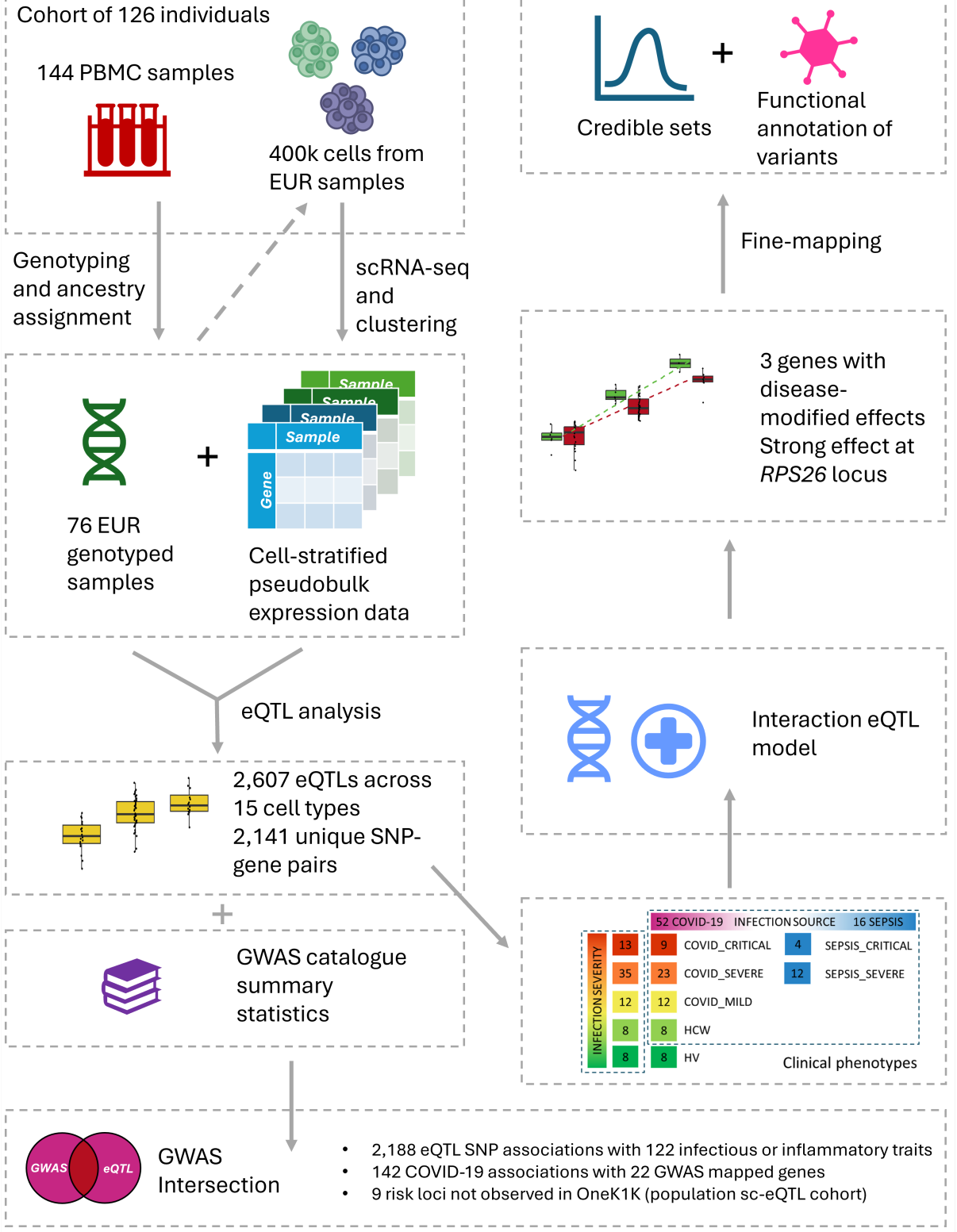

Figure 1:

Schematic summarizing data, workflow and key results. scRNA−seq and clustering was previously described by the COMBAT consortium prior to this work (COMBAT Consortium, 2022). SNPs were genotyped and data were integrated for single−cell eQTL analysis.

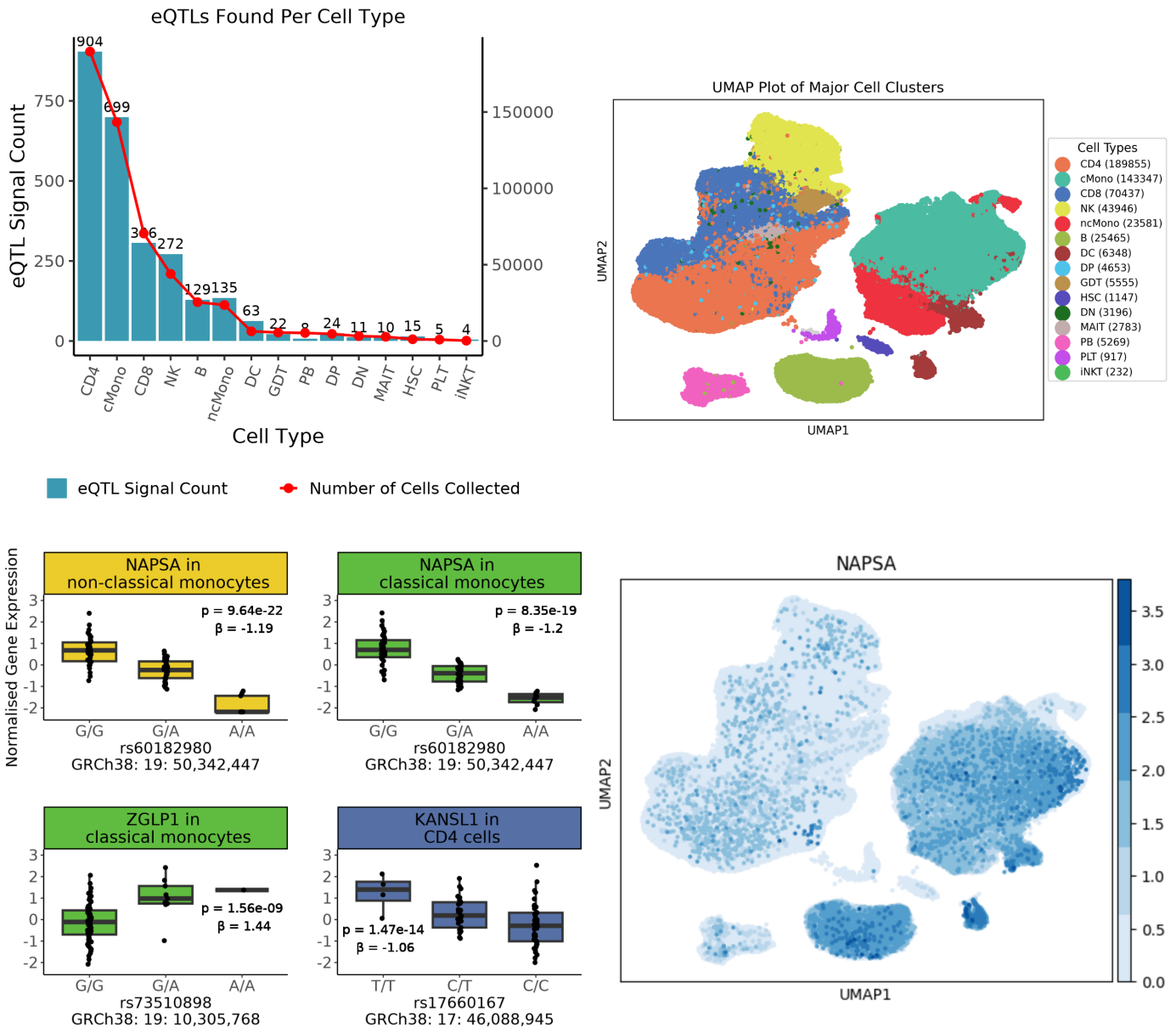

Figure 2:

An overview of eQTL results a) eQTL signal counts (y−axis left) and cell counts (y−axis right) across 15 cell types (x−axis) b) UMAP of 526,731 cells across 76 individuals with 15 annotated cell types. The abreviations for each cell type are displayed in Table S8 with cell counts for each cell type c) eQTL boxplots for COVID−risk variants with risk−alleles on the right. The boxplots show the distribution of normalized gene expression (y−axis) across genotype categories (x−axis). The box represents the interquartile range (IQR), with the horizontal line indicating the median and the whiskers extending to 1.5×IQR. P−value and beta are derived from a linear model assessing the association between genotype and gene expression d) UMAP with differential expression of NAPSA (higher expression in B cells and monocytes).

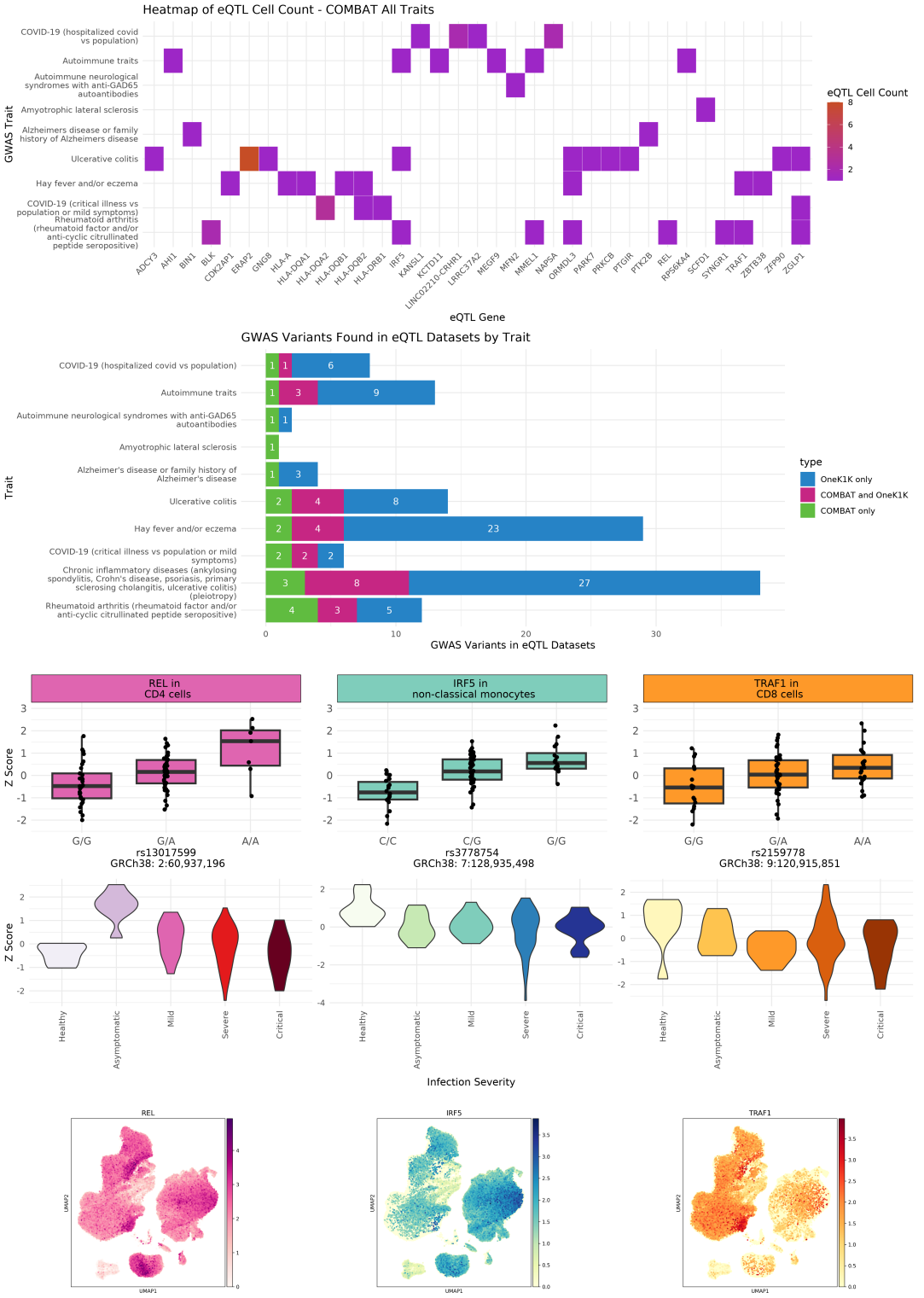

Figure 3:

Colocalization of eQTL and GWAS variants a) COMBAT eQTL SNPS colocalizing with GWAS risk variants for infectious and inflammatory traits according to the GWAS catalogue downloaded on 30/05/2024 (Cerezo et al., 2025) b) Overlap between lead SNPs of the eQTL analysis and GWAS traits (infectious and immune) in COMBAT and OneK1K c) Boxplots of strongest REL, IRF5 and TRAF1 eQTLs. The boxplots show the distribution of normalized gene expression (y−axis) across genotype categories (x−axis). The box represents the interquartile range (IQR), with the horizontal line indicating the median and the whiskers extending to 1.5×IQR d) Violin plots showing expression of REL, IRF5 and TRAF1 stratified by infection severity, over the categories healthy (healthy volunteers), asymptomatic (individuals with no symptoms but a positive COVID−9 test), Mild (hospitalized with mild COVID−19 or sepsis infection), Severe (hospitalized with severe COVID−19 or sepsis infection and requiring no ventilation or non−invasive ventilation) and Critical (hospitalization with critical COVID−19 or sepsis infection requiring intubation) e Single−cell expression of REL, IRF5, TRAF1 reflected on a UMAP.

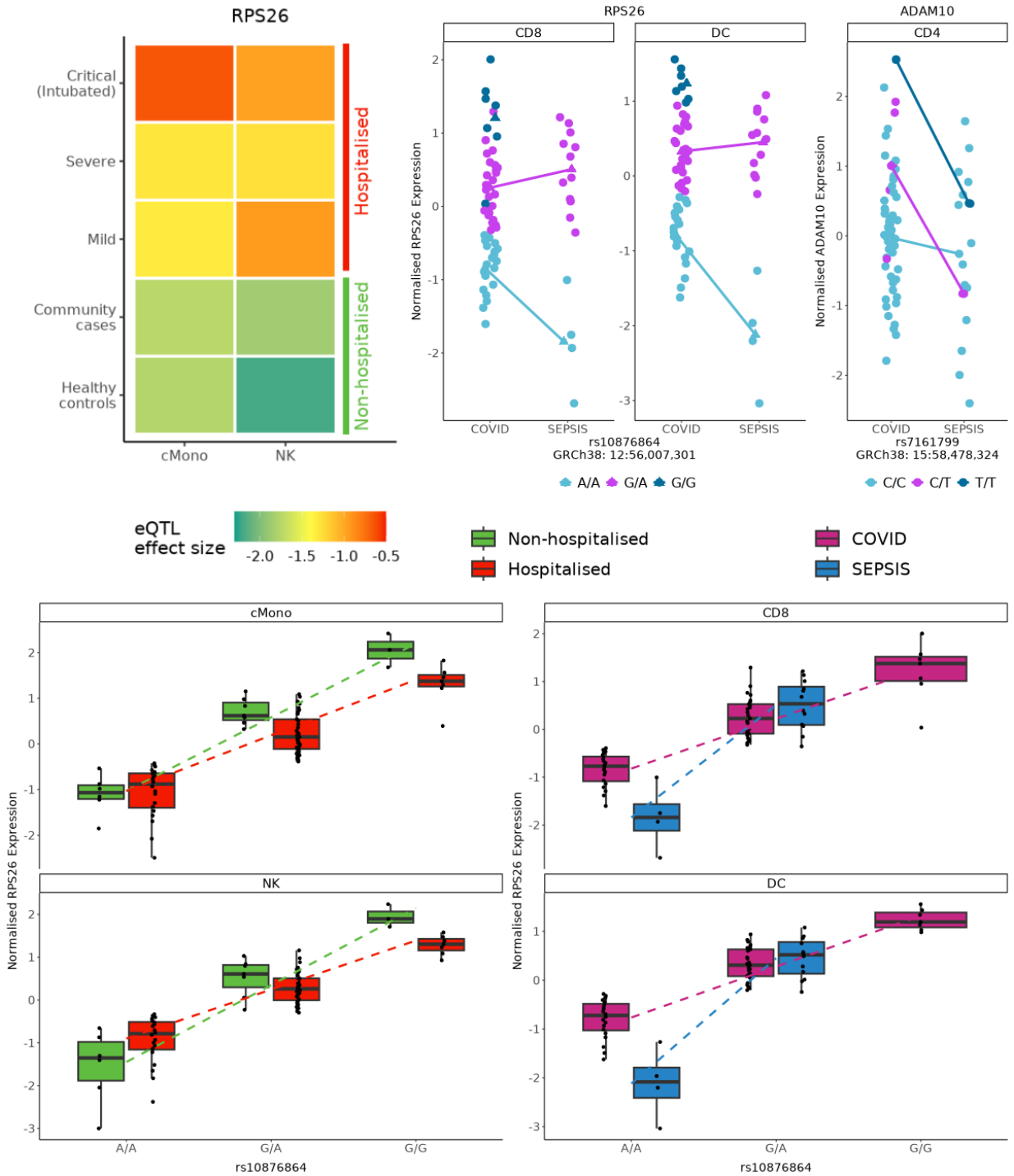

Figure 4:

Context−modified eQTLs RPS26 and ADAM10 a) Heatmap shows the magnitude of effect size of rs10876864−RPS26 decreases s infection severity increases in classical monocytes and NK cell. Heatmap colours denote betas of eQTL effect from the regression model b) Plot shows source of infection modifies eQTL effect at RPS26 (CD8+ and DC) and ADAM10 (CD4+) loci. Normalized gene expression was stratfied by two phenotypes (COVID−19 and Sepsis), coloured by individuals... genotype of the lead eQTL variant for RPS26 and ADAM10. c) Genotype (x−axis) association with normalized RPS26 expression (y−axis) modified by severity and source of infection. The box represents the interquartile range (IQR), with the horizontal line indicating the median and the whiskers extending to 1.5×IQR. The two boxplots on the left show the eQTL effect in green for non−hospitalized (healthy and asymptomatic) and red for hospitalized (mild, critical and severe infection) in cMono and NK cells. The two boxplots on the right show the eQTL effect in pink for COVID−19 and blue for sepsis for CD8+ and dendritic cells (DC). A/A genotypes show increased expression in hospitalized individuals whereas RPS26 expression decreases in hospitalized G/G and heterozygous individuals. A similar relationship is seen with COVID−19 vs sepsis infection.