**Results**

**Cellular Composition in Moderate and Critical COVID-19 Patients**

We first examined the cellular landscape of nasopharyngeal and bronchial samples from patients with moderate (n=14) and critical (n=13) COVID-19. Our analysis revealed a diverse cellular composition comprising 13 distinct cell types, including B cells, basal cells, basophils/mast cells, ciliated cells, dendritic cells, fibroblasts, goblet cells, intermediate cells, macrophages, monocytes, neutrophils, T cells, and unassigned cells (Figure 1).

Notably, the cellular proportions varied significantly between moderate and critical patients. Neutrophils, goblet cells, and T cells emerged as the predominant cell types across both severity groups. The stacked bar plot visualization highlighted subtle but potentially meaningful differences in cellular proportions between moderate and critical patient samples, suggesting that the cellular landscape might be dynamically altered during different stages of COVID-19 progression.

**Differential Cell-Cell Communication Patterns**

To understand the molecular mechanisms underlying COVID-19 severity, we performed a comprehensive cell-cell communication analysis using CellChat. By comparing the interaction patterns between moderate and critical patients, we uncovered distinct communication signatures that differentiate these two disease states (Figure 2).

The comparative heatmap revealed nuanced differences in inter-cellular communication:

1. In moderate patients, we observed a pronounced interaction between goblet cells (as sender cells) and other immune cells, particularly neutrophils, monocytes, and T cells. The top ligand-receptor interactions in this group included:
   * ANXA1-FPR1 interaction between goblet and neutrophil cells (probability: 0.49)
   * HLA-B/A/C with CD8A/B interactions between goblet and T cells (probabilities: 0.33-0.36)
2. In contrast, critical patients exhibited a markedly different communication profile, characterized by:
   * Enhanced communication between monocytes and neutrophils
   * Top interactions included ANXA1-FPR1 (probability: 0.35), CCL3-CCR1 (probability: 0.34), and CXCL3-CXCR2 (probability: 0.32)

These findings suggest that the severity of COVID-19 is associated with distinct cellular communication landscapes, potentially reflecting different inflammatory and immune responses.

**Key Molecular Interactions**

The ligand-receptor analysis revealed several noteworthy interactions:

**Moderate Patients**

* Goblet cells demonstrated extensive communication with immune cells, particularly through:
  + ANXA1 (Annexin A1) interactions with formyl peptide receptors (FPR1, FPR2)
  + HLA molecules (HLA-A, B, C) interacting with CD8 molecules on T cells
  + MIF (Macrophage Migration Inhibitory Factor) interactions via CD74 and CD44

**Critical Patients**

* Monocyte-neutrophil interactions dominated, mediated by:
  + Chemokine-receptor interactions (e.g., CCL3-CCR1, CXCL2/3/5-CXCR1/2)
  + Inflammatory molecules like ANXA1, IL1B, and SPP1
  + Adhesion molecule interactions involving integrins and CD44

These molecular interactions provide insights into the potential mechanisms driving inflammatory responses and immune cell recruitment during different stages of COVID-19.

**Biological Implications**

The observed differences in cell-cell communication suggest that:

1. Moderate COVID-19 cases might exhibit a more balanced immune response, with goblet cells playing a central communication role
2. Critical cases demonstrate a more inflammatory profile, characterized by enhanced monocyte-neutrophil interactions and pro-inflammatory signaling

These findings contribute to our understanding of the complex cellular and molecular dynamics underlying COVID-19 severity and may provide potential therapeutic targets for future interventions.