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Risk for Subsequent SARS-CoV-2 Infection and Severe COVID-19 Among Community-Dwellers With Pre-Existing Cervicocephalic Atherosclerosis: A Population-Based Study

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Abstract

Background: COVID-19 patients may develop atherosclerosis-related complications. Whether a proportion of these patients already had asymptomatic cervicocephalic atherosclerosis before SARS-CoV-2 infection is not known. This study assessed whether pre-existing cervicocephalic atherosclerosis increased the susceptibility to SARS-CoV-2 infection or resulted in more severe or fatal COVID-19. **Methods:** Individuals enrolled in the Atahualpa Project cohort who received head CT (for assessing carotid siphon calcifications) and B-mode ultrasounds (for measurement of the carotid intima-media thickness) prior to the pandemic were eligible for this study. Among this cohort, those who also received serological tests for detection of SARS-CoV-2 antibodies and clinical evaluations for assessment of COVID-19 severity were enrolled. Multivariate logistic regression and exposure-effect models were fitted to assess the association between pre-existing atherosclerosis biomarkers, and SARS-CoV-2 seropositivity and COVID-19 severity. **Results:** Overall, 154 of 519 study participants (30%) had evidence of cervicocephalic atherosclerosis. A total of 325 (63%) individuals became SARS-CoV-2 positive, and 65 (23.5%) of seropositive individuals had severe or fatal COVID-19. The risk of SARS-CoV-2 seropositive status did not differ across individuals with and without atherosclerosis biomarkers ($P = .360$). Likewise, seropositive individuals with pre-existing atherosclerosis were not more prone to develop severe or fatal COVID-19 than those without evidence of atherosclerosis ($P = .274$). Average estimated exposure effects of pre-existing cervicocephalic atherosclerosis versus no atherosclerosis over SARS-CoV-2 seropositivity and COVID-19 severity were not significant. **Conclusions:** Pre-existing cervicocephalic atherosclerosis does not increase the risk of acquiring SARS-CoV-2 infection nor the severity of COVID-19 among seropositive individuals.

Keywords

cervicocephalic atherosclerosis, SARS-CoV-2, COVID-19, risk factors, population-based study

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Introduction

According to an expert panel of the World Health Organization, a stroke may occur in about 5% (95% C.I.: 2.8%-8.7%) of patients with Coronavirus Disease 2019 (COVID-19).[1] With more than 250 million people infected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) up of November 2021, the global burden of stroke has likely increased during the pandemic. While pathogenetic mechanisms responsible for stroke occurrence among COVID-19 patients are complex and not well

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understood, recent reviews suggest that the vast majority of strokes are ischemic and related to either a hypercoagulable state, vasculitis, or cardiomyopathy; in addition, a sizable proportion of strokes are of undetermined origin.[2,3] Intracranial atherosclerotic disease (ICAD) has been conjectured to be the most likely mechanism underlying stroke in some COVID-19 patients.[4,5] Whether a proportion of such patients had asymptomatic cervicocephalic atherosclerosis prior to infection and whether this predisposes to SARS-CoV-2 infection or to a more severe COVID-19 is not known.

Atahualpa—a rural Ecuadorian village—was struck by the pandemic from March to May 2020. A massive outbreak infection was evidenced by a sudden increase in COVID-19-related deaths,[6] a SARS-CoV-2 seroprevalence of 45% among adults living in the community,[7] and an incidence rate ratio of 7.4 per 100 person-months of virus exposure.[8] Utilizing the well-established Atahualpa Project cohort, this study assessed whether pre-existing cervicocephalic atherosclerosis increased the susceptibility to SARS-CoV-2 infection or, if in the subset of seropositive individuals, resulted in a more severe or fatal illness.

Material and Methods

Study Population

This study was carried out in middle-aged and older adults residing in Atahualpa where several epidemiological studies on SARS-CoV-2 infection have been conducted.[6-11] As detailed elsewhere, Atahualpa residents are racially homogeneous (Amerindian ancestry), and share characteristics regarding socio-economic status and dietary habits; in addition, the migration rate is low, which makes this village an ideal setting for the follow-up of cohort studies.[12]

Study Design

Following a population-based prospective longitudinal study design, all individuals actively enrolled in the Atahualpa Project Cohort as of May 2020, who previously had assessments of intracranial and extracranial carotid artery atherosclerosis biomarkers, were eligible for this study. Those who also signed an informed consent for determination of SARS-CoV-2 IgM and IgG antibodies were enrolled. Several rounds of antibody testing and repeated clinical evaluations were performed until the end of the follow-up period in order to assess the independent association between pre-existing atherosclerosis biomarkers (as exposures) and SARS-CoV-2 seropositivity and COVID-19 severity (as outcomes). The study was approved by the I.R.B. of our Institution.

Intracranial Atherosclerosis Evaluation

Imaging studies were performed with a Philips Brilliance 64 CT scanner (Philips Medical Systems, Eindhoven, the Netherlands). Slice thickness was 3 mm with no gap between slices. CT digital images were viewed using the Osirix Medical Imaging software (Pixmeo, Geneva, Switzerland) with the bone windows setting to grade carotid siphon calcifications. As detailed elsewhere,[13] Grade 1 was defined as the absence or near-absence of calcification, Grade 2 as tiny scattered calcifications, Grade 3 as thick interrupted or thin confluent calcifications, and Grade 4 as thick contiguous calcifications. Individuals were further classified into those with low (Grades 1 and 2) and high (Grades 3 and 4) calcium content in carotid siphons. All scans were read by an experienced neurologist and a neuroradiologist. Kappa coefficients for inter-rater agreements were .81 for the presence of high calcium content in carotid siphons, and discrepancies were resolved by consensus.[14]

Extracranial Carotid Artery Atherosclerosis Evaluation

B-mode ultrasound exams were performed in each carotid artery in 3 segments to assess the carotid intima-media thickness (cIMT).[15] Carotid ultrasounds were performed by an experienced sonographer (blinded to the other information). All exams were subsequently reviewed by another sonographer blinded to previous readings.[14] If the measurements of the total cIMT from the 2 readers differed by 1 standard deviation from the mean (0.2 mm), images were again reviewed by the 2 readers for consensus.

Serological Tests

Detection of SARS-CoV-2 IgM and IgG antibodies was performed using the BIOHIT SARS-CoV-2 antibody test kit, colloidal gold method (BIOHIT Health Care Ltd., Cheshire, UK). Reliability of this test is high, as detailed elsewhere.[16] A total of 5 rounds of tests were performed—May 2020, June 2020, September 2020, January 2021, and April 2021—using the same trained personnel, kits, and procedures. All tests were independently read by 2 of the authors, blinded to any individual information. Overall, the Kappa coefficient for interrater agreement was .91, and discrepancies were resolved by consensus.

COVID-19 Severity Assessment

We used previously described criteria to define severe COVID-19.[17] Study participants who had a positive serological test for the SARS-CoV-2 antibodies received frequent home visits and clinical examinations to determine if they developed severe COVID-19-related symptomatology. Those who had been hospitalized were visited at nearby community hospitals where Atahualpa individuals with severe COVID-19 were admitted, and medical records were reviewed together with the hospital medical staff. We also took into account patients with severe COVID-19 who were

not hospitalized and remained at home receiving oxygen therapy and other treatments. Individuals who died as a result of the disease during the observation period were also tabulated.

Clinical Covariates Investigated

Covariates were selected if they are suspected to play a role in modifying the susceptibility to SARS-CoV-2 infection or the severity of COVID-19. These include demographics (age and sex) as well as the complete set of cardiovascular risk factors according to the criteria of the American Heart Association (AHA), which included: a poor smoking status if the subject was a current smoker, a poor diet if the individual had 0-1 component of the AHA healthy diet, a poor physical activity if there was no moderate or vigorous activity, a poor body mass index if $\geq 30\,kg/m^2$, a poor blood pressure if $\geq 140/90$ mmHg, a poor fasting glucose if ≥ 126 mg/dL, and a poor total cholesterol blood level if ≥ 240 mg/dL.[18] Our determination of these factors was updated during an annual survey conducted 3 months before the start of the pandemic in the village. Socio-economic factors deemed relevant to the pandemic were also used as covariates. These included the number of persons living in the household, the number of bedrooms per house, and a period of home confinement for at least 2 months during the pandemic.[7,8]

Statistical Analysis

Data analyses were carried out by using STATA version 17 (College Station, TX, USA). In unadjusted analyses, continuous variables were compared by linear models and categorical variables by the chi-squared or Fisher exact test, as appropriate. Separate multivariate logistic regression models were fitted to estimate the independent association between pre-existing cervicocephalic atherosclerosis and seropositivity to SARS-CoV-2 antibodies and severity of COVID-19 as the dependent variables, after adjusting for all the above-mentioned covariates. To further assess the relationship of pre-existing cervicocephalic atherosclerosis with SARS-CoV-2-related seropositivity and COVID-19 severity (outcomes), we used treatment effects methodology computing inverse probability of exposure (treatment effect) weighting to address and adjust for the effect of confounders on cervicocephalic atherosclerosis. Estimates of the adjusted odds of atherosclerosis on SARS-CoV-2 seropositivity and severe COVID-19 are provided.

Results

Enrollment Process

Figure 1 is a flowchart depicting enrollment and the reasons for not participating at each stage of this process. In brief, from a total of 933 individuals aged ≥ 40 years enrolled in the Atahualpa Project cohort from June 2012 to May 2019, 590 received both a CT for assessment of calcium content in the carotid siphons and B-mode ultrasounds for cIMT evaluation before the pandemic. Of these, 57 had died or emigrated before the invitation to receive serological tests for detection of SARS-CoV-2 antibodies. Fourteen of the remaining 533 subjects actively enrolled as of May 2020 refused the tests, leaving a total of 519 individuals enrolled in the study.

Overall Characteristics of Participants

The mean ($\pm$SD) age of study participants was 61.8 ± 12 years (median age: 61 years) and 304 (59%) were women. Twenty individuals (4%) were current smokers, 145 (28%) had a body mass index $\geq 30\,kg/m^2$, 27 (5%) had poor physical activity, 23 (4%) had a poor diet, 166 (32%) had blood pressure $\geq 140/90$ mmHg, 132 (25%) had fasting glucose ≥ 126 mg/dL, and 57 (11%) had total cholesterol levels ≥ 240 mg/dL. Regarding socio-economic factors of relevance to the pandemic, the mean number of individuals and bedrooms per house were 5.4 ± 3.3 and 2.5 ± 1.1, respectively, and 210 (40%) had been confined to home for at least 2 months.

A total of 112 individuals (22%) had high calcium content in the carotid siphons. The mean cIMT was 0.85 ± 0.19 mm, with 69 subjects (13%) having a cIMT >1 mm. Overall, 154 study participants (30%) had evidence of cervicocephalic atherosclerosis (high calcium content in the carotid siphons, increased cIMT, or both). Seropositivity for SARS-CoV-2 antibodies was determined in 325 (63%) persons. Of them, 222 (68%) were seropositive in May 2020, and the remaining 103 individuals seroconverted to positive in one of the subsequent rounds of serological test (23 in June 2020, 28 in September 2020, 23 in January 2021, and 29 in April 2021). COVID-19-related symptomatology was recalled by 277 out of 325 seropositive individuals (85%) individuals. Of the 277 symptomatic individuals, 65 (23.5%) had severe COVID-19, including 8 who died as the result of the disease.

Association Between Pre-Existing Cervicocephalic Atherosclerosis and Susceptibility to SARS-CoV-2 Infection

In unadjusted analyses, individuals with cervicocephalic atherosclerosis (any biomarker) were older, more often male, had worse physical activity, had more often hypertension, high fasting glucose levels, and were more often confined to home than those without biomarkers. In addition, the body mass index was inversely associated with cervicocephalic atherosclerosis (due to a mechanism termed the "obesity paradox," as previously reported in this population).[19] Overall,

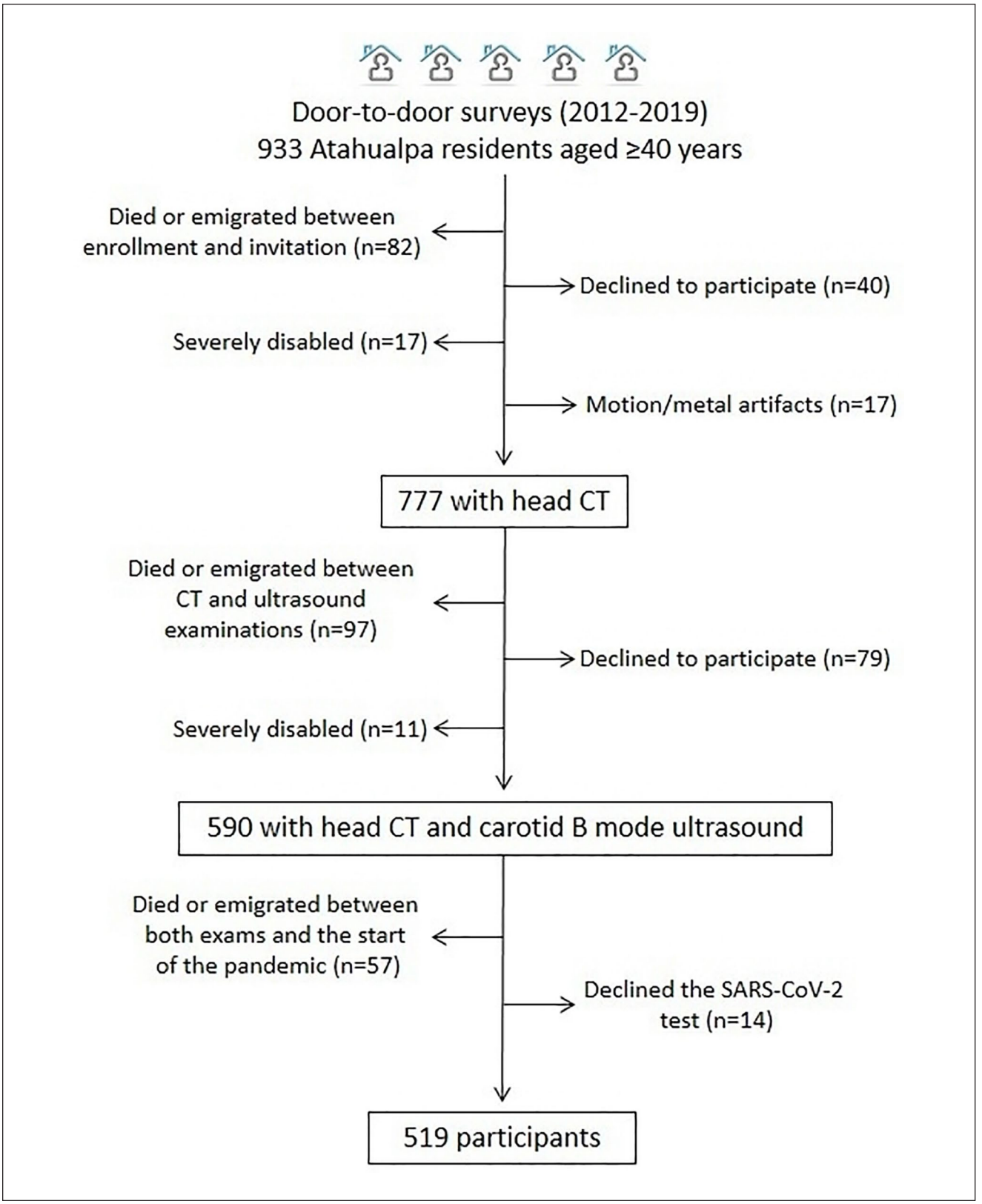

Figure 1. Flowchart depicting enrollment and the reasons for not participating at each stage of this process.

Table 1. Characteristics of Atahualpa Residents Across Individuals With and Without Pre-Existing Cervicocephalic Atherosclerosis (Unadjusted Analyses).

Variable	Total series (n = 519)	Pre-existing cervicocephalic atherosclerosis		
		No (n = 365)	Yes (n = 154)	*P* value
Age, years (mean ± SD)	61.8 ± 12	58.7 ± 11	69.1 ± 11	<.001*
Female gender, n (%)	304 (59)	230 (63)	74 (48)	.002*
Current smoker, n (%)	20 (4)	13 (4)	7 (5)	.595
Body mass index ≥30 kg/m^2, n (%)	145 (28)	118 (32)	27 (18)	<.001*
Poor physical activity, n (%)	27 (5)	13 (4)	14 (9)	.009*
Poor diet, n (%)	23 (4)	14 (4)	9 (6)	.309
Blood pressure ≥140/90 mmHg, n (%)	166 (32)	90 (25)	76 (49)	<.001*
Fasting glucose ≥126 mg/dL, n (%)	132 (25)	73 (20)	59 (38)	<.001*
Total cholesterol ≥240 mg/dL, n (%)	57 (11)	35 (10)	22 (14)	.118
Individuals per house, mean ± SD	5.4 ± 3.3	5.6 ± 3.2	5.0 ± 3.4	.056
Bedrooms per house, mean ± SD	2.5 ± 1.1	2.6 ± 1.1	2.4 ± 1.0	.053
Home confinement, n (%)	210 (40)	131 (36)	79 (51)	.001*
SARS-CoV-2 seropositive status, n (%)	325 (63)	234 (64)	91 (59)	.280

*Statistically significant result.

Table 2. Multivariate Logistic Regression Model Showing That SARS-CoV-2 Serological Status (Dependent Variable) is Not Predicted by Pre-Existing Cervicocephalic Atherosclerosis and Other Baseline Covariates. Log likelihood = −335.40298.

Serological status	Odds ratio	95% confidence interval	*P* value
Cervicocephalic atherosclerosis	0.81	0.52-1.27	.360
Age	1.01	0.99-1.02	.510
Being female	1.15	0.77-1.73	.500
Current smokers	0.63	0.24-1.62	.335
Body mass index ≥30 kg/m^2	1.08	0.71-1.66	.707
Poor physical activity	0.71	0.31-1.61	.411
Poor diet	0.51	0.21-1.22	.131
Blood pressure ≥140/90 mmHg	1.13	0.74-1.72	.571
Fasting glucose ≥126 mg/dL	0.93	0.61-1.42	.732
Total cholesterol ≥240 mg/dL	1.59	0.86-2.96	.138
Number of persons per house	1.06	0.99-1.13	.084
Bedrooms per house	0.82	0.68-1.00	.055
Home confinement	0.82	0.54-1.23	.334
Constant	1.42	0.43-4.75	.567

the risk of SARS-CoV-2 seropositive status did not differ across individuals with and without atherosclerosis biomarkers (Table 1). There was also no difference in the frequency of atherosclerosis biomarkers across individuals who seroconverted early in the course of the pandemic (May-June, 2020) versus those who seroconverted after September 2020 (71 of 245 [29%] vs 20 of 80 [25%]; $P = .491$). A multivariate logistic regression model did not disclose any significant association between pre-existing atherosclerosis and increased susceptibility to SAPS-CoV-2 infection; in this model, none of the investigated covariates reached independent significance (Table 2). The average estimated exposure effect of pre-existing cervicocephalic atherosclerosis versus no atherosclerosis over SARS-CoV-2 seropositivity was not significant (β: .004; 95% C.I.: −0.114 to 0.120; $P = .952$).

Association Between Pre-Existing Cervicocephalic Atherosclerosis and COVID-19 Severity in SARS-CoV-2 Seropositive Individuals

When only the subset of SARS-CoV-2 seropositive individuals were considered for analyses, disease severity was not associated with the presence of cervicocephalic atherosclerosis in unadjusted analysis. In such univariate models, individuals with atherosclerosis were older, more frequent males, had more often hypertension, high fasting

Table 3. Characteristics of SARS-CoV-2 Seropositive Individuals With and Without Pre-Existing Cervicocephalic Atherosclerosis (Unadjusted Analyses).

Variable	Total series (n = 325)	Pre-existing cervicocephalic atherosclerosis		
		No (n = 234)	Yes (n = 91)	*P* value
Age, years (mean ± SD)	61.8 ± 11.9	59.2 ± 11.3	68.6 ± 10.7	<.001*
Female gender, n (%)	196 (60)	151 (65)	45 (49)	.013*
Current smoker, n (%)	10 (3)	5 (2)	5 (5)	.150
Body mass index ≥30 kg/m^2, n (%)	92 (28)	73 (31)	19 (21)	.638
Poor physical activity, n (%)	14 (4)	7 (3)	7 (8)	.609
Poor diet, n (%)	10 (3)	9 (4)	1 (1)	.293
Blood pressure ≥140/90 mmHg, n (%)	105 (32)	60 (26)	45 (49)	<.001*
Fasting glucose ≥126 mg/dL, n (%)	82 (25)	47 (20)	34 (37)	.001*
Total cholesterol ≥240 mg/dL, n (%)	41 (13)	27 (12)	14 (15)	.211
Individuals per house, mean ± SD	5.5 ± 3.3	5.7 ± 3.3	5.1 ± 3.3	.142
Bedrooms per house, mean ± SD	2.5 ± 1.0	2.5 ± 1.0	2.5 ± 1.1	. . .
Home confinement, n (%)	127 (39)	82 (35)	45 (49)	.017*
Severe COVID-19, including deaths, n (%)	65 (20)	46 (20)	19 (21)	.804

*Statistically significant result.

Table 4. Multivariate Logistic Regression Model Showing That COVID-19 Severity (Dependent Variable) is Not Predicted Among SARS-CoV-2 Seropositive Individuals by Pre-Existing Cervicocephalic Atherosclerosis. Only Increased Age Remained Independently Significant in This Model. Log likelihood = −153.62458.

Serological status	Odds ratio	95% confidence interval	*P* value
Cervicocephalic atherosclerosis	0.68	0.34-1.36	.274
Age	1.03	1.00-1.06	.026*
Being female	0.67	0.36-1.26	.218
Current smokers	3.24	0.80-13.1	.099
Body mass index ≥30 kg/m^2	0.71	0.35-1.45	.344
Poor physical activity	1.57	0.39-6.36	.530
Poor diet	0.38	0.04-3.28	.378
Blood pressure ≥140/90 mmHg	0.76	0.39-1.46	.407
Fasting glucose ≥126 mg/dL	1.21	0.63-2.34	.560
Total cholesterol ≥240 mg/dL	1.35	0.60-3.03	.469
Number of persons per house	0.92	0.82-1.02	.126
Bedrooms per house	1.22	0.89-1.69	.219
Home confinement	0.74	0.38-1.44	.376
Constant	0.05	0.01-0.35	.003

*Statistically significant result.

glucose levels, and were more often confined to home than those without biomarkers (Table 3). A multivariate logistic regression model did not reveal any significant association between pre-existing atherosclerosis and COVID-19 severity in SARS-CoV-2 seropositive individuals; in this model, only increased age reached independent significance (Table 4). Among seropositive individuals, the estimated average exposure effect of pre-existing cervicocephalic atherosclerosis versus no atherosclerosis over COVID-19 severity was not significant (β: −.033; 95% C.I.: −0.157 to 0.089; $P = .592$).

Discussion

Study results show that susceptibility to SARS-CoV-2 infection and COVID-19 severity are not modified by the presence of cervicocephalic atherosclerosis. The lack of association in univariate and multivariate adjusted models was confirmed in exposure-effects models that took into account covariates related to atherosclerosis, viral infection, or both. As previously noted, the latter models were fitted with cervicocephalic atherosclerosis as the exposure and SARS-CoV-2 infection and COVID-19 severity as the outcomes.

While several studies have attempted to assess the relationship between atherosclerosis and SARS-CoV-2 infection, biomarkers of atherosclerosis were measured after the infection and the reported associations may have been the result of newly developed atherosclerosis following SARS-CoV-2 infection.[20,21] There are some reports of occlusion of large intra- or extracranial arteries soon after SARS-CoV-2 infection, and some patients who present these complications had cardiovascular risk factors prior to the infection; nevertheless, specific biomarkers of pre-existing atherosclerosis have not been determined.[22-24] To the best of our knowledge, no previous study has systematically evaluated the impact of pre-existing atherosclerosis on these outcomes.

Atherosclerosis is a chronic inflammatory disease causing endothelial dysfunction and, as such, may act as a substrate for high viral replication as well as for the occurrence and progression of SARS-CoV-2-related cytokine storms which, in turn, are one of the chief causes of organ injury during the acute phase of COVID-19.[25] Based on this reasoning, pre-existing atherosclerotic disease could influence COVID-19 severity in susceptible individuals.[26,27] A systematic review of studies reporting brain histopathological findings of COVID-19 patients found atherosclerotic changes in about one third of cases; however, it was not possible to determine whether those changes were already present before the infection or if they occurred as a result of the deleterious effect of the virus on endothelial cells.[4] In addition, increased expression of the angiotensin converting enzyme2 (ACE2), observed in patients with pre-existing hypertension and cardiovascular diseases, may render individuals with pre-existing atherosclerosis more susceptible to infection since SARS-CoV-2 uses this enzyme as the portal of entry to human cells.[28] It has also been postulated that individuals with an established SARS-CoV-2 infection are more prone to develop new-onset atherosclerosis; in this scenario, the virus results in endothelial dysfunction that would favor the occurrence of atherosclerosis.[29] Similar adverse effects of SARS-CoV-2 have been described in other viral infections, namely HIV, hepatitis C virus, human T cell leukemia virus-1, among others.[30,31]

A major strength of the present study is that it provides the opportunity to assess the role of cervicocephalic atherosclerosis in the acquisition of SARS-CoV-2 infection and the severity of COVID-19. Another strength is the inclusion of participants of the Atahualpa Project cohort in whom cardiovascular and other risk factors have previously been assessed. This reduces the likelihood of unexpected confounders that may occur when 2 different populations are compared. The homogeneity of study participants, in terms of race/ethnicity and living conditions is a potential limitation since our results may not be comparable to other populations. In addition, while the antibody test we used is reliable, we cannot totally dismiss misclassifications due to false positive or false negative results,[7] or the eventual possibility of cross-reactions with other regional-endemic viruses.[32] Moreover, as only the intracranial and carotid artery extracranial arterial beds were investigated, it is possible that some individuals without cervicocephalic atherosclerosis had other compromised vascular beds, for example, coronary and peripheral arteries. Further studies of individuals from other geographical locations who received systematic investigation of the presence of atherosclerotic biomarkers prior to the pandemic are warranted to support our findings.

In conclusion, this population study conducted in community-dwelling middle-aged and older adults living in a rural village severely struck by the pandemic, shows that pre-existing cervicocephalic atherosclerosis does not increase the susceptibility to SARS-CoV-2 infection nor the severity of COVID-19 among seropositive individuals. Ongoing longitudinal studies in this cohort with repeated determinations of cervicocephalic atherosclerosis biomarkers will help to evaluate the effects of SARS-CoV-2 infection and severe COVID-19 on the subsequent development of atherosclerosis.

Author Contributions

OHD: study design, imaging readings, manuscript drafting; RMM: statistical analysis, significant intellectual contribution to manuscript content; VJD: imaging readings, significant intellectual contribution to manuscript content; BYR: study coordinator, data collection, and analysis; DAR: data collection and analysis; AFC: data collection and analysis; MJS: significant intellectual contribution to manuscript content.

Declaration of Conflicting Interests

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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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