CorSalud 2020 Apr-Jun;12(2):129-137

CorSalud

Cuban Society of Cardiology

Original Article

Cardiocentro Ernesto Che Guevara Santa Clara Cuba

Epidemiological and laboratory aspects in patients with underlying cardiovascular disease and diagnosis of COVID-19 in Santa Clara (Cuba)

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: 17 de mayo de 2020
Accepted: 18 de junio de 2020

Competing interests
The authors declare no competing interests

Abbreviations
COVID-19: coronavirus disease 2019
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
WHO: World Health Organization

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ABSTRACT

Introduction: In March 2020, COVID-19 is declared a pandemic. The transmissibility of SARS-CoV-2 in asymptomatic patients, who could infect others, greatly complicates the detection of new cases.

Objectives: We sought to identify the degree of association of epidemiological factors and comorbidities associated with asymptomatic and symptomatic states, as well as ascertain the main manifestations in these individuals and determine the behavior of laboratory test results.

Methods: A cross-sectional descriptive study was conducted on a sample of 52 patients with underlying cardiovascular disease, diagnosed with COVID-19 and admitted to the Hospital Universitario Celestino Hernández Robau in Santa Clara (Cuba), a facility exclusively devoted to the care of such patients during the pandemic.

Results: High blood pressure predominated among the associated comorbidities (32.7%) and dry cough was the most frequent symptom (75%), followed by fever (25%). None of the subjects developed severe symptoms of COVID-19, nor did they die. The highest proportion of cases corresponded to asymptomatic patients (61.5%). Hypercholesterolemia was close to but not yet significant (OR=0.97; CI 0.82-1.16; p=0.06). Mean erythrocyte sedimentation values were higher in asymptomatic than symptomatic patients (CI 8.45-33.74; p=0.02).

Conclusions: In individuals with heart disease the relationship between epidemiological factors and associated comorbidities was similar in asymptomatic and symptomatic states. Results of most laboratory tests yielded no differences between the two types of patients.

Keywords: COVID-19, SARS-CoV-2, Signs and symptoms, Cardiovascular diseases, Comorbidity

Aspectos epidemiológicos y de laboratorio en pacientes con cardiopatía y diagnóstico de COVID-19 en Santa Clara (Cuba)

RESUMEN

Introducción: En marzo de 2020 la COVID-19 se declara pandemia. La capacidad de transmisibilidad del SARS-CoV-2 en pacientes asintomáticos, que podrían con-

Authors' contribution
GAPF and GIS: Research conception and design; data collection, analysis, interpretation, and manuscript writing.
LMR and RSH: Research conception, data analysis and interpretation.
ERG and JSR: Obtaining raw data and help in manuscript writing.
The manuscript was reviewed and unanimously approved by the authors.

tagiar a otros, hace muy compleja la detección de nuevos casos.
Objetivo: Identificar el grado de asociación de los factores epidemiológicos y las comorbilidades asociadas a los estados asintomático y sintomático. Conocer, en estos pacientes, las principales manifestaciones clínicas y determinar el comportamiento de los resultados de los exámenes de laboratorio.
Método: Se realizó un estudio descriptivo de carácter transversal a una muestra de 52 pacientes con cardiopatía, diagnosticados de COVID-19 e ingresados en el Hospital Universitario Celestino Hernández Robau de Santa Clara (Cuba), centro dedicado exclusivamente a la atención de este tipo de pacientes durante la pandemia.
Resultados: Entre las comorbilidades asociadas predominó la hipertensión arterial (32,7%) y la tos seca fue el síntoma más frecuente (75%), seguido de la fiebre (25%). Ninguno de los pacientes desarrolló síntomas graves de COVID-19, ni falleció. La mayor proporción de casos correspondió a los asintomáticos (61,5%). La comorbilidad que más se acercó a la significación, sin llegar a alcanzarla, fue la hipercolesterolemia (OR=0,97; IC 0,82-1,16; p=0,06). Los valores medios de eritrosedimentación fueron más elevados en los pacientes asintomáticos respecto a los sintomáticos (IC 8,45-33,74; p=0,02).
Conclusiones: En el paciente con cardiopatía la relación entre los factores epidemiológicos y las comorbilidades asociadas fueron similares en los estados asintomático y sintomático. No existieron diferencias en los resultados de la mayoría de los exámenes de laboratorio entre ambos tipos de pacientes.
Palabras clave: COVID-19, SARS-CoV-2, Signos y síntomas, Enfermedades cardiovasculares, Comorbilidad

INTRODUCTION

Several massive viral epidemics such as (SARS-CoV) severe acute respiratory syndrome coronavirus from 2002 to 2003, H1N1 influenza in 2009 and most recently MERS-CoV Middle East respiratory syndrome identified in Saudi Arabia in 2012 have been striking around the globe[1].

The outbreak of a number of cases with pneumonia of unknown etiology in the Wuhan province, China on December 2019 drew the attention of the global medical community. That same year, the World Health Organization (WHO) identified a new coronavirus as the causal agent of this type of pneumonia and provisionally called it novel coronavirus (2019-nCoV).

On February 11, 2020 WHO Director General Dr Tedros Adhanom Ghebreyesus announced the name of COVID-19 for any manifestation caused by this unknown causal agent, which has similar characteristics to the coronavirus that causes severe acute respiratory syndrome coronavirus or SARS-CoV reason why it was appointed as SARS-CoV-2[2].

On January 2020, the World Health Organization (WHO) declared COVID-19 a "public health emergency of international concern" reported by that time in 18 countries. By March 2020, there were 118.000 cases in 114 countries and more than 4.000 deaths. By then, the WHO declared COVID-19 as a pandemic[1,3].

While this article was being written (May 2020) there were, according to official figures, 184 countries with cases of COVID-19 reporting 3.986.119 confirmed cases and 278.817 deaths for a worldwide lethality of 6.99%[4].

Cuba reports a prevalence of 2.6% of positive cases to COVID-19 (1783 positive samples) with a lethality of less than 5% and where a prevalence of asymptomatic cases has been found to vary from 20-50% since the first positive case was known in the country on March 11, 2020. Nearly 211 positive cases have been diagnosed to date in the province of Villa Clara. Of these, 136 are from the city of Santa Clara, accounting for 64.4% of cases in the province and 7.6% nationwide[4].

One of the aspects that has been a true challenge for health systems around the world, even those highly developed such as that of China, Europe and the United States, is the transmissibility of SARS-CoV-2 in asymptomatic patients that could infect others, complicating the detection of new cases and thus, fostering the "hidden" spread and perpetuation of COVID-19[5].

Recent epidemiological studies have reported

that patients with COVID-19 who also have cardiovascular comorbidities and risk factors such as high blood pressure, diabetes mellitus, ischemic heart disease, cerebrovascular disease, among others, are indeed exposed to greater risk[3]. However, the literature reviewed indicates that the degree of association between cardiovascular comorbidity and presenting symptoms at the time of diagnosis have not hitherto been determined for this specific type of patient. Therefore, in this paper, we sought to identify the degree of association between epidemiological factors and comorbidities associated with asymptomatic and symptomatic states of patients with COVID-19 and previous heart disease. We also specified the main clinical symptoms found in these patients and the behavior of the laboratory test results among those asymptomatic and symptomatic as well.

METHOD

A cross-sectional descriptive study was conducted on a sample of 52 patients with underlying cardiovascular disease, diagnosed with COVID-19 from early April to May 2020, admitted to the *Hospital Universitario Celestino Hernández Robau* in Santa Clara, Villa Clara, a facility exclusively devoted to the care of such patients during the pandemic.

Variables

Any patient who did not report symptoms during the epidemiological survey at the time of diagnosis of COVID-19 or during his/her hospital stay was defined as asymptomatic; while anyone who reported the presence of symptoms in any of the above scenarios was identified as a symptomatic case.

All patients with cardiovascular disease prior to the diagnosis of COVID-19 were defined as cardiac patients.

The associated cardiovascular comorbidities were found in the anamnesis of the clinical histories of the patients, also including those diagnosed by the corresponding laboratory tests: hypercholesterolemia when fasting cholesterol higher than 5.7 mmol/l was determined and hypertriglyceridemia when the triglyceride level was higher than 2.2 mmol/l[6].

Procedure

A review of the epidemiological surveys and clinical records of each patient was carried out in order to obtain the most relevant epidemiological, clinical and laboratory information according to the objectives of the present study.

Real-time PCR (polymerase chain reaction) test by nasopharyngeal scrapings was performed on all patients to diagnose COVID-19.

All laboratory tests were performed on fasting patients using the standard-routine techniques in the country's clinical laboratories.

Analysis and processing

The data were analyzed using the SPSS version 17 software for statistical applications and descriptive statistics –absolute frequencies for qualitative variables and central tendency and dispersion measures for quantitative variables– were applied.

Table 1. Characterization of the study sample (n=52).

Variables	Nº	%
Age groups* (years)		
18 – 39	14	26.9
40 – 59	20	38.5
60 and older	18	34.6
Sex		
Male	27	51.9
Female	25	48.1
Skin color		
White	43	82.7
Non-white	9	17.3
Associated comorbidities		
High blood pressure	17	32.7
Hypertriglyceridemia	15	28.8
Hypercholesterolemia	8	15.4
Type 2 diabetes mellitus	6	11.5
Obesity	7	13.5
Ischemic heart disease	6	11.5

Average age: 53.10 ± 20.48

Contingency tables were used to determine the association between variables (Chi-square) and OR *odd ratio* (cross-product or probability ratio) in order to establish relationships between variables.

The significance threshold used was alpha = 0.05. Statistical significance was considered for any value of p<alpha.

RESULTS

Table 1 presents a characterization of the study sample. The average age found was 53.10±20.48 years with predominance of the group from 40 to 59 years (38.5%) followed by the group of 60 years and older, which represented 34.6%. White (82.7%) and male patients (51.9%) predominated. Among the associated comorbidities, high blood pressure was predominant in 32.7% of cases, followed by hypertriglyceridemia (28.8%) and hypercholesterolemia (15.4%). Type 2 diabetes mellitus and ischemic heart disease were present in 11.5% of cases each.

Dry cough was the most frequent symptom reported upon admission in 75% of the cases studied (**Figure 1**), followed by fever (25%), headache (25%) and general malaise (20%). None of the patients developed severe symptoms of COVID-19, nor

Table 2. Association of the variables studied in asymptomatic and symptomatic patients with underlying cardiovascular disease and diagnosis of COVID-19.

Variable	Presence of symptoms				Total	OR (CI 95 %)	χ^2	p
	Asymptomatic (n=32)		Symptomatic (n=20)					
	Nº	%	Nº	%	Nº			
Sex								
Female	15	60.0	10	40.0	25	0.92 (0.46-1.84)	0.48	0.82
Male	17	63.0	10	37.0	27			
Skin color								
White	26	60.5	17	39.5	43	1.18 (0.43-3.20)	0.12	0.72
Non-white	6	66.7	3	33.3	9			
High blood pressure								
Yes	9	52.9	8	47.1	17	1.37 (0.69-2.71)	0.78	0.37
No	23	65.7	12	34.3	35			
Hypertriglyceridemia								
Yes	9	60.0	6	40.0	15	0.94 (0.44-1.99)	0.21	0.88
No	23	62.2	14	37.8	37			
Hypercholesterolemia								
Yes	6	75.0	2	25.0	8	0.97 (0.82-1.16)	0.06	0.79
No	26	59.1	18	40.9	44			
Diabetes mellitus								
Yes	3	50.0	3	50.0	6	1.35 (0.55-3.27)	0.38	0.53
No	29	63.0	17	37.0	46			
Obesity								
Yes	4	57.1	3	42.9	7	1.13 (0.44-2.88)	0.66	0.79
No	28	62.2	17	37.8	45			
Ischemic heart disease								
Yes	5	83.3	1	16.7	6	0.40 (0.65-2.49)	1.36	0.24
No	27	58.7	19	41.3	46			

CI, confidence interval; OR, odd ratio or cross-product ratio; χ^2, Chi-square
Source: Medical records.

did they die. The highest proportion of cases, as shown in **figure 2**, was asymptomatic (61.5%).

When analyzing the association between the variables studied according to the presence or not of symptoms in patients with COVID-19 (**Table 2**), significant differences were not observed in terms of sex (p=0.48; OR=0.92) and skin color (p=0.12; OR=1.18). Hypercholesterolemia was the comorbidity that came closest to significance, though not reaching it, (p=0.06; OR= 0.97). The rest of the studied comorbidities did not show significant association with the presence or not of symptoms.

When comparing the mean values of laboratory tests (**Table 3**), a significant superiority of the mean values of erythrocyte sedimentation in asymptomatic patients over symptomatic patients (p=0.02) becomes apparent. No significant differences were found between those with and without symptoms in relation to the rest of the variables.

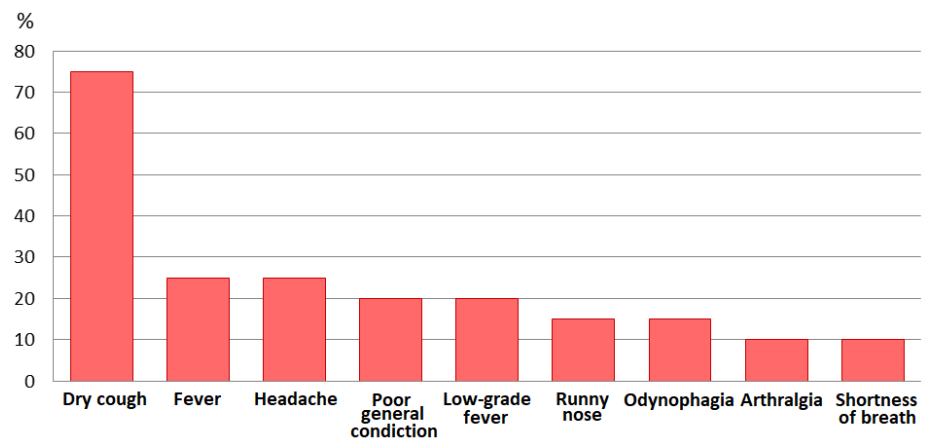

Figure 1. Most frequent symptoms reported upon admission by Covid-19 positive patients with cardiovascular involvement in the study sample
Source: Medical records.

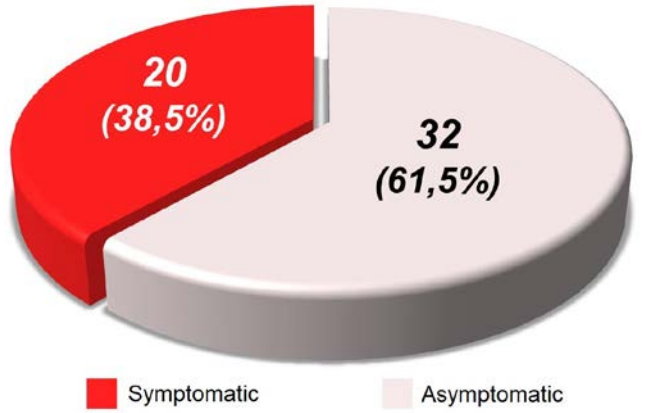

Figure 2. Percentage of asymptomatic and symptomatic COVID-19 patients with cardiovascular involvement in the study sample.
Source: Medical records.

DISCUSSION

The COVID-19 pandemic as a global public health emergency has impacted the world in an unprecedented way. Hence the importance of accurate epidemiological recognition in order to foster smart health strategies in the population.

In the present study, both average age of 53.1 years and most affected age groups coincide with a number of papers reporting similar results[7,8]. Early descriptions of COVID-19 positive patients reported that the disease occurred almost exclusively in those over 60 years of age primarily due to an aging-related compromised immune system[9]. The age alone has not been shown to be related to the possibility of being infected by the SARS-CoV-2 virus, although there is a proportional relationship with the adverse clinical course of the disease, along with other factors such as associated comorbidities[10].

Compared to women, men appear to be more susceptible to developing COVID-19 and experience a more rapid progression of the disease[11]. The explanation is found in the studies published on male mice infected with the SARS-CoV virus, which presents very similar characteristics to SARS-CoV-2, responsible for COVID-19, which presented significant correlations between viral load and accumulation of macrophages and neutrophils in the lungs. Likewise, mortality was increased when female mice were administered with an estrogen receptor blocker. This suggests that estrogens would possibly protect females from a more lethal course of infection[12]. Higher concentrations of angiotensin-receptor blocker have been recently found in females; which has

Table 3. Comparison of mean values of laboratory tests performed on patients with heart disease and asymptomatic and symptomatic COVID-19 diagnosis.

Variable	Asymptomatic	Nº	Mean	SD	t	df	p	CI (95%)
Packed cell volume	Yes	32	40.16	4.17	1.222	50	0.227	-1.60 - 6.57
	No	20	37.67	10.27				
Leukogram	Yes	32	7.9644	1.161	-1.700	50	0.095	-1.408 - 0.117
	No	20	8.610	1.571				
Polymorphs	Yes	32	0.5356	0.123	0.126	50	0.901	-0.069 - 0.078
	No	20	0.5310	0.1381				
Lymphocytes	Yes	32	0.4694	0.0981	0.994	50	0.325	-0.033 - 0.097
	No	20	0.4370	0.136				
Eosinophils	Yes	32	0.035	0.13	0.85	50	0.23	-0.022 - 0.081
	No	20	0.027	0.14				
Platelet count (µ/L)	Yes	32	203.13	38.787	-0.818	50	0.417	-35.8 - 15.1
	No	20	213.50	52.54				
Erythrocyte sedimentation rate (mm/h)	Yes	32	39.25	26.085	3.353	50	0.002	8.45 - 33.74
	No	20	18.15	13.14				
Glycemia (mmol/L)	Yes	32	5.1519	0.8196	-1.359	50	0.180	-1.058 - 0.204
	No	20	5.5790	1.44				
Creatinine (µmol/L)	Yes	32	91.25	38.67	0.636	50	0.527	-13.46 - 25.95
	No	20	85.01	26.04				
Uric acid (mmol/L)	Yes	32	309.06	87.72	-0.491	50	0.625	-66.34 - 40.26
	No	20	322.10	101.26				
Cholesterol (mmol/L)	Yes	32	5.4906	0.92	1.023	50	0.311	-0.25613 - 0.78
	No	20	5.2250	0.89				
Triglycerides (mmol/L)	Yes	32	1.9031	0.617	0.876	50	0.385	-0.21726 - 0.55
	No	20	1.7350	0.755				
TGP (UI/L)	Yes	32	34.53	22.35	0.137	50	0.891	-10.64 - 12.20
	No	20	33.75	15.24				
TGO (UI/L)	Yes	32	32.09	16.84	-0.036	50	0.972	-8.91 - 8.60
	No	20	32.25	12.36				
LDH (UI/L)	Yes	32	336.63	176.44	1.234	50	0.223	-37.7 - 158.19
	No	20	276.45	161.98				
GGT (UI/L)	Yes	32	57.19	47.140	-0.363	50	0.719	-35.72 - 24.80
	No	20	62.65	61.063				
C-reactive protein (UI/L)	Yes	32	9.02	20.159	1.145	50	0.258	-3.96 - 14.46
	No	20	3.77	4.350				

CI, confidence interval; df, degrees of freedom; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; SD, standard deviation; t, student's t-statistic; TGO, glutamic-oxalacetic transaminase; TGP, glutamic-pyruvic transaminase.
Source: Medical records.

been shown to play an anti-inflammatory role in lung injury and is currently being studied in order to find optimal solutions for treating COVID-19[13].

The disease was initially termed as "Chinese Virus" because it was mistakenly thought to affect only Asian people and that, consequently, African Americans individuals would be exempt from being infected. Such a myth was later dispelled when cases began to appear in the United States showing that this ethnic group would be one of the most severely affected in cities with a high prevalence of African-American people such as New York, Boston, Chicago, Detroit, New Orleans and Philadelphia. Publications on the ethnicity of COVID-19 are still relatively limited and no studies have been published addressing specific mechanisms within the human body that directly involve any of the races with increased susceptibility to COVID-19[14].

It is known that the presence of associated comorbidities substantially worsens patients' prognosis[10,11]. High blood pressure is one of the most reported in the literature reviewed, which is consistent with what we found in our work; as well as diabetes mellitus and chronic obstructive pulmonary disease, according to a recent meta-analysis enrolling 1558 COVID-19 positive patients, published by Wang *et al*[15]. The study also found cardiovascular and cerebrovascular conditions as aggravating risk factors for COVID-19[15], which significantly doubled the risk of complications associated with the course of this viral disease.

The most frequent symptoms found in our work coincide mostly with those reported in literature, with predominance of dry cough, fever and general malaise in a high percentage of symptomatic patients at the onset of the disease[2,11]. Similar findings were obtained by Adhikari *et al*[16], after analyzing the results of 65 epidemiological studies on COVID-19, published up to January 2020.

Traditional infection control and public health strategies rely primarily on early detection of disease to stop transmission. When the first cases of COVID-19 were detected, officers and managers of major public health systems worldwide applied the same response strategies that were successfully used to control SARS in 2003, including detecting cases with respiratory symptoms and subsequently performing diagnostic tests to manage isolation and quarantine.

This initial approach was based on the similarities between SARS-CoV-1 and SARS-CoV-2 viruses, which include transmission through saliva droplets, frequency of similar respiratory symptoms, and an almost identical mean incubation period of 5 days after exposure. However, these two epidemics have followed completely different trajectories. The SARS was controlled in 8 months, after SARS-CoV-1 virus had infected approximately 8100 people in limited geographic areas; while SARS-CoV-2, has infected millions of people in 5 months and has continued to spread around the globe. The explanation lies on the high presence of SARS-CoV-2 in the upper respiratory tract in asymptomatic subjects with COVID-19, which makes it different from SARS-CoV-1 where the process takes place in the lower respiratory tract, making SARS-CoV-2 transmissible before the onset of symptoms and greatly hindering the identification of cases[17].

The prevalence of patients with asymptomatic COVID-19 is variable and ranges from 10% to 60%[4,5,18], similar to what was observed in our study sample, where there were no differences between epidemiological factors and associated cardiovascular comorbidities with regard to their relationship with asymptomatic or symptomatic states. No research was found where this type of comparison was made in order to discuss the above result. It is therefore evident how difficult it is to individualize a patient with COVID-19 from an epidemiological perspective where the previous cardiovascular involvement is not decisive in the presence of symptoms at the initial diagnosis; although it is known to play a significant role in the clinical course after diagnosis[8,10].

According to the literature reviewed, the most frequent laboratory alterations in patients with COVID-19 are: lymphopenia, increased C-reactive protein and elevated transaminases[19,20]. In our cases, no significant differences were found in most of the mean values of such tests –performed during hospital admission– among symptomatic or asymptomatic individuals. This confirms the epidemiological and laboratory similarity of both clinical states in cardiac patients.

Undoubtedly, understanding the characteristics of those who do not have symptoms is crucial. The identification of asymptomatic patients with COVID-19 has put a strain on health systems around the world, including Cuba's, which to date has managed to flatten the infection curve and is steadily working to achieve greater control of the pandemic in the country[4].

According to the literature reviewed, our paper is the first to compare the symptomatic and asymptomatic states from the epidemiological and laboratory point of view in patients with heart disease and diagnosis of COVID-19 in our setting.

CONCLUSIONS

The relationship between epidemiological factors and cardiovascular comorbidities studied was similar in asymptomatic and symptomatic states in patients with heart disease who are positive to COVID-19. The main clinical manifestations found were dry cough, fever, headache and general malaise. There were no significant differences in the results of most laboratory tests between asymptomatic and symptomatic patients.

LIMITATIONS OF THE STUDY

The small sample size is the main limitation of our study, reason why its statistical power is low, although the statistical precision obtained was adequate. Further studies with larger samples and more variables will be required to confirm the results of our research.

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