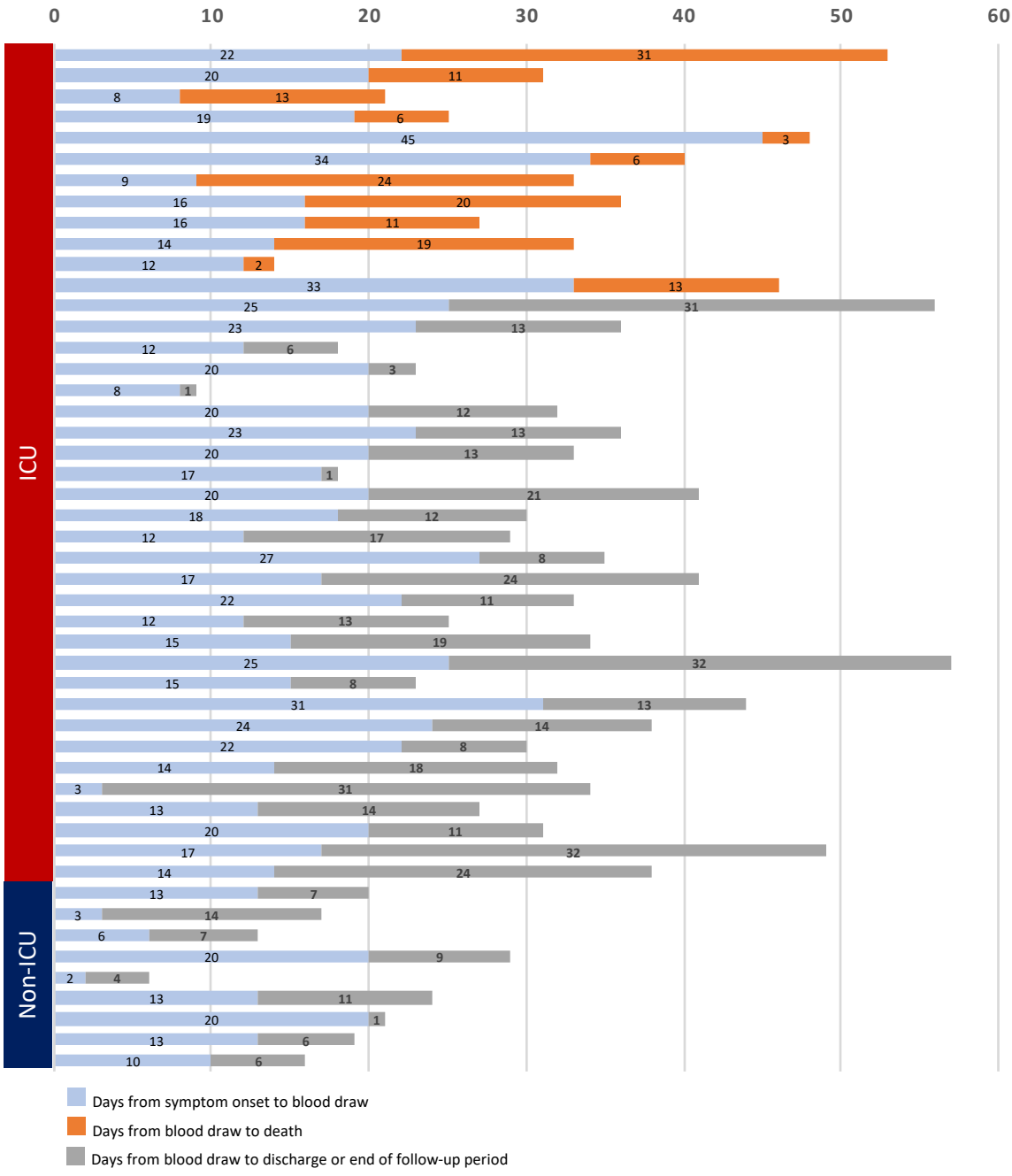
Supplementary Table 1. Intensive Care Unit Admission Criteria

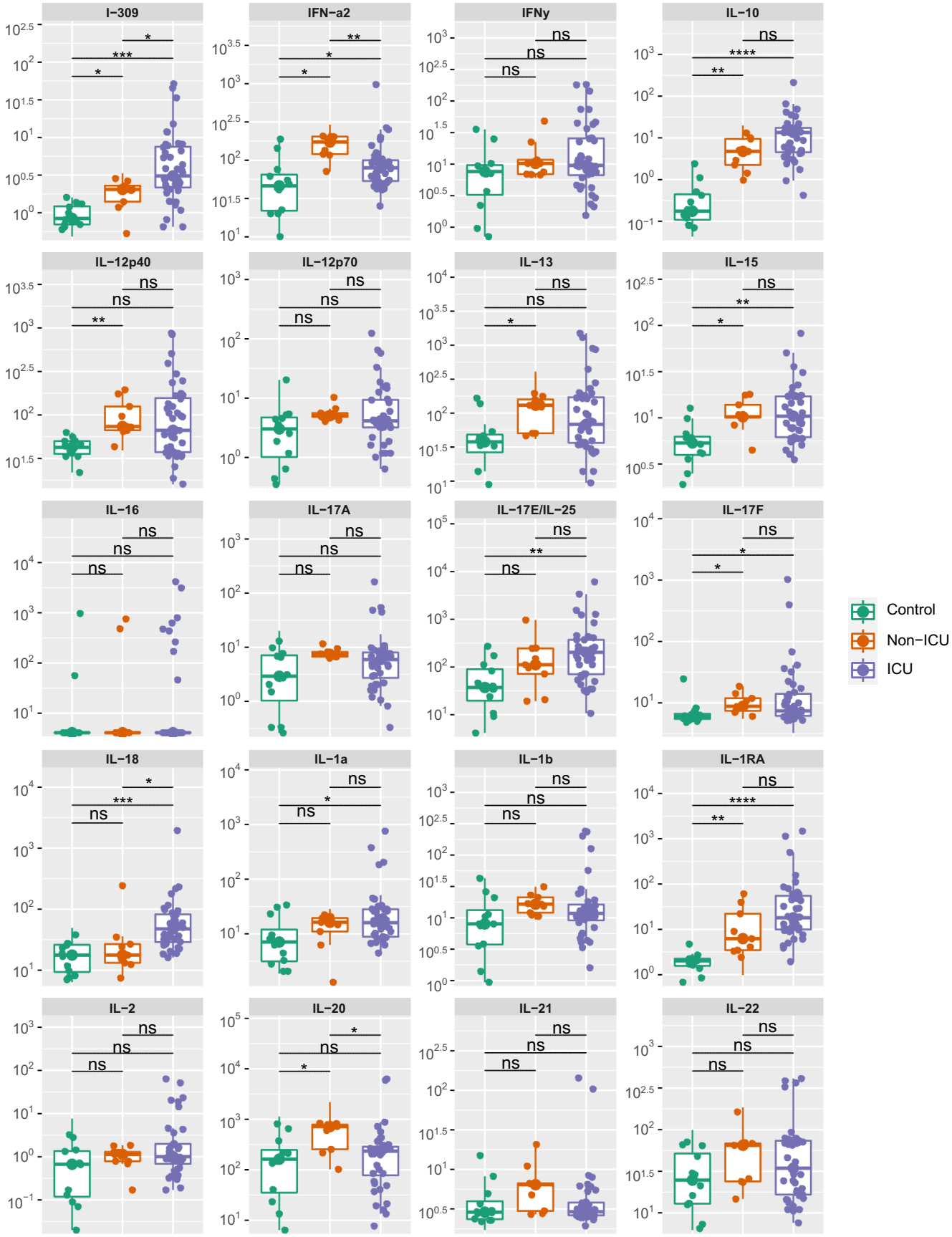
Criteria for Respiratory Failure
1. Mechanical ventilation
2. Hypoxia with inability to wean FiO2 to less than 60% to maintain SPO_2 >90%
3. Hypercapnia with pH<7.32
4. Initiation of high flow nasal cannula (HFNC)
5. Initiation of BiPAP or CPAP

Supplementary Figure 1



Supplementary Figure 1. Time course depicting duration from symptom onset to blood draw and duration from blood draw to death, discharge, or end of follow-up period for each patient in the cross-sectional cohort.

Supplementary Figure 2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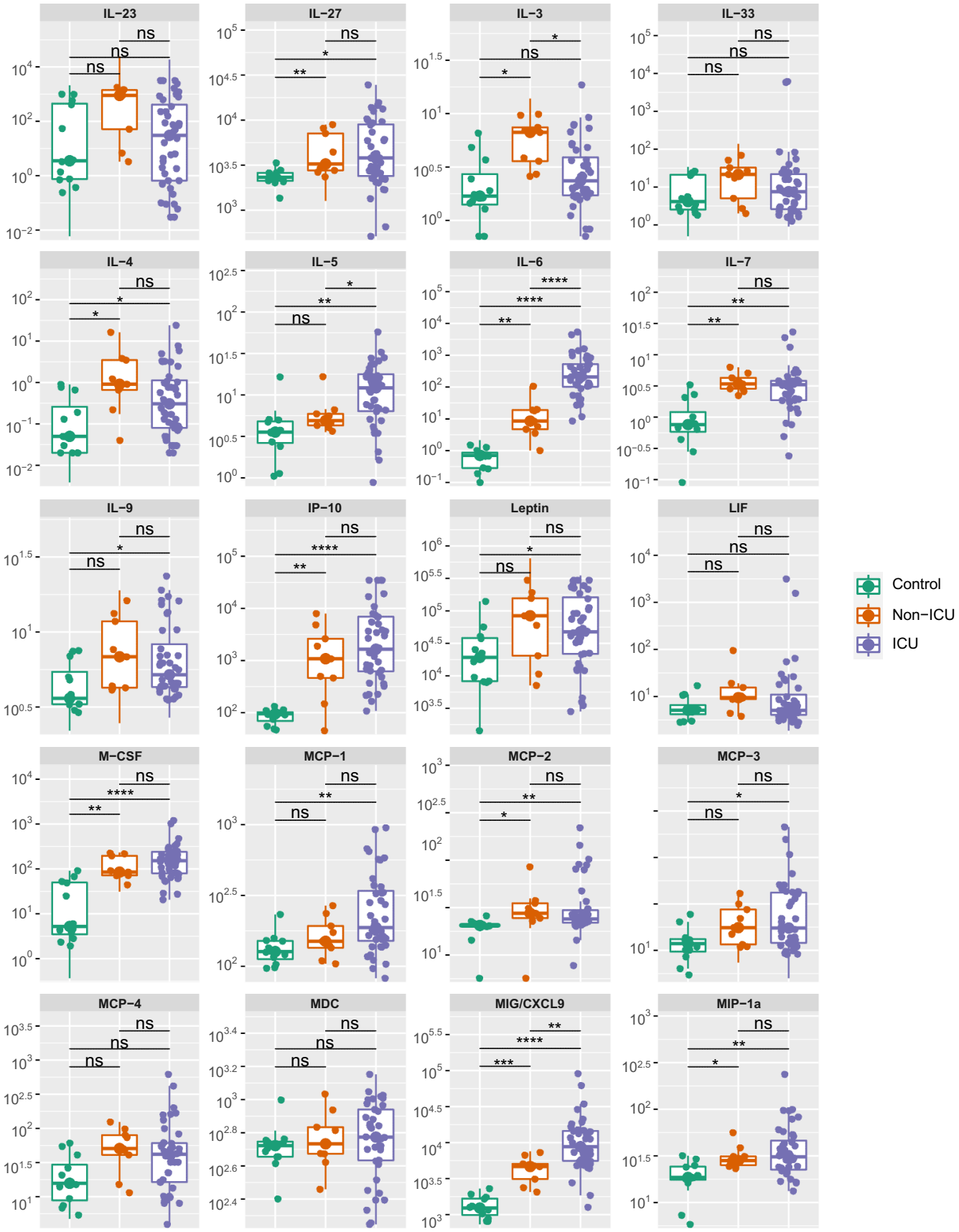
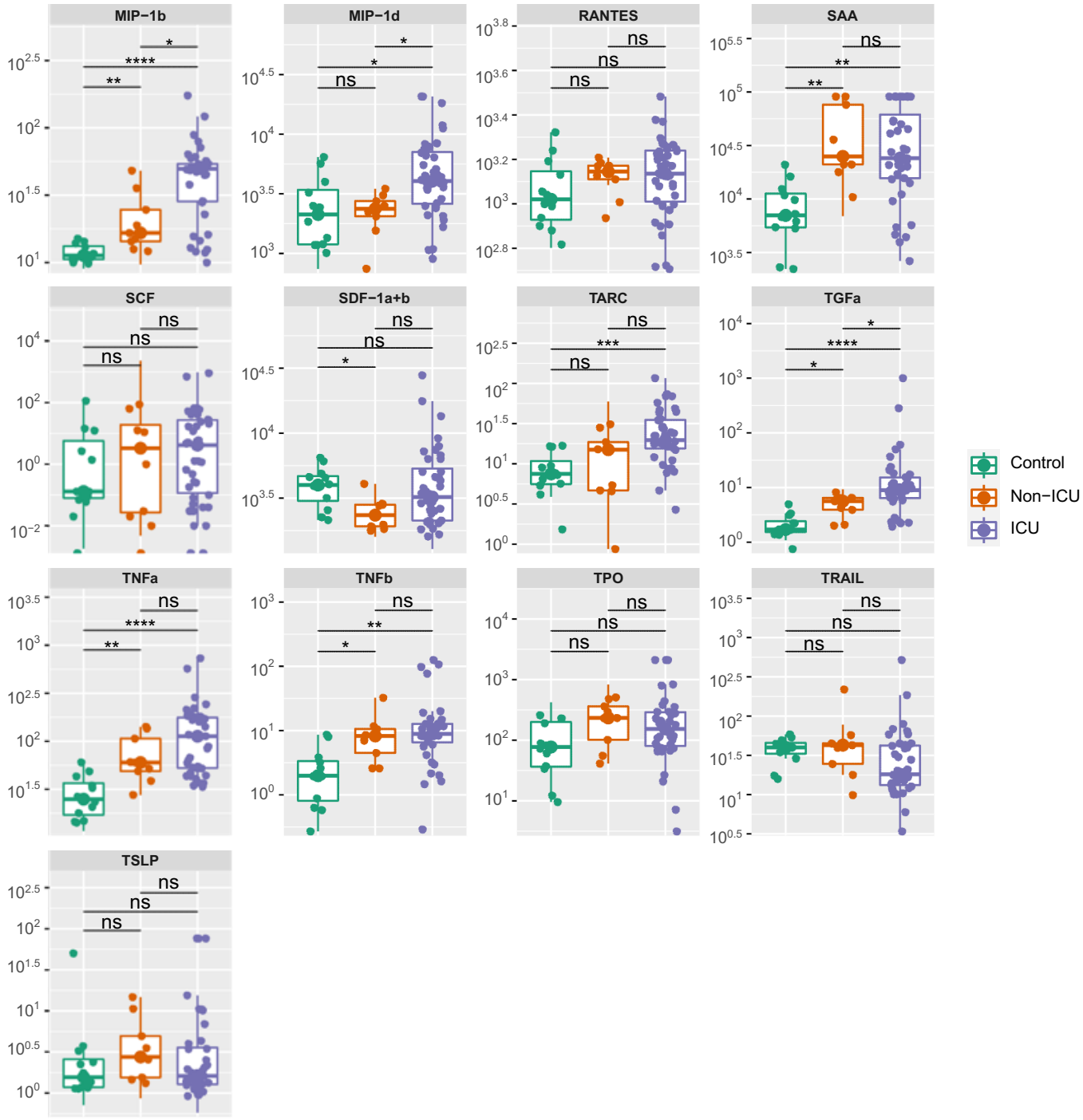
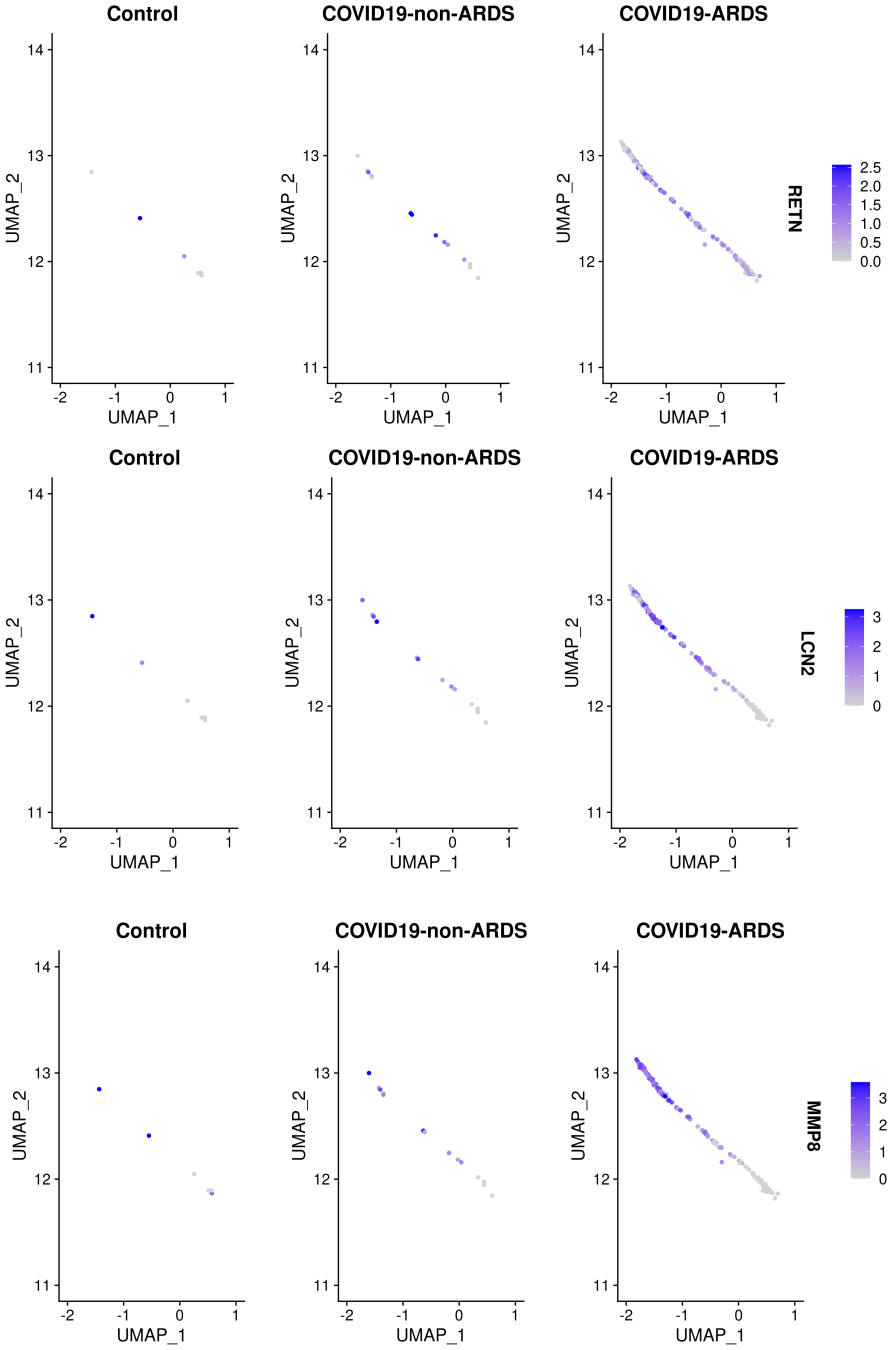
IFN−a2
IFNy
IL−10
IL−12p40
IL−12p70
IL−13
IL−15
IL−16
IL−17A
IL−17E/IL−25
IL−17F
IL−18
IL−1a
IL−1b
IL−1RA
IL−2
IL−20
IL−21
IL−22
Control
Non−ICU
ICU


IL−23
IL−27
IL−3
IL−33
IL−4
IL−5
IL−6
IL−7
IL−9
IP−10
Leptin
LIF
M−CSF
MCP−1
MCP−2
MCP−3
MCP−4
MDC
MIG/CXCL9
MIP−1a
Control
Non−ICU
ICU



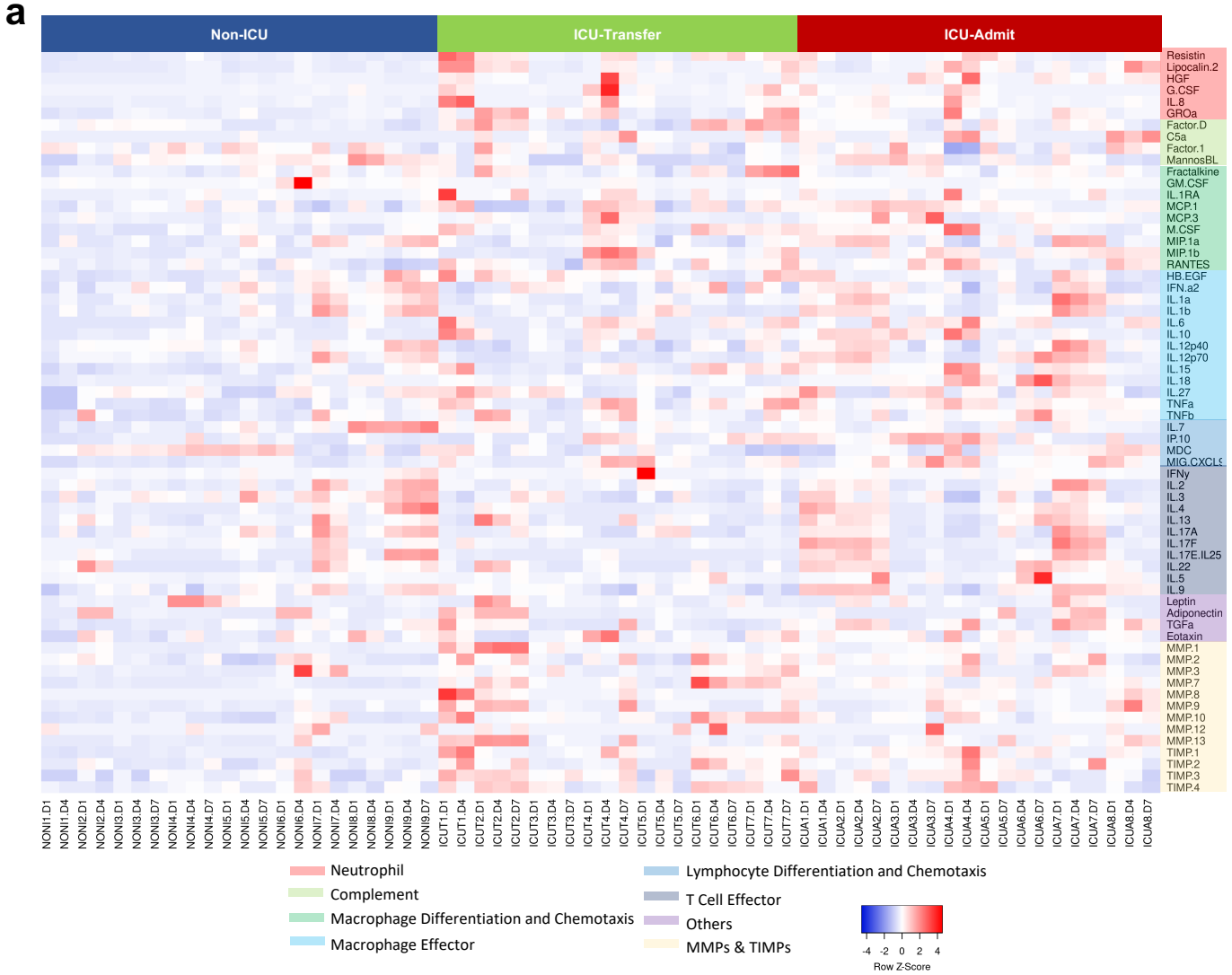
Supplementary Figure 2. Circulating levels of all measured biomarkers in the cross-sectional cohort, comparing: 1) controls, 2) non-ICU COVID-19, and 3) ICU COVID-19 patients. Asterisks denote statistically significant differences between groups (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$). All values are concentrations in pg/mL, except for C1q, C3, C4, CFB, CFH, CF1, and Adipsin, which are reported as ng/mL. ICU: intensive care unit.

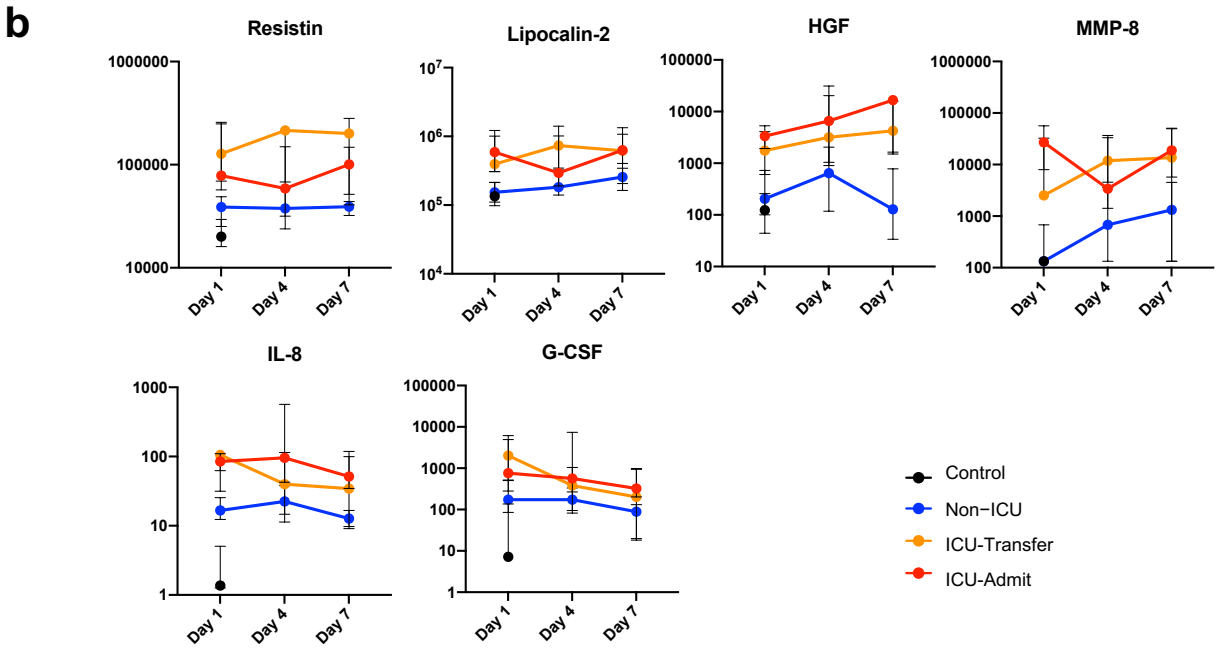
Supplementary Figure 3



Supplementary Figure 3. Feature plot representation of neutrophil markers resistin (RETN), lipocalin-2 (LCN2), and matrix metallopeptidase 8 (MMP8) in the 'Developing neutrophil' population, re-analyzed from scRNAseq data published by Wilk et al, split by COVID-19 and ARDS status. The 'Developing neutrophil' population is mainly composed of cells from the COVID-19 ARDS samples (n=186) and includes few cells from the COVID19-non-ARDS (n=14) and Control (n=6) samples. The 'Developing neutrophil' population was subsetted from the larger single-cell RNAseq dataset of peripheral blood mononuclear cells from patients with COVID-19.[3]

Supplementary Figure 4

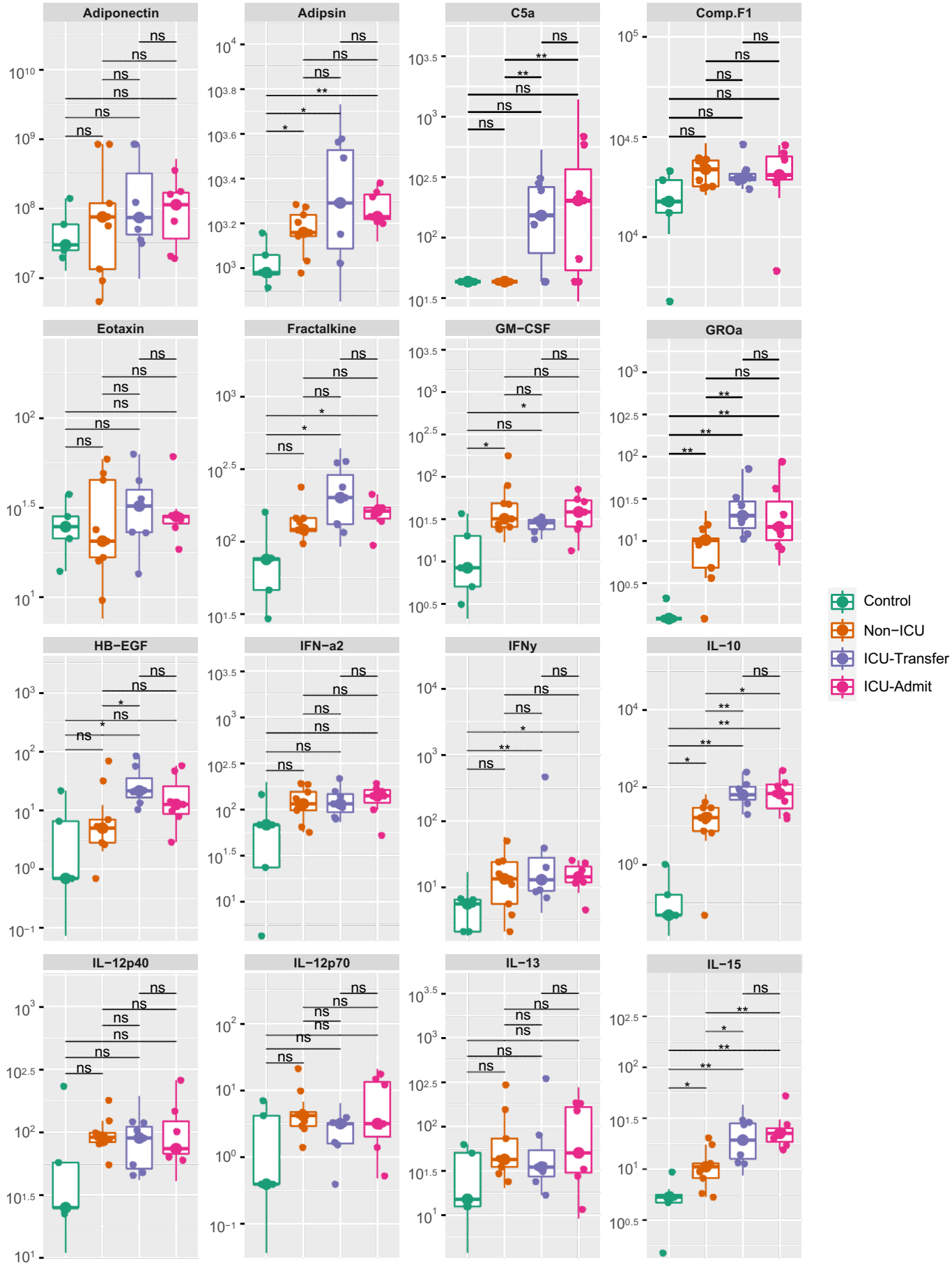


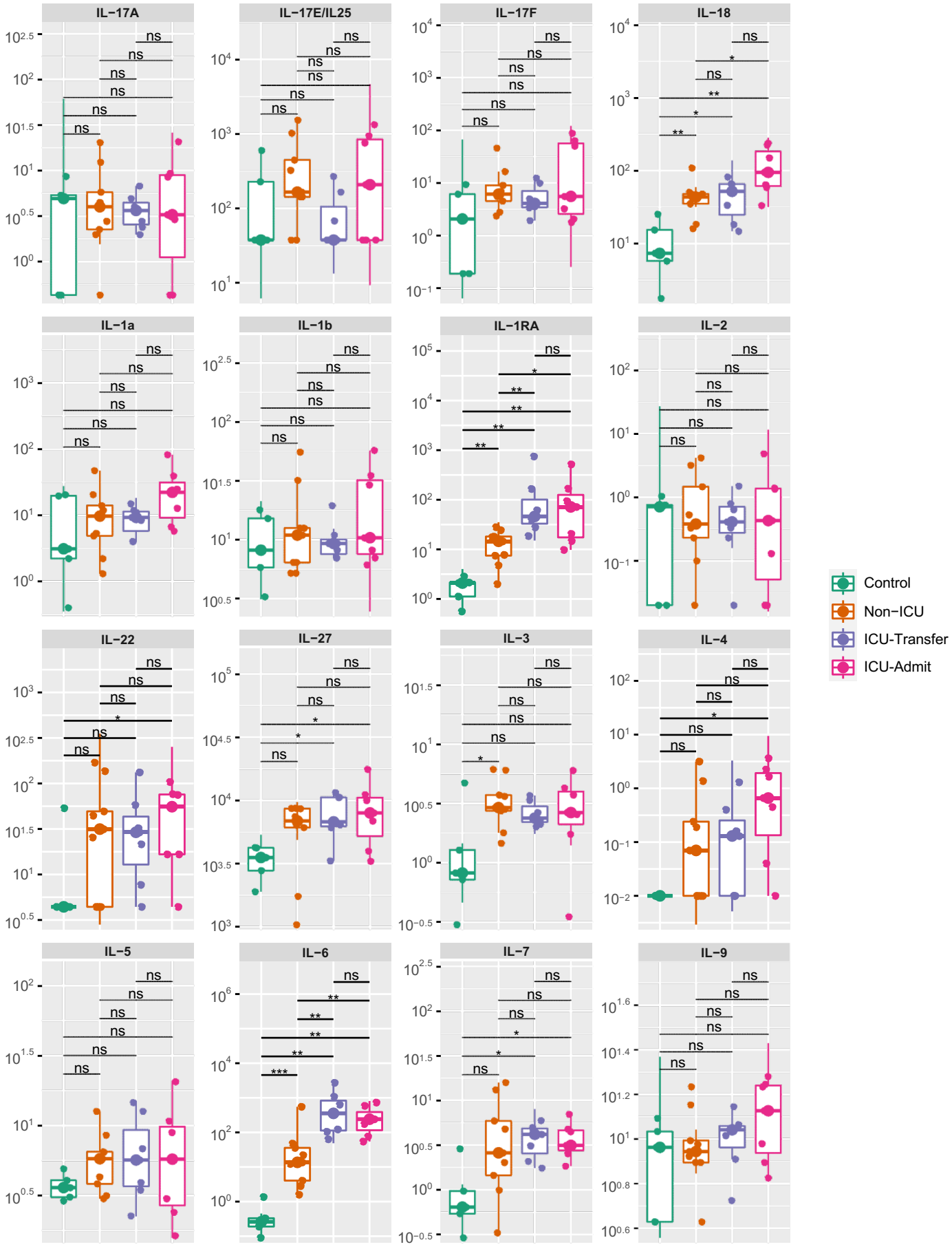


Supplementary Figure 4. (a) Heatmap indicating relative protein levels detected in each subject of the longitudinal cohort at specified timepoints during hospitalization (columns) for all biomarkers tested (rows). Proteins are categorized by biological function and samples are labeled according to patient category (NONI: non-ICU, ICUT: ICU-Transfer, ICUA: ICU-Admit), numerical patient identifier within that category (1-9), and timepoint (D1: day 1, D4: day 4, D7: day 7). (b) Circulating levels of the neutrophil activation markers measured in the longitudinal cohort over time, comparing subjects categorized as: 1) controls, 2) non-ICU, 3) ICU-Transfer, and 4) ICU-Admit. 'Non-ICU' indicates patients who remained in a non-ICU unit until discharge; 'ICU-Transfer' indicates patients who were admitted to a non-ICU unit and were transferred to an ICU unit during hospitalization; 'ICU-Admit' indicates patients who were admitted directly to an ICU unit. Data is shown as median w/ interquartile range. All values are concentrations in pg/mL.

Supplementary Figure 5

a

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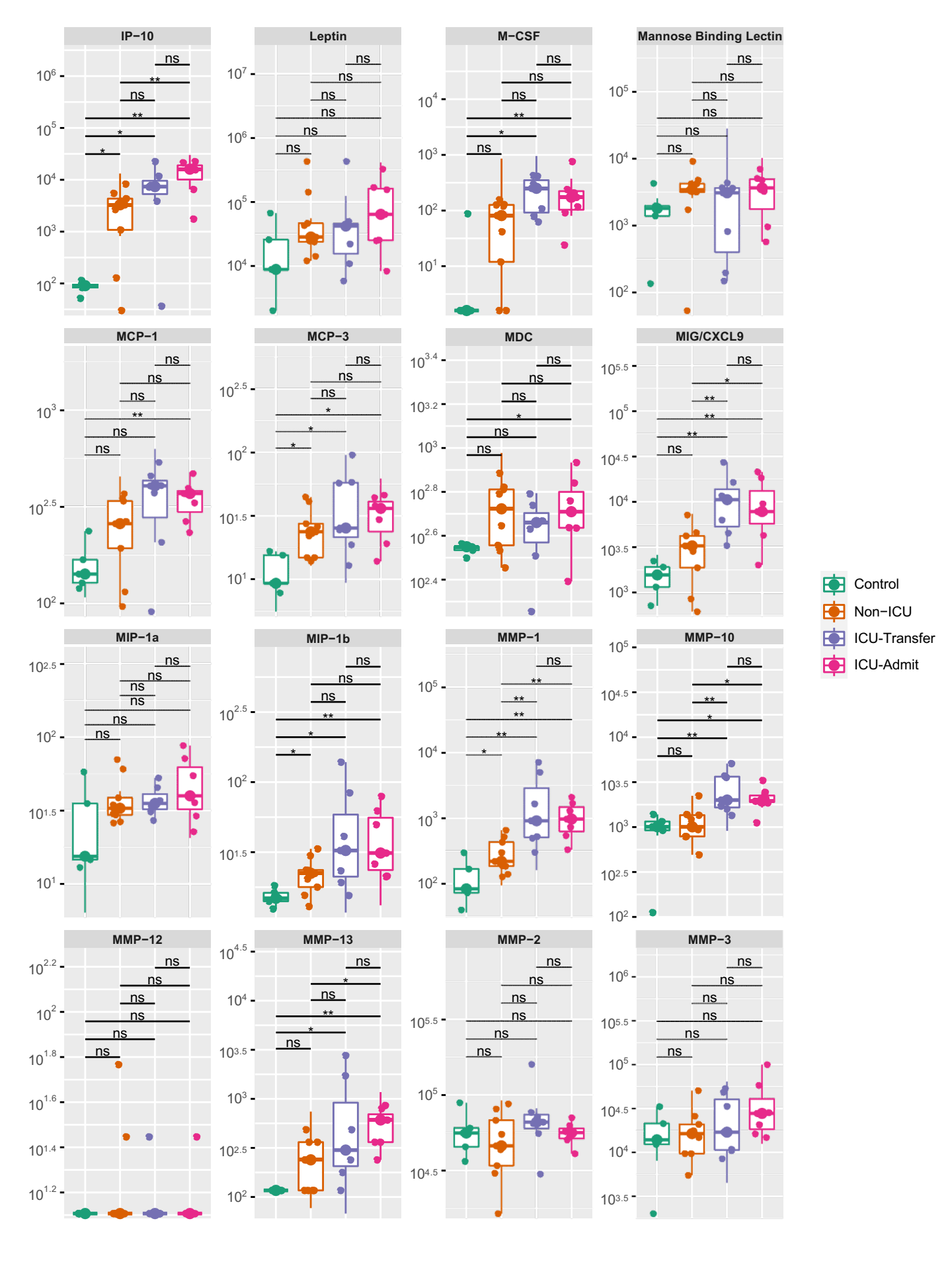
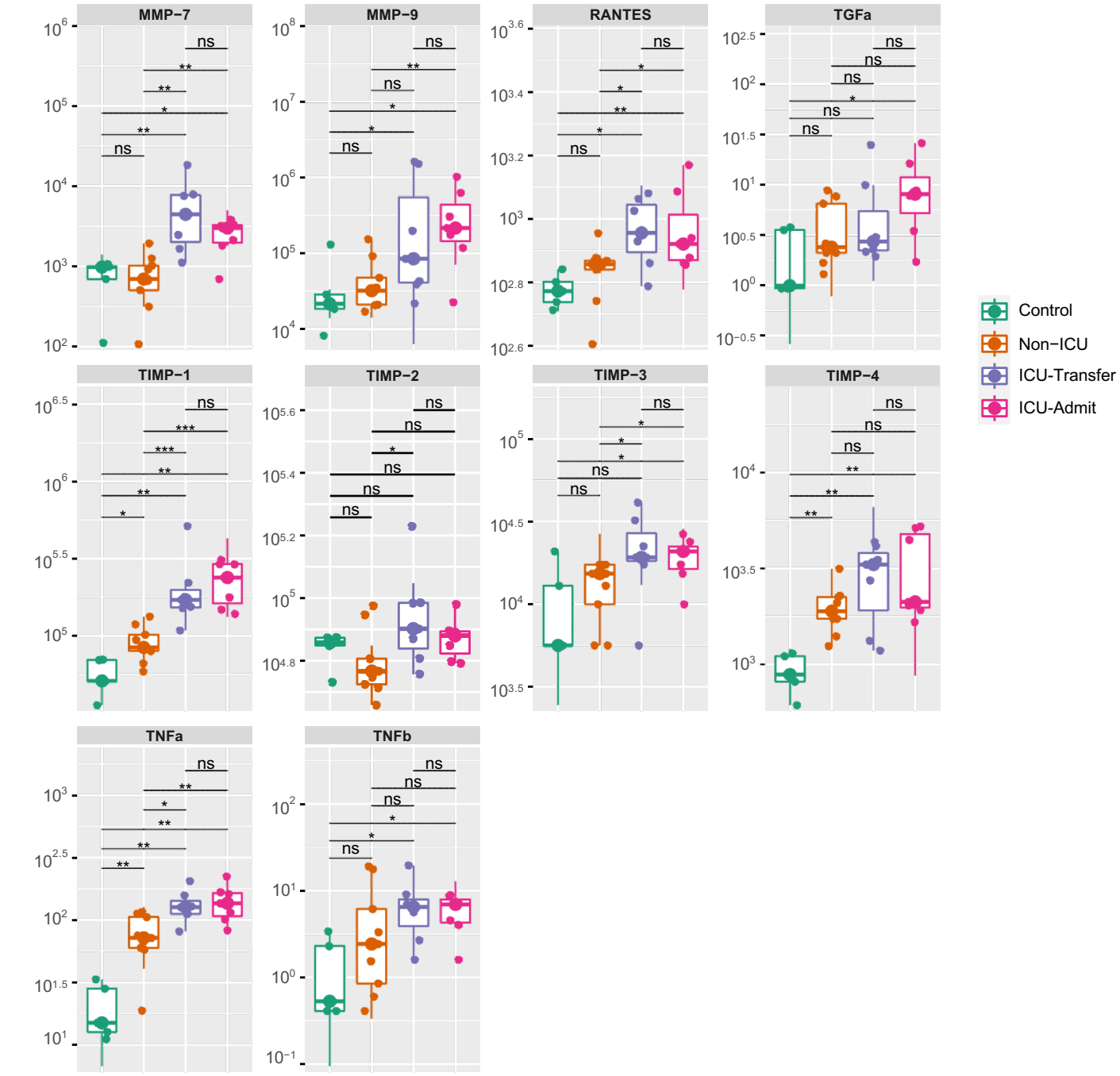
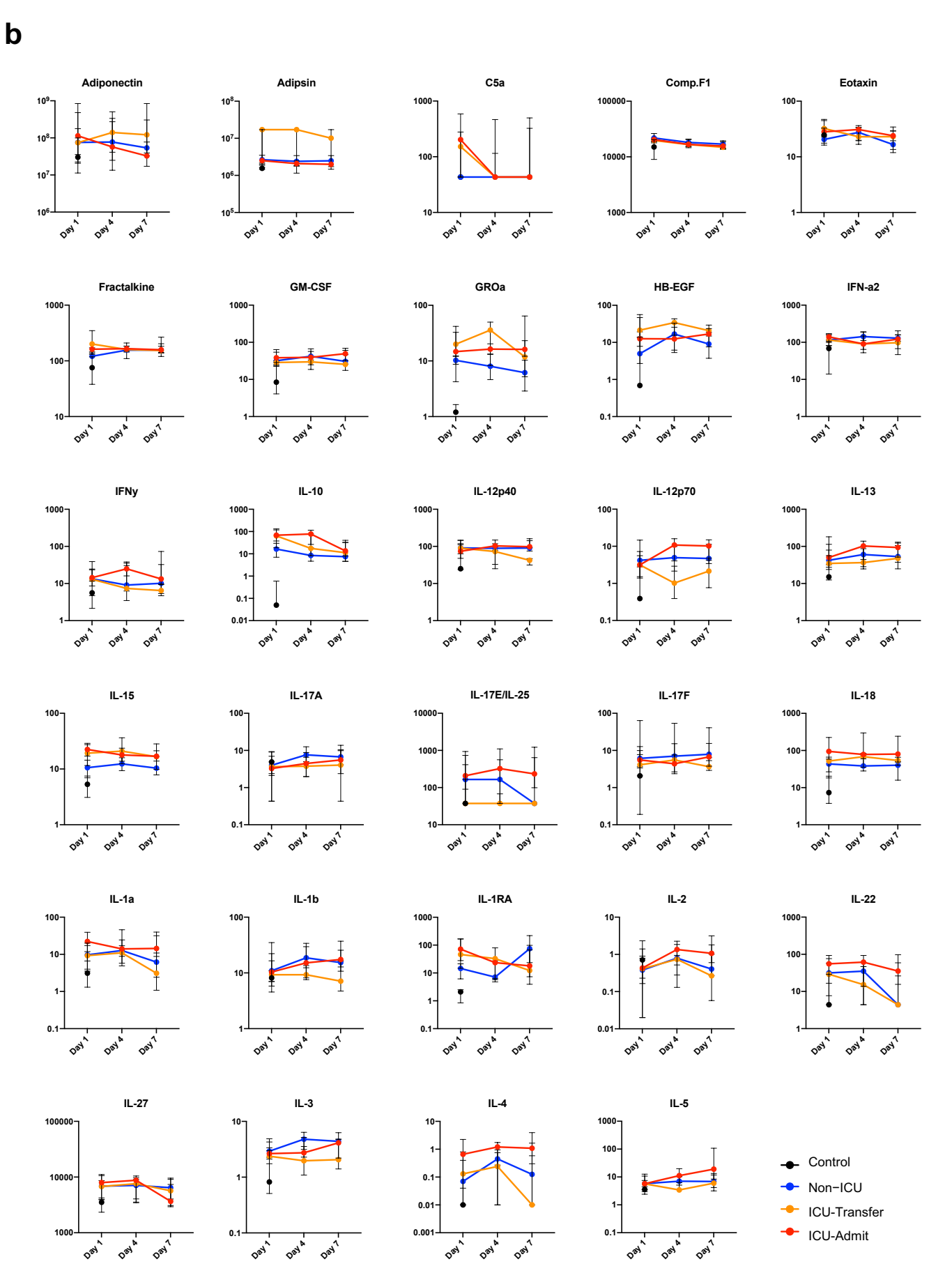
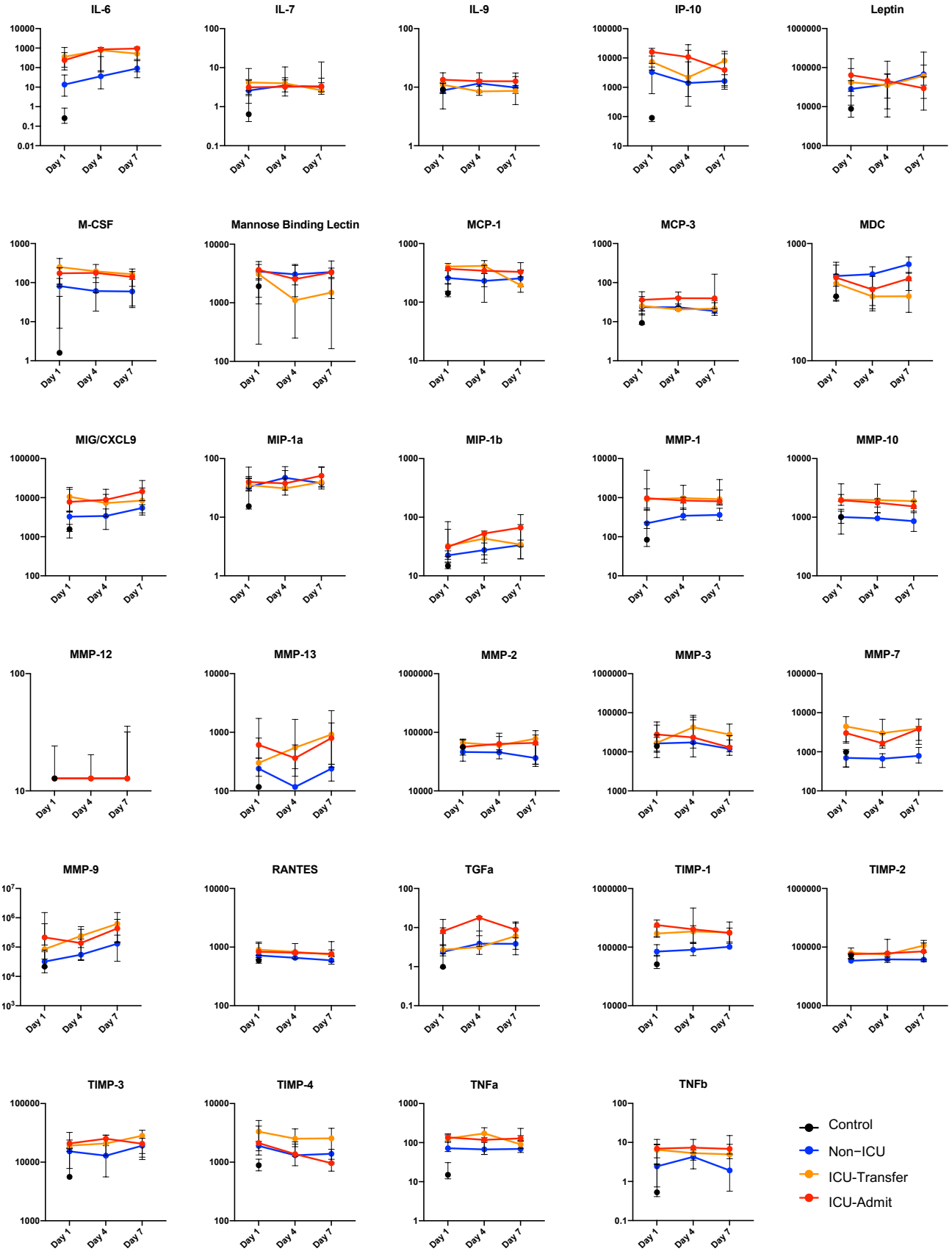
IL−17E/IL25
IL−17F
IL−18
IL−1a
IL−1b
IL−1RA
IL−2
IL−22
IL−27
IL−3
IL−4
IL−5
IL−6
IL−7
IL−9
Control
Non−ICU
ICU−Transfer
ICU−Admit


IP−10
Leptin
M−CSF
Mannose Binding Lectin
MCP−1
MCP−3
MDC
MIG/CXCL9
MIP−1a
MIP−1b
MMP−1
MMP−10
MMP−12
MMP−13
MMP−2
MMP−3
Control
Non−ICU
ICU−Transfer
ICU−Admit

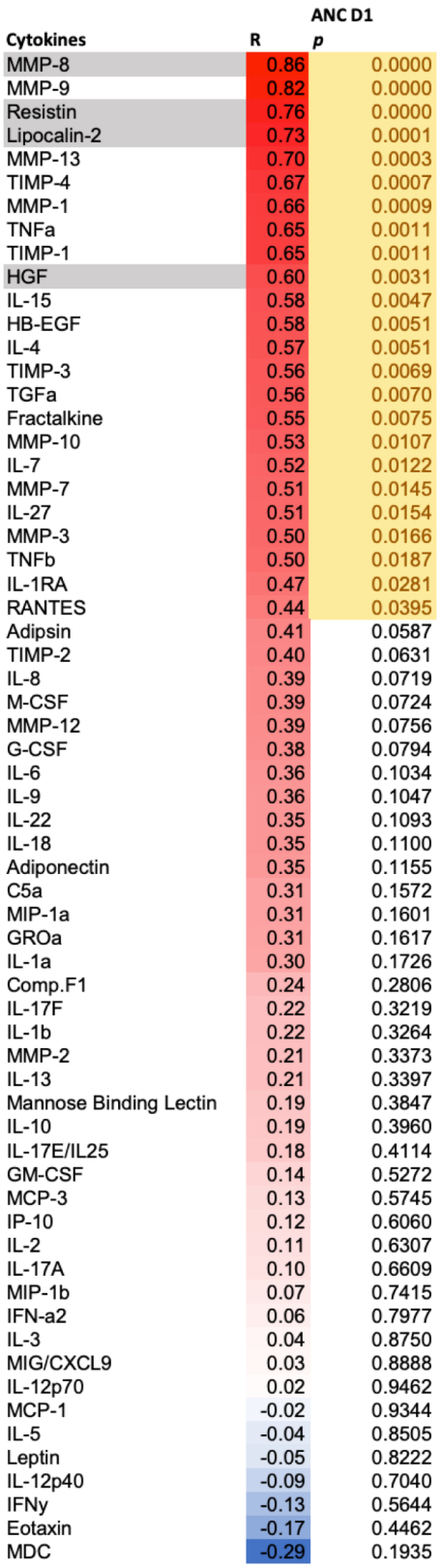

MMP−7
MMP−9
RANTES
TGFa
TIMP−1
TIMP−2
TIMP−3
TIMP−4
TNFa
TNFb
Control
Non−ICU
ICU−Transfer
ICU−Admit


b
Adiponectin
Adipsin
C5a
Comp.F1
Eotaxin
Fractalkine
GM-CSF
GROa
HB-EGF
IFN-a2
IFNy
IL-10
IL-12p40
IL-12p70
IL-13
IL-15
IL-17A
IL-17E/IL-25
IL-17F
IL-18
IL-1a
IL-1b
IL-1RA
IL-2
IL-22
IL-27
IL-3
IL-4
IL-5
Day 1
Day 4
Day 7
Control
Non−ICU
ICU-Transfer
ICU-Admit


IL-6
IL-7
IL-9
IP-10
Leptin
M-CSF
Mannose Binding Lectin
MCP-1
MCP-3
MDC
MIG/CXCL9
MIP-1a
MIP-1b
MMP-1
MMP-10
MMP-12
MMP-13
MMP-2
MMP-3
MMP-7
MMP-9
RANTES
TGFa
TIMP-1
TIMP-2
TIMP-3
TIMP-4
TNFa
TNFb
Day 1
Day 4
Day 7
Control
Non−ICU
ICU-Transfer
ICU-Admit

Supplemental Figure 5. Circulating levels of all measured biomarkers in the longitudinal cohort on (a) day 1, and (b) days 1, 4, and 7 of hospitalization, comparing subjects categorized as: 1) controls, 2) non-ICU, 3) ICU-Transfer, and 4) ICU-Admit. 'Non-ICU' indicates patients who remained in a non-ICU unit until discharge; 'ICU-Transfer' indicates patients who were admitted to a non-ICU unit and were transferred to an ICU unit during hospitalization; 'ICU-Admit' indicates patients who were admitted directly to an ICU unit. For Day 1 samples, asterisks denote statistically significant differences between groups (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). Data is shown as median with interquartile range. All values are concentrations in pg/mL, except for CF1, adipsin, and mannose binding lectin, which are reported as ng/mL.

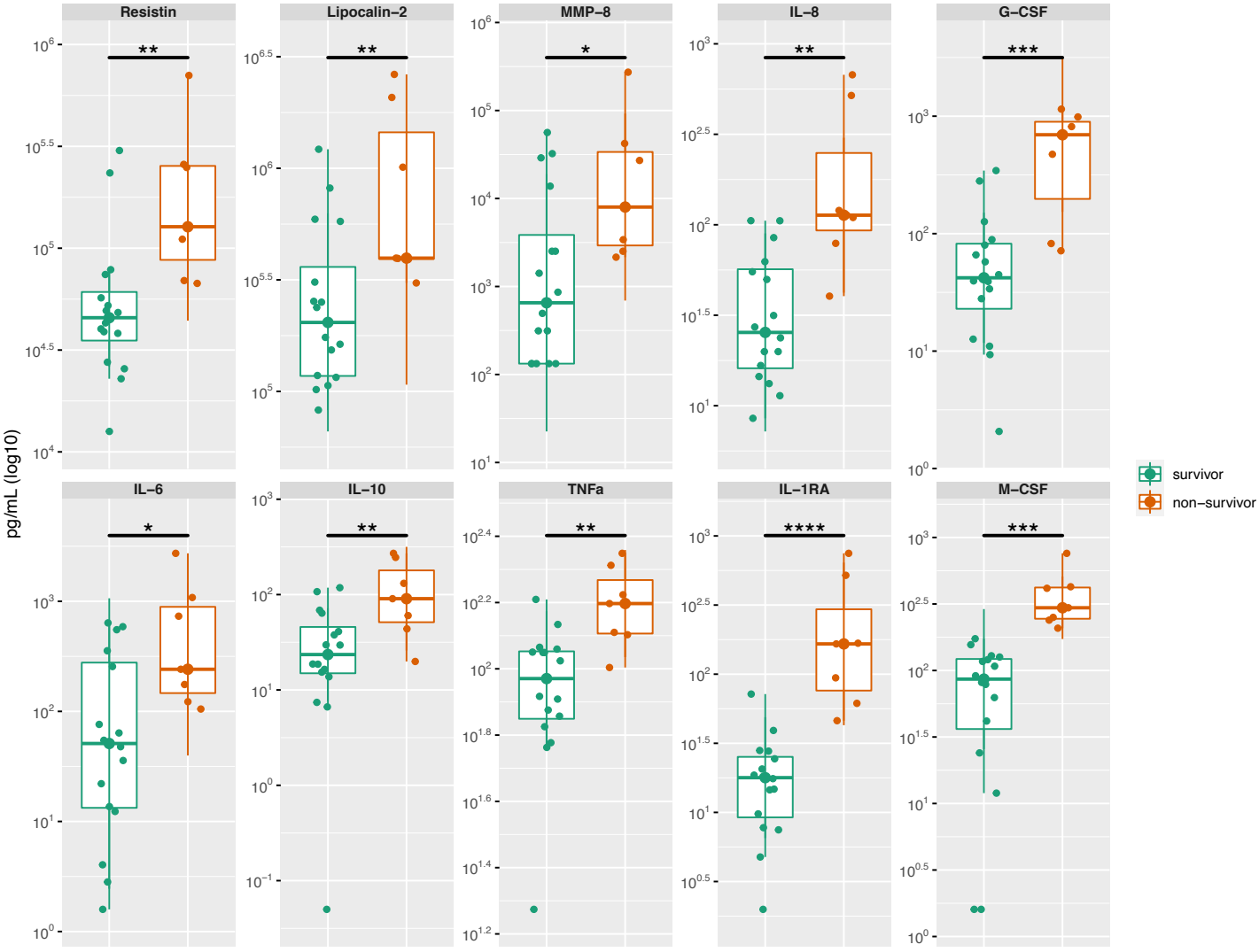
Supplementary Figure 6



Cytokines	ANC D1 R	ANC D1 *p*
MMP-8	0.86	0.0000
MMP-9	0.82	0.0000
Resistin	0.76	0.0000
Lipocalin-2	0.73	0.0001
MMP-13	0.70	0.0003
TIMP-4	0.67	0.0007
MMP-1	0.66	0.0009
TNFa	0.65	0.0011
TIMP-1	0.65	0.0011
HGF	0.60	0.0031
IL-15	0.58	0.0047
HB-EGF	0.58	0.0051
IL-4	0.57	0.0051
TIMP-3	0.56	0.0069
TGFa	0.56	0.0070
Fractalkine	0.55	0.0075
MMP-10	0.53	0.0107
IL-7	0.52	0.0122
MMP-7	0.51	0.0145
IL-27	0.51	0.0154
MMP-3	0.50	0.0166
TNFb	0.50	0.0187
IL-1RA	0.47	0.0281
RANTES	0.44	0.0395
Adipsin	0.41	0.0587
TIMP-2	0.40	0.0631
IL-8	0.39	0.0719
M-CSF	0.39	0.0724
MMP-12	0.39	0.0756
G-CSF	0.38	0.0794
IL-6	0.36	0.1034
IL-9	0.36	0.1047
IL-22	0.35	0.1093
IL-18	0.35	0.1100
Adiponectin	0.35	0.1155
C5a	0.31	0.1572
MIP-1a	0.31	0.1601
GROa	0.31	0.1617
IL-1a	0.30	0.1726
Comp.F1	0.24	0.2806
IL-17F	0.22	0.3219
IL-1b	0.22	0.3264
MMP-2	0.21	0.3373
IL-13	0.21	0.3397
Mannose Binding Lectin	0.19	0.3847
IL-10	0.19	0.3960
IL-17E/IL25	0.18	0.4114
GM-CSF	0.14	0.5272
MCP-3	0.13	0.5745
IP-10	0.12	0.6060
IL-2	0.11	0.6307
IL-17A	0.10	0.6609
MIP-1b	0.07	0.7415
IFN-a2	0.06	0.7977
IL-3	0.04	0.8750
MIG/CXCL9	0.03	0.8888
IL-12p70	0.02	0.9462
MCP-1	-0.02	0.9344
IL-5	-0.04	0.8505
Leptin	-0.05	0.8222
IL-12p40	-0.09	0.7040
IFNy	-0.13	0.5644
Eotaxin	-0.17	0.4462
MDC	-0.29	0.1935

Supplementary Figure 6. Correlations of all measured biomarkers with absolute neutrophil count (ANC) in blood samples collected within 24 hours of hospital admission (day 1) for the longitudinal cohort. R, Spearman's rank correlation coefficient; *p*, p-value.

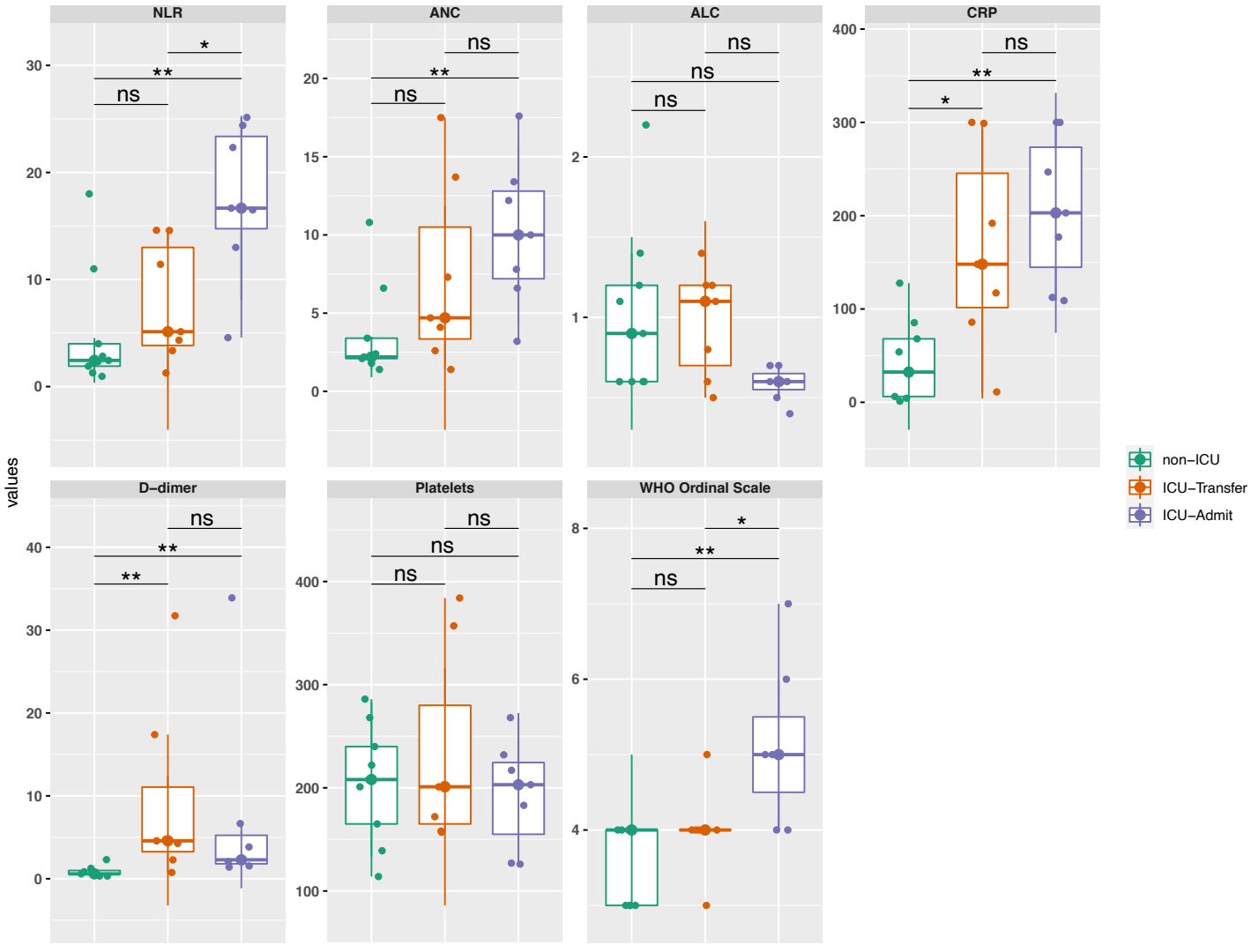
Supplementary Figure 7

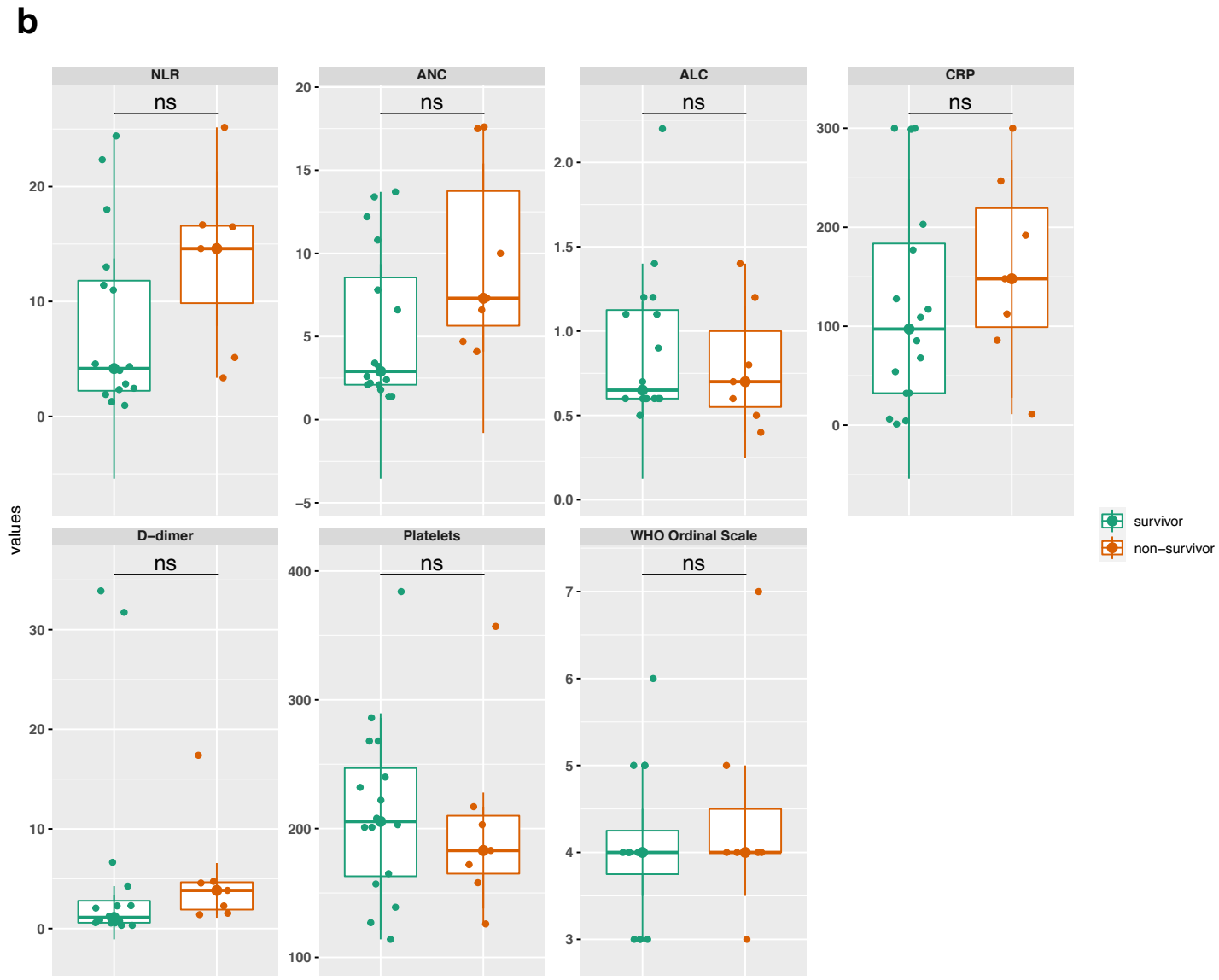


Supplementary Figure 7. Levels of neutrophil (row 1) and macrophage (row 2) activation markers from blood samples collected within 24 hours of hospitalization (day 1) for the longitudinal cohort, comparing patients who were discharged alive (survivors) and those who died (non-survivors). Asterisks denote statistically significant differences between groups (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). Data is shown as median with interquartile range. All values are concentrations in pg/mL.

Supplementary Figure 8

a





Supplementary Figure 8. Established clinical markers of disease severity in COVID-19 were assessed from blood samples collected on day 1 in the longitudinal cohort, and the WHO Ordinal Scale was assessed based on oxygen requirements at the time of day 1 blood draw, comparing (a) patients categorized as 1) non-ICU, 2) ICU-Transfer, and 3) ICU-Admit, and (b) patients who were discharged alive (survivors) and those who died (non-survivors). 'Non-ICU' indicates patients who remained in a non-ICU unit until discharge; 'ICU-Transfer' indicates patients who were admitted to a non-ICU unit and were transferred to an ICU unit during hospitalization; 'ICU-Admit' indicates patients who were admitted directly to an ICU unit. Asterisks denote statistically significant differences between groups (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). Data is shown as median with interquartile range. ALC: Absolute lymphocyte count; ANC: Absolute neutrophil count; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; WHO: World Health Organization.