

Correlation of echocardiographic variables and biomarkers in severely ill COVID-19 patients

Correlación de variables ecocardiográficas y biomarcadores en pacientes graves con COVID-19

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Abstract

Objective: To describe echocardiographic variables and their correlation with biomarkers and mortality in COVID-19 patients. **Method:** Observational, descriptive, longitudinal, and retrospective study. **Results:** 70% (n = 21) corresponded to the male gender; means of age and body mass index were 59 (46-67) years and 30.1 (27.3-32.4) kg/m², respectively. In the evaluation of the left ventricular systolic function, an appropriate correlation between MAPSE (mitral annular plane systolic excursion) and the left ventricular ejection fraction ($r^2 = 0.508$, $p = 0.004$) was observed. In the evaluation of the right ventricular systolic function, an optimum correlation between TAPSE (tricuspid annular plane systolic excursion) and the right ventricular outflow tract fractional shortening ($r^2 = 0.649$, $p = \leq 0.0001$) was observed. No correlation between biomarkers and echocardiographic variables between surviving and non-surviving patients was found, except for MAPSE and serum lactate dehydrogenase values ($r^2 = -0.427$, $p = 0.019$). The mortality rate was 16% (n = 5). **Conclusion:** An appropriate correlation between echocardiographic variables of both left and right ventricular systolic function was found, as well as between MAPSE and serum LDH values.

Keywords: Biomarkers. COVID-19. Echocardiography. MAPSE. Mortality. TAPSE.

Resumen

Objetivo: Describir las variables ecocardiográficas de los pacientes con COVID-19 y su correlación con biomarcadores y mortalidad. **Método:** Estudio observacional, descriptivo, longitudinal y retrospectivo. **Resultados:** El 70% (n = 21) eran de sexo masculino, el promedio de edad fue de 59 (46-67) años y el índice de masa corporal fue de 30.1 (27.3-32.4) kg/m². En la evaluación de la función sistólica del ventrículo izquierdo se observó una adecuada correlación entre la excursión

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sistólica del plano del anillo mitral (MAPSE) y la fracción de eyección del ventrículo izquierdo ($r^2 = 0.508$, $p = 0.004$). La evaluación de la función sistólica del ventrículo derecho indicó una óptima correlación entre la excursión sistólica del plano del anillo tricuspídeo (TAPSE) y la fracción de acortamiento del ventrículo derecho ($r^2 = 0.649$, $p = \leq 0.0001$). No hubo correlación de los biomarcadores y las variables ecocardiográficas entre los pacientes sobrevivientes y no sobrevivientes, a excepción del MAPSE y las concentraciones séricas de deshidrogenasa láctica ($r^2 = -0.427$, $p = 0.019$). La tasa de mortalidad fue del 16% ($n = 5$). **Conclusión:** Existe una adecuada correlación entre las variables ecocardiográficas de la función sistólica del ventrículo izquierdo y del ventrículo derecho, así como también entre la MAPSE y los valores séricos de DHL.

Palabras clave: Biomarcadores. COVID-19. Ecocardiografía. MAPSE. Mortalidad. TAPSE.

Introduction

Towards the end of December 2019, the first case of pneumonia of unknown origin was identified in Wuhan, capital of the Hubei province in China¹. The causative microorganism, a new beta-coronavirus, the RNA² chain of which was identified, was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)³. Infection with this virus has a wide range of symptoms, from asymptomatic presentations to mild, moderate or severe symptoms⁴⁻⁸.

The prevalence of cardiovascular diseases in patients with COVID-19 is common, and they are associated with a higher risk of severity and complications, with hypertension being the most common⁹⁻¹¹. In Mexico, the prevalence of hypertension in seriously ill COVID-19 patients is 37.5%¹².

The most common cardiac complications related to COVID-19 are myocardial injury and myocarditis, acute myocardial infarction, acute heart failure and cardiomyopathy, arrhythmias and venous thromboembolic events¹³.

Echocardiography can help to quickly identify patient hemodynamic status, with the most frequent findings being hyperdynamic heart function, stress-induced cardiomyopathy (Takotsubo), pulmonary hypertension and diffuse myocardial inhibition secondary to hypoxia¹⁴.

The purpose of the study herein presented is to describe echocardiographic variables in patients diagnosed with severe COVID-19 pneumonia and their correlation with biomarkers and mortality at the intensive care unit (ICU).

Method

Observational, descriptive, longitudinal, retrospective study, which was carried out at *Médica Sur* Hospital ICU, from March to June 2020, after authorization by the Research Ethics Committee of the Hospital

(2020-EXT-461) and informed consent signature by the patient or his/her legal representative.

The inclusion criteria were: adult patients of both genders, older than 18 years, with respiratory function progressive deterioration manifested by dyspnea and hypoxemia, with increased oxygen supply requirements and suspected or confirmed diagnosis of COVID-19 by clinical and radiological data consistent with COVID-19 and with polymerase chain reaction (PCR) positive test for SARS-CoV-2 from a nasopharyngeal sample, who were admitted to the ICU for advanced airway management and invasive mechanical ventilation. Pregnant patients were excluded.

Evaluated variables included age, gender, body mass index (BMI), clinical-demographic characteristics, ventilatory management, echocardiographic variables, biomarkers (lymphocytes, platelets, fibrinogen, D-dimer, lactic dehydrogenase [LDH], triglycerides, ferritin and C-reactive protein) and mortality. Data were retrospectively obtained from the medical record at admission, and paraclinical tests were carried out and targeted treatment administered at admission and during patient hospitalization until discharge from the ICU due to improvement or death or cutoff date on June 10, 2020.

Data distribution was determined with Kolmogorov-Smirnov test. Categorical data are shown as percentages, while continuous data are expressed as medians and interquartile ranges. Differences between categorical variables were analyzed using the chi-square test and Fisher's exact test, while differences between continuous data were evaluated with Mann-Whitney's U-test. Correlations between echocardiographic variables and biochemical data were performed using Spearman's correlation. Statistical analysis was carried out with the SPSS v.20 statistical package.

Results

In the period from March to June, 65 patients diagnosed with severe COVID-19 pneumonia were

Table 1. Echocardiographic variables in severely ill COVID-19 patients

Variable	Total patients (n = 30) % (n), M [IQR]	Survivors (n = 25) % (n), M [IQR]	Non-survivors (n = 5) % (n), M [IQR]	p
Age, years	59 [46-67]	59.5 [46.7-67]	63 [41-77]	1.000
Gender (M/F)	70% (21)/30% (9)	72% (18)/28% (7)	60% (3)/40% (2)	1.000
BMI	30 [27.1-33.7]	29.7 [26.8-33.7]	32 [28.1-46.6]	0.315
Mortality (%)	5 (16%)	-	-	
Obesity	30% (9)	28% (7)	40% (2)	0.563
Hypertension	23.3% (7)	20% (5)	40% (2)	0.225
Diabetes	13.3% (4)	16% (4)	0%	1.000
Echocardiography				
Diameter (S/D)	28 [26-33]	28 [26.7-33]	26 [21-32.5]	0.613
Mass/m ²	69 [55-78]	66.5 [55-78]	73 [53.5-83.5]	0.598
LVEF	60 [57.5-61]	60 [57.3-61]	59.5 [57.5-65.2]	0.631
MAPSE	10.2 [12.2-13.7]	12.2 [10.2-14]	12.3 [10-13]	1.000
TAPSE	19.1 [18.2-20.9]	18.9 [18-20.2]	20.9 [20.2-23.2]	0.099
RV free wall thickness	4.7 [4.0-5.0]	4.6 [4-5]	4.9 [4.2-5.7]	0.598
RVSF	40 [37.3-45]	40 [36.5-41.2]	42.5 [40-45]	0.283
Dilated RV	66% (20)	64% (16)	80% (4)	0.272
RV basal diameter	43.5 [39.5-45.2]	43.1 [37.9-45.2]	44.8 [43.4-45.7]	0.598
PASP	27.5 [23.7-32.7]	27 [23.7-32]	31.5 [16.8-38.2]	1.000
E/A ratio	0.89 [0.72-1.2]	0.87 [0.72-1.2]	1.1 [0.63-1.2]	0.597
LV mobility alterations	13.3% (4)	4% (1)	60% (3)	0.454
RV mobility alterations	13.3% (4)	12% (3)	20% (1)	0.454
Stress-induced cardiomyopathy	10% (3)	12% (3)	0%	0.768
IVM				
PEEP	10 [8-12]	10 [8-12]	10 [10-13]	1.000

BMI: body mass index; IQR: interquartile range; IVM: invasive mechanical ventilation; LV: left ventricle; LVEF: left ventricular ejection fraction; M: median; MAPSE: mitral annular plane systolic excursion; M/F: male/female; PASP: pulmonary artery systolic pressure; PEEP: positive end-expiratory pressure; RV: right ventricle; RVSF: right ventricular shortening fraction; S/D: systolic/diastolic diameter; TAPSE: tricuspid annular plane systolic excursion.

admitted to *Médica Sur* Hospital ICU, out of whom 30 (46%) underwent transthoracic echocardiogram.

Of the 30 evaluated patients, 70% (n = 21) were males, mean age was 59 (46-67) years and BMI was 30.1 (27.3-32.4) kg/m². Main comorbid conditions were obesity (30%, n = 9), hypertension (23%, n = 7) and diabetes (13%, n = 4).

The echocardiographic variables evaluated in patients with severe COVID-19 pneumonia showed no significant differences between surviving and non-surviving patients (Table 1).

In left ventricular systolic function evaluation, an appropriate correlation was observed between mitral annular plane systolic excursion (MAPSE) and left ventricular ejection fraction values ($r^2 = 0.508$, $p = 0.004$) (Fig. 1). Similarly, in right ventricular systolic function evaluation, an appropriate correlation was observed between tricuspid annular plane systolic excursion (TAPSE) and right ventricular shortening fraction determination ($r^2 = 0.649$, $p = \leq 0.0001$)

(Fig. 2). However, no statistically significant difference was found between right ventricular diameter and thickness ($r^2 = 0.354$, $p = 0.055$).

Among the evaluated patients, 100% were on orotracheal intubation and invasive mechanical ventilation at the time transthoracic echocardiogram was carried out, without a statistically significant correlation being found between the levels of positive end-expiratory pressure and those of pulmonary artery systolic pressure, with a correlation $r^2 = -0.059$; $p = 0.755$.

On the other hand, serum biomarkers determination in patients who underwent transthoracic echocardiography showed no differences between survivors and non-survivors (Table 2). However, when biomarkers and echocardiographic variables were compared, a correlation was found between MAPSE and serum LDH values ($r^2 = -0.427$; $p = 0.019$) (Fig. 3).

The mortality rate was 16% (n = 5), and 40% of the patients who died had obesity and hypertension as comorbid conditions.

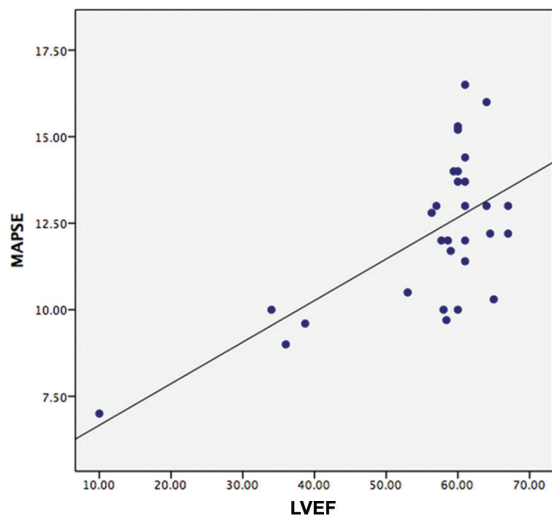


Figure 1. Correlation between mitral annular plane systolic excursion (MAPSE) and left ventricular ejection fraction (LVEF).

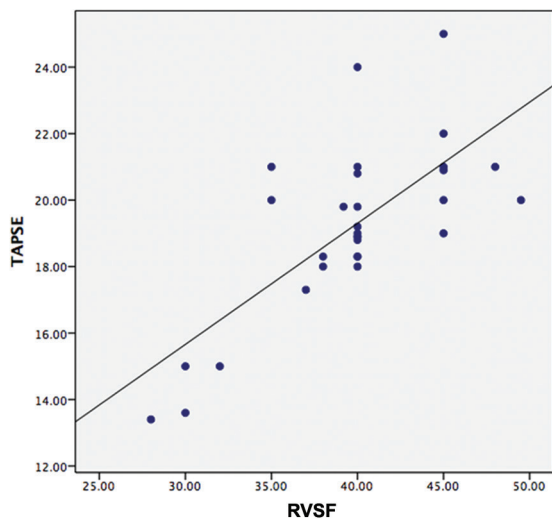


Figure 2. Correlation between tricuspid annular plane systolic excursion (TAPSE) and right ventricular shortening fraction (RVSF).

Discussion

Studied patients had similar clinical and demographic characteristics to those of other studies in the general population and in the ICU, with advanced age and the presence of obesity and hypertension standing out as the most important comorbid conditions^{10,15,16}.

Within the echocardiographic variables that were obtained, there were no statistically significant differences between surviving and non-surviving patients, but it should be pointed out that 13.3% (n = 4)

and 26.6% (n = 8) had a low left ventricular ejection fraction (< 40%) and decreased MAPSE (< 12 mm), respectively, similar to findings reported by Ruan et al.¹⁷; however, this was not correlated with a mortality increase as Rath et al.¹⁸ and Li et al.¹⁹ described. On the other hand, 10% (n = 3) of the patients had typical stress-induced cardiomyopathy (Takotsubo), out of whom all survived, as in other case series reports^{20,21}.

Six patients (20%) had pulmonary arterial pressure elevation (> 35 mmHg), and 66% (n = 20), right ventricular dilation that was not associated with chronicity, with this percentage being higher than that reported by Rath et al.¹⁸, which was 48.9% in a similar population. Taking right ventricular free wall thickness into consideration, only 6.6% of patients had myocardial hypertrophy, which would indicate a low probability of previous pulmonary hypertension, same as the findings made by Li et al.¹⁹ in their study.

In addition, a significant proportion of patients (26.6%) were observed to have low MAPSE without an ejection fraction decrease, which could perhaps indicate subclinical left ventricular systolic dysfunction, which would impact on their clinical conditions; among them, half had pulmonary arterial pressure elevation.

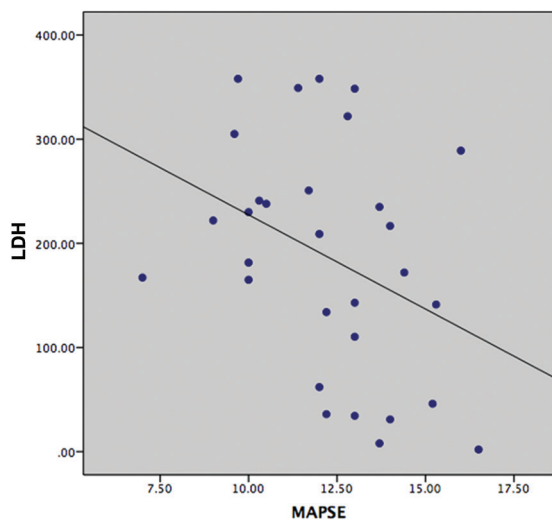
The correlation of echocardiographic variables with biomarkers of inflammation and thrombosis in evaluated patients showed no statistically significant differences with mortality, as were the results reported in other case series¹⁸⁻²², in which a mortality increase is described in patients with C-reactive protein elevation. In the study by Rath et al.¹⁸, no correlation was found between D-dimer elevation and left and right ventricular systolic dysfunction either; however, unlike the observations reported by Li et al.¹⁹ who did find a correlation between high D-dimer values and right ventricular systolic dysfunction, regarded as an independent mortality predictor.

It is important mentioning that, in the study population, a correlation was observed between LDH elevated values and MAPSE low values in patients with severe COVID-19 pneumonia, which may be useful for left ventricular systolic function to be determined in places where echocardiography is not accessible or available.

Mortality in our population was 16.6% (n = 5), with previous history of cardiovascular disease, mainly hypertension, as published in other patient series^{18,22}, with mortality being higher than that reported by Rath et al.¹⁸, which was 13%, and lower than that reported by Guo et al.²², which was 23%.

Table 2. Correlation of echocardiographic variables with biomarkers in severely ill COVID-19 patients

Biomarker	Total patients	Survivors	Non-survivors	p
Lymphopenia ($\times 10^3/\mu\text{L}$)	750 [400-100]	600 [375-1000]	950 [525-1600]	0.598
Platelets ($\times 10^3/\mu$)	249 [204-309]	256.5 [204-309.5]	234 [183.5-331.7]	0.702
Fibrinogen (mg/dL)	699 [493-759.7]	699 [488-759.5]	579 [493-868]	1.000
D-dimer (ng/mL)	1380 [925-6750]	1210 [865-5657]	6270 [1332-216,467]	0.157
Lactate dehydrogenase (U/L)	195.2 [98.2-260.3]	212.8 [98.2-293]	162.2 [61.5-233.4]	0.617
Triglycerides (mg/dL)	183 [123-278.5]	183 [123-278.5]	191.5 [131.9-314.8]	1.000
Ferritin (ng/mL)	850 [258.7-1508.7]	941 [258.7-1517.5]	565.6 [196.4-1334.3]	0.391
C-reactive protein (ng/mL)	338.5 [244.7-514.7]	335.5 [243.7-492.2]	433.5 [259.2-646]	0.461

**Figure 3.** Correlation between mitral annular plane systolic excursion (MAPSE) and lactate dehydrogenase (LDH).

The main limitations of the study are that it is retrospective, single-center and with a small sample size, and the results of the correlation measurements between different interventions should therefore be taken with caution until a larger number of patients are available.

Conclusions

Main characteristics of the critically ill patients evaluated with echocardiography were the presence of obesity and hypertension, with an appropriate correlation being found between the echocardiographic variables of the left and right ventricular systolic function, as well as between MAPSE and LDH serum values. Undoubtedly, echocardiography is a highly

useful tool for seriously ill COVID-19 patients global, real-time, bedside evaluation.

Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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