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Relationship Between COVID-19 and MINOCA: A Pilot Cross-Sectional Study

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Abstract

Introduction: *Evidence suggests that COVID-19 infection increases the likelihood of myocardial infarction with no obstructive coronary arteries (MINOCA), particularly in females. This study hypothesizes that patients with COVID-19 and acute myocardial infarction (AMI) who underwent coronary angiography will have a higher proportion of MINOCA than those with AMI without COVID-19.*

Objective: *This study aimed to assess if COVID-19 infection is associated with MINOCA in patients who underwent coronary catheterization.*

Methods: *This was a single-center cross-sectional pilot study that gathered information using the electronic medical records of a tertiary care institution between February 2020 and October 2021. Patients were divided into two groups: those with AMI and COVID-19 (AMICOVID+) and those with AMI without COVID-19 (AMICOVID-). The primary outcome was to evaluate the relationship between COVID-19 and MINOCA, expressed in relative frequencies and p-values calculated by the Chi-squared test and corroborated by a sensitivity analysis using logistic regression.*

Results: *Of the 28 patients that met the inclusion criteria, 14 (50%) had AMICOVID+, and 14 (50%) had AMICOVID-. MINOCA was significantly higher in the group with AMICOVID+ compared to AMICOVID- (85.7% vs. 21.4%. p = 0.001), showing no effect modification when sensitivity analysis was carried on. The raw data for statistical analyses was also included in the appendices.*

Conclusion: *MINOCA was in a significantly higher proportion in the AMICOVID+ group than in the AMICOVID- group. However, this study had a small sample size; therefore, these results must be corroborated in different populations with larger sample sizes.*

Introduction

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus belonging to the coronaviridae family that causes Coronavirus-19 disease (COVID-19) and is responsible for thousands of infections and deaths. The average incubation time of the SARS-CoV-2 virus is 14 days; the condition can debut in many ways, ranging from asymptomatic infection to the appearance of various symptoms, like malaise, fever, and cough (Herrera Ortiz et al., 2020; Quiroz Alfaro et al., 2022). Myocardial infarction with no obstructive coronary arteries (MINOCA) refers to an acute myocardial infarction (AMI), as defined by the fourth universal definition of myocardial infarction, wherein there is no obstructive disease during the coronary angiography and other clinical conditions that may lead to myocardial injury without ischemia have been ruled out (Tamis-Holland et al., 2019).

The proportion of MINOCA among patients with AMI varies between 3% and 15% (Yildiz et al., 2022). MINOCA also tends to present more commonly in younger and less comorbid patients than those with AMI with coronary artery disease (CAD) and is more common in Black and Hispanic populations (Yildiz

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et al., 2022).

Up to 12% of patients diagnosed with COVID-19 may have some degree of cardiac injury (Tajbakhsh et al., 2021). Evidence suggests that 33% of females and 18% of males with COVID-19 infection and ST-segment elevation AMI have MINOCA, compared to 3.5% in patients without COVID-19 infection (Andersson et al., 2018; Quesada et al., 2022).

During the pandemic, there has been a worldwide drop in acute coronary syndrome hospital admissions due to fear of contracting the infection, limiting the number of patients exposed to coronary angiography and, consequently, the knowledge we have about coronary findings in patients with COVID-19 (Piccolo & Esposito, 2021).

Although patients presenting with MINOCA tend to have a more favorable prognosis than patients with AMI and obstructive CAD, patients with MINOCA still have a significant all-cause mortality rate of 3.4% at 12 months (Pasupathy et al., 2021). Therefore, we have decided to perform a cross-sectional pilot study to assess the relationship between COVID-19 active infection and MINOCA in Hispanic patients. We hypothesize that individuals with AMI and COVID-19 (AMICOVID+) who underwent coronary angiography will have a higher proportion of MINOCA than those with AMI without COVID-19 (AMICOVID-).

Materials and Methods

This is a single-center cross-sectional pilot study that gathered information through convenience sampling using the electronic medical records of a tertiary care institution (Instituto Cardiovascular del Cesar, Valledupar-Colombia) to identify patients with AMICOVID+ and patients with AMICOVID- who underwent coronary angiography during the pandemic. This cross-sectional study was written based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Sample

The inclusion criteria were Hispanic patients of $\geq$18 years of age diagnosed with AMI who had a COVID-19 test performed upon admission and underwent coronary angiography between February 2020 and October 2021.

AMI was defined (according to the fourth universal definition of myocardial infarction) as symptoms of acute myocardial ischemia with acute myocardial injury (cardiac troponin values rise and/or fall, with at least one value above the 99th percentile), and at least one of the following criteria: new ischemic Electrocardiographic (EKG) changes or new imaging evidence of regional wall motion abnormality or loss of viable myocardium consistent with ischemic etiology (Thygesen et al., 2018).

MINOCA was defined as AMI (as above) in a patient presenting with a percentage of luminal stenosis $\leq$50% during coronary angiography and in which other clinical conditions that may lead to myocardial injury without ischemia had been ruled out (specifically sepsis, pulmonary embolism, cardiac contusion, spontaneous coronary artery dissection, spontaneous coronary vasospasm) (Tamis-Holland et al., 2019).

A confirmed COVID-19 case was defined as a positive COVID-19 assay test (real-time reverse transcription polymerase chain reaction or antigen test) from a nasopharyngeal or oral swab.

The exclusion criteria were patients with a clinical history of thrombophilia, cancer, pregnancy, autoimmune diseases, or incomplete clinical records. The local ethics committee approved (Institutional Review Board Approval: INV-BPC-F-037) this study in strict adherence to national laws (Article 5, law 8430 of 1993) and the Helsinki Declaration. As the data was collected after patients were discharged, informed consent was waived.

Data Extraction and Missing Data

Patients were divided into two groups: those with AMICOVID+ and those with AMICOVID- who underwent coronary angiography. The variables extracted from the medical records were gender, age, hypertension, diabetes, smoking status, obesity, chronic kidney disease, EKG findings, cardiac dominance, other diagnoses detected during angiography, number of arteries affected by atherosclerosis, culprit coronary artery of myocardial infarction, complications during angiography, myocardial infarction type, percentage of luminal stenosis in the culprit artery, diagnosis of MINOCA, thrombus burden and left ventricular ejection fraction. Two authors collected the data in a data extraction table.

If missing data was present, it was assumed to be "missing at random"; therefore, the multiple imputation technique was carried out for missing numerical data, and hot-deck imputation was carried out for categorical missing data (Haukoos & Newgard, 2007; Newgard & Haukoos, 2007).

Outcome

The primary outcome was to evaluate the relationship between COVID-19 and MINOCA among Hispanic patients with AMI who underwent coronary angiography.

Statistical Analysis

All statistical analyses were done using STATA 17 (StataCorp LLC, College Station, TX). Categorical variables were summarized using absolute and relative frequencies. Numerical variables were first assessed for normality through histograms and the Shapiro-Wilk test; if a normal distribution was demonstrated, means and standard deviations were utilized. In contrast, numerical variables with no normal distribution were expressed through medians and interquartile range (IQR).

The variables between the AMICOVID+ and AMICOVID- groups were compared using t-student or Mann-Whitney tests for parametric and non-parametric numerical data, respectively, and with the Chi-squared test or Fisher test for categorical variables based on the expected frequencies contingency table. The comparison between variables was planned to assess if a statistically significant difference between the two groups existed.

The association between COVID-19 and MINOCA was assessed using the Chi-squared or Fisher test based on the abovementioned conditions. A statistically significant p-value was set as ≤ 0.05. The variables with statistically significant results underwent a sensitivity analysis using logistic regression to adjust for one covariate (one each time). Due to the small sample size, adjusting multiple variables simultaneously was considered inappropriate.

Angiographic Procedure

All patients received 300 mg of aspirin and 300 mg of clopidogrel per os before the intervention. Coronary angiography was performed through a femoral or radial approach. Unfractionated heparin (100 IU/kg/IV) was administered if the approach was radial or a primary percutaneous coronary intervention was performed.

The thrombus burden was determined using Sianos et al. (2010) classification (G0 = no thrombus, G1 = possible thrombus, G2 = small thrombus [most significant dimension $\leq$ 1/2 vessel diameter (VD)], G3 = moderate thrombus (> 1/2 but < 2VD), G4 = large thrombus ($\geq$ 2VD), G5 = unable to assess thrombus burden due to vessel occlusion (Sianos et al., 2010). High thrombus burden was defined by the presence of a large thrombus ($\geq$ G4).

Ejection fraction calculation

The left ventricular ejection fraction was calculated using the biplane summation technique with a General Electric S70N echocardiograph or during left ventricular contrast ventriculography using the Dodge-Sandler area-length method (Dodge et al., 1960; Lang et al., 2015).

Results

Of the 96 patients with AMI and a COVID-19 test performed upon admission who underwent coronary angiography between February 2020 and October 2021, only 28 (29%) met the inclusion criteria (Figure 1).

Baseline characteristics of AMICOVID+ and AMICOVID- groups are outlined in (Table 1); no statistically significant differences were found in the groups' baseline characteristics. Three patients of the AMICOVID+ group did not have ejection fraction data; therefore, hot-deck imputation was carried out. MINOCA was significantly higher in the AMICOVID+ group compared to the AMICOVID- group (85.7% vs 21.4%. p = 0.001), showing no effect modification when sensitivity analysis was carried out (Appendix A).

Discussion

The main finding of this pilot study is that MINOCA was present in a significantly higher proportion in the AMICOVID+ group compared to the AMICOVID- group. It is hypothesized that the biological mechanism under MINOCA is due to dysfunctional microcirculation that leads to cardiac necrosis or the compression of the lumen of the artery secondary to myocardial edema (Niccoli & Camici, 2020). According to John et al. (2022), MINOCA in patients infected with COVID-19 can result from myocarditis, takotsubo cardiomyopathy, coronary vasospasm, and sepsis (John et al., 2022).

In our study, all patients had an AMI with a clinical presentation highly suggestive of acute myocardial ischemia; we hypothesize that the MINOCA cases were primarily due to direct cardiomyocyte damage by SARS-CoV2, leading to myocardial edema, and subsequently producing arterial lumen compression, causing infarction (John et al., 2022; Niccoli & Camici, 2020). This theory is backed up by the fact that none of our patients in the AMICOVID+ group had sepsis nor coronary vasospasm detected during angiography, and only one patient had takotsubo cardiomyopathy.

The relationship between COVID-19 and MINOCA has been found previously in other studies; the incidence of MINOCA in patients with COVID-19 is at least four times higher (22%) than in patients without COVID-19 (6%) (Alasnag et al., 2022). In our study, we found similar results showing that MINOCA was

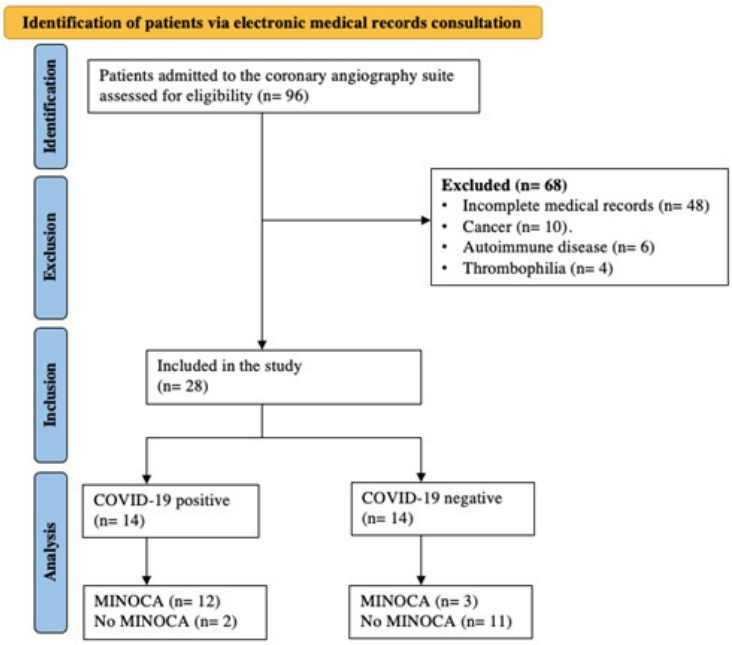

Figure 1: *STROBE flow chart.*

four times higher in the AMICOVID+ group compared to the AMICOVID- group (85.7% vs. 21.4%); however, we found a higher proportion of MINOCA cases in our sample compared to what has been previously reported in the literature.

A study by Modin et al. (2020) showed that there was a nearly fivefold increase in the incidence of AMI within the 14 days following a COVID-19 diagnosis compared to the 180 days preceding the diagnosis within the same group of patients (Modin et al., 2020). On the other hand, a manuscript by Katsoularis et al. (2021) found that the risk of AMI was almost twofold higher during the initial 14 days after a COVID-19 diagnosis (Katsoularis et al., 2021). However, this effect was temporary, as the risk in the third and fourth weeks did not show a significant increase compared to the same patients 90 days before their COVID-19 diagnosis. These findings suggest that COVID-19 may pose a potential risk factor for the development of AMI in the first two weeks after diagnosis (Katsoularis et al., 2021).

Montero-Cabezas et al. (2022) included 57 patients with COVID-19 and AMI who underwent coronary angiography; they identified 42% of cases with a high thrombus burden. These results differ significantly from our study's findings, where only 7.1% of patients in the AMICOVID+ group had a high thrombus burden (Montero-Cabezas et al., 2022). These differences can be explained by the fact that in the study by Montero-Cabezas et al. (2022), the patients were more comorbid with higher degrees of renal insufficiency; moreover, most of the patients included in their study were males (82%), and it has been described that MINOCA is more frequent in females, which represented more than 50% of our sample (Montero-Cabezas et al., 2022). The main strength of this study is that it is based on the Latin American (Hispanic) population, which is a region needing more research data, making our results novel; also, we had a comparison group without COVID-19 infection and low rates of missing data. The limitations of this study are the low sample size, which can provide high heterogeneity and low robustness of data. Another limitation is that the patients were recruited from a single center using convenience sampling, which can lead to bias, affecting our results' external validity. Additionally, when the patients' electronic medical records were accessed, no information was available about their vaccination status. However, considering their age ranges, the time when the vaccinations started in Colombia (February 20, 2021), and the limited number of doses available, it is likely that most were either unvaccinated or had received only a single dose.

One of the most significant limitations of this study is that simultaneous multiple covariates adjustment could not be performed due to the low sample size. However, the variables with statistically significant results underwent a sensitivity analysis using logistic regression to adjust for one covariate (one each time), showing that the effect persisted in being statistically significant in "MINOCA," "percentage of luminal stenosis," and "number of arteries affected by atherosclerosis." The result changed to non-statistically significant in "culprit coronary artery" when clinically significant variables were ad-

Variables n (%)	Subgroup	AMICOVID+ (n=14; 50%)	AMICOVID- (n=14; 50%)	P-value
Age, median (IQR)		69 years (IQR= 80 – 63)	71 years (IQR = 80 - 64)	0.66
Gender	Male	5 (35.7)	4 (28.6)	0.99
	Female	9 (64.3)	10 (71.4)	
Hypertension	Yes	10 (71.5)	13 (92.9)	
	No	4 (28.5)	1 (7.1)	0.32
Diabetes	Yes	3 (21)	6 (42.9)	0.42
	No	11 (79)	8 (57.1)	
Smoker	Yes	6 (43)	11 (78.6)	0.12
	No	8 (57)	3 (21.4)	
Obesity	Yes	4 (29)	3 (21.4)	0.99
	No	10 (71)	11 (78.6)	
Chronic kidney disease	Yes	0 (0)	4 (28.6)	
	No	14 (100)	10 (71.4)	0.09
EKG findings	ST-segment elevation	1 (7.1)	1 (7.1)	
	ST-segment dynamic abnormalities	6 (42.9)	2 (14.3)	0.38
	Non-specific abnormalities	2 (14.3)	6 (42.9)	
	Bradyarrhythmias	3 (21.4)	3 (21.4)	
	Tachyarrhythmias	2 (14.3)	2 (14.3)	
Type of myocardial infarction	ST-segment elevation	1 (7.1)	1 (7.1)	0.99
	Non-ST-segment elevation	13 (92.9)	13 (92.9)	
Cardiac dominance	Right coronary artery	12 (85.7)	12 (85.7)	0.99
	Left coronary artery	2 (14.3)	2 (14.3)	
Number of arteries affected by atherosclerosis	0	4 (28.6)	0 (0)	0.019*
	1	5 (35.7)	2 (14.3)	
	2	3 (21.4)	3 (21.4)	
	≥3	2 (14.3)	9 (64.3)	
Culprit coronary artery	LADA	1 (7.1)	5 (35.7)	0.02+
	PDA	0 (0)	1 (7.1)	
	OMA	0 (0)	0 (0)	
	CA	0 (0)	1 (7.1)	
	RCA	1 (7.1)	3 (21.4)	
	PLA	0 (0)	1 (7.1)	
	No culprit coronary artery	12 (85.7)	3 (21.4)	
Percentage of luminal stenosis of the culprit artery	0%	6 (42.9)	3 (21.4)	0.002*
	>0 - ≤50%	6 (42.9)	0 (0)	
	>50 - ≤99%	1 (7.1)	7 (50)	
	100%	1 (7.1)	4 (28.6)	
MINOCA	Yes	12 (85.7)	3 (21.4)	0.001*
	No	2 (14.3)	11 (78.6)	
High thrombus burden	Yes	1 (7.1)	5 (35.7)	0.16
	No	13 (92.9)	9 (64.3)	
Left ventricular ejection fraction	≤ 40%	2 (14.3)	5 (35.7)	0.38
	> 40%	12 (85.7)	9 (64.3)	
Other diagnoses during angiography	Takotsubo syndrome	1 (7.1)	1 (7.1)	0.99
	None	13 (92.9)	13 (92.9)	
Complications during angiography	Yes	0 (0)	0 (0)	0.99
	No	14 (100)	14 (100)	

Numerical data are presented as medians and IQR. Categorical data are presented as absolute (n) and relative frequencies (%). **LADA:** Left anterior descending artery; **PDA:** Posterior descending artery; **OMA:** Obtuse marginal artery; **CA:** Circumflex artery; **RCA:** Right coronary artery; **PLA:** Posterolateral artery.

* The result continued to be statistically significant when sensitivity analysis was performed

+ The result changed to non-statistically significant when sensitivity analysis was performed

Table 1: *Baseline characteristics of the sample.*

justed.

Since this study is cross-sectional, it cannot demonstrate causality between COVID-19 and MINOCA; therefore, further studies are needed to increase the robustness of the evidence.

Conclusion

MINOCA was found in a significantly higher proportion in the AMICOVID+ group than in the AMICOVID- group. However, this was a single-center cross-sectional study with a small sample size; therefore, these results must be corroborated in different populations with larger sample sizes.

Abbreviations

MINOCA: Myocardial infarction with no obstructive coronary arteries.
AMI: Acute myocardial infarction.
AMICOVID+: Acute myocardial infarction and COVID-19 group.
AMICOVID-: Acute myocardial infarction without COVID-19 group.
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.
COVID-19: Coronavirus-19 disease.
CAD: Coronary artery disease.
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology Guidelines.
IQR: Interquartile range.
VD: Vessel diameter.

Supplementary materials

Appendix A, B.

Author Contributions

All the named authors participated significantly during the manuscript elaboration to take responsibility for it.

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Conflicts of Interest

The authors declare no conflict of interest.

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