RETROSPECTIVE COHORT STUDY OF THE CARDIOVASCULAR RISK 6 MONTHS AFTER COVID-19 INFECTION COMPARED TO THE GENERAL POPULATION OF CATALONIA.

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ABSTRACT *(English)*

Background: The cardiovascular system is a target for the SARS-Cov-2 virus and therefore is largely affected. Few studies have analyzed the incidence of cardiovascular (CV) events in patients with coronavirus disease (COVID-19) in a large population-based cohort.

Aim: This study aimed at calculating the risk of CV events and all-cause mortality in patients that had a positive COVID-19 test compared to individuals that did not, during the 9-12 months after the infection/inclusion in the study. Secondary objectives were to compare risk factor prevalence between individuals with and without a positive COVID-19 test.

Methods: All individuals registered in the public healthcare system in Catalonia who had a positive COVID-19 test during March-June 2020 were included as well as a random selection of non-positive individuals. Data was obtained from the PADRIS Program. Incidence of CV events and mortality was compared between individuals with and without a positive COVID-19 test using crude and adjusted odds ratios (OR). Adjusted ORs took into account age, sex, hypertension, hypercholesterolemia, diabetes, and smoking.

Results: angina, atrial fibrillation & flutter, bypass surgery, death, heart failure, myocardial infarction, myocarditis, peripheral arterial disease, revascularization, stroke, tachycardia, thrombosis, and transient ischemic attack (TIA) had a higher possibility of happening in the COVID-19 positive group (adjusted ORs range= 2.7-17.2).

Conclusions: This study confirms the hypothesis that patients who had been infected by SARS-CoV-2 present a higher incidence of CV events and mortality than the general population. Thrombosis and tachycardia appeared to be the outcomes most influenced by the SARS-CoV-2 infection.

RESUM (Català)

Antecedents: El sistema cardiovascular és una diana del virus SARS-CoV-2 i per tant es veu afectat. Pocs estudis han analitzat la incidència d'esdeveniments cardiovasculars en pacients amb la malaltia del coronavirus (COVID-19) en una gran cohort poblacional.

Objectiu: Aquest estudi tenia com a objectiu calcular el risc d'esdeveniments cardiovasculars i de mortalitat en pacients que han tingut COVID-19 en comparació amb individus que no l'han tingut, durant els 9-12 mesos posteriors a la infecció/incorporació a l'estudi. Els objectius secundaris eren comparar la prevalença dels factors de risc en aquests individus.

Mètodes: Es van incloure tots els individus positius per COVID-19 entre març-juny de 2020 a Catalunya, i una selecció aleatòria d'individus sense COVID-19. Les dades es van obtenir del Programa PADRIS. Es va comparar la incidència d'esdeveniments cardiovasculars i de mortalitat entre els individus amb i sense una prova positiva de la COVID-19 utilitzant odds ratios (OR) crus i ajustats. Els ORs ajustats tenien en compte l'edat, el sexe, la hipertensió, la hipercolesterolèmia, la diabetis i el tabaquisme.

Resultats: L'angina de pit, la fibril·lació auricular, la cirurgia de bypass, la mort, la insuficiència cardíaca, l'infart de miocardi, la miocarditis, la malaltia arterial perifèrica, la revascularització, l'ictus, la taquicàrdia, la trombosi i l'atac isquèmic transitori tenien una major probabilitat de donar-se en el grup que havia tingut COVID-19 (rang dels ORs ajustats= 2,7-17,2).

Conclusions: Aquest estudi confirma la hipòtesi que els pacients que han estat infectats per SARS-CoV-2 presenten una major incidència d'esdeveniments cardiovasculars i de mortalitat que la població general. La trombosi i la taquicàrdia semblen ser els resultats més influïts per la infecció per SARS-CoV-2.

RESUMEN (Castellano)

Antecedentes: El sistema cardiovascular es una diana del virus SARS-CoV-2y, por lo tanto, se ve ampliamente afectado. Pocos estudios han analizado la incidencia de eventos cardiovasculares en pacientes con la enfermedad del coronavirus (COVID-19) en una cohorte basada en la poblacional.

Objetivo: Este estudio tenía como objetivo calcular el riesgo de eventos cardiovasculares i de mortalidad en pacientes que han tenido COVID-19 en comparación con individuos que no lo han tenido, durante los 9-12 meses posteriores a la infección/inclusión en el estudio, en la población general de Cataluña. Los objetivos secundarios eran comparar la prevalencia de factores de riesgo entre estos individuos.

Métodos: Se incluyeron todos los individuos positivos por COVID-19 entre marzo-junio de 2020 en Cataluña, y una selección aleatoria de individuos sin COVID-19. Los datos se obtuvieron del Programa PADRIS. Se comparó la incidencia de eventos cardiovasculares y de mortalidad entre individuos con y sin una prueba positiva de COVID-19 utilizando odds ratio (OR) crudos y ajustadas. Las OR ajustadas tuvieron en cuenta la edad, el sexo, la hipertensión, la hipercolesterolemia, la diabetes y el tabaquismo.

Resultados: La angina de pecho, la fibrilación auricular, la cirugía de bypass, la muerte, la insuficiencia cardíaca, el infarto de miocardio, la miocarditis, la enfermedad arterial periférica, la revascularización, el ictus, la taquicardia, la trombosis y el ataque isquémico transitorio (AIT) tenían una mayor probabilidad de ocurrir en el grupo que había tenido COVID-19 (rango OR ajustadas = 2,7-17,2).

Conclusiones: Este estudio confirma la hipótesis de que los pacientes que han sido infectados por SARS-CoV-2 presentan una mayor incidencia de eventos cardiovasculares y de mortalidad que la población general. La trombosis y la taquicardia parecen ser los resultados más influenciados por la infección por SARS-CoV-2.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a respiratory infection which can lead to pneumonia and acute respiratory distress syndrome. In addition, SARS-CoV-2 infection can also cause a cytokine storm and systemic inflammation, which leads to multiorgan damage, and coagulation abnormalities, which can cause thromboembolic events (1–3).

Early studies of coronavirus disease 19 (COVID-19) patients reported an association between COVID-19 and cardiovascular disease (CVD). COVID-19 patients had a 10-30% higher prevalence of CVD and of CVD risk factors, particularly coronary heart disease, hypertension, and diabetes mellitus (4–8). COVID-19 can cause cardiovascular disorders such as myocardial injury, arrhythmias, acute coronary syndrome, heart failure, coagulation abnormalities and thrombosis (9–11).

The data on cardiovascular disease after the hospitalization period is scarce. This is particularly important because there could be short- and long-term effects on CVD due to the systemic inflammation as it is associated with increased troponin levels, myocarditis, heart failure, acute coronary syndrome, arrhythmia, and thrombosis among others (12). In line with this hypothesis, myocardial inflammation, myocarditis, and pericarditis have been observed in patients after having COVID-19 (13–15), suggesting long-term CVD effects after SARS-CoV-2 infection.

There are studies that show how SARS-CoV-2 enters the host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor found in vascular endothelial cells, cardiac myocytes, and type 2 alveolar pneumocytes, which would explain why these tissues are affected the most (16). After internalization in the cell the virus proliferates, duplicates, and downregulates ACE2, which leads to a lower angiotensin level in the blood and high angiotensin II level in the circulatory system causing inflammation, vasoconstriction, myocardial injury, and thrombosis (17,18). Therefore, patients with preexisting risk factors may not only have a higher morbidity and mortality rate but also may directly present with cardiovascular complications (17).

A study found a 6.25% incidence of cardiovascular events the first year after hospitalization, and a third of these occurred during the first 30 days. The events included acute coronary syndrome, cerebrovascular accident, venous thromboembolic disease (the earliest to appear), hospitalization due to cardiac insufficiency (the most frequent) and cardiovascular death (19).

Hypothesis and objectives

We hypothesized that cardiovascular (CV) risk factors would be higher in patients that had been infected with SARS-CoV-2 compared to those who weren't in a large population cohort of Catalonia. We also hypothesized, that infected patients would present a higher number of CV events and mortality than the general population during a follow-up of 9-12 months, that certain CV events would be more associated with having COVID-19 than others, and that CV risk factors may explain some of these associations.

The objectives were:

- to study baseline CV risk factors' prevalence in patients who had been infected with SARS-CoV-2 compared to the general population.
- to analyze CV event incidence and mortality in infected patients and general population 9-12 months after SARS-CoV-2 infection or inclusion.
- to examine whether CV risk factors explained part of the association between CV incidence and COVID-19 disease.

METHODS

Study design

Retrospective cohort study of general population of Catalonia with data in the public healthcare system.

Subjects

The selected individuals were patients with a positive COVID-19 PCR registered in the public health system between March 1st, 2020, and May 31st, 2020. And individuals without a positive COVID-19 test, who had information on risk factors between March 2017 and March 2020. Non-infected individuals were randomly selected based on age and sex distributions at a 4:1 ratio.

The inclusion criteria were:

- age >44 years old.
- COVID-19 patients should have a positive PCR/antigen test/rapid test between March 1st to May 31st, 2020.
- non-infected participants should have no positive COVID-19 test.
- cohort participants needed to have follow-up data after recovery from COVID-19 of at least 9 months after inclusion.
- participants should have risk factor data at the start of data collection.

The exclusion criteria were:

- having a CV event previous to March 1st 2020,
- non-infected participants with negative COVID-19 tests but labelled as suspicious by epidemiologists/clinicians.
- COVID-19 patients without a positive COVID-19 test or diagnosis

Follow-up was obtained until March 31st of 2021, between 9 and 12 months after the inclusion or positive PCR result for each cohort participant. Any CV event or death that occurred up to that date was registered in the database.

Data collection

The data was obtained from a Program created to promote research and innovation in health by making available to researchers anonymized data from the health system (Data analytics program for health research and innovation, PADRIS), which pertains to the agency that evaluates and controls the healthcare quality in Catalonia (Health Quality and Assessment Agency of Catalonia, AQUAS). Data was gathered from primary care, the minimal shared basic information database (CMBD), pharmacy retrievals and the mortality register.

If participants had more than one laboratory result within a year, the annual average value was calculated. The most recent data on CV risk factors prior to inclusion was selected for baseline examination.

The project was approved by the ethics committees of the Hospital del Mar Medical Research Institute (IMIM) and PADRIS. The data used in this project was anonymized.

Included variables

The exposure variable was SARS-CoV-2 infection. COVID-19 was coded positive if there was a positive report in the medical records or a positive test (antigen, PCR or rapid test). COVID-19 was coded negative if all tests were negative and participants were not labelled as suspicious by epidemiologists/clinicians.

The outcome variables were CV disease incidence during the follow-up. The CV outcomes under study were: angina, atrial fibrillation/flutter, bypass surgery, heart failure, myocardial infarction, myocarditis, peripheral artery disease, revascularization, stroke, tachycardia, thrombosis, and transient ischemic attack. We also analyzed all-cause mortality during the follow-up.

Other variables under study included demographic characteristics (age and sex) and CV risk factor variables (body mass index (BMI), diabetes, hypertension, hypercholesterolemia, and smoking). BMI was weight in Kg divided by squared height in m.

Diabetes/hypertension/hypercholesterolemia were coded positive if participants were previously diagnosed, if they had been or were on treatment for the condition, or if their glucose/blood pressure/cholesterol levels were above a defined threshold. The threshold was 126 mg/dL for glucose, 140/90 mm Hg for systolic/diastolic blood pressure, and 200 mg/dL for total cholesterol. Smoking was coded positive if recorded either in primary care or in the CMBD. We also analyzed glucose concentration and the lipid profile (high-density lipoprotein cholesterol [HDL-cholesterol], low-density lipoprotein cholesterol [LDL-chol], triglycerides, and total cholesterol).

Outcome and risk factor data was obtained with defined international classification of diseases (ICD) codes, while treatment data was obtained with defined Anatomical Therapeutic Chemical (ATC) codes.

Statistical analysis

Missing data was analyzed in the main variables included in the study. Supplementary Figure 1 shows each variable's missing values.

Quantitative variables were described with the mean and the standard deviation if variables followed a normal distribution, or with the median and the interquartile range otherwise. Categorical variables were presented with absolute and relative frequencies.

To compare quantitative variables between the 2 study groups (COVID-19 patients and general population), we used unpaired T-tests for normal distributed variables and Mann-Whitney U tests otherwise. To compare categorical variables between groups we used Chi squared tests if all cell combinations had more than 4 expected cases and exact tests otherwise.

Cardiovascular event incidence in COVID-19 patients and control participants was analyzed with crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). Adjusted ORs were obtained from logistic regression models adjusted for demographic and CV risk factors. The following logistic model assumptions were confirmed: linear association between the log odds and the quantitative predictors (using an interaction term= ln(age)*age), absence of influential outliers (Cook's distance <1), and absence of correlation between the model predictor variables (Spearman correlation <0.7).

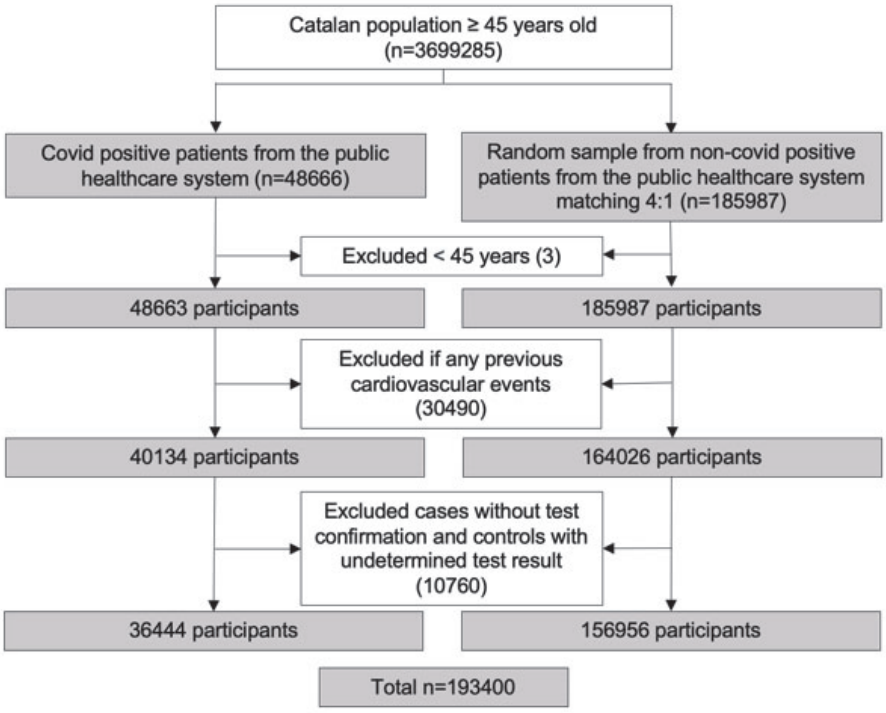
We used the R software v.4.2.1 for database preparation and quality control, and the IBM SPSS program for data analysis Statistics v.28. For descriptive analyses we considered as statistically significant a p-value <0.05. For crude and adjusted ORs, due to the high number

of outcomes examined, we applied the Bonferroni correction and defined as statistically significant a p-value < 0.004.

RESULTS

A total of 48666 patients with a positive COVID-19 test were recruited and a total of 185987 non-infected individuals were randomly selected. There were three individuals excluded as they were 44 years old, 30490 were excluded because of previous CV events, and 10760 were excluded for being labelled as infected but having no positive COVID-19 test result or diagnosis, or for having negative tests results but labelled as suspicious. The positive COVID-19 group ended up with 36444 individuals and the control group with 156956 individuals (Figure 1).

Figure 1. Flowchart of the participants included in the study.



As seen in Table 1 the characteristics from each group were compared finding statistically significant differences for each variable analyzed. Being the COVID-19 positive group on average a year older, having higher BMI, and higher prevalence of smoking, hypertension, hypercholesterolemia, and diabetes. And the COVID-19 negative group having higher concentration of glucose, triglycerides and cholesterol (HDL-cholesterol, LDL-cholesterol, and total cholesterol).

The two CV risk factors with the largest difference between groups were diabetes (8.4%) and hypertension (5.6%).

Table 1. Descriptive analysis of the study participants characteristics at inclusion.

	COVID-19 negative *N=156956*	COVID-19 positive *N=36444*	p. overall
Age (years), median [IQR]	66.0 [55.0;81.0]	67.0 [55.0;83.0]	<0.001
Sex: Women, n (%)	91429 (58.3%)	21531 (59.1%)	0.004
SBP (mmHg), median [IQR]	131 [122;139]	130 [120;138]	<0.001
DBP (mmHg), median [IQR]	76.0 [70.0;82.0]	75.0 [69.0;82.0]	<0.001
Height (cm), median [IQR]	162 [155;170]	161 [154;168]	<0.001
Weight (kg), median [IQR]	71.8 [62.0;82.0]	73.0 [62.8;84.0]	<0.001
BMI (kg/m^2), median [IQR]	27.4 [24.6;30.7]	28.0 [25.0;31.5]	<0.001
Smoker: Yes, n (%)	15524 (9.89%)	3990 (10.9%)	<0.001
Hypertension: Yes, n (%)	47799 (44.9%)	13190 (50.5%)	<0.001
Hypercholesterolemia: Yes, n (%)	80270 (51.1%)	19841 (54.4%)	<0.001
Diabetes: Yes, n (%)	90701 (57.8%)	24144 (66.2%)	<0.001
LDL cholesterol (mg/dL) median [IQR]	125 [102;150]	121 [98.6;146]	<0.001
HDL cholesterol (mg/dL) median [IQR]	56.6 [47.3;69.0]	53.6 [44.9;65.4]	<0.001
Total cholesterol (mg/dL) median [IQR]	207 [181;236]	200 [173;230]	<0.001
Triglycerides (mg/dL) median [IQR]	62.0 [50.0;100]	60.0 [47.5;96.0]	<0.001
Glucose (mg/dL) median [IQR]	96.3 [87.5;116]	95.2 [86.3;113]	<0.001

IQR: interquartile range, n/N: number of individuals. *SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein.*

Table 2 displays the number of individuals that had each outcome and the corresponding percentage in that group. The percentages are all higher in the COVID-19 positive group. Certain outcomes, such as bypass surgery, atrial fibrillation & flutter, peripheral arterial disease, and myocarditis even have a higher number of cases in the COVID-19 positive group than in the negative group.

Table 2. Crude incidence of each outcome in both study groups.

Outcome	COVID-19 negative *N=156956*	COVID-19 positive *N=36444*
Angina: Yes, n (%)	81 (0.1%)	72 (0.2%)
Atrial fibrillation & flutter: Yes, n (%)	1035 (0.7%)	1281 (3.5%)
Bypass surgery: Yes, n (%)	29 (0.0%)	36 (0.1%)
Death: Yes, n (%)	3912 (2.5%)	6387 (17.5%)
Heart failure: Yes, n (%)	916 (0.6%)	912 (2.5%)
Myocardial infarction: Yes, n (%)	214 (0.1%)	133 (0.4%)
Myocarditis: Yes, n (%)	1 (0.0%)	4 (0.0%)
Peripheral Arterial Disease: Yes, n (%)	314 (0.2%)	361 (1.0%)
Revascularization: Yes, n (%)	109 (0.1%)	143 (0.4%)
Stroke: Yes, n (%)	314 (0.2%)	221 (0.6%)
Tachycardia: Yes, n (%)	113 (0.1%)	386 (1.1%)
Thrombosis: Yes, n (%)	105 (0.1%)	336 (0.9%)
Transient ischemic attack (TIA): Yes, n (%)	64 (0.0%)	41 (0.1%)

Table 3 presents the crude ORs and their 95% CIs from the associations between having COVID-19 disease and CV event incidence or all-cause mortality. SARS-CoV-2 infection was associated with a higher incidence of all CV events under study, except for myocarditis, and with a higher all-cause mortality. Depending on the outcome, the possibility of having the described CV events or death was 2-14 times higher in the COVID-19 disease positive group compared to the control group. The events that had more possibilities of occurring in the SARS-CoV-2 infected group were tachycardia, thrombosis, and death.

Table 3. Crude ORs and 95% CIs of the associations between SARS-CoV-2 infection and CV event incidence and all-cause mortality.

Outcome	OR [95% CI]	p-value
Angina	3.83 [2.79-5.26]	<0.001
Atrial fibrillation & flutter	5.48 [5.05-5.96]	<0.001
Bypass surgery	5.35 [3.28-8.72]	<0.001
Death	8.31 [7.97-8.66]	<0.001
Heart failure	4.37 [3.98-4.79]	<0.001
Myocardial infarction	2.68 [2.16-3.33]	<0.001
Myocarditis	17.22 [1.92-154.14]	0.005

Peripheral Arterial Disease	4.99 [4.28-5.80]	<0.001
Revascularization	5.66 [4.41-7.27]	<0.001
Stroke	3.04 [2.56-3.61]	<0.001
Tachycardia	14.85 [12.04-18.33]	<0.001
Thrombosis	13.90 [11.16-17.31]	<0.001
Transient ischemic attack (TIA)	2.76 [1.86-4.08]	<0.001

Table 4 shows the adjusted ORs and their 95% CIs. ORs were adjusted for age, sex, smoking, hypertension, hypercholesterolemia, and diabetes. The adjusted results were similar to the crude results. Adjusted analysis indicated higher possibilities of having all CV events after having COVID-19, ranging from 2 to 14 times higher, except for myocarditis, as well as higher possibilities of all-cause mortality (10 times higher). The outcomes presenting higher possibilities of occurring in the COVID-19 positive group compared to the control were also tachycardia, thrombosis, and death. ORs were slightly lower than those presented in table 2. Supplementary figure 2 and 3 show the logistic model assumptions that were tested.

Table 4. Adjusted ORs and 95% CIs of the associations between SARS-CoV-2 infection and CV event incidence and all-cause mortality.

Outcome	OR [95% CI]	p-value
Angina	3.50 [2.54-4.82]	<0.001
Atrial fibrillation & flutter	5.21 [4.79-5.67]	<0.001
Bypass surgery	5.00 [3.06-8.18]	<0.001
Death	10.10 [9.65-10.58]	<0.001
Heart failure	3.98 [3.63-4.38]	<0.001
Myocardial infarction	2.53 [2.03-3.15]	<0.001
Myocarditis	15.31 [1.70-137.33]	0.015
Peripheral arterial disease	4.68 [4.02-5.46]	<0.001
Revascularization	5.18 [4.03-6.66]	<0.001
Stroke	2.84 [2.39-3.39]	<0.001
Tachycardia	14.63 [11.85-18.06]	<0.001
Thrombosis	13.54 [10.86-16.88]	<0.001
Transient ischemic attack (TIA)	2.58 [1.74-3.83]	<0.001

Analysis were performed with logistic regression models adjusted for group, sex, age, hypercholesterolemia, diabetes, hypertension, and smoking. CI: confidence interval, OR: odds ratio.

DISCUSSION

This study shows a higher prevalence of CV risk factors such as BMI, smoking, hypertension, hypercholesterolemia, and diabetes in patients who were infected with SARS-CoV-2 compared to those who were not. The results also show lower concentration of glucose, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol in COVID-19 patients, probably due to higher treatment rates. COVID-19 patients also had higher odds of having CV events, except for myocarditis, even after adjustment for CV risk factors. The largest differences in CV events were observed for tachycardia and thrombosis. All-cause mortality was also higher in COVID-19 patients compared to controls. ORs were almost unchanged after adjustment for CV risk factors.

Previous studies also found higher odds of presenting major cardiovascular events after COVID-19 infection (20–22). Weijie Wang et al. studied long-term cardiovascular outcomes in COVID-19 survivors versus matched non-infected patients finding the highest odds ratios in myocarditis (HR [95%CI] = 4.40 [2.89-6.71]), ischemic cardiomyopathy (HR [95%CI] = 2.81 [2.47-3.19]), and pulmonary embolism (HR [95%CI] = 2.64 [2.44-2.87]) (21). Weijie Wang et al. included international data although most was from the US. So they had data from a few other countries and were able to analyze regional differences, finding transient ischemic attacks to be the outcome with highest risk in the Middle Eastern countries (21). These differences may justify the difference between studies. L.F. Reyes et al. studied patients with severe COVID-19 and compared those who presented a MACE versus those who didn't. The most frequent diagnosis were cardiac arrythmias, cardiac arrest and heart failure (22). Charlotte Warren et al. studied COVID-19 survivors depending on their CV risk using the QRISK3 score and their hypertension values. They found a gradient in the occurrence of severe COVID-19 outcomes by underlying CV risk profile among people without preexisting CVD (20). Deaths were also attenuated but remained present when stratified by 15-year age groups (20).

CV risk factors have been previously associated with COVID-19 (23,24). Hyperglycemia enhances SARS-CoV-2 replication in monocytes, increases ACE2 expression, and augments the monocyte pro-inflammatory cytokine response *ex vivo* (23). This probably explains why the degree of glycemic control is proportionally associated with increased risk of multiple infections and infection-related morbidity and mortality (23). Also, in animal studies, the expression of ACE2, which is where SARS-CoV-2 binds, in markedly increased in patients with diabetes, hypertension and heart failure as an adaptative response (23,24).

The results indicate that COVID-19 disease is itself a cardiovascular risk factor even when adjusted for CV risk factors. These findings can be explained altogether understanding that

ACE2 is expressed in vascular endothelial cells, cardiac myocytes, and type 2 alveolar pneumocytes. Thus, ACE2 is not only a SARS-CoV-2 receptor but also a regulator of the renin-angiotensin system (RAS), which has significant roles in the cardiovascular and immune systems (16). More specifically each individual finding has its own explanation. Heart failure and other diseases due to myocardial damage occur as a result of different myocardial aggression mechanisms such as direct myocardial injury by viral action, indirect and direct inflammatory damage, O_2 supply-demand imbalance, and increase of atherothrombotic events due to inflammatory destabilization of atheromatous plaques resulting in acute myocardial dysfunction (7,26,27). Prothrombotic states and ischemic events can be understood by the exacerbated inflammation, hypoxemia, and immobilization (26,28). These findings add to a growing body of data highlighting a broad variety of symptoms from brain fog and exercise fatigue to heart-related issues that some patients experience past the initial phase of SARS-CoV-2 infection (26,28–30).

This study has several strengths. First, it included a large cohort of COVID-19 patients and control participants from Catalonia's general population. Second, data was gathered from primary care, hospital admissions, mortality, and pharmacy records. Third, a large number of CV events were analyzed using adjusted models.

This study has limitations that should be considered. First, the data obtained was not complete for all study individuals (Supplementary figure 1) and missing values for dichotomic variables were assumed as non-pathological. Second, as the study analyzed electronic health records, misclassification bias and residual confounding cannot be excluded. Third, not all COVID-19 negative patients were tested for the infection and therefore it cannot be excluded that they may have suffered asymptomatic infections. Fourth, the ethnicity and socioeconomic group each individual belonged to was unknown and could have a role in disease evolution and prognosis. Furthermore, severity of the disease was not recorded and therefore could not be analyzed, COVID-19 severity could have been a risk stratification factor. Finally, most of the data of this study was obtained before the vaccines were commercialized and therefore do not take into consideration the prevention of complications the vaccination has.

These results would require further in-depth studies that analyze CVD with laboratory markers and/or imaging techniques to better diagnose diseases and disease subtypes. And also be to analyze outcomes stratified by CV risk or COVID severity.

CONCLUSIONS

Overall, the importance of this study lies in the demonstration of COVID-19 disease as an independent cardiovascular risk factor, particularly for tachycardia and thrombosis. These results would suggest that screening and monitoring infected patients would allow prevention and treatment of complications therefore reducing CV events caused by the infection.

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SUPPLEMENTARY MATERIALS

Supplementary Figure 1. Missing values for each variable.

VARIABLE	MISSING VALUES
Age	0
Sex	0
SBP	0
DBP	0
Height	0
Weight	0
BMI	0
Smoker	78552
LDL cholesterol	85000
HDL cholesterol	75427
Total cholesterol	75427
Triacylglycerides	75427
Glucose	60561
Transient ischemic attack (TIA)	187826
Angina	187826
Bypass surgery	187826
Atrial fibrillation & flutter	187826
Stroke	187826

Supplementary Figure 1. Missing values for each variable.

VARIABLE	MISSING VALUES
Myocardial infarction	187826
Heart failure	187826
Peripheral arterial disease	187826
Myocarditis	187826
Revascularization	187826
Tachycardia	187826
Thrombosis	187826
Death	187826

Supplementary Figure 2. Analysis of correlation coefficients in the regression models.

		Hypertension	Diabetes	Hypercholesterolemia	Smoking	Sex	Age
Hypertension	Correlation Coefficient		.216	.220	.058	-.004	.391
	Sig. (2-tailed)		<.001	<.001	<.001	.110	<.001
Diabetes	Correlation Coefficient	.216		.515	.078	.073	.191
	Sig. (2-tailed)	<.001		<.001	<.001	<.001	<.001
Hypercholesterolemia	Correlation Coefficient	.220	.515		.088	.076	.212
	Sig. (2-tailed)	<.001	<.001		<.001	<.001	<.001
Smoking	Correlation Coefficient	.058	.078	.088		-.175	-.018
	Sig. (2-tailed)	<.001	<.001	<.001		<.001	<.001
Sex	Correlation Coefficient	-.004	.073	.076	-.175		.073
	Sig. (2-tailed)	.110	<.001	<.001	<.001		<.001
Age	Correlation Coefficient	.391	.191	.212	-.018	.073	
	Sig. (2-tailed)	<.001	<.001	<.001	<.001	<.001	

Supplementary Figure 3. Analysis of observations influence in the regression models.

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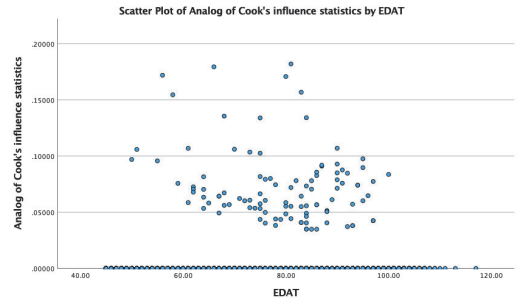
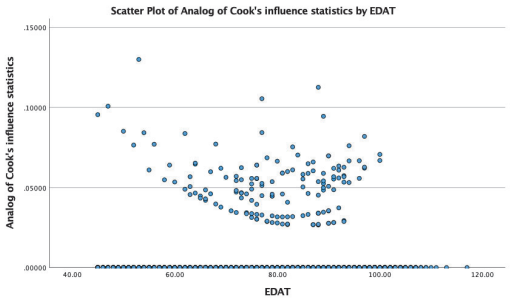
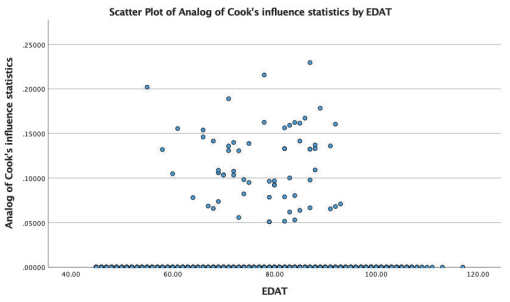


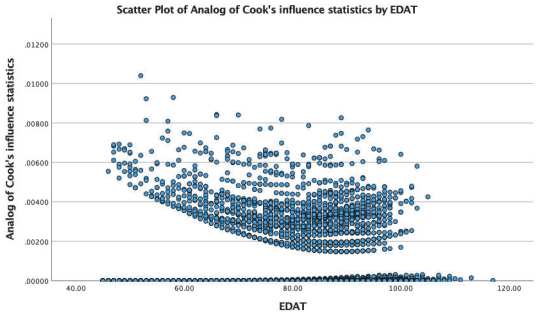
ANGINA



BYPASS



FIBRILLATION & FLUTTER



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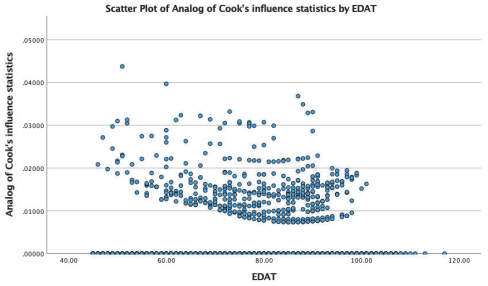

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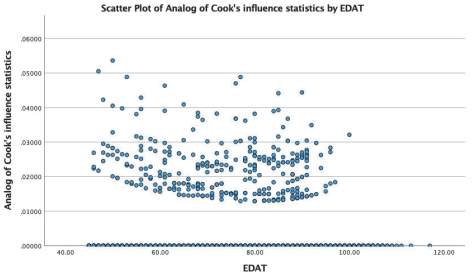

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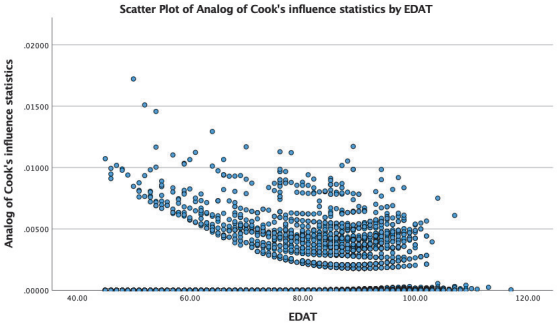

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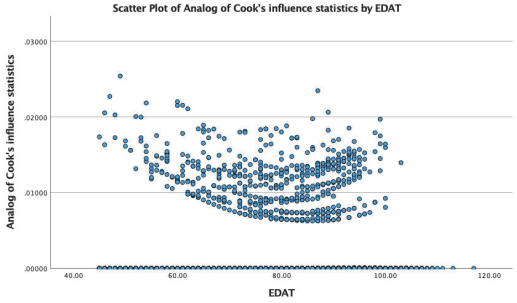
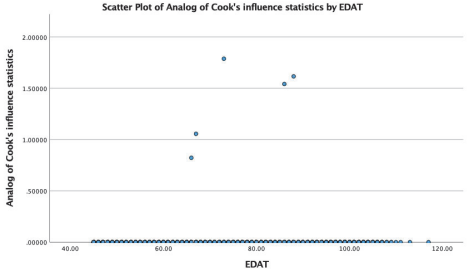
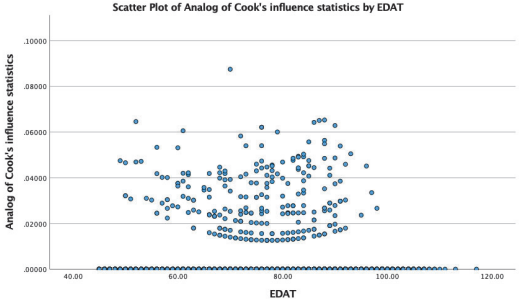


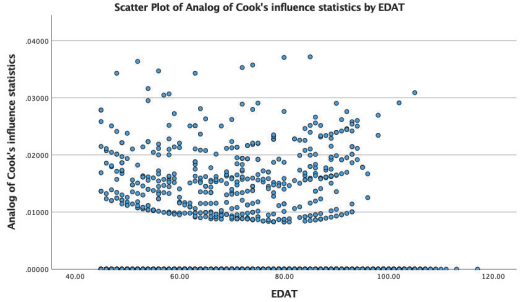
MYOCARDITIS



REVASCULARIZATION



TACHYCARDIA



THROMBOSIS