Clinical and cardiovascular characteristics from subjects with in COVID-19 and viral outbreaks

Arturo Orea-Tejeda PhD1, Óscar Ubald Martínez-Reyna MD1, Dulce González-Islas PhD1, Rafael Hernández-Zenteno PhD2, Rocío Sánchez-Santillán MSc1, Aimee Flores-Vargas MD3, Alan Ibarra-Fernández MD3, Ilse Pérez-García BChD1, Justino Pineda-Regalado PhD4, Juan José Orozco-Gutierrez MD1

A Orea-Tejeda, OU Martínez-Reyna, D González-Islas, R Hernández-Zenteno, R Sánchez-Santillán, A Flores-Vargas, A Ibarra-Fernández, I Pérez-García, J Pineda-Regalado, JJ Orozco-Gutierrez. Clinical and cardiovascular characteristics from subjects with in COVID-19 and viral outbreaks. Can J Respir Ther 2022;58:39–43. doi: 10.29390/cjrt-2021-042.

Introduction: Lower respiratory tract infections remain the deadliest communicable disease worldwide. The relationship between cardiovascular diseases and viral infections is well known; for example, during the AH1N1 influenza pandemic, many patients developed acute cardiovascular disease. In the SARS-CoV2 pandemic, cardiovascular health has again become a challenge, with early reports showing cardiac damage in these patients.

Objective: The study aims to describe the clinical characteristics of COVID-19 patients with an emphasis on cardiovascular complications, compared with past outbreaks of influenza AH1N1, to identify prognostic factors of severity.

Methods: A cross-sectional study of 72 subjects with a confirmed diagnosis of COVID-19 was conducted. Subjects were evaluated in two groups: 38 hospitalized patients and 34 patients in the Intensive Care Unit (ICU). Data from different outbreaks of influenza AH1N1 were then compared with this group.

Results: The 34 subjects in the ICU had higher levels of high sensible troponin, D dimer, creatinine, and leukocytes compared with the 38 hospitalized subjects. The lymphocytes count was diminished in 85.29% of ICU subjects. When compared with AH1N1 patients, it was found that SARS-CoV2 patients were 10 years older on average. The proportion of overweight and obese SARS-CoV2 patients was double that in the influenza outbreaks. In addition, it was observed that a high number of SARS-CoV2 subjects presented with diabetes mellitus.

Conclusion: There were various clinical and severity differences between each of these outbreaks. However, viral respiratory infection diseases such as SARS-CoV2 are a significant risk factor for acute ischemic, functional, and structural cardiovascular complications. The only way to combat this risk is a prevention approach, specifically through vaccines, but also through measures that force drastic changes in health policies to reduce perhaps the worst of pandemics, obesity, and its metabolic consequences.

Key Words: SARS-CoV2 infection; influenza; cardiovascular disease; disease outbreaks

INTRODUCTION

Lower respiratory tract infections remain the deadliest communicable disease worldwide. Since the 2009 AH1N1 influenza pandemic, evidence has shown the association between acute viral respiratory infections and the risk of developing acute cardiovascular disease, including ischemic events [1, 2].

Histological data from autopsies of patients with acute influenza reveal that 30%-50% had injuries characterized by cell infiltration and necrosis without any previous evidence of clinical cardiac damage [3]. Viruses are the most common infectious cause of myocarditis, characterized by a temporary increase in troponin levels and/or changes in the electrocardiogram after a respiratory disease [4].

There are isolated case reports of myocarditis in patients who contracted emergent respiratory viruses like SARS-CoV in 2003 (Severe Acute Respiratory Syndrome coronavirus) and MERS-CoV (Middle East Respiratory coronavirus) in 2012 [5, 6]. An association between respiratory infection caused by influenza and acute myocardial infarction (AMI) has been described. Most of the AMI takes place during the first 7 days after the onset of acute respiratory disease, with no difference in incidence related to age [3, 7].

In December 2019, China reported a new coronavirus producing a syndrome called COVID-19 caused by a new type of coronavirus called SARS-CoV2. In March 2020, the Worldwide Health Organization declared COVID-19 a pandemic. As of 28 March 2020, 614,884 cases worldwide were diagnosed, with 28,687 deaths (4.6%) [8]. And, in Mexico, by 27 March 2020, 707 cases were reported, with 12 deaths (1.7%) [9]. From 2010 to 2017, the National Institute of Respiratory Diseases, Ismael Cosío Villegas, saw more than 35,000 hospitalized cases of respiratory viruses.

Of the 35,000 patients hospitalized by respiratory viruses such as AH1N1 at Ismael Cosío Villegas, 20% had cardiovascular damage. The most common was systemic arterial hypertension, pulmonary...

1Heart Failure and Respiratory Distress Clinic, Cardiology Department, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
2Department of Research in Tobacco Smoking and COPD, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
3Pneumology resident, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
4Subdirection for Medical Care in Pneumology at Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
Correspondence: Dulce González-Islas, Coordinator of Research Projects of the Cardiology Department at Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”, Calzada de Tlalpan 4502 Col Sec XVI CP 14080 Del Tlalpan, Mexico City, Mexico, Tel: 52 555487 1700 Ext 5506, E-mail: gzz.dulce@gmail.com
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thromboembolic disease with or without pulmonary arterial hypertension, ischemic cardiopathy, and heart failure. The number of cardiovascular comorbidities in patients with these respiratory viruses was higher than the sum of cancer and interstitial lung disease during winter of each year, only (barely) exceeded by pneumonia [10].

This study aims to describe the demographic and clinical characteristics of subjects with COVID-19, with an emphasis on cardiovascular compromises. In addition, the study also compares the demographic, clinical, laboratory, and severity variables between outbreaks of influenza AH1N1 and SARS-CoV2.

METHODS

A cross-sectional study was conducted at the National Institute of Respiratory Disease, Ismael Cosío Villegas, which was designated as the primary hospital for COVID-19 patients. The data came from the first patients with a diagnosis of COVID-19.

Subjects

The study is assessed in two parts. The first part compares two groups of COVID-19 patients, those who required hospitalization and those who required the Intensive Care Unit (ICU).

Diagnosis of COVID-19 was confirmed by reactive polymerase chain (PCR) according to the criteria established by the Diagnosis and Reference Epidemiology Institute (InDRE, Instituto de Diagnóstico y Referencia Epidemiológico) [11]. Subjects were recruited from 17 March 2020 to 10 April of 2020. Patients presented at the emergency department, where the physician decided the treatment. The treatment was individualized and all the data were obtained from clinical records.

Of the patients admitted to ICU, the second part of the study looked at those who needed invasive mechanical ventilation (IMV), especially those who required monitoring of invasive mechanical ventilation (IMV) with transesophageal balloon. The second part is a comparison between COVID-19 patients and influenza outbreaks AH1N1. Data from three outbreaks of influenza AH1N1 (April 2009, 1 September to 2 December 2010, and 1 January to 30 March 2012) were taken from Velázquez et al. [12].

Data collection

Clinical data were extracted from electronic medical records. The data collected were age, sex, and comorbidities as diabetes mellitus, hypertension, cardiovascular diseases, smoking, and obesity and overweight. Laboratory data such as white and red blood cells, C reactive Protein, D Dimer, creatine phosphokinase (CPK), myoglobin, and high sensibly troponin were obtained from routine measurements performed on patients during their stay in the ICU or during hospitalization.

Ethics approval

This study was conducted according to the Declaration of Helsinki and was approved by the Research Ethics Committee (approval number E06-20) of the National Institute of Respiratory Disease, Ismael Cosío Villegas. Written informed consent was not required by the ethics committee due to the observational nature of the study.

Statistical analysis

Categorical variables are given in frequencies and percentages. The Shapiro–Wilk test was used to determine the normality of quantitative variables. Those with normal distribution are presented as a mean and standard deviation; otherwise, median and percentiles 25–75 were shown. Chi-square or Fisher test was used to compare the difference between groups on categorical variables and the t-student test or Mann–Whitney U test was used for quantitative variables, as applicable. Statistical analysis was made by the STATA software version 14 (Stata Corporation, College Station, Texas, USA). Statistical significance with a P < 0.05 was considered.

RESULTS

Seventy-two patients with a diagnosis of COVID-19 were admitted, of whom 34 required ICU and 38 required hospitalization. 61.1% were men, with a mean age of 51.38 ± 11.72 years. Forty-three percent had diabetes, 23.61% had hypertension, 26.39% had obesity, and 25% were smokers. More than half had hypoxemia, 70.97% of patients in the ICU and 60.00% of those hospitalized.

With respect to the biomarkers of cardiac damage, subjects in the ICU had greater levels of high sensitivity troponin, D dimer, creatinine, and leukocytosis, than the 38 hospitalized subjects. The lymphocytes count was diminished in 85.2% in subjects in the ICU (see Table 1).

The second part of the study compares data from influenza outbreaks (AH1N1) and patients with SARS-CoV2 disease. Patients with SARS-CoV2 disease were on average older than AH1N1 influenza.
TABLE 2
Clinical characteristics of influenza AH1N1 outbreaks [8]

| Age, years | 2009 outbreak, n = 146 | 2010 outbreak, n = 61 | 2012 outbreak, n = 51 | P      |
|------------|------------------------|-----------------------|-----------------------|--------|
| Men, n (%) | 41 ± 12                | 42 ± 12               | 45 ± 13               | 0.17   |
| Tobacco use n (%) | 97 (66) | 27 (61)           | 37 (53)               | 0.22   |
| Never      | 57 (50)                | 17 (28)               | 29 (62)               | 0.001  |
| Smoker     | 57 (50)                | 29 (34)               | 6 (17)                | 0.001  |
| Former smoker | —                   | 14 (23)              | 10 (21)               | 0.22   |
| BMI class, n (%) | 31.4 ± 6.6 | 31.5 ± 6.8         | 32.1 ± 6.6            | 0.79   |
| Normal     | 22 (15)                | 11 (18)               | 2 (4)                 |        |
| Overweight | 48 (33)                | 17 (28)               | 12 (23)               | 0.001  |
| Obesity    | 73 (50)                | 32 (52)               | 18 (35)               | 0.13   |
| Mortal obesity | 15 (10)         | 5 (8)                | 3 (6)                 | 0.62   |
| Comorbidities, n (%) |       |                      |                       |        |
| COPD       | 3 (2)                  | 2 (3)                 | —                     | 0.46   |
| Asthma     | 18 (14)                | 7 (12)                | 8 (17)                | 0.79   |
| Diabete    | 7 (5)                  | 1 (2)                 | 4 (8)                 | 0.29   |
| OSAS       | 7 (5)                  | 5 (9)                 | 6 (13)                | 0.26   |
| Cardiovascular disease | 17 (15) | 4 (7)          | —                     | 0.01   |
| Onset of symptoms before attending to urgency service | 12 ± 10 | 7 ± 3         | 6 ± 5                 | 0.01   |
| Intra-hospital stay days | 13 ± 11 | 14 ± 11     | 8 ± 5                 | 0.01   |
| Invasive mechanical ventilation | 46 (33) | 17 (31)   | 7 (15)                | 0.05   |
| Complications, n (%) |       |                      |                       |        |
| ARDS       | 99 (67)                | 36 (59)               | 7 (15)                | <0.001 |
| Pneumonia  | 118 (81)               | 48 (79)               | 36 (77)               |        |
| Mortality  | 14 (10)                | 3 (5)                 | 2 (4)                 | 0.19   |

Note: ARDS = Acute Respiratory Distress Syndrome; BMI = body mass index; COPD = Chronic Obstructive Pulmonary Disease; OSAS = Obstructive Sleep Apnea Syndrome.

patients (outbreak 1) by more than a decade (51.38 ± 1.7 vs. 41 ± 12, P < 0.001). However, the proportion of overweight patients was higher in the influenza outbreaks than SARS-CoV2 (33% vs. 28% vs. 23% vs. 9.7% P = 0.03). In addition, it was observed that a high proportion of SARS-CoV2 subjects presented with diabetes mellitus than influenza outbreaks (43.06% vs. 5% vs 2% vs. 8%, P < 0.001), respectively (see Table 2). Of the 47.2% of patients admitted to the ICU, the proportion was higher than in the three AH1N1 outbreaks of 2009, 2010, and 2012 (31.5% vs. 27.8% vs. 13.7%, P < 0.034), respectively.

DISCUSSION

The main finding showed that greater cardiac damage was seen in subjects in the ICU as compared with hospitalized subjects. These patients in the ICU also showed higher levels of high sensitivity troponin, D dimer, creatinine, and leukocytes. In general, subjects with an increased risk of disease are older than 70 years; have a history of cardiovascular, respiratory, and metabolic chronic diseases; and are immunosuppressed subjects [9].

A retrospective study looking at 1,884,985 cases of acute myocardial infarction (AMI) reports that 1.1% had a concomitant respiratory infection disease (0.5% influenza, 0.6% other respiratory infection). People with influenza had a greater proportion of ST-segment-elevation myocardial infarction than patients with a different respiratory infection and those without a respiratory infection disease (90.3% vs. 84.9% vs. 74.6% respectively, P < 0.001). ST is a clinical syndrome defined by myocardial ischemia symptoms; persistent elevation in the ST segments of the electrocardiogram and release of biomarkers of myocardial necrosis (e.g., elevated troponin levels). In the same study, there were double the cases of shock and acute respiratory failure in the AMI and influenza group compared with those without influenza, regardless of age, gender, or previous comorbidities (including cardiovascular disease) [13].

Besides the clinical and severity differences between the outbreaks of influenza reported by Velázquez et al. [12], in the third outbreak, the in-hospital stay was shorter despite the similarities of comorbidities: obesity, asthma, obstructive sleep apnea syndrome (OSAS), diabetes. Most importantly, hospitalized patients were not vaccinated, and more than 50% were obese [8].

A big difference between the outbreak of SARS-CoV in 2003 and SARS-CoV2 is the higher transmission rate, making SARS-CoV2 more difficult to control and prevent. Respiratory symptoms are the main manifestation, but severe cardiovascular damage has also been reported. SARS-CoV2 patients with a pre-existing cardiovascular disease [14] have a higher risk of mortality. The mean age of SARS-CoV2 patients was greater than that seen during SARS-CoV. In addition, patients who were smokers and obese patients were less prevalent during SARS-CoV. However, the proportion of diabetics was higher. There were no differences between hospitalization and ICU in those patients.

MERS CoV is also related to the coronavirus family, and can induce myocarditis and heart failure [7]. Both SARS-CoV2 and MERS-CoV have similarities in their pathogenic and viral effects on the myocardium, increasing the risk of complications, interfering with the treatment, and adversely affecting the prognosis. Along with other members of the coronavirus family, it can produce septic shock and multi-organ failure [15].

SARS-CoV had a lower mortality rate of 10%, unlike MERS-CoV, with a 37% mortality rate [16, 17]. With COVID-19, those with a history of cardiovascular diseases have the worst prognosis [18] with a 40% mortality rate due to acute myocarditis, myocardial infarction, and acute heart failure [18]. During the outbreaks of SARS and MERS, patients with heart failure and reduced ejection fraction had higher mechanical ventilation requirements [19].

Early reports about the clinical characteristics of COVID-19 have shown that almost 20% of patients infected with SARS-CoV2 had cardiac damage (defined as an increase in cardiac biomarkers, high sensitivity Troponin I (cTnI), CK-MB, Myo hemoglobin). Moreover, in those subjects with cardiac damage, the 30-day mortality increased by 10 times compared with those without cardiac damage (51% vs. 4.5%, P < 0.001) [20].

In one study with a total of 138 patients with a SARS-CoV2 diagnosis, 36 required ICU treatment. In those patients, biomarkers of cardiovascular damage were higher (CPK-MB = 18 U/L versus 14 U/L, P < 0.001; cTnl =11.0 pg/mL versus 5.1 pg/mL, P = 0.004) than those who...
did not require ICU, suggesting an association between severe symptoms and acute myocardial complications [21].

Zheng et al. [18] looked at 41 patients with a SARS-CoV2 diagnosis and documented myocardial damage in five subjects (12%) measured by the cTnI > 28 pg/mL. Four of the five subjects required ICU treatment.

It is outstanding that in our cases, 47% required ICU management. Of these, 40% had markers of poor prognosis with CPK elevations (almost twice as high) in an opposite ratio of significantly decreased lymphocytes cTnI elevation (4 times more), as well as CRP. Likewise, there was an increase in creatinine, in which our cases were higher in the ICU patients [8, 21].

Currently, the physiopathology of the SARS-CoV2 is not clear; nevertheless, there are some suggestions about an increase of inflammatory cytokines levels such as interleukin-1, gamma interferon, and monocyte chemoattractant protein, producing an overwhelming response to Thelper lymphocytes [16].

In agreement with other studies [23, 27, 30], in this population, cardiac injury markers were found in those admitted to ICU, particularly Dimer, suggesting the possibility of a systemic thrombotic process playing a phytotypathogenic role in the multi-organ damage. There is increasing evidence that COVID-19 affects (directly or through the infection process) the hypoxic status, hemostatic alterations, or inclusive disseminated intravascular coagulation [22, 23], generating thromboembolic disease. As Tang et al. [21] reported, the levels of D-Dimer and fibrin degradation, as well as prothrombin prolongation time, were elevated in those who died compared with survivors.

Another possibility is that coagulation abnormalities can be related to the cytokine storm, as was observed in several viral processes [24, 25]. Also, an increased incidence of deep venous thrombosis and pulmonary embolism (PE) was noted in the SARS-CoV2 and SARS-CoV-V1 outbreak in 2014 [26]. In our cases, increased D-dimer levels were observed in those patients admitted to ICU. D-dimer was associated with the requirement for mechanical ventilation or death [27]. Fifty percent of patients with D-dimer higher than 1 µg/mL had an increased incidence of thrombosis and the worst prognosis [28, 29]. However, obesity, chronic immobility, cardiovascular preexisting abnormalities, and hospitalization, per se, increase thrombosis and PE [30].

Another study [31] in patients with SARS-CoV2 and elevated cardiac troponin reported a higher level of interleukin 6. The cause of death was documented as fulminant myocarditis [31], probably due to the cytokine storm.

An additional problem is the relation between the cardiovascular system and viral respiratory infections as a long-term effect. A study by Wu et al. [32] followed 25 recovered SARS-CoV patients after 12 years and reported that 68% developed hyperlipemia, 44% cardiovascular abnormalities, and 60% alterations in glucose metabolism. In our population, with the highest proportion of diabetics and obesity, this will be an increased risk for myocardial infarction in the short term for survivors.

In this pandemic, cardiovascular damage is one more consequence of a systemic inflammatory process. In the case of these outbreaks, it is accentuated by the viral load and the immune response in susceptible subjects—despite being younger—and implies a worse prognosis, even in those who do not die. Cardiovascular damage can accelerate the existing metabolic and microvascular damage.

Limitations
The authors acknowledge this study has some limitations. These include the small size of the sample, the inherent limitations to cross-sectional design, the absence of laboratory data on some patients, and the difficulty of accessing the subject’s file for being considered as contaminated and, therefore, the impossibility of evaluating the electrocardiographic records. Also, because of limited resources, serial monitoring of the quantification of markers of cardiac damage such as troponins and B-type natriuretic peptides was difficult. However, aside from these significant limitations, the authors feel there is importance in reporting and recognizing the reality of this situation: the severe panorama of cardiovascular health deterioration that has developed in Mexico and the rest of the world and the obesity pandemic and its metabolic sequels.

CONCLUSION
Viral respiratory infection disease is an important risk factor for acute ischemic events. Pre-existing thrombotic status or the excessive inflammatory response to viral infection allow [31] us to speculate if it is an important factor in the outcome of critically affected patients.

The emergence of new viruses causing respiratory infections will continue to represent a challenge for health and medical systems. The only way to combat this risk is a prevention approach, specifically through vaccines, but also through measures that force drastic changes in health policies to reduce perhaps the worst of pandemics, obesity, and its metabolic consequences.

DISCLOSURES
Contributors
Conception and design (AO, OR, DG); data acquisition (AV, AI, IP, RH, JR, JO); data analysis and interpretation (DG, RS, RH); preparation of the draft manuscript (AO, OR, DG, RS); revisions or critique and overall and/or sectional scientific management (AO, OR, DG, RH, RS, AV, AI, IP, JR, JO); final manuscript approval (AO, OR, DG, RH, RS, AV, AI, IP, JR, JO).

Conflict of Interest
The authors declare they have no conflict of interest.

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Ethical approval
This study was conducted under the Declaration of Helsinki, and approved by the Research Ethics Committee (approval number E-06-20) of the National Institute of Respiratory Disease, Ismael Costio Villegas.

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