Data S5: Compositional Analysis of CITE-seq Data, Related to STAR Methods

Related to **STAR Methods**: CITE-seq: composition analysis.

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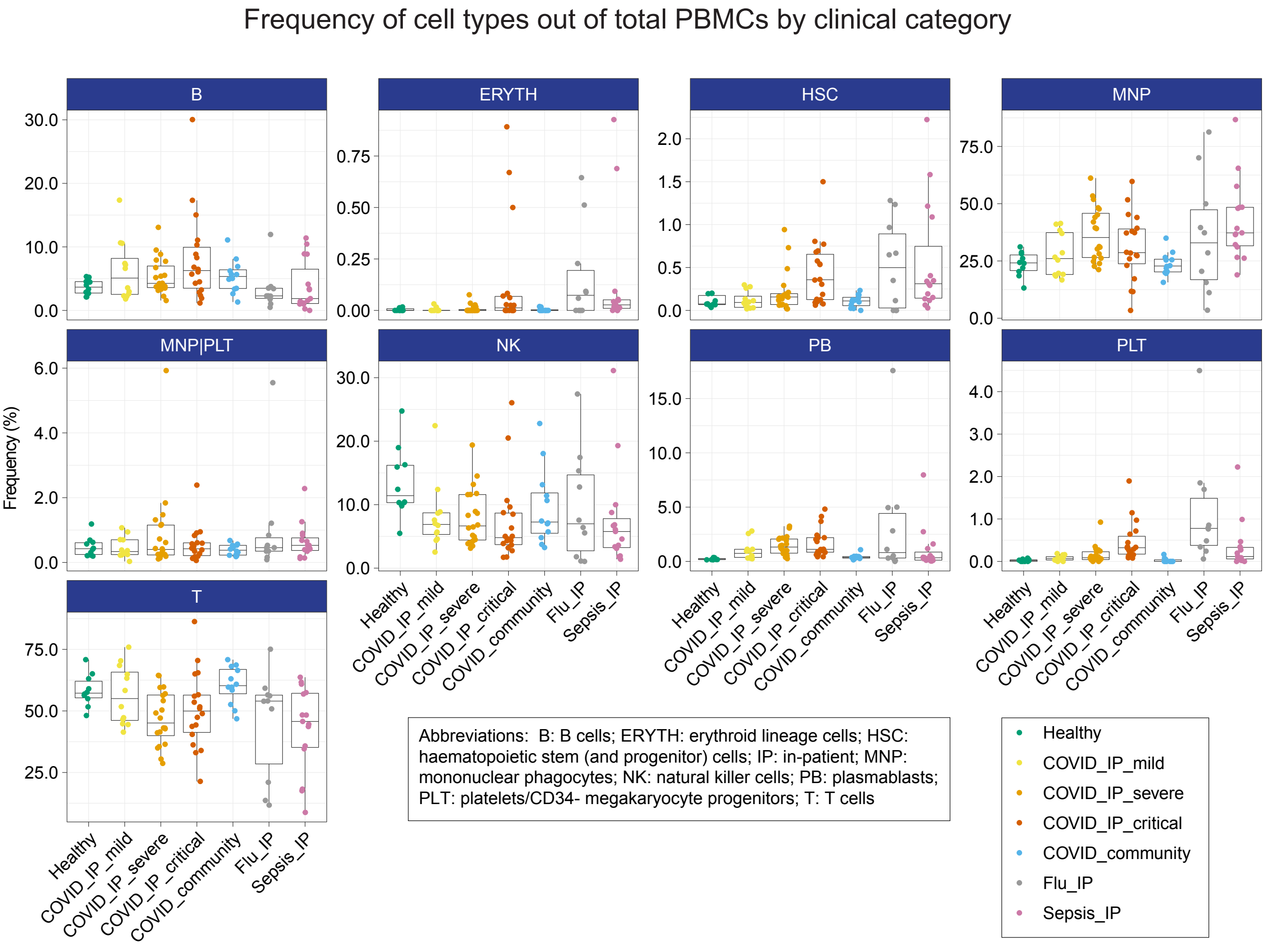
Composition analysis

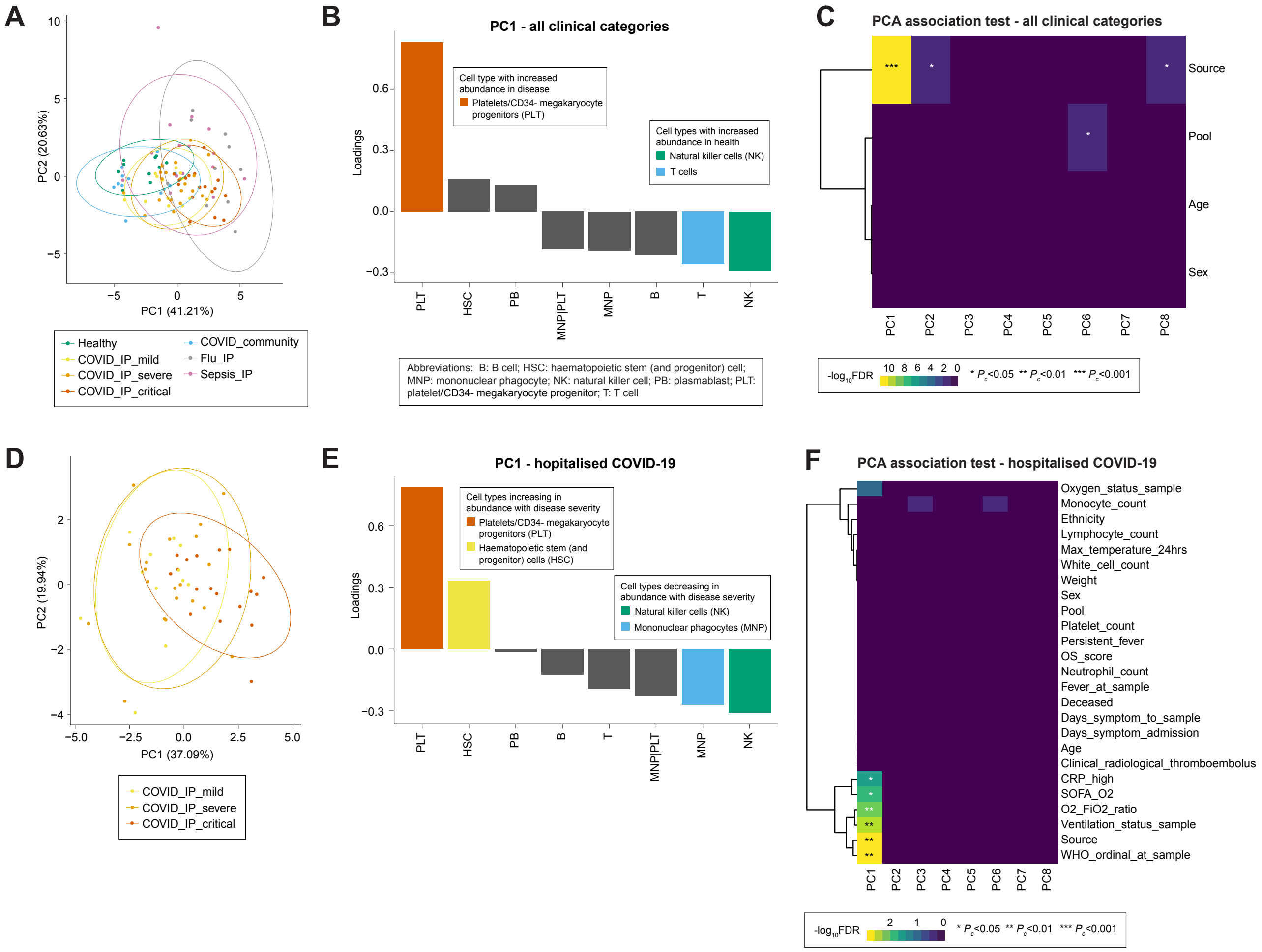
Composition analysis of cell types



Abbreviations: B: B cells; ERYTH: erythroid lineage cells; HSC: haematopoietic stem (and progenitor) cells; IP: in-patient; MNP: mononuclear phagocytes; NK: natural killer cells; PB: plasmablasts; PLT: platelets/CD34- megakaryocyte progenitors; T: T cells

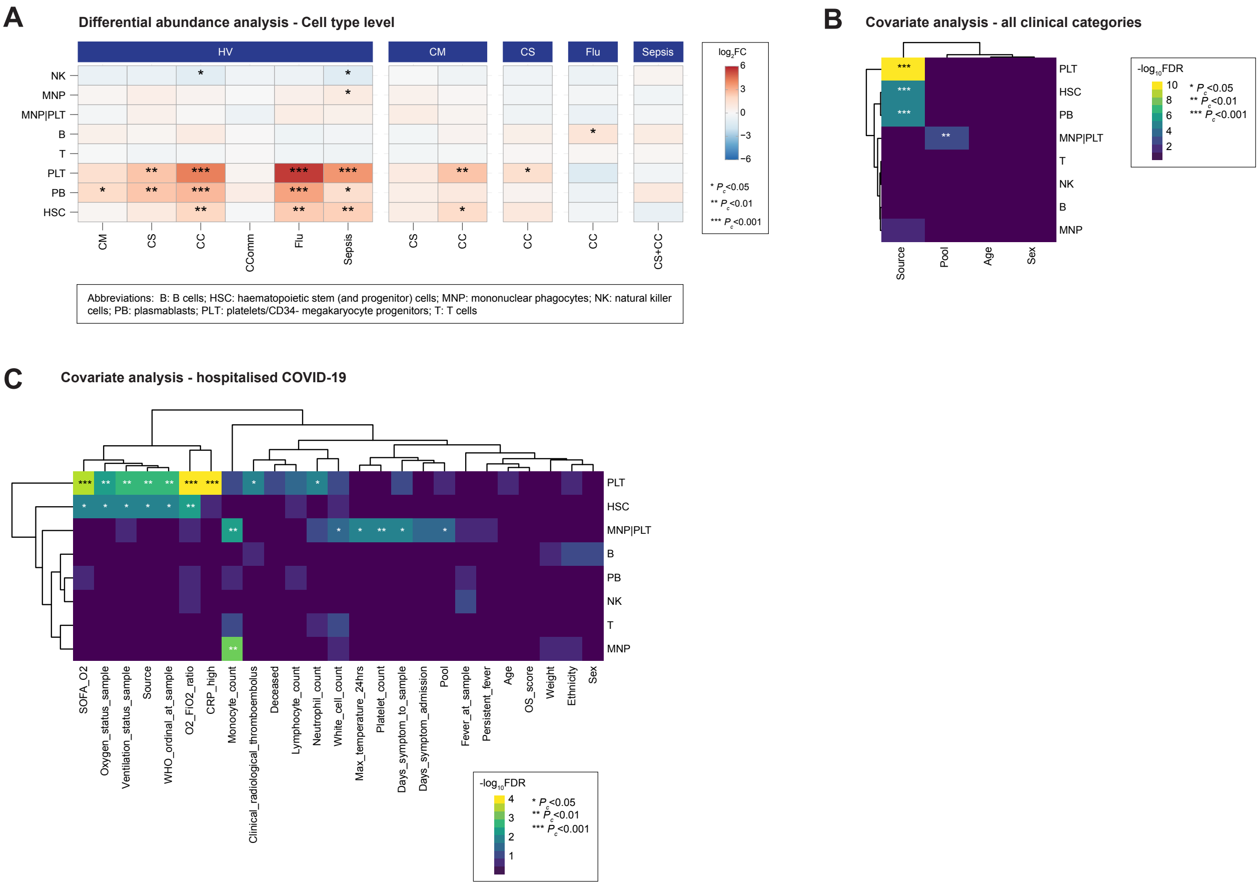
1: Cell type frequency by clinical category. The box plots show the median and the first and third quartiles; whiskers show 1.5 × the interquartile range above and below the box. Cell types are ordered alphabetically. Related to STAR Methods: CITE-seq: composition analysis.

Cell types - PCA



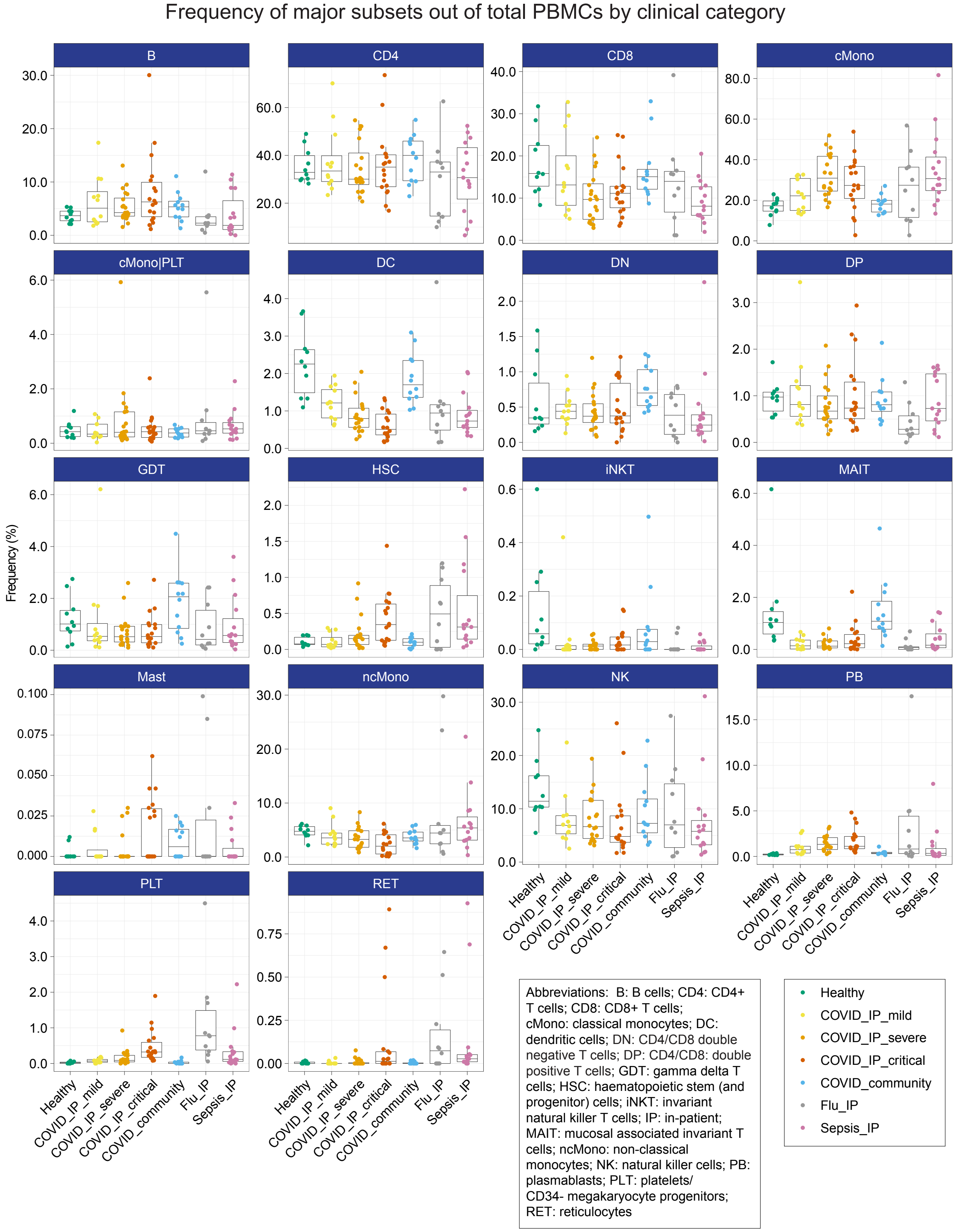
2: Cell type PCA and association tests. (A) PCA plot for all clinical categories. Percentage of variance explained by each PC is shown in the brackets. (B) Loadings of cell types on PC1 from analysis including all clinical categories. (C) Association test between top PCs and source (clinical category), age, sex, and sample pool for all clinical categories. (D) PCA plot for hospitalized COVID-19. Percentage of variance explained by each PC is shown in the brackets. (E) Loadings of cell types on PC1 from analysis of hospitalized COVID-19 cases. (F) Association test between top PCs and clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Cell types - edgeR differential abundance analysis



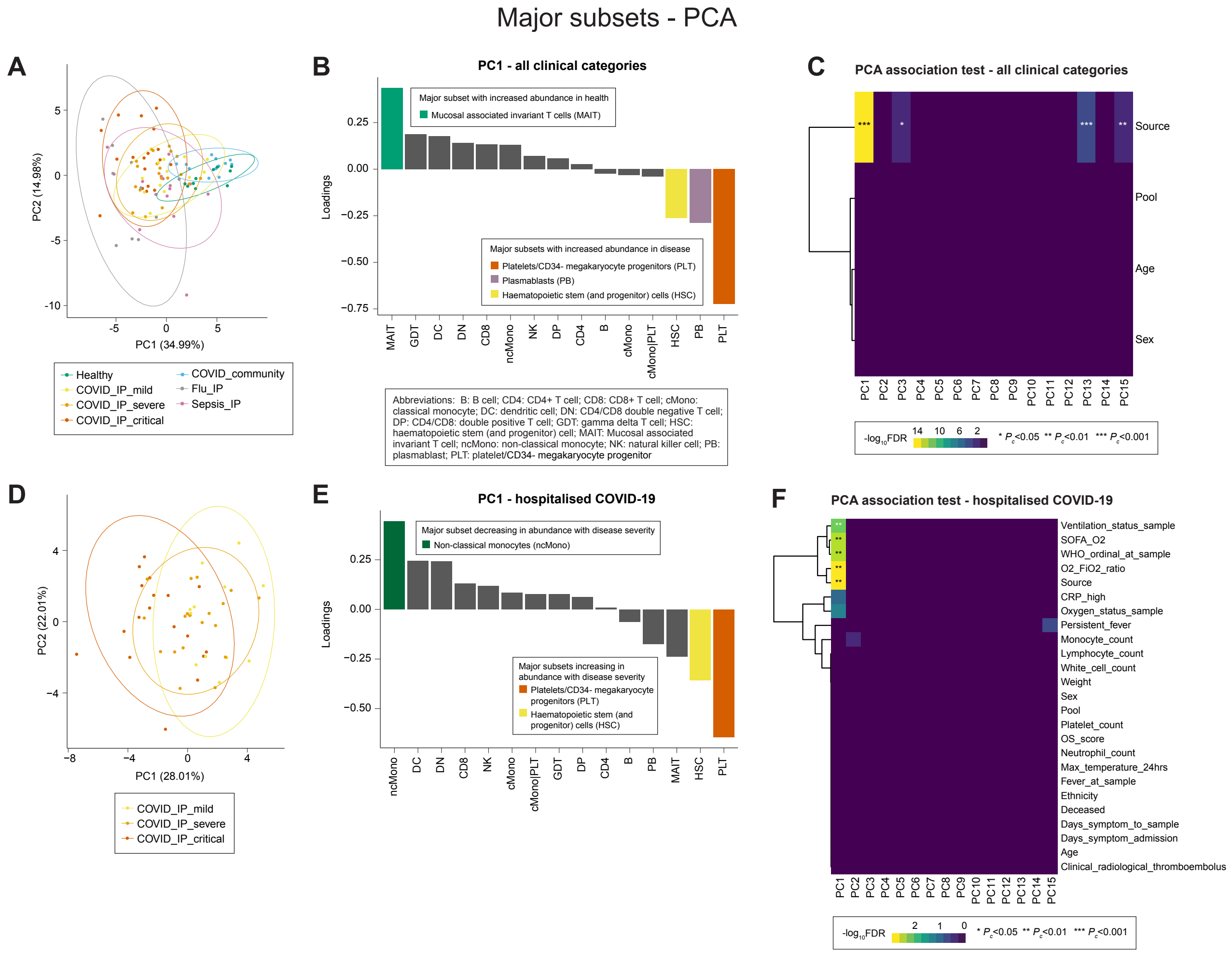
3: Cell type differential abundance analysis. (A) Cell type differential abundance analysis between clinical categories, controlling for age, sex and sample pool effects. (B) Cell type covariate analysis for source (clinical category), age, sex and sample pool for all clinical categories. (C) Cell type covariate analysis for clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Composition analysis of major cell subsets



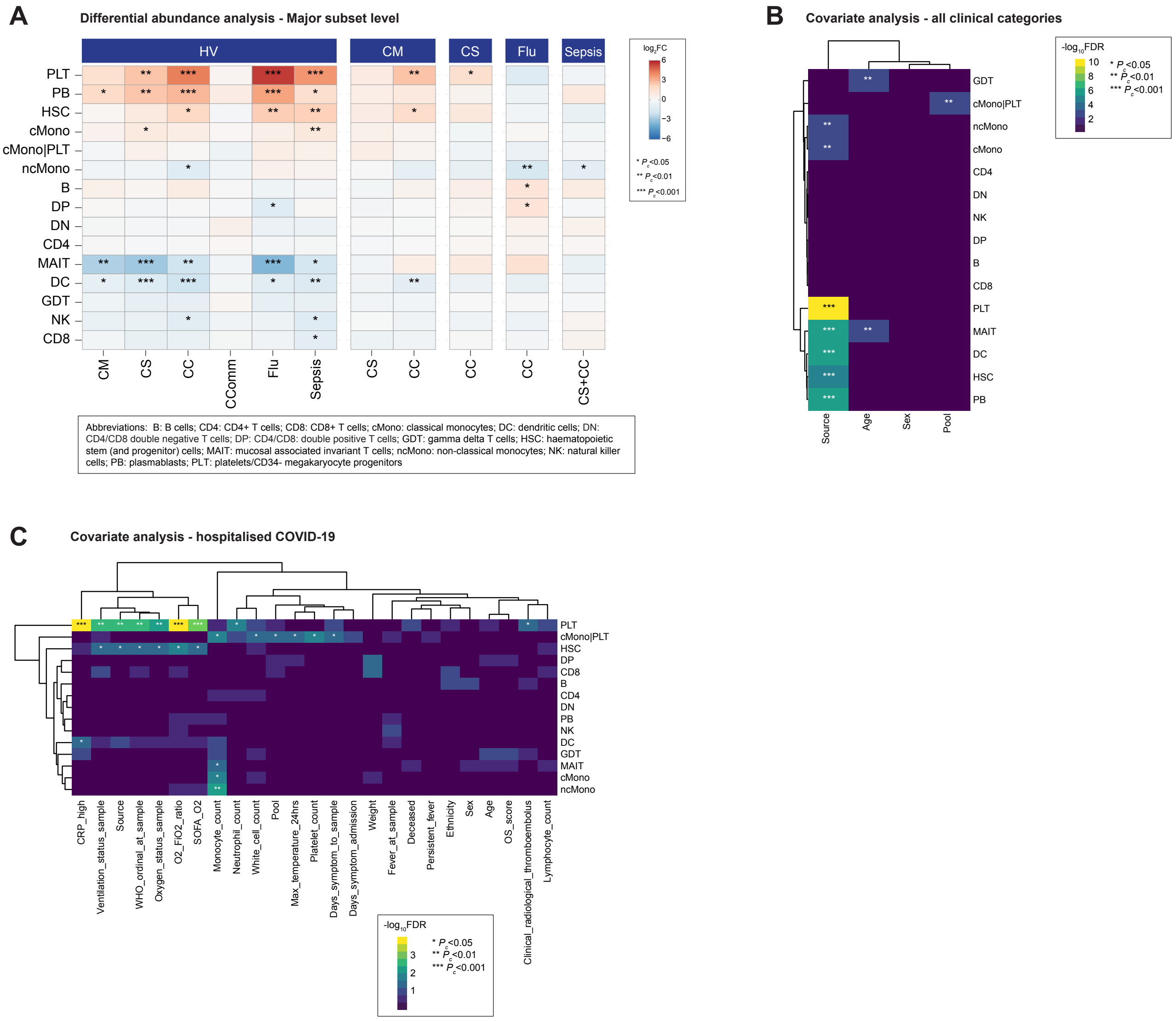
Abbreviations: B: B cells; CD4: CD4+ T cells; CD8: CD8+ T cells; cMono: classical monocytes; DC: dendritic cells; DN: CD4/CD8 double negative T cells; DP: CD4/CD8: double positive T cells; GDT: gamma delta T cells; HSC: haematopoietic stem (and progenitor) cells; iNKT: invariant natural killer T cells; IP: in-patient; MAIT: mucosal associated invariant T cells; ncMono: non-classical monocytes; NK: natural killer cells; PB: plasmablasts; PLT: platelets/ CD34- megakaryocyte progenitors; RET: reticulocytes

4: Major cell subset frequency by clinical category. Box plots show the median and the first and third quartiles; whiskers show 1.5 × the interquartile range above and below the box. Major subsets are ordered alphabetically. Related to STAR Methods: CITE-seq: composition analysis.



5: Major cell subset PCA and association tests. (A) PCA plot for all clinical categories. Percentage of variance explained by each PC is shown in the brackets. (B) Loadings of major subsets on PC1 from analysis including all clinical categories. (C) Association test between top PCs and source (clinical category), age, sex, and sample pool for all clinical categories. (D) PCA plot for hospitalized COVID-19. Percentage of variance explained by each PC is shown in the brackets. (E) Loadings of major subsets on PC1 from analysis of hospitalized COVID-19 cases. (F) Association test between top PCs and clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

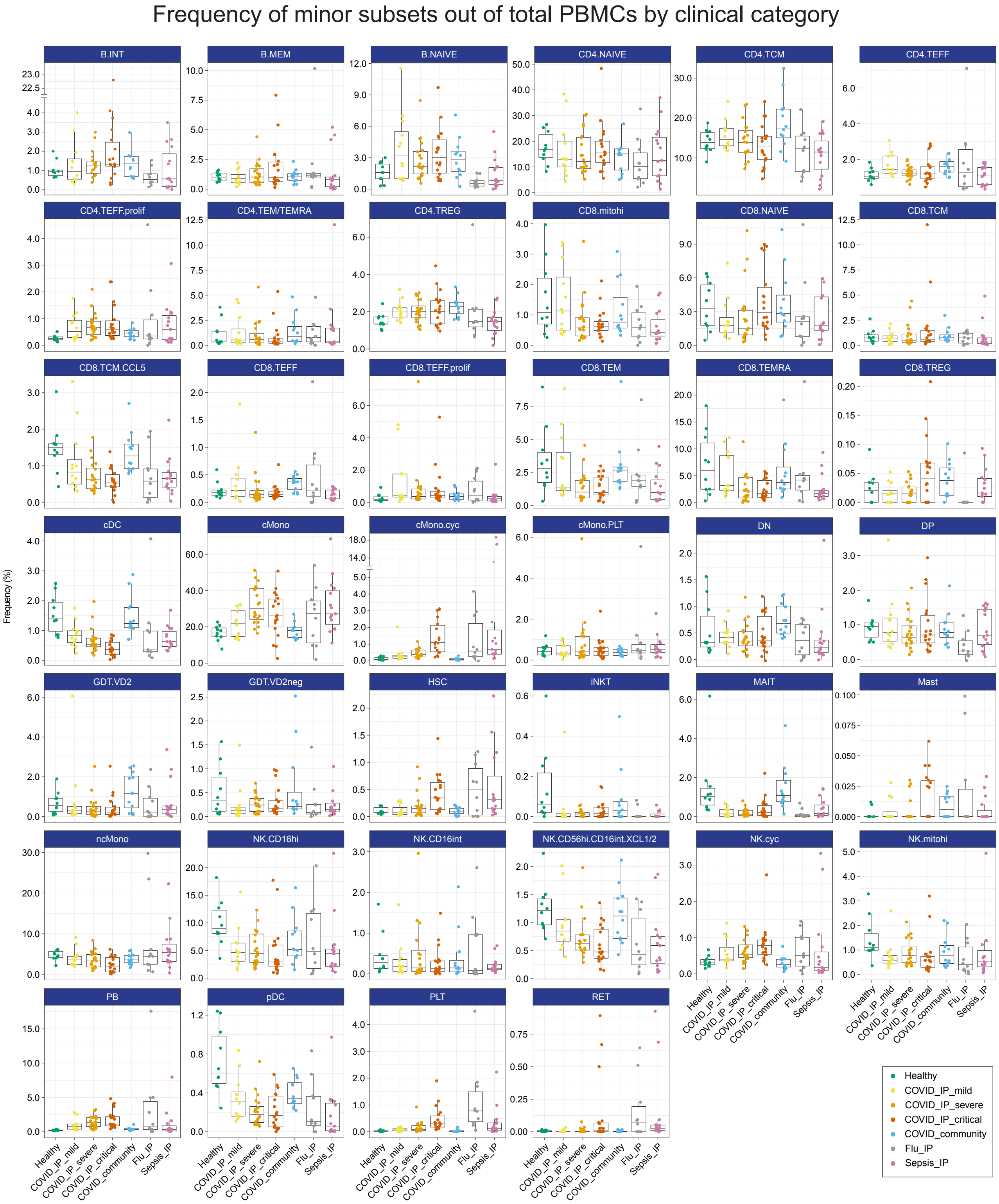
Major subsets - edgeR differential abundance analysis



Abbreviations: B: B cells; CD4: CD4+ T cells; CD8: CD8+ T cells; cMono: classical monocytes; DC: dendritic cells; DN: CD4/CD8 double negative T cells; DP: CD4/CD8: double positive T cells; GDT: gamma delta T cells; HSC: haematopoietic stem (and progenitor) cells; MAIT: mucosal associated invariant T cells; ncMono: non-classical monocytes; NK: natural killer cells; PB: plasmablasts; PLT: platelets/CD34- megakaryocyte progenitors

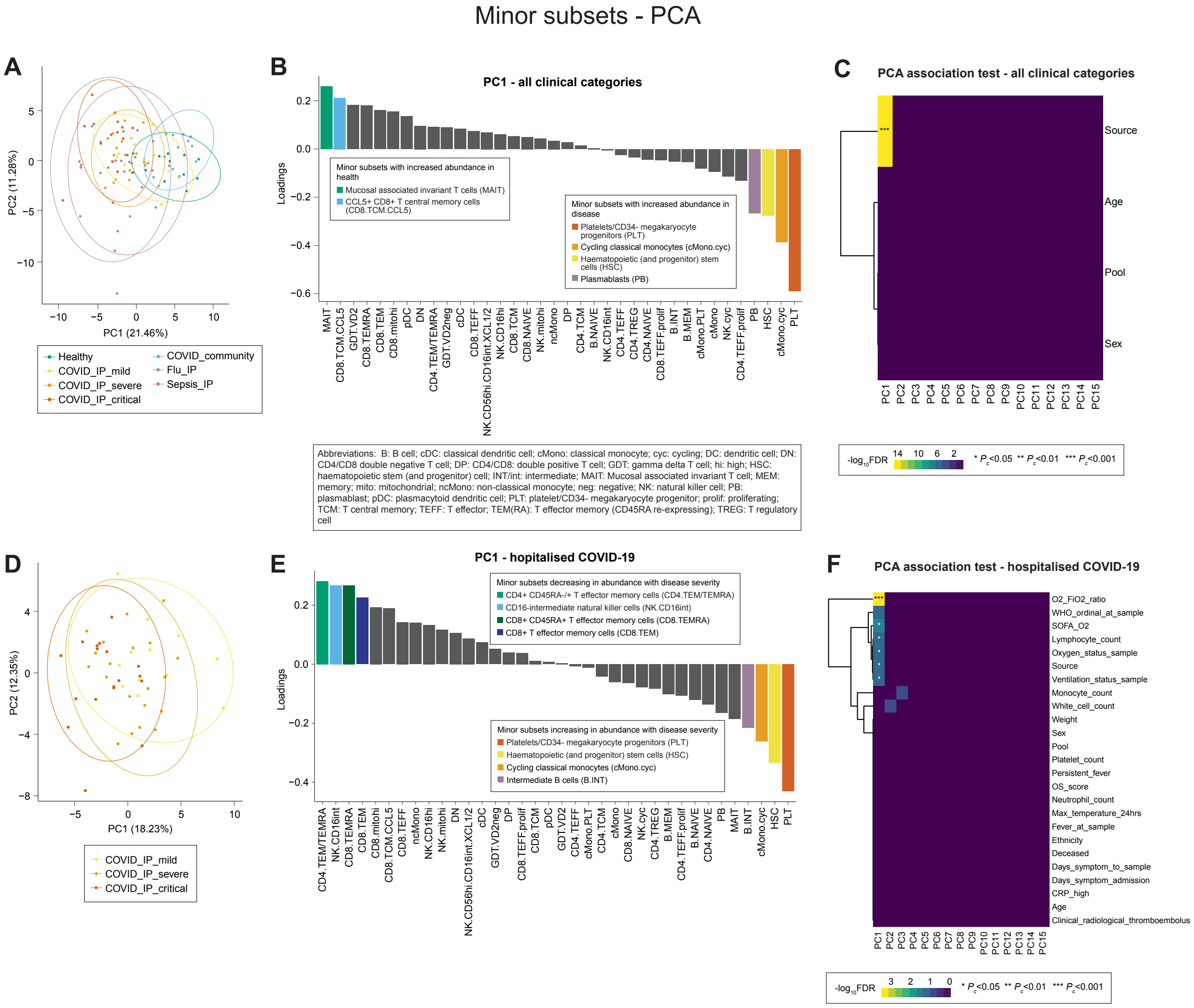
6: Major cell subset differential abundance analysis. (A) Major subset differential abundance analysis between clinical categories, controlling for age, sex and sample pool. (B) Major subset covariate analysis for source (clinical category), age, sex and pool for all clinical categories. (C) Major subset covariate analysis for clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Composition analysis of minor cell subsets


Frequency of minor subsets out of total PBMCs by clinical category

Abbreviations: B: B cell; cDC: classical dendritic cell; cMono: classical monocyte; cyc: cycling; DN: CD4/CD8 double negative T cell; DP: CD4/CD8: double positive T cell; GDT: gamma delta T cell; hi: high; HSC: haematopoietic stem (and progenitor) cell; iNKT: invariant NKT cell; INT/int: intermediate; IP: in-patient; MAIT: mucosal associated invariant T cell; MEM: memory; mito: mitochondrial; ncMono: non-classical monocyte; neg: negative; NK: natural killer cell; PB: plasmablast; pDC: plasmacytoid dendritic cell; PLT: platelet/CD34- megakaryocyte progenitor; prolif: proliferating; TCM: T central memory; TEFF: T effector; TEM(RA): T effector memory (CD45RA re-expressing); TREG: T regulatory cell; RET: reticulocytes

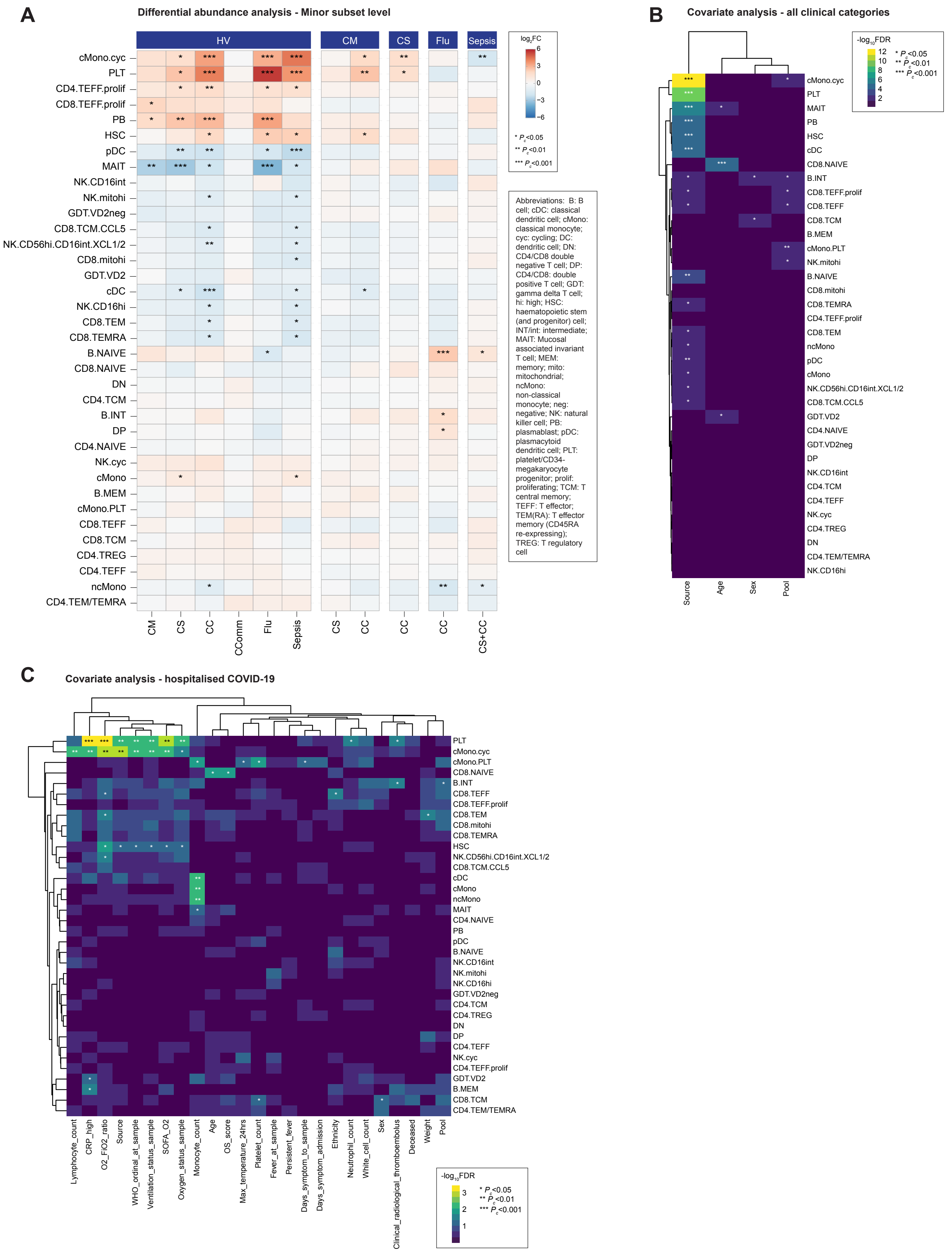
7: Minor cell subset frequency by clinical category. Box plots show the median and the first and third quartiles; whiskers show 1.5 × the interquartile range above and below the box. Minor subsets are ordered alphabetically. Related to STAR Methods: CITE-seq: composition analysis.



Abbreviations: B: B cell; cDC: classical dendritic cell; cMono: classical monocyte; cyc: cycling; DC: dendritic cell; DN: CD4/CD8 double negative T cell; DP: CD4/CD8: double positive T cell; GDT: gamma delta T cell; hi: high; HSC: haematopoietic stem (and progenitor) cell; INT/int: intermediate; MAIT: Mucosal associated invariant T cell; MEM: memory; mito: mitochondrial; ncMono: non-classical monocyte; neg: negative; NK: natural killer cell; PB: plasmablast; pDC: plasmacytoid dendritic cell; PLT: platelet/CD34- megakaryocyte progenitor; prolif: proliferating; TCM: T central memory; TEFF: T effector; TEM(RA): T effector memory (CD45RA re-expressing); TREG: T regulatory cell

8: Minor cell subset PCA and association tests. (A) PCA plot for all clinical categories. Percentage of variance explained by each PC is shown in the brackets. (B) Loadings of minor subsets on PC1 from analysis including all clinical categories. (C) Association test between top PCs and source (clinical category), age, sex, and sample pool for all clinical categories. (D) PCA plot for hospitalized COVID-19. Percentage of variance explained by each PC is shown in the brackets. (E) Loadings of minor subsets on PC1 from analysis of hospitalized COVID-19 cases. (F) Association test between top PCs and clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Minor subsets - edgeR differential abundance analysis

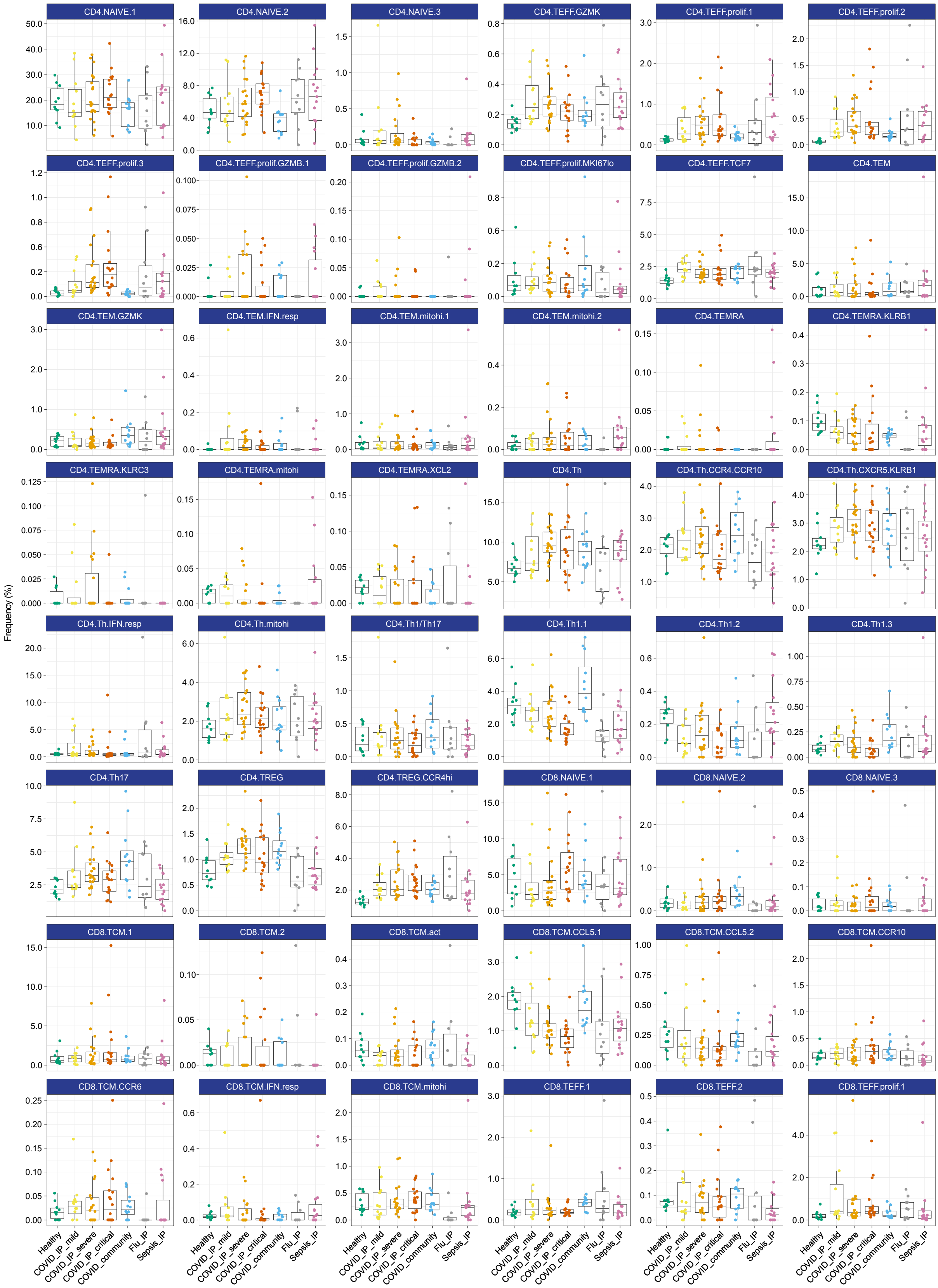


Abbreviations: B: B cell; cDC: classical dendritic cell; cMono: classical monocyte; cyc: cycling; DC: dendritic cell; DN: CD4/CD8 double negative T cell; DP: CD4/CD8: double positive T cell; GDT: gamma delta T cell; hi: high; HSC: haematopoietic stem (and progenitor) cell; INT/int: intermediate; MAIT: Mucosal associated invariant T cell; MEM: memory; mito: mitochondrial; ncMono: non-classical monocyte; neg: negative; NK: natural killer cell; PB: plasmablast; pDC: plasmacytoid dendritic cell; PLT: platelet/CD34- megakaryocyte progenitor; prolif: proliferating; TCM: T central memory; TEFF: T effector; TEM(RA): T effector memory (CD45RA re-expressing); TREG: T regulatory cell

9: Minor cell subset differential abundance analysis. (A) Minor subset differential abundance analysis between clinical categories, controlling for age, sex and sample pool. (B) Minor subset covariate analysis for source (clinical category), age, sex and pool for all clinical categories. (C) Minor subset covariate analysis for clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Composition analysis of T and natural killer cell clusters

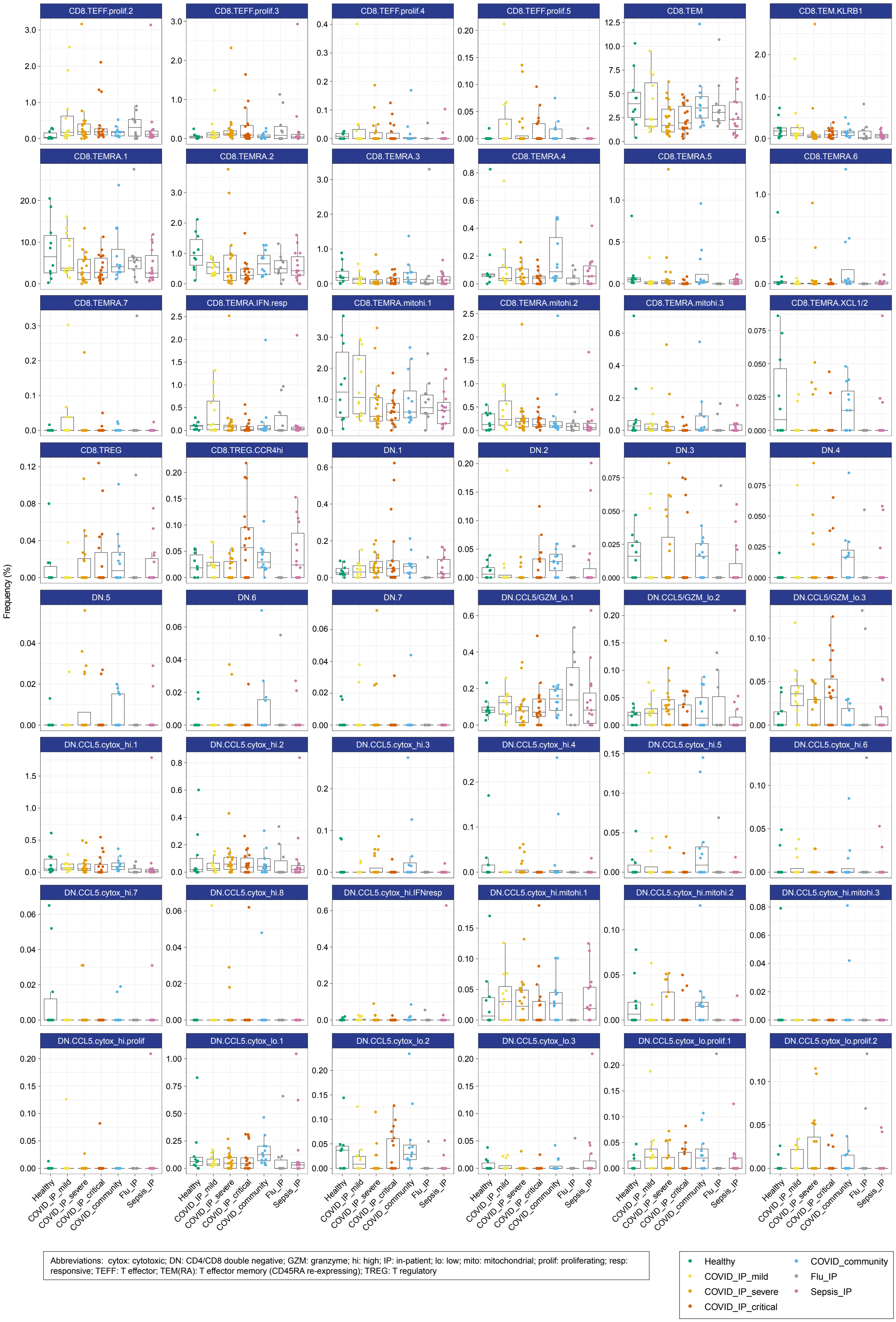
Frequency of clusters out of total T and natural killer cells by clinical category (1)



Abbreviations: act: activated; hi: high; IP: in-patient; lo: low; mito: mitochondrial; prolif: proliferating; resp: responsive; TCM: T central memory; TEFF: T effector; TEM(RA): T effector memory (CD45RA re-expressing); Th: T helper; TREG: T regulatory

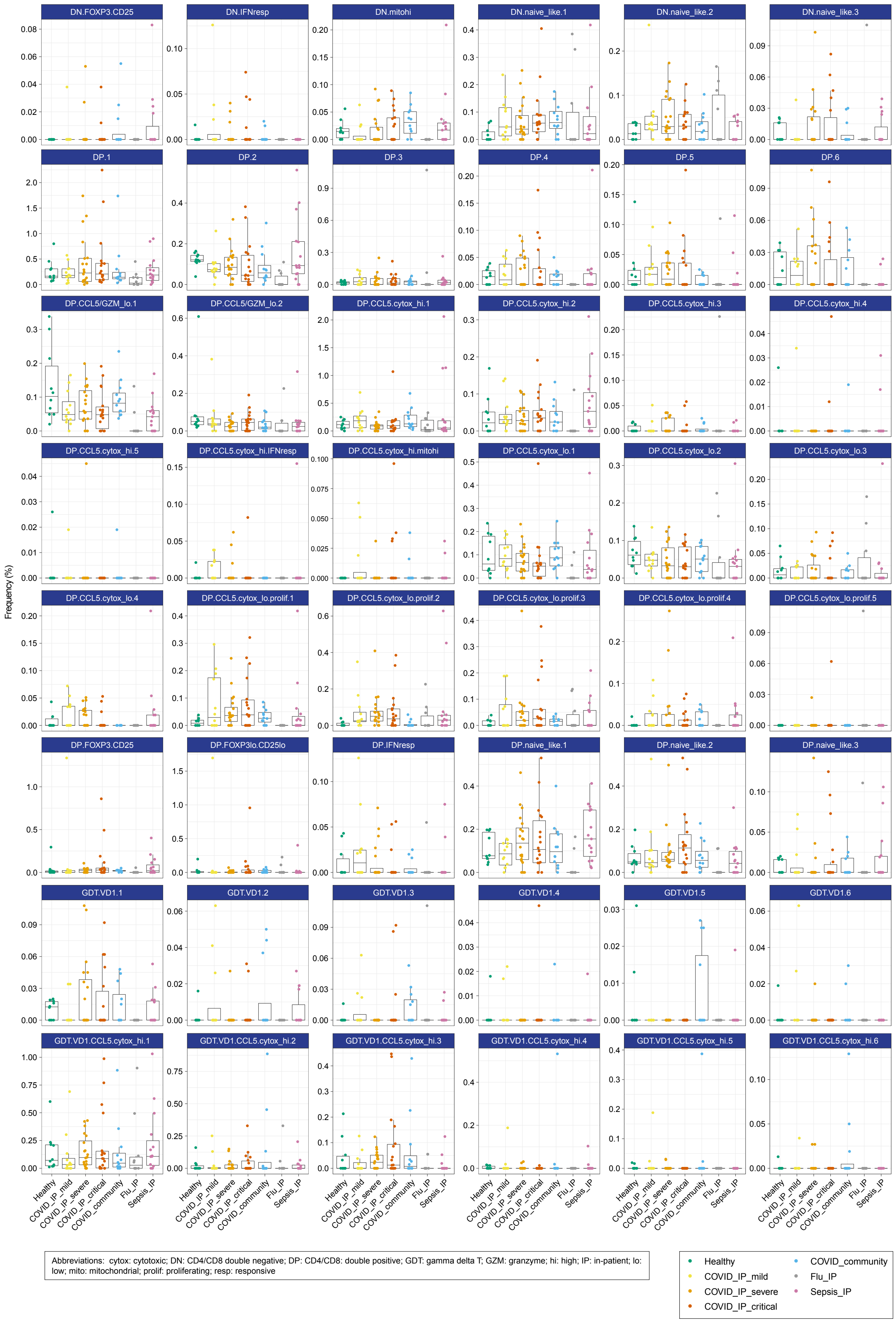
● Healthy	● COVID_community
● COVID_IP_mild	● Flu_IP
● COVID_IP_severe	● Sepsis_IP
● COVID_IP_critical	

Frequency of clusters out of total T and natural killer cells by clinical category (2)



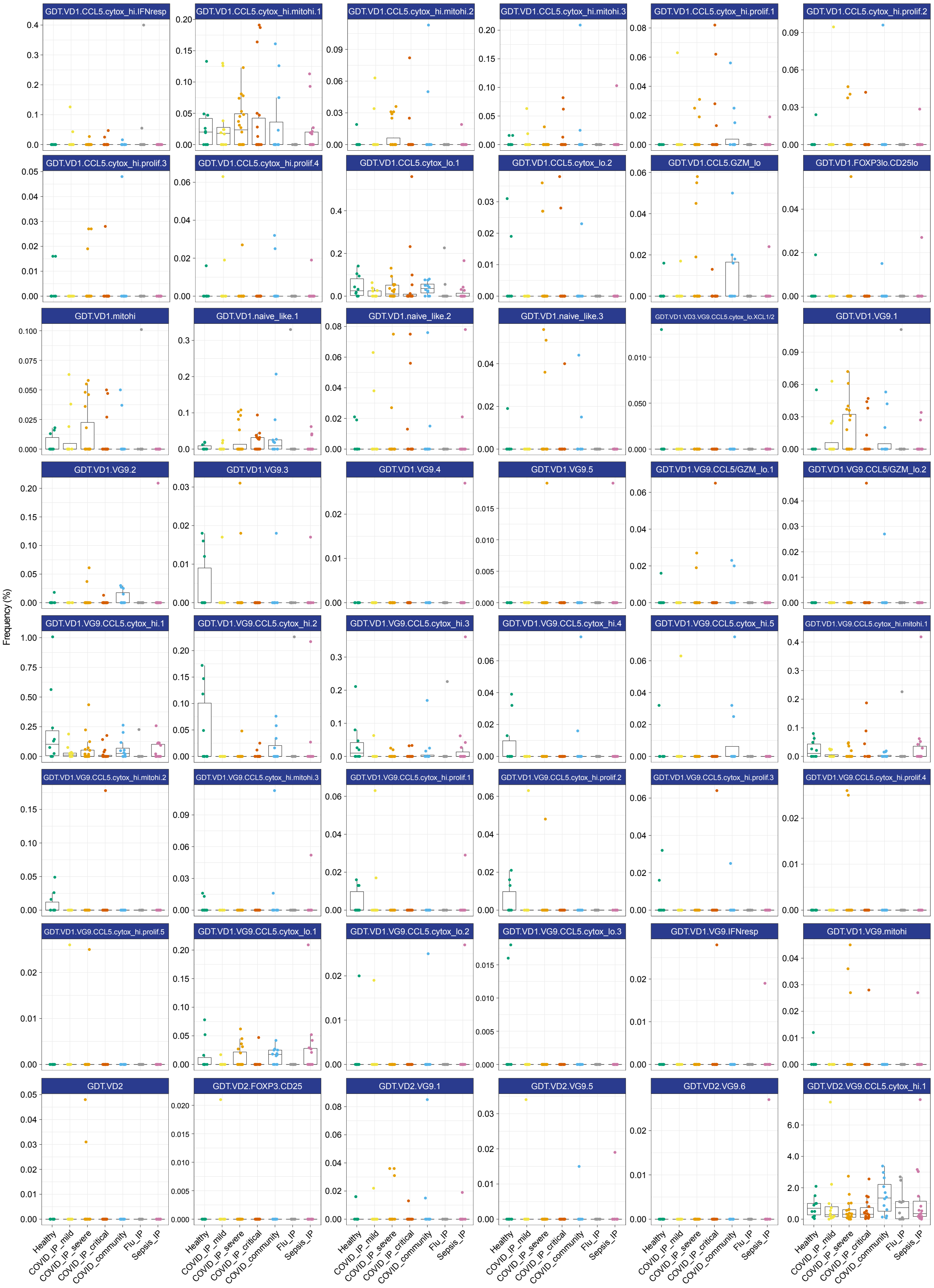
Abbreviations: cytox: cytotoxic; DN: CD4/CD8 double negative; GZM: granzyme; hi: high; IP: in-patient; lo: low; mito: mitochondrial; prolif: proliferating; resp: responsive; TEFF: T effector; TEM(RA): T effector memory (CD45RA re-expressing); TREG: T regulatory

Frequency of clusters out of total T and natural killer cells by clinical category (3)



Abbreviations: cytox: cytotoxic; DN: CD4/CD8 double negative; DP: CD4/CD8: double positive; GDT: gamma delta T; GZM: granzyme; hi: high; IP: in-patient; lo: low; mito: mitochondrial; prolif: proliferating; resp: responsive

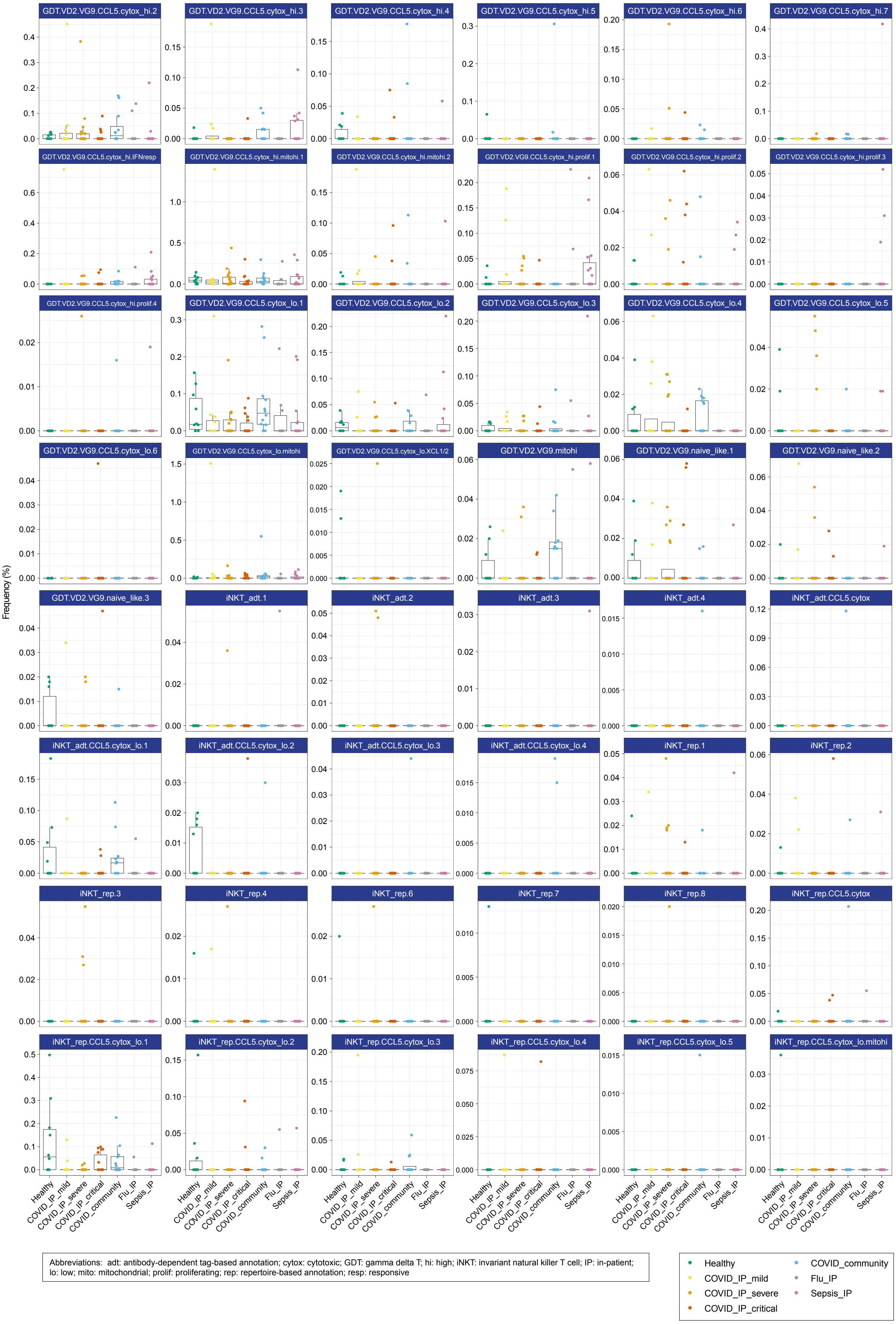
Frequency of clusters out of total T and natural killer cells by clinical category (4)



Abbreviations: cytox: cytotoxic; GDT: gamma delta T; GZM: granzyme; hi: high; IP: in-patient; lo: low; mito: mitochondrial; prolif: proliferating; resp: responsive

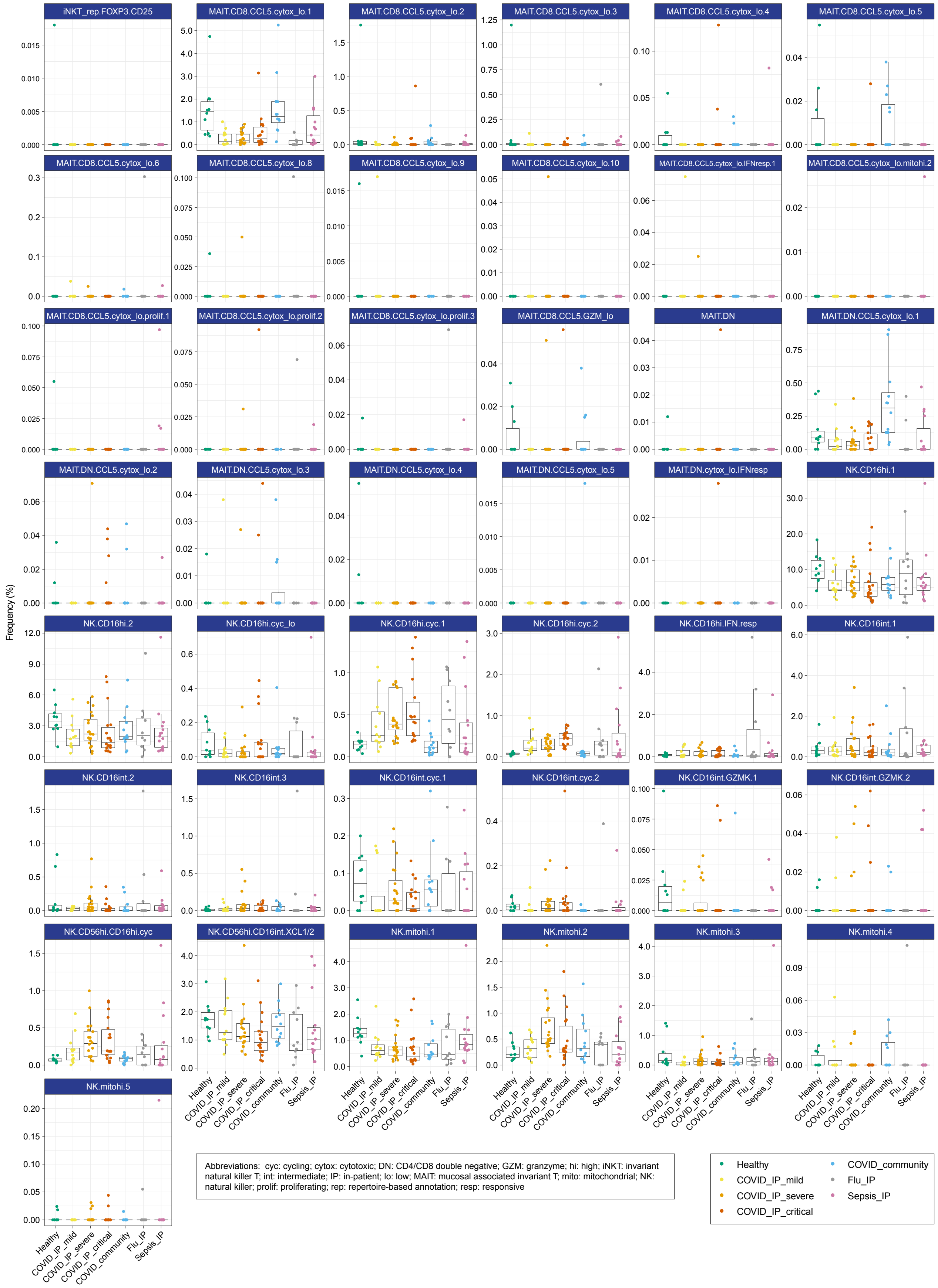
● Healthy	● COVID_community
● COVID_IP_mild	● Flu_IP
● COVID_IP_severe	● Sepsis_IP
● COVID_IP_critical	

Frequency of clusters out of total T and natural killer cells by clinical category (5)



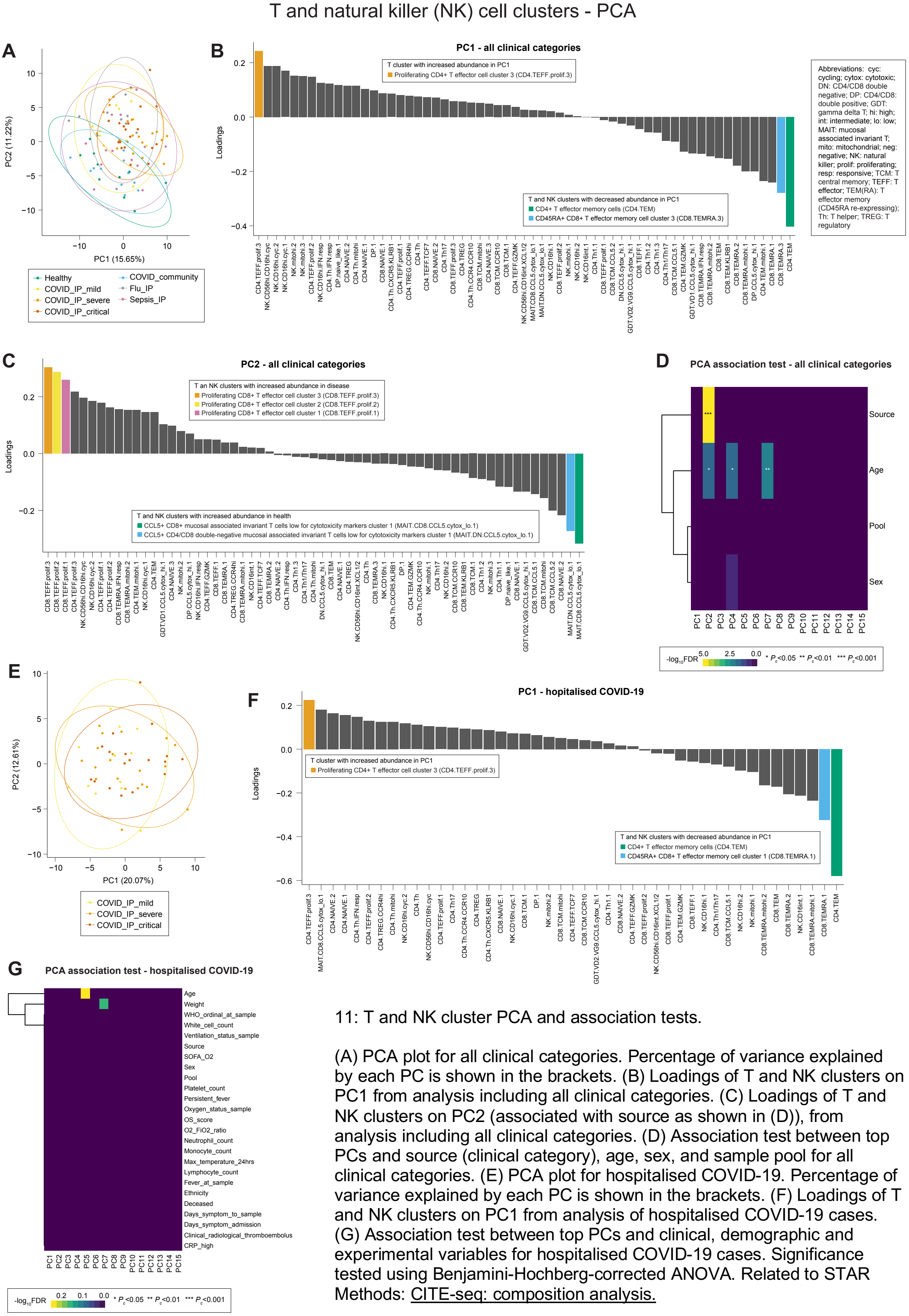
Abbreviations: adt: antibody-dependent tag-based annotation; cytox: cytotoxic; GDT: gamma delta T; hi: high; iNKT: invariant natural killer T cell; IP: in-patient; lo: low; mito: mitochondrial; prolif: proliferating; rep: repertoire-based annotation; resp: responsive

Frequency of clusters out of total T and natural killer cells by clinical category (6)



Abbreviations: cyc: cycling; cytox: cytotoxic; DN: CD4/CD8 double negative; GZM: granzyme; hi: high; iNKT: invariant natural killer T; int: intermediate; IP: in-patient; lo: low; MAIT: mucosal associated invariant T; mito: mitochondrial; NK: natural killer; prolif: proliferating; rep: repertoire-based annotation; resp: responsive

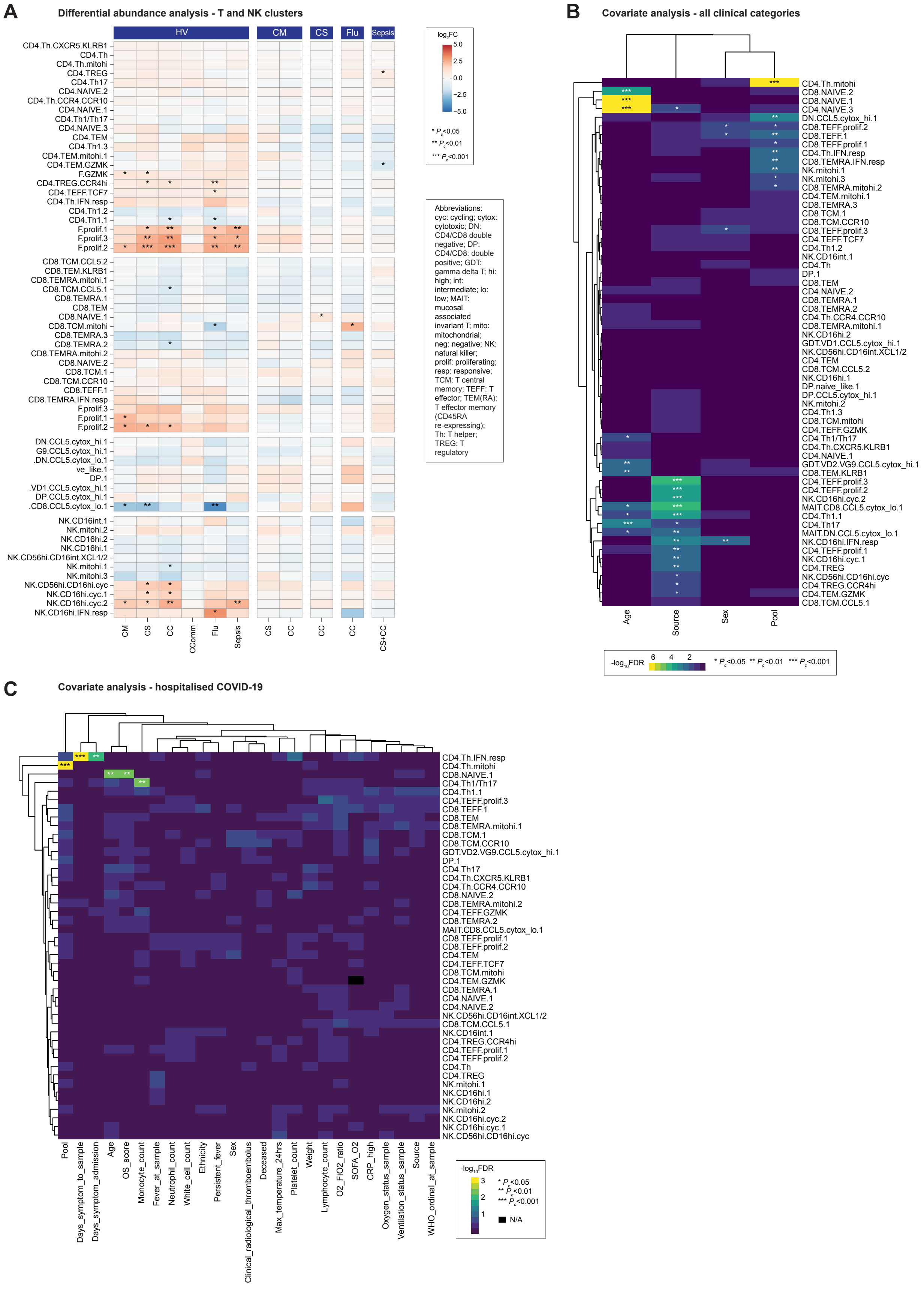
10: T and NK cluster frequency by clinical category. Box plots show the median and the first and third quartiles; whiskers show 1.5 × the interquartile range above and below the box. Clusters are ordered alphabetically. Related to STAR Methods: CITE-seq: composition analysis.


T and natural killer (NK) cell clusters - PCA

11: T and NK cluster PCA and association tests.

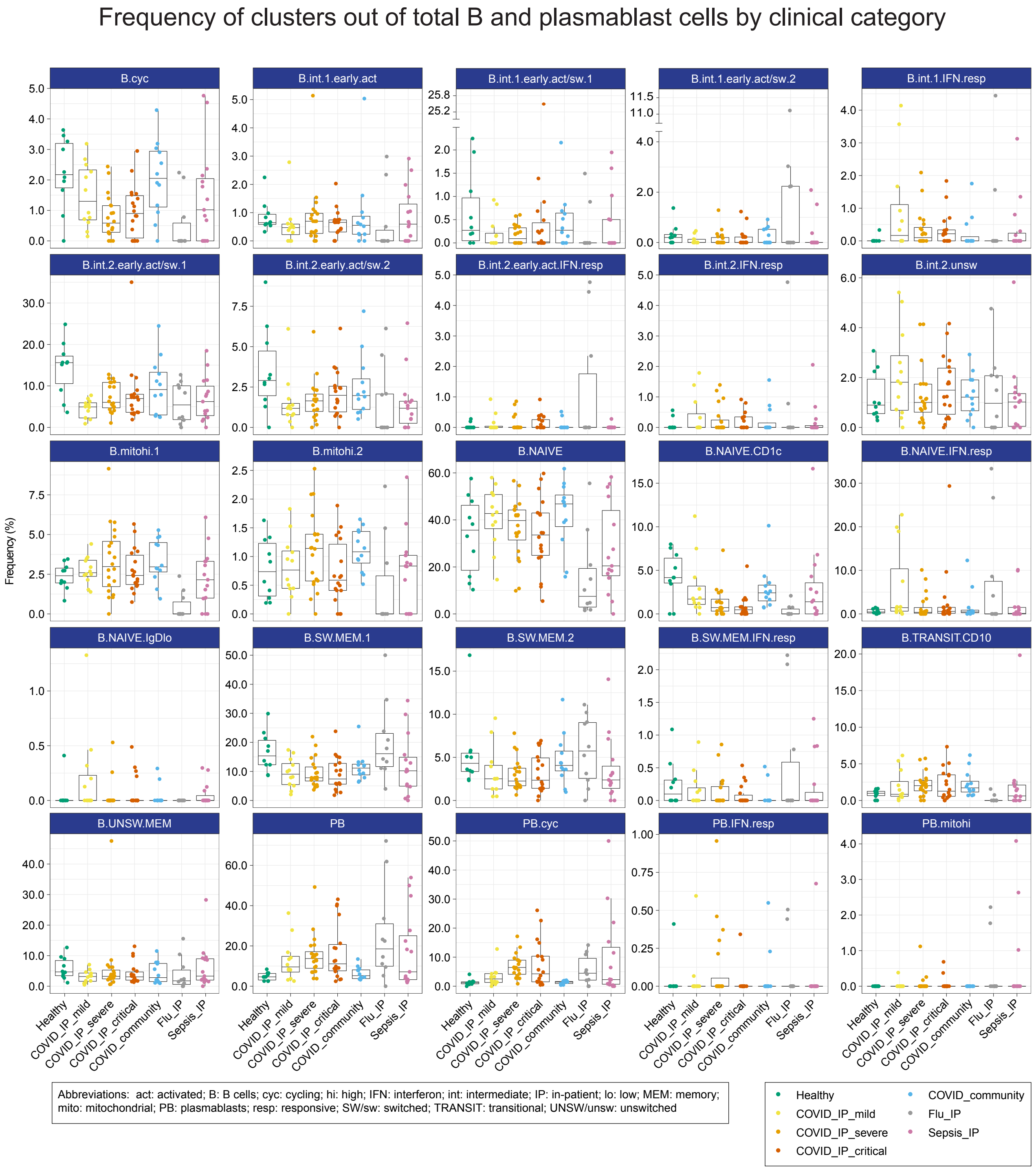
(A) PCA plot for all clinical categories. Percentage of variance explained by each PC is shown in the brackets. (B) Loadings of T and NK clusters on PC1 from analysis including all clinical categories. (C) Loadings of T and NK clusters on PC2 (associated with source as shown in (D)), from analysis including all clinical categories. (D) Association test between top PCs and source (clinical category), age, sex, and sample pool for all clinical categories. (E) PCA plot for hospitalised COVID-19. Percentage of variance explained by each PC is shown in the brackets. (F) Loadings of T and NK clusters on PC1 from analysis of hospitalised COVID-19 cases. (G) Association test between top PCs and clinical, demographic and experimental variables for hospitalised COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

T and natural killer (NK) cell clusters - edgeR differential abundance analysis



12: T and NK cluster differential abundance analysis. (A) T and NK cluster differential abundance analysis between clinical categories, controlling for age, sex, and sample pool. (B) T and NK cluster covariate analysis for source (clinical category), age, sex and pool for all clinical categories. (C) T and NK cluster covariate analysis for clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

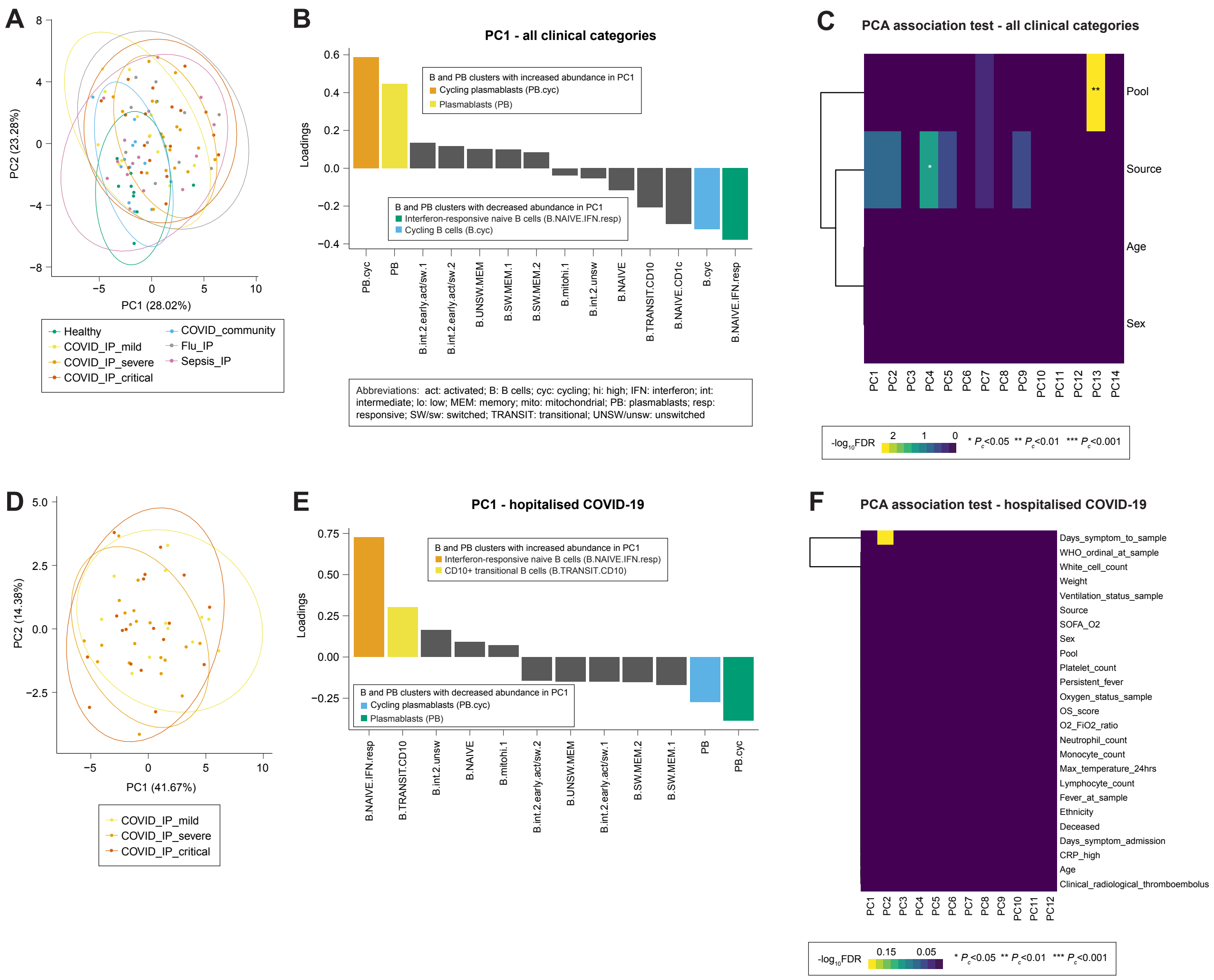
Composition analysis of B and plasmablast cell clusters



Abbreviations: act: activated; B: B cells; cyc: cycling; hi: high; IFN: interferon; int: intermediate; IP: in-patient; lo: low; MEM: memory; mito: mitochondrial; PB: plasmablasts; resp: responsive; SW/sw: switched; TRANSIT: transitional; UNSW/unsw: unswitched

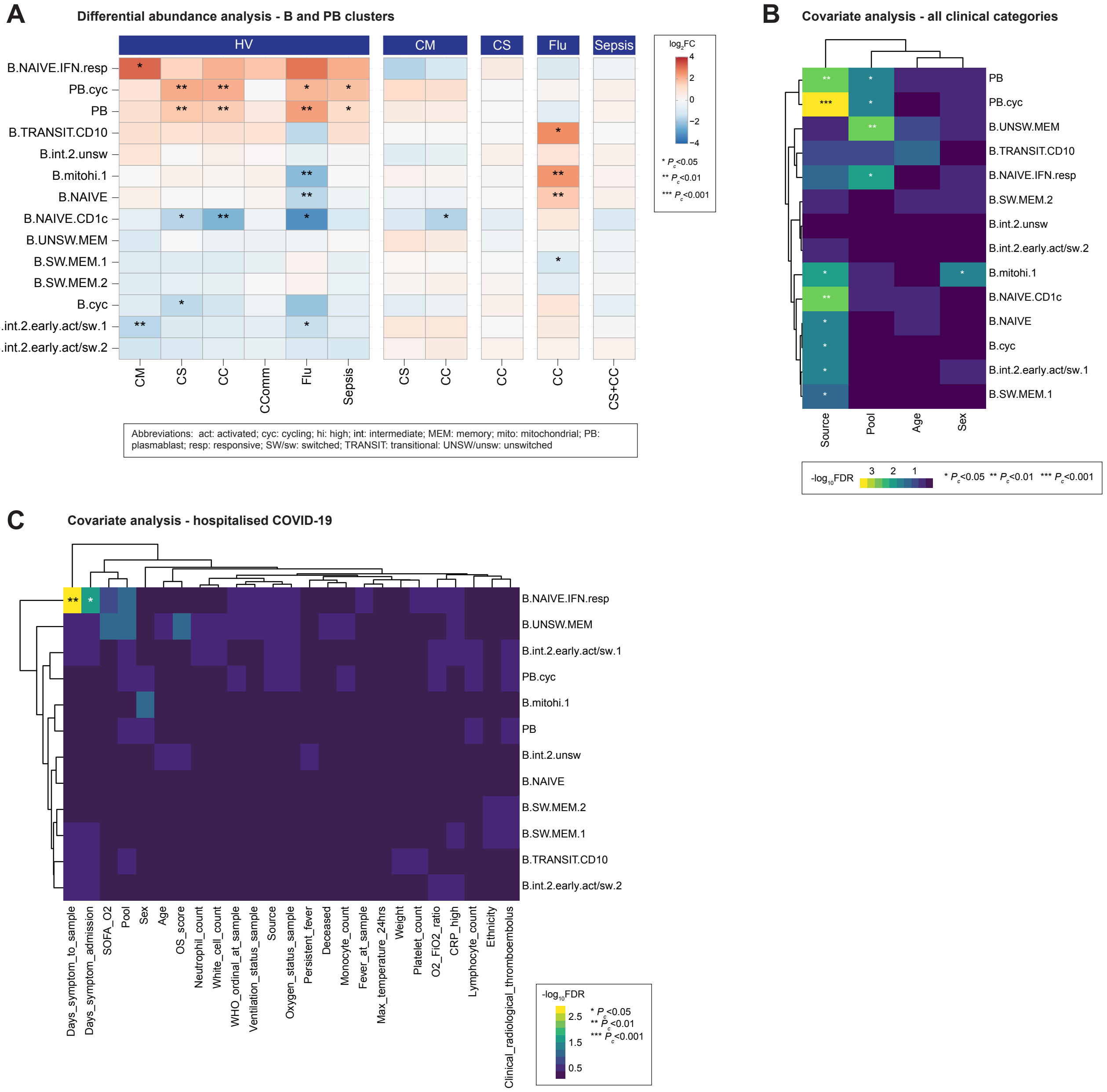
13: B and PB cluster frequency by clinical category. Box plots show the median and the first and third quartiles; whiskers show 1.5 × the interquartile range above and below the box. Clusters are ordered alphabetically. Related to STAR Methods: CITE-seq: composition analysis.

B and plasmablast (PB) cell clusters - PCA



14: B and PB PCA and association tests. (A) PCA plot for all clinical categories. Percentage of variance explained by each PC is shown in the brackets. (B) Loadings of B and PB clusters on PC1 from analysis including all clinical categories. (C) Association test between top PCs and source (clinical category), age, sex, and sample pool for all clinical categories. (D) PCA plot for hospitalized COVID-19. Percentage of variance explained by each PC is shown in the brackets. (E) Loadings of B and PB clusters on PC1 from analysis of hospitalized COVID-19 cases. (F) Association test between top PCs and clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

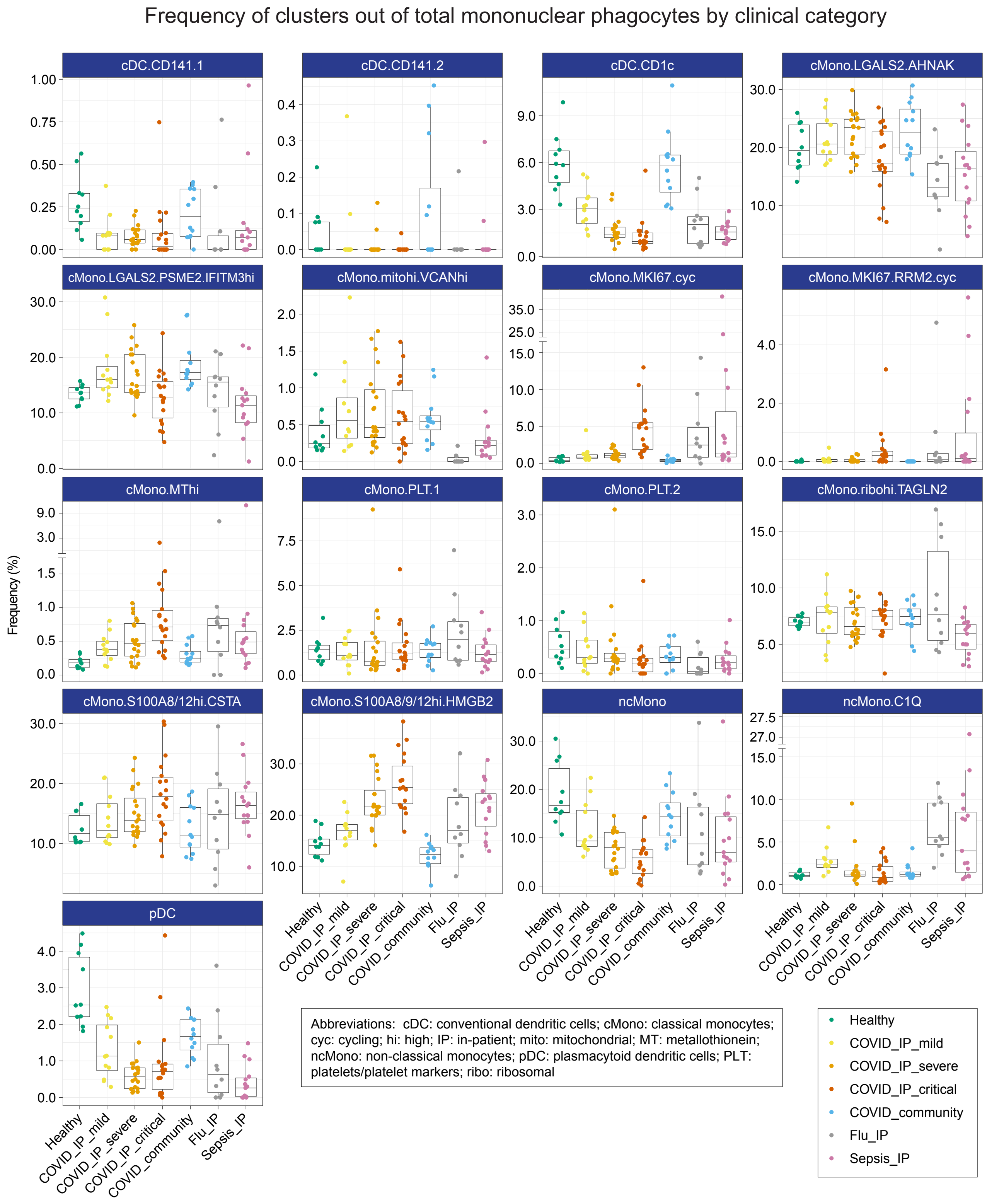
B and plasmablast (PB) cell clusters - edgeR differential abundance analysis



Abbreviations: act: activated; cyc: cycling; hi: high; int: intermediate; MEM: memory; mito: mitochondrial; PB: plasmablast; resp: responsive; SW/sw: switched; TRANSIT: transitional: UNSW/unsw: unswitched

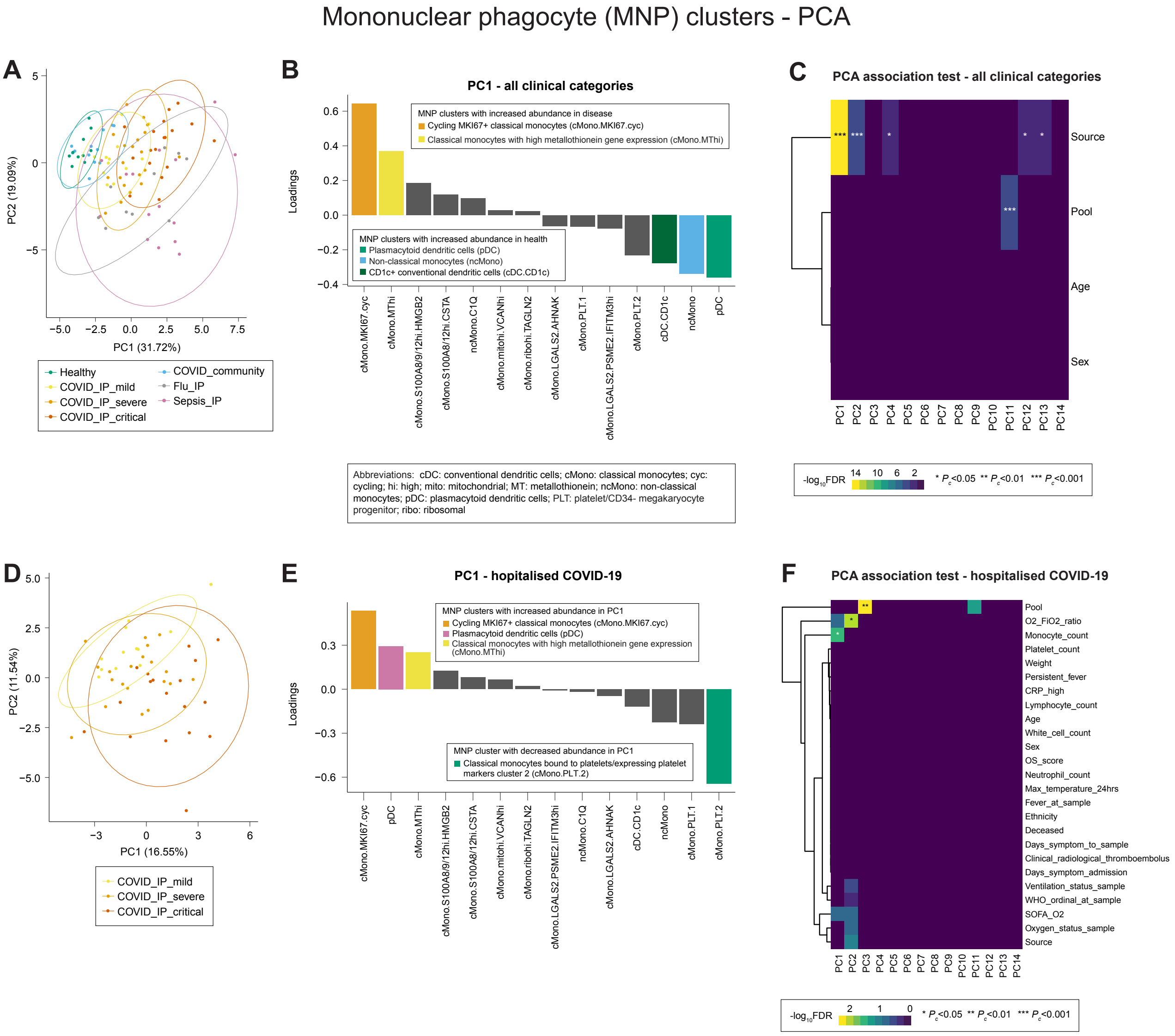
15: B and PB cluster differential abundance analysis. (A) B and PB cluster differential abundance analysis between clinical categories, controlling for age, sex and sample pool. (B) B and PB cluster covariate analysis for source (clinical category), age, sex and pool for all clinical categories. (C) B and PB cluster covariate analysis for clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Composition analysis of mononuclear phagocyte clusters



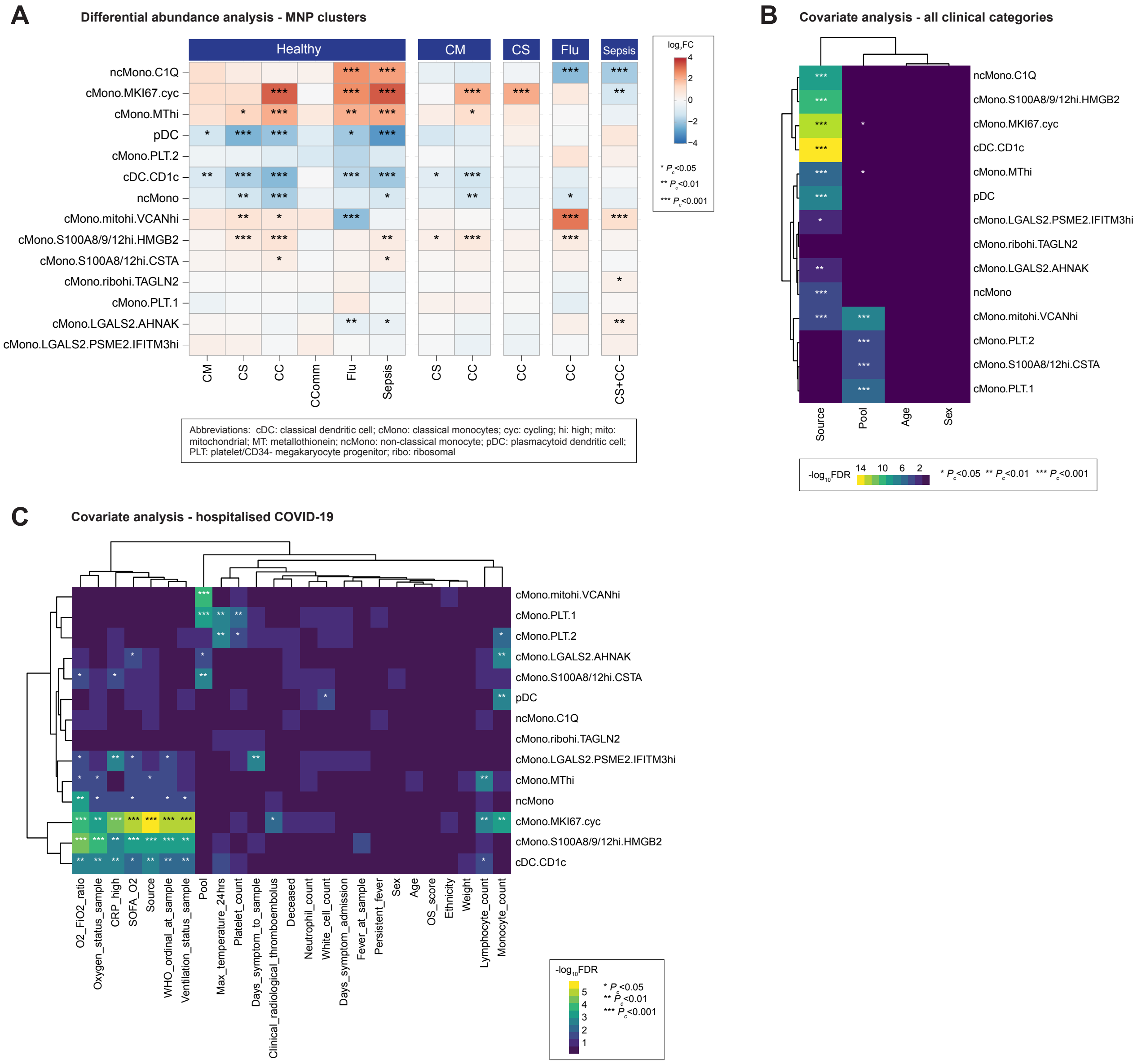
Abbreviations: cDC: conventional dendritic cells; cMono: classical monocytes; cyc: cycling; hi: high; IP: in-patient; mito: mitochondrial; MT: metallothionein; ncMono: non-classical monocytes; pDC: plasmacytoid dendritic cells; PLT: platelets/platelet markers; ribo: ribosomal

16: MNP cluster frequency by clinical category. Box plots show the median and the first and third quartiles; whiskers show 1.5 × the interquartile range above and below the box. Clusters are ordered alphabetically. Related to STAR Methods: CITE-seq: composition analysis.



17: MNP cluster PCA and association tests. (A) PCA plot for all clinical categories. Percentage of variance explained by each PC is shown in the brackets. (B) Loadings of MNP clusters on PC1 from analysis including all clinical categories. (C) Association test between top PCs and source (clinical category), age, sex, and sample pool for all clinical categories. (D) PCA plot for hospitalized COVID-19. Percentage of variance explained by each PC is shown in the brackets. (E) Loadings of MNP clusters on PC1 from analysis of hospitalized COVID-19 cases. (F) Association test between top PCs and clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.

Mononuclear phagocyte (MNP) clusters - edgeR differential abundance analysis



Abbreviations: cDC: classical dendritic cell; cMono: classical monocytes; cyc: cycling; hi: high; mito: mitochondrial; MT: metallothionein; ncMono: non-classical monocyte; pDC: plasmacytoid dendritic cell; PLT: platelet/CD34- megakaryocyte progenitor; ribo: ribosomal

18: MNP cluster differential abundance analysis. (A) MNP cluster differential abundance analysis between clinical categories, controlling for age, sex and sample pool. (B) MNP cluster covariate analysis for source (clinical category), age, sex and pool for all clinical categories. (C) MNP cluster covariate analysis for clinical, demographic and experimental variables for hospitalized COVID-19 cases. Significance tested using Benjamini-Hochberg-corrected ANOVA. Related to STAR Methods: CITE-seq: composition analysis.