# Serum protein profiling reveals a specific upregulation of the immunomodulatory protein progranulin in COVID-19

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Summary: Specific upregulation in COVID-19 warrants further evaluation of progranulin as a potential biomarker and its impact on interferon signaling, virus elimination, and virus-induced lung tissue damage.

**Conflict of interest:** none

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**Abstract**

**Background**: Severe courses of COVID-19 are associated with elevated levels of interleukin 6. However, there is a growing body of evidence pointing to a broad and more complex disorder of pro-inflammatory and anti-viral responses with disturbed interferon signaling in COVID-19.

**Methods:** In this prospective single-center registry, we included SARS-CoV-2 positive patients and patients with similar symptoms and severity of disease but negative for SARS-CoV-2 admitted to the emergency department and compared their serum protein expression profiles.

**Results:** Interleukin-6 abundance was similar in SARS-CoV-2 positive patients (n = 24) compared to SARS-CoV-2 negative control (n = 61). In contrast, we observed a specific upregulation of the immunomodulatory protein progranulin (GRN). High GRN abundance was associated with adverse outcomes and increased expression of interleukin-6 in COVID-19.

**Conclusion:** The data from this registry reveals that GRN is specifically upregulated in SARS-CoV-2 positive patients while interleukin-6 may serve as marker for disease severity. The potential of GRN as a biomarker and a possible impact of increased GRN expression on interferon signaling, virus elimination, and virus-induced lung tissue damage in COVID-19 should be further explored.

**Key words:** COVID-19, SARS-CoV-2, proteome, interferon, biomarker

## Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with substantial pulmonary disease up to acute respiratory failure. However, there is a broad range of extrapulmonary manifestations, including thromboembolism, bleeding, myocardial injury, renal failure, gastrointestinal symptoms, neurological disorders, and others [1]. The spectrum of clinical presentations ranges from asymptomatic or mild courses to severe and life-threatening illness requiring intensive care treatment [2].

Early during the ongoing pandemic, severe courses of COVID-19 have been linked to what is often referred to as cytokine storm and elevated levels of interleukin 6 (IL-6) have been associated with adverse outcomes [3-6]. Subsequently, inhibition of the IL-6 signaling pathway has been proposed for treatment of COVID-19 and clinical trials evaluating the use of antibodies against IL-6 or IL-6 receptor are ongoing [7]. However, increased levels of IL-6 have been described in numerous conditions including trauma, surgery, sepsis, respiratory failure, myocardial infarction, or post-resuscitation syndrome [8] and can be considered as a general indicator of disease severity. Unraveling distinct changes in serum protein abundance may facilitate our understanding of COVID-19. However, many studies investigating the pathophysiology of SARS-CoV-2 focused on critically ill patients with COVID-19 compared to patients with COVID-19 and moderate symptoms or to healthy individuals. Thus, the goal of the present study was to identify distinct protein expression in serum of patients with COVID-19 versus patients presenting with comparable symptoms and disease severity but tested negative for SARS-CoV-2.

## Methods

We performed an investigator-initiated, prospective single-center registry study to evaluate changes in serum protein expression associated with COVID-19 (DRKS00021206, Deutsches Register klinische Studien (DRKS)) conducted at the University Medical Center – University of Freiburg. The protocol of this study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethical committee of the University of Freiburg (EK 153/20).

### Study population

All-comers admitted to the department of emergency medicine of the University Medical Center – University of Freiburg undergoing a throat swab for PCR testing of suspected SARS-CoV-2 infection at the physicians discretion were eligible for inclusion. Written informed consent was obtained from all participants prior to inclusion and before the test results were available. Patients with a negative PCR-test for SARS-CoV-2 served as control group. We analyzed 24 SARS-CoV-2 positive and 61 negative patients that were recruited between the 2nd of April 2020 and the 8th of May 2020.

### Study procedures

Characteristics such as medical history, clinical symptoms or previous medication were obtained from all patients enrolled in the study. The severity of illness was assessed using the Sequential Organ Failure Assessment (SOFA) score [9]. Serum samples were obtained at the time point of hospital admission. In addition to the determination of clinical routine parameters, serum samples were analyzed with proximity extension assay (PEA) technology for protein detection and quantification. We performed a standardized 30-days follow-up period after study inclusion. All clinical data gathered during this period was obtained from the electronic patient file. During follow-up, no interventions were conducted for the purpose of this study and all therapeutic and diagnostic procedures were applied as part of standard

care at the discretion of the treating physicians. Finally, participants were contacted by phone and asked about the course of disease. Patients who required ICU treatment or died were categorized as severe, inpatients not requiring ICU were categorized as moderate, and outpatients were categorized as mild course of disease.

**Proximity extension assay**

Protein abundance in serum was determined by proximity extension assay [10] using the Olink® Cardiovascular III panel (Olink Proteomics, Uppsala, Sweden, Supplemental table 1) according to the manufacturer's instructions. Briefly, the protein of interest is targeted by oligonucleotide-labeled antibody probes. By binding to the target protein, a pair of probes is brought into close proximity allowing the oligonucleotides to hybridize. The resulting DNA template is detected and quantified by real-time PCR. Relative abundance of each target protein is presented in arbitrary units (Normalized Protein eXpression, NPX), allowing comparison between samples. Proximity extension assay was performed at the ARCADIA core facility at UMC Utrecht (NL) as an Olink certified service provider and technicians were blind for SARS-CoV-2 status of the samples.

**Data analysis**

For analysis, data were blinded to patient identity. Statistical analyses were performed using SPSS (version 25, IBM, SPSS Statistics, Armonk, USA) and GraphPad Prism 8 (GraphPad Software, San Diego, USA). Continuous variables were tested for normal distribution by using the Shapiro-Wilk test. Data are presented as mean ± standard deviation if found to follow a Gaussian distribution or otherwise as median with interquartile range. Variables following Gaussian distribution were compared using student's t-test, non-normally distributed continuous values by using Mann-Whitney-U test. NPX data was analyzed by student's t-test with Benjamini and Hochberg correction of false discovery rate. Categorical

variables were assessed by chi-square test or Fisher's exact test as appropriate. Correlation analysis was performed using the Spearman test for non-parametric data.

## Results

### Baseline characteristics and clinical outcomes

Of the 85 patients analyzed, 24 were SARS-CoV-2 positive and 61 SARS-CoV-2 negative. Main diagnoses for hospital admission of SARS-CoV-2 negative patients included non-COVID-19 infectious diseases, cancer, cardiac disease, and others (Fig. 1A). Median age, body mass index, and sex ratio were similar in both groups (Table 1). We observed a statistically non-significant trend towards a higher occurrence of cough or fever in SARS-CoV-2 positive patients. In addition, blood pressure, respiratory rate, temperature and disease severity as assessed by SOFA score were comparable in SARS-CoV-2 positive and negative patients (Table 1). Evaluation of medical history, potential risk factors, and preexisting medication revealed no difference except for a higher rate of premedication with oral anticoagulants or antiplatelet agents in the SARS-CoV-2 negative group (Table 1). Outcome categories and detailed outcome parameters (rate of hospital admission, rate of ICU-admission, need of ventilation, mortality) were comparable between both groups (Fig. 1B, Table 1). Of all routine laboratory parameters obtained at the time of admission to the emergency department, hemoglobin, hematocrit, AST and ALT were significantly higher in the SARS-CoV-2 positive group compared to SARS-CoV-2 negative patients. In contrast, Troponin T and proBNP levels were significantly higher in the control group (Table 2), likely reflecting the rate of acute coronary syndromes and heart failure as reasons for hospital admission in SARS-CoV-2 negative patients (Fig 1A). Importantly, we did not find differences in IL-6 expression between SARS-CoV-2 positive and negative patients (Fig.1C).

**Protein expression profiling**

To identify potentially COVID-19-related proteins, we performed a proximity extension assay-based screening of 92 candidate proteins from serum samples taken at hospital admission (Figure 2A-B, Supplemental Figure 1). Sample-to-sample correlation was significantly higher in the SARS-CoV-2 positive group compared to the control group (Supplemental Figure 1A-B), indicating a common response pattern in patients with COVID-19. However, we observed only few differences in absolute protein expression between both groups. After correction for false discovery rate, we identified two differentially abundant proteins: Progranulin (GRN) was 1.94-fold upregulated while TNF receptor superfamily member 10C (TNFRSF10C) was 1.99-fold downregulated in serum from SARS-CoV-2 positive compared to SARS-CoV-2 negative patients (Fig. 2C-D). Of note, a similar pattern of regulation was observed when SARS-CoV-2 positive patients were compared to a subgroup of patients with other type of pneumonia or infectious disease but negative for SARS-CoV-2 (Supplemental Figure 2), suggesting specificity for SARS-CoV-2.

**Association of GRN abundance with disease severity**

Interestingly, GRN was excessively increased (3.3-fold above mean of SARS-CoV-2 positive patients) in the one COVID-19 patient that died during the 30-days follow-up period (Fig. 2C). To follow this finding, we assessed outcomes of SARS-CoV-2 positive patients with high (above 50$^{th}$ percentile) or low (below 50$^{th}$ percentile) GRN expression. The rate of severe courses was significantly higher in patients with high GRN expression (Fig. 3A). Patients with high GRN expression showed higher maximum serum creatinine and IL-6 levels as surrogate parameters for disease severity (Fig. 3B-C). Interestingly, levels of GRN and maximum IL-6 in SARS-CoV-2 positive patients were strongly correlated with each other (Figure 3D). To identify potential pathophysiological processes associated with increased

GRN expression, we searched for other co-expressed factors in serum of SARS-CoV-2 positive patients (Fig. 4). Among the proteins showing the most significant positive correlation with GRN were growth/differentiation factor 15 (GDF-15), urokinase-type plasminogen activator (uPA) and urokinase-type plasminogen activator receptor (U-PAR). Furthermore tumor necrosis factor receptors 1 and 2 (TNF-R1, TNF-R2), that serve as GRN receptors as well, were strongly correlated with GRN abundance (Fig. 4).

**Cellular source of GRN in COVID-19**

We observed a higher number of monocytes in blood from SARS-CoV-2 positive patients with high GRN expression (Fig 5A) and GRN expression was significantly correlated with monocyte count (Fig. 5B). To confirm the cellular source of GRN in SARS-CoV-2 positive patients we assessed a very recently published dataset [11] on single cell mRNA expression in peripheral blood mononuclear cells from COVID-19 patients and healthy donors (Fig. 5C). In monocytes from patients with a moderate or severe course of COVID-19, *GRN* expression was 2.0- or 1.9-fold increased, respectively, when compared to healthy individuals (Fig. 5C). In contrast, no or only minor changes in *GRN* expression were detectable in natural killer cells, T cells, or B cells from patients with COVID-19 (Fig. 5C).

**Discussion**

In this study, we compared serum protein expression in patients with COVID-19 to patients with comparable symptoms and disease severity but negative for SARS-CoV-2. We identified the immunomodulatory factor progranulin (GRN) and TNFRSF10C to be specifically regulated in patients with COVID-19.

We observed a specific upregulation of GRN in SARS-CoV-2 positive patients compared to patients with comparable symptoms and disease severity but negative for SARS-CoV-2. This supports an earlier report describing an upregulation of GRN in patients with severe COVID-19 but not in patients with other diseases when compared to healthy controls [12]. In contrast, we found no difference in IL-6 abundance in SARS-CoV-2 positive versus negative patients. This important finding is in line with a recent report describing that the plasma cytokine profile of severe COVID-19 was similar to ARDS or sepsis [13]. Thus, while IL-6 might serve as a marker for disease severity in COVID-19, it is in contrast to GRN not specifically upregulated in patients with moderate symptoms. However, though promising, the usability of GRN as a biomarker in COVID-19 requires further investigation, including patients with a broader spectrum of disease severity.

There is a growing body of evidence pointing to a broad and more complex disorder of pro-inflammatory and anti-viral responses in COVID-19 [7]. Recent studies have shown that interferon signaling seems to take a critical role in COVID-19. Interferons are crucial for the immune response to viral infections as they induce the synthesis of proteins interfering with viral replication [14]. Upon viral infection, most cell types are able to secret interferons type I (IFN-α and IFN-β), whereas interferon type II (INF-γ) is only produced by NK cells and activated T cells [14, 15]. Studies on SARS coronavirus (SARS-CoV), causing the 2003 pandemic, demonstrated antiviral effects of IFN-β at high concentrations [16, 17]. Likewise, treatment with type I and III interferons reduced virus replication in cell cultures infected with SARS-CoV-2 [18, 19]. However, current research shows that induction of interferons in cells infected with SARS-CoV-2 is impaired [18, 20, 21]. Transcriptional profiling of human airway epithelial cells revealed an upregulation of IL-6 and other pro-inflammatory cytokines but a repression of interferon I and III signaling after SARS-CoV-2 infection [18]. In patients with COVID-19, interferon production by mononuclear cells was reduced [22, 23]. Suppression of the translational machinery by SARS-CoV-2 [24] and auto-antibodies against type I interferons [25] have been proposed as potential mechanisms involved. The lack of

interferons is associated with a persistent blood viral load and an increase of TNF-α and IL-6 [26], suggesting that the diminished interferon response contributes to impaired virus elimination and disease progression in COVID-19. Early clinical data indicate a potential benefit of subcutaneously administered interferon beta on the course of COVID-19 and further studies are currently ongoing [27]. However, the optimal IFN-I subtype, dose, timing, and route of administration appear to be crucial and remain to be investigated [27].

GRN is the common precursor of the granulin peptide family [28]. It is a pleiotrophic growth factor and immune-regulatory molecule expressed in a broad range of tissues and cell types such as epithelia, bone marrow and various immune cells including T-cells, DCs, monocytes and macrophages [28]. In SARS-CoV-2 positive patients, GRN abundance was associated with higher blood monocyte counts. Single cell data shows an upregulation of *GRN* mRNA expression in blood monocytes [11] and in pulmonary macrophages after SARS-CoV-2 infection [29], suggesting that myeloid cells are the primary source of GRN in COVID-19. By binding to the membrane bound receptors TNF-R1, TNF-R2 or TLR9, GRN exhibits a variety of functions in the innate and adaptive immune system [28]. In the adaptive immune system, GRN is crucial for T-cell regulation since it promotes the differentiation of CD4+ T cells into Foxp3+ Tregs and protects Tregs from negative regulation by TNF-alpha [30]. GRN prevents regulatory NK cell cytotoxicity against antiviral T cells [31] and inhibits LPS-mediated IL-6 and TNF-α secretion from macrophages [32, 33].

GRN has contrasting roles in bacterial or viral infections that may contribute to the pathophysiology of COVID-19: GRN contributes to host defense against bacterial pneumonia and sepsis by promoting macrophage recruitment and bacterial clearance [34, 35]. On the other hand, it was shown that GRN mRNA is induced in the lungs of mice after influenza infection [36] and that GRN is upregulated in clinical and experimental influenza in a disease-severity dependent manner [37], similar to what we observed here in COVID-19. The upregulation of GRN in influenza is associated with aggravated virus-induced lung injury

and mortality due to an enhanced influx of neutrophils and monocytes/macrophages and a consequently significant increase of pulmonary IL-6 and other cytokines [37]. In line with this, we observed a positive correlation of GRN with IL-6 abundance and disease severity in patients with COVID-19. Importantly, deterioration of viral infections by GRN are accompanied by an impaired type I interferon production due to inhibition of NF-κB and IRF3 signaling [38], similar to what has been described in SARS-CoV-2 infection [26]. GRN neutralizing antibodies protect against influenza virus-induced lethality in mice [38]. Thus, we conclude that restoring interferon signaling by inhibition of GRN may have beneficial effects on COVID-19 that should be further explored.

Among others, GRN exerts its downstream effects by activation of TNF-R1 and TNF-R2 [28]. Interestingly, upregulation of GRN was associated with increased abundance of TNF-R1 and TNF-R2 in SARS-CoV-2 positive patients, implying a possible feed forward mechanism. Moreover, we found that another member of the TNF-receptor superfamily, TNFRSF10C, was downregulated in COVID-19. TNFRSF10C is a decoy receptor and thought to function as an antagonistic receptor that protects cells from TRAIL (TNF-related apoptosis-inducing ligand)-induced apoptosis. It is known from other viral infections such as influenza that TRAIL signaling is involved in the induction of apoptosis and necrosis of fibroblasts, dendritic cells and lung epithelial cells, thus contributing to virus-induced lung damage [39]. A downregulation of TNFRSF10C in COVID-19 might therefore contribute to enhanced SARS-CoV-2-induced lung injury.

Finally, GRN might be involved in extrapulmonary manifestations of COVID-19. We observed a strong correlation of GRN with uPA and U-PAR, which might be related to the coagulopathy observed in COVID-19, and with GDF-15, a well established predictive biomarker of all-cause mortality and adverse cardiovascular events [40].

## Conclusion

In conclusion, the data from this prospective registry reveals that GRN is specifically upregulated in SARS-CoV-2 positive patients compared to patients presenting with comparable symptoms and disease severity but tested negative for SARS-CoV-2. The potential of GRN as a biomarker and a possible impact of increased GRN expression on interferon signaling, virus elimination, and virus-induced lung tissue damage in COVID-19 should be further explored.

**Author contributions:**

M.R., D.D. and A.L. designed the study, M.R., A.L., L.W., L.P., M. J., I.G., N.B., B.S., H-J.B., M.H., R.T. and S.R. acquired data and samples, M.R., D.D., W.K., C.B. and A.L. analyzed and interpreted data, M.R. and A.L. wrote the manuscript.

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| | SARS-CoV-2 positive | SARS-CoV-2 negative | P value |
|---|---|---|---|
| **patients characteristics** | | | |
| sex [male] | 10 (41.7%)[c] | 31 (50.8%)[c] | 0.479[f] |
| age [years] | 58.5 ± 15.5[a] | 66.0 ± 30.0[a] | 0.2432[e] |
| BMI [kg/m$^2$] | 25.7 ± 6.5[a] | 24.4 ± 5.4[a] | 0.2877[e] |
| **symptoms at admission** | | | |
| dyspnoe | 10 (41.7%)[c] | 35 (57.4%)[c] | 0.232[f] |
| cough | 14 (58.3%)[c] | 23 (37.7%)[c] | 0.085[f] |
| fever | 18 (75.0%)[c] | 30 (49.2%)[c] | 0.051[f] |
| **clinical presentation at admission** | | | |
| systolic blood pressure [mmHg] | 128.6 ± 17.6[b] | 139.0 ± 25.3[b] | 0.9414[d] |
| diastolic blood pressure [mmHg] | 82.0 ± 11.2[b] | 79.4 ± 16.1[b] | 0.4797[d] |
| mean arterial pressure [mmHg] | 100.6 ± 12.3[b] | 99.1 ± 16.4[b] | 0.6723[d] |
| heart rate [per minute] | 90.4 ± 15.0[b] | 88.5 ± 19.8[b] | 0.6750[d] |
| respiratory rate [per minute] | 24.0 ± 17.0[a] | 23.0 ± 12.0[a] | 0.6117[e] |
| temperature | 37.5 ± 1.4[a] | 37.3 ± 1.1[a] | 0.4568[e] |
| SOFA-Score | 1.0 ± 3.0[a] | 1.0 ± 2.0[a] | 0.5292[e] |
| **medical history / risk factors** | | | |
| smoking | 4 (16.7%)[c] | 12 (19.7%)[c] | 0.948[f] |
| hypertension | 8 (33.3%)[c] | 31 (50.8%)[c] | 0.158[f] |
| diabetes | 4 (16.7%)[c] | 9 (14.8%)[c] | 1.0[f] |
| chronic heart failure | 1 (4.2%)[c] | 2 (3.3%)[c] | 1.0[f] |
| coronary artery disease | 2 (8.3%)[c] | 8 (13.1%)[c] | 0.718[f] |
| chronic kidney disease | 2 (8.3%)[c] | 7 (11.5%)[c] | 1.0[f] |
| oncological disease | 6 (25.0%)[c] | 21 (34.4%)[c] | 0.450[f] |
| pulmonary disease | 5 (20.8%)[c] | 16 (26.2%)[c] | 0.782[f] |
| **Preexisting medication** | | | |
| antibiotic therapy prior to admission | 0 (0%)[c] | 4 (6.6%)[c] | 0.573[f] |
| immunosuppressive therapy | 3 (12.5%)[c] | 4 (6.6%)[c] | 0.397[f] |
| antidiabetic medication | 3 (12.5%)[c] | 5 (8.2%)[c] | 0.682[f] |
| **Anticoagulation / antiplatelet therapy** | **3 (12.5%)[c]** | **27 (44.3%)[c]** | **0.006[f]** |
| **Outcome** | | | |
| hospital admission | 18 (75.0%)[c] | 45 (73.8%)[c] | 1.0[f] |
| length of hospital stay [days] | 15.0 ± 17.5[a] | 9.0 ± 10.5[a] | 0.0703[e] |
| ICU admission | 2 (8.3%)[c] | 6 (9.8%)[c] | 1.0[f] |
| length of ICU stay [days] | 14.0 ± 8.0[a] | 4.0 ± 6.0[a] | |
| need of non-invasive / invasive ventilation | 2 (8.3%)[c] | 4 (6.6%)[c] | 1.0[f] |
| days on non-invasive ventilation | 13.0 ± 10.0[a] | 3.5 ± 6.75[a] | |
| death during 30-days follow-up | 1 (4.2%)[c] | 5 (8.2%)[c] | 0.671[f] |

**Table 1: Patient characteristics and outcome.** P values refer to the comparison between the SARS-CoV-2 negative and the SARS-CoV-2 positive patients. a presented as median ± interquartile range, b presented as mean ± standard deviation, c number of patients (with percentage based on the total number of patients), d based on student's t-test for variables following a Gaussian distribution, e based on Mann-Whitney-U test for nonparametric variables, f based on chi-square test / Fisher's exact test as appropriate for categorical variables.

| Laboratory findings at admission | | SARS-CoV-2 positive | SARS-CoV-2 negative | P value |
|---|---|---|---|---|
| | **leukocyte count [$10^3$/µl]** | **4.765 ± 3.383** | **8.92 ± 7.45** | **0.0003** |
| | platelet count [$10^3$/µl] | 185.5 ± 86.0 | 233.0 ± 156.0 | 0.0622 |
| | **haemoglobin [g/dl]** | **13.5 ± 2.98** | **11.7 ± 4.65** | **0.0093** |
| | **hematocrit [%]** | **37.85 ± 6.58** | **34.2 ± 11.55** | **0.0321** |
| | creatinine [mg/dl] | 0.87 ± 0.5155 | 0.97 ± 0.625 | 0.2335 |
| | urea [mg/dl] | 30.5 ± 16.0 | 36.0 ± 33.0 | 0.2635 |
| | CRP [mg/dl] | 25.55 ± 68.83 | 29.5 ± 76.25 | 0.6103 |
| | PCT [ng/ml] | 0.08 ± 0.095 | 0.08 ± 0.305 | 0.5264 |
| | **AST [U/l]** | **34.5 ± 29.25** | **25.0 ± 18.5** | **0.0019** |
| | **ALT [U/l]** | **27.0 ± 20.25** | **19.0 ± 17.5** | **0.0085** |
| | y-GT [U/l] | 44.0 ± 59.0 | 34.0 ± 66.0 | 0.5036 |
| | LDH [U/l] | 304.5 ± 177.0 | 235.0 ± 104.0 | 0.0576 |
| | bilirubin [mg/dl] | 0.4 ± 0.35 | 0.5 ± 0.6 | 0.1091 |
| | CK [U/l] | 79.0 ± 104.0 | 69.0 ± 71.0 | 0.4763 |
| | **troponin T [ng/l]** | **7.0 ± 5.9** | **14.3 ± 33.3** | **0.0279** |
| | **proBNP [pg/ml]** | **129.5 ± 354.0** | **327.5 ± 3595.75** | **0.0219** |
| | myoglobin [ng/ml] | 56.0 ± 54.0 | 52.0 ± 67.5 | 0.9960 |
| | D-Dimers [mg/l] | 1.17 ± 1.64 | 1.175 ± 1.805 | 0.6520 |
| | vWF-antigen [%] | 277.0 ± 151.0 | 218.0 ± 200.5 | 0.1183 |
| | vWF-activity [%] | 266.0 ± 114.0 | 216.5 ± 184.0 | 0.2016 |
| | IL-6 [pg/ml] | 18.15 ± 47.705 | 26.2 ± 107.05 | 0.2336 |
| | Clauss fibrinogen [mg/dl] | 303.0 ± 124.5 | 374.0 ± 325.8 | 0.1489 |

**Table 2: Laboratory findings at the time of study inclusion.** P values refer to the comparison between the SARS-CoV-2 negative and the SARS-CoV-2 positive patients. All values are presented as median ± interquartile range, comparisons are based on Mann-Whitney-U test for nonparametric variables.

**Figure legends:**

**Figure 1: Patient characteristics and clinical outcomes.** Patients with COVID-19 (n = 24) and patients with other main diagnosis but negative for SARS-CoV-2 (n = 61) admitted to the emergency department were included in a prospective registry (A). Patient outcomes were categorized as mild, moderate or severe (B). Serum levels of interleukin-6 was determined in routine testing (C).

**Figure 2: Impact of COVID-19 on serum protein expression.** Serum expression of 92 candidate proteins in patients with COVID-19 (n = 24) and patients with other main diagnosis but negative for SARS-CoV-2 (n = 61) was determined by proximity extension assay (A). Volcano plot indicating fold change and q value of the candidate proteins (B). Serum expression of progranulin (GRN) and TNF receptor superfamily member 10C (TNFRSF10C) was significantly altered in COVID-19 compared to control patients (C-D). *q<0.05; ***q<0.001 vs. SARS-CoV-2 negative. NPX, normalized protein expression.

**Figure 3: Correlation of progranulin expression with clinical outcome and biomarkers in COVID-19.** According to GRN expression, SARS-CoV-2 positive patients (n = 24) were allocated to GRN low (GRN < $50^{th}$ percentile) or GRN high (GRN > $50^{th}$ percentile) groups. After 30 days of follow-up, outcome of SARS-CoV-2 positive patients was categorized as mild, moderate, or severe (A, * P<0.05 by chi-square). Serum creatinine and IL-6 levels in GRN low or high SARS-CoV-2 positive patients (B-C; **P<0.01 by student's t-test) and Pearson correlation of IL-6 with GRN expression were determined.

**Figure 4: Correlation of progranulin expression with other serum proteins in COVID-19.** Volcano plot indicating correlation of GRN and other protein expression in serum of SARS-CoV-2 positive patients. GDF-15, growth/differentiation factor 15; uPA, urokinase-type plasminogen activator; U-PAR, urokinase-type plasminogen activator receptor; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2.

**Figure 5: Cellular source of progranulin in COVID-19.** Blood monocyte count in GRN low or high SARS-CoV-2 positive patients (A; *P<0.05 by student's t-test) and Pearson correlation of blood monocyte count with GRN expression (B) were determined. Cell type-specific changes in GRN mRNA expression were derived from a previously published single cell RNA-seq [11] from peripheral blood mononuclear cells from patients with moderate (n=7) or severe (n=4) COVID-19 and healthy donors (n=5) (C).

Figure 1

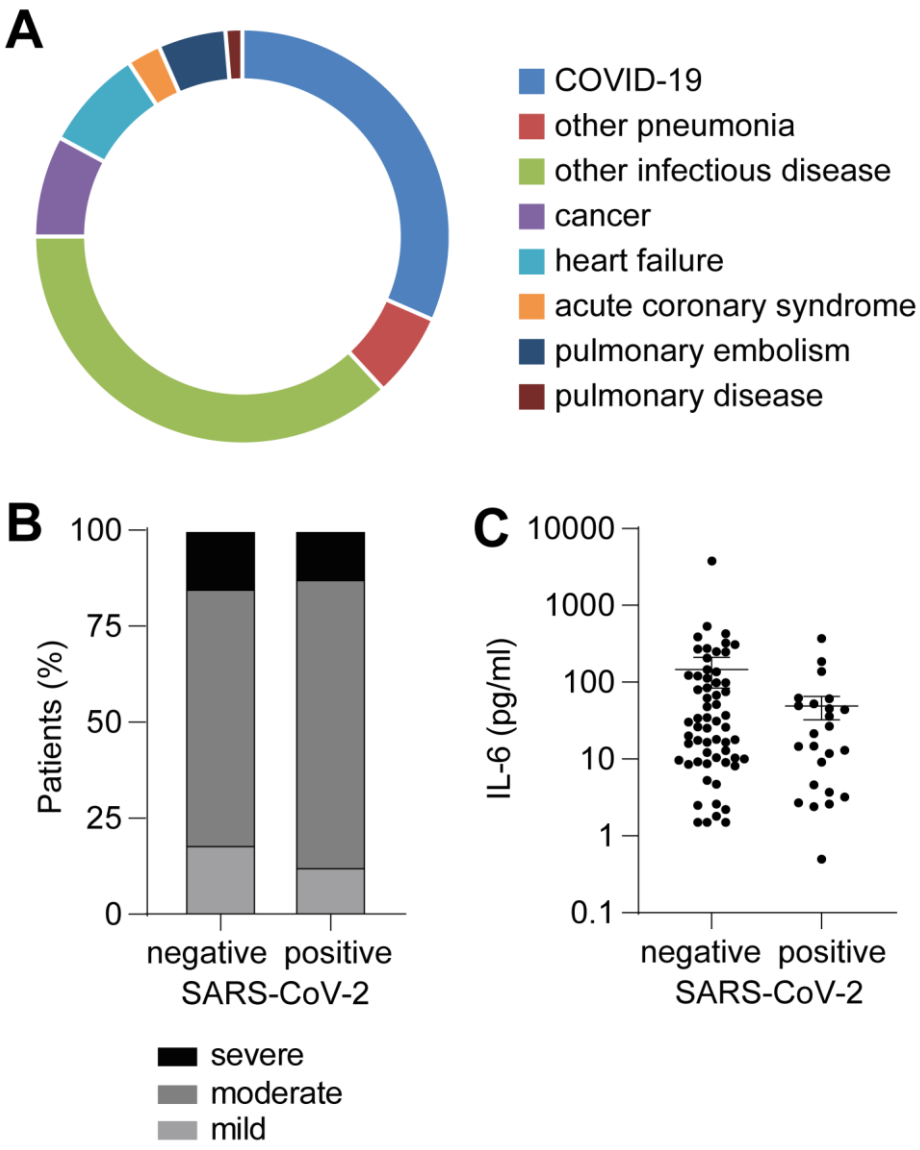
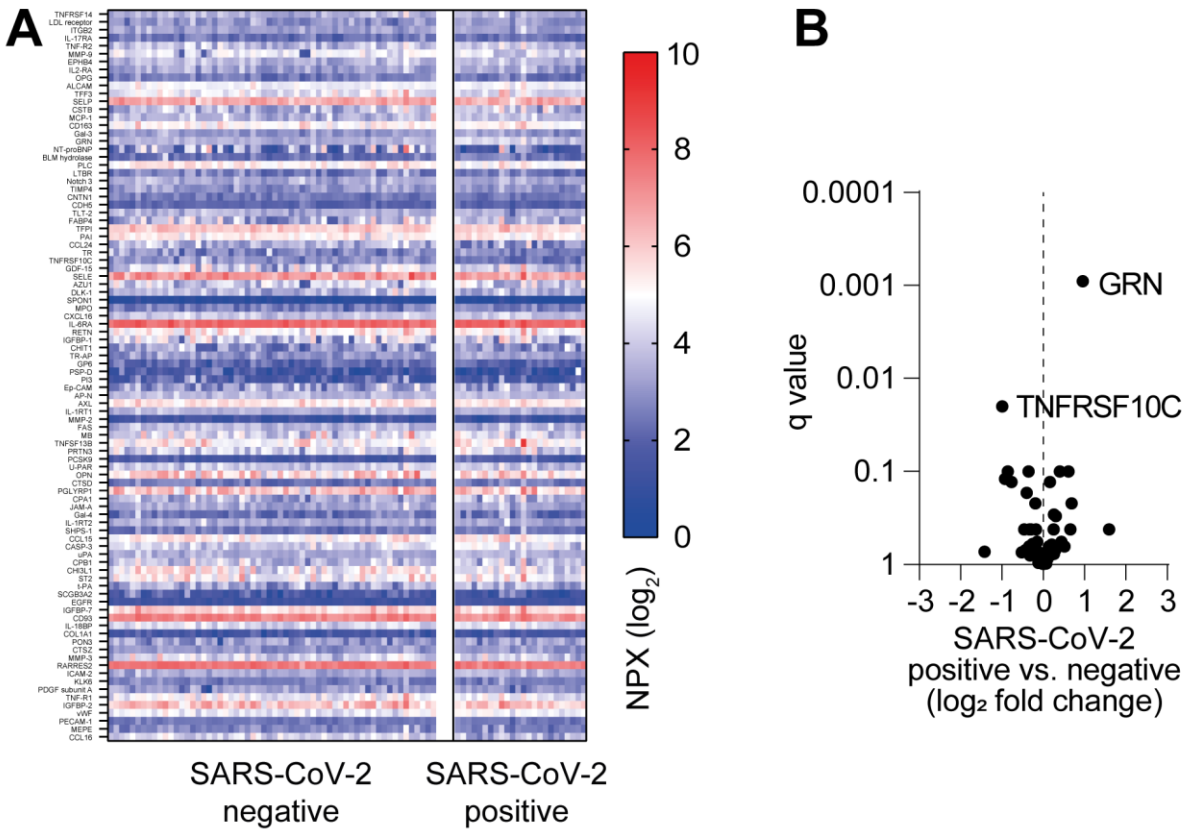


Figure 2


A
B
10
8
6
4
2
0
NPX (log2)
SARS-CoV-2 negative
SARS-CoV-2 positive
0.0001
0.001
0.01
0.1
1
q value
GRN
TNFRSF10C
-3 -2 -1 0 1 2 3
SARS-CoV-2 positive vs. negative (log2 fold change)

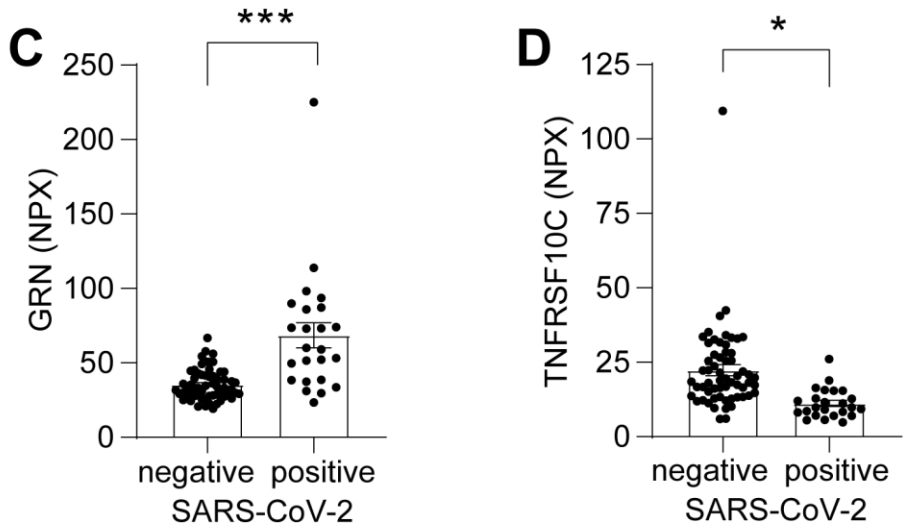

C
***
250
200
150
100
50
0
GRN (NPX)
negative positive
SARS-CoV-2
D
*
125
100
75
50
25
0
TNFRSF10C (NPX)
negative positive
SARS-CoV-2

Figure 3

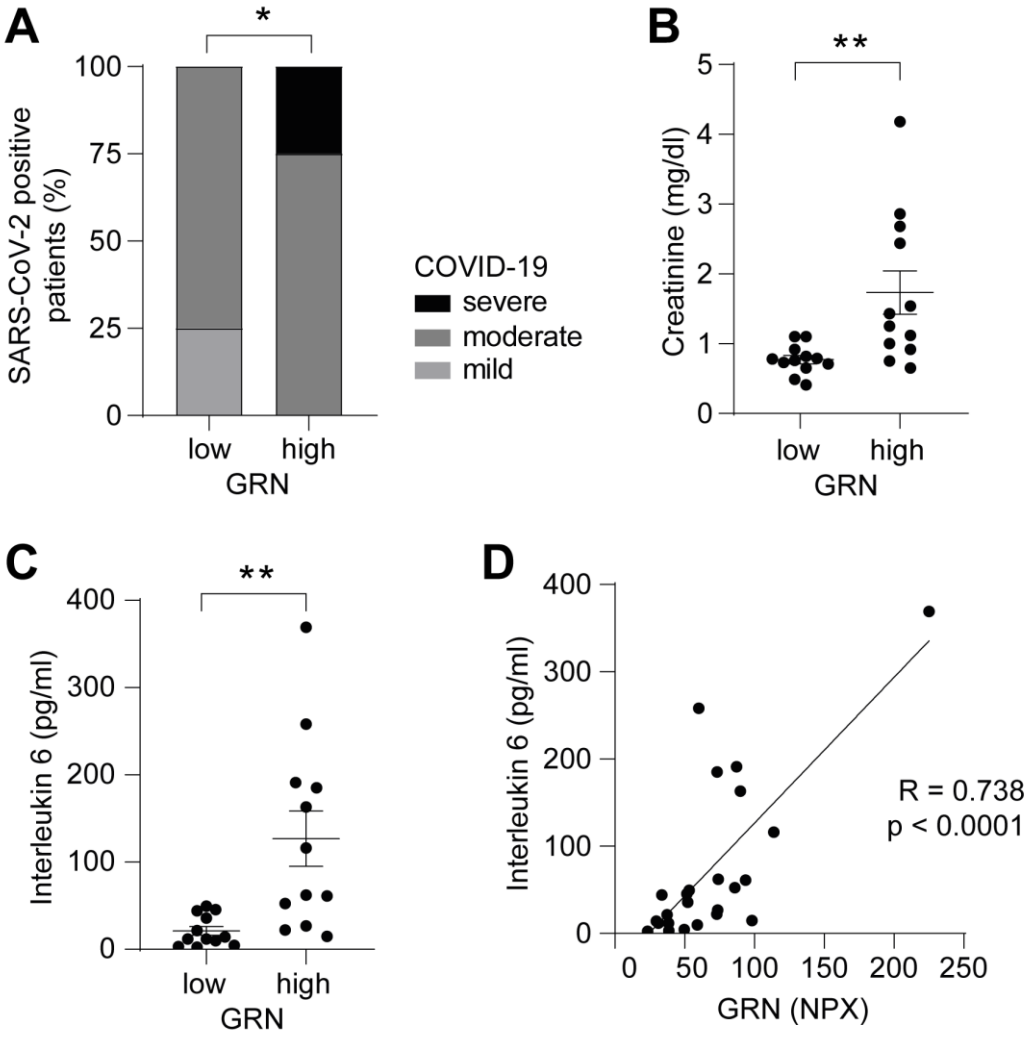


Figure 4

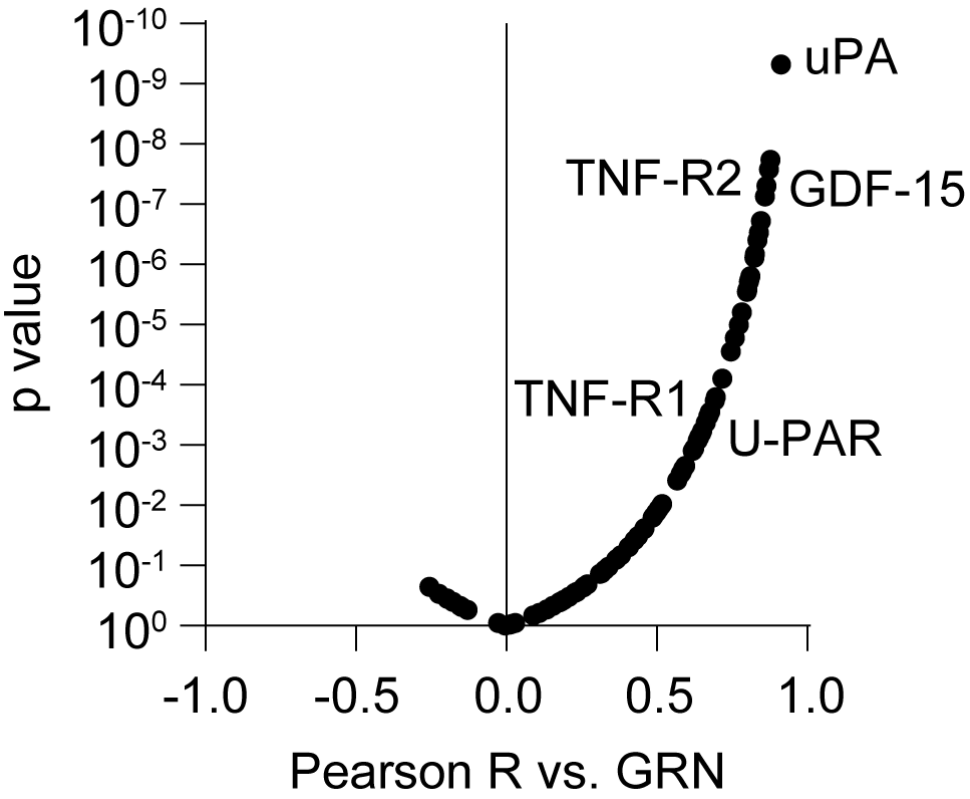
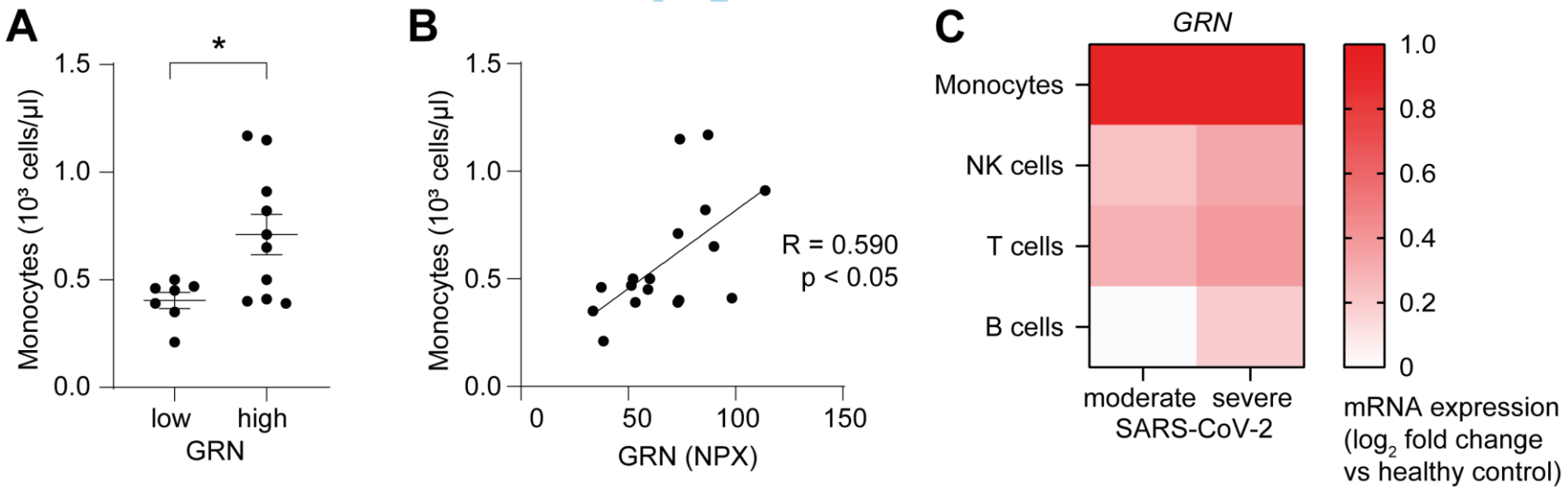


Figure 5


A
*
Monocytes (10³ cells/µl)
1.5
1.0
0.5
0.0
low
high
GRN
B
Monocytes (10³ cells/µl)
1.5
1.0
0.5
0.0
0
50
100
150
GRN (NPX)
R = 0.590
p < 0.05
C
GRN
Monocytes
NK cells
T cells
B cells
moderate
severe
SARS-CoV-2
1.0
0.8
0.6
0.4
0.2
0
mRNA expression
(log2 fold change
vs healthy control)