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V.M. Kovalenko, E.G. Nesukay, T.V. Talaieva, O.S. Sychov, S.V. Cherniuk, R.M. Kirichenko, I.V. Tretiak
SI "National scientific center "The M.D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Sciences of Ukraine", Kyiv

FEATURES OF THE DEBUT OF ACUTE MYOCARDITIS IN PATIENTS AFTER COVID-19 INFECTION

e-mail: nesukay@yahoo.com

The purpose of the study was to perform a comparative assessment and analysis of the relationship between parameters of immune status and the structural and functional state of the heart in patients with acute myocarditis who had or did not have a history of COVID-19 infection. According to the results of the study, patients with acute myocarditis and a history of COVID-19 infection were characterized by a larger volume of inflammatory and fibrotic damage to the myocardium and more pronounced violations of the contractility of the left ventricle compared to patients who did not have a history of coronavirus infection. In addition, patients with myocarditis and previous coronavirus infection were characterized by a more pronounced activation of immunopathological reactions, which was accompanied by a higher level of C-reactive protein, pro-inflammatory interleukin-6, ferritin and troponin I as a marker of cardiomyocyte damage. The use of factor analysis made it possible to establish the limit values of instrumental and laboratory indicators associated with the presence of widespread inflammatory/fibrotic lesions of the left ventricle in patients with acute myocarditis and history of COVID-19: the values of left ventricle longitudinal, global systolic strain of the ≤9.0 % and the left ventricle end-diastolic volume index ≥95 ml/m^2, as well as the content of tumor necrosis factor-α ≥7.5 pg/mL and C-reactive protein ≥12.0 mcg/ml in blood serum.

Key words: acute myocarditis, coronavirus infection, immunopathological reactions, left ventricle global systolic strain, inflammatory and fibrotic changes in the heart.

В.М. Коваленко, О.Г. Несукай, Т.В. Талаєва, О.С. Сичов, С.В. Чернюк, Р.М. Кириченко, І.В. Третяк

ОСОБЛИВОСТІ ДЕБЮТУ ГОСТРОГО МІОКАРДИТУ У ХВОРИХ, ЯКІ ПЕРЕНЕСЛИ COVID-19 ІНФЕКЦІЮ

Метою дослідження була порівняльна оцінка та аналіз взаємозв'язку показників імунного статусу та структурно-функціонального стану серця у хворих з гострим міокардитом, які перенесли або не мали COVID-19 інфекцію в анамнезі. Згідно результатів проведених досліджень пацієнти з гострим міокардитом і перенесеною в анамнезі COVID-19 інфекцією характеризувались більш значним об'ємом запального і фібротичного ураження міокарду та більш вираженими порушеннями скоротливої здатності лівого шлуночка в порівнянні з хворими, які не мали коронавірусної інфекції в анамнезі. Окрім цього, пацієнти з міокардитом та перенесеною коронавірусною інфекцією характеризувались більш вираженою активацією імунопатологічних реакцій, що супроводжувалось вищим рівнем С-реактивного протеїну, прозапального інтерлейкіну-6, феритину та тропоніну І як маркера ураження кардіоміоцитів. Застосування факторного аналізу дозволило встановити граничні значення інструментальних та лабораторних показників, що асоціювались з наявністю розповсюдженого запального/фібротичного ураження лівого шлуночка у хворих з гострим міокардитом та COVID-19 в анамнезі: величини поздовжньої глобальної систолічної деформації лівого шлуночка ≤9,0 % та індекс кінцево-діастолічного об'єму лівого шлуночка ≥95 мл/м^2, а також вміст фактора некрозу пухлини-α ≥7,5 пг/мл та С-реактивного протеїну ≥12,0 мкг/мл в сироватці крові.

Ключові слова: гострий міокардит, коронавірусна інфекція, імунопатологічні реакції, глобальна систолічна деформація лівого шлуночка, запальні та фібротичні зміни серця.

The study is a fragment of the research project "To establish the influence of stress factors on the course and long-term consequences of myocarditis in martial law conditions and to develop new approaches to its treatment", state registration number 0119U202079.

Coronavirus disease (COVID-19) is associated with a wide range of cardiovascular complications, including acute coronary syndrome, cardiac arrhythmias, acute heart failure (HF), acute myocarditis (AM), and sudden cardiac death. In patients with COVID-19, myocardial damage occurs in 7–23 % of cases and is associated with a higher mortality rate [4, 15]. Myocarditis in patients after COVID-19 infection can manifest as arrhythmias, right and left ventricular dysfunction, cardiogenic shock, and sudden cardiac death [14, 15]. In some cases, the debut of myocarditis after the transferred COVID-19 infection can occur under the mask of acute coronary syndrome, dysfunction of the heart's conduction system, thromboembolism of pulmonary arteries, and acute HF [2, 4]. At the same time, the issues of the onset and course of myocarditis in patients who have had a COVID-19 infection, compared with those without a history of COVID-19, are insufficiently studied. In particular, it is relevant to conduct a comparative and correlational analysis of the state of immunity, contractility of the heart, localization and volume of inflammatory and cardiac fibrosis

in groups of patients with myocarditis who have suffered from COVID-19 and in patients without a history of coronavirus infection.

The purpose of the study was to perform a comparative assessment and analysis of the relationship between parameters of immune status and the structural and functional state of the heart in patients with acute myocarditis who had or did not have a history of COVID-19 infection.

Material and methods. 46 patients with acute myocarditis (AM) were examined and were divided into two groups. Group 1 included 26 patients with AM, which developed on average 1.5 ± 0.5 months after COVID-19 infection: 15 (57.6 %) men and 11 (42.4 %) women, aged on average (38.3±2.7) years. Group 2 included 20 patients with AM and without COVID-19: 12 (60.0 %) men and 8 (40.0 %) women, mean age (40.9±3.0) years, who were examined and inpatient treatment in the Department of non-coronary heart diseases, rheumatology and therapy of the SI "National scientific center "The M.D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Sciences of Ukraine". All patients signed informed consent to participate in the study.

The diagnosis of acute myocarditis was established based on the Standards for diagnosing and treating cardiovascular diseases and the recommendations for diagnosing and treating myocarditis of the Ukrainian Association of Cardiology [1, 2].

To confirm the diagnosis of acute myocarditis, all patients underwent magnetic resonance imaging (MRI) of the heart on a Toshiba Vantage Titan HSR 1.5 Tesla device (Japan). Images of the heart along the short and long axis were evaluated in 3 modes: before the administration of a contrast agent (Gadovist, Bayer AG., Germany) to detect the area of edema in the myocardium within 3–5 min after administration (early contrast) and delayed contrast mode after 10–15 min after the administration of contrast agent [3].

Cardiohemodynamic parameters were assessed using transthoracic echocardiography (EchoCG) using the ultrasound system Aplio Artida SSH – 880 CV (Toshiba Medical System Corporation, Japan). In the B-mode, the end-diastolic (EDV) and end-systolic (ESV) volumes of the left ventricle (LV) were determined, which were indexed to the body surface area (EDVI, ESVI). The ejection fraction (EF) of the LV was calculated using the biplane method of discs (modified Simpson's rule) [11].

Speckle-tracking echocardiography (STE) using the Wall Motion Tracking software package was used to assess the geometry of heart chamber contraction. Parameters of LV global longitudinal, circumferential and radial systolic strain (respectively GLS, GCS and GRS) and left atrial systolic strain (LASS) were determined. LV twist (difference between apical and basal LV rotations) was assessed using video clips-images recorded in the parasternal view along the short axis at the level of the LV apex and the mitral valve [11].

The content of high-sensitivity C-reactive protein, tumor necrosis factor α, interleukin-6, ferritin, troponin I and D-dimer was determined on the ThunderBolt enzyme-linked immunosorbent assay system using the Storm Software Suite. Parameters were determined using enzyme immunoassay kits from IBL International (Germany), LDN Labor Diagnostika (Germany), Monobind Inc. (USA).

The results were processed using the Excel XP software (Microsoft Office, USA) and the statistical program Statistica 10.0 Portable (Statsoft, USA). Statistical analysis of the obtained results was carried out using descriptive statistics and parametric (Student) statistical criteria; $p<0.05$ was considered the criterion for the probability of discrepancies. The relationship between variables was determined using parametric correlation analysis. Limit values of indicators associated with the presence of certain structural and functional disorders were determined based on the Student's test using multivariate regression analysis.

Results of the study and their discussion. Comparative analysis of echocardiogram (EchoCG) data allowed us to establish that the groups of patients were comparable in terms of LV volumes and LV EF. At the same time, the patients of Group 1 had more pronounced changes in the geometry of contraction compared to those in Group 2, namely according to the results of STE, it was established that in the 1st group, the values of LV GLS and GCS were, respectively, on average by 18.9 and 17.5 % lower than those in Group 2 ($p<0.05$), the values of LV GRS were comparable (Table 1).

In Group 1, the value of the LASS index was lower on average by 22.3 % compared to that in the 2nd group ($p<0.01$), which indicated a decrease in the reservoir function of the LA. When studying the rotation indices, it was found that the patients of Group 1 had more significant violations in the values of the LV twisting indices compared to Group 2. In patients of Group 1 compared to Group 2, the LV rotational deformation index value was 25.3 % lower on average: 8.3±0.6 and 11.1±0.8 ^{0}/s, respectively ($p<0.01$).

Table 1

Results of echocardiography and cardiac MRI in groups of patients with AM

Parameters	Parameter value (M±m) in groups	
	1st (n=26)	2nd (n=20)
LV EDVI, ml/m²	102.1± 8.2	98.6±6.3
LV ESVI, ml/m²	68.2±6.8	62.2±5.4
LV EF, %	33.9±2.2	36.4±3.1
GLS	8.2±0.6	10.1±0.7*
GCS, %	7.5 ±0.6	9.1±0.7*
GRS, %	16.7±1.4	18.6±1.2
Early contrast on T1 images (hyperemia), %	86.6	70.0
Signal intensity amplification on T2 images (edema), %	73.3	60.0
Delayed contrast on T1 images (necrosis/fibrosis), %	60.0	40.0
Number of segments with inflammatory changes (edema and/or hyperemia)	7.20±0.68	5.41±0.54*
Number of segments with fibrotic changes (delayed contrast)	4.22±0.42	2.54±0.38**
Total lesion volume by inflammatory and fibrotic changes (segments)	11.42±0.88	7.91±0.72**

Note. The difference in indices is significant compared to those in Group 1: * $p < 0.05$, ** – $p < 0.01$.

According to cardiac MRI data, a larger volume of inflammatory and fibrotic lesions of the LV was found in patients of the 1st group compared to patients of the 2nd group. In particular, early contrast on T1 images, which indicates inflammatory hyperemia in patients of Group 1, was found in 86.6 % of cases; increased signal intensity on T2 images, reflecting myocardial edema – in 73.3 % of cases; delayed accumulation of contrast, which indicates necrotic and/or fibrotic changes, was noted in 60 % of cases. In patients of the 2nd group, hyperemia and edema were detected less often – in 70 and 40 % of cases, respectively, and fibrotic changes of the myocardium in 40 %. At the same time, in patients of the 1st group, the mean number of segments affected by inflammatory changes was 25 % more ($p < 0.05$) than in patients of the 2nd group. At the same time, the number of segments affected by fibrotic changes in this cohort of patients was higher by 40.5 % ($p < 0.01$), and the total volume affected by inflammatory and fibrotic changes by 30.7 % ($p < 0.01$) higher than in patients without a history of COVID 19.

The analysis of the localization of pathological changes showed that in patients of Group 1, inflammatory lesions of the interventricular septum (IVS) prevailed (in 75 % of cases) and zones of delayed accumulation of contrast – in 37.5 % of patients. Inflammatory changes in the lateral region of the LV were detected in 40.6 % and the posterior wall in 34.4 % of cases, while delayed contrast in the lateral and posterior region was detected in 28.1 and 25.0 % of cases, respectively. In Group 2, the frequency of inflammatory lesions of the IVS and the lateral region of the LV was the same and amounted to 50 %. The involvement of the posterior wall in the inflammatory process was observed at 40 %. Delayed contrast in the IVS and the back wall of the LV in patients of the 2nd group was detected in 20 % of cases, and in the lateral region in 30 % of patients.

According to the results of laboratory tests, it was established that the level of troponin I in patients of Group 1 was 13 % higher than in the individuals of the 2nd group and was 0.62±0.03 and 0.55±0.02 ng/ml respectively ($p<0.05$). The activity of systemic inflammation in the patients of Group 1 was higher compared to the patients of Group 2. In particular, the average values of C reactive protein (CRP) were higher by 12.1 % ($p<0.05$), ferritin – by 41.5 % ($p<0.01$), IL-6 – 93.8 % ($p<0.01$) of the corresponding indices in patients of Group 2. The average levels of TNFα and D-dimer in patients of the 1st and 2nd groups were not significantly different (Table 2).

Table 2

Levels of CRP, IL-6, TNF-α, ferritin, troponin I and D-dimer in patients with AM

Parameters	Parameter value (M±m) in groups	
	1st (n=26)	2nd (n=20)
CRP, mcg/ml	12.4±0.7	10.9±0.6*****
IL-6, pg/ml	6.6±0.4	3.4±0.2******
TNF α, pg/ml	7.7±0.6	7.3±0.6
Ferritin, ng/mL	114.5±10.8	80.9±3.6******
D-dimer, ng/mL	512.7±44.9	498.3±23.5

Note: The difference in indices is reliable compared to those in patients of the 1st group: * – $p < 0.05$, ** – $p < 0.01$.

Parametric correlation analysis revealed significant inverse correlations between inflammatory and fibrotic changes in the myocardium and GLS in Group 1 (r=-0.67; p<0.01) and (r=-0.53; p<0.05), respectively, a decrease in GLS was also associated with a large number of LV segments affected by inflammatory (r=-0.66; p<0.02) and fibrotic changes (r=-0.36; p<0.05). At the same time, a decrease in GCS in Group 1 had a significant relationship with the presence of delayed contrast (r=-0.39; p<0.05) and the number of LV segments affected by fibrotic changes (r=-0.38; p<0.05). In the 2nd group, compared with the 1st, fewer associative links were found between pathological changes in cardiac MRI and STE indicators: a decrease in GLS correlated only with the presence of myocardial edema (r=-0.42; p<0.05) and the number of LV segments affected by the inflammatory process (r=-0.34; p<0.05), and GCS did not have any associative links with pathological changes in MRI at all.

To study the relationship between the activity of autoimmune reactions and the violation of the structural and functional state of the heart in both groups of patients, a correlation analysis was performed between immunological markers and the volume of inflammatory lesions of the LV myocardium. In the patients of the 1st group, reliable direct correlations were found between the level of CRP and IL-6 and the number of segments with signs of edema and hyperemia detected during early contrast (r=0.63, p<0.05 and r=0 .55, p<0.05, respectively).

In order to determine the limit values of immunological biomarkers and indices of the structural and functional state of the heart, which are associated with the presence of widespread LV damage with inflammatory and fibrotic changes, which was characterized by involvement in the pathological process of ≥ 6 segments of the LV according to cardiac MRI data, in the 1st group statistical processing of the results was carried out using multivariate regression analysis.

In general, the regression model was as follows:

$y=a_0+a_1x_1+a_2x_2+….+a_nx_n$,

Where y is the original function of the model (lesion ≥ 6 LV segments), $x_1, \ldots x_n$ – independent variables (limit values of factors), $a_0, \ldots, a_n$ – model coefficients.

The adequacy of the model was sufficiently high (F=7.06). The model was accurate (r=0.86) and reliable (p=0.024).

According to the values of β coefficients, the greatest contribution to the presence of widespread inflammatory/fibrotic lesions of the LV among the studied parameters was: GLS value ≤9.0 % (b=0.884; p=0.002), the value of LV EDVI≥95 ml/m^2 (b=0.546; p=0.012), as well as the content of TNF-α≥7.5 pg/ml (b=0.384; p=0.032) and CRP≥12.0 mcg/ml (b=0.355; p=0.044).

A similar regression model was built to establish the limit values of the indices associated with a pronounced violation of the contractile capacity of the LV (output function of the model – GLS≤9.0), the model was accurate (r=0.88) and reliable (p=0.031). The presence of a significant violation of the contractile capacity of the LV according to the GLS index ≤9.0 % had a direct connection with a significant volume of inflammatory and fibrotic lesions of the LV. It was characterized by the involvement of ≥ 6 LV segments in the pathological process (b=0.922; p=0.001), LV dilation – LV EDVI≥95 ml/m^2 (b=0.674; p=0.011), an increase in the CRP content ≥12.0 mcg/ml (b=0.387; p=0.039) and IL-6 ≥6.0 pg/ml (b=0.401; p=0.042). The results of the multivariate regression analysis indicate a clear relationship between a significant volume of inflammatory and fibrotic lesions of the LV and a decrease in GLS. This confirms the high informativeness and diagnostic accuracy of STE and MRI for assessing the structural and functional state of the heart in patients with myocarditis after COVID-19 infection.

In the discussion of the obtained results, it should be noted that the detected decrease in global longitudinal deformation in both groups of patients reflects a significant disruption of the work of the subepicardial fibres of the myocardium. According to the latest literature data, it correlates with the localization and zones of damage according to cardiac MRI data [7, 10]. In a recent study, in patients with myocarditis who suffered from COVID-19, in addition to the violation of longitudinal deformation indices, changes in the geometry of contraction in the circular direction and the processes of LV twisting were found, which require further study [8]. Violation of LV global strain in myocarditis, caused by damage to the subendocardial and subepicardial fibers, can be a decisive diagnostic approach to AM, especially in patients after COVID-19 infection.

Predominant damage to the myocardium outer and its middle layers in myocarditis, especially after suffering from COVID-19, leads to a violation of circular and rotational deformation. It could potentially

be a new diagnostic STE criterion for this pathology and a method of selecting patients for additional diagnostic procedures, particularly cardiac MRI [3]. Thus, the use of STE made it possible to identify additional signs of a more significant violation of the mechanics of LV contraction and a decrease in the LV reservoir function in patients with myocarditis with reduced LV EF who had a history of COVID-19 infection compared to patients without a history of COVID-19 infection.

The results of correlation and multivariate regression analysis in patients of the 1st group give grounds to assert that the violation of longitudinal LV strain was associated with the presence of both inflammatory and fibrotic changes in the myocardium and with the volume of LV damage and the violation of circular LV strain with the presence of only fibrotic changes and their volume. On the other hand, in the patients of the 2nd group, a relationship was found between the violation of longitudinal strain and the presence of only inflammatory changes of the LV. The obtained data may indicate a more significant role of fibrotic changes of the myocardium in patients with AM who suffered from COVID-19 in the pathogenesis of impaired LV contractility compared to patients with myocarditis who did not have a history of COVID-19.

According to the results of recent studies, an increase in the content of ferritin, which is a complex protein complex (iron protein), accompanies various acute, in particular viral, infections, indicates an acute reaction and belongs to the markers of the acute phase of the systemic inflammatory response. Accumulated data indicate the role of ferritin as a signalling molecule and a direct mediator of the immune system. At the same time, inflammation and oxidative stress have been shown to activate ferritin synthesis in many cells, including macrophages [9]. Inflammatory stimuli, particularly IL-6, can induce ferritin synthesis. The existence of different feedback mechanisms between ferritin and cytokines regarding the control of pro- and anti-inflammatory mediators is discussed [13]. High ferritin levels are considered as a prognostic marker of severe COVID-19 [9]. According to our data, patients with AM with a history of COVID-19 were characterized by a high content of this biomarker, associated with a more severe course of the disease.

The data obtained during the laboratory study indicated a more severe course of AM in patients of the 1st group because, according to modern ideas, troponins are considered absolute specific biomarkers of myocardial damage [6]. The direct cytotoxic effect of viruses on cardiomyocytes (cytokine-induced cytotoxicity) is considered the main mechanism of an increase in cardio markers, including troponins, in myocarditis. The time that troponins remain elevated is associated with the severity of inflammation, which can be used to assess further the progression of cardiovascular remodelling changes in cytoarchitectonics and the risk of an unfavourable prognosis in patients with AM [6]. An increase in the level of CRP and increased content of IL-6 is associated with the more excellent activity of the inflammatory process and indicated more significant damage to cardiomyocytes and vascular endothelial cells in patients of the 1st group, which was also confirmed by a higher level of troponin I. In addition, it is now known that high concentrations of IL-6 in patients with COVID-19 correlate with the severe course of the disease [12]. In our study, it was established that patients with myocarditis who suffered from COVID-19 were characterized not only by high levels of IL-6 and CRP but also by the association of these markers of systemic inflammation with the number of LV segments in which edema and heperemia were detected during MRI. The created multivariate regression models also indicate a statistically significant role of the high content of such laboratory biomarkers as IL-6, TNF-α, and CRP in the violation of the contractile capacity of the LV and the prevalence of its inflammatory lesions in patients with AM who suffered from COVID-19.

Conclusions

1. Patients with acute myocarditis and a history of COVID-19 infection were characterized by a more significant volume of inflammatory and fibrotic damage to the myocardium and more pronounced violations of the contractile ability of the LV. This was evidenced by a 30.7 % higher number of affected LV segments detected by cardiac MRI, lower rates of longitudinal and circular global LV strain by 18.9 and 17.6 %, respectively, and a 22.3 % lower rate of LV systolic strain compared with patients who did not have a history of coronavirus infection.

2. In patients with acute myocarditis and a previous coronavirus infection, a more pronounced activation of immunopathological reactions was noted, which was accompanied by a higher level of C-reactive protein, pro-inflammatory interleukin-6, ferritin and troponin I as a marker of cardiomyocyte

damage. This was associated with a more pronounced violation of the structural and functional state of the heart compared to patients without a history of COVID-19.

3. When conducting a correlation analysis in patients with myocarditis who suffered from COVID-19, reliable relationships were established between the number of LV segments affected by inflammatory changes and GLS ($r = -0.66$; $p<0.02$), as well as by the number of segments with fibrotic changes and GLS and GCS – ($r = -0.36$; $p<0.05$) and ($r = -0.38$; $p<0.05$), respectively. According to the results of the factor analysis, the presence of a widespread inflammatory/fibrotic lesion of the LV involving 6 or more segments in patients with myocarditis and a history of COVID-19 had a direct relationship with the values of GLS≤9.0 % and LV EDVI≥95 ml/m^2, and also with TNF-α content ≥7.5 pg/ml and CRP≥12.0 μg/ml.

References

1. Kovalenko VM, Lutay MI, Sirenko YuM, Sychov OS, redaktory. Sertsevo-sudynni zakhvoryuvannya: klasyfikatsiya, standarty diahnostyky ta likuvannya. Kyiv: MORION. 2020; 239 s. [in Ukrainian]

2. Kovalenko VM, Nesukay OH, Chernyuk SV, Kozlyuk AS, Kyrychenko RM. Diahnostyka ta likuvannya miokardytu. Rekomendatsiyi Vseukrayinskoyi asotsiatsiyi kardiolohiv Ukrayiny. Ukrayinskyy kardiolohichnyy zhurnal. 2021; 32(3):67–88.doi:10.31928/1608-635X-2021.3.6788 [in Ukrainian]

3. Arnold JR, McCann GP. Cardiovascular Magnetic Resonance: Applications and Practical Considerations for the General Cardiologist. Heart. 2020; 106(3):174–181. doi: 10.1136/heartjnl-2019-314856.

4. Azevedo RB, Botelho BG, de Hollanda JVG, Ferreira LVL, Junqueira de Andrade LZ, Oei SSML et al. "Covid-19 and the cardiovascular system: a comprehensive review," J Hum Hypertens. 2020; 35(1):4–11. doi: 10.1038/s41371-020-0387-4.

5. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB et al. Current state of knowledge on aetiology, diagnosis, management and therapy of myocarditis: a position statement of the ESC Working group on myocardial and pericardial diseases. Eur Heart J. 2013; 34(33): 2636–48. doi: 10.1093/eurheartj/eht210.

6. Chaulin AM. The Metabolic Pathway of Cardiac Troponins Release: Mechanisms and Diagnostic Role. Cardiol Res. 2022; 13(4):190-205. doi: 10.14740/cr1351. Epub 2022 Aug 15. PMID: 36128422; PMCID: PMC9451590

7. González-Ruiz FJ, Lazcano-Díaz EA, Vásquez-Ortiz ZY, Bernal-Ceballos F. Comprehensive Left Ventricular Mechanics Analysis by Speckle Tracking Echocardiography in COVID-19. World Journal of Cardiovascular Diseases. 2021; 11:113–125. doi: 10.4236/wjcd.2021.112013.

8. Goody P, Zimmer S, Zimmer A, Kreuz J, Becher M, Isaak A et al. 3D-speckle-tracking echocardiography correlates with CMR diagnosis of acute myocarditis. Int J Cardiol Heart Vasc. 2021; 17:549–563. doi: 10.22541/au.161359840.05297135/v1.

9. Kaushal K, Kaur H, Sarma P, Bhattacharyya A, Sharma DJ, Prajapat M et al. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. J Crit Care. 2022; 67:172–181. doi:10.1016/j.jcrc.2021.09.023.

10. Kostakou PM, Kostopoulos VS, Tryfou ES, Giannaris VD, Rodis IE, Olympios CD et al. Subclinical left ventricular dysfunction and correlation with regional strain analysis in myocarditis with normal ejection fraction. A new diagnostic criterion. Int J Cardiol. 2018; 259:116–121. doi: 10.1016/j.ijcard.2018.01.058.

11. Lang R, Badano LP, Mor-Avi V, Afilalo J, Armstron A, Ernande L et al. Recommendations for cardiac chamber quantification in adults: an update from the American Society of echocardiography and European Asssociation of cardiovascular imaging. J. Am. Soc. Echocardiogr. 2015; 28(1):1–38. doi: 10.1016/j.echo.2014.10.003.

12. Liu T, Zhang J, Yang Y, Ma H, Li Z, Cheng J et al. X. The potential role of IL-6 in monitoring severe case of coronavirus disease. EMBO Mol Med. 2020; 12(7): e12421. doi: 10.15252/emmm.202012421. Epub 2020 Jun 5. PMID: 32428990 PMCID: PMC7280589

13. Para O, Caruso L, Pestelli G, Tangianu F, Carrara D, Maddaluni L et al. Ferritin as prognostic marker in COVID-19: the FerVid study. Postgrad Med. 2022; 134(1):58–63. doi: 10.1080/00325481.2021.1990091. Epub 2021 Oct 17. PMID: 34613875; PMCID: PMC8544665.

14. Tschöpe C, Ammirati E, Bozkurt B, Caforio AL, Cooper LT, Felix SB, Hare JM et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol. 2021; 18(3):169–193. doi: 10.1038/s41569-020-00435-x.

15. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 2020; 17(5):259–260. doi: 10.1038/s41569-020-0360-5.

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