**Title: COVID-19 and immune transcriptomes in relation to severity or disease time course - A Systematic Review**

**Search method:**

Searched **PubMed** using search term “**covid AND SARS AND transcriptomic\* AND immune**“ on 1 Dec 2021

151 results

110 excluded after abstract review, 41 included for full text review

Of the 41 included for full text review, 29 excluded after full text review, **12** included for metaanalysis

Searched **Web of Science** using search term “**covid AND SARS AND transcriptomic\* AND immune**“ on 27 Dec 2021

109 results

5 included after abstract review and excluding duplicates

Of the 5 included for full text review, 4 excluded after full text review, **1** included for metaanalysis

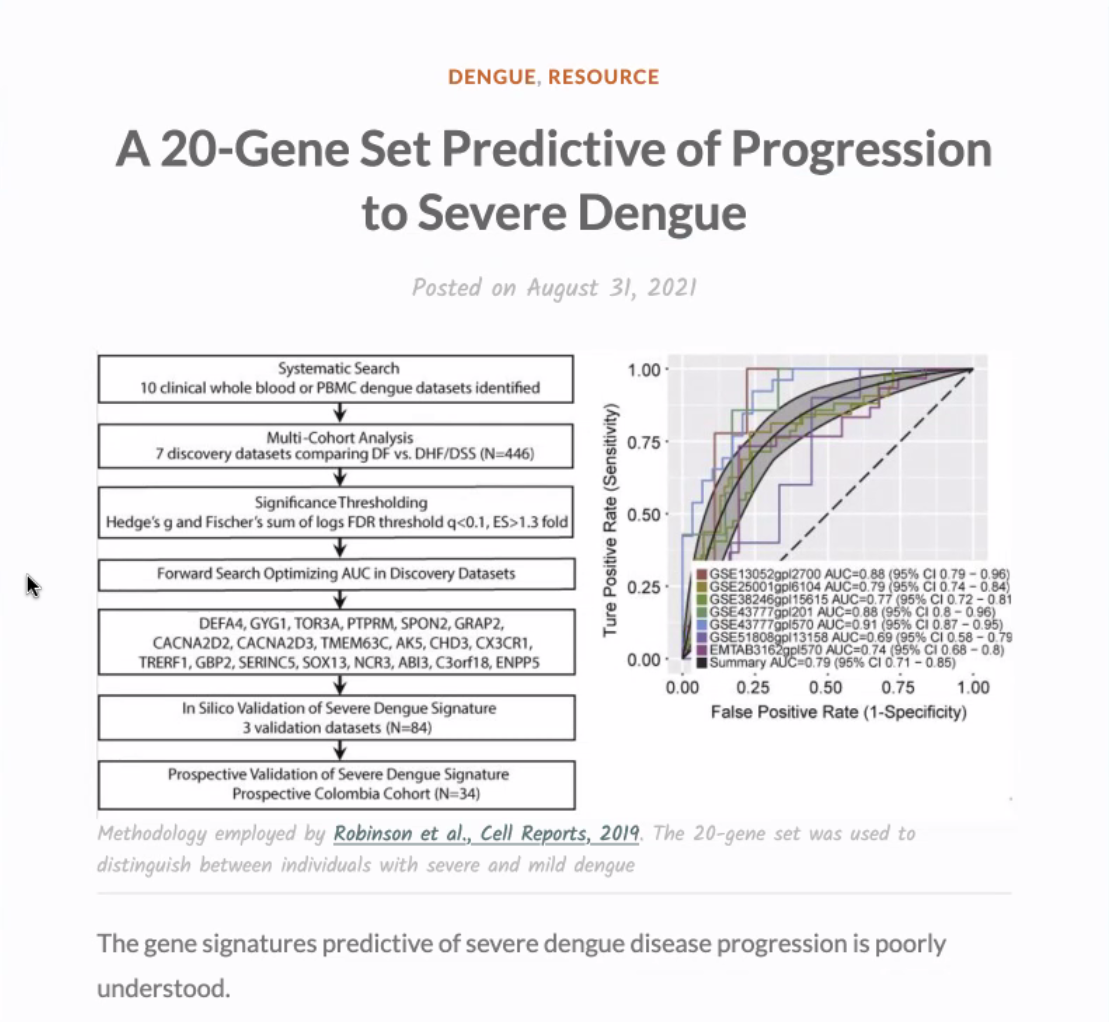
Searched **Scopus** using search term “**covid AND SARS AND transcriptomic\* AND immune** **AND NOT single-cell**“ in Article title, abstract, keywords on 27 Dec 2021

147 results

24 included after abstract review and excluding duplicates

20 excluded after abstract review, 4 included for full text review

Of the 4 included for full text review, 0 excluded after full text review, **4** included for metaanalysis



| **No** | **Author, publication, year** | **Database availability** | **Type of study (Time series?)** | **Number of samples and tool used** | **Type of sample** | **Search term used** | **Other important description** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | [Ong et al., eBioMedicine, 2021](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7937043/) | E-MTAB-9721 | Time series | 6 severe, 4 non-severe, across 15 time-points (Microarray) | Whole blood | Transcriptomics, temporal, COVID-19l | Time-points before and after nadir are sampled |
| 2 | Fong SW et al, J Clin Immunol. 2021 | [GSE155454](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE155454)  RNAseq - Counts provided | Acute and convalescent samples | 14 wild-type, severity unknown  (RNAseq) | Whole blood |  | Acute vs convalescent  Data also compared with Δ382 Variant |
| 3 | Zhang J, et al. Front Immunol. 2021 | [GSE179627](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE179627)  RNAseq - Counts provided | Acute samples | 8 asymptomatic, 13 symptomatic, 15 recovered, 12 re-test positive  (RNAseq) | PBMC |  | Compared with healthy controls |
| 4 | Prokop JW, et al. Front Immunol. 2021 | Found at [supplementary data](https://figshare.com/articles/dataset/Prokop_2021_COVID_RNAseq_Data_xlsx/13524275)  RNAseq - Counts and processed data provided | Acute samples | 23 mild-moderate, 13 on mechanical ventilation  (RNAseq) | Whole blood |  | Compared with asymptomatic COVID-19 negative controls |
| 5 | Bibert S, et al. Front Immunol. 2021 | http://dx.doi.org/10.17632/8wxhhykfnh.2 | Acute samples | 23 mild, 40 moderate, 40 severe | Whole blood |  | Compared with healthy controls and Influenza patients |
| 6 | Wilk AJ, et al. J Exp Med. 2021 | GSE174072 | Acute samples | 8 mild, 11 moderate, 8 severe, 6 fatal  (RNAseq) | PBMC |  | Compare full range of severity |
| 7 | Chan YH, et al. EMBO Mol Med. 2021 | GSE155454 and GSE166424 | Acute samples | 9 mild, 10 moderate, 7 severe, 30 asymptomatic  (RNAseq) | PBMC |  | Compare range of severity |
| 8 | McClain MT, et al. Nat Commun. 2021 | GSE161731  RNAseq - Counts provided | Various time points collected  Early ≤10 days, middle 11–21 days, late >21 days | 34 moderate, 12 severe  (RNAseq) | Whole blood |  | Compared with other viral and bacterial pneumonias and healthy controls |
| 9 | Aschenbrenner AC, et al. Genome Med. 2021 | EGAS00001004503 | Acute samples | 39 mild and severe  (RNAseq) | Whole blood |  | Compared with healthy controls |
| 1- | Thair SA, et al. IScience. 2021 | GSE152641 | Acute samples | 62 patients (severity unknown)  (RNAseq) | Whole blood |  | Compared with non-COVID19 viral profile and HC |
| 11 | Chen YM, et al. EMBO J. 2020 | RNA‐Seq and exRNA‐Seq Data: NODE OEP000868 | Time series | Healthy control, n = 14; mild, n = 179; severe, n = 37  (RNAseq) | Whole blood |  | Compared with healthy controls |
| 12 | Ong EZ, et al. Cell Host Microbe. 2020 | Lab | Time series | 3 mild  (Nanostring) | Whole blood |  | Early time points sampled  Compared with participants in MMR vaccination study |
| 13 | Xiong Y, et al. Emerg Microbes Infect. 2020 | CRA002390 | Acute samples | 3 patients  (RNAseq) | PBMC, BALF |  | Compared with healthy controls |
| 14 | Chu CF, et al. Front Immunol. 2021 | GSE181032 | Acute samples | 3 mild, 2 severe  (RNAseq) | Sorted CD3+ CD45RA– memory T cells |  | Severe compared with mild |
| 15 | Martín-Sánchez E, et al. Front Immunol. 2021 | GSE153610 and GSE155897 | Acute samples | 11 patients (severity not stated, but analysed as favourable vs fatal)  (RNAseq) | Myeloid and DC subsets isolated by FACS |  | Favourable vs fatal  Compared also to healthy controls |
| 16 | Galani IE, et al. Nat Immunol. 2021 | PRJNA638753 | Time course starting from day 1 of entry to the ward or ICU and at different time points thereafter | 5 noncritically and 4 critically ill  (RNAseq) | Whole blood |  | Critically ill and noncritically ill vs healthy controls  Critically ill vs nonciritically ill |
| 17 | Zheng HY, et al Signal Transduct Target Ther. 2020 | Within paper as supplementary files | Time course  (treatment, convalescence, and rehabilitation stages) | 6 mild, 7 moderate, 5 severe  (RNAseq) | Whole blood |  | Compared across stages |

In detail points:

**Ong EZ, Kalimuddin S, Chia WC, et al. Temporal dynamics of the host molecular responses underlying severe COVID-19 progression and disease resolution. EBioMedicine. 2021;65:103262. doi:10.1016/j.ebiom.2021.103262**

Purpose:

To define the principal drivers of pulmonary dysfunction in COVID-19 patients, we focused our attention on the host response to SARS-CoV-2 infection around the period of the nadir of respiratory function. We hypothesised that the principal drivers of COVID-19 severity must track tightly with respiratory function and must resolve in sync with respiratory improvement. Thus, instead of time interval analysis [14], [15], [16], we performed daily transcriptomic profiling to obtain a detailed continuum of the host immune response in COVID-19 patients before, during and after the nadir of respiratory function.

Patients:

* To interrogate the transcriptomic changes spanning the nadir of respiratory function nadir, we sampled daily, where possible, whole blood from COVID-19 patients ranging from -4 days to 13 days, with the nadir being day 0
* For the 5 patients that needed non-invasive ventilation (NIV) or MV, the day of respiratory function nadir was defined as the day the patient was initiated on NIV or MV. For P6, the patient with moderately severe COVID-19, day of respiratory function nadir was defined as the day when arterial oxygen saturation was lowest at 93%

Findings:

* The expression of genes that tracked most closely in temporal terms relative to disease progression and resolution were in clusters 3 and 4 (Fig. 2a). Neutrophil mediated immunity and neutrophil activation were the top 2 enriched pathways in cluster 3 (Fig. 2c). Other enriched pathways in cluster 3 were cellular response to mechanical stimulus, regulation of NFkB transcription factor activity, pattern recognition receptor signaling and IFN-gamma-mediated signaling pathways (Fig. 2c). Cluster 4 only had neutrophil mediated immunity pathway being significantly modulated. Combining both clusters 3 and 4, we identified 87 genes involved in neutrophil mediated immunity that showed peak expression during the nadir of respiratory function; expression waned with upswing in respiratory function
* Collectively, increased expression of serine-threonine kinases over time suggests a protective role for these kinases in COVID-19 disease resolution.

Summary:

* We found that the neutrophil activation pathway, but not type-I IFN signaling pathways, showed a direct inverted relationship with respiratory function – genes in this pathway increased and peaked during the nadir of respiratory function and then declined during the recovery phase. On the other hand, transcripts associated with protein phosphorylation pathways, particularly the serine threonine kinases involved in cell cycle progression and T cell development increased at convalescence.

**Fong SW, Yeo NK, Chan YH, Goh YS, Amrun SN, Ang N, Rajapakse MP, Lum J, Foo S, Lee CY, Carissimo G, Chee RS, Torres-Ruesta A, Tay MZ, Chang ZW, Poh CM, Young BE, Tambyah PA, Kalimuddin S, Leo YS, Lye DC, Lee B, Biswas S, Howland SW, Renia L, Ng LFP. Robust Virus-Specific Adaptive Immunity in COVID-19 Patients with SARS-CoV-2 Δ382 Variant Infection. J Clin Immunol. 2021 Oct 30:1–16. doi: 10.1007/s10875-021-01142-z. Epub ahead of print. Erratum in: J Clin Immunol. 2021 Nov 27;: PMID: 34716845; PMCID: PMC8556776.**

Purpose:

To uncover the molecular mechanisms underlying the milder disease phenotype in Δ382 SARS-CoV-2 infections

Patients:

* 66 patients (WT, *n* = 36 and Δ382, *n* = 30) who tested PCR-positive for SARS-CoV-2 in nasopharyngeal swab samples was recruited into the study from February to April 2020.
* RNA-seq of whole blood from 25 COVID-19 patients was performed (WT, *n* = 14 and Δ382, *n* = 11).
* Acute (SARS-CoV-2 PCR-positive, median 8 days post-illness onset [PIO]) and recovered (SARS-CoV-2 PCR-negative, median 21 days PIO)

Findings:

* Less stringent criteria of *p* < 0.01 and |FC|> 2 was applied to pathway and Gene Ontology (GO) analyses [[34](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8556776/#CR34)]. This yielded 491 significant transcripts, in which 241 differentially expressed genes (DEGs) were found to be enriched, whereas 250 were downregulated during the acute phase of infection.
* Gene functional enrichment analysis revealed that robust type I IFN, classical complement, and humoral and cellular immune responses were induced, whereas biological processes such as “target of rapamycin (TOR) signaling,” “protein catabolic process,” and “positive regulation of autophagy” were shown to be downregulated in the acute phase of WT SARS-CoV-2 infection..
* IPA analysis revealed IFN signaling, IFN regulatory factor (IRF) activation, pattern recognition receptors (PRR)-induced signaling and salvage pathway of ribonucleotides as the top canonical pathways induced upon SARS-CoV-2 infection.

Summary:

Overall, the results showed that antiviral IFN responses and virus sensing PRR signaling pathways were activated following WT SARS-CoV-2 infection

**Zhang J, Lin D, Li K, et al. Transcriptome Analysis of Peripheral Blood Mononuclear Cells Reveals Distinct Immune Response in Asymptomatic and Re-Detectable Positive COVID-19 Patients. Front Immunol. 2021;12:716075. Published 2021 Jul 29. doi:10.3389/fimmu.2021.716075**

Purpose:

To compare the transcriptome profiles of PBMCs from COVID-19 patients including asymptomatic, symptomatic, recovered, and RP groups

Patients:

* 8 asymptomatic, 13 symptomatic, 15 recovered and 12 RP patients
* PBMC samples were collected within 4 days of admission from asymptomatic and symptomatic groups to maintain uniformity of timing for comparison between groups.
* Recruited from March through May in 2020

Findings:

* The level of IFN response and complement activation in asymptomatic patients was lower than in the symptomatic patients.
* ssGSEA analysis revealed that the interferon-alpha response and interferon-gamma response activity are significantly higher in the symptomatic group compared with the healthy donors. The levels of interferon response in the asymptomatic group were comparable with those of the healthy group and significantly lower than in the symptomatic group, indicating a lower level of IFN in the serum of asymptomatic patients.
* GSEA analysis revealed down-regulation of IFN response and complement activation in the asymptomatic patients, indicating a weaker immune response of the PBMCs in asymptomatic patients. Interestingly, some cell cycle related pathways were down-regulated and NGF related pathways up-regulated in the asymptomatic patients.
* WGCNA analysis revealed the genes in the red co-expression module were enriched in the humoral immune response. The red module was found to be positively correlated with the symptomatic patients but not asymptomatic patients, suggesting a high level of humoral immune response in the symptomatic patients.

Summary:

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**Prokop JW, Hartog NL, Chesla D, et al. High-Density Blood Transcriptomics Reveals Precision Immune Signatures of SARS-CoV-2 Infection in Hospitalized Individuals. Front Immunol. 2021;12:694243. Published 2021 Jul 16. doi:10.3389/fimmu.2021.694243**

Purpose:

To produce the highest density (most sequenced bases per patient) blood PAXgene tube transcriptome analysis of severely ill patients hospitalized with COVID-19.

Patients:

* 15 were suspected COVID-19 negative (asymptomatic controls), and 36 were COVID-19 positive. 11 out of 36 COVID-19 positive patients died.
* Period of recruitment of COVID-19 patients unstated

Findings:

* This current study generated an average of 45 billion bases of sequencing for each patient, more than 10 billion higher than any other study performed to date.
* Multiple enriched terms of genes higher in COVID-19 samples are connected to neutrophil processes, including secretory granules, neutrophil activation, and neutrophil extracellular traps (NETs).
* All COVID-19 patients show strong downregulation of genes and clonal expansion of the acquired immune system.
* One group of COVID-19 patients have the highest activation of our significant gene list, suggesting an overactive immune system that might benefit the most from immune-suppressive drugs.
* The second group of COVID-19 patients have strong suppression of Type I IFN response and an elevation of RN7SL2 and RN7SL1 genes collectively known as 7SL RNA, both connected to viral packing and trafficking and known to interact with the SARS-CoV-2 NSP8 and NSP9 proteins to impact viral trafficking to the cell membrane. This group of patients may benefit from higher suspicion for nosocomial infections and respond better to immune-stimulating agents that activate the Type I IFN response, such as convalescent serum, as they appear to be an immune-suppressed group.

Summary:

* An improved understanding of severe COVID-19 disease pathogenesis and the patient’s physiologic and immunologic state could help identify patients at significant risk for complications, guiding precision therapeutic approaches.

**Wilk AJ, Lee MJ, Wei B, et al. Multi-omic profiling reveals widespread dysregulation of innate immunity and hematopoiesis in COVID-19. J Exp Med. 2021;218(8):e20210582. doi:10.1084/jem.20210582**

Purpose:

Multi-omic single-cell immune profiling of 64 COVID-19 patients across the full range of disease severity, from outpatients with mild disease to fatal cases

Patients:

* Performed single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq), single-cell RNA sequencing (scRNA-seq), and cytometry by time of flight (CyTOF) on the peripheral immune cells of a cohort of COVID-19 patients across the entire spectrum of disease severity, tomap the immune response at the epigenetic, transcriptional, and proteomic levels.
* 64 patients with COVID-19 and 12 healthy controls, 8 mild, 11 moderate, 8 severe, 6 fatal
* Patients were recruited March to June 2020

Findings:

* Depletion of CD16 monocytes, dendritic cells (DCs), and NK cells, as well as increases in plasmablasts (PBs) was observed in patients with severe and fatal COVID-19. The cell subset proportions that were altered in moderate and severe disease were generally unchanged in mild cases, with the exception of plasmacytoid DCs (pDCs), which were depleted in all severity groups
* cDC2 cells as the principal remodeled DC subset in COVID-19; these cells are depleted in severe disease and have the greatest disease severity–associated perturbation.
* CD8 TEM cells also displayed severity-associated transcriptional perturbations.
* The proportion of activated NK cells was significantly increased in moderate and severe COVID-19. NK cells from moderate and severe, but not mild, COVID-19 cases also displayed transcriptional evidence of exhaustion
* Profiling fresh whole blood rather than isolated PBMCs reveals a prominent neutrophil hyperactivation signature in severe and fatal COVID-19.
* Multiple IFN-stimulated genes (ISGs) and markers of immature and tolerogenic monocytes, such as CD163, PLAC8, and MPO, were up-regulated with increasing disease severity. Suppressive and dysfunctional monocytes were a feature of severe and fatal COVID-19. Importantly, mild COVID-19 generally did not lead to this shift toward suppressive and dysfunctional monocytes.
* Minimal expression of key monocyte-derived pro-inflammatory cytokine–encoding genes, particularly in severe and fatal COVID-19 patients. Aberrant decreases in NF-κB activity in severe COVID-19 may result in loss of accessibility at putative enhancers of key cytokine genes.

Summary:

* Transcriptomic, epigenomic, and proteomic analyses revealed widespread dysfunction of peripheral innate immunity in severe and fatal COVID-19, including prominent hyperactivation signatures in neutrophils and NK cells.
* We also identified chromatin accessibility changes at NF-κB binding sites within cytokine gene loci as a potential mechanism for the striking lack of pro-inflammatory cytokine production observed in monocytes in severe and fatal COVID-19.
* We further demonstrated that emergency myelopoiesis is a prominent feature of fatal COVID-19.

**Chan YH, Fong SW, Poh CM, et al. Asymptomatic COVID-19: disease tolerance with efficient anti-viral immunity against SARS-CoV-2. EMBO Mol Med. 2021;13(6):e14045. doi:10.15252/emmm.202114045**

Purpose:

Immunophenotyping during active infection between asymptomatic and symptomatic patients in the Singapore COVID‐19 cohort.

Patients:

* 48 asymptomatic COVID‐19 patients and 172 symptomatic patients
* Recruited January to August 2020
* 26 symptomatic patients with varying disease severity outcomes (mild, symptomatic without pneumonia, n = 9; moderate, pneumonia without oxygen requirement, n = 10; and severe, pneumonia with oxygen requirement, n = 7) and 30 asymptomatic patients with RNA integrity number more than 6 were included in this analysis

Findings:

* Due to the differences in timing of diagnosis and hospitalization, blood sample collections were performed at varying stages of the acute phase, which could influence the observed transcriptomic profiles in symptomatic patients.
* 215 differentially expressed genes (DEGs) under‐expressed and 952 over‐expressed in symptomatic patients during acute phase of infection when we compared symptomatic and asymptomatic patients.
* Asymptomatic COVID‐19 patients had less robust response to type‐I interferon, classical complement, innate, and humoral immune responses, but presented with upregulation of processes such as cytosolic ribosomal activity, positive regulation of cell killing, T‐cell, and TNF receptor activities, and regulation of B‐cell proliferation during the acute phase of SARS‐CoV‐2 infection
* There was a higher expression of activated neutrophil‐associated genes, inflammatory monocyte‐associated genes and pro‐inflammatory cytokine and chemokine genes in symptomatic patients.

Summary:

* Asymptomatic patients mount a different immune response against SARS‐CoV‐2 from their symptomatic counterparts, characterized by a less severe myeloid compartment dysregulation, less systemic inflammation, a more robust SARS‐CoV‐2 peptide‐specific Th17 response, and higher levels of tissue healing mediators.
* While a lower neutralizing antibody capacity was observed in asymptomatic patients, they were still able to neutralize virus infection against SARS‐CoV‐2 wild‐type (D614) and the more virulent G614 variants.

**McClain MT, Constantine FJ, Henao R, et al. Dysregulated transcriptional responses to SARS-CoV-2 in the periphery. Nat Commun. 2021;12(1):1079. Published 2021 Feb 17. doi:10.1038/s41467-021-21289-y**

Purpose:

To further define unique components of the host immune response in subjects with COVID-19, we performed RNA sequencing on whole blood samples from 46 individuals with PCR-positive, symptomatic SARS-CoV-2 infection and compared them directly to subjects with other respiratory infections and healthy controls.

Patients:

* Samples from subjects with COVID-19 were assigned to three groups based on time from symptom onset (early ≤10 days, middle 11–21 days, late >21 days).
* Fourteen of the SARS-CoV-2 subjects with mild/moderate disease consented to sampling at multiple timepoints, and these were each separated into the appropriate time bin and utilized to control for temporal dynamics of the host response

Findings:

* At early timepoints (≤10 days of symptoms), the response of most patients was dominated by upregulation of interferon-response signals that have some similarity to those described for other common viral ARIs
* In early mild-moderate infections, there was marked dysregulation of IL1, JAK/STAT, IL6, and IL10 signaling pathways compared to other infections. There is predominantly muted expression of these pathways, where expression levels more closely resemble healthy controls than seasonal coronavirus or influenza,, which is consistent with permissive hypoinflammatory responses described elsewhere.
* Severely ill subjects (n = 12) exhibited even more marked transcriptional heterogeneity, but showed a trend towards greater IL12 and IFN-response activation along with neutrophil activation, degranulation, and translation initiation, but muted IL1 and IL6 signaling. They also demonstrate further elevation in plasmablasts/plasma cells compared to mild disease, but decreased proportions of CD8 + T cells.

Summary:

* SARS-CoV-2 triggers inflammatory and humoral immune response pathways in ways that are distinct from those seen in other common respiratory infections.

**Aschenbrenner AC, Mouktaroudi M, Krämer B, et al. Disease severity-specific neutrophil signatures in blood transcriptomes stratify COVID-19 patients. Genome Med. 2021;13(1):7. Published 2021 Jan 13. doi:10.1186/s13073-020-00823-5**

Purpose:

To characterize molecular subtypes within the immune response of COVID-19 patients beyond distinguishing mild and severe cases only.

Patients:

* Granulocytes were sequenced and transcriptomes were analyzed from 16 longitudinally sampled patients (8 mild, 9 severe), resulting in 17 mild and 27 severe COVID-19 samples
* Used the CoCena2 modules from the whole blood analysis (Fig. 2c) to identify modules that are actually driven by alterations in neutrophil activation instead of a mere increase in the neutrophil population
* Patients recruited between March 13 and March 30, 2020

Findings:

* Granulocytes from severe COVID-19 patients show a simultaneous increase in inflammatory and suppressive signatures. Differential expression analysis identified 2289 upregulated and 912 downregulated genes comparing COVID-19 and control samples (FC > |2|, padj < 0.05; Fig. 1b). Upregulated genes showed greater fold changes than the downregulated genes (Fig. 1c). Of note, CD177, markedly expressed in neutrophils [67, 68], was the most prominently upregulated gene with the lowest p value.
* Although all samples from COVID-19 patients showed functional enrichment for granulocyte/neutrophil activation-associated terms in general, direct comparison of severe and mild COVID-19 patients revealed this to be a heightened characteristic of the immunoprofiles in severe COVID-19
* Collectively, co-expression analysis (CoCena2) in whole blood transcriptomes reveals at least five molecular phenotypes of the host’s immune response in COVID-19 patients with at least two different groups in clinically described severe COVID-19 patients. The two molecularly defined groups G1 and G2 are transcriptionally characterized by a pronounced neutrophilic signature, at the same time distinct in other cellular characteristics.
* Whole blood transcriptome analysis showed enrichment of neutrophil activation-associated signatures (Fig. 2). Excluding the bias of alterations in neutrophil population size across conditions, gene set enrichment analysis on granulocyte samples now uncovered that differentially expressed genes between severe and mild COVID-19 patients are indeed characterized by an increase in granulocyte activation-associated factor
* CD177 is part of the granulocyte activation gene set and was indeed markedly increased in severe (day 1–10) compared to mild (day 1–10) COVID-19 samples. Also, the alarmin S100A12 exhibited heightened expression in granulocytes from severe COVID-19 patients..
* Premature/immature, severe inflammatory, and severe suppressive subset marker genes were markedly enriched in granulocytes from severe COVID-19 patients
* Integration with signatures from other diseases reveals COVID-19-specific characteristics.

Summary:

* Analysis of granulocyte samples from COVID-19 patients proved that, in addition to the relative increase in neutrophils in severe COVID-19 cases, there are indeed alterations in the transcriptional program of these cells themselves.
* We found enrichment of signatures typical of pre-/immature neutrophils and evidence of simultaneous inflammatory and suppressive features, arguing for a dysregulation in the peripheral granulocyte compartment.
* Importantly, transferring these findings back to the whole blood analysis showed that the granulocyte phenotypes were still observable within the whole blood transcriptomes.
* Classical bioinformatic assessment of blood transcriptome data comparing defined groups, in this study represented by control individuals and samples derived from either mild or severe COVID-19 patients, already revealed important biology of the systemic immune response.
* Indeed, co-expression network analysis in a data-driven fashion allowed us to define five patient subgroups (G1–5) defined by 10 distinct transcriptional modules, which was corroborated in a second independent cohort

**Chen YM, Zheng Y, Yu Y, et al. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. EMBO J. 2020;39(24):e105896. doi:10.15252/embj.2020105896**

Purpose:

Using a multi‐omics approach employing cutting‐edge transcriptomic, proteomic, and metabolomic technologies, we identified significant molecular alterations in patients with COVID‐19 compared with uninfected controls in this study.

Patients:

* Healthy control, n = 14; mild, n = 179; severe, n = 37
* Patients enrolled between January 31 and April 7, 2020.
* Multiple timepoints collected for 65 patients over a 5 week period

Findings:

* Analysis of whole blood transcriptomic data revealed that gene sets, including an antiviral IFN signature (M75 module), were enriched at the first sampling timepoint (Fig [6A](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737620/figure/embj2020105896-fig-0006/), Dataset [EV7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737620/#embj2020105896-sup-0009)). Notably, IFN signaling was continuously activated in severe patients during the entire period of hospitalization (Fig [6A](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737620/figure/embj2020105896-fig-0006/)), while negative regulators of innate immune signaling (e.g. TRIM59, USP21, and NLRC3) were downregulated (Fig [EV4A](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737620/figure/embj2020105896-fig-0004ev/)). Additionally, clinical data showed significant increases of IL‐6, IL‐8, and IL‐10 levels in severe patients compared with mild patients (Figs [2F](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737620/figure/embj2020105896-fig-0002/) and [EV4B](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737620/figure/embj2020105896-fig-0004ev/)). Combined, these data suggest that the continuous activation of IFN‐I signaling and a high level of inflammatory cytokines likely impact COVID‐19 immunopathology.

Summary:

* Our longitudinal analyses provided evidence that patients with mild or severe symptoms who succeeded in T‐cell mobilization promptly controlled SARS‐CoV‐2 infection and symptoms (Figs 2C and 6A and C). In contrast, those (especially severe‐fatal) patients that failed to mount a sound T‐cell response maintained a continuous pro‐inflammatory response and suffered from cytokine storms as well as excess NETs (Figs 6A and B), both of which are known to cause systematic tissue damages (Akiyama et al, 2019; Bohmwald et al, 2019). In sum, our data indicate that T cells play a key role in controlling SARS‐CoV‐2 infection.

**Ong EZ, Chan YFZ, Leong WY, et al. A Dynamic Immune Response Shapes COVID-19 Progression. Cell Host Microbe. 2020;27(6):879-882.e2. doi:10.1016/j.chom.2020.03.021**

Purpose:

Our goal in this study is to ask whether the inflammatory and immune responses to SARS-CoV-2 infection, especially in the early phase of illness, are indeed dynamic in order to guide hypotheses generation and design of studies to address disease pathogenesis and therapeutic interventions.

Patients:

* 3 patients with mild COVID-19 recruited in Jan 2020

Findings:

* Analysis of RNA extracted from whole blood revealed a highly dynamic pro-inflammatory response in Case 1. Expression of pro-inflammatory genes in Case 1 (Figure 2 A), represented by cluster 4 and consisting of mostly genes driving the Toll-like receptor (TLR) and inflammatory response as well as cytokine signaling pathways (Figure S1), was notably higher than in healthy controls (Table S1). Expression of most of these genes peaked on day 6 of illness. This peak in pro-inflammatory gene expression thus lagged behind the nadir of respiratory function on day 5 of illness

Summary:

* We found a highly dynamic expression of pro-inflammatory genes. Expression of most of these genes peaked after the nadir of respiratory function, which calls into question the cytokine storm hypothesis. Instead, our data hints at the possibility that the IL1 pathway may be a more suitable correlate of severe respiratory disease. In addition, the attenuated cytokine expression associated with mild infection could also delay T cell immunity against SARS-CoV-2, which prolongs infection; this suggests the possibility that afebrile and undifferentiated COVID-19 cases may drive virus spread in the community.

**Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect. 2020;9(1):761-770. doi:10.1080/22221751.2020.1747363**

Purpose:

In this study, we use RNA sequencing techniques to investigate the transcriptional changes in BALF and PBMC specimens of COVID-19 patients.

Patients:

* We got samples from Zhongnan Hospital of Wuhan University, including BALF samples from two patients (WHU01-2), and blood samples from 3 patients (P1-3) and 3 healthy individuals (N1-3). The data for 3 BALF healthy samples (Ctrl1-3) were from a previous study

Findings:

* For BALF samples, the up-regulated genes are related to invasion of the virus (Figure 2(A) and Supplementary File 2). Viral infection-induced changes in various membrane structures and endoplasmic reticulum. Indeed, the most enriched biological processes are “cotranslational protein targeting to membrane”, “protein targeting to ER”, and “viral transcription”.
* However, up-regulated genes in PBMC are mainly enriched in “complement activation”, “humoral immune response mediated by circulating immunoglobulin”, and “B cell mediated immunity” (Figure 2(B) and Supplementary File 2), indicating activated immune activity in PMBC. In addition, a series of inflammation-related processes was activated, such as “regulation of acute inflammatory response” and “acute inflammatory response” (Supplementary File 2).

Summary:

* SARS-CoV-2 virus infection stimulates a unique transcriptome profile in COVID-19 patients BALF and PBMC. Additionally, the cytokine expression profile suggests excessive pro-inflammatory cytokine release might be a hallmark of COVID-19 patients.

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From the first detection of the novel SARS-CoV-2 COVID-19 in Wuhan, China, to the global spread of COVID-19, this pandemic has already resulted in extreme healthcare, societal, economic and political disruption across the globe. Despite widespread vaccination efforts, the rapid global waves of infection with variants such as the highly transmissible Delta and Omicron variants continue to pose significant threats. Rapid surges in infection rates place acute strains on international healthcare systems and resources. Therefore there is a need to identify biomarkers predictive of severe COVID-19.

COVID-19 presents with a spectrum of clinical phenotypes. Most patients exhibit symptoms such as fever, cough, fatigue and dyspnoea. The severity of disease progresses from the initial onset of the first symptoms, with approximately 15% experiencing a deterioration in health requiring hospitalisation within a week. In a minority, this can be followed by the development of acute distress syndrome (ARDS) even necessitating ICU admission and/or mechanical ventilation in a short time period. Case fatality ranges between 4.3% - 15%. The heterogeneity of COVID-19 results in the differing onsets and severity of symptoms between patients, making it challenging to identify disease severity-specific biomarkers. The underlying cause of this difference is unknown, but they are thought to be due to dysregulated or maladaptive immune responses to SARS-CoV-2.

Risk factors for severe COVID-19 include age and comorbidities. In assessing predictors for intubation, clinical features such as tachypnoea and need for supplemental oxygen, higher Sequential Organ Failure Assessment (SOFA), involvement of multiple lung lobes and pleural effusion, and biochemical markers of elevated CRP, decreased lymphocyte count (especially in CD8+ T cells) and D-dimer greater than 1 μg/ml are reliable predictors for the need for invasive mechanical ventilation.

Transcriptomics of peripheral blood cells has been a powerful tool to characterise human immune responses to diverse pathogens, including respiratory viruses. There is an abundance of transcriptomic data from studies carried out in COVID-19 patients, however their use is limited by the confounding factors pertaining to each study. Gene expression profiling by different analytical platforms and sample types have revealed that COVID-19 patients exhibit (a) activation of humoral immunity, hypercytokinaemia, apoptosis, and dynamic toll-like receptor signaling in peripheral blood; (b) induction of interferon stimulated genes (ISGs), chemokines and inflammation of the lower respiratory tract. Of importance, the results and interpretation of these data were based on \_\_\_, in which significance.

The transcriptional response of peripheral leukocytes reflects the systemic adaptations to the inflammatory environment imposed by SARS-CoV-2 infection. The renalaysis of all these datasets in a unified approach should help in understanding of the molecular basis of COVID-19 disease progression and immunopathology. This should allow for the identification of COVID-19 biomarkers expressed in patients and the presence of markers specific to disease severity and condition. Understanding the immunological mechanisms underlying the diverse clinical presentations of COVID-19 is a crucial step in the design of rational therapeutic strategies.

In this study, we aim to use the multiple publicly available transcriptomic datasets to identify consistently differentially expressed genes in peripheral blood in different severities and time points of COVID-19. We expect that several factors will contribute to the differences in transcriptional profiles of larger cohorts of COVID-19 patients.

To gain further insights on host immune responses to SARS-CoV-2 infection based on severity, we

To gain further insights on host immune responses to SARS-CoV-2 infection related to time.