Folia Cardiologica 2024, 19
DOI: 10.5603/fc.100542
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ISSN 2353–7752
e-ISSN 2353–7760

Coronary artery calcium score predicts outcome in patients with COVID-19

Wynik uwapnienia w tętnicy wieńcowej pozwala przewidzieć wynik leczenia pacjentów z Covid-19

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Abstract

Purpose. Coronary artery calcium (CAC) score is a proven prognostic cardiovascular risk marker. This study aims to evaluate the prognostic value of the CAC score on standard chest computed tomography (CT) in patients admitted with COVID-19.

Methods. Enrolled were 144 consecutive patients (mean age 67 ± 13 years, 60.7% male) hospitalized with COVID-19. On admission, they underwent chest CT to detect and assess pulmonary involvement. Two investigators blinded to the patient›s clinical data calculated the CAC score. Patients were followed up for an average of 14 months after their admission.

Results. 106 patients (mean age 66.5 ± 14 years, 66% male) had image quality sufficient for analysis. The median CAC score was 249 Agatston units (interquartile range 658). Thirty-three deaths were recorded in the study group during the follow-up period. The median values of CAC of patients who died during the study period and of the survivors were 592 (interquartile range 1492) and 142 (interquartile range 400), respectively. The difference in CAC between these two subgroups was statistically significant (p = 0.0001). The area under the ROC curve for the CAC score for predicting all-cause mortality was 0.738 (95% CI 0.644 to 0.819). The criterion with the highest prognostic accuracy was CAC score > 143 Agatston units (positive and negative predictive values were 44.4% and 88.4%, respectively). The presence of this criterion was associated with a 3.9 times higher relative risk (RR) of mortality (95% CI 1.66–9.41; p = 0.0019).

Conclusion. CAC score measurement based on standard chest CT performed on admission in patients with COVID-19 to detect pulmonary involvement is a prognostic marker of increased mortality during the 14-month follow-up.

Keywords: SARS-COV2, chest computed tomography, coronary artery calcium score, coronary artery disease

Folia Cardiologica 2024; 19: 158–163

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Received: 05.05.2024 Accepted: 25.05.2024 Early publication date: 08.07.2024

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Introduction

Since the onset of the COVID-19 pandemic, scientific literature has extensively examined risk factors related to clinical outcomes and the pathophysiology of COVID-19 pneumonia. Factors previously regarded as the most common and best-linked risk factors for adverse outcomes in patients with cardiovascular diseases, such as age, arterial hypertension, obesity, and diabetes mellitus, have quickly been recognized to be strongly associated with the clinical course and outcomes in patients with COVID-19, mainly affecting the risk of hospitalization and mortality [1–3].

Patients with COVID-19 suffering from a high disease burden routinely undergo non-gated computed tomography (CT) analysis to assess disease severity. These CT images can be used to evaluate the severity of coronary artery calcium (CAC) as a marker of atheromatous plaque burden in the coronary arteries. The prognostic significance of this marker for patients with stable coronary artery disease (CAD) has been established [4]. Analysing CAC scores on non-gated CT images in patients with other diseases with lung involvement, for example, chronic obstructive pulmonary disease (COPD), has been shown to closely correlate to gated CT studies in assessments of the CAC burden [5].

Several cohort studies and subsequent meta-analyses have associated CAC scoring with an increased risk of all-cause mortality in patients infected with COVID-19 pneumonia [6]. The ability to risk stratify patients with the help of CAC analysis into groups at greater risk for needing mechanical ventilation or intensive care has been assessed [7]. The exact pathophysiologic mechanism behind this observation and what Agatston score cut-off point should be used remains a topic of discussion. The precise role of this tool in stratifying at-risk patients remains to be determined.

Methods and Materials

Between October and December 2020, 144 patients were admitted to the study department because of COVID-19 infection confirmed by real-time polymerase chain reaction (RT-PCR). All patients underwent standard non-gated chest CT at admission and were scanned with a Siemens SOMATOTOM top-64 row device (with a slice thickness of 1.5 mm). Patients were then followed up for a mean time of 14 months. Thirty-seven patients had to be excluded due to insufficient image quality. The main primary endpoint was identified as all-cause mortality till January 2022.

Two different observers assessed CAC scoring. During observation, each of the four coronary arteries was identified: Right Coronary Artery (RCA), Left Main Artery (LMA), Left Anterior Descending Artery (LAD), and Left Circumflex Artery (LCx). CAC analysis was performed offline (vitrea FX software) using CAC score analysis software (V score). Agatston score was defined as a visual score of 2 different

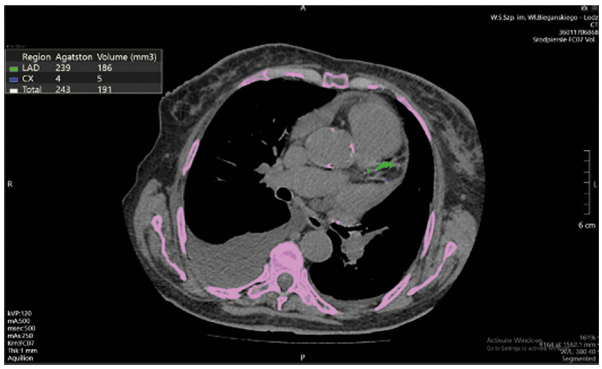

Figure 1. Coronary Artery Calcium (CAC) analysis on a native CT scan

voxels with a density of more than 130 hertz. Figure 1 demonstrates the measurement of the CAC score on a native CT scan.

The clinical characteristics of the patients were recorded according to the medical records of the hospital database. Clinical characteristics of the patient cohort are included in Table 1.

The present study was approved by the Ethics Committee of the Medical University of Lodz (12.06.2022/RNN/166/22/KE) and was performed according to the Declaration of Helsinki principles. As this study was retrospective, informed consent was waived.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) if the sample is normally distributed. If the distribution is not normal, values are given as medians, including the lower and upper interquartile ranges. To compare medians, the Mann–Whitney test was used. The Receiver-Operating Characteristics (ROC) curve analysis was performed with the obtained Agatston scores to establish a criterion with the highest prognostic value. This criterion allowed us to classify the patients into two groups. Relative risk (RR) for patients with an Agatston score higher than the cut-off point was calculated for death, use of catecholamines, intubation, and intensive care unit (ICU) admission.

The Cox proportional hazards regression model was used to analyse the impact of various factors on mortality rates. Findings were deemed significant at a p-value of less than 0.05. All statistical analyses were conducted using MedCalc software, version 12.2.1.

Results

Of the 144 patients (mean age 67 ± 13 years, 60.7% male), 106 patients (mean age 66.5 ± 13.5 years, 63% male) had image quality sufficient to be included in the analysis. The median CAC score was 249 Agatston units (interquartile

Table 1. Patient clinical characteristics according to a Coronary artery calcium (CAC) score greater or lower than 143 Agatston units. The highest values of cardiac biomarkers recorded during the hospital stay are expressed as the medians (1st and 3rd quartile)

Clinical Characteristics (n = 106)	Number (prevalence%)	CAC < 143 (n = 43)	CAC > 143 (n = 63)	P value
Diabetes Mellitus type 2	28 (26.4)	6	29	0.001
Arterial Hypertension	61 (57.6)	29	53	0.075
Hypercholesterolemia	36 (34)	12	20	0.835
Obesity	13 (12.3)	8	5	0.179
Smoking	9 (8.5)	5	6	0.98
Hypertriglyceridemia	1 (0.9)	0	1	< 0,001
Congestive Heart Failure	32 (30.2)	8	25	0.037
Coronary Artery Disease	40 (37.7)	7	33	0.00037
Previous Myocardial Infarction	20 (18.9)	4	16	0.068
STEMI	10 (9.4)	4	6	0.764
NSTEMI	10 (9.4)	0	10	< 0,001
Atrial Fibrillation	23 (21.7)	10	21	0.367
Pulmonary Disease	12 (11.3)	4	8	0.818
COPD	4 (3.8)	2	2	0.899
Asthma Bronchiale	5 (4.7)	1	4	0.622
Chronic Kidney Disease	8 (7.5)	2	6	0.577
Previous Interventions				
Coronary Artery Bypass Graft	8 (7.5)	0	8	< 0,001
Percutaneous Coronary Intervention	27 (25.5)	6	21	0.043
Implantable Cardioverter Defibrillator	2 (1.9)	0	2	< 0,001
Cardiac Biomarkers				
NT-pro BNP (pg/mL)		534 (107–1944)	1311 (480–3740)	0.0065
Troponin T (ng/ml)		0.025 (0.009–0,088)	0.04 (0.02–0.317)	0.0451

COPD — chronic obstructive pulmonary disease; NSTEMI — Non-ST elevation myocardial infarction; NT-proBNP — B-type Natriuretic peptide; STEMI — ST-elevation myocardial infarction

range 658). Overall, 33 patients (31%) in the present study group met the primary endpoint. Out of the 33 patients, 24 died during the initial hospital stay after an average of 11 days. Out of these 24 patients, 20 patients (83%) died because of respiratory insufficiency in the intensive care unit due to COVID-19 pneumonia, with 3 patients (12%) being additionally diagnosed with an acute heart failure exacerbation and one patient (0.5%) with a chronic obstructive pulmonary disease (COPD) exacerbation. Of the patients who were followed up beyond the initial hospital stay, 4 patients died from various causes (meningitis, stroke, oesophagus carcinoma, myocardial infarction). In 5 patients, the cause of death is unknown.

The most common comorbidity in the patient population is arterial hypertension (57.6%), followed by hypercholesterolemia (34%) and diabetes mellitus type 2 (DM2; 26.4%).

ROC curve analysis was employed to evaluate the prognostic significance of CAC scoring (Figure 2). The area under the ROC curve for the CAC score for predicting all-cause mortality was 0.738 (95% CI 0.644 to 0.819). The criterion with the highest prognostic accuracy was CAC score > 143 Agatston units (positive and negative predictive values were 44.4% and 88,4%, respectively), with a sensitivity of 84.8% and a specificity of 52.1%. Baseline clinical characteristics according to the patient's CAC are listed in Table 1. 63 out of the 106 patients included in the study had a CAC > 143 Agatston units. These patients were more likely to have DM2 (p = 0.001) and CAD (p = 0.00037) than the 43 patients with a CAC score of less than 143 Agatston units.

Calculated were the RR of death, use of catecholamines, intubation, and ICU admission in patients with an Agatston score greater than 143. Patients with an Agatston score of greater than 143 had a significantly increased risk of mortality 3.9 (95% CI 1.66–9.41) p = 0.0019, but no significant increase in RR of the use of catecholamine 1.62 (95% CI 0.80–3.83) p = 0.16; intubation 1.71 (95% CI 0.72–4.05) p = 0.22, and ICU admission: 1.82 (95% CI 0.69–4.83) p = 0.22 during hospitalization.

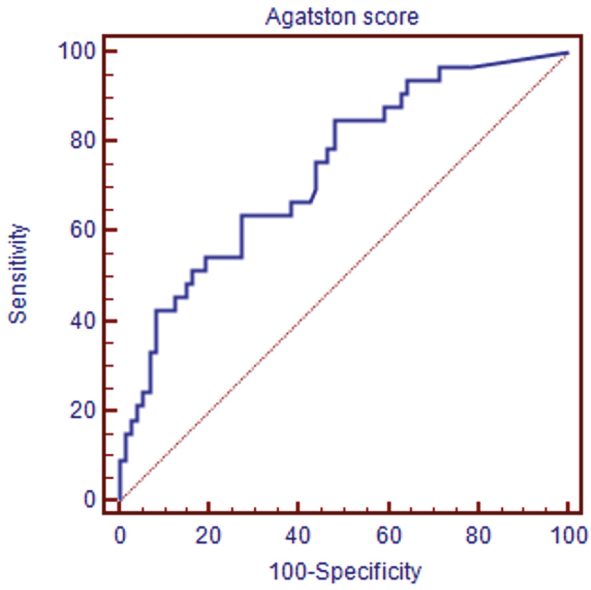

Figure 2. Receiver-operator characteristics (ROC) curve analysis. The Criterion with the highest prognostic accuracy was an Agatston score of more than 143.

On multivariable analysis using the Cox proportional hazard regression model, the CAC score of more than 143 Agatston units, maximum troponin level, and maximum level of pro-b-type natriuretic peptide (NT-proBNP) were compared. Maximum Median Troponin and NT-proBNP values recorded during the hospital stay (according to the CAC score) are shown in Table 1. A CAC score of more than 143 Agatston units conferred a hazard ratio (HR) of 10.64 (1.93–58.5 95% CI) p = 0.0068, compared to troponin with a HR of 2.62 (1.21–5.71) p = 0.02 and NT-proBNP with a HR of 1 (0.99–1) p = 0.5026.

Discussion

CAC scoring is an established cardiovascular risk marker, and its predictive value supports decision-making in asymptomatic patients with cardiovascular risk factors [8]. Since the start of the COVID-19 pandemic, numerous research findings have indicated that patients with a higher CAC score who are admitted with COVID-19 pneumonia tend to have a poorer prognosis. In a comprehensive review of 18 studies, a high CAC score was associated with a higher rate of adverse outcomes [9]. In the patient population, a similar relationship was observed. The RR of a patient with an Agatston score of over 143 to meet the primary outcome (14-month mortality) was 3.9. In a small study of 89 patients admitted with COVID-19, Fervers et al. [10] showed that combined CAC scoring with age and clinical risk factors yielded the most accurate predictor of ICU admission. However, in the following study, a CAC score of over 143 Agatston units could not statistically significantly predict an increased RR of admission to the ICU or intubation.

Notably, all the patients in the study population underwent routine chest CTs to assess the severity of lung changes due to COVID-19 pneumonia. Many studies previously assessing CAC in this scenario used a visual assessment carried out by experienced observers to quantify plaque burden subjectively [11, 12]. However, a universally accepted method of CAC assessment to predict worse outcomes in patients with COVID-19 has yet to be defined.

Interestingly, Govino et al. [13] suggest using an Agatston score of more than 400 as a cut-off point. An Agatston score of over 400 units indicates severe calcification of the coronary arteries [14]. In the present patient population, the criterion with the highest AUC was a CAC score of more than 143 Agatston units. This implies that individuals with underlying CAD are at an increased risk of experiencing severe complications from COVID-19 pneumonia. As chronic coronary syndrome (CCS) becomes more and more prevalent in the population, the prevalence of mild to moderate CAC also increases [15]. Indeed, 63 out of the 106 patients in the present study group had a CAC score of more than 143. Patients with a CAC score of over 143 were more likely to suffer from DM type 2, congestive heart failure, and CAD. The relationship of lower CAC with better outcomes was also demonstrated by Luchian et al. [16], who found that the absence of CAC had a negative predictive value for a major adverse cardiovascular event (MACE), independent of other cardiovascular risk factors.

In the present study group, 24 out of 34 deaths occurred during the first fourteen days of hospitalization. On multivariate analysis, a CAC score of more than 143 yielded a predictor of mortality with a HR of 10.64. In a large Italian cohort study on patients with COVID-19 undergoing non-gated CT scan and CAC analysis, patients with subclinical CAD had a 10-day in-hospital mortality of 27.3%, according to the Agatston score [18].

Other cardiovascular markers to access outcomes in patients with COVID-19 have also been previously assessed, and troponin has been suggested as a biomarker to show myocardial injury in patients infected with COVID-19, which was associated with an increased risk of mortality [18]. According to Pergola et al. [19], high-sensitive troponin (HS-trop) was a more accurate predictor of outcome than CAC scoring. The authors attributed this finding to the pro-inflammatory environment a COVID-19 infection creates and its subsequent effect on the myocardium. It is important to note, however, that Pergola et al. [19] excluded patients who previously underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). This contrasts with the findings of the present study, where the CAC score had a more significant HR compared to the maximum troponin level during hospitalization. However, in the present study population, 35 patients had received

previous myocardial revascularization, either through PCI or CABG, showing a high plaque burden in the coronary arteries.

Limitations

This was a single-centre study, and the CT examinations were performed using one scanner. Moreover, several patients had to be excluded, as the central line catheter caused artifacts, and the images could not be reliably analysed.

Conclusion

Patients often undergo chest CTs to assess the severity of COVID-19 pneumonia. Currently, the guidelines do not indicate the benefit of routine CT-based CAC analysis for patients hospitalized with COVID-19. In this study, compared to other cardiovascular risk markers, a high CAC score has been associated with increased mortality risks of patients hospitalized for COVID-19 pneumonia. Therefore, CAC can be regarded as an additional complementary risk marker. Whether this will impact clinical decision-making remains to be seen.

Additional information

Conflict of interests

The authors declare no conflict of interest.

Funding

None declared.

Streszczenie

Cel. Wynik uwapnienia w tętnicy wieńcowej (CAC) jest udowodnionym prognostycznym markerem ryzyka sercowo-naczyniowego. Celem tego badania jest ocena wartości prognostycznej wyniku CAC w standardowej tomografii komputerowej klatki piersiowej (CT) u pacjentów przyjętych z powodu COVID-19.

Metody. Do badania włączono 144 kolejnych pacjentów (średni wiek 67 ± 13 lat, 60,7% mężczyzn) hospitalizowanych z powodu Covid-19. Przy przyjęciu wykonano im tomografię komputerową klatki piersiowej w celu wykrycia i oceny zajęcia płuc. Dwóch badaczy, nie znających danych klinicznych pacjenta, obliczyło wynik CAC. Pacjenci byli obserwowani średnio przez 14 miesięcy od przyjęcia.

Wyniki. U 106 pacjentów (średnia wieku 66,5 ± 14 lat, 66% mężczyzn) jakość obrazu była wystarczająca do analizy. Mediana wyniku CAC wyniosła 249 jednostek Agatstona (przedział międzykwartylowy 658). W okresie obserwacji w grupie badanej odnotowano 33 zgony. Mediana wartości CAC pacjentów, którzy zmarli w okresie badania i pacjentów, którzy przeżyli, wyniosła odpowiednio 592 (rozstęp międzykwartylowy 1492) i 142 (rozstęp międzykwartylowy 400). Różnica w CAC pomiędzy tymi dwiema podgrupami była istotna statystycznie (p = 0,0001). Pole pod krzywą ROC dla wyniku CAC służącego do przewidywania śmiertelności z jakiejkolwiek przyczyny wynosiło 0,738 (95% CI 0,644 do 0,819). Kryterium charakteryzującym się największą trafnością prognostyczną był wynik CAC > 143 jednostek Agatstona (dodatnie i ujemne wartości predykcyjne wynosiły odpowiednio 44,4% i 88,4%). Obecność tego kryterium wiązała się z 3,9-krotnie większym względnym ryzykiem zgonu (95% CI 1,66–9,41; p = 0,0019).

Wniosek. Pomiar wyniku CAC w oparciu o standardową tomografię komputerową klatki piersiowej wykonywaną przy przyjęciu u pacjentów z COVID-19 w celu wykrycia zajęcia płuc jest prognostycznym markerem zwiększonej śmiertelności w trakcie 14-miesięcznej obserwacji.

Słowa kluczowe: SARS-COV2, tomografia komputerowa klatki piersiowej, ocena uwapnienia tętnic wieńcowych, choroba wieńcowa

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References

1. Visseren FLJ, Mach F, Smulders YM, et al. ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Rev Esp Cardiol (Engl Ed). 2022; 75(5): 429, doi: 10.1016/j.rec.2022.04.003, indexed in Pubmed: 35525570.
2. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018; 72(4): 434–447, doi: 10.1016/j.jacc.2018.05.027, indexed in Pubmed: 30025580.

3. Ko JY, Danielson ML, Town M, et al. COVID-NET Surveillance Team. Risk Factors for Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. Clin Infect Dis. 2021; 72(11): e695–e703, doi: 10.1093/cid/ciaa1419, indexed in Pubmed: 32945846.
4. Budoff MJ, Mayrhofer T, Ferencik M, et al. PROMISE Investigators. Prognostic value of coronary artery calcium in the PROMISE study (prospective multicenter imaging study for evaluation of chest pain). Circulation. 2017; 136(21): 1993–2005, doi: 10.1161/CIRCULATIONAHA.117.030578, indexed in Pubmed: 28847895.
5. Budoff MJ, Nasir K, Kinney GL, et al. Coronary artery and thoracic calcium on noncontrast thoracic CT scans: comparison of ungated and gated examinations in patients from the COPD Gene cohort. J Cardiovasc Comput Tomogr. 2011; 5(2): 113–118, doi: 10.1016/j.jcct.2010.11.002, indexed in Pubmed: 21167806.
6. Cereda A, Toselli M, Palmisano A, et al. Coronary calcium score as a predictor of outcomes in the hypertensive Covid-19 population: results from the Italian (S) Core-Covid-19 Registry. Hypertens Res. 2022; 45(2): 333–343, doi: 10.1038/s41440-021-00798-9, indexed in Pubmed: 34789917.
7. Lee KK, Rahimi O, Lee CK, et al. A meta-analysis: coronary artery calcium score and COVID-19 prognosis. Med Sci (Basel). 2022; 10(1), doi: 10.3390/medsci10010005, indexed in Pubmed: 35225939.
8. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018; 72(4): 434–447, doi: 10.1016/j.jacc.2018.05.027, indexed in Pubmed: 30025580.
9. Yousefimoghaddam F, Goudarzi E, Ramandi A, et al. Coronary artery calcium score as a prognostic factor of adverse outcomes in patients with COVID-19: a comprehensive review. Curr Probl Cardiol. 2023; 48(8), doi: 10.1016/j.cpcardiol.2022.101175, indexed in Pubmed: 35339532.
10. Fervers P, Kottlors J, Große Hokamp N, et al. Coronary artery calcification on low-dose chest CT is an early predictor of severe progression of COVID-19-A multi-center, multi-vendor study. PLoS One. 2021; 16(7): e0255045, doi: 10.1371/journal.pone.0255045, indexed in Pubmed: 34288966.
11. Chiles C, Duan F, Gladish G, et al. Association of Coronary Artery Calcification and Mortality in the National Lung Screening Trial: A Comparison of Three Scoring Methods. Radiology. 2015; 276(1): 82–90, doi: 10.1148/radiol.15142062, indexed in Pubmed: 25759972.
12. Le Hir AS, Fayol A, Mousseaux E, et al. Association between coronary artery calcifications and 6-month mortality in hospitalized patients with COVID-19. Diagn Interv Imaging. 2021; 102(12): 717–725, doi: 10.1016/j.diii.2021.06.007, indexed in Pubmed: 34312110.
13. Nai Fovino L, Cademartiri F, Tarantini G. Subclinical coronary artery disease in COVID-19 patients. Eur Heart J Cardiovasc Imaging. 2020; 21(9): 1055–1056, doi: 10.1093/ehjci/jeaa202, indexed in Pubmed: 32671381.
14. Kim JY, Suh YJ, Han K, et al. Reliability of coronary artery calcium severity assessment on non-electrocardiogram-gated CT: a meta-analysis. Korean J Radiol. 2021; 22(7): 1034–1043, doi: 10.3348/kjr.2020.1047, indexed in Pubmed: 33856134.
15. Sanchis-Gomar F, Perez-Quilis C, Leischik R, et al. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016; 4(13): 256, doi: 10.21037/atm.2016.06.33, indexed in Pubmed: 27500157.
16. Luchian ML, Lochy S, Motoc A, et al. Prognostic value of coronary artery calcium score in hospitalized COVID-19 patients. Front Cardiovasc Med. 2021; 8, doi: 10.3389/fcvm.2021.684528, indexed in Pubmed: 34307498.
17. Scoccia A, Gallone G, Cereda A, et al. Impact of clinical and subclinical coronary artery disease as assessed by coronary artery calcium in COVID-19. Atherosclerosis. 2021; 328: 136–143, doi: 10.1016/j.atherosclerosis.2021.03.041, indexed in Pubmed: 33883086.
18. Ferrante G, Fazzari F, Cozzi O, et al. Risk factors for myocardial injury and death in patients with COVID-19: insights from a cohort study with chest computed tomography. Cardiovasc Res. 2020; 116(14): 2239–2246, doi: 10.1093/cvr/cvaa193, indexed in Pubmed: 32637999.
19. Pergola V, Cabrelle G, Previtero M, et al. Impact of the „atherosclerotic pabulum" on in-hospital mortality for SARS-CoV-2 infection. Is calcium score able to identify at-risk patients? Clin Cardiol. 2022; 45(6): 629–640, doi: 10.1002/clc.23809, indexed in Pubmed: 35355295.