Classic and genetic cardiovascular risk burden and case-fatality from SARS-CoV-2 virus infection. The CARGENCORS study

A. Camps-Vilaro[1], I. R Degano[2], R. Brugada[3], M. Pinsach[3], R. Elosua[1], R. Ramos[4], R. Marti[4], I. Subirana[5], X. Nogues[6], J.R. Masclans[7], J. Marin[7], R. Guerri[8], H. Tizon[9], B. Vaquerizo[9], J. Marrugat[1]

[1]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [2]University of Vic-Central University of Catalonia (UVic-UCC), Vic, Spain; [3]Girona Biomedical Research Institute, Girona, Spain; [4]Primary Care Research Institute (IDIAP), Barcelona, Spain; [5]Health Institute Carlos III, CIBER CV, Madrid, Spain; [6]Hospital del Mar, Internal Medicine Department, Barcelona, Spain; [7]Hospital del Mar, Critical Care Department, Barcelona, Spain; [8]Hospital del Mar, Infectious Diseases Department, Barcelona, Spain; [9]Hospital del Mar, Cardiology Department, Barcelona, Spain

On behalf of CARGENCORS investigators

Funding Acknowledgement: Type of funding sources: Other. Main funding source(s): Carlos III Health Institute and the European Regional Development FundAgency for Management of University and Research GrantsCrue-CSIC-Santander FONDO SUPERA COVID-19

Background: The disease presentation of the severe acute respiratory syndrome coronavirus 2 infection (COVID-19) ranges from asymptomatic to fatal. COVID-19 patients with pre-existing coronary artery disease (CAD) risk factors or overt cardiovascular disease more often develop severe COVID-19, which are also related to thrombotic, inflammatory, and to viral infectivity response. We hypothesised that despite some genetic predisposition, especially in COVID-19 severity, the main determinants of fatal complications in COVID-19 patients are related to comorbidity.

Purpose: To determine the role of genetics and cardiovascular comorbidity in mortality from COVID-19.

Methods: We conducted a retrospective cohort study including 3,120 patients with positive COVID-19 test from several hospitals and primary care between February 2020 and June 2021. Among them 1,096 required hospitalization, and 121 died within 3 months after symptom onset. Standard parametric and non-parametric methods, as required, were used to compare patient characteristics by vital status. Individual genotypes for 32 CAD, 14 thrombosis, 19 inflammation, and 11 viral infectivity single nucleotide variants (SNV), as well as, 2 COVID-19 SNVs already published were tested for association with mortality with Cochran-Armitage statistics and p-values corrected for multiple comparisons. The mutually-adjusted odds ratio (OR) and 95% confidence interval (95% CI) of fatal COVID-19 was analysed for SNVs significantly associated to case-fatality, with their adverse alleles count (0, 1 or 2), and for comorbidity factors with logistic regression adjusted for age and sex. The discrimination of the models was also estimated by the area under the curve (AUC).

Results: Fatal and non-fatal cases' characteristics are compared in Table 1. Fatal cases had a more adverse cardiovascular and anthropometric risk profile. After correcting for multiple testing by Benjamini-Hochberg method, we observed the inflammation-related rs6993770 SNV to be significantly associated with COVID-19 fatality (p-value = 0.04). The CAD-related rs9982601 and rs2505083 SNVs, and the thrombosis-related rs7853989 SNV were moderately associated with COVID-19 fatality (p-value $\leq$0.1). On Figure 1 we show the adjusted OR for rs6993770 (OR: 1.02; 95% CI 1.01–1.03 per risk allele) and that for clinical factors related to COVID-19 case-fatality. The AUC of the model was 0.85 (95% CI 0.81–0.88), which not improved that of a model with clinical risk factors alone (AUC: 0.84; 95% CI 0.81–0.87).

Conclusion: The rs6993770 inflammation (interleukin measurement trait)-related SNV was independently associated to case fatality; however the outcome was mainly driven by age, male sex, diabetes, and glomerular filtration rate.

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

	Dead from COVID-19 N=121	COVID-19 survivors N=2,999	p.overall
Age, years *	**71 (9)**	**58 (13)**	**<0.001**
Sex, men	**80 (66.1%)**	**1404 (46.8%)**	**<0.001**
Smoking	9 (7.83%)	267 (8.99%)	0.793
Diabetes	**47 (38.8%)**	**405 (13.5%)**	**<0.001**
Hypertension	**85 (70.2%)**	**999 (33.3%)**	**<0.001**
Systolic blood pressure, mmHg *	129 (18.5)	130 (17)	0.742
Diastolic blood pressure, mmHg *	**73 (12)**	**77 (11)**	**<0.001**
Glycaemia, mg/dL (median [IQR])	**108 [93;139]**	**94 [86;106]**	**<0.001**
Total cholesterol, mg/dL *	**186 (48)**	**198 (42)**	**0.009**
HDL cholesterol, mg/dL *	**50 (15)**	**56 (16)**	**<0.001**
LDL cholesterol, mg/dL *	**110 (42)**	**121 (36)**	**0.011**
Triglycerides, mg/dL (median [IQR])	**124 [87;173]**	**109 [77;155]**	**0.008**
Glomerular filtration rate, mL/min/1,73m^2 *	**76.1 (32.8)**	**94.3 (25.6)**	**<0.001**
Body mass index, kg/m^2 *	**29.3 (5.55)**	**28.0 (5.23)**	**0.015**
Coronary artery disease risk, % *	**6.40 (5.17)**	**3.47 (2.82)**	**<0.001**
History of coronary artery disease	**14 (11.7%)**	**124 (4.14%)**	**<0.001**
History of stroke	**8 (6.67%)**	**74 (2.48%)**	**0.013**
History of thrombosis	**8 (6.61%)**	**65 (2.17%)**	**0.007**
History of neoplasia	**25 (20.7%)**	**276 (9.20%)**	**<0.001**
History of immune disease	14 (11.6%)	248 (8.27%)	0.265
History of COPD	**14 (11.6%)**	**71 (2.37%)**	**<0.001**
History of mental/cognitive illness	23 (19.2%)	614 (20.5%)	0.812

* Mean (standard deviation). COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; IQR, Inter-Quartile Range; LDL, low-density lipoprotein.

Figure 1. Adjusted odds ratio and 95% confidence intervals (95% CI) of COVID-19 mortality for genetic and classic risk factors