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Genetic risk score for risk stratification of patients positive for SARS-CoV-2 virus. The CARGENCORS study

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Background: The disease presentation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ranges from asymptomatic to fatal. COVID-19 patients with pre-existing coronary artery disease (CAD) risk factors or overt cardiovascular disease are at particular risk of severe disease. We hypothesised that a specific genetic risk score (GRS) based on single nucleotide polymorphisms (SNPs) allele count to score COVID-19 severity might include SNPs counts related to CAD incidence and to thrombosis, inflammation, and viral infectivity determinants involved in the severity of SARS-CoV-2. Such GRS could improve the early risk stratification of COVID-19 patients and optimize treatment strategies.

Purpose: To evaluate the capacity of a genetic risk score (GRS) with candidate genes to predict COVID-19 severity.

Methods: We conducted an age- and sex-matched case-control study with 1:2 ratio recruitment involving 2454 patients from Catalan hospitals and primary care. Cases were hospitalized severe (requiring at least oxygen treatment) or fatal COVID-19 patients; and controls were moderate-symptom and asymptomatic patients treated at home. Standard parametric and non-parametric methods, as required, were used to compare patient characteristics by severity. Individual genotypes for 33 CAD, 14 thrombosis, 22 inflammation, 15 viral infectivity SNPs and 2 COVID-19 SNPs already published were tested for association with severity with Cochran-Armitage statistics and p-values corrected for multiple comparisons. GRS was computed as the unweighted count of adverse alleles (0, 1 or 2). The odds ratio of severe COVID-19 was analysed for GRS (and its component SNPs) with logistic regression models adjusted for potential confounding factors. Area under the curve (AUC) improvement and net reclassification index (NRI) for GRS was estimated from a basic model including CAD and COVID-19 severity risk factors. Models' performance was measured with the Akaike information criterion.

Results: SNPs identifications are not shown to prevent patent conflict. Cases and control characteristics are compared in Table 1. Cases had a more adverse cardiovascular and anthropometric risk profile. After correcting for multiple testing by Benjamini-Hochberg criteria, we observed 13 SNPs to be significantly associated with severity. After excluding the close SNPs in linkage disequilibrium, 7 were retained in the GRS model, which yielded the discrimination and reclassification characteristics described in Table 2.

Conclusion: A GRS with 7 SNPs related to CAD, thrombosis and inflammation significantly improves the severe COVID-19 risk assessment done with age, sex, comorbidity, and anthropometry alone.

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Table 1. Demographic, anthropometry and cardiovascular risk prevalences in severe and non-severe COVID-19 patients.

	Severe COVID-19 N=818	Non-severe COVID-19 N=1636	p-value
Age (mean (SD))	60.6 (12.3)	59.8 (12.0)	0.121
Sex, men (n (%))	413 (50.5%)	826 (50.5%)	1.000
Smoker (n (%))	31 (3.87%)	177 (10.9%)	<0.001
Diabetes (n (%))	188 (23.0%)	174 (10.6%)	<0.001
Hypertension (n (%))	381 (46.6%)	521 (31.8%)	<0.001
Systolic blood pressure, mmHg (mean (SD))	132 (18)	130 (16)	<0.001
Diastolic blood pressure, mmHg (mean (SD))	76 (12)	78 (11)	0.005
Glycaemia, mg/dL (mean (SD))	111 (35.7)	98.8 (24.6)	<0.001
Total cholesterol, mg/dL (mean (SD))	201 (46.7)	200 (39.7)	0.583
HDL cholesterol, mg/dL (mean (SD))	51.4 (14.9)	57.2 (15.9)	<0.001
LDL cholesterol, mg/dL (mean (SD))	124 (40.2)	121 (33.9)	0.133
Triglycerides, mg/dL (mean (SD))	158 (98.1)	118 (61.4)	<0.001
Glomerular filtration rate, mL/min/1,73m^2 (mean (SD))	93.2 (31.0)	92.4 (22.7)	0.507
Coronary artery disease risk, (%)	4.29 (3.36)	3.47 (2.57)	<0.001
Body mass index, kg/m^2 (mean (SD))	29.8 (5.72)	27.3 (4.84)	<0.001
History of coronary heart disease, (n (%))	37 (4.53%)	69 (4.22%)	0.801

SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

CV and anthropometric risk profile

Table 2. Adjusted odds ratio of COVID-19 severity for a 7-SNP Genetic Risk Score in the CARGENCORS case-control study matched for age and sex. Discrimination, calibration and reclassification of a model with risk factors plus the GRS is presented.

	Model 1	Model 2		Model comparison
			p-value	p-value
GRS odds ratio (95% CI)		1.05 (1.04-1.06)	<0.001	
AUC	0.71 (0.69-0.73)	0.74 (0.71-0.76)		<0.001
AIC	2475	2394		
Continuous NRI, %		30 (22-40)		<0.001

Model 1 included as predictor variables diabetes, smoking, blood pressure, total cholesterol, HDL-cholesterol and body mass index. Model 2 included the variables of Model 1 plus the GRS. NRI is showing the reclassification of Model 2 compared to Model 1. GRS, genetic risk score; CI, confidence interval; AUC, area under the receiver operating characteristic curve; AIC, Akaike information criterion; NRI, net reclassification index.

OR of COVID-19 severity for a 7-SNP GRS