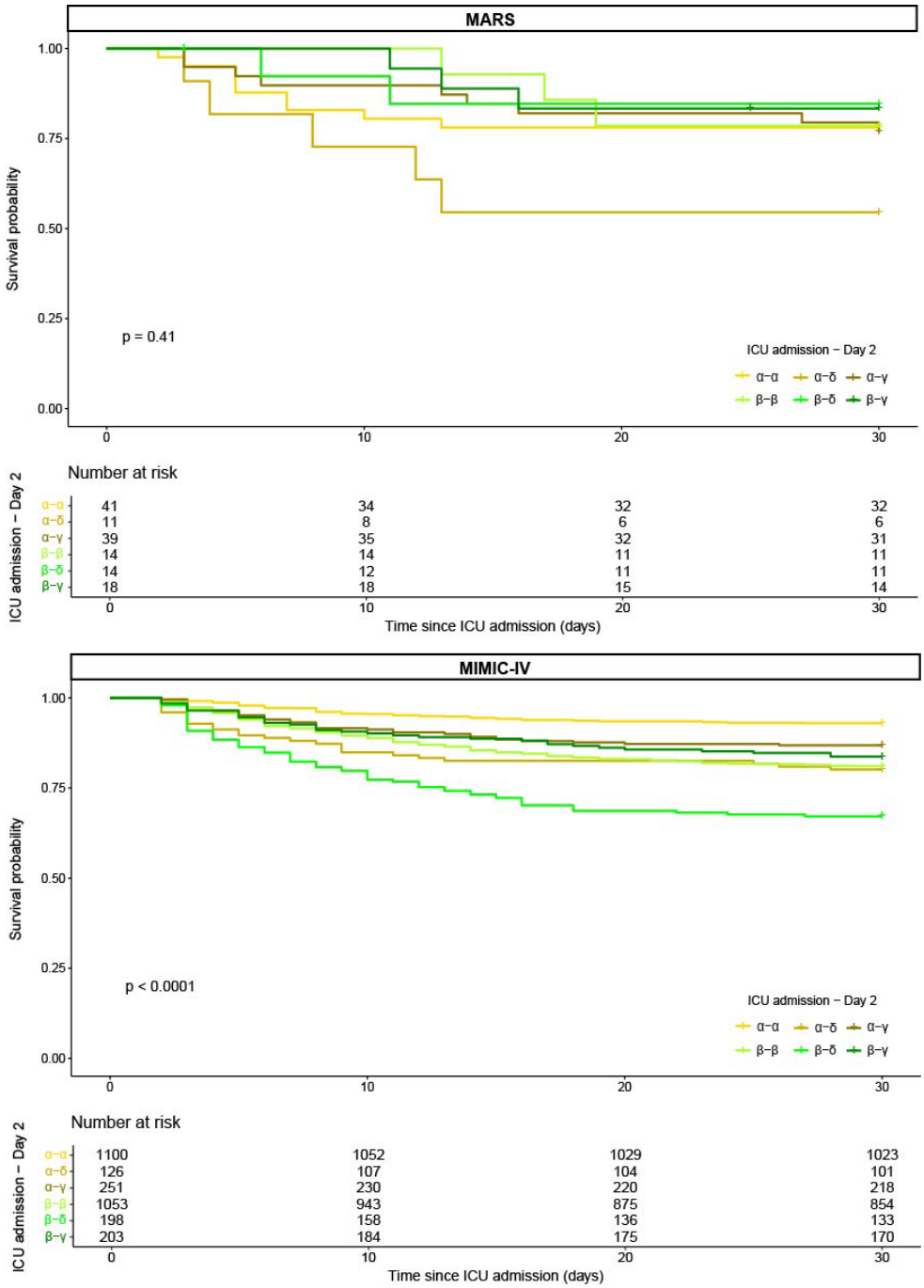
The red dashed line indicates the limit, which was applied to include variables for the subtype adjudication, only variables with <80% missing on ICU admission were used for subtype adjudication; resulting in the exclusion of CRP and ESR. Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ERS, erythrocyte sedimentation rate; GCS, Glasgow Coma Scale; INR, international normalized ratio; Po2, Partial pressure of oxygen; SBP, systolic blood pressure; Spo2, oxygen saturation; WBC, white blood cell count.

Supplementary Figure 4. Percentage of the missing variables on day 2, 4 and 7 in the MIMIC-IV cohort



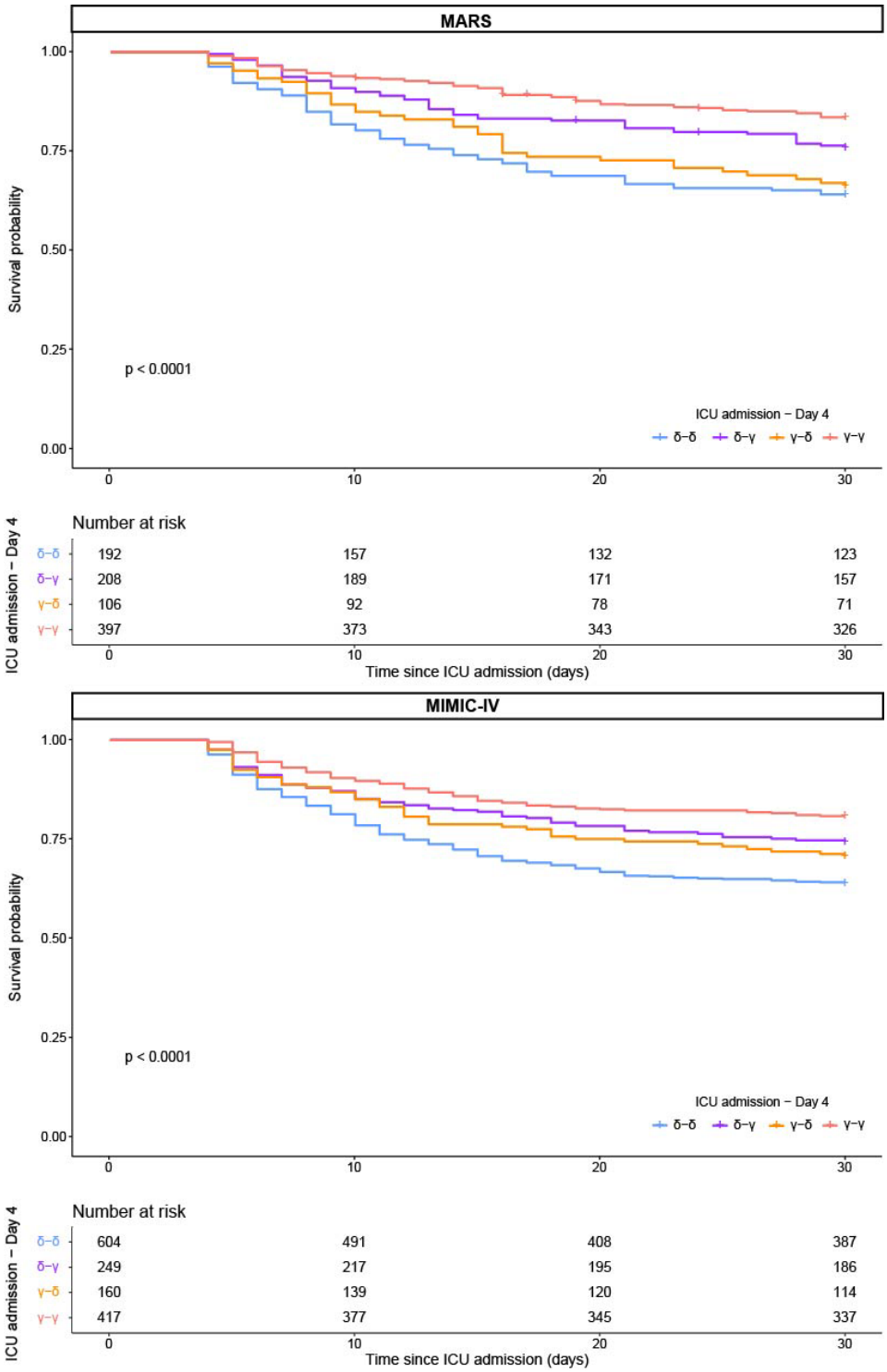
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ERS, erythrocyte sedimentation rate; GCS, Glasgow Coma Scale; INR, international normalized ratio; Po2, Partial pressure of oxygen; SBP, systolic blood pressure; Spo2, oxygen saturation; WBC, white blood cell count.

Supplementary Figure 5. 30-day survival curves according to the subtypes on ICU admission and day 2 in patients with subtype α or β on admission



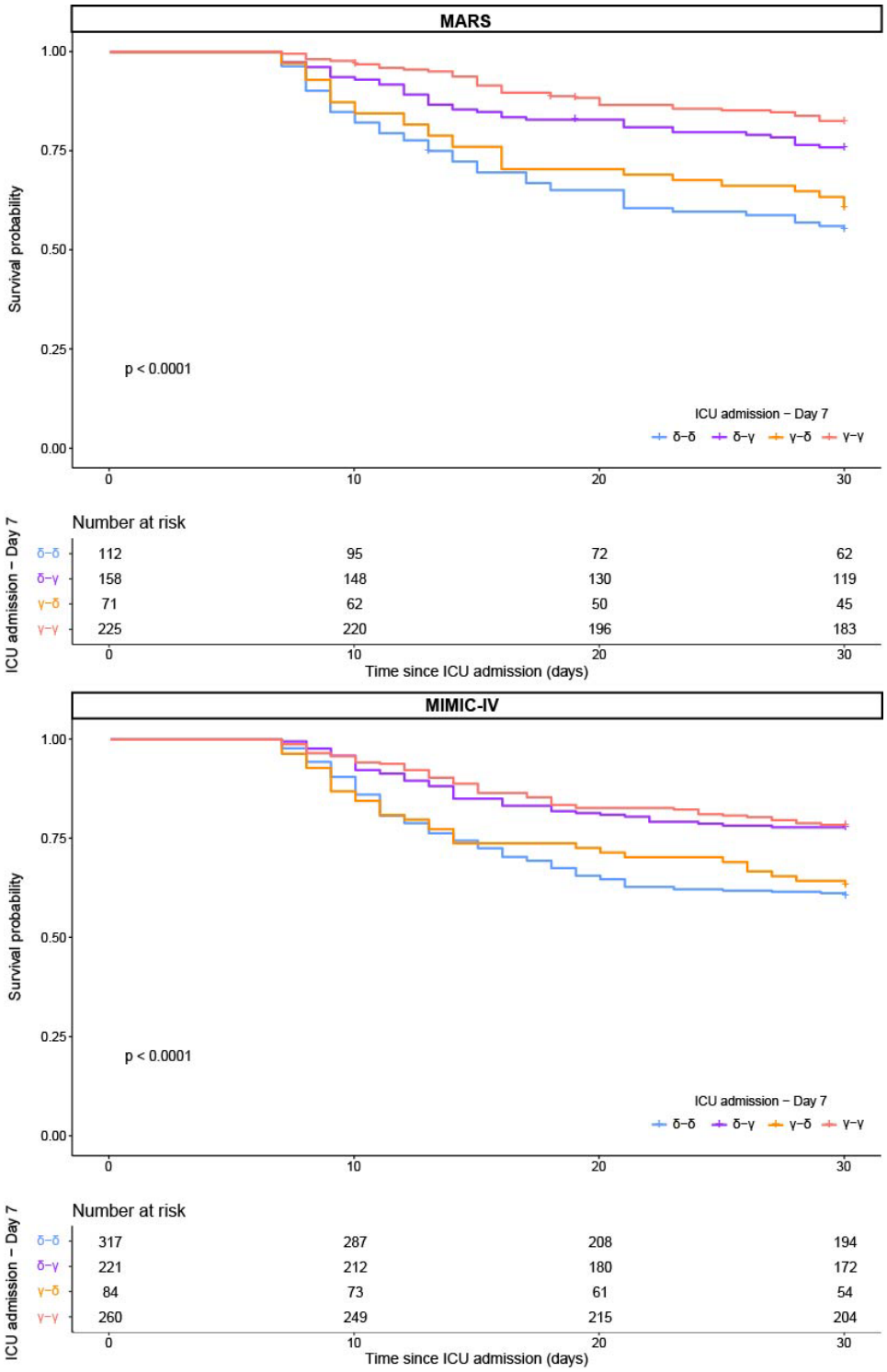
The 30-day survival curves are displayed according to the subtypes on ICU admission and day 2 in the MARS and MIMIC-IV cohort in patients transitioning from α-α to α-γ and α-δ and in β-β to β-γ and β-δ. An unadjusted logistic regression model between the survival curves of the patients with consistent subtype on ICU admission versus those exhibiting a changed subtype by day 2 is shown. Abbreviations: ICU, intensive care unit.

Supplementary Figure 6. 30-day survival curves according to the subtypes on ICU admission and day 4



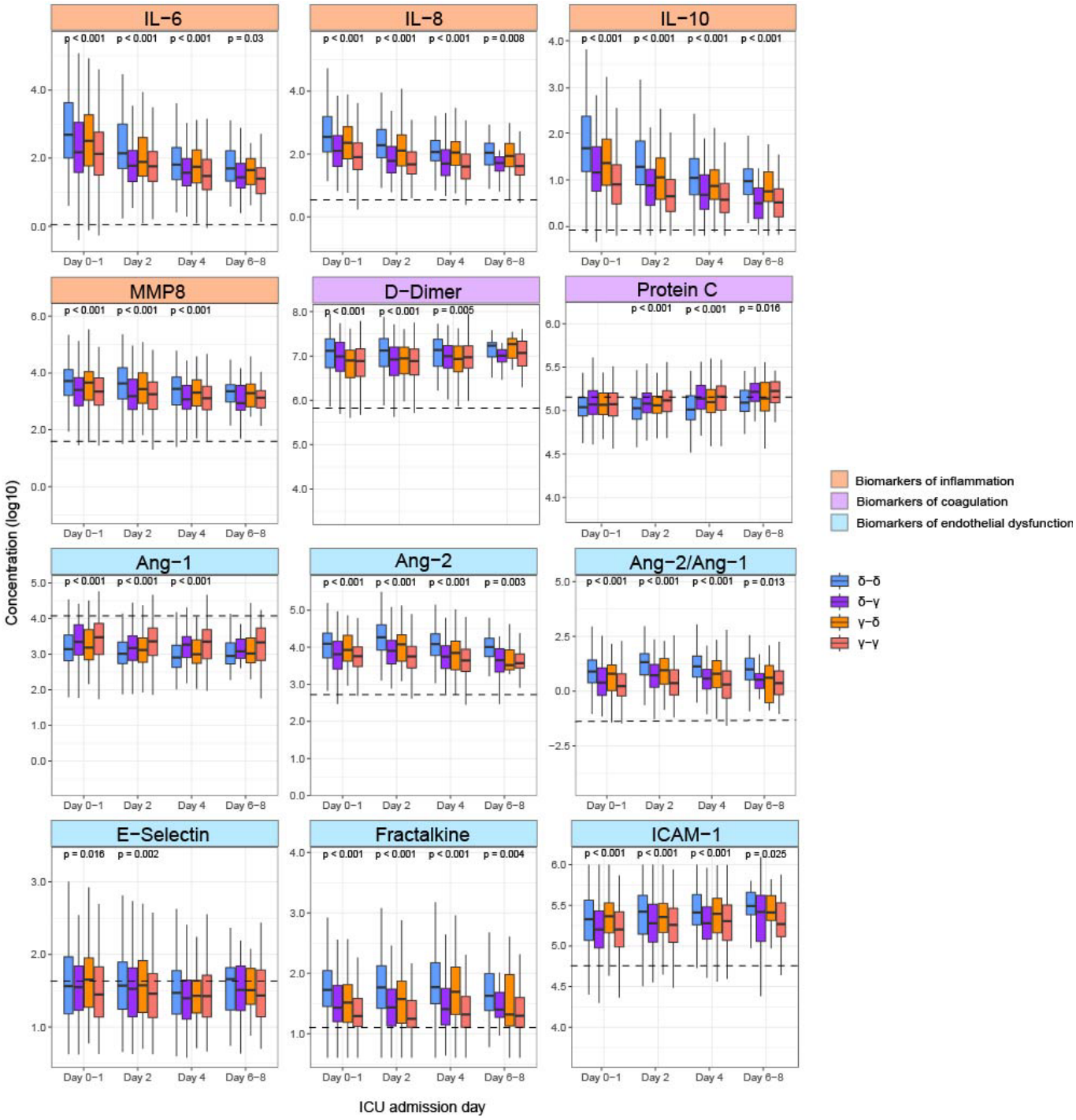
The 30-day survival curves are displayed according to the subtypes on ICU admission and day 4 in the MARS and MIMIC-IV cohort. Only patients with the δ and γ subtype were included in this figure, since the α and γ subtype were only present in a small proportion of the MARS (on baseline α 6.2% and β 2.9%). An unadjusted logistic regression model between the survival curves of the patients with consistent subtype on ICU admission versus those exhibiting a changed subtype by day 4 is shown. Abbreviations: ICU, intensive care unit.

Supplementary Figure 7. 30-day survival curves according to the subtypes on ICU admission and day 7



The 30-day survival curves are displayed according to the subtypes on ICU admission and day 7 in the MARS and MIMIC-IV cohort. Only patients with the δ and γ subtype were included in this figure, since the α and γ subtype were only present in a small proportion of the MARS (on baseline α 6.2% and β 2.9%). An unadjusted logistic regression model between the survival curves of the patients with consistent subtype on ICU admission versus those exhibiting a changed subtype by day 4 is shown. Abbreviations: ICU, intensive care unit.

Supplementary Figure 8. Host response biomarkers



The host response biomarkers during ICU admission are displayed according to the subtypes on ICU admission and day 2 in the MARS cohort. Boxplots displaying biomarker concentrations (pg/ml), after log10 transformation. Horizontal line is the median concentration of healthy volunteers (n = 25). Biomarkers are grouped by domain (Inflammation, Coagulation, and Endothelial dysfunction). Abbreviations: ang, angiopoietin; IL, interleukin; MMP, matrix metalloproteinase; ICAM, intercellular adhesion molecule.

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