UDC 616.12-073.7:616.98:578.834.1-036.8 doi: https://doi.org/10.15407/ubj96.02.100

ECG PATTERNS IN POST-COVID-19 PATIENTS

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Received: 06 January 2024; **Revised:** 17 March 2024; **Accepted:** 17 March 2024

COVID-19 has been associated with a wide range of cardiac sequelae after the acute phase. The goal of the study is to evaluate the spectrum of arrhythmias in the aspects of age, comorbidity, and survival rate using electrocardiography (ECG) patterns in patients after COVID-19 during two months of recovery. ECG data of 758 patients were examined and analyzed, including 256 (33.6%) males and 503 (66.4%) females ages 15 to 90 (52.99 ± 11.68) years. A total of 848 ECGs were performed in acute period and recovery. ECG changes were classified according to the Minnesota code (MC) classes. It was found that age, sex, severity of COVID-19, presence of concomitant hypertension and diabetes mellitus have a significant impact on ECG changes. Age correlated with the severity of COVID-19 ($r = 0.485$, $P < 0.001$), concomitant hypertension ($r = 0.471$, $P < 0.001$), diabetes ($r = 0.346$, $P < 0.001$) and obesity ($r = 0.179$, $P < 0.001$). Correlations were established between age and the presence of baseline previous pathological ECGs ($r = 0.290$, $P < 0.0001$). We established that heart rhythm disorders related to the severity of the COVID-19 course are significantly influenced by oxygen saturation ($r = -0.211$, $P < 0.001$) and, to a lesser extent, the percentage of lung damage according to computed tomography data ($r = 0.127$, $P = 0.060$). The results of the arrhythmias screening in patients with COVID-19 demonstrate the association mainly with the severity of the disease and comorbidity, especially diabetes mellitus. So, we may consider arrhythmogenesis in COVID-19 through the prism of inflammation, intoxication, hypoxia, metabolic disorders, and drug effects.

K e y w o r d s: post-COVID-19, arrhythmias, electrocardiography, Minnesota code (MC) classes.

Post-coronavirus disease syndrome involves the presentation of various new, returning, or ongoing symptoms, especially for the cardiovascular system and heart conductivity. Electrocardiography (ECG) is one of the available routine methods for the primary detection of arrhythmias. It is still a relevant research method to evaluate coronavirus disease 2019 (COVID-19) pandemic-induced changes to the heart. According to the European Society of Cardiology (ESC) guidelines (2021) [1], any infection, including the coronavirus, may exacerbate chronic diseases, which obviously explains the frequent cardiac complications in severe COVID-19 since cardiovascular diseases (CVD) is the most common of diseases in modern civilization.

COVID-19 is a viral infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, more than 670 million people around the world have been affected by COVID-19, and it has been attributed to approximately 7 million deaths. An interplay between COVID-19 and CVD has been suggested by recent evidence. COVID-19 may serve as an underappreciated risk modifier for CVD as well as diabetes mellitus and arterial hypertension. To date, scientific data on arrhythmias in patients with COVID-19 infection are quite limited and contradictory. As stated in the latest ESC guidelines, the true prevalence and origin of arrhythmias in patients with COVID-19 as well as the presence of ECG changes remain unknown, therefore careful observation of long-term manifestations of COVID-19 is essential.

The aim of our research is arrhythmias screening based on the analysis of electrocardiograms

recorded during the acute period of the disease and within 1–60 days after the last negative polymerase chain reaction test result for SARS-CoV-2.

Materials and Methods

A total of 758 patients with COVID-19 were examined, including 255 (33.6%) males and 503 (66.4%) females ages 15 to 90 (52.99 ± 11.68) years. Healthcare workers represented 35.8% (271) of the cohort. The control group consisted of 78 persons who did not have any clinical or laboratory manifestations of COVID-19 and were seronegative. Medical records of an outpatient/hospitalized patient and the results of a clinical examination with re-registration of the ECG of seropositive persons in 1–60 days after a negative test for COVID-19 were used for the analysis.

According to the severity of COVID-19, all patients were divided into the following groups: HQM – Home Quarantined with Mild disease course, HMO – Hospitalized with Moderate course, HSV – Hospitalized oxygen-dependent patients with Severe symptoms and HCR – Hospitalized Critical patients in ICU departments with artificial ventilation.

A total of 848 ECGs were performed. ECG changes were classified according to the Minnesota code (MC) classes. Statistical analysis was performed with SPSS 21.0 software (SPSS Inc., Chicago, Illinois, USA) using univariate and multivariate tests (Chi-square, Fisher's exact test, Mann-Whitney U, one-way ANOVA and Kruskal-Wallis ANOVA tests). Analysis of the survival of hospitalized patients with COVID-19 was carried out using the Kaplan-Meier method, and the difference in indicators was evaluated using the logarithmic rank test (χ^2). Independent predictors of cardiovascular events were determined using univariate and multivariate regression analysis by creating Cox-intensive proportionality models with stepwise backward extraction of indicators. The threshold of *P*-value for inclusion of the indicator in the model was 0.05, and that for extraction from the model was 0.10. Results are presented as hazard ratio (HR) (95% confidence interval).

Results and Discussion

Most patients with COVID-19 had a mild (HQM, 42.4%) or moderate (HMO, 38.4%) form of the disease. The HSV group with 17.4% of patients required oxygen support during coronavirus diseases, and the HCR group with 1.8% of those whom we were able to examine after discharge, were critically ill during the acute period of the disease and required invasive oxygen therapy.

In 35.8% of the examined cohort, changes in the ECG were not detected, which corresponds to the previous data (33.1%) of only one epidemiological 25-year study of the Ukrainian adult population [2]. Age, sex, severity of COVID-19, presence of concomitant hypertension and diabetes mellitus have a significant impact on ECG changes.

In general, age impacts most of the investigated indicators. Thus, the age correlated with the severity of COVID-19 ($r = 0.485$, $P < 0.001$), concomitant hypertension ($r = 0.471$, $P < 0.001$), diabetes ($r = 0.346$, $P < 0.001$) and obesity ($r = 0.179$, $P < 0.001$). Correlations were established between age and the presence of baseline previous pathological ECGs ($r = 0.290$, $P < 0.0001$), negative ECG dynamics during follow-up ($r = 0.317$, $P = 0.003$) and changes in several MC classes: infarction changes (MC 1) $r = 0.175$, $P < 0.001$; atrioventricular conduction disorders (MC 6) $r = 0.118$, $P < 0.001$; supraventricular and ventricular extrasystoles (MC 8-1-1,8-1-2) $r = 0.196$, $P < 0.001$; atrial fibrillation (AF) (MC 8-3) $r = 0.259$, $P < 0.001$; ST segment changes (MC 4) $r = 0.120$, $P = 0.001$ and T wave changes (MC 5) $r = 0.180$, $P < 0.001$. In general, age had a significant effect on "major" arrhythmic episodes (MC 6-2; 6-3; 6-4; 6-8; 7-1; 7-2; 7-4; 7-8; 8-3; 8-4-2; prolonged QT) $r = 0.485$, $P < 0.001$. Therefore, we made standardization by age simultaneously with further assessing the changes in individual parameters.

Hypertension was the most common comorbidity (316 people or 41.7% of the cohort). It was diagnosed for the first time during COVID-19 in 1.3% of persons. Patients with diabetes mellitus formed 9.4% of the cohort, and 5.1% of patients were discharged from the hospital with a diagnosis of diabetes detected for the first time and 2.5% with glucose intolerance. However, regarding hypertension rate, the group of patients with COVID-19 did not differ significantly from the control group at 30.8% ($P = 0.078$) and, in general, corresponds to the average population level – in Ukraine, according to the STEPS study, an increase in blood pressure (BP) was detected in one-third of the population (34.8%) [3]. Correlation analysis (pairwise correlations) revealed the dependence of the severity of the course of COVID-19 with the presence of hypertension and the duration of history of hypertension ($r = 0.248$;

$P < 0.001$), diabetes mellitus ($r = 0.331$; $P < 0.001$) and obesity ($r = 0.188$, $P < 0.001$). However, when determining the partial correlation excluding the effect of age, the relationship between the severity of the course of COVID-19 and hypertension is lost, but there is a relation with diabetes ($r = 0.215$, $P < 0.001$) and the presence of obesity ($r = 0.123$, $P < 0.001$).

At the same time, a correlation was established between the severity of COVID-19 and changes in the ECG ($r = 0.106$, $P = 0.015$), in particular, MC class 6 – changes in atrioventricular conduction ($r = -0.666$, $P = 0.001$), class 8 – arrhythmias ($r = 0.113$, $P = 0.010$), as well as changes in the QRS complex ($r = -0.148$, $P = 0.005$) and MC class 5 – changes in the T wave ($r = -0.103$, $P = 0.049$).

A detailed analysis of the ECG in the patients of the groups under study revealed a predominance of pathological changes in hospitalized patients compared to persons who were treated on an outpatient basis, respectively, 74.1% versus 57.8% ($P < 0.001$). An increase in the proportion of patients with pathological changes on the ECG was observed among patients with severe COVID-19 (HSV, 83.9%) and critical patients (HCR, 89.3%) compared to patients with moderate symptoms (66.6 %, respectively, $P < 0.001$ and $P = 0.013$).

The analysis of ECG changes by separate classes of MC is shown in Table 1.

A significant predominance among hospitalized patients of a deviation of the axis to the left (angle $\alpha = -30°$), i.e., the presence of blockade of the anterior branch of the left bundle branch (MC 2-1) and voltage criteria of left ventricular hypertrophy (MC 3), is associated with the presence of hypertension in most of these patients (55.5% vs. 29.7% in HQM, $P < 0.001$). Repolarization processes disturbance (MC 4 and MC 5) is difficult to interpret without the context of a specific clinical situation, but still, in severely ill patients, changes in the T wave (MC 5) were more often detected, which was associated with infectious-toxic inflammatory effects (correlation with changes in cardiotocography – $r = 0.116$, $P = 0.05$), electrolyte and metabolic disorders, hypoxia (correlation with SpO_2 – $r = -0.247$, $P < 0.0001$).

As can be seen from Table 1, atrioventricular conduction (MC 6) and disturbance of impulse conduction along the bundle of His (MC 7) did not differ significantly in the groups. However, in a detailed analysis of changes within a separate class of MC, the situation in terms of the significance of the detected disturbances is quite unequal. Whereas in the outpatients (HQM), symptoms of PQ shortening prevailed (Clerc-Levy-Cristesco, Wolff-Parkinson-White, MC 6-5; 6-4), and there were cases of presence of pacemaker (MC 6-8), in the hospitalized patients, atrioventricular blocks of the first and second degree were mainly observed (MC 6-3, 6-2). At the same time, in the latter, the dependence of the frequency of atrioventricular blocks on the severity of COVID-19 was established, with HMO, HSV and HCR – 1.0, 3.1 and 7.1% (pHMO-HCR = 0.011), respectively. Changes in MC 7 in hospitalized patients were associated with complete blockade of the left or

Table 1. Changes in ECG according to separate classes of the Minnesota code among outpatients and hospitalized patients (%)

MC class	Outpatients (HQM) $n = 283$ ECG	Hospitalized patients (HMO+HSV+HCR) $n = 565$ ECG	*P* value
MC2-1 (∟α=-30°, blockade of the anterior branch of the left bundle branch)	6.9	13.2	0.014
MC3	3.2	11.9	<0.001 (0.0002)
MC4	14.2	17.6	NS*
MC5	19.7	31.0	0.002
MC6	3.2	4,8	NS
MC7	7.8	12.5	(0.0637)
MC8	15.6	26.1	0.002

Note. *NS – not significant; MC – Minnesota code; HQM – Home Quarantined with Mild disease course; HMO – Hospitalized with Moderate course; HSV – Hospitalized oxygen-dependent patients with Severe symptoms; ECG – Electrocardiography

right bundle branch (2.4%, $P = 0.009$), while in outpatients, non-specific disturbances of intraventricular conduction prevailed (MC 7-4) as well as incomplete blockade of the right bundle branch (MC 7-3).

Arrhythmias (MC 8) occurred quite often both in the HQM group and especially in hospitalized patients, 15.6 and 26.1% ($P = 0.002$), respectively. According to the observations of individual researchers, the frequency of arrhythmias in hospitalized patients was about 17% and increased to 44% in intensive care unit patients [4]. However, in the final ESC guidelines updated in November 2021 [1], it is reported that the incidence of arrhythmias in stable patients with COVID-19 is low. Conversely, the frequency of arrhythmias increases significantly in patients in critical condition. However, data from various reports are quite contradictory.

We established that heart rhythm disorders (HRD) related to the severity of the COVID-19 course are significantly influenced by oxygen saturation ($r = -0.211$, $P < 0.001$) and, to a lesser extent, the percentage of lung damage according to computed tomography data ($r = 0.127$, $P = 0.060$). However, the nature of arrhythmias is quite heterogeneous both in terms of electrophysiological characteristics and their clinical significance and depends on some factors, such as age, gender and severity of the course of COVID-19; therefore, it requires separate consideration (Table 2).

Supraventricular and ventricular extrasystoles are the most frequent types of arrhythmias in both outpatients and hospitalized patients (5.5 and 10.2%, $P = 0.040$), moreover, in severe forms of supraventricular extrasystole (8-1-1), the detection increased by 3–5 times, a tendency to increase ventricular (8-1-2) ectopy was also observed.

Given that supraventricular extrasystole is a precursor to AF, the occurrence of this arrhythmia in patients with COVID-19 and its progression in severe forms of the disease is expected. According to

Table 2. Heart rhythm disorders by separate classes of the Minnesota code among outpatients and hospitalized patients (%)

MC class	(1) HQM 283 ECGs	HMO+HSV+HCR 565 ECGs	(2) HMO 329 ECGs	(3) HSV 202 ECGs	(4) HCR 34 ECGs
Supraventricular extrasystole (8-1-1)	2.3	5.6	3.3	9.9	14.7
	$P = 0.051$		$P_{2-3} = 0.002$; $P_{3-4} > 0.05$; $P_{2-4} = 0.002$		
Ventricular extrasystole (8-1-2)	3.7	5.4	5.0	5.2	10.7
	$P > 0.05$		$P_{2-3-4} > 0.05$		
Atrial fibrillation (8-3)	0.9	7.5	3.6	12.0	14.7
	$P < 0.001$		$P_{2-3} < 0.001$; $P_{3-}4 > 0.05$; $P_{2-4} = 0.004$		
- a permanent form of atrial fibrillation	0.5	4.2	1.7	6.3	11.8
	$P = 0.008$		$P_{2-3} < 0.001$; $P_{3-4} > 0.05$; $P_{2-4} < 0.001$		
"Major" arrhythmias	0.9	13.4	8.3	20.3	17.8
	$P < 0.001$		$P_{2-3} < 0.001$; $P_{3-4} > 0.05$; $P_{2-4} < 0.001$		
"Minor" arrhythmias	22.5	25.9	22.5	27.1	53.6
	$P > 0.05$		$P_{2-3} > 0.05$; $P_{3-4} = 0.004$; $P_{2-4} < 0.001$		
Sinus tachycardia (8-7)	5.0	8.2	4.6	10.4	32.1
	$P > 0.05$		$P_{2-3} = 0.013$; $P_{3-4} = 0.001$; $P_{2-4} < 0.001$		
Sinus bradycardia (8-8)	2.8	2.5	2.3	2.1	10.7
	$P > 0.05$		P_{2}-3 > 0.05; $P_{3-4} = 0.016$; $P_{2-4} = 0.013$		

Notes. MC – Minnesota code; HQM – Home Quarantined with Mild disease course; HMO – Hospitalized with Moderate course; HSV – Hospitalized oxygen-dependent patients with Severe symptoms; HCR – Hospitalized Critical patients in ICU departments with artificial ventilation; ECG – Electrocardiography

our observations, AF was registered more often in hospitalized patients (Table 2). Similar ratios were preserved both in the paroxysmal form (0.5 and 3.4%, $P = 0.022$) and in patients with chronic AF (0.5 and 4.2%, $P = 0.008$). Among all patients with COVID-19 and AF, the chronic form occurred in almost half of the examined patients (47.4%), and the frequency of detection of the latter increased with the severity of the course. The relationship between the occurrence or presence of AF and the severity of COVID-19 is confirmed by the correlation with SpO_2 ($r = -0.189$, $P < 0.0001$), which was also observed when the AF paroxysm occurred ($r = -0.102$, $P < 0.016$). According to previous studies [4, 5], arterial hypoxemia itself increases the likelihood of developing AF, especially in elderly patients.

Indeed, the age factor is a long-proven factor of AF [6, 7]. However, according to our analysis, when patients were standardized by age, the relationship between AF (MC 8-3) and blood oxygen saturation was preserved ($r = -0.110$, $P < 0.009$), the effect of age was more significant only in cases of paroxysmal AF in the acute period of the disease. In addition, it was confirmed that the incidence of AF was predominantly influenced by the presence of comorbid hypertension. Among patients with concomitant hypertension, the proportion of AF was 6.9%, against 1.0% in normotensive patients ($P = 0.0004$).

Cumulative analysis of the so-called "major" arrhythmias (6-1,6-2,6-4,6-8; 7-1,7-2,7-4,7-8; 8-3, 8-4-2, Q-T prolongation) confirmed the correlation with the severity of the course of COVID-19 – $r = 236$, $P < 0.0001$ and was accompanied by an increase in the proportion of HRD with increasing severity of the disease.

Similar regularities were observed with "minor" arrhythmias (6-3,6-5; 7-3; 8-7,8-8,8-1-1,8-1-2,8-1-3); however, this was more relevant for HCR group patients, in whom the indicated HRD were detected in almost every second patient ($P < 0.001$).

Among the rhythm disorders, such seemingly commonplace disorders as sinus tachycardia (MC 8-7) and sinus bradycardia (MC 8-8) attract attention. In general, the occurrence of those disorders did not statistically differ between outpatients and hospitalized patients, 8.7 and 10.9%, respectively. However, among hospitalized patients, the percentage of heart rate acceleration above 100 bpm was growing. The basis for abnormal sinus tachycardia is probably the autonomous regulation changes of the sinus node with an imbalance of sympathetic and

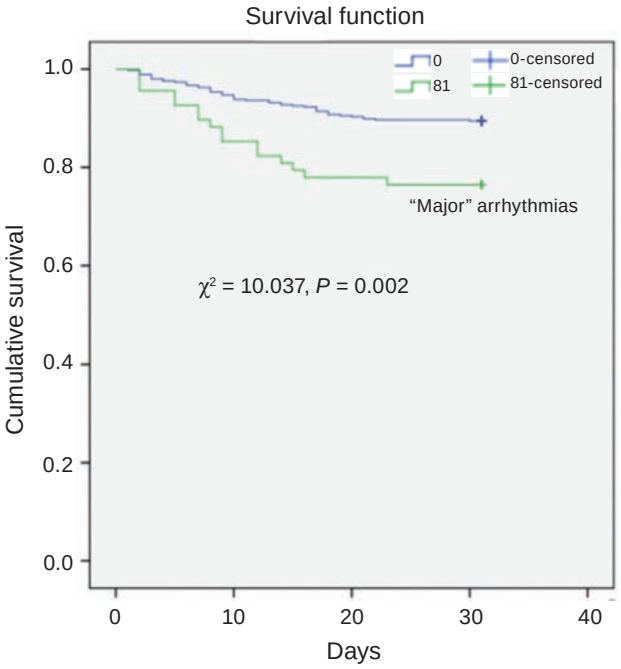

Fig. 1. Survival rate of patients with COVID-19 depending on the registration of "Major" arrhythmias

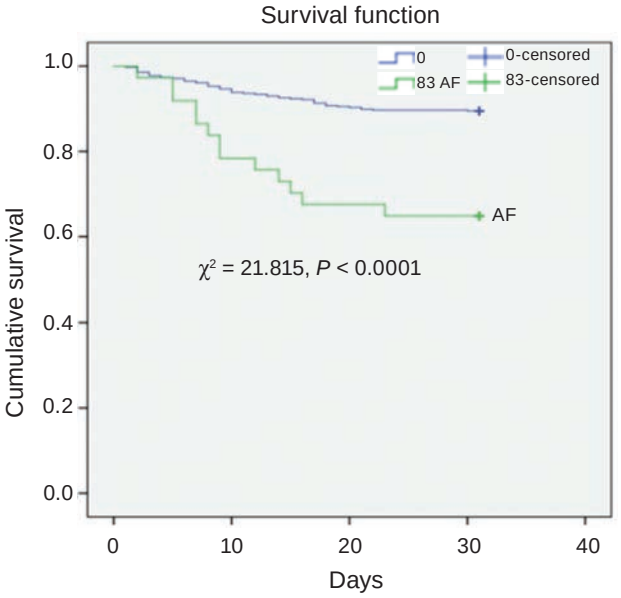

Fig. 2. Survival of patients with COVID-19 depending on the registration of atrial fibrillation

parasympathetic functions against the background of viral load, inflammation, toxic effects and drug interaction, and in the distant period reflected post-infectious asthenia. The five-times higher frequency of severe bradycardia in patients in critical condition (HCR) compared to other groups of inpatients

(HMO, HSV) was probably provoked by invasive lung ventilation.

To assess the prognostic value of arrhythmias in hospitalized patients, in-patient mortality and survival of patients over 30 days and their relationship with various HRD were monitored. The Kaplan-Meier method was used to estimate the survival rate. Fig. 1 and Fig. 2 show the survival curves of hospitalized patients depending on the development of "major" arrhythmias or separately – atrial fibrillation.

Analysis of the survival rate of patients with COVID-19 according to the Kaplan-Meier method revealed an effect of HRD on in-hospital mortality ("major" arrhythmias, $\chi^2 = 10.037$, $P = 0.002$), in particular, AF ($\chi^2 = 21.815$, $P < 0.0001$). The relationship between mortality and AF was maintained both for the paroxysmal ($\chi^2 = 8.999$, $P = 0.003$) and for the permanent form ($\chi^2 = 12.175$, $P < 0.0001$).

For other rhythm and conduction disorders, similar survival curves were obtained only for supraventricular extrasystoles (MC 8-1-1, $\chi^2 = 6.269$, $P = 0.012$) and sinus tachycardia (MC 8-7, $\chi^2 = 64.055$, $P < 0.0001$). Our data on the impact of AF and supraventricular ectopic activity on mortality correlate with the results of another study [8], according to which the presence of atrial arrhythmias was associated with higher levels of inflammatory markers and higher 30-day mortality.

Ventricular ectopy, as a known leading factor in sudden cardiac death, had no significant prognostic value in the patients we examined, and in-hospital cardiac arrest and COVID-19 was, as a rule, secondary. According to pathomorphological studies, the main causes of death of patients with COVID-19 were acute respiratory failure, acute respiratory distress syndrome (59.09%), multiple organ failure (28.79%) and cardiopulmonary failure (12.12%).

To establish possible predictors of a fatal outcome in hospitalized patients with COVID-19, the Cox proportional hazards model was used. The model included such parameters as age, history of concomitant high blood pressure, diabetes, obesity and HRD – supraventricular extrasystoles, AF groups of "major" and "minor" arrhythmias. In the process of univariate and multivariate analysis, the following were found to be independent predictors of in-hospital mortality: age (HR 1.077, 1.049–1.106, 95% cardiac index (CI)), diabetes (HR 0.484, 0.286–0.820, 95% CI), AF from the group of "major" arrhythmias (HR 0.287, 0.136–0.604, 95% CI) and "minor" arrhythmias (BP 0.221, 0.124–0.394, 95% CI). The reliability of the model of fatal events was $\chi^2 = 89.241$, $P < 0.0001$.

Although it was not possible to establish a reliable specific effect of COVID-19 and the most common arrhythmias (i.e., AF), on the arrhythmogenesis, however, out of all patients with supraventricular myocardial activity disorders, 47% of patients required non-invasive oxygen support compared to 24% of HQM patients and 29 % of HMO patients. In addition, the SARS-CoV-2 infection is often a trigger for the development of arrhythmias. This is especially clearly manifested in the case of a severe course of COVID-19, as indicated by the prevalence of arrhythmias in patients who are in resuscitation and intensive care units – 44.4% versus 6.9% of other hospitalized patients [9].

Conclusion. The results of the preliminary analysis of arrhythmias in patients with COVID-19 in aspects of the severity of the course of the disease, the presence of comorbidity, especially with diabetes, provide grounds for considering arrhythmogenesis with underlying SARS-CoV-2 infection through the prism of the pathogenetic influence of inflammation, intoxication syndrome, hypoxia, metabolic disorders and drugs effects.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. The study was supported by the RECOOP Research Grant #023 "Impacts of COVID-19 infection on patients with high blood pressure using angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARBs)," the RECOOP Research Grant #024 "Vascular dysfunction in post-infected COVID-19 patients" and the Ministry of Health of Ukraine Grant #0121U100305.

Institutional review board statement. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of the I. Horbachevsky Ternopil National Medical University, Protocol N 59 of 6 May 2020.

Informed consent statement. Informed consent was obtained from all subjects involved in the study.

ЕКГ ПАТЕРНИ У ПОСТКОВІДНИХ ПАЦІЄНТІВ

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COVID-19 асоціюється з широким спектром негативних наслідків для серцево-судинної системи. Мета дослідження: оцінити спектр аритмій залежно від віку, коморбідної патології та виживаності за даними ЕКГ у пацієнтів, які перенесли COVID-19, протягом 2 місяців після одужання. Обстежено та проаналізовано дані ЕКГ 758 пацієнтів у гострому періоді та періоді реконвалесценції, серед яких 256 (33,6%) чоловіків та 503 (66,4%) жінки у віці від 15 до 90 (52,99 ± 11,68) років. Всього було виконано 848 ЕКГ. Зміни на ЕКГ класифікували відповідно до класів Міннесотського кодексу (МК). Встановлено, що вік, стать, тяжкість перенесеного COVID-19, наявність супутньої артеріальної гіпертензії та цукрового діабету мають значний вплив на зміни ЕКГ. Вік корелює з тяжкістю COVID-19 (r = 0,485, P < 0,001), супутньою артеріальною гіпертензією (r = 0,471, P < 0,001), цукровим діабетом (r = 0,346, P < 0,001) та ожирінням (r = 0,179, P < 0,001). Встановлено кореляцію між віком та наявністю попередніх патологічних ЕКГ (r = 0,290, P < 0,0001). Встановлено, що порушення серцевого ритму, пов'язані з тяжкістю перебігу COVID-19, значно впливають на рівень сатурації (r = -0,211, P < 0,001), а в меншій мірі – на відсоток ураження легень за даними комп'ютерної томографії (r = 0,127, P = 0,060). Результати скринінгу аритмій у хворих на COVID-19 демонструють зв'язок переважно з тяжкістю перебігу захворювання та коморбідною патологією, особливо цукровим діабетом. Отже, ми можемо розглядати аритмогенез при COVID-19 через призму запалення, інтоксикації, гіпоксії, метаболічних порушень та медикаментозних впливів.

Ключові слова: постковідний період, аритмії, електрокардіографія, класи Міннесотського коду.

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