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ACUTE MYOCARDIAL INJURY AS AN INDEPENDENT FACTOR OF POOR PROGNOSIS IN SEVERE COVID 19 DISEASE

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ABSTRACT

In 2020, coronavirus disease 2019 (COVID-19) was one of the main causes of morbidity and mortality worldwide. During the pandemic, research focused on identifying risk factors that are associated with serious illness and biochemical markers that predict mortality. This study aims to determine if acute myocardial injury is an independent factor of poor prognosis in severe COVID-19 disease by measuring high-sensitivity troponin I. A retrospective, observational, analytical and cross-sectional case-control clinical study was carried out including patients with COVID-19, which were divided into two groups: those who presented troponin I values of high sensitivity within normal parameters and patients with seric values above the 99th percentile (>25ng/l). Variables studied were sociodemographic, clinical and laboratory data recorded at hospital admission. Parametric and non-parametric statistical tests were used to compare both groups and the OR of troponin I was calculated. A total of 285 patients were included, of which 225 were recruited into the control group and 60 in the problem group. We determined that those patients with high levels of troponin I have a 5 time greater risk of dying during their hospital stay, so troponin I can be used as an independent predictor of mortality in patients with SARS-CoV-2 infection.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been one of the main current causes of mortality in the last years worldwide. Thats why it is considered a public health problem for it is necessary to implement measures in order to diminish progression risk of the disease towards severity and death (1). It has been estimated that 20% of patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will require hospital care and 5% will be admitted to the Intensive Care Unit (ICU).

Currently, different poor prognostic factors have been identified, including age ≥65 years, male gender, comorbidities (cardiovascular, respiratory diseases, and diabetes), and altered biochemical parameters upon hospital admission such as lactic dehydrogenase (LDH) >245U/L, elevated C-reactive protein (CRP), interleukin 6 (IL-6), D-dimer, serum ferritin, brain natriuretic peptide, and troponin I (2). Increases of cardiac markers is associated with the ability of SARS-CoV-2 to invade and damage cardiac tissue, leading to acute myocardial injury (3).

The American Heart Association defines acute myocardial injury as the presence of elevated cardiac troponin above the upper reference limit of the 99th percentile (4). It has been described that seriously ill patients with COVID-19 present elevated troponin I during their hospital stay in the absence of pre-existing heart disease, so it has been proposed that this cardiac marker may be associated with a higher risk of the disease, complications and mortality (5). This study aims to determine if acute myocardial injury is an independent factor of poor prognosis in severe COVID-19 disease.

METHODOLOGY

A retrospective, observational, analytical and cross-sectional case-control clinical study was designed including patients over 16 years of age with a clinical diagnosis of COVID-19 confirmed by reverse transcriptase polymerase chain reaction (PCR-RT), which were admitted at a third level hospital in a nine-month observation period during 2020. Patients with a previous history of acute heart failure, ischemic heart disease, or cardiovascular accident were excluded from the study.

All recruited patients were divided into two groups according to the concentrations of high-sensitivity troponin I taken in the first 24 hours of admission: those who presented acute myocardial injury determined by elevation of high-sensitivity troponin I (cases) and those who did not had acute myocardial injury (controls). The cut-off point established by the institutional laboratory to determine serum elevation of high-sensitivity troponin I was >25 ng/dl, a value that is standardized above the upper reference limit of the 99th percentile. Sociodemographic and clinical data recorded during hospital admission were obtained from the electronic clinical records of each patient. To support the clinical severity of patients with elevated troponin I, laboratory determination of blood count, blood chemistry, lipid profile and inflammatory markers was performed. This study was approved by the Institutional Research and Ethics Research Committees.

Statistic Analysis

The information collected was recorded in an electronic Excel spreadsheet. Statistical analysis was performed using SPSS v.25.0 statistical software. Continuous variables are expressed as mean ± standard deviation with minimum and maximum values of variability. Categorical variables are expressed as frequency and percentage in relation to the population at risk of each study group. The Student T test was used to compare numerical variables with normal distribution, and the Chi Square test was used to compare categorical variables, calculating the odds ratio with a 95% confidence interval. Mann Whitney U test was used to compare numerical variables without normal distribution. A $p < 0.05$ was considered statistically significant. The high-sensitivity troponin I values were analyzed and an Odds ratio (OR) value was subsequently calculated.

RESULTS

During the study period, a total of 285 patients were included, which were distributed into two groups. In Group 1 (controls) 225 (78.9%) patients were recruited and in Group 2 (cases) there were 60 (21.1%) patients. **Table 1** shows sociodemographic characteristics of the study groups, where statistically significant differences in age and type 2 diabetes mellitus (DM-2) were detected. Age is higher in the problem group. Regarding comorbidities, DM-2 is the most frequent comorbidity in both groups, although in the control group it occurs to a greater extent compared to the problem group. Male was the gender that was most frequently observed in the study population. Regarding somatometry, it is shown that in

both groups BMI correspond to overweight according to the WHO (6). **Table 2** shows the clinical variables recorded at hospital admission, where significant differences are observed in temperature, oxygen saturation (SO_2), capillary refill, the presence of tachypnea, polypnea and days of hospital stay. The temperature and SO_2 are lower in the problem group. Although SO_2 is lower in the problem group, no differences are observed in the use of oxygen therapy and devices to administer oxygen (O_2). Tachypnea was more frequent in the problem group and hospital stay in days was shorter in the problem group. **Table 3** shows higher mortality in patients in the problem group which presented high-sensitivity troponin I values >25ng/l with an OR of 4.7 (1.2-4.2).

To corroborate the severity of the COVID-19 disease in the problem group, laboratory values were determined, which are presented in Table 4. Significant differences can be observed in the values of leukocytes, neutrophils, glucose, BUN, creatinine, and high-density lipoprotein (HDL), low-density lipoprotein (LDL), CRP, high-sensitivity troponin I, D-Dimer, IL-6 and LDH. In the blood count and blood chemistry it is observed that the values of leukocytes, neutrophils, glucose, BUN and creatinine were higher in the problem group. Lipid profile showed lower concentrations of LDH and LDL in the problem group. Troponin I, D-dimer, IL-6 and LDH and CRP were significantly higher in the problem group.

DISCUSSION

COVID-19 is caused by SARS-CoV-2, which is a single-stranded RNA Betacoronavirus that mainly affects respiratory system. The virus enters into host cells by means of the angiotensin-converting enzyme 2 (ACE2) receptor. The S protein of the virus binds to the receptor through the transmembrane protease serine 2 (TMPRSS2) that promotes endocytosis of the virus into the cell. ACE2 receptor is expressed mainly in type II pneumocytes, in the bronchial epithelium and the ciliated cells of the nasal epithelium. This is the reason because respiratory tract is the main target for SARS-CoV-2 (7,8). The expression of the ACE2 receptor is not limited to the respiratory tract, but is also found in bowel, brain, kidneys and heart muscle, which allows the virus to affect these organs and cause extrapulmonary symptoms.

Damage to the cardiovascular system occurs in the majority of severe cases due to COVID-19, generates direct myocardium damage due to the entry of the virus through the ACE2 receptor and, indirectly promotes an inflammatory response associated with hipoxemia. This activates the immune system, which attracts proinflammatory cells that unestabilizes cardiac environment, leading to an increase in oxidative stress and, promoting acute myocardial injury (9, 10). The heart expresses a greater number of ACE2 receptors than the lungs, making it a very susceptible organ to SARS-CoV-2 infection, which causes acute damage to cardiac tissue and elevation of cardiac biomarkers, including troponin I (11). It has been documented that elevated troponin I associated with acute myocardial injury is a strong independent predictor of in-hospital mortality in patients with COVID-19 (12,13). In this study, it was identified that those patients who present an increase in high-sensitivity troponin I levels above the 99th percentile during their hospital stay have five times the risk of dying during their hospital stay than those who present levels within normal parameters. Therefore, the acute myocardial injury associated with SARS-CoV-2 infection and the consequent elevation of troponin I are poor prognostic factors that can help to promptly identify those patients who are at a greater risk of progression to severe COVID-19 disease and death.

It was observed that those patients who presented higher troponin I concentrations upon hospital admission were significantly older, which is a cardiovascular risk factor that makes the patient more susceptible to acute myocardial damage associated with SARS-CoV-2 infection. The prevalence of chronic degenerative diseases and their complications increase with age and promote in patients a constant and chronic pro-inflammatory state that favors an altered immune response and increases the risk of presenting an uncontrolled cytokine storm (14,15). In our study the cases were significantly older compared to the controls and among the comorbidities, type 2 diabetes occurs more frequently in both groups, affecting patients in the problem group in a greater number. This comorbidity is capable of accelerating the production of oxygen radicals promoted by SARS-CoV-2 infection, which makes both diseases work synergistically in the pathogenesis of cardiac injury (16). Patients with DM-2 have a 3 time increased risk of myocardial damage associated with ischemic heart disease. Metabolic disturbance increases oxidative and inflammatory stress, which is further altered with coronavirus infection (17). We can propose that patients with DM-2 are a population with a higher risk of presenting troponin I elevation and acute myocardial injury, as shown in this study.

Among clinical manifestations, it is expected that those patients who present some type of infection will have an elevated temperature. On the contrary, in this study the problem group had a significantly lower body temperature compared to the control group. This is associated with the fact that the autonomic thermoregulatory neurons found in the preoptic region lose their thermoregulatory capacity in older adults, which causes a decrease in thermal sensation and in conditions where the temperature should be raised, it can remain normal or even lower than normal as expected (18). In the problem group, the patients are older compared to the control group, which explains why the thermoregulatory response is affected and the response to the infection does not present with fever or increased temperature.

Dyspnea is an early symptom due to hipoxemia, which is associated with a higher risk of mortality. Both study groups presented severe hypoxemia recorded by SO_2, but the problem group had significantly lower levels. Despite this, we can say that hypoxemia was not a mortality risk factor in this study, since upon hospital admission the patients received oxygen therapy opportunely and it has been documented that for every unit that SO_2 increases the risk of mortality decreases up to 8% (19). In addition we can observe that dyspnea was not a common symptom presented in the problem group. On the contrary, it was seen that there were no statistical differences in its classification. It has been reported as well, that patients with elevated troponin I are more likely to require oxygen therapy and even use of invasive mechanical ventilation (IMV) (20). In our study groups, no significant differences were observed in the use of oxygen (O_2) and devices. In both, the reservoir mask was used more frequently followed by the nasal prongs despite the fact that oxygen saturation (SO_2) was significantly minor in the problem group.

The results of laboratory studies taken during hospital admission show that those patients with elevated troponin I have a greater risk of progressing to a serious condition and consequently death. The significant increase in leukocytes due neutrophils elevations associated with a high level of C-reactive protein is associated with severity of the inflammatory response and predicts an unfavorable outcome for the patient. The increase in proinflammatory cytokines promotes apoptosis mainly of the epithelial cells of the respiratory system and alveoli, which serves as a predictor of respiratory failure. It has been reported that leukocyte values remain with a tendency to rise in seriously ill patients and those who have leukopenia present a mild to moderate disease. Likewise, D-dimer is an acute phase reactant that is significantly elevated in acute inflammatory diseases and is commonly elevated in severe cases of COVID-19 and has been considered a predictor of mortality (21). LDH is an enzyme that also shows significant elevations in the problem

group, which is known to increase after a cellular injury associated with inflammation or hypoxemia and in the same way this marker is used as a predictor of severity (22). Elevation of troponin I is an independent marker of poor prognosis in patients with COVID-19 who present acute myocardial injury, which is corroborated by laboratory results and elevation of markers that have already been associated with poor prognosis such as CRP, D-dimer and LDH, which presented with statistically significant elevations in the problem group. These patients present with severe inflammatory activity that not only damages the respiratory system, but also affects cardiac tissue with the consequent exaggerated immune response that can even progress to a cytokine storm. That is why troponin I can be used as a predictive biomarker of mortality in patients with COVID-19.

CONCLUSION

Troponin I is a biomarker that is mainly elevated in acute myocardial injury. It has been described that those patients who have COVID-19 and an elevation of this marker above the 99th percentile (>25 ng/l) during their hospital admission have a 5 times greater risk of dying during their hospital stay. Therefore, troponin I can be used as an independent predictor of mortality in patients with SARS-CoV-2 infection.

Tables

Table 1. Comparison Of The Sociodemographic Variables Of The Study Groups

Variables	CONTROL Group (n=225) n (%) / Mean ± SD (Min - Max)	PROBLEM Group (n=60) n (%) / Mean ± SD (Min - Max)	p
Age (years)	51 ± 14 (16-84)	57 ± 14 (24-81)	0.008
Gender			
Male	150 (66.7%)	42 (70%)	NS
Female	75 (33.3%)	18 (30%)	NS
Comorbidity			
SAH	57 (25.3%)	20 (33.3%)	NS
DM2	66 (29.3%)	26 (43.3%)	0.0393
Asthma	3 (1.3%)	0 (0%)	NS
COPD	3 (1.3%)	1 (1.7%)	NS
Smoking	36 (16%)	14 (23.3%)	NS
HIV	1 (0.4%)	0 (0%)	NS
Somatometry			
Weight	79 ± 16 (40-142)	76 ± 19 (45-118)	NS
Size	1.64 ± 0.09 (1.40-1.87)	1.62 ± 0.09 (1.44-1.81)	NS
BMI	29.41 ± 5.37 (17.78-49.31)	28.91 ± 6.03 (18.73-46.09)	NS

Abbreviations: *SAH = Systemic arterial hypertension, DM2 = Diabetes mellitus type 2, HIV = Human Immunodeficiency Virus, COPD = Chronic Obstructive Pulmonary Disease, BMI = Body Mass Index*

Table 2. Clinical Variables Of The Study Groups

Variables	CONTROL Group (n=225) n (%) / Mean ± SD (Min - Max)	PROBLEM Group (n=60) n (%) / Mean ± SD (Min - Max)	p
Temperature (°C)	37.3 ± 0.90 (35-39.9)	37 ± 0.8 (35.5-39.3)	0.044
Blood pressure (mmHg)			
Systolic	115 ± 16 (60-162)	117 ± 19 (60-160)	NS
Diastolic	70 ± 10 (33-95)	70 ± 11 (35-96)	NS
HR (bpm)	101 ± 18 (55-195)	103 ± 18 (62-149)	NS
RR (bpm)	27 ± 7 (15-48)	29 ± 7 (15-48)	NS
SO2 (%)	81 ± 13 (25-100)	66 ± 18 (34-98)	< 0.0001
Capillary refill(s)	2 ± 1 (1-6)	3 ± 1 (2-4)	0.008
Glasgow	15 ± 1 (6-15)	15 ± 1 (9-15)	NS
Oxygen therapy	186 (82.7%)	50 (83.3%)	NS
O2 supply			
Nasal prongs	85 (37.8%)	17 (28.3%)	NS
Simple mask	3 (1.3%)	1 (1.7%)	NS
Reservoir mask	95 (42.2%)	30 (50%)	NS
IMV	4 (1.8%)	1 (1.7%)	NS
Tachypnea	64 (28.4%)	25 (41.7%)	0.05
Dyspnoea			
Mild	91 (40.5%)	18 (30%)	NS
Moderate	66 (29.3%)	25 (41.7%)	NS
Severe	23 (10.2%)	10 (16.7%)	NS
Hospitalization (days)	17 ± 31 (0-220)	14 ± 31 (1-220)	0.031

Abbreviations: *°C = degrees Celsius, mmHg = millimeters of mercury, HR = heart rate, bpm = beats per minute, RR = Respiratory rate, bpm = breaths per minute, SO_2 = oxygen saturation, s = seconds, O_2 = oxygen, IMV = invasive mechanical ventilation*

Table 3. Contingency Table For Mortality And High-sensitivity Troponin I.

	Control	Problem		
Mortality	<25ng/l	>25ng/l	p	OR (95% CI)
YES	81 (36%)	43 (71.7%)	< 0.0001	4.7 (1.2-4.2)
NO	144 (64%)	17 (28.3%)		

Abbreviations: *ng = nanograms, l = liters*

Table 4. Laboratory Variables Of The Study Groups

	n (%) / Mean ± SD (Min - Max)	n (%) / Mean ± SD (Min - Max)	
Hematic biometry			
Hemoglobin (g/dl)	14.6 ± 2.9 (0.8 - 29.5)	14.3 ± 2.4 (6.6 - 18.9)	NS
Leu (cell/mm³)	10.5 ± 5.2 (0.6 - 39.7)	13.3 ± 6 (0.6 - 29.4)	< 0.0001
Neu (cell/mm³)	9.94 ± 9.68 (0.03 - 87.30)	11.6 ± 5.9 (0.2 - 28.3)	< 0.0001
Lymph (cell/mm³)	1.72 ± 8.21 (0.09 - 122)	1.19 ± 1.28 (0.17 - 10)	NS
Blood chemistry			
Glucose (mg/dl)	151 ± 97 (45 - 592)	192 ± 187 (21 - 1178)	0.045
BUN (mg/dl)	20.1 ± 14.4 (0.8 - 112.9)	33.8 ± 26.3 (5.4 - 129.4)	< 0.0001
Creatinine (mg/dl)	1.0 ± 0.8 (0.3 - 8.8)	2.3 ± 3.7 (0.6 - 17.9)	< 0.0001
Lipid profile			
Cholesterol (mg/dl)	136 ± 41 (15 - 373)	132 ± 41 (63 - 275)	NS
HDL (mg/dl)	31 ± 13 (2 - 138)	27 ± 12 (3 - 60)	0.016
LDL (mg/dl)	72 ± 31 (10 - 252)	65 ± 32 (9 - 194)	0.041
CRP (mg/dl)	166.07 ± 128.13 (0.77 - 1306)	220.59 ± 123.34 (1.87 -705.49)	< 0.0001
D-dimer (ng/ml)	2419.5 ± 5097.2 (1.8 - 35200)	6269.78 ± 9051.35 (225 -35200)	< 0.0001
IL-6 (pg/ml)	106.4 ± 141.3 (2 - 935)	226.2 ± 293.1 (2 -1000)	< 0.0001
DHL (UI/L)	390 ± 160 (105 - 1552)	532 ± 212 (172 -1121)	< 0.0001
Ferritin (mcg/L)	952.35 ± 911.74 (3.5 - 7500)	1500.7 ± 2284.7 (25.1 -14054)	NS

Abbreviations: *Leu = leukocytes, Neu = neutrophils, Linf = lymphocytes, g = grams, dl = deciliter, cell = cells, mm³ = cubic, mcg = micrograms, BUN = Blood urea nitrogen, HDL = high-density lipoprotein, LDL = low-density lipoprotein, CRP = C-reactive protein, IL-6 = Interleucin -6*

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