Online data supplement

Immunomodulation and endothelial barrier protection mediate the association between oral imatinib and mortality in hospitalised COVID-19 patients

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Table S1. Biomarkers measured.

	Abbreviation
Endothelial cell activation and function	
Angiopoietin-1	Ang-1
Angiopoietin-2	Ang-2
E-selectin	E-selectin
Fractalkine	Fractalkine
Intracellular adhesion molecule 1	ICAM-1
Syndecan-1	Syndecan-1
Syndecan-4	Syndecan-4
Thrombomodulin	Thrombomodulin
Vascular cell adhesion molecule 1	VCAM-1
Cytokine release	
Interferon gamma	IFNγ
Interleukin-2	IL-2
Interleukin-6	IL-6
Interleukin-8	IL-8
Interleukin-10	IL-10
Interleukin-17	IL-17
Tumour necrosis factor alpha	TNFα
Epithelial cell activation and function	
Receptor for advanced glycation end products	RAGE
Surfactant protein D	SP-D
Systemic inflammation	
Platelet-derived growth factor AB	PDGF-AB
Pentraxin-3	PTX-3
Procalcitonin	Procalcitonin
Tumour necrosis factor receptor I	TNFRI
Coagulation	
D-dimer	D-dimer
Tissue factor	TF
Von Willebrand factor	vWF

Table S2. Quality assessment of biomarker measurements.

Biomarker	Within all limits	> ULQ *	< LLQ †	< 25 beads measured ‡
Angiopoietin-1	695 (97.9)	8 (1.1)	..	7 (1.0)
Angiopoietin-2	701 (98.7)	..	..	9 (1.3)
D-dimer	614 (86.5)	61 (8.6)	..	35 (4.9)
E-selectin	703 (99.0)	..	..	7 (1.0)
Fractalkine	165 (23.2)	2 (0.3)	5 (0.7)	538 (75.8)
ICAM-1	702 (98.9)	..	1 (0.1)	7 (1.0)
IFNγ	692 (97.5)	..	11 (1.5)	7 (1.0)
IL-2	618 (87.0)	..	85 (12.0)	7 (1.0)
IL-6	696 (98.0)	..	7 (1.0)	7 (1.0)
IL-8	702 (98.9)	..	1 (0.1)	7 (1.0)
IL-10	519 (73.1)	..	184 (25.9)	7 (1.0)
IL-17	411 (57.9)	..	297 (41.8)	2 (0.3)
PDGF-AB	710 (100)	..	..	..
Pentraxin-3	693 (97.6)	..	11 (1.5)	6 (8.4)
Procalcitonin	690 (97.2)	5 (0.7)	..	15 (2.1)
RAGE	702 (98.9)	..	1 (0.1)	7 (1.0)
SP-D	706 (99.4)	2 (0.3)	..	2 (0.3)
Syndecan-1	675 (95.1)	..	1 (0.1)	34 (4.8)
Syndecan-4	703 (99.0)	..	..	7 (1.0)
Thrombomodulin	703 (99.0)	..	..	7 (1.0)
Tissue factor	703 (99.0)	..	..	7 (1.0)
TNFα	703 (99.0)	..	..	7 (1.0)
TNFRI	710 (100)	..	..	..
VCAM-1	524 (73.8)	183 (25.8)	..	3 (0.4)
Von Willebrand factor	701 (98.7)	..	..	9 (1.3)

Data are n (%). Total N = 710. Abbreviations: ULQ = upper limit of quantification, LLQ = lower limit of quantification, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1. * Values above the upper limit of the calibration curve are extrapolated based on the standard curve. † Values below the lower limit of the calibration curve were set to the lower limit of quantification. ‡ Measurements with less than 25 beads measured were excluded from analysis.

Table S3. Number of samples measured per time point.

	Sample measured	Measurement missed *	Patient deceased	Patient discharged
Baseline	296 (76.9)	89 (23.1)	..	..
Day 2/3	256 (66.5)	100 (26.0)	2 (0.5)	27 (7.0)
Day 5	136 (35.3)	95 (24.7)	17 (4.4)	137 (35.6)

Data are n (%). Total N = 385. * Reasons for a missed measurement include: no blood withdrawal in participating center, failure of withdrawal, patient refusal, logistic difficulties.

Table S4. Comparison of clinical characteristics between patients included and excluded in the secondary analysis.

	Included in secondary analysis n = 332	**Excluded in secondary analysis** n = 53	**p value**
Randomisation, n (%)			
Imatinib group	169 (50.9)	28 (52.8)	0.91
Placebo group	163 (49.1)	25 (47.2)	0.91
Demographics			
Age, years, n (%)	64 [56-73]	62 [56-70]	0.65
Male gender, n (%)	234 (70.5)	30 (56.6)	0.06
BMI, kg/m^2, median [IQR]	28.4 [25.5-32.4]	28.7 [25.7-30.9]	1.00
Comorbidities, n (%) *			
Current or former smoker	130 (41.0)	23 (46.0)	0.61
BMI of > 30 kg/m^2	113 (38.4)	15 (30.6)	0.37
Diabetes	88 (26.5)	12 (22.6)	0.67
Cardiovascular disease †	77 (23.2)	6 (11.3)	0.08
Hypertension	122 (36.7)	23 (43.4)	0.44
COPD or asthma	62 (18.7)	9 (17.0)	0.92
Venous thromboembolism	5 (1.5)	5 (9.4)	**< 0.01**
Renal failure	12 (3.6)	2 (3.8)	1.00
Hepatic disease	2 (0.6)	0 (0.0)	1.00
Rheumatic disease	23 (6.9)	6 (11.3)	0.40
Heart failure	11 (3.3)	1 (1.9)	0.90
Medical treatments, n (%) ‡			
Glucose lowering drugs	83 (25.0)	11 (20.8)	0.62
Antihypertensive treatment	170 (51.2)	23 (43.4)	0.36
ACE or ARB	104 (31.3)	17 (32.1)	1.00
Statins	108 (32.5)	19 (35.8)	0.75
Platelet inhibitors	72 (21.7)	10 (18.9)	0.78
Oral anticoagulants	33 (9.9)	5 (9.4)	1.00
Laboratory values at admission, median [IQR]			
Hemoglobin, mmol/L	8.5 [7.9-9.1]	8.3 [7.5-9.0]	0.10
Leukocytes, x 10^9 cells/L	7.7 [5.7-10.3]	7.1 [5.7-9.3]	0.53
Neutrophils, x 10^9 cells/L	6.0 [4.3-8.5]	5.6 [3.9-8.1]	0.44
Lymphocytes, x 10^9 cells/L	0.90 [0.60-1.20]	1.10 [0.70-1.27]	0.11
Thrombocytes, x 10^9 cells/L	238 [189-315]	257 [190-322]	0.60
Urea, mmol/L	6.6 [4.8-8.8]	6.6 [4.9-8.1]	0.70
Creatinine, µmol/L	77 [65-91]	77 [65-90]	0.93
C-reactive protein, mg/L	99 [47-155]	95 [38-128]	0.41
Medication initiated at admission, n (%)			
Low-molecular-weight heparin	271 (81.6)	46 (86.8)	0.47
Oral anticoagulants	27 (8.1)	3 (5.7)	0.73
Antibiotics	132 (39.6)	29 (54.7)	0.05
Dexamethasone	242 (72.9)	34 (64.2)	0.25
Remdesivir	66 (19.9)	14 (26.4)	0.37
(Hydroxy)chloroquine	26 (7.8)	3 (5.7)	0.78
Clinical outcomes			
28-day mortality, n (%)	37 (11.1)	5 (9.4)	0.89

90-day mortality, n (%)	43 (13.0)	6 (11.3)	0.91
Time to discontinuation of oxygen support, days, median [IQR] §	7 [5-11]	5 [3-8]	< **0.01**
Duration of hospital admission, days, median [IQR]	7 [4-11]	5 [3-12]	0.19
Need for mechanical ventilation, n (%)	47 (14.2)	9 (17.0)	0.74
Duration of mechanical ventilation, days, median [IQR]	10 [5-18]	7 [4-10]	0.41
Duration of ICU admission, days, median [IQR]	9 [5-18]	9 [8-10]	0.92

Data are median [interquartile range] or n (%). ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit, IQR = interquartile range. * Comorbidities as reported at admission or present in the patient's medical record. † Cardiovascular diseases included arrhythmias (predominantly atrial fibrillation), valvular disease, coronary artery disease and conduction disorders. ‡ Medical treatment (or home medication) as reported at admission or present in the patient's medical record. § Time to discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours, while being alive during a 28-day period after randomisation.

Table S5. Clinical characteristics of patients with baseline biomarker data available (i.e. moderation analysis cohort).

	Imatinib group n = 154	**Placebo group** n = 142
Demographics		
Age, years, median [IQR]	65 [57-74]	64 [56-74]
Male gender, n (%)	116 (75.3)	93 (65.5)
BMI, kg/m^2, median [IQR]	27.4 [25.2-31.1]	29.7 [25.7-32.9]
Comorbidities, n (%) *		
Current or former smoker	59 (39.6)	58 (43.3)
BMI of > 30 kg/m^2	39 (28.5)	61 (48.4)
Diabetes	31 (20.1)	42 (29.6)
Cardiovascular disease †	31 (20.1)	38 (26.8)
Hypertension	52 (33.8)	54 (38.0)
COPD or asthma	28 (18.2)	30 (21.1)
Venous thromboembolism	2 (1.3)	2 (1.4)
Renal failure	5 (3.2)	5 (3.5)
Hepatic disease	1 (0.6)	1 (0.7)
Rheumatic disease	8 (5.2)	12 (8.5)
Heart failure	8 (5.2)	3 (2.1)
Medical treatments, n (%) ‡		
Glucose lowering drugs	30 (19.5)	38 (26.8)
Antihypertensive treatment	70 (45.5)	80 (56.3)
ACE or ARB	39 (25.3)	55 (38.7)
Statins	47 (30.5)	51 (35.9)
Platelet inhibitors	33 (21.4)	33 (23.2)
Oral anticoagulants	15 (9.7)	17 (12.0)
Laboratory values at admission, median [IQR]		
Hemoglobin, mmol/L	8.5 [7.8-9.1]	8.6 [7.9-9.1]
Leukocytes, x 10^9 cells/L	7.7 [5.6-10.4]	7.8 [6.0-10.1]
Neutrophils, x 10^9 cells/L	6.0 [4.2-8.6]	6.1 [4.4-8.2]
Lymphocytes, x 10^9 cells/L	0.90 [0.60-1.10]	0.90 [0.60-1.22]
Thrombocytes, x 10^9 cells/L	240 [184-322]	232 [189-311]
Urea, mmol/L	6.6 [4.7-8.8]	6.6 [5.0-8.7]
Creatinine, µmol/L	77 [64-89]	78 [66-92]
C-reactive protein, mg/L	104 [47-161]	91 [45-142]
Medication initiated at admission, n (%)		
Low-molecular-weight heparin	132 (85.7)	111 (78.2)
Oral anticoagulants	8 (5.2)	13 (9.2)
Antibiotics	61 (39.6)	51 (35.9)
Dexamethasone	115 (74.7)	103 (72.5)
Remdesivir	30 (19.5)	30 (21.1)
(Hydroxy)chloroquine	13 (8.4)	10 (7.0)

Data are median [interquartile range] or n (%). No p values are shown for baseline data, since data is obtained from a randomised controlled trial. ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit, IQR = interquartile range. * Comorbidities as reported at admission or present in the patient's medical record. † Cardiovascular diseases included arrhythmias (predominantly atrial fibrillation), valvular disease, coronary artery disease and conduction disorders. ‡ Medical treatment (or home medication) as reported at admission or present in the patient's medical record.

Table S6. Baseline (pre-treatment) plasma biomarker concentrations, stratified by treatment group.

	Imatinib group n = 154	**Placebo group** n = 142	**BH adjusted p value**
Endothelial cell activation and function			
Ang-2/Ang-1	0.20 [0.13 – 0.37]	0.20 [0.11 – 0.37]	0.78
E-selectin, ng/mL	23.32 [16.42 – 31.69]	26.11 [18.41 – 34.06]	0.30
ICAM-1, ng/mL	275.93 [213.70 – 388.37]	337.53 [243.18 – 496.03]	0.07
Syndecan-1, ng/mL	6.63 [4.65 – 9.35]	6.79 [4.60 – 9.65]	0.79
Syndecan-4, ng/mL	0.73 [0.49 – 1.11]	0.70 [0.49 – 1.03]	0.79
Thrombomodulin, ng/mL	5.11 [3.77 – 6.91]	5.50 [4.34 – 7.43]	0.29
VCAM-1, µg/mL	3.22 [2.08 – 6.53]	3.40 [2.15 – 5.96]	0.80
Cytokine release			
IFNγ, pg/mL	18.05 [10.79 – 24.83]	18.05 [11.20 – 30.27]	0.60
IL-2, pg/mL	6.64 [2.37 – 10.96]	7.68 [3.46 – 10.96]	0.48
IL-6, pg/mL	10.46 [6.03 – 17.00]	11.32 [7.47 – 24.31]	0.30
IL-8, pg/mL	12.99 [7.27 – 22.09]	14.47 [9.62 – 25.09]	0.29
IL-10, pg/mL	7.68 [1.09 – 13.24]	8.46 [2.68 – 13.24]	0.79
IL-17, pg/mL	2.49 [0.53 – 5.86]	2.49 [0.53 – 8.80]	0.59
TNFα, pg/mL	11.22 [8.58 – 13.84]	11.99 [9.64 – 15.41]	0.30
Epithelial cell activation and function			
RAGE, ng/mL	3.79 [2.00 – 7.28]	3.99 [2.50 – 7.85]	0.48
SP-D, ng/mL	8.15 [3.57 – 16.48]	9.31 [4.03 – 22.37]	0.48
Systemic inflammation			
PDGF-AB, ng/mL	0.91 [0.53 – 1.41]	0.92 [0.64 – 1.40]	0.80
Pentraxin-3, ng/mL	6.53 [3.39 – 1.11]	6.14 [3.25 – 10.83]	0.59
Procalcitonin, pg/mL	73.10 [44.95 – 121.03]	80.55 [49.21 – 138.50]	0.78
TNFRI, ng/mL	1.90 [1.37 – 2.36]	1.98 [1.50 – 2.68]	0.48
Coagulation			
D-dimer, µg/mL	3.17 [2.21 – 4.71]	3.59 [2.02 – 5.62]	0.48
Tissue factor, pg/mL	42.70 [30.05 – 61.79]	45.73 [34.19 – 68.27]	0.31
Von Willebrand factor, ng/mL	5.51 [3.68 – 7.88]	5.67 [3.94 – 7.80]	0.79

Results are presented as median [interquartile range]. Ang = angiopoietin, BH = Benjamini–Hochberg, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1.

Table S7. Clinical characteristics of patients with baseline biomarker data available, stratified by subphenotype.

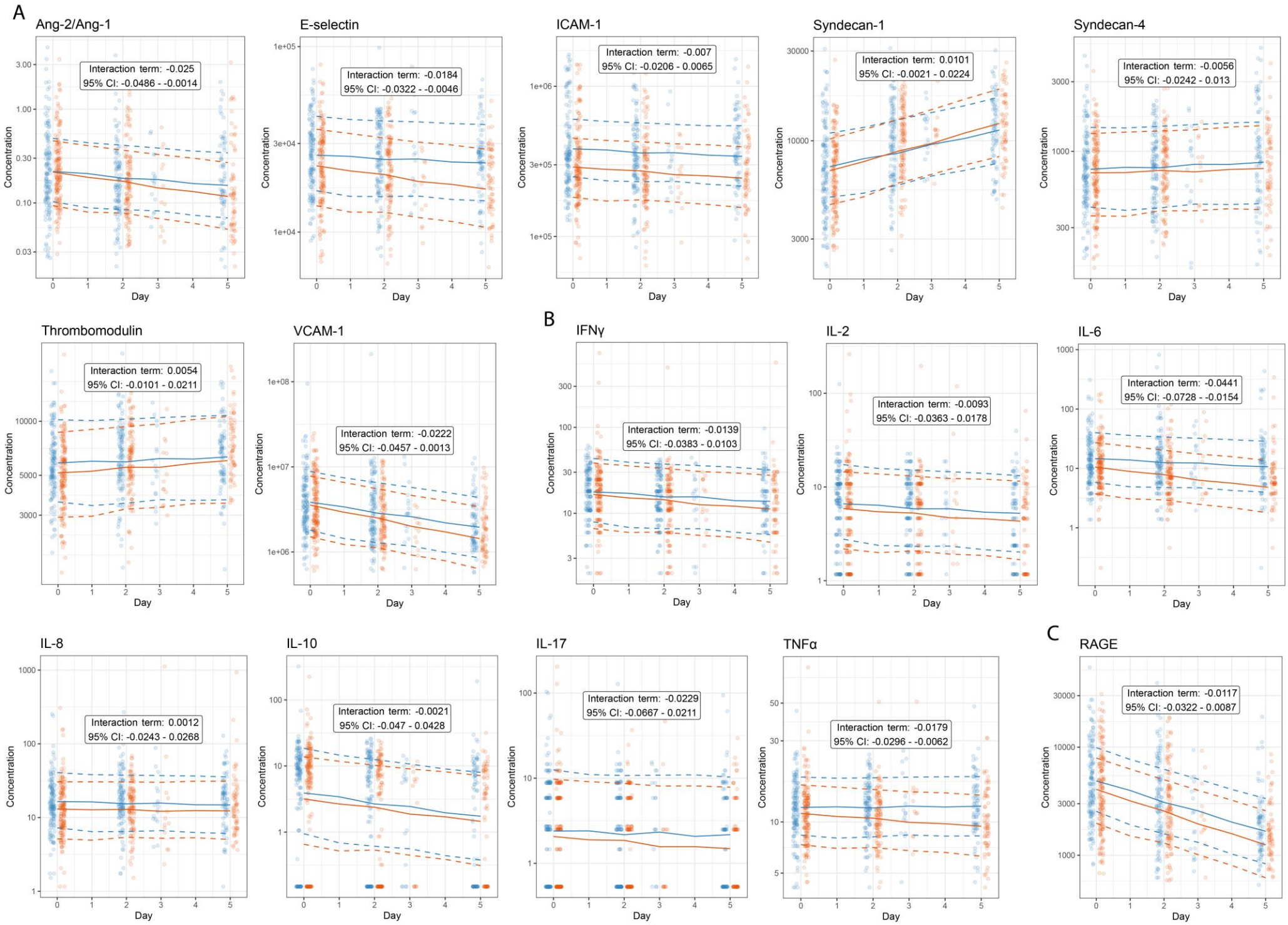
	Cluster 1 n = 102	**Cluster 2** n = 70	**Cluster 3** n = 122	**p value**
Randomisation, n (%)				
Imatinib group	55 (53.9)	39 (55.7)	59 (48.4)	0.55
Placebo group	47 (46.1)	31 (44.3)	63 (51.6)	0.55
Demographics				
Age, years, median [IQR]	65 [57-74]	61 [52-67]	68 [58-76]	**0.01**
Male gender, n (%)	78 (76.5)	37 (52.9)	93 (76.2)	**< 0.01**
BMI, kg/m^2, median [IQR]	28.7 [25.6-31.9]	28.6 [25.6-33.1]	27.8 [25.2-31.6]	0.72
Medical treatments, n (%) *				
Glucose lowering drugs	30 (29.4)	13 (18.6)	25 (20.5)	0.17
Antihypertensive treatment	58 (56.9)	33 (47.1)	59 (48.4)	0.34
ACE or ARB	34 (33.3)	23 (32.9)	37 (30.3)	0.88
Statins	37 (36.3)	18 (25.7)	43 (35.2)	0.30
Platelet inhibitors	23 (22.5)	10 (14.3)	32 (26.2)	0.16
Oral anticoagulants	9 (8.8)	7 (10.0)	16 (13.1)	0.57
Vital signs at admission, median [IQR]				
Mean arterial pressure, mm Hg	90 [84-101]	90 [83-99]	90 [85-98]	0.80
Heart rate, beats per min	81 [70-91]	74 [66-83]	79 [69-87]	**0.01**
Peripheral oxygen saturation, %	94 [92-96]	94 [93-96]	94 [92-95]	0.23
Oxygen support, L/min	5 [3-10]	3 [2-5]	5 [3-10]	**0.01**
Respiratory rate, /min	22 [18-27]	18 [16-21]	20 [18-24]	**< 0.01**
Temperature, °C	36.8 [36.3-37.5]	36.7 [36.4-37.1]	36.7 [36.3-37.2]	0.22
Laboratory values at admission, median [IQR]				
Hemoglobin, mmol/L	8.6 [7.9-9.2]	8.6 [8.0-9.1]	8.4 [7.8-9.1]	0.36
Leukocytes, x 10^9 cells/L	8.0 [5.6-10.8]	6.7 [5.2-9.0]	8.1 [6.3-10.7]	**0.01**
Neutrophils, x 10^9 cells/L	6.2 [4.0-9.0]	5.0 [3.7-6.5]	6.6 [4.6-9.3]	**< 0.01**
Lymphocytes, x 10^9 cells/L	0.84 [0.60-1.03]	1.00 [0.83-1.37]	0.80 [0.60-1.10]	**< 0.01**
Thrombocytes, x 10^9 cells/L	220 [178-270]	256 [199-331]	240 [192-330]	**0.01**
Urea, mmol/L	7.1 [5.5-10.4]	5.5 [4.2-7.0]	6.8 [5.0-8.6]	**< 0.01**
Creatinine, µmol/L	81 [71-100]	69 [58-83]	76 [64-89]	**< 0.01**
C-reactive protein, mg/L	116 [66-171]	63 [32-125]	104 [50-150]	**< 0.01**
Medication initiated at admission, n (%)				
Low-molecular-weight heparin	85 (83.3)	58 (82.9)	98 (80.3)	0.82
Oral anticoagulants	5 (4.9)	3 (4.3)	13 (10.7)	0.14
Antibiotics	35 (34.3)	21 (30.0)	55 (45.1)	0.08
Dexamethasone	77 (75.5)	47 (67.1)	93 (76.2)	0.35
Remdesivir	25 (24.5)	13 (18.6)	21 (17.2)	0.37
(Hydroxy)chloroquine	6 (5.9)	7 (10.0)	10 (8.2)	0.60
Clinical outcomes				
28-day mortality, n (%)	16 (15.7)	2 (2.9)	15 (12.3)	**0.03**
90-day mortality, n (%)	18 (17.6)	4 (5.7)	17 (13.9)	0.07
Time to discontinuation of oxygen support, days, median [IQR] †	8 [5-13]	6 [4-9]	8 [5-11]	**0.01**
Duration of hospital admission, days, median [IQR]	7 [4-15]	4 [3-8]	7 [4-11]	**< 0.01**
Need for mechanical ventilation, n (%)	21 (20.6)	2 (2.9)	14 (11.5)	**< 0.01**
Duration of mechanical ventilation, days, median [IQR]	11 [6-19]	22 [21-24]	6 [3-11]	0.07
Duration of ICU admission, days, median [IQR]	12 [6-21]	23 [18-24]	7 [5-11]	0.07

Data are median [interquartile range] or n (%). ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit, IQR = interquartile range. * Medical treatment (or home medication) as reported at admission or present in the patient's medical record. † Time to discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours, while being alive during a 28-day period after randomisation.

Table S8. Clinical outcome of patients with baseline biomarker data available, stratified by subphenotype.

	Cluster 1 n = 102	**Cluster 2** n = 70	**Cluster 3** n = 122
90-day mortality			
Unadjusted	0.83 (0.33 – 2.09)	0.81 (0.11 – 5.78)	0.30 (0.10 – 0.92)
Adjusted for sex, BMI, diabetes and cardiovascular disease	0.61 (0.22 – 1.75)	1.06 (0.12 – 9.27)	0.20 (0.05 – 0.70)

Data are HR (95% CI). All HRs are for the imatinib group versus placebo group. HRs and 95% CIs were calculated by use of Cox regression analysis. HR = hazard ratio. CI = confidence interval. BMI = body mass index.


A
Ang-2/Ang-1
Interaction term: -0.025
95% CI: -0.0486 - -0.0014
E-selectin
Interaction term: -0.0184
95% CI: -0.0322 - -0.0046
ICAM-1
Interaction term: -0.007
95% CI: -0.0206 - 0.0065
Syndecan-1
Interaction term: 0.0101
95% CI: -0.0021 - 0.0224
Syndecan-4
Interaction term: -0.0056
95% CI: -0.0242 - 0.013
Thrombomodulin
Interaction term: 0.0054
95% CI: -0.0101 - 0.0211
VCAM-1
Interaction term: -0.0222
95% CI: -0.0457 - 0.0013
B
IFNγ
Interaction term: -0.0139
95% CI: -0.0383 - 0.0103
IL-2
Interaction term: -0.0093
95% CI: -0.0363 - 0.0178
IL-6
Interaction term: -0.0441
95% CI: -0.0728 - -0.0154
IL-8
Interaction term: 0.0012
95% CI: -0.0243 - 0.0268
IL-10
Interaction term: -0.0021
95% CI: -0.047 - 0.0428
IL-17
Interaction term: -0.0229
95% CI: -0.0667 - 0.0211
TNFα
Interaction term: -0.0179
95% CI: -0.0296 - -0.0062
C
RAGE
Interaction term: -0.0117
95% CI: -0.0322 - 0.0087
Concentration
Day

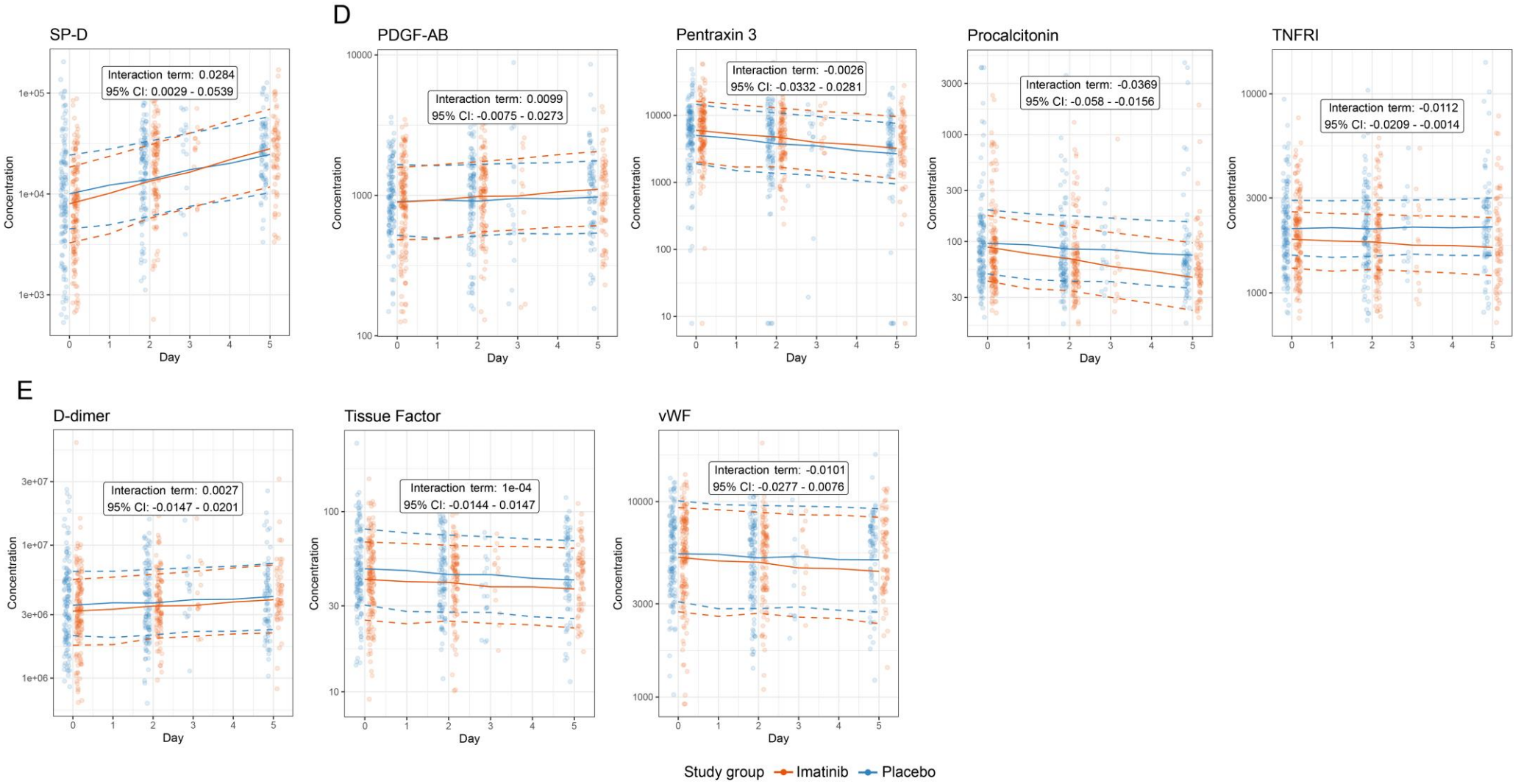


Figure S1. Longitudinal plasma concentrations of biomarkers reflective of host response pathways implicated in COVID-19 pathogenesis, stratified by treatment group. A = endothelial cell activation and function, B = cytokine release, C = epithelial cell activation and function, D = systemic inflammation, E = coagulation. Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1, vWF = Von Willebrand factor.

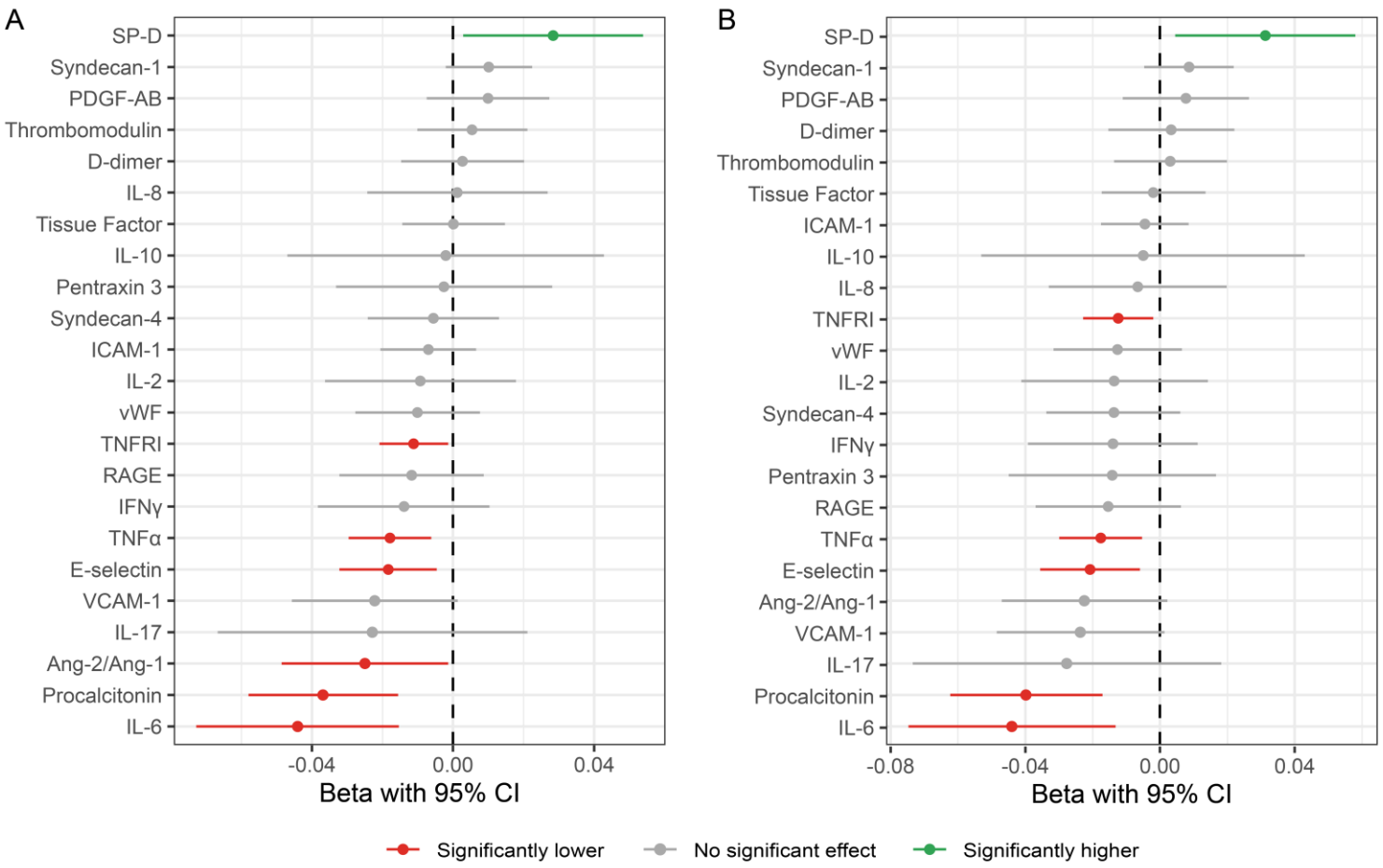


Figure S2A: The effect of imatinib on the biomarker concentration over time, when compared to placebo. **S2B**: The effect of imatinib on the biomarker concentration over time, corrected for body mass index, age, cardiovascular disease and diabetes. SP-D = surfactant protein D, PDGF-AB = platelet-derived growth factor AB, IL = interleukin, ICAM-1 = intracellular adhesion molecule 1, vWF = Von Willebrand factor, TNFRI = tumour necrosis factor receptor I, RAGE = receptor for advanced glycation end products, IFNγ = interferon gamma, TNFα = tumour necrosis factor alpha, VCAM-1 = vascular cell adhesion molecule 1, Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1.

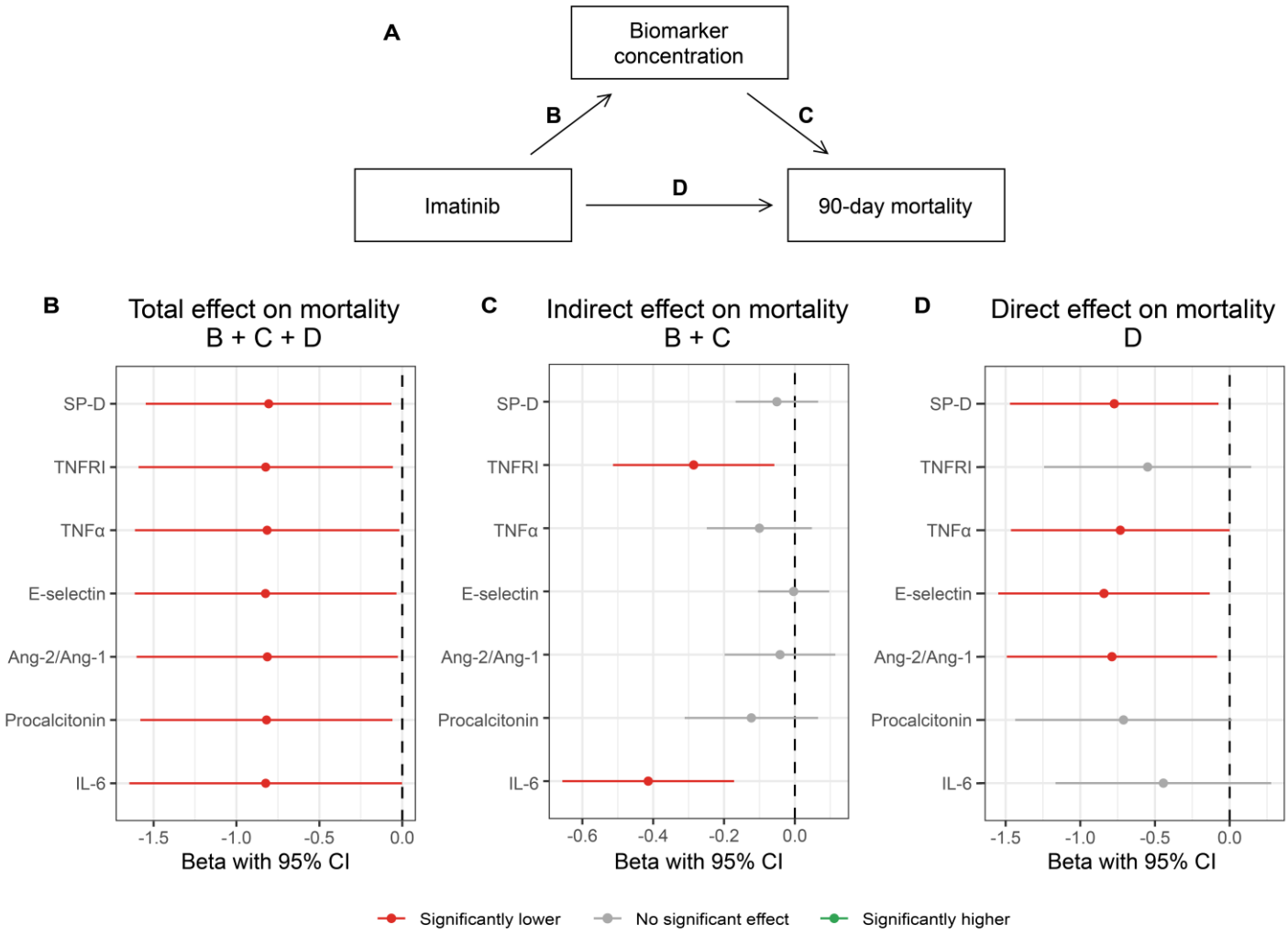


Figure S3A: Visualisation of mediation analysis with natural effects. **3B**: The total effect of imatinib on 90-day mortality, when compared to placebo, including its effects through the biomarker. **3C:** The indirect effect of imatinib on 90-day mortality, i.e. the effect of imatinib on 90-day mortality that is mediated by a change in biomarker concentration. **3D:** The effect of imatinib on 90-day mortality, when the effect of the biomarkers is left out. Abbreviations: SP-D = surfactant protein D, TNFRI = tumour necrosis factor receptor I, TNFα = tumour necrosis factor alpha, Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, IL-6 = interleukin-6.

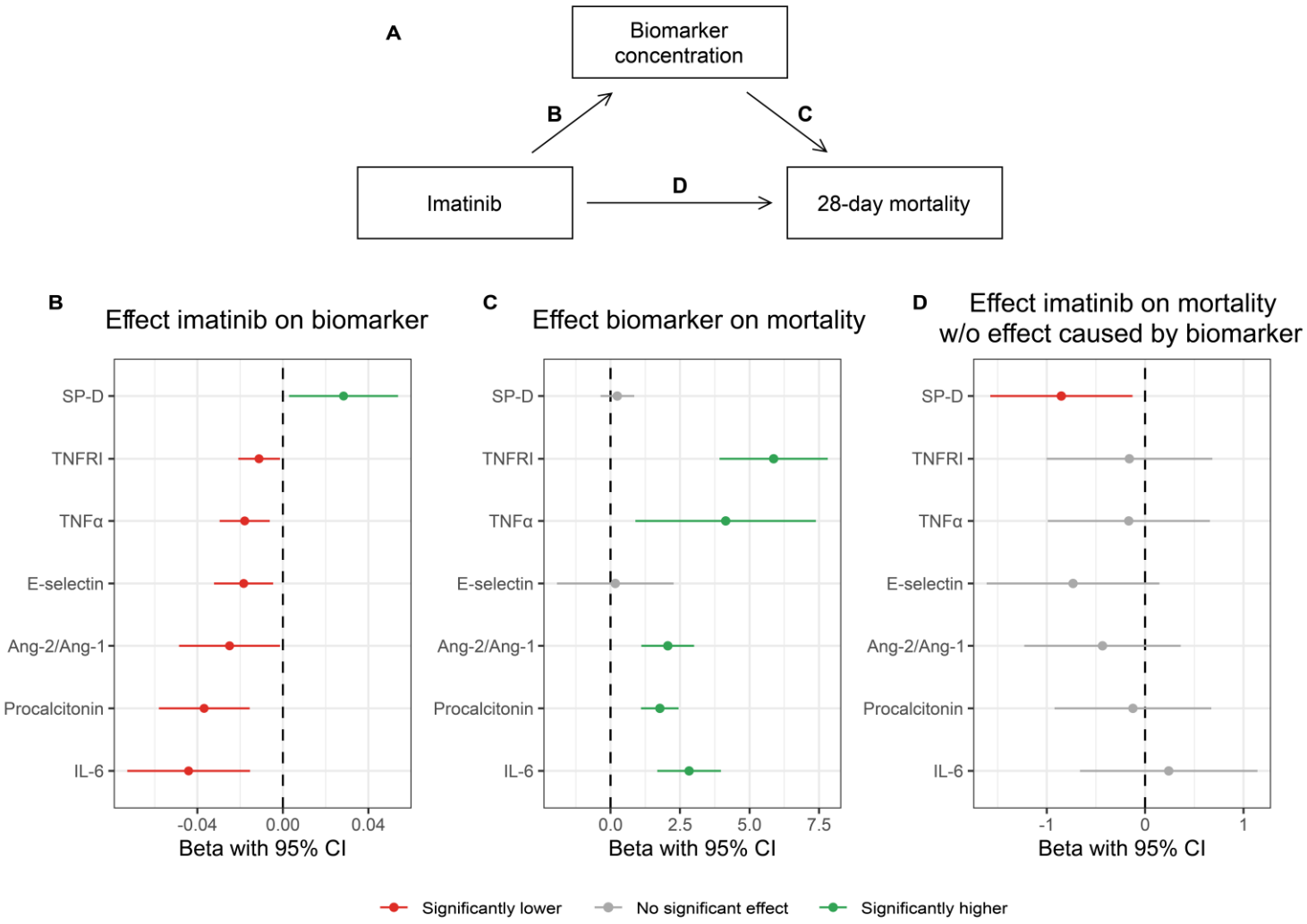


Figure S4A: Visualisation of mediation analysis. **4B:** The effect of imatinib on the biomarker concentration over time, when compared to placebo. **4C:** The effect of an increased biomarker concentration over time on 28-day mortality. **4D:** The effect of imatinib on 28-day mortality, when the effect of the biomarkers is left out. The effect of imatinib on 28-day mortality is completely mediated by changes in TNFRI, TNFα, E-selectin, Ang-2/Ang-1, procalcitonin and IL-6. Abbreviations: SP-D = surfactant protein D, TNFRI = tumour necrosis factor receptor I, TNFα = tumour necrosis factor alpha, Ang-2/Ang-1 = angiopoietin 2 to 1 ratio, IL-6 = interleukin-6.

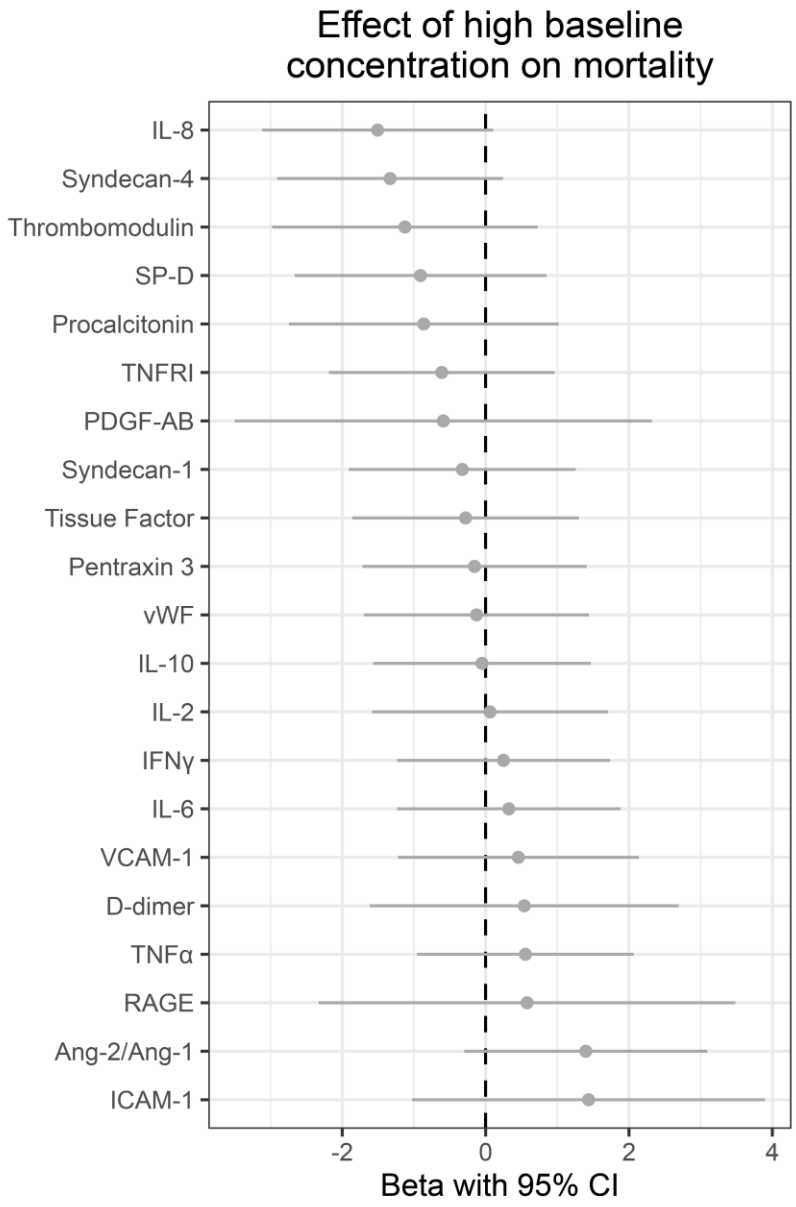


Figure S5. The effect of having a high baseline biomarker concentration on 90-day mortality in patients treated with imatinib, when compared to placebo. Dichotomisation between high and low biomarker concentrations was done by maximally selected rank statistics. Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1, vWF = Von Willebrand factor.

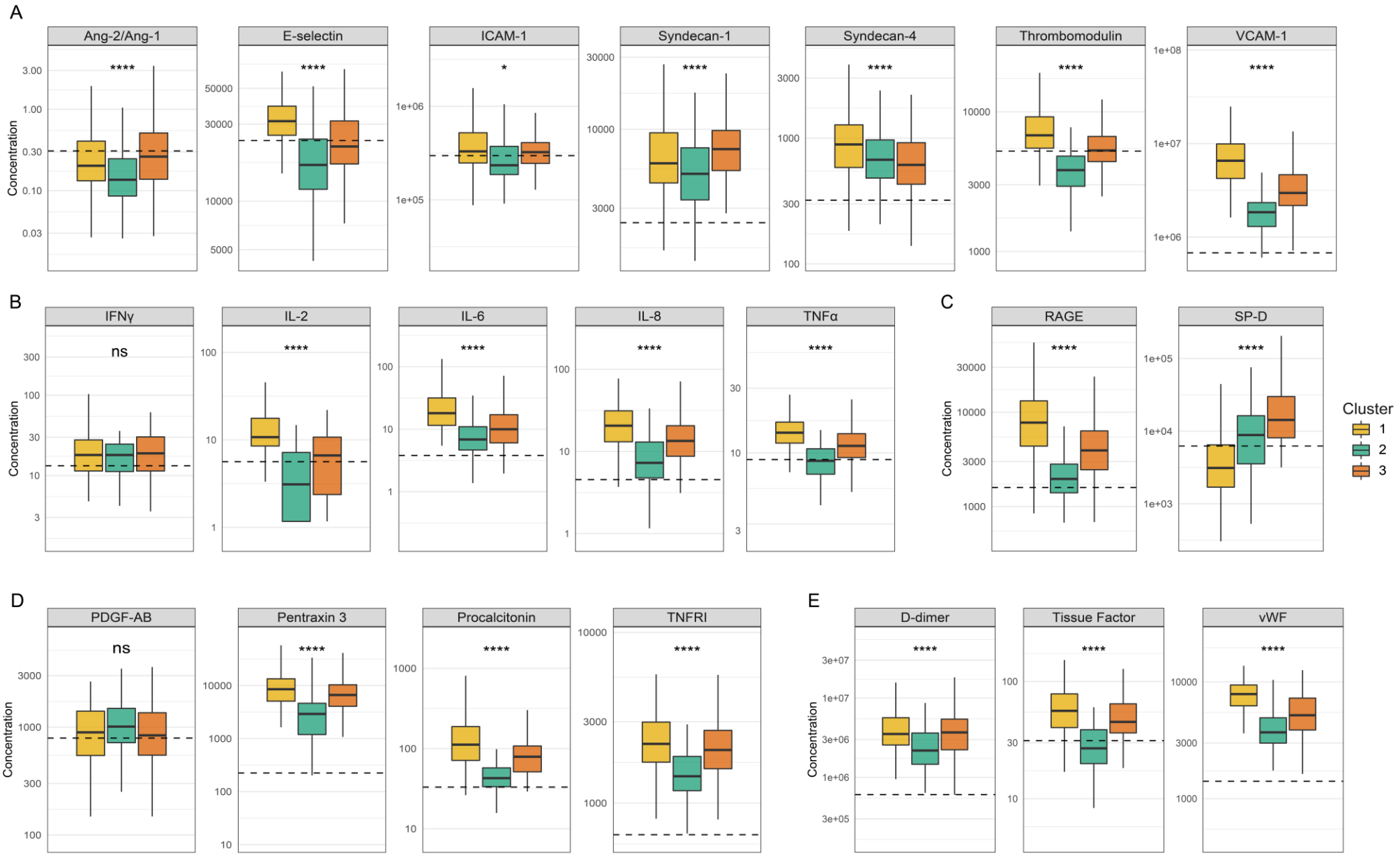
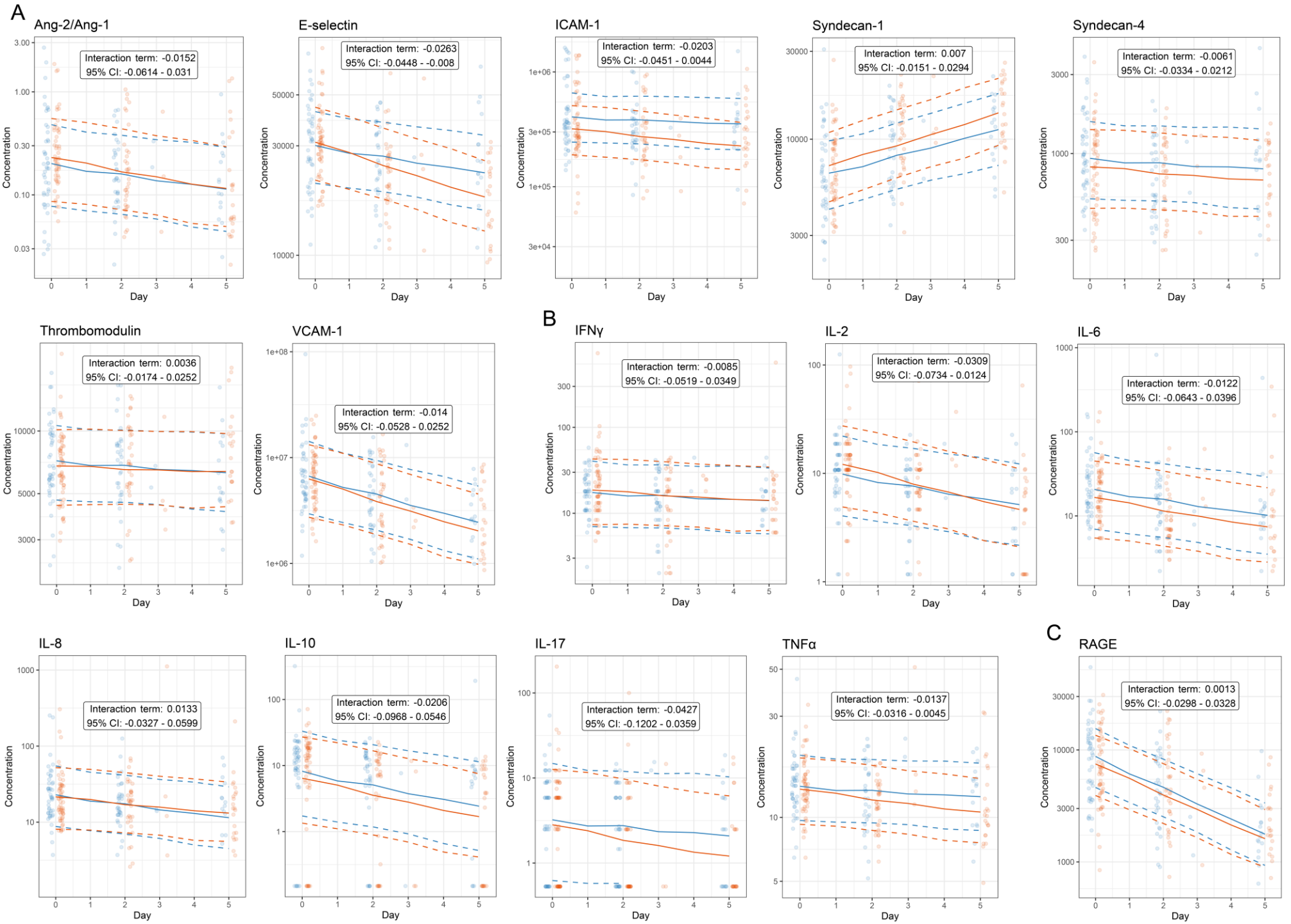


Figure S6. Baseline plasma biomarkers reflective of host response pathways implicated in COVID-19 pathogenesis, stratified according to subphenotype. Data is depicted as box and whisker plots. A = endothelial cell activation and function, B = cytokine release, C = epithelial cell activation and function, D = systemic inflammation, E = coagulation. Dotted lines indicate median values obtained in healthy controls. Asterisks indicates statistical significance by analysis of

variance (ANOVA) tests. **** $p < 0.0001$. *** $p < 0.001$. ** $p < 0.01$. * $p < 0.05$. ns = not significant. Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1, vWF = Von Willebrand factor.


A
Ang-2/Ang-1
Interaction term: -0.0152
95% CI: -0.0614 - 0.031
E-selectin
Interaction term: -0.0263
95% CI: -0.0448 - -0.008
ICAM-1
Interaction term: -0.0203
95% CI: -0.0451 - 0.0044
Syndecan-1
Interaction term: 0.007
95% CI: -0.0151 - 0.0294
Syndecan-4
Interaction term: -0.0061
95% CI: -0.0334 - 0.0212
Thrombomodulin
Interaction term: 0.0036
95% CI: -0.0174 - 0.0252
VCAM-1
Interaction term: -0.014
95% CI: -0.0528 - 0.0252
B
IFNγ
Interaction term: -0.0085
95% CI: -0.0519 - 0.0349
IL-2
Interaction term: -0.0309
95% CI: -0.0734 - 0.0124
IL-6
Interaction term: -0.0122
95% CI: -0.0643 - 0.0396
IL-8
Interaction term: 0.0133
95% CI: -0.0327 - 0.0599
IL-10
Interaction term: -0.0206
95% CI: -0.0968 - 0.0546
IL-17
Interaction term: -0.0427
95% CI: -0.1202 - 0.0359
TNFα
Interaction term: -0.0137
95% CI: -0.0316 - 0.0045
C
RAGE
Interaction term: 0.0013
95% CI: -0.0298 - 0.0328
Concentration
Day

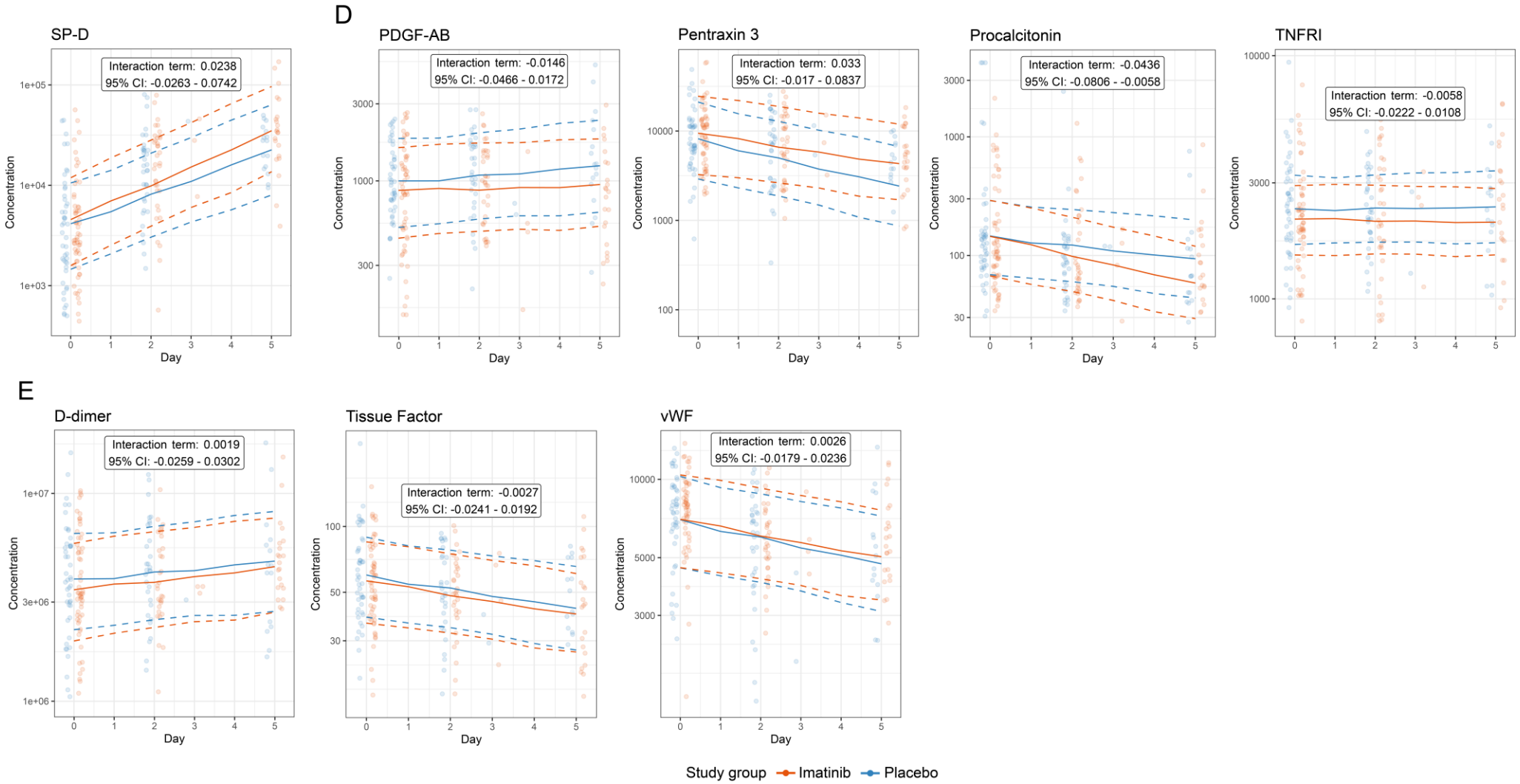
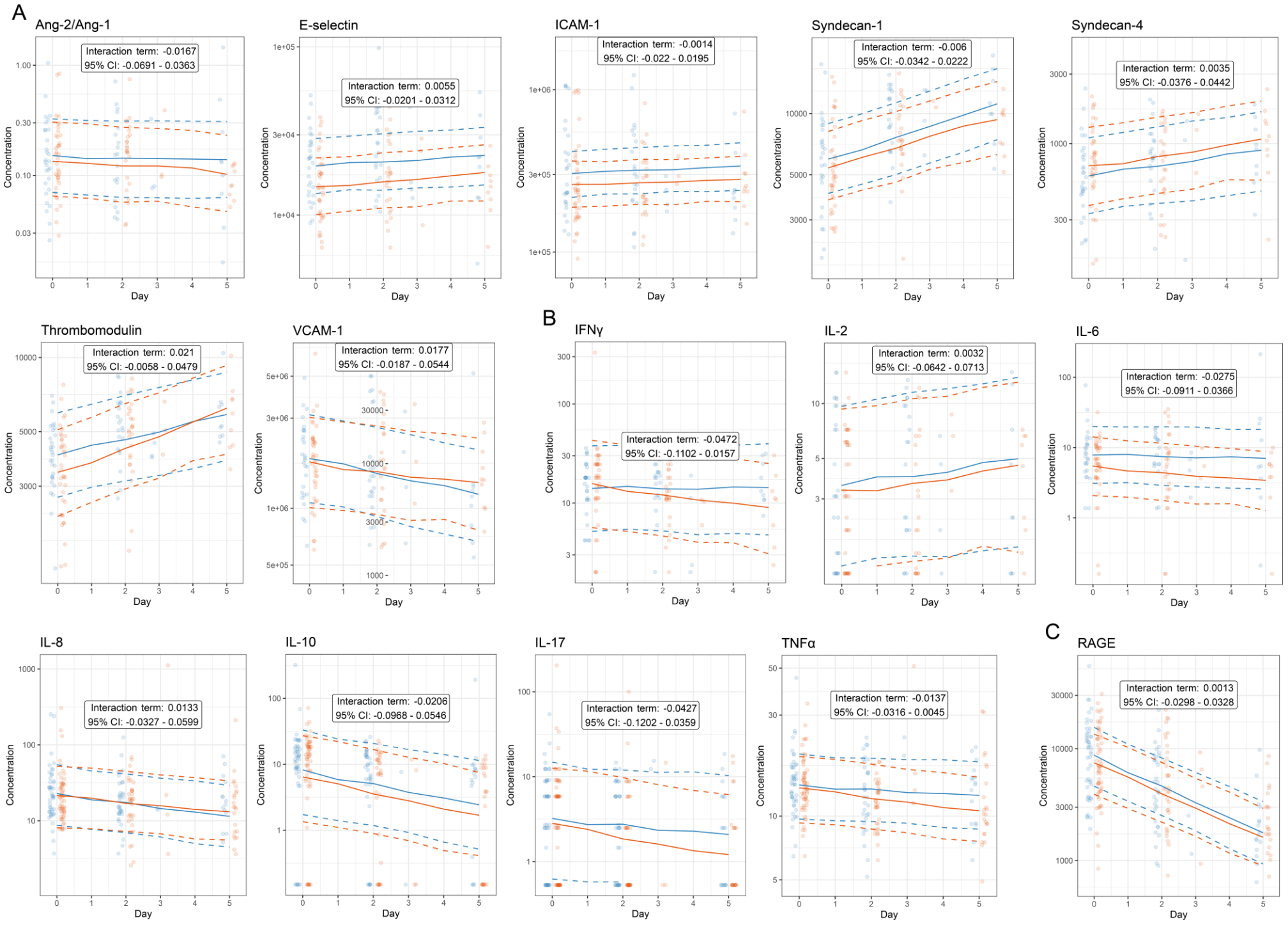


Figure S7. Longitudinal plasma biomarker concentrations in patients assigned to cluster 1, stratified by treatment group. A = endothelial cell activation and function, B = cytokine release, C = epithelial cell activation and function, D = systemic inflammation, E = coagulation. Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1, vWF = Von Willebrand factor.


A
Ang-2/Ang-1
Interaction term: -0.0167
95% CI: -0.0691 - 0.0363
E-selectin
Interaction term: 0.0055
95% CI: -0.0201 - 0.0312
ICAM-1
Interaction term: -0.0014
95% CI: -0.022 - 0.0195
Syndecan-1
Interaction term: -0.006
95% CI: -0.0342 - 0.0222
Syndecan-4
Interaction term: 0.0035
95% CI: -0.0376 - 0.0442
Thrombomodulin
Interaction term: 0.021
95% CI: -0.0058 - 0.0479
VCAM-1
Interaction term: 0.0177
95% CI: -0.0187 - 0.0544
B
IFNγ
Interaction term: -0.0472
95% CI: -0.1102 - 0.0157
IL-2
Interaction term: 0.0032
95% CI: -0.0642 - 0.0713
IL-6
Interaction term: -0.0275
95% CI: -0.0911 - 0.0366
IL-8
Interaction term: 0.0133
95% CI: -0.0327 - 0.0599
IL-10
Interaction term: -0.0206
95% CI: -0.0968 - 0.0546
IL-17
Interaction term: -0.0427
95% CI: -0.1202 - 0.0359
TNFα
Interaction term: -0.0137
95% CI: -0.0316 - 0.0045
C
RAGE
Interaction term: 0.0013
95% CI: -0.0298 - 0.0328
Concentration
Day

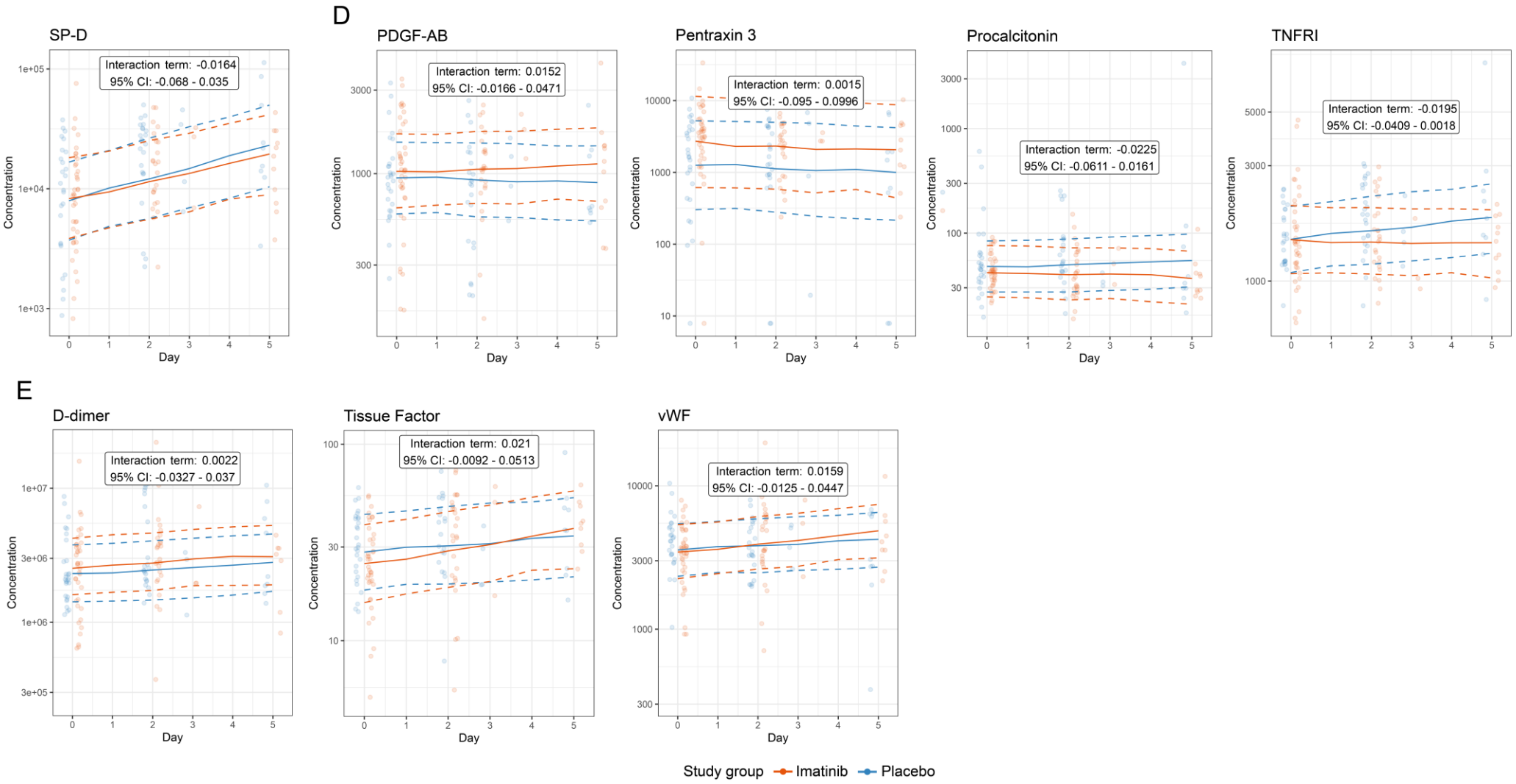
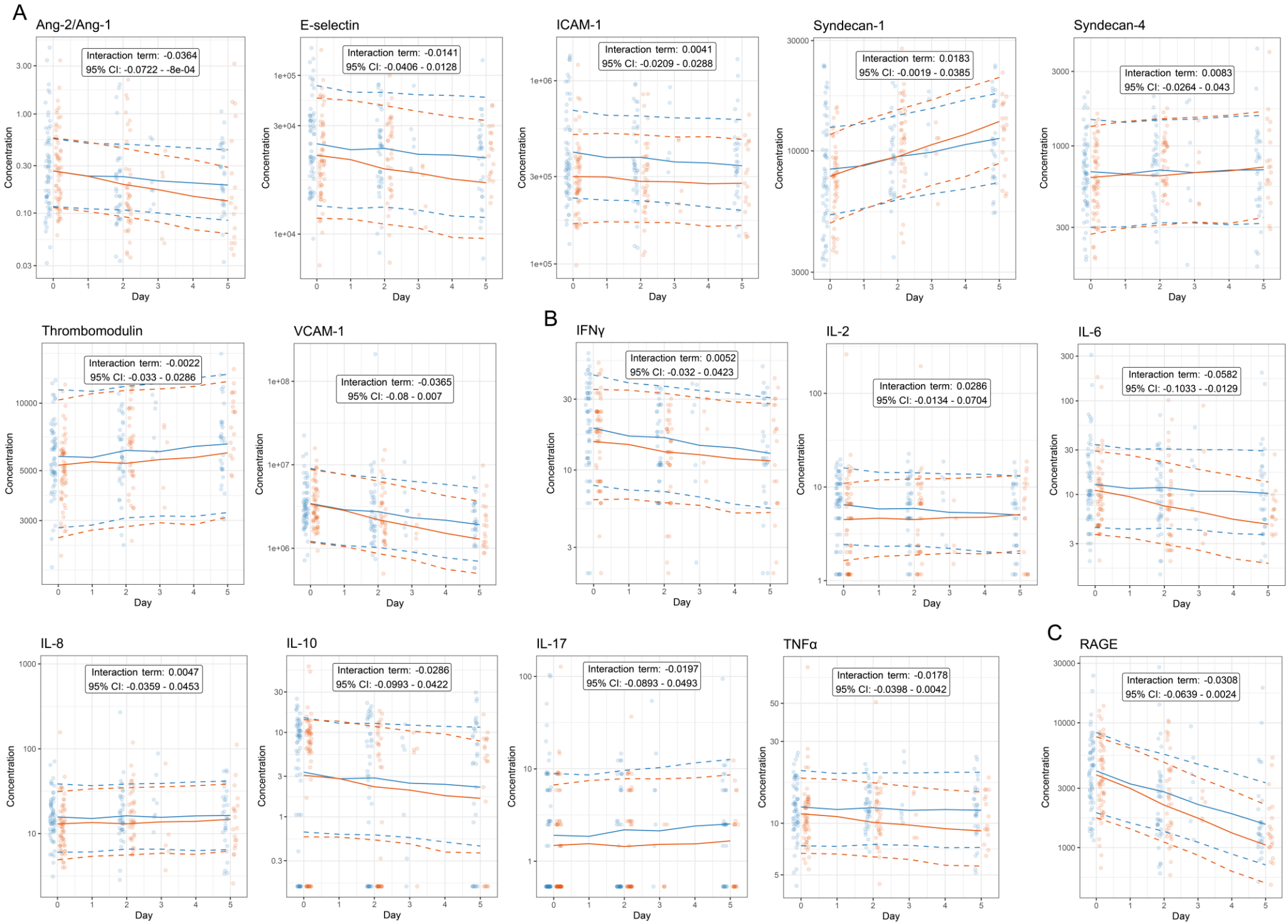


Figure S8. Longitudinal plasma biomarker concentrations in patients assigned to cluster 2, stratified by treatment group. A = endothelial cell activation and function, B = cytokine release, C = epithelial cell activation and function, D = systemic inflammation, E = coagulation. Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1, vWF = Von Willebrand factor.


A
Ang-2/Ang-1
Interaction term: -0.0364
95% CI: -0.0722 - -8e-04
E-selectin
Interaction term: -0.0141
95% CI: -0.0406 - 0.0128
ICAM-1
Interaction term: 0.0041
95% CI: -0.0209 - 0.0288
Syndecan-1
Interaction term: 0.0183
95% CI: -0.0019 - 0.0385
Syndecan-4
Interaction term: 0.0083
95% CI: -0.0264 - 0.043
Thrombomodulin
Interaction term: -0.0022
95% CI: -0.033 - 0.0286
VCAM-1
Interaction term: -0.0365
95% CI: -0.08 - 0.007
B
IFNγ
Interaction term: 0.0052
95% CI: -0.032 - 0.0423
IL-2
Interaction term: 0.0286
95% CI: -0.0134 - 0.0704
IL-6
Interaction term: -0.0582
95% CI: -0.1033 - -0.0129
IL-8
Interaction term: 0.0047
95% CI: -0.0359 - 0.0453
IL-10
Interaction term: -0.0286
95% CI: -0.0993 - 0.0422
IL-17
Interaction term: -0.0197
95% CI: -0.0893 - 0.0493
TNFα
Interaction term: -0.0178
95% CI: -0.0398 - 0.0042
C
RAGE
Interaction term: -0.0308
95% CI: -0.0639 - 0.0024
Concentration
Day

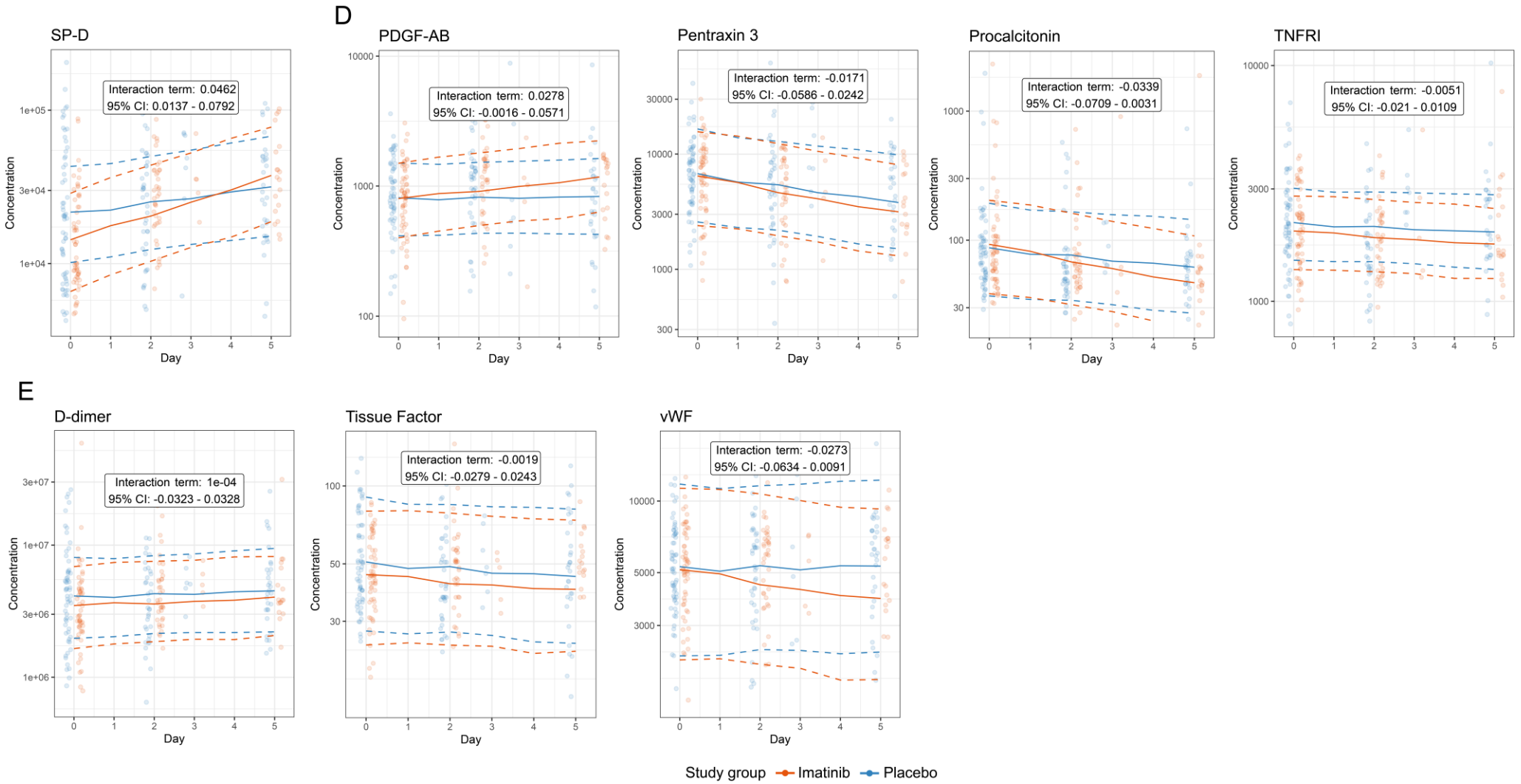


Figure S9. Longitudinal plasma biomarker concentrations in patients assigned to cluster 3, stratified by treatment group. A = endothelial cell activation and function, B = cytokine release, C = epithelial cell activation and function, D = systemic inflammation, E = coagulation. Ang-2/Ang-1 = the ratio of angiopoietin 2 to 1, ICAM-1 = intracellular adhesion molecule 1, IFNγ = interferon gamma, IL = interleukin, PDGF-AB = platelet-derived growth factor AB, RAGE = receptor for advanced glycation end products, SP-D = surfactant protein D, TNFα = tumour necrosis factor alpha, TNFRI = tumour necrosis factor receptor I, VCAM-1 = vascular cell adhesion molecule 1, vWF = Von Willebrand factor.

Supplementary methods

Luminex assay quality assessment

Data quality was assessed by evaluation of the beads count (the number of replicates counted per sample). A minimum bead count of 25 was considered to be acceptable. Values below the lowest point of the calibration point were set to the lower limit of quantification. Samples above the highest calibration point were extrapolated based on the algorithms available in the Luminex software. More than 50% of the fractalkine measurements were judged to be unreliable because of stringent quality criteria and were therefore excluded from analysis.

Model assumptions

- There is a linear change in biomarker concentration in the days after treatment with either placebo or imatinib.
- There is no unmeasured confounder between treatment allocation and mediator or outcome due to randomisation.
- There is no effect of the outcome or mediator on the treatment group due to randomisation.
- There is no measurement error in treatment allocation, the mediator and the outcome.
- There is no moderating effect of the mediators, which was tested.