

Article

Structural Variants in Severe COVID-19: Clinical Impact Assessment

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Abstract

Background: Several genes and genomic regions have been implicated in COVID-19 susceptibility and severity, but their clinical relevance remains uncertain. We comprehensively assessed both copy number variants (CNVs) and single-nucleotide variants (SNVs) disrupting genes implicated in COVID-19 in a Swedish cohort of ICU-treated COVID-19 patients with detailed phenotype data. **Methods:** Patients ($n = 301$) with severe COVID-19 treated in intensive care units (ICU) between March 2020 and January 2021 at two large Swedish university hospitals were included. Whole exome sequencing (WES) was performed to identify both large copy number variations (CNVs) and single-nucleotide variants (SNVs), including small indels, using the Genome Analysis Toolkit (GATK) pipelines. We focused our analyses on variants disrupting coding genes implicated in severe COVID-19, but also assessed variants known to cause human disease. **Results:** We identified 11 rare CNVs and several SNVs potentially linked to severe COVID-19. Patients carrying a CNV spanning a COVID-19-implicated gene had higher levels of the heart failure marker NT-proBNP (median 4440 [1558–8160] vs. 1170 [329–3152], $p = 0.017$), worse renal function at ICU admission ($p = 0.0026$), and a higher need for continuous renal replacement therapy (CRRT) (28% vs. 10%, $p = 0.045$) compared to patients without a potentially damaging CNV. **Conclusions:** Although patients with a potentially damaging CNV or SNV exhibited some differences in cardiac and renal markers, our findings do not support broad genetic screening as a predictive tool for COVID-19 severity.



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Keywords: COVID-19 severity; copy number variants (CNVs); single nucleotide variants (SNVs); intensive care patients; whole exome sequencing (WES); phenotype data; genetic susceptibility

1. Introduction

Susceptibility to SARS-CoV-2 and variation in disease severity of COVID-19 have been shown to have a genetic component, where genes related to lung function, cardiovascular dysfunction, coagulation deficiencies, and immune response have been implicated [1–6]. However, most research initiatives have focused on common genetic variants and rare single-nucleotide variants (SNVs), while the importance of structural variants (SVs), including copy number variations (CNVs), has not been equally explored.

The COVID-19 Host Genomics Initiative (HGI), a global effort aimed at identifying genetic factors important in severe COVID-19 [7,8], and other large initiatives [9,10] have identified genes involved in the pathogenesis of COVID-19, significantly improving our understanding of the underlying genetic pathogenesis. The additive effect of common genetic variation explains only about 1% of severe COVID-19 [4] and thus lacks clinical utility on an individual level. Studies on rare SNVs and COVID-19 severity have suggested potential clinical relevance [11], but findings have been inconsistent [12].

Here, leveraging prior knowledge, we investigate the clinical relevance of genetic findings by comprehensively analyzing both CNVs and SNVs in a cohort of 301 critically ill Swedish COVID-19 patients. Using whole-exome sequencing data and detailed clinical ICU data, genetic factors implicated in COVID-19 are scrutinized in a clinical context.

2. Materials and Methods

2.1. Study Cohort

Clinical data and blood samples were collected from 301 individuals, 24% women, and three pairs of first-degree relatives with severe COVID-19 (all patients were included individually and not as relatives). Severe COVID-19 was defined as intensive care unit (ICU) treatment. Patients were recruited from two large university hospitals in Sweden during the initial wave of COVID-19 (March 2020–January 2021) prior to available SARS-CoV-2 vaccines. Whole exome sequencing (WES) was performed to identify rare genetic variants (both small and large) potentially influencing disease severity.

2.2. Variant Calling and Annotation

Variant calling from short-read, Illumina-generated, exome sequencing data was performed using the Genome Analysis Toolkit (GATK) suite. The new GATK-gCNV algorithm, especially developed to accurately identify rare CNVs in exome data, was used to call CNVs [13], while the Haplotype Caller was used for calling SNVs and short indels [14]. Quality control was performed separately for the two analyses, with cutoffs as suggested by the software authors [Supplementary Material]. Variants were aligned to the genomic build GRCh38, and the Variant Effect Predictor (VEP) [15] was used to annotate the quality-controlled VCF files. Population frequencies from gnomAD were used, and updated ClinVar annotations were downloaded from the official NCBI FTP site (<https://ftp.ncbi.nlm.nih.gov/pub/clinvar/>, accessed on 10 March 2025).

2.3. CNV Prioritization and Filtering

Only gene transcripts annotated by VEP as ‘canonical transcript’ were considered for both the CNV and SNV analysis. Because CNV calling is less accurate for certain

genomic regions when WES data is used, only the 15,734 genes assessed by the Exome Aggregation Consortium (ExAC) as technically reliable for CNV calling in WES data were investigated [16]. Further, because the study focused on clinically actionable CNVs, we restricted the analysis to gene deletions only. This was performed for two reasons: firstly, it is more difficult to confidently detect duplicated genomic segments in WES data [17], and secondly, the functional impact of a genomic duplication is harder to predict and leads to uncertain interpretations. After quality control, we filtered for rare CNVs disrupting coding genes using a frequency cut-off of <0.5%, as suggested by gnomAD [16].

Unfortunately, samples from one sub-site ($n = 96$, batch 1) had a read depth variability that was too high for confident CNV calling, and these samples were therefore excluded from the CNV analysis but could be kept for the SNV analysis. Therefore, a total of 205 ICU-treated COVID-19 patients were assessed for disrupting CNVs in genes linked to COVID-19.

To identify potential clinically relevant gene deletion, we employed a filtering strategy with three arms [details in Supplementary Material]. We identified all gene deletions that spanned the canonical transcript of genes in

- (1) The curated (green-listed) COVID-19 research gene panel from PanelApp (<https://panelapp.genomicsengland.co.uk>, accessed on 10 November 2024), Genomics England.
- (2) The Online Mendelian Inheritance in Man (OMIM) morbid map (4442 genes) [18], which is a comprehensive resource that catalogs all known genetic diseases and describes what is known about their molecular pathogenesis.
- (3) A condensed list of genes implicated in COVID-19 pathogenesis from the largest GWASs and candidate gene studies to date [Supplementary Material].

2.4. SNV Prioritization and Filtering

Because knowledge about SNVs and short indels is much greater than for CNVs, we leveraged prior knowledge and focused on rare SNVs that have previously been classified as either pathogenic or likely pathogenic (non-conflicting evidence) in the curated NCBI database ClinVar [19]. Both pathogenic and likely pathogenic variants are considered clinically actionable by the American College of Medical Genetics (ACMG) [20]. Here, we used a more stringent frequency cutoff (0.1%) to define a rare variant. This was performed because allele frequencies for SNVs are much more likely to be correct due to larger reference databases. As shown by Lek et al., virtually all known disease variants will be captured, even for recessive disorders, using a frequency cutoff < 0.1% [21]. For the SNV analysis, we also explored variants unknown to ClinVar where predicted loss-of-function (pLoF) variants resided in genes likely to be haploinsufficient (LOUEF score cutoff < 0.35) and thus most likely to cause a clinical disorder on an individual level.

2.5. Clinical Data

Clinical phenotype data were available for all patients. This detailed information was collected during each patient's ICU stay and consisted of over a hundred variables, including age, sex, BMI, preexisting medical conditions, length of stay (LOS) in the ICU, time on ventilator, need for vasoactive treatment and continuous renal replacement therapy, 90-day survival, and numerous common laboratory results.

2.6. Data Analysis

All figures and downstream analyses were performed in R (version 4.3.2). Statistical inference was performed using linear and/or logistic regression models adjusted for age and sex. Normality of continuous variables was assessed using histograms and Q-Q plots, and variables were transformed when appropriate to meet model assumptions. For genetic

comparisons involving small numbers of observations or low expected counts, Fisher’s exact test was used. A two-sided p -value < 0.05 was considered statistically significant.

2.7. Ethics Statement

Ethical approval was granted by the Swedish Ethical Review Authority [Supplementary Material]. Informed written consent was obtained from severely ill COVID-19 patients or their next of kin, if the patient was unable to give consent. Blood samples were collected and pseudonymized prior to analysis to maximize patient confidentiality.

3. Results

A total of 301 ICU-treated COVID-19 patients were included. To assess disease severity, detailed clinical ICU data were collected and analyzed [Section 2]. The newly developed GATK-gCNV algorithm was used to identify CNVs, while HaplotypeCaller was used to call SNVs. Given the low overall heritability of severe COVID-19 ($\approx 1\%$) [4], we hypothesized that relevant genetic variants (i.e., clinically actionable) must be rare in the general population. Using previously published cutoffs, we therefore focused on variants with a population frequency $< 0.5\%$ for CNVs and $< 0.1\%$ for SNVs that disrupted coding genes implicated in COVID-19 or associated with human disease [Section 2].

3.1. CNV Analysis

Common and rare SNVs have been extensively studied in relation to COVID-19 [7–10], but the impact of CNVs in severe cases remains less understood. In our cohort of ICU-treated patients, we identified 61 rare CNVs (deletions with an allele frequency below 0.5%) disrupting coding genes. To identify potentially clinically relevant CNVs, we applied three different filter strategies [details in Section 2]. After filtering, 11 separate deletions in 14 individuals were identified, all with potential clinical relevance. Three deletions, in three separate individuals, disrupted genes previously implicated in COVID-19 severity, while eight large deletions involved genes classified as disease-associated in OMIM (Figure 1 and Table 1).

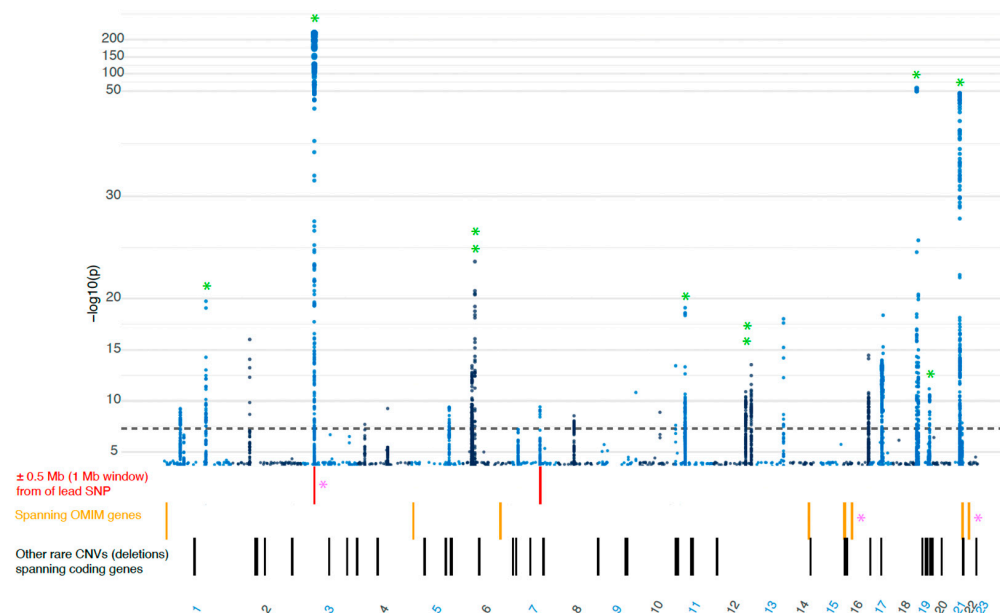


Figure 1. The genomic location of the 61 rare deletions identified in our COVID-19 cohort, plotted in relationship to the largest GWAS focused on severe COVID-19 (cases = 21,294, controls = 2,182,461, COVID-19 Host Genetics Initiative, Release 7) [22] * PINK = genes implicated in COVID-19, * GREEN = locus also overlaps with COVID-19 susceptibility locus. SNP, single nucleotide polymorphism; OMIM, Online Mendelian Inheritance in Man database; CNV, copy number variation.

Table 1. CNV findings are listed by location and annotations. PINK = COVID-19 implicated ORANGE = OMIM genes not linked to COVID-19. OMIM, Online Mendelian Inheritance in Man; Louef, loss-of-function observed/expected upper bound fraction; CNV, copy number variation; AR, autosomal recessive; AD, autosomal dominant; LoF, loss of function; GoF, gain of function.

Location	Genes (Filtered)	Associated Disorders (Inheritance)	Louef (LoF Intolerance)	Likely Disease Mechanism	CNV Length (kbp)	Disease Causing in Decipher
3p21.31	XCR1	Gene not described in OMIM	1.73	-	5.487	-
16p11.2	ALDOA	Glycogen storage disease (AR)	0.82	LoF	526.596	Yes
	CORO1A	Immunodeficiency 8 (AR)	0.57	Lof		
	KIF22	Spondyloepimetaphyseal dysplasia (AD)	1.03	GoF		
	TBX6	Spondylocostal dysostosis 5 (AR, AD)	0.94	LoF		
22q11.21	LZTR1	Noonan syndrome (AD, AR)	2.00	GoF in AD mode	2024.745	Yes
	SCARF2	Van den Ende-Gaupa Syndrome (AR)	0.99	LoF		
	SNAP29	Cerebral dysgenesis, neuropathy (AR)	0.83	LoF		
	SLC25A1	Myasthenic syndrome, congenital (AR) Metabolic	1.04	LoF		
	TANGO2	encephalomyopathic crises (AR)	0.92	LoF		
	TBX1	22q11 syndrome (DiGeorge syndrome) (AD)	0.70	LoF		
1p36.21	CELA2A	Metabolic syndrome (AD)	1.16	Dominant negative	17.9	Only biallelic
5p15.31	NSUN2	Intellectual developmental disorder (AR)	0.97	LoF	1283.985	-
6q23.2	ARG1	Argininemia (AR)	0.83	LoF	322.429	Only biallelic
	ENPP1	Metabolic disorders, Cole disease (AR, AD)	0.73	LoF/GoF in AD mode		
	MED23	Intellectual developmental disorder (AR)	0.77	LoF		
14q31.3	GALC	Krabbe disease (AR)	1.02	LoF	18.233	Only biallelic
16p13.3	GFER	Congenital cataract and developmental delay (AR)	1.87	LoF	18.647	-
16p13.3	ALG1	Congenital disorder of glycosylation (AR)	1.42	LoF	26.488	Only biallelic
21q22.3	CRYAA	Cataract 9 (AR, AD)	NA	LoF/GoF in AD mode	247.324	-
21q22.3	TRAPPC10	Neurodevelopmental disorder (AR)	0.27	LoF	1108.704	-

Two of the large deletions, found on 22q11 and 16p11, matched two well-described syndromes. (1) The first individual had a deletion known to cause 22q11 deletion syndrome, also known as DiGeorge syndrome [23]. The deletion larger than 2 Mbp spanned the gene *TBX1*, which has previously been implicated in COVID-19 severity, but evidence for its action in COVID-19 pathogenesis is limited [24,25]. (2) The second individual had a deletion matching the 16p11.2 recurrent deletion syndrome [26] and spanned the gene *CORO1A*, which has also been implicated in COVID-19 severity [27,28]. The third deletion spanned the entire *XCR1* gene, which has been suggested to be one of the candidate genes to underlie the strong GWAS signal(s) on chromosome 3p21 [29–31]. The deletion of *XCR1* was located in the 3p21 GWAS locus, very close (<0.5 Mb) to the lead SNP [22] (Figure 1). Additionally, in a fourth individual, we identified a deletion of the gene *CNPY4*, which also localized to

a previously known GWAS locus on 7q22.1. However, the gene *CNPY4* has not previously been implicated in COVID-19 [Supplementary Material].

3.2. Clinical Presentation (CNV Patients)

The clinical presentation of each patient with a CNV finding is summarized in (Table 2). Characteristics of patients without a potentially damaging CNV or SNV are summarized in (Table 3). There was no difference in the ICU length of stay (LOS) (median 10 days); however, the CNV patients required more supportive care compared to patients without a potentially damaging CNV. Time on a ventilator differed between the groups (median 3.2 days for the CNV patients vs. 1 day for the non-CNV group), and so did the 90-day survival rate (57% vs. 72%), although none of these results were statistically significant when adjusting for age and sex. The CNV group had worse renal function at ICU admission, measured as creatinine concentration (median 91 μmol/L [76–536] vs. 75 μmol/L [61–98], $p = 0.0026$) and had a significantly higher need for continuous renal replacement therapy (CRRT) (28% vs. 10%, $p = 0.045$). The CNV patients also displayed a significantly higher NT-proBNP (median 4440 ng/L [1558–8160] vs. 1170 ng/L [429–3155], $p = 0.017$) compared to patients without a potentially damaging CNV.

Table 2. CNV patient characteristics before, during, and after intensive care, including intensive care outcome. ACEi, angiotensin-converting enzyme inhibitor; BMI, body mass index; CNV, copy number variation; eGFR, estimated glomerular filtration rate; LOS, length of stay; BNP/NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PFI, fraction of inspired oxygen ratio (PaO₂/FiO₂); SAPS, simplified acute physiology score.

CNV Variant	Baseline Data	ICU	Labs	Complications
3p21.31 (XCR1)	70 years old. BMI 28 Previous malignant disease. eGFR 90	COVID-day 13. LOS 10 d. SAPS 69 4 d ventilator and 1d vasoactive treatment.	PFI min 9.5 kPa. CRP max 200, pct max 4.4. TropI max 76, BNP max 2050.	Secondary infection. (<i>C. albicans</i>) 90-day survivor.
16p11.2 (ALDOA, CORO1A, KIF22, TBX6)	50 years old. BMI 66. Asthma, smoker. eGFR 90	COVID-day 12, LOS 4 d. SAPS 34 No ventilator och vasoactive treatment.	PFI min 20 kPa. CRP max 121, pct 0.1. TropI max 4.8, BNP max 650.	None 90-day survivor
22q11.21 (LZTR1, SCARF2, SNAP29, SLC25A1, TANGO2, TBX1)	25 years old. BMI 28. Psychiatric disease, smoker. eGFR 90.	Los 11 d. SAPS 50 7 d ventilator and 7 d vasoactive treatment.	PFI min 7 kPa CRP max 263, pct 0.71. TropI max 147, BNP max 927	None 90-day survivor
1p36.21 (CELA2A)	65 years old. BMI 33. Hypertension, diabetes, CKD, former smoker. eGFR 18.	COVID-day 6, Los 15 d. SAPS 66 11 d ventilator and vasoactive treatment. 10 days CRRT.	PFI min 13 kPa. CRP max 198, pct max 1.9, ferritin 1551. TropI max 501 BNP max 10800. D-dimer 38.	Died day 13. Tromboembolic event. Critical illness and secondary infection (<i>S. aureus</i>)
5p15.31 (NSUN2)	80 years old. BMI 26. Hypertension, diabetes, peripheral vessel disease, smoker. Anticoagulant and steroid treatment. eGFR 54.	COVID-day 11. Los 8 d. No ventilator, vasoactive tratment or dialysis.	PFI min 8 kPa. CRP max 97, pct max 1. TropI max 15, BNP max 1540.	Died day 8 due to hypoxia. GI-bleeding, secondary infection and sepsis. (<i>S. epidermidis</i>).

Table 2. Cont.

CNV Variant	Baseline Data	ICU	Labs	Complications
6q23.2 (ARG1, ENPP1, MED 23)	70 years old. BMI 40. Hypertension, diabetes, former smoker. Anticoagulant treatment. eGFR 71.	Los 2 d, mainly due to heart failure. No ventilator or vasoactive treatment.	PFI min 15 kPa. CRP max 61. TropI max 48, BNP max 7140.	Lower urine tract infection. (<i>Citro bacteria</i>) 90-day survivor
14q31.3 (GALC)	75 years old. BMI 33. Hypertension, ischemic heart disease. Former smoker. ACEi and anticoagulant treatment. eGFR 74.	COVID-day 7. Los 17 d. SAPS 63. 15 d ventilator and 17 d vasoactive treatment.	PFI min 11 kPa. CRP max 367, pct max 4.3. TropI max 73, BNP max 617.	Died day 17. AKI and secondary infection. (<i>C. albicans</i>)
14q31.3 (GALC)	80 years old. BMI 27 Asthma, hypertension, smoker. ACEi treatment. eGFR 59.	Los 9 d. SAPS 69. 8 d ventilator and 5 days vasoactive treatment.	PFI min 9 kPa. CRP max 286, pct max 3.4. TropI max 242, BNP max 5500.	Died day 9. AKI and secondary infection. (<i>E. coli</i>).
14q31.3 (GALC)	75 years old male. BMI 27. Hypertension, malignant disease, former smoker. Anticoagulant treatment. eGFR 73.	COVID day 7. Los 7 d. SAPS 60 CRRT 4 d. No ventilator or vasoactive treatment.	PFI min 15 kPa. CRP max 289, pct max 16. GFR min 6. TropI max 133, BNP max 53000	AKI. 90-day survivor
16p13.3 (GFER)	80 years old. BMI 23. Chronic hematologic disease. eGFR 56.	COVID-day 11. Los 6 d. SAPS 66 No ventilator or vasoactive treatment.	PFI min 11 kPa. CRP max 280, pct max 0.7 TropI max 27, BNP max 3360.	None 90-day survivor
16p13.3 (ALG1)	80 years old. BMI 28. Hypertension. Smoker. ACEi and Anticoagulant treatment. eGFR 60.	COVID day 6. Los 3 d. No ventilator or vasoactive treatment.	PFI min 15 kPa. CRP max 352, pct max 25. BNP max 6090.	Died day 3.
21q22.3 (CRYAA)	70 years old. BMI 25. Asthma, hypertension, diabetes, CDK. Former smoker. ACEi, anticoagulant and steroid treatment. eGFR 12.	COVID-day 7. Los 10 d. No ventilator or vasoactive treatment. 4 d CRRT.	PFI min 14 kPa. CRP max 194. pct max 42. TropI max 1620, BNP max 25900.	AKI. 90-day survivor
21q22.3 (TRAPPC10)	65 years old. BMI 26. eGFR 90	COVID day 17. Los 6 d. SAPS 66 1 d ventilator, 3 days vasoactive treatment.	PFI min 12 kPa. CRP max 286, pct max 7.4. TropI max 112, BNP max 8500	Lower urine tract infection. (<i>S. agalactiae</i>) 90-day survivor
21q22.3 (TRAPPC10)	85 years old. BMI 31. Hypertension. ACEi treatment. eGFR 57.	COVID day 9. Los 4 d. SAPS 55 No ventilator or vasoactive treatment.	PFI min 11 kPa. CRP max 276, pct max 8.9 TropI max 176, BNP max 1610	Died day 4.

Table 3. Patient characteristics for those without rare, potentially damaging copy number variants (CNVs) or single-nucleotide variants (SNVs). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; LOS, length of stay; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Patient Characteristics	<i>n</i> = 172 ¹
Age (years)	64 (55, 74)
Sex	
Female	41 (24%)
Male	131 (76%)
BMI	29 (26, 33)
Smoker (current)	7 (4.1%)
Former smoker	45 (27%)
Never smoked	117 (69%)
Pre-existing co-morbidities	
Lung disease (COPD or asthma)	44 (26%)
Diabetes	54 (31%)
Ischemic heart disease	22 (13%)
Hypertension	107 (62%)
Heart failure	14 (8.1%)
Previous thromboembolic disease	25 (15%)
ACEi or ARB treatment	75 (44%)
Anticoagulant treatment	53 (31%)
ICU parameters	
COVID day at arrival	10.0 (8.0, 12.0)
Length of stay (LOS) in days	9 (5, 16)
Days with vasoactive treatment	1 (0, 6)
Days with ventilator	1 (0, 10)
Dialysis (CRRT)	20 (12%)
90-day survival	123 (72%)
CRP max	234 (156, 334)
Procalcitonin max	0.9 (0.3, 3.9)
Troponin I max	24 (9, 90)
NT-proBNP max	1170 (429, 3155)
eGFR Krea min	61 (37, 80)

¹ Median (Q1, Q3); *n* (%).

3.3. SNV Analysis

We also performed an analysis focused on rare coding sequence variants (SNVs and small indels) [Methods]—focusing on those with known clinical relevance. Unlike CNVs, the contribution of SNVs to disease is better understood and supported by larger reference datasets. We chose to concentrate on the >2.4 million variants that consistently have been labeled as either pathogenic (P) or likely pathogenic (LP) in the National Institutes of Health's (NIH) curated variant database ClinVar [19].

3.4. No Enrichment of Pathogenic Variants in Severe COVID-19

Confining our analysis to rare, non-conflicting ClinVar P/LP variants (i.e., clinically actionable variants), we identified 404 alleles (353 unique variants) affecting 296 separate genes in 301 ICU-treated patients—an average of 1.34 previously known clinically actionable variants per person. However, this number did not differ from our population-based [32] control group (SweGen), where an average of 1.37 variants/person was observed ($p = 0.80$) [Supplementary Material]. Similarly, 8.4% of these variants affected COVID-

19-related genes vs. 9.1% in controls ($p = 0.69$). Naturally, many of these variants reside in genes known to cause recessive disease and might therefore be of less interest. When instead focusing on predicted loss-of-function (pLoF) variants in genes likely to be haploinsufficient (LOEUF < 0.35), we noted a non-significant enrichment in the severe COVID-19 cohort (OR = 2.21 [0.18–19.4], $p = 0.33$). Although the overall proportion of clinically actionable variants did not differ, gene-specific effects could exist since a large proportion of the pathogenic variants (~35%) in our COVID-19 cohort resided in genes not disrupted in the population controls [Supplementary Material].

3.5. SNV Findings

We identified 28 variants (13 missense, 3 indels, and 12 pLoF) likely to cause a dominant clinical condition, including porphyria, polycystic kidney disease, metabolic disorders, and coagulation defects [Supplementary Material]. In an extended analysis, we also explored genetic variations not previously classified as disease-causing in ClinVar, but where loss-of-function had been described to cause a dominant disorder (i.e., haploinsufficiency), implicated in COVID-19 pathogenesis [Section 2]. Applying these criteria, we identified 12 additional pLoF variants in 12 different genes, where only *SRP54* (signal recognition particle 54), known to be a cause of neutropenia with dominant inheritance [33], had been described in COVID-19 severity [34] [Supplementary Material].

4. Discussion

Here, in a cohort of severely ill, ICU-treated COVID-19 patients, we have explored the prevalence of disrupting copy number variants (CNVs) and single-nucleotide variants (SNVs) potentially affecting COVID-19 severity. Our goal was to identify clinically significant genetic variants influencing disease severity through the combined analysis of whole-exome sequencing data and detailed clinical phenotypes. We focused on rare genetic variants disrupting genes implicated in COVID-19 pathogenesis or known to cause human diseases using three filtering strategies: OMIM haploinsufficient genes, PanelApp (Genomics England), and candidate genes from large COVID-19 GWAS studies. This approach allowed us to provide a comprehensive exploration of the genetic landscape and integrate well-established genetic knowledge while also considering emerging research to enhance the robustness of our findings.

During the first and second waves of COVID-19, approximately 11% of all hospitalized Swedish patients required ICU care [35]. Despite finding no enrichment of pathogenic variants in ICU-treated patients, a significant proportion of the ICU cohort (17%) carried at least one genetic variant of potential relevance. We also identified several individuals with variants (both CNVs and SNVs) likely to cause clinical disease. Our results showed that patients with a potentially damaging CNV had a significantly worse renal function at ICU admission and a greater need for continuous renal replacement therapy during their ICU stay. They also had a significantly higher NT-proBNP than patients without a damaging CNV, indicating an increased cardiac load. Although an elevated NT-proBNP is foremost a marker of heart failure, it is also often elevated in chronic kidney disease (CKD) [36–38]. Hence, it is not unexpected that both impaired renal function and signs of increased cardiac load co-exist. Severe COVID-19 has been associated with both acute kidney injury and progression of chronic kidney disease [39]. Moreover, elevated NT-proBNP levels are thought to indicate higher risks in CKD patients than in non-CKD patients [40]. Two out of the four CNV patients who needed CRRT had gene deletions with plausible biological relevance. One individual had a deletion in the gene *CRYAA*, which is almost exclusively expressed in the eye and kidney, but only known to cause a dominant form of cataract in humans. The second individual had a deletion of the

gene *CELA2A*, where heterozygous deleterious variants are associated with early-onset metabolic syndrome and atherosclerosis [41]. This patient had chronic kidney failure before ICU admission, and his metabolic profile (including hypertension, diabetes, and obesity in addition to CKD) conforms to the genetic finding.

Although we cannot demonstrate causality, the clinical presentation varied widely, and we observed that a subset of the CNV patients developed a more severe disease course. First, the deletion of *XCR1* was found within the strongest GWAS locus found to date (3p21), associated with both susceptibility, severity, and hospitalizations in COVID-19 cases [3,29,30,42]. This GWAS locus involves multiple immune-related genes, but the underlying effector gene has not yet been established. *XCR1*, encoding a chemokine receptor expressed by dendritic cells [43], has been suggested as a candidate gene to underlie the strong GWAS signal [29,30]. The patient carrying the *XCR1* deletion spent 10 days at the ICU with the need for both invasive mechanical ventilation and vasoactive treatment. This patient also had elevated troponin I and NT-proBNP (Table 2), indicating cardiac injury, which has been associated with a lower survival rate [44].

Another notable finding was in the patient carrying a deletion in *CELA2A*, a gene associated with metabolic syndrome [41], which is a known risk factor for severe COVID-19. The affected patient was obese (BMI 33) and had hypertension, chronic kidney disease, and diabetes—all components of the metabolic syndrome. This patient stayed 15 days in intensive care and 11 days on a ventilator.

Similarly, the deletion in the *CNPY4* gene on chromosome 7, also within a GWAS locus, could be relevant as it regulates immune function, and hyperinflammation is one of the cardinal symptoms of severe COVID-19 [45]. Variants in genes regulating any of these steps are therefore highly interesting when exploring COVID-19 severity. The CNV analysis also identified two patients with two separate known syndromes, the 22q11 deletion syndrome and the 16p11.2 recurrent deletion syndrome. These syndromes can affect an individual's general health and could, as such, increase the risk of severe COVID-19. Interestingly, both these deletion syndromes are associated with immunodeficiency [23,28] and include genes previously implicated in COVID-19 severity (*TBX1* [24] on chromosome 22q11 and *CORO1A* [46] on chromosome 16p11.2). The young, less than 30-year-old, individual who carried the 22q11 deletion had no other risk factors for severe COVID-19, suggesting that the deletion syndrome may have increased his vulnerability. He stayed 11 days in the ICU, including 7 days on a ventilator with vasoactive treatment. This considerably longer need for invasive supportive care compared to patients without a CNV is notable, given his young age.

In contrast, the patient with a 16p11.2 deletion (associated with immunodeficiency 8) had an extreme BMI of 66, which likely contributed to the ICU admission. Interestingly, the deletion breakpoint was just 0.7 Mb from the gene *SH2B1*, known to cause monogenic childhood-onset obesity [47,48], and sometimes spanned by the recurrent deletions at this chromosomal location (16p11.2) [49]. Although deletions can be identified using WES data, the exact deletion breakpoints are less accurately called compared to whole genome sequencing (WGS), which is why a genetic cause of her high BMI cannot be excluded.

The CNV- and SNV-related conditions were, however, mostly isolated to individual cases and spread over a wide range of genes with different functions. This indicates that rare genetic variants may not directly contribute to COVID-19 severity, but instead, as with high age, male sex, pre-existing medical conditions, and socioeconomic factors [50–53], affect an individual's overall frailty. Frailty, a term constructed to capture a person's general health and well-being, is often impacted in rare diseases and genetic syndromes [54], but it is also a known and important risk factor for ICU-treated patients [55].

5. Conclusions

In our cohort with ICU-treated COVID-19 patients, we identified both CNVs and SNVs likely to cause clinical conditions, suggesting that rare genetic variants may contribute to COVID-19 disease severity in specific cases. However, the overall heterogeneity of our findings, with individually isolated and varying genetic conditions, does not support a direct impact on COVID-19 pathogenesis but possibly an increased overall frailty, making their clinical utility low.

6. Limitations

This study has several limitations that should be considered when interpreting the findings. First, the overall sample size was moderate, which may limit the statistical power to detect smaller effects and reduce the generalizability of the results. In addition, only a small proportion of patients were identified as having a clinically significant CNV ($n = 14$), which further restricts the robustness of the analysis. The absence of a suitable comparison group, such as patients with a mild COVID-19 disease course, limits our ability to directly assess whether the observed genetic findings are specific to the severe disease or represent broader background variation. Further, our analysis was limited to CNVs detectable by WES, i.e., spanning exonic regions. Patients classified as ‘not having a CNV’ could therefore have carried structural variants relevant for disease affecting regulatory and/or other non-coding regions.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/covid6010010/s1>, Figures S1 and S2: Quality control and variant prioritization; Databases for filtering; Figure S3: COVID-19 condensed list; Table S1: Pathogenic variants in patients and controls; CNVs implicated in COVID-19; Table S2: Chromosomal location of CNVs; No enrichment of pathogenic variants in severe COVID-19; SNV findings; Figure S4 and Table S3: Several individuals had genetic variants known to cause a clinical condition; Table S4: Exploratory SNV analysis; Table S5: SNV patient characteristics; Ethical permits; Supplementary references.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study, or their next of kin, if the patient was unable to give consent.

Data Availability Statement: The data presented in this study may be made available upon reasonable request from the corresponding author, due to privacy and/or ethical restrictions.

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Abbreviations

The following abbreviations are used in this manuscript:

ACMG	American College of Medical Genetics and Genomics
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CNV	Copy Number Variant
CRRT	Continuous renal replacement therapy
COVID-19	Coronavirus disease 2019
ExAC	Exome Aggregation Consortium
FTP	File Transfer Protocol
GATK	Genome Analysis Toolkit
gnomAD	The Genome Aggregation Database
GWAS	Genome-wide association study
HGI	COVID-19 Host Genetics Initiative
ICU	Intensive care unit
Indel	Insertion/deletion
IFN	Interferon
LOEUF	Loss-of-function observed/expected upper bound fraction
LOS	Length of stay
MB/Mb	Megabase
NCBI	National Center for Biotechnology Information
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OMIM	Online Mendelian Inheritance in Man
<i>p</i>	<i>p</i> -value
PFI	fraction of inspired oxygen ratio (PaO ₂ /FiO ₂)
pLoF	Predicted loss-of-function
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SNV	Single-nucleotide variant
SV	Structural variant
VEP	Variant Effect Predictor
WES	Whole exome sequencing
WGAS	Whole genome sequencing

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