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Clinical and cardiovascular differences from epidemic outbreaks viral diseases

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Abstract

Background: The lower respiratory tract infections remained the deadliest communicable disease worldwide. The relationship between cardiovascular diseases and viral infections is well known, namely myocarditis. AH1N1 influenza pandemic showed an association with developing acute cardiovascular disease, including ischemic events. Besides, the new pandemic of SARS-CoV2 became a new challenge for cardiovascular health. In early reports showed cardiac damage in patients infected with SARS-CoV2. This study aimed to describe the clinical characteristics with an emphasis on cardiovascular compromises of COVID-19 patients. Moreover, to compare with outbreaks of influenza AH1N1 to identify prognostic factors of severity. Methods: A cross-sectional study, 72 subjects with a confirmed diagnosis of COVID-19 was included, Subjects were evaluated in two groups; those hospitalized and those who required Intensive Care Unite (ICU). The data from different AH1N1 outbreaks were obtained from Velazquez et al. Results: Thirty-four subjects were admitted to ICU. Subjects at ICU, have greater levels of high sensible troponin, D dimer, creatinine, and leukocytes, than hospitalized subjects. The lymphocytes count where diminished in 85.29% of ICU subjects. SARS-CoV2 disease patients were more than one-decade older than patients in the influenza outbreaks. In SARS-CoV2 subjects the overweight and obesity proportion is half than in the influenza outbreaks; there is a big proportion, more than 6 times, of diabetes mellitus in SARS-CoV2 subjects. Conclusions: Viral respiratory infection disease as SARS-CoV2 is a significant risk factor for acute ischemic, functional, and structural cardiovascular complications.

Introduction

The most frequent cause of death is cardiovascular disease followed by chronic obstructive pulmonary disease, and lower respiratory tract infection [1].

Importantly, the lower respiratory tract infections remained as the deadliest communicable disease worldwide. The relationship between cardiovascular diseases and viral infections is well known, namely myocarditis. Beyond the AH1N1 influenza pandemic (2009), there is more evidence about the association between an acute viral respiratory infection and the risk of developing acute cardiovascular disease, including ischemic events [2].

In the Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas" between 2010 and 2017 had more than 35,000 of hospitalized cases, the 20% of them had some cardiovascular damage, between the most common were: systemic arterial hypertension, pulmonary thromboembolic disease with or without pulmonary arterial hypertension, ischemic cardiopathy and heart failure. The cardiovascular comorbidity was higher than the sum of cancer and interstitial lung disease and barely overcome by pneumonia during the winter season of each year.[3]

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In December 2019, the new pandemic of SARS-CoV2 (Severe Acute Respiratory Syndrome Coronavirus 2) became a new challenge for cardiovascular health. Histological data from autopsies of patients with acute influenza reveals that 30 - 50% of them have injuries characterized by cell infiltration and necrosis without any previous evidence of clinical cardiac damage [4].

The respiratory viruses associated with myocarditis are Influenza A and B, Coxsackie, Cytomegalovirus, Epstein-Barr, Adenovirus, Respiratory Syncytial Virus (RSV), Parvovirus B19, y Rhinovirus [5]. There are some isolated case reports of myocarditis with the new emergent respiratory viruses like the SAR-CoV in 2003 (Severe acute respiratory síndrome coronavirus) and MERS-CoV (Middle East Respiratory coronavirus) in 2012 [6,7].

Viruses are the most common infectious causes of myocarditis, which is characterized by a temporary increase of troponin levels and/or changes in the electrocardiogram after a respiratory disease[5].

An association between respiratory infection caused by influenza and acute myocardial infarction (AMI), has been described. Most of the AMI takes place on the first seven days after the onset of acute respiratory disease, and the incidence of cases, not differ between younger or older (>65 years old) people. [4,8].

A retrospective study with more than 1,884,985 cases of AMI reports that 1.1% of them 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 the other respiratory infections and those without respiratory infection disease (90.3% vs. 84.9% vs. 74.6% respectively, p <0.001). In the same study, there was a double proportion of cases with shock and acute respiratory failure in the AMI and influenza group comparing with those without influenza, regardless of age, gender, previous comorbidities (including cardiovascular disease) [9].

The aim of the study was to described the demographic and clinical characteristics with an emphasis on cardiovascular compromises of the subjects with Coronavirus Infectious Disease 2019 (COVID-19) diagnosis. Moreover, to compare the demographic, clinical, laboratories, and severity variables between different outbreaks of influenza AH1N1 and SARS-CoV2 and to identify prognostic factors of severity.

Methods and Material

A cross-sectional study at the Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas," which was designated as the number one hospital to care for COVID-19 patients. The data came from the first patients with a diagnosis of COVID-19 and hospitalized between March 17 and April 10 of 2020. Diagnosis of COVID-19 was confirmed according to the criteria established by the Diagnosis and Reference Epidemiology Institute (InDRE, Instituto de Diagnóstico y Referencia Epidemiológicos) [10]. Subjects with the confirmed diagnosis were evaluated in two groups; those hospitalized and those who required Intensive Care Unite (ICU). Demographic, laboratories, and comorbidities variables were taken from the data record of the patients.

Data from different outbreaks of influenza AH1N1 were taken from Velázquez et al, (11), the first one April 2009, the second, between September 1 and December 2 of 2010, and the last one between January 1 and march the 30th. of 2012 There were clinical and severity differences between each of these outbreaks.

This study was conducted under the Declaration of Helsinki. This study was approved by the Research Ethics Committee (approval number E-06-20) at Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas."

Statistics Analysis

Categorical variables are given in frequencies and percentages. 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 was shown. Chi-square or F-Fisher test was used to compare the difference between group on categoric variables and t-student test or Mann-Whitney U test for

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quantitative variables, as applicable. Statistical analysis was made by the STATA version 14 program (Stata Corporation, College Station, Texas, USA). Statistical significance with a $p<0.05$ was considered.

Results

Seventy-two hospitalized patients with COVID were considered, 61.11 % were men, with a mean of age of 51.38 ± 11.72, 43% were diabetic, and 23.61 % have systemic arterial hypertension. A total of 26.93 % of patients have obesity, and 9.72 % overweight. About 25 % were smokers. More than half have hypoxemia.

Thirty-four subjects were admitted to ICU. From the laboratory view, the biomarkers of cardiac damage in subjects at ICU, have greater levels of high sensibly troponin, D dimer, creatinine, and leukocytes, than hospitalized subjects. The lymphocytes count where diminished in 85.29% of them. (Table 1).

SARS-CoV2 disease patients were more than one-decade older respect patients in the influenza outbreaks. Interestingly, although the overweight and obesity proportion is half than in the influenza outbreaks, there is a big proportion, more than 6 times, of diabetes mellitus in SARS-CoV2 subjects. (Table 2)

In case of COVID-19 disease, in this preliminary communication, the proportion of cases admitted to ICU at the moment is 47%, which is lower than in the firsts outbreaks due influenza AH1N1.

Discussion

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 declare COVID-19 as a pandemic outbreak. In march 28 of 2020, 614, 884 cases were diagnosis worldwide, with 28,687 (4.6%) cases of death [12]. At the same time, México has 707 cases, with 12 deaths (1.7%)[12].

At present, the subjects with an increased risk of several diseases are older than 70 years, with a history of cardiovascular, respiratory, and metabolic chronic diseases, as well as immunosuppressed subjects[13].

Besides the clinical and severity differences between the outbreaks of influenza, it has to be emphasized that in the third outbreak, the intra-hospital stay was lower, despite the similarities of comorbidities: obesity, asthma, OSAS, diabetes. It has to be highlighted that most hospitalized patients did not was vaccinated and more than 50 percent were obese [11]

Important differences between the outbreak of SARS-CoV in 2003 and the actual SARS-CoV2, it is the higher transmissibility rate of the last one, making it difficult to control and prevent. Respiratory symptoms are the main manifestation of it; nevertheless, severe cardiovascular damage has been reported. Likewise, they have a higher risk of mortality with a preexisting cardiovascular disease [14] Moreover, and, remarkably, the mean age of this outbreak is greater. However, the smokers and obesity are lesser prevalent, the proportion of diabetics is higher and accords with the increased hospitalized patients in those over 40 years old and a bigger proportion of them in the ICU.

Additionally, the Middle East respiratory syndrome (MERS CoV) also related to the coronavirus family induces myocarditis and heart failure[7]. Both SARS-CoV2 and MERS-Cov have similarities in their pathogenic and the viral effects over the myocardium, increasing the risk of complications, interfering with the treatment, and adversely affect the prognosis. As well as other members of the coronavirus family, it can produce septic shock and multi organic failure [15].

SARS-CoV was a lower specter of the disease with a mortality of 10%, unlike MERS-CoV, with 37% of mortality [16,17]. Nevertheless, in COVID-19 and with history of cardiovascular diseases, the prognosis is worst [18] with over 40% of mortality due to acute myocarditis, myocardial infarction and acute heart failure[18], because according to the outbreaks of SARS and MERS, patients with heart failure with reduced ejection fraction (HFrEF) had higher mechanical ventilation requirements[19].

In early reports about the clinical characteristics of COVID-19 have shown that almost 20% of the patients infected with SARS-CoV2 had cardiac damage (define as an increase in cardiac biomarkers, high sensibility

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Troponin I (cTnI), CK-MB, Myo hemoglobin). In those subjects with cardiac damage, the 30 days mortality increased ten times than in those without cardiac damage (51% vs. 4.5%, 0<0.001)[20]

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

Still, other research with 41 patients with SARS-CoV2 diagnosis documented myocardial damage in 5 subjects (12%) measured by the cTnI > 28 pg/ml, four of them required ICU treatment[18]It is striking that in our cases, 47% required ICU management and of these 40% had CPK elevations (almost twice as high), cTnI (4 times more), as well as CRP, leukocytes, and creatinine in opposite relation to the lymphocyte count that showed a marked decrease, all of the markers of worse prognosis in other studies. [11,21].

For the moment, 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, monocyte chemoattractant protein, producing an overwhelmed respond to T-helper lymphocytes [16].

In agreement with other authors, in this population, the finding of cardiac injury markers was present in those admitted to ICU, particularly D Dimer, suggesting the possibility of a systemic thrombotic process playing a fisio-pathogenic roll in the multiorgan damage.

At the moment, there are increasing evidence that COVID-19 affects direct or thought infection process hypoxemic status, hemostatic alterations or inclusive disseminated intravascular coagulation[22,23] Generating thromboembolic disease as some authors are reporting, in whom patients died were elevated levels of D-Dimer and fibrin degradation as well as prothrombin prolongation time compared with survives [23] Another possibility is that coagulation abnormalities be related to the cytokine storm as has been observed in several viral processes [24,25] Also, it was observed as increased incidence of deep venous thrombosis and pulmonary embolism (PE) in SARS-CoV-2 and SARS-CoV-1 outbreak of 2014[26] In our cases, increased D-dimer levels were observed in those patients admitted to ICU, D- dimer is associated to requiring mechanical ventilation or death [27]. Although 50% of patients with D-dimer higher than1 μg/Ml had increased incidence of thrombosis and worst prognosis [28,29]

However, the obesity, chronic immobility, cardiovascular preexisting abnormalities, and hospitalization, per se, increase thrombosis and PE[30]

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

An additional problem is a relation between the cardiovascular system and the viral respiratory infection as a long-term effect. In one study with 25 recovered patients or SARS-CoV with twelve years followed time reports that 68% developed hyperlipemia, 44% cardiovascular abnormalities, and 60% metabolism glucose alterations[32], situation, in which, in our population with the highest proportion of diabetics and obesity will be an increased risk of myocardial infarction in the short term in those survivors.

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

Limitations

Limitations, the main one being the small size of the sample, the absence of laboratory data on some patients, and the difficulty of accessing the subject's file because it was considered contaminated and, therefore, the impossibility of evaluating the electrocardiographic records. Also, due to limited resources, are difficult serial monitoring of the quantification of markers of cardiac damage such as troponins and BNP.

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In counterpart to these significant limitations, the recognition of our reality and in it, the severe panorama of cardiovascular health deterioration that has developed in our country and in the rest of the world, the obesity pandemic and its metabolic sequelae, particularly in our country, diabetes

Conclusions

Viral respiratory infection disease is an important risk factor for acute ischemic, functional, and structural cardiovascular complications.

Thrombotic status preexistent or induced by the inflammatory virus response could be an important factor to improve the outcome of patients critically affected

The emergence of new viruses causing respiratory infections will continue to represent a challenge for the health and medical systems.

Until now, the only way to combat this risk is the prevention approach, specifically through vaccines (influenza), as well as measures that force drastic changes in health policies to reduce, perhaps the worst of pandemics, obesity, and its metabolic consequences.

Changes in health policies to reduce, perhaps the worst of pandemics, obesity, and its metabolic consequences, are absolutely essentials

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	All n = 72	**ICU n = 34**	**Hospitalized n =38**	**p**	**Reference Value**
Men, n (%)	44 (61.11)	22 (64.71)	22 (57.89)	0.554	-
Age, years	51.38 ± 1.72	52.73 ± 2.39	50.13 ± 15.11	0.455	-
Diabetes Mellitus, n (%)	31 (43.06)	14 (41.18)	17 (44.74)	0.761	-
Hypertension, n (%)	17 (23.61)	10 (29.41)	7 (10.42)	0.273	-
Overweight, n (%)	7 (9.72)	1 (2.94)	6 (15.79)	0.081	-
Obesity, n (%)	19 (26.39)	12 (35.29)	7 (18.42)		-
Smoking, n (%)	18 (25.00)	11 (32.35)	7 (18.42)	0.173	-
PO2, mmHg	57.42 ± 14.86	54.84 ± 15.03	60.09 ± 14.45	0.170	
Myoglobin, ng/ml * n = 27	61.9 [32- 150.7]	61.95 [50.2 - 333.9]	46.4 [29.5 - 74.6]	0.145	0.0-150 ng/ml
CPK, UI/L	110 [53.15 - 291.25]	137 [58.9- 1147.2]	78.5 [50 - 177]	0.079	M: 38-234 UI/L H: 49-397 UI/L
CPK, high levels, n (%) *n= 64	16 (25.00)	11 (40.74)	5 (13.51)	0.013	-
High sensibly tropinine pg/ml *n=40	2.2 [1.55 - 9.9]	7.8 [2.5 - 22.7]	2 [1.3 - 2.4]	0.004	28.9-39.2pg/ml
D Dimer, µg/mL	1.13 [0.57 - 2.6]	1.7 [1.08 - 5.37]	0.6 [0.41 - 1.32]	<0.001	< 0.5 ug/mL
D Dimer > 0.5 µg/mL, n (%) *n = 57	46 (80.70)	27 (93.10)	19 (67.86)	0.016	-
Procalcitonina, ng/ml,	0.09 [0.05 - 0.41]	0.16 [0.07 - 0.41]	0.08 [0.03 - 0.6]	0.325	< 0.5 ng/ml
C reactive protein mg/dL	10.5 [3.7 - 20.94]	12.06[5.21 - 24.73]	9 [2.54- 18.1]	0.119	< 1 mg/dL
Lymphocytes, $10^3/mm^3$,	0.8 [0.55 - 1.15]	0.6 [0.5 - 0.9]	0.9 [0.7 - 1.2]	0.005	1- 4, 10ˆ3/mm^3
Lymphocytes < 1, $10^3/mm^3$, n (%)	52 (72.22)	29 (85.29)	23 (60.53)	0.019	-
Leukocytes, $10^3/mm^3$	7.2 [5.75 - 9.2]	7.8 [6.5 - 9.3]	7 [5.1 - 9.1]	0.034	4-10,10ˆ3/mm^3
Creatinine, mg/dl	0.9 [0.72- 1.31]	1.22 [0.85 - 1.52]	0.81 [0.65 - 0.93]	0.001	0.7 - 1.2 mg/dl

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	All n = 72	**ICU n = 34**	**Hospitalized n =38**	**p**	**Reference Value**
BMI.- Body Mass Index, CPK.- creatine phosphokinasa	BMI.- Body Mass Index, CPK.- creatine phosphokinasa	BMI.- Body Mass Index, CPK.- creatine phosphokinasa	BMI.- Body Mass Index, CPK.- creatine phosphokinasa	BMI.- Body Mass Index, CPK.- creatine phosphokinasa	BMI.- Body Mass Index, CPK.- creatine phosphokinasa

Table 1. Clinical characteristics of COVID-19 diagnosis patients.

Table 2. Clinical characteristics of influenza AH1N1 outbreaks[11]

	1º outbreak n = 146	**2º outbreak n = 61**	**3º outbreak n = 51**	**p**
Age, years	41 ± 12	42 ± 12	45 ± 13	0.17
Men, n(%)	97 (66)	27 (61)	37 (53)	0.22
Tobacco use n(%) never smoker former smoker	57 (50) 57(50) -	17 (28) 29 (34) 14 (23)	29 (62) 8 (17) 10 (21)	0.001 0.001 0.22
BMI class, n(%) Normal Overweight Obesity Morbid obesity	31.4 ± 6.6 22 (15) 48 (33) 73 (50) 15 (10)	31.5 ± 6.8 11 (18) 17 (28) 32 (52) 5 (8)	32.1 ± 6.6 2 (4) 12n (23) 18 (35) 3 (6)	0.79 0.001 0.001 0.13 0.62
Comorbidities, n(%) COPD Asthma Diabetes OSAS Cardiovascular disease	3 (2) 18 (14) 7 (5) 7 (5) 17 (15)	2 (3) 7 (12) 1 (2) 5 (9) 4 (7)	- 8 (17) 4 (8) 6 (13) -	0.46 0.79 0.29 0.26 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
Non invasive mechanical ventilation	46 (33)	17 (31)	7 (15)	0.05
Complications, n(%) ARDS Renal insufciciency Pneumoniia	99 (67) 20 (21) 118 (81)	36 (59) 1 (2) 48 (79)	7 (15) 2 (4) 36 (77)	<0.001
Mortaliity	14 (10)	3 (5)	2 (4)	0.19

	1º outbreak n = 146	2º outbreak n = 61	3º outbreak n = 51	p
ARDS Acute Respiratory Distress Syndrome, BMI body mass index, COPD Chronic Obstructive Pulmonary Disease, OSAS Obstructive Sleep Apnea Syndrome.	ARDS Acute Respiratory Distress Syndrome, BMI body mass index, COPD Chronic Obstructive Pulmonary Disease, OSAS Obstructive Sleep Apnea Syndrome.	ARDS Acute Respiratory Distress Syndrome, BMI body mass index, COPD Chronic Obstructive Pulmonary Disease, OSAS Obstructive Sleep Apnea Syndrome.	ARDS Acute Respiratory Distress Syndrome, BMI body mass index, COPD Chronic Obstructive Pulmonary Disease, OSAS Obstructive Sleep Apnea Syndrome.	ARDS Acute Respiratory Distress Syndrome, BMI body mass index, COPD Chronic Obstructive Pulmonary Disease, OSAS Obstructive Sleep Apnea Syndrome.

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