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RESEARCH ARTICLE

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Genetic characteristics involved in COVID-19 severity. The CARGENCORS case-control study and meta-analysis

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Abstract

Pre-existing coronary artery disease (CAD), and thrombotic, inflammatory, or virus infectivity response phenomena have been associated with COVID-19 disease severity. However, the association of candidate single nucleotide variants (SNVs) related to mechanisms of COVID-19 complications has been seldom analysed. Our aim was to test and validate the effect of candidate SNVs on COVID-19 severity. CARGENCORS (*CARdiovascular GENetic risk score for Risk Stratification of patients positive for SARS-CoV-2 [COVID-19] virus*) is an age- and sex-matched case-control study with 818 COVID-19 cases hospitalized with hypoxemia, and 1636 controls with COVID-19 treated at home. The association between severity and SNVs related to CAD ($n = 32$), inflammation ($n = 19$), thrombosis ($n = 14$), virus infectivity ($n = 11$), and two published to be related to COVID-19 severity was tested with adjusted logistic regression models. Two external independent cohorts were used for meta-analysis (SCOURGE and UK Biobank). After adjustment for potential confounders, 14 new SNVs were associated with COVID-19 severity in the CARGENCORS Study. These SNVs were related to CAD ($n = 10$), thrombosis ($n = 2$), and inflammation ($n = 2$). We also confirmed eight SNVs previously related to severe COVID-19 and virus infectivity. The meta-analysis showed five SNVs associated with severe COVID-19 in adjusted analyses (rs11385942, rs1561198, rs6632704, rs6629110, and rs12329760). We identified 14 novel SNVs and confirmed eight previously related to COVID-19 severity in the CARGENCORS data. In the meta-analysis, five SNVs were significantly associated to COVID-19 severity, one of them previously related to CAD.

KEYWORDS
COVID-19, genetics, SARS-CoV-2, severity, single nucleotide variants, SNVs

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) reached pandemic level in March 2020. As of July 2023, more than 768 million people have been infected, and almost seven million have died from COVID-19 worldwide.[1] Vaccination has decreased hospitalizations and mortality.[2] However, severe and fatal cases still exist due to unvaccinated population, more infective SARS-CoV-2 variants, and individual susceptibility and comorbidity.[3–6]

The SARS-CoV-2 enters host cells by binding to transmembrane angiotensin-converting enzyme 2 (ACE2). The virus initially infects epithelial cells in the nasopharynx before spreading to the alveolar space.[7,8] In some cases, a hyperactive immune response and sustained inflammation can cause severe pneumonia and multiorgan dysfunction. Additionally, the virus can contribute to the destabilization of atherosclerotic plaques and lead to acute coronary syndromes due to its potential for blood clot formation and hyperinflammation.[9–13]

Clinical presentation of COVID-19 ranges from asymptomatic (40%) to fatal (1.5%).[1,14] Patients with pre-existing cardiovascular (CV) risk factors (e.g., older age, male sex, hypertension, obesity, diabetes, chronic kidney disease) or with overt CV disease are at higher risk of severe COVID-19 presentation.[9,15–18] Although clinical risk factors have been identified for COVID-19, they do not fully account for the broad spectrum of clinical presentations of the disease.

Multiple genome-wide association studies (GWAS) have identified a gene cluster at locus 3p21.31 as having the strongest association with severe COVID-19. This gene cluster comprises six genes, some of which are known to be associated with transporters that interact with ACE2 receptor, and they are primarily expressed in lung cells.[19–21] Moreover, the *ACE2* gene has demonstrated a strong association with both susceptibility and severity of COVID-19.[22,23] However, the underlying mechanisms for COVID-19 complications are not fully understood.[9,13,19] Some studies suggest that an atypical type I interferon response and elevated expression of inflammatory genes play a significant role in severe COVID-19 development.[19,24,25]

While some single nucleotide variants (SNVs) have been associated with COVID-19 severity,[19–21,23] the association of candidate SNVs related to mechanisms of COVID-19 complications has been seldom analysed.[19,21] We hypothesized that SNVs in genes related to coronary artery disease (CAD), virus infectivity (ACE2 receptor genes and genes regulating cell cycle or apoptosis), inflammatory response to microbial agents, and thrombosis or related pathways are associated to COVID-19 severity.

The objectives of the present study were to test the association of candidate SNVs on COVID-19 severity in the CARGENCORS Study, and to validate our results in external cohorts.

2 | METHODS

2.1 | Study design and participants

An age- and sex-matched case-control study with a 1:2 recruitment ratio was carried out in Catalonia, north-eastern Spain, as part of the CARGENCORS [*CARdiovascular GENetic risk score for Risk Stratification of patients positive for SARS-CoV-2 (COvid-19) virus*] study. We recruited 3314 patients aged 35–85 years. Participants had tested positive for SARS-CoV-2 (reverse-transcription polymerase chain reaction, rapid antigen, or immunoglobulin G test results) between February 2020 and June 2021. Cases were consecutively hospitalized patients receiving oxygen treatment due to respiratory frequency ≥30 times/min, blood oxygen saturation ≤93%, PaO_2/FiO_2 ratio or P/F(1) <300 mmHg, infiltrates in >50% of pulmonary fields within 24–48 h of symptom onset, severe pneumonia diagnosis, required mechanical ventilation, or died at hospital admission. Controls were patients with mild or no symptoms, treated at home, and not requiring oxygen therapy. DNA was early collected after admission in all patients but very specially from critically ill ones. Participants were excluded if no clinical data were available in the electronic medical record of the Catalan health system (universal coverage) or if they were vaccinated against COVID-19 before the diagnosis.

2.2 | Data collection and management

Blood samples were obtained from cases as soon as possible during hospitalization. Controls were directed to an outpatient clinic, where trained nurses performed the examinations and collected blood or saliva samples to extract DNA.

Data on age, sex, height, weight, and blood pressure were collected during admission (cases) or at the outpatient clinic (controls). Clinical data before the COVID-19 infection were collected from electronic medical records including the most recent glycemia, cholesterol, and triglycerides values, glomerular filtration rate, and history of smoking, arterial hypertension, dyslipidemia, diabetes, CAD, stroke, thromboembolism, and chronic obstructive pulmonary disease (COPD). Ten-year CAD risk was estimated using the REGICOR risk function.[26]

2.3 | Single Nucleotide Variants

SNVs from candidate genes were selected from previous publications of GWAS studies for their association with: CAD[27–29] (n = 33), thrombosis[30,31] (n = 15), inflammation[32,33] (n = 21), virus infectivity[34] (n = 15), and COVID-19 severity[20] (n = 2). Details about all SNVs considered in the study, and their mapped genes are provided in Table S1.

2.4 | Genomic DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood collected in 4-mL ethylenediaminetetraacetic acid Anti-Coagulant BD Vacutainer tubes or from saliva collected in DANASALIVA Sample Collection kit (DANAGEN). DNA extraction was performed using either a Chemagic™ DNA Blood 7k Kit H12 (PerkinElmer) on a Chemagic MSM I instrument or a FlexiGene DNA Kit (Qiagen).

DNA samples were genotyped by TaqMan Open Array Technology. Fluorescence data was collected on a Fluidigm EP1 Reader, and data were analysed using Fluidigm SNV Genotyping Analysis Software to obtain genotype calls. Hardy–Weinberg equilibrium was tested for all SNVs among control participants. We provide more details on DNA extraction, genotyping, and quality-control procedures in the Supporting Information Methods section of the Supporting Information Material.

2.5 | Sample size

Accepting an alpha risk of 0.05% and 80% statistical power in a two-sided test, we estimated that 809 COVID-19 severe cases and 1618 COVID-19 nonsevere controls were needed to recognize as statistically significant an odds ratio (OR) >1.3, assuming that 30% of controls were risk allele carriers.

2.6 | Statistical analyses

Patient characteristics were reported as frequencies for categorical variables, and as means and standard deviation or median and quartiles for continuous normally and nonnormally distributed variables, respectively. Means and medians were compared between cases and controls by Student t-test or Mann–Whitney tests, respectively, and frequencies by Chi-square test. Crude association of each SNV and case/control status was examined with an additive inheritance model with the Cochran–Armitage test. The resulting p-values were corrected for multiple comparisons with the Benjamini–Hochberg (BH) method. Crude associations were further adjusted for diabetes, blood pressure, lipid profile, body mass index, and smoking using a multivariate logistic regression model.

SNVs located on the X chromosome were examined separately by sex to prove the consistency of the results. Moreover, sensitivity analyses with all participants before pairing by sex and age were performed.

Considering the limited statistical power in CARGENCORS case-control study we selected for meta-analysis candidate SNVs with BH corrected $p < 0.2$ to ensure we were not missing any important relationship. Statistical significance in the meta-analysis was defined as BH corrected $p < 0.05$. All statistical analyses were performed with R software version 4.2.1, the SNPassoc (v2.1-0), and the meta (v6.2-1) R packages.[35]

2.7 | Meta-analysis using SCOURGE and UK biobank cohorts

To validate our findings, a meta-analysis of COVID-19 severity was conducted using data from the CARGENCORS study, along with data from two additional European cohorts: SCOURGE and UK Biobank. The SCOURGE (Spanish Coalition to Unlock Research on Host Genetics on COVID-19) consortium recruited over 11000 COVID-19 patients from 34 medical centres across Spain during 2020. This study aimed to identify prognostic and evolutionary biomarkers of significant impact on clinical and therapeutic COVID-19 management. We used 9184 COVID-19 patients from SCOURGE of the same age range as in CARGENCORS.[21] Similarly, in the UK Biobank, a population-based cohort consisting of over 500 000 participants recruited between 2006 and 2010, we identified 8478 SARS-CoV-2 positive participants, who

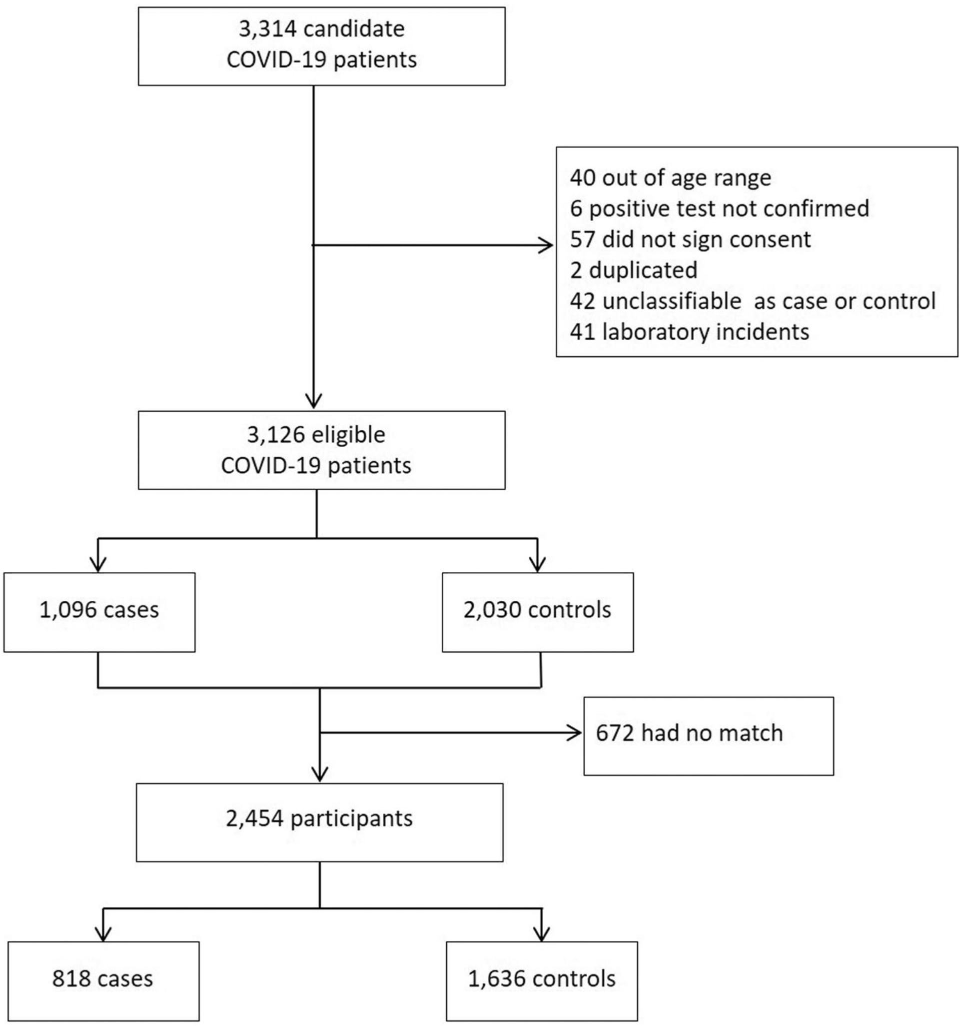

FIGURE 1 Assessment of eligibility.

were aged 50–85 years during 2020.[36] Cases (hospitalized) and controls (nonhospitalized) COVID-19 patients were similarly defined in SCOURGE, UK Biobank, and CARGENCORS studies, ensuring comparability. We meta-analysed the effect of all the SNVs selected in CARGENCORS, in the three cohorts using fixed- and random-effect models, as appropriate, based on heterogeneity *I*-squared index.

2.8 | Ethical aspects

All participants were duly informed and provided their consent to participate in the CARGENCORS study, which was approved by the Ethics Committees of *Parc de Salut Mar* (#2020/9297/I), *Doctor Josep Trueta* University Hospital of Girona (#2020/058), Foundation University Institute for Primary Health Care Research *Jordi Gol i Gurina* (IDIAPJGol) (#2021/084-PCV), and *Fundació d'Osona per a la Recerca i l'Educació Sanitàries* (FORES) (#2020152/PR283). The study followed all international regulations for biomedical research. This research was also conducted using the SCOURGE and UK Biobank resources. The SCOURGE project was approved by the Galician Ethical Committee (#2020/197); and the UK Biobank Study received approval from the National Information Governance Board for Health and Social Care and the National Health Service North West Multicentre Research Ethics Committee.

3 | RESULTS

3.1 | Participants

We recruited 3314 candidate COVID-19 patients in the CARGENCORS study. After excluding those who did not meet inclusion criteria (n = 188), 818 (90 fatal) and 1636 age- and sex-matched cases and controls, were retained in the analysis, respectively (Figure 1). Table S2 shows the risk factors and clinical characteristics in matched and nonmatched patients.

TABLE 1 Demographic profile, anthropometry and cardiovascular risk prevalence in matched patients with severe (cases) and nonsevere (controls) COVID-19.

	Severe COVID-19 *N* = 818	Non-severe COVID-19 *N* = 1636	*p*-value
Age, years*	60.6 (12.2)	59.7 (11.9)	0.091
<60 years	47.4%	47.1%	0.920
Sex, male	50.1%	50.1%	1.000
Current smoker	3.75%	10.4%	<0.001
Diabetes mellitus	22.4%	10.5%	<0.001
Hypertension	45.5%	31.5%	<0.001
Systolic blood pressure, mmHg*	132 (18)	130 (16)	0.001
Diastolic blood pressure, mmHg*	76 (12)	78 (11)	0.009
Glycemia, mg/dL (median [IQR])	100 [90; 117]	93 [86; 103]	<0.001
Total cholesterol, mg/dL*	200 (47)	200 (40)	0.971
HDL cholesterol, mg/dL*	51 (15)	57 (16)	<0.001
LDL cholesterol, mg/dL*	124 (40)	122 (34)	0.117
Triglycerides, mg/dL (median [IQR])	133 [99; 184]	103 [75; 142]	<0.001
Glomerular filtration rate, mL/min/1.73 m^2*	93.6 (31.0)	92.5 (22.8)	0.370
Body mass index, kg/m^2*	29.8 (5.69)	27.4 (4.77)	<0.001
Coronary artery disease risk, %*	4.24 (3.23)	3.49 (2.56)	<0.001
History of coronary artery disease	5.39%	4.35%	0.295
History of stroke	3.82%	2.02%	0.013
History of thrombosis	4.17%	1.71%	<0.001
History of neoplasia	11.9%	8.56%	0.011
History of immune disease	8.56%	8.80%	0.899
History of COPD	4.04%	1.35%	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; IQR, inter-quartile range; LDL, low-density lipoprotein.
*Mean (standard deviation).

Demographic, anthropometric, and clinical characteristics of cases and controls are shown in Table 1. Cases had significantly higher prevalence of diabetes and hypertension, and more often had previous stroke, thrombosis, neoplasia, and COPD history. Levels of systolic blood pressure, glycemia, triglycerides, body mass index, and CAD risk were also higher in cases. Although both cases and controls had a low smoking prevalence, cases had a significantly lower proportion of smokers than controls. Cases also had lower diastolic blood pressure and high-density lipoprotein cholesterol levels.

3.2 | SNVs associated with COVID-19 severity in the CARGENCORS study

From the 86 initially selected SNVs, eight were discarded (9.3%): six had more than 5% of missing data, and two showed a disrupted Hardy-Weinberg equilibrium ($p < 0.001$).

Of the 78 SNVs finally analysed, 14 novel SNVs were associated with severe COVID-19 in the adjusted models: rs12190287, rs1746048, rs2246833, rs17465637, rs10507391, rs4252120, rs974819, rs9982601, rs1561198, and rs2047009 related to CAD; rs1801020 and rs13109457, associated to thrombotic events or pathways; rs4961252 and rs75885714 involved in inflammation. We also confirmed previously published associations between rs11385942, rs1561198, rs6632704, rs6629110, rs12329760, and severe COVID-19 (Table 2). SNVs located on the X chromosome exhibited comparable results in males and females (Table S3). Furthermore, sensitivity analyses with all participants showed similar results compared to the matched cohort (Table S4).

3.3 | Meta-analysis

To validate our findings, we used individual data from the SCOURGE and the UK Biobank. A description of the SCOURGE cohort has been published previously,[21] and that of the selected UK Biobank participants is presented in Table S5.

We conducted a meta-analysis of all the significant SNVs of the CARGENCORS study. Among these SNVs, we identified five that showed consistent effects on COVID-19 severity across all three cohorts, considering all participants (rs11385942, rs1561198, rs6632704, rs6629110, and rs12329760) (Figure 2). These SNVs have been previously related to COVID-19 severity and CAD, respectively.

4 | DISCUSSION

In the CARGENCORS cohort, 14 SNVs correlated with CAD, thrombosis, and inflammation were significantly associated with COVID-19 severity for the first time. We also validated eight other SNVs already published. The meta-analysis confirmed that five SNVs were associated with COVID-19 severity in the three cohorts, one of these had not been previously reported and has been related with CAD. Individuals who carried a single risk allele of the most significantly associated SNVs exhibited a notable 1.61-fold increased odds of developing severe COVID-19. These results highlight the importance of genetic variation, in influencing the severity of COVID-19.

The most significant COVID-19 severity-associated SNVs identified in the CARGENCORS case-control are located in a group of genes associated with atherosclerosis, hemostasis, and involved in immune and inflammation responses: rs13109457 annotates the *FGA*, and *FGG* genes, which encode the alpha and gamma subunits, respectively, of fibrinogen, which is a primary factor in coagulation and also involved in antimicrobial host defense.[37] rs1801020 is present in the *F12* gene and is accountable for the considerable diversity observed in Factor XII levels, a crucial coagulation factor; moreover, it serves as a reliable predictor for the risk of venous thromboembolism.[30,38] rs12190287 is found in the *TCF21* gene implicated in epithelial differentiation during lung morphogenesis and regulates epicardial cell and coronary vasculature differentiation.[39] rs17465637 is presented in the *MIA3* gene, which plays a role in collagen secretion, vascular smooth muscle cell proliferation, fibrous cap thickness, and plaque stability.[40] Finally, rs11385942 variant is located within the 3p21.31 locus, which contains a cluster of genes that exhibit the most significant association with COVID-19 severity.[20,41,42] Among these genes, some are related to transporters that interact with the ACE2 receptor.[41,42] In the meta-analysis, the association between rs11385942, rs1561198, rs6632704, rs6629110, rs12329760, and COVID-19 severity was confirmed, and that of rs1561198 emerged as significant. This SNV is located in the genomic region between the *VAMP5* and *VAMP8* genes. These genes are involved in multiple processes related to vesicle trafficking, including cytokine release and phagocytosis.[43] Previous studies have linked this variant to the levels of interleukin 6[44] and its association with CAD incidence.[45,46] Our study confirms the robust correlation between CAD-related genetic variants and the severity of COVID-19. It is important to note that while some discrepancies were observed between the results obtained from our CARGENCORS analysis and the meta-analysis, both pointed to the same direction. In our first analysis, our focus was on selecting SNVs that reached significance according to the BH-method. Although there were variations in the significant SNVs, the direction of the effects was consistent between the two analyses. Variations in certain SNVs observed within the meta-analysis across populations may stem from multiple factors. These could arise from the distinct demographic backgrounds. Alternatively, dissimilarities in age distribution could contribute, given that participants in the UK Biobank cohort were notably older than those in the other two cohorts.

As for comorbidities of COVID-19 patients, cases had a worse CV risk factor profile, except for smoking, which had a low prevalence in all participants, particularly in severe cases. In a previous meta-analysis, COVID-19 patients had a lower prevalence of smoking than general population.[47] However, our study was not

TABLE 2 Single nucleotide variants (SNVs) and susceptibility loci associated with severe COVID-19, ordered by Benjamini–Hochberg-corrected p-value and limited to $p < 0.20$ in the adjusted models of matched participants within the whole CARGENCORS population.

								Nonadjusted		Adjusted for risk factors*	
SNV	Chr	Genes	Alleles	MAF	Risk allele	RAF	Reference phenotype	OR (95% CI)	BH p-value	OR (95% CI)	BH p-value
rs11385942	3	SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1	AA/AAA	0.08	AAA	0.08	Severe COVID-19	1.73 (1.42–2.12)	<0.001	1.73 (1.37–2.17)	<0.001
rs13109457	4	FGA, FGG	G/A	0.21	A	0.21	D-dimer levels	1.32 (1.14–1.52)	0.003	1.36 (1.15–1.60)	0.004
rs1801020	5	F12, GRK6	G/A	0.24	A	0.24	Plasma factor XII concentration	1.31 (1.15–1.49)	0.001	1.35 (1.16–1.57)	0.004
rs12190287	6	TCF21	C/G	0.37	G	0.37	Coronary artery disease	1.32 (1.17–1.49)	<0.001	1.31 (1.14–1.50)	0.004
rs17465637	1	MIA3	C/A	0.33	A	0.33	Coronary artery disease	1.24 (1.10–1.40)	0.005	1.31 (1.13–1.51)	0.004
rs4961252	8	PTK2, DENND3	A/G	0.42	G	0.42	Response to interferon beta	1.25 (1.11–1.41)	0.003	1.31 (1.13–1.50)	0.004
rs2246833	10	LIPA	C/T	0.33	T	0.33	Coronary artery disease	1.24 (1.10–1.41)	0.005	1.29 (1.12–1.50)	0.006
rs1746048	10	LINC02881, CXCL12	C/T	0.17	T	0.17	Coronary artery disease	1.33 (1.15–1.54)	0.003	1.36 (1.14–1.62)	0.006
rs5936011	X	ACE2	T/C	0.45	T	0.55	ACE2 expression	1.19 (1.09–1.32)	0.003	1.20 (1.08–1.35)	0.012
rs4830974	X	ACE2	A/G	0.46	A	0.54	ACE2 expression	1.19 (1.08–1.30)	0.005	1.19 (1.08–1.33)	0.013
rs6632704	X	ACE2	A/C	0.46	A	0.54	ACE2 expression	1.18 (1.06–1.30)	0.007	1.19 (1.06–1.33)	0.013
rs10507391	13	ALOX5AP	T/A	0.39	A	0.39	Coronary artery disease	1.16 (1.03–1.31)	0.081	1.25 (1.08–1.43)	0.015
rs6629110	X	ACE2	C/T	0.47	C	0.53	ACE2 expression	1.16 (1.05–1.28)	0.011	1.18 (1.04–1.32)	0.036
rs2158082	X	ACE2	A/G	0.44	A	0.56	ACE2 expression	1.18 (1.06–1.28)	0.008	1.16 (1.04–1.30)	0.044
rs4252120	6	PLG	T/C	0.27	T	0.74	Coronary artery disease	1.18 (1.03–1.35)	0.081	1.23 (1.05–1.43)	0.052
rs75885714	3	PLCL2	A/C	0.05	C	0.05	Interleukin measurement	1.46 (1.16–1.84)	0.081	1.38 (1.06–1.80)	0.079
rs974819	11	PDGFD	C/T	0.33	C	0.67	Coronary artery disease	1.16 (1.02–1.32)	0.091	1.19 (1.03–1.39)	0.095
rs12329760	21	TMPRSS2	C/T	0.19	C	0.82	TMPRSS2 measurement	1.12 (0.96–1.32)	0.296	1.22 (1.02–1.45)	0.113
rs9982601	21	SLC5A3, LINC00310, KCNE2	C/T	0.11	C	0.89	Coronary artery disease	1.22 (1.01–1.49)	0.139	1.28 (1.01–1.61)	0.142
rs4646127	X	ACE2	G/A	0.35	G	0.66	ACE2 expression	1.11 (1.00–1.23)	0.167	1.12 (1.00–1.27)	0.189
rs1561198	2	VAMP5, VAMP8, GGCX	C/T	0.49	C	0.51	Coronary artery disease	1.10 (0.98–1.23)	0.271	1.14 (1.00–1.32)	0.190
rs2047009	10	CXCL12	T/G	0.47	T	0.53	Coronary artery disease	1.11 (0.99–1.25)	0.176	1.15 (1.00–1.32)	0.190

Abbreviations: BH, Benjamini-Hochberg method; Chr, chromosome; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; RAF, risk allele frequency; SNV, single nucleotide variant.

*Diabetes, blood pressure, smoking, high-density lipoprotein-cholesterol, total cholesterol, and body mass index.

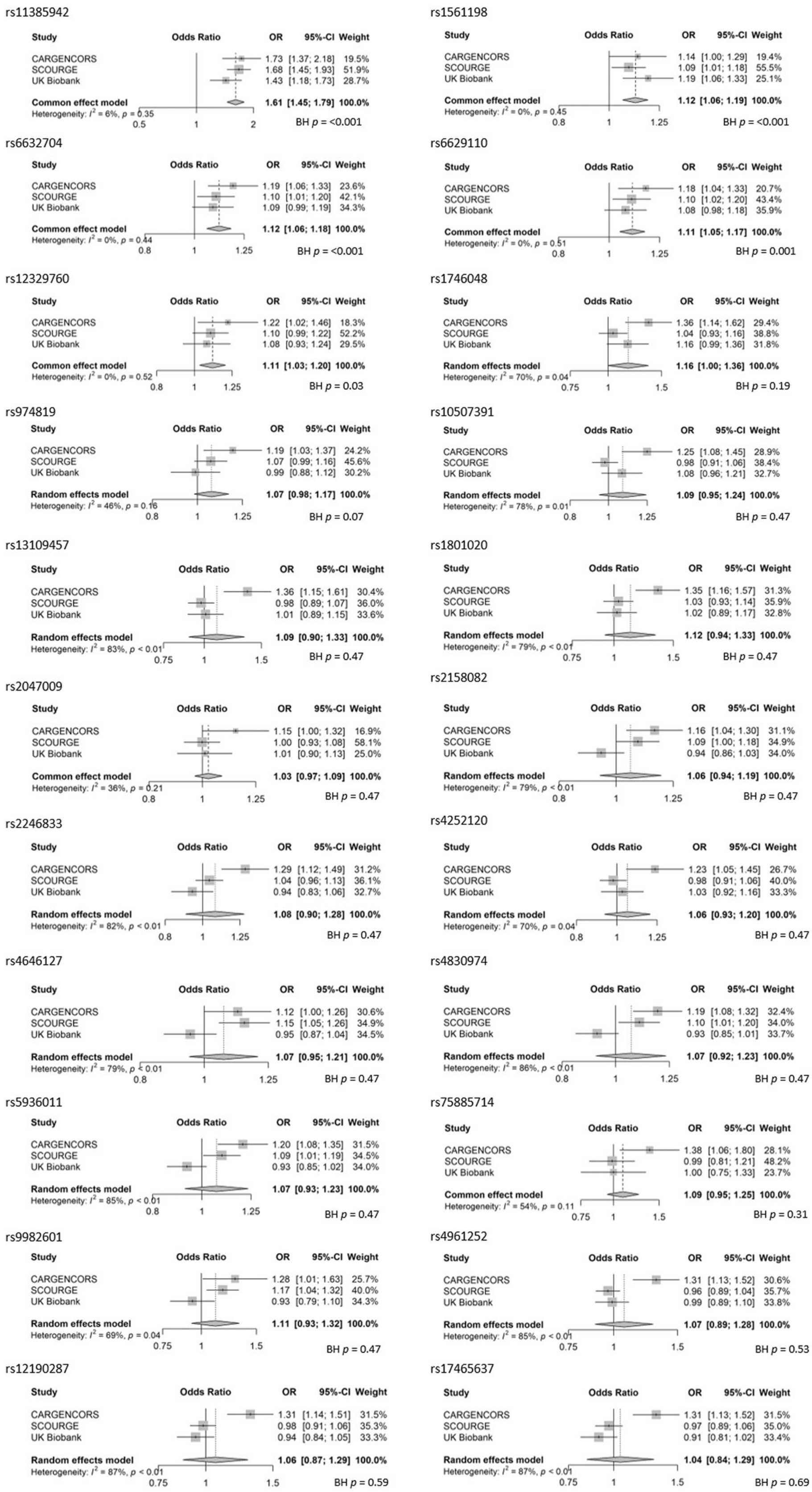

FIGURE 2 Odds ratio of the fixed (common) or random effect model in the meta-analysis of the CARGENCORS, SCOURGE and UK Biobank cohorts for the 22 selected single nucleotide variants associated with COVID-19 severity. BH *p*, Benjamini Hochberg *p*-value.

designed to explore the role of smoking in COVID-19 severity. Several circumstances may explain the differences in smoking prevalence between COVID-19 patients and general population. For example, competitive causes of death and disease may be related to smoking early in life, residual confounding, and collider bias.[48]

Our study has several strengths, including its robust design and the large sample size of the derivation and validation cohorts. Participants were well characterized, with a strict method of inclusion and definition of cases (severity) and controls. In addition, we used individual data with high-quality genotyping and CV risk factor information. There are also study limitations that must be taken into consideration. First, we used a case-control design that does not represent the real-life proportion of severe COVID-19 cases (~10%). Second, the majority of our participants were of European descent, with only 20% representing individuals from South America, Asia, and Africa. Also, we were unable to incorporate adjustments based on the first 10 ancestry-specific principal components in our analysis. Recognizing this limitation, we conducted a meta-analysis to test the robustness and generalizability of our findings. Third, although the adjustments made in the three cohorts were comparable, in the SCOURGE cohort, adjustment for smoking and cholesterol levels could not be performed.

In summary, we provide evidence of 14 new genetic variants and loci, and eight previously published variants that are related to COVID-19 severity. But more importantly, we provide five SNVs associated with COVID-19 severity, one of them previously related to CAD, in three independent cohorts. The identified SNVs could be candidates for future polygenetic risk scores for risk stratification, which could guide screening, vaccine boosting, or prioritization of patients to receive new COVID-19 antiviral therapies.

AUTHOR CONTRIBUTIONS

Jaume Marrugat, **Irene R. Degano**, **Rafel Ramos**, and **Ramon Brugada**: Conceptualization. **Jaume Marrugat**, **Roberto Elosua**, **Irene R. Degano**, **Isaac Subirana**, **Rafel Ramos**, **Ruth Martí-Lluch**, **Ramon Brugada**, and **Mel·lina Pinsach-Abuin**: Methodology. **Ruth Martí-Lluch**, **Mel·lina Pinsach-Abuin**, **Anna Camps-Vilaró**, **Clàudia Solà-Richarte**, **Ingrid Vilaró**, **Raquel Cruz**, **Silvia Diz-de Almeida**, **Xavier Nogues**, **Joan R. Masclans**, **Roberto Güerri-Fernández**, **Judith Marin**, **Helena Tizon-Marcos**, and **Beatriz Vaquerizo**: Investigation. **Anna Camps-Vilaró**, **Isaac Subirana**, **Ruth Martí-Lluch**, and **Mel·lina Pinsach-Abuin**: Data curation. **Anna Camps-Vilaró**: Writing—original draft preparation. **Jaume Marrugat**, **Roberto Elosua**, **Irene R. Degano**, **Isaac Subirana**, **Rafel Ramos**, **Ruth Martí-Lluch**, **Ramon Brugada**, and **Mel·lina Pinsach-Abuin**: Writing—review and editing. **Jaume Marrugat**: Visualization. **Jaume Marrugat**, **Irene R. Degano**, **Rafel Ramos**, and **Ramon Brugada**: Supervision. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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