Russian Journal of Cardiology 2023;28(S2):5357
doi:10.15829/1560-4071-2023-5357
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)
ISSN 2782-2257 (online)

Hypertensive disease after moderate coronavirus infection. The results of six-month follow-up

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Aim. This study aims to assess the clinical specificity of course of hypertensive disease (HD) during the first 6 months after new coronavirus infection (COVID-19) and to investigate prognostic significance of laboratory and instrumental parameters for organ dysfunctions in acute period of COVID-19 in patients with HD.

Material and methods. The study included 82 patients. The main group included 50 patients with HD duration of at least 3 years, who received antihypertensive therapy and had confirmed moderate COVID-19. The control group included 32 patients with HD and without COVID-19. The mean age was 63,6±7,9 years and 66,6±10,3 years, respectively. The standard parameters of carbohydrate and lipid metabolism, inflammatory markers, hematological indicators, glomerular filtration rate (GFR) were measured, and also arterial pressure, Ps, t° C, SpO_2, peak expiratory flow rate (PEFR) were recorded. In 6 months we contacted by phone to conduct a survey concerning the 6-month period after hospitalization or outpatient examination with filling the questionnaire form SF-36.

Results. Before inclusion, 76,5% and 83,3% of the patients in the main and control groups, respectively, took 1 hypotensive drug; 17,7% and 16,6% — 2-3 drugs; 5,9% ($p<0,05$) of the patients from the COVID-19 group took the drugs irregularly before hospitalization. In 6 months, 3% in each group took 1 hypotensive drug, 50% — 2 drugs, and 47% — 3 drugs. For the control group this was: 77% — 2 and 20% — 3, respectively. After analyzing the SF-36 form, we found that the worsening of emotional health in the group with HD and COVID-19 correlated ($p<0,05$) with initial SpO_2 (r=-0,623), t° C (r=-0,371), PEFR (r=0,423), and the degree of improvement — with GFR (r=0,339), total cholesterol (r=0,471) and platelet count (r=0,414). SF-36 also showed that in the main group, the worsening of physical health was associated with lower ALB (r=0,512), the higher increase of lactate dehydrogenase (r=0,342) and RBC (r=0,393).

Conclusion. In 6 months after moderate COVID-19, the patients develop pronounced emotional and physical disorders as well as the worsening of HD clinical course. Regarding to this, the parameters reflecting severity of systemic inflammation, impairment of liver function and changes in brain function in acute COVID-19 possessed the prognostic significance.

Keywords: hypertensive disease, novel coronavirus infection.

Relationships and Activities: none.

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Received: 05.02.2023
Revision Received: 06.03.2023
Accepted: 19.05.2023

For citation: Fedoseeva D. O., Sokolov I. M., Shvarts Yu. G. Hypertensive disease after moderate coronavirus infection. The results of six-month follow-up. *Russian Journal of Cardiology*. 2023;28(2S):5357. doi:10.15829/1560-4071-2023-5357. EDN RZSZQF

Key messages

- Moderate COVID-19 worsens the course of hypertensive disease: it increases the frequency of hypertensive crisis and causes the requirement of the larger number of the drugs due to development of microvascular damage and imbalance between pressor and depressor mechanisms.
- In 6 months after moderate COVID-19, the patients with HD develop more pronounced emotional and physical disorders.
- The found changes in total cholesterol levels, platelet count, glomerular filtration rate, albumin and lactate dehydrogenase levels may be used as the predictors. The listed indicators are associated with severity of systemic inflammation, impairment of liver function and changes in brain function in acute COVID-19.

Currently, cardiovascular diseases are one of the most common comorbid pathological conditions in patients with novel coronavirus infection (COVID-19); almost every second patient with COVID-19 infection and concomitant cardiovascular diseases has hypertensive disease (HD) [1]. And some authors note the role of HD as a risk factor of more severe course of COVID-19 [1, 2].

To date, relatively little is known about clinical and laboratory-instrumental features of the HD course against the background of COVID-19. In addition, there is no enough understanding of long-term systemic effects, including cardiovascular, of COVID-19 on the organs in HD. The clinical features of the development of HD after COVID-19 infection are not completely clear, in particular, in patients with moderate course of COVID-19.

The data of the fact that the clinical symptoms named Long-COVID can persist after COVID-19 infection from several weeks to several moths are being accumulated [2-6]. It is described that the Long-COVID manifestations may be associated with viral or immuno-mediated disorder of the autonomic nervous system, functional disorders of some organs and endocrine system disorders [5, 6]. The latter may have a relation to HD progression too.

In this regard, our study was mainly aimed to assess the clinical features of the HD course during first 6 months after COVID-19 infection as well as to investigate the prognostic values of laboratory and instrumental parameters which characterize organ dysfunction in acute period of COVID-19 in patients with HD.

Material and methods

The total number of patients involved in the prospective study was 82. The inclusion of patients was carried out from November 2020 to February 2021. The investigated group included 50 patients with HD stages II-III and very high risk of the development of cardiovascular complications (according to SCORE-2), with duration of HD at least 3 years, received antihypertensive therapy and with confirmed moderate COVID-19 according to the criteria of the temporary methodological recommendations for prevention, diagnostics and treatment of COVID-19 (the Ministry of Health of Russian Federation version 9 from 26.10.2020), who received hospital treatment in the infectious department of S. R. Mirotvortsev University hospital № 1 of Saratov State Medical University. The HD diagnosis was verified in accordance with the clinical recommendations "Arterial hypertension in adults 2020" of the Russian Society of Cardiology [7]. The age of patients varied from 38 to 80 years (the mean age was 63,6±7,9 years), of them 28 women and 22 men.

The comparison group included 32 patients (19 women and 13 men) with confirmed HD stages II-III and very high risk of the development of cardiovascular complications, with duration of HD ⩾3 years, received constant basic hypotensive therapy (the diagnosis was verified similarly to the research group) and without COVID-19, who were under outpatient supervision in the Clinical center of Saratov State Medical University at the time of the study conduction and applied for a planned consultation due to various problems, against the background of satisfactory control of arterial pressure (AP) level. The age of patients varied from 39 to 80 years (the mean age was 66,6±10,3 years).

The exclusion criteria for both groups were: uncontrolled or resistant HD, hypertensive crisis (HC) before hospitalization or at admission to the hospital as well as before outpatient supervision, secondary arterial hypertension; acute or decompensated chronic heart failure, acute coronary syndrome and its complications, the rhythm disturbances with hemodynamic impairment, acute cerebrovascular accident and/or transient ischemic attack at the moment of hospitalization or examination of outpatients; the presence of acute inflammatory processes of any other localization; oncological diseases at

Table 1

The main initial laboratory parameters (Me [25%; 75%])

Parameters	Investigated group HD+COVID-19 (n=50)	Control group HD (n=32)	Value p
SpO_2, %	95,5 [94,0; 97,0]	97,0 [96,0; 97,0]	0,001
SAP, mm Hg	121,0 [113,0; 132,0]	135,0 [125,0;143,0]	0,00009
DAP, mm Hg	71,0 [65,0; 84,0]	80,0 [72,0; 89,0]	0,04
Pulse, beats/min	69,0 [60,0; 80,0]	65,5 [60,0; 72,0]	0,1
PEFRmean l/min	223,3 [170,0; 331,7]	255,0 [205,0; 328,3]	0,2
White blood cell count, 10*9/l	8,0 [5,9; 9,8]	7,3 [6,3; 8,5]	0,7
Redd blood cell count, 10*12/l	4,6 [4,1; 4,9]	4,7 [4,4; 5,2]	0,2
Platelet count, 10*9/l	222,5 [184,0; 318,0]	221,5 [183,0; 266,5]	0,2
Hemoglobin, g/l	135,5 [124,5; 141,0]	123,5 [112,5; 138,5]	0,9
Ferritin, µg/l	400,0 [380,9; 400,0]	–	–
Glucose, mmol/l	8,3 [6,0; 10,6]	5,8 [4,7; 6,2]	0,00002
Albumin, g/l	32,1 [28,5; 34,1]	36,0 [33,1; 37,1]	0,00001
Urea, mmol/l	7,0 [5,1; 8,6]	6,8 [5,2; 8,7]	0,9
Creatinine, µmol/l	79,6 [71,2; 90,0]	88,6 [81,4; 100,0]	0,002
LDH, u/l	308,1 [224,2; 363,0]	187,3 [150,5; 233,5]	0,00000001
ALT, u/l	38,7 [19,5; 77,2]	23,6 [14,6; 28,4]	0,00009
AST, u/l	33,2 [26,0; 42,6]	22,6 [18,8; 27,5]	0,0006
Cholesterol, mmol/l	4,9 [4,0; 5,4]	4,5 [3,7; 5,1]	0,00009
Total protein, g/l	67,9 [64,0; 71,0]	69,0 [64,5; 70,1]	0,2
Potassium, mmol/l	5,6 [5,1; 5,9]	5,0 [4,6; 5,5]	0,00000001
Sodium, mmol/l	136,7 [134,7; 139,0]	140,3 [136,9; 141,7]	0,003

Abbreviations: ALT — alanine aminotransferase, AST — aspartate aminotransferase, HD — hypertensive disease, DAP — diastolic arterial pressure, LDH — lactate dehydrogenase, PEFR mean. — peak expiratory flow rate, mean value, SAP — systolic arterial pressure, COVID-19 — novel coronavirus infection, SpO_2 — oxygen saturation.

present and in the anamnesis; severe kidney pathology (including chronic kidney disease stage 3); decompensation of liver diseases.

Blood sampling and measurement of laboratory and instrumental parameters were performed to all hospitalized patients starting from the second day of hospital treatment, in the morning, from 06:30 to 07:30. Blood sampling was performed on an empty stomach and before oral and parenteral administration of drugs.

In 30-40 min after blood sampling, a doctor measured the level of AP in accordance with ESC, pulse, body temperature (t° C), blood oxygen level (SpO_2), peak expiratory flow rate (PEFR). SpO_2 was measured using a pulse oximeter Riester Ri-fox N. PEFR measurement was performed with a peak flow meter Omron PF20 three times for further determination of the mean value and maximum value. The outpatient examination was performed similarly.

The parameters of carbohydrate and lipid metabolism were investigated, and the analysis of inflammatory markers (C-reactive protein, ferritin) was performed. The standard laboratory blood parameters — hematological and biochemical were tested: total protein, albumin (ALB), total bilirubin, urea, glucose, cholesterol, alanine aminotransferase, aspartate aminotransferase, potassium and sodium, creatinine and glomerular filtration rate (GFR).

In 6 months after primary examination, we contacted the patients by phone to conduct a survey concerning the 6-month period after hospitalization or outpatient examination. The patients informed the doctor about significant changes in their health condition: hospitalizations for HD or consultation with doctor for this reason, the development of hypertensive crisis [8], and following recommendations for HD treatment. To record the symptomatic hypotonic episodes (SHEs) we conditionally accepted a temporary decrease in AP level below 100 and 60 mm Hg [8, 9] and the presence of the clinical symptoms (heaviness in the head, headache, dizziness, cardialgia, shortness of breath, general weakness) with duration >10 min [8].

In the hospital and immediately after patient`s consultation with doctor, the received therapy was corrected. In 6 months, a number of antihyperten-

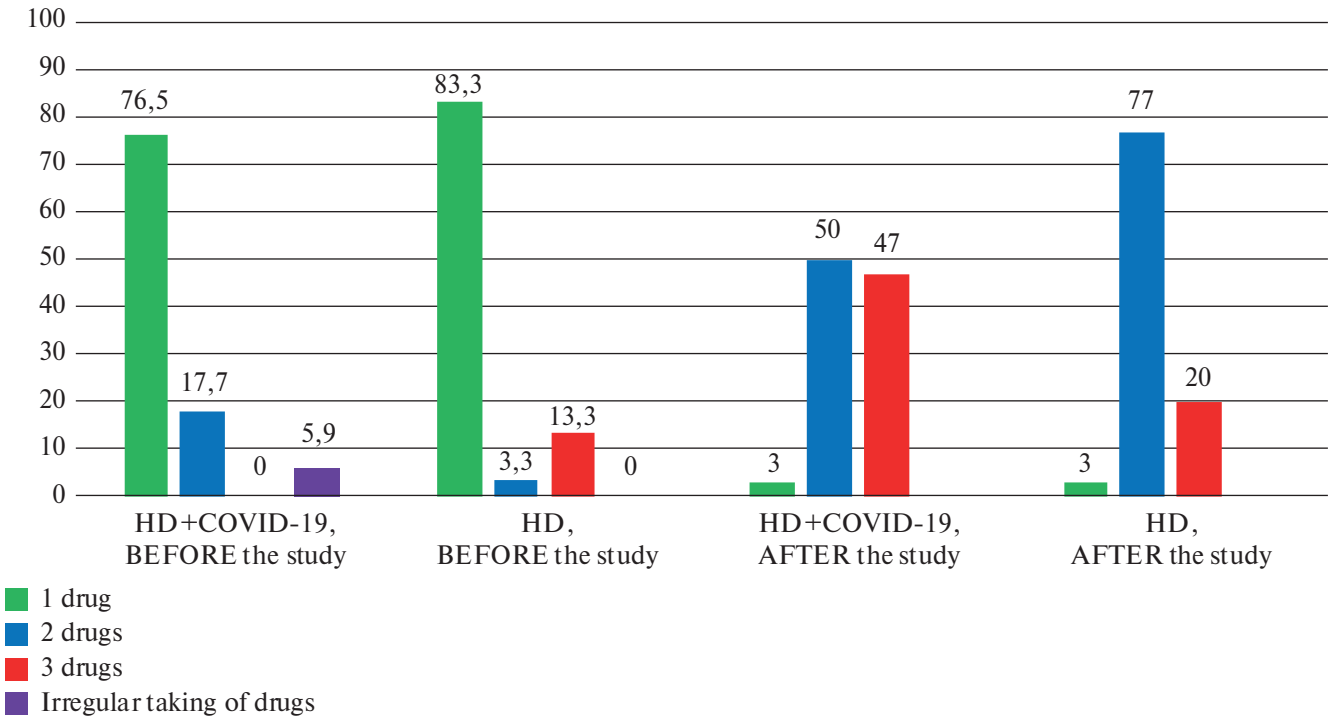

Figure 1. The number of antihypertensive drugs (%) taken by patients before and 6 months after the inclusion into the study in the main (HD and COVID-19) and control (HD without COVID-19) groups.
Abbreviations: HD — hypertensive disease, COVID-19 — novel coronavirus infection.

sive drugs used by a patient at the time of the survey was analyzed. During the telephone contact, the SF-36 questionnaire "Assessment of quality of life" was filled out. The analysis was made on the basis of percentage indicators from 0 to 100 points relative to the maximum possible for each scale, and then the general parameters were calculated: general physical health (physical status) and general mental health (emotional status).

We assessed an improvement or worsening of physical and emotional state, i.e. the assessment of these characteristics by the patients themselves for the last 6 months. When assessing the dynamics of physical state, we considered it appropriate to take into account the increase or decrease in the clinical symptoms of the main disease and the restoration of physical productivity. When assessing the emotional state, we based on the own opinion of the patients in the regard of the presence of changes according to the parameters which are assessed using the SF-36 questionnaire.

Statistical processing of the obtained results using methods of graphical analysis, analysis of variance with the determination of M±SD, with abnormal data distribution — Kruskal-Wallis ANOVA with the determination of Me, Q25 and Q75, cross-tabulation using the Fisher and χ^2 criteria, as well as nonparametric correlation with the determination of the Kendall coefficient, was carried out using the application software package "STATISTICA 10.0" (StatSoftUSA) and MicrosoftExcel. We give and discuss below only statistically significant correlation coefficients ($p<0,05$).

Results

The mean duration of HD in the examined patients in the group with HD and COVID-19 was 11,5±4,72 years. 14 patients from the same group also had a form of chronic ischemic heart disease — exertional angina pectoris (3 patients had myocardial infarction in the anamnesis), 5 patients had atrial fibrillation, 43 — had different degree of obesity (mean body mass index was 29,4±3,5 kg/m^2), and 17 patients had type 2 diabetes mellitus. Most patients were hospitalized in average on the fifth day from the onset of the clinical symptoms of COVID-19. All patients of this group received oxygen therapy; moistened oxygen was delivered through a nasal cannula at a flow rate of 5 l/min. During treatment, glucocorticosteroids were administered parenterally twice a day. The dose varied according to temporary guidelines for prevention, diagnostics and treatment of COVID-19 (the Ministry of Health of Russian Federation version 9 from 26.10.2020).

In the group of patients with HD and without COVID-19, the mean duration of HD was

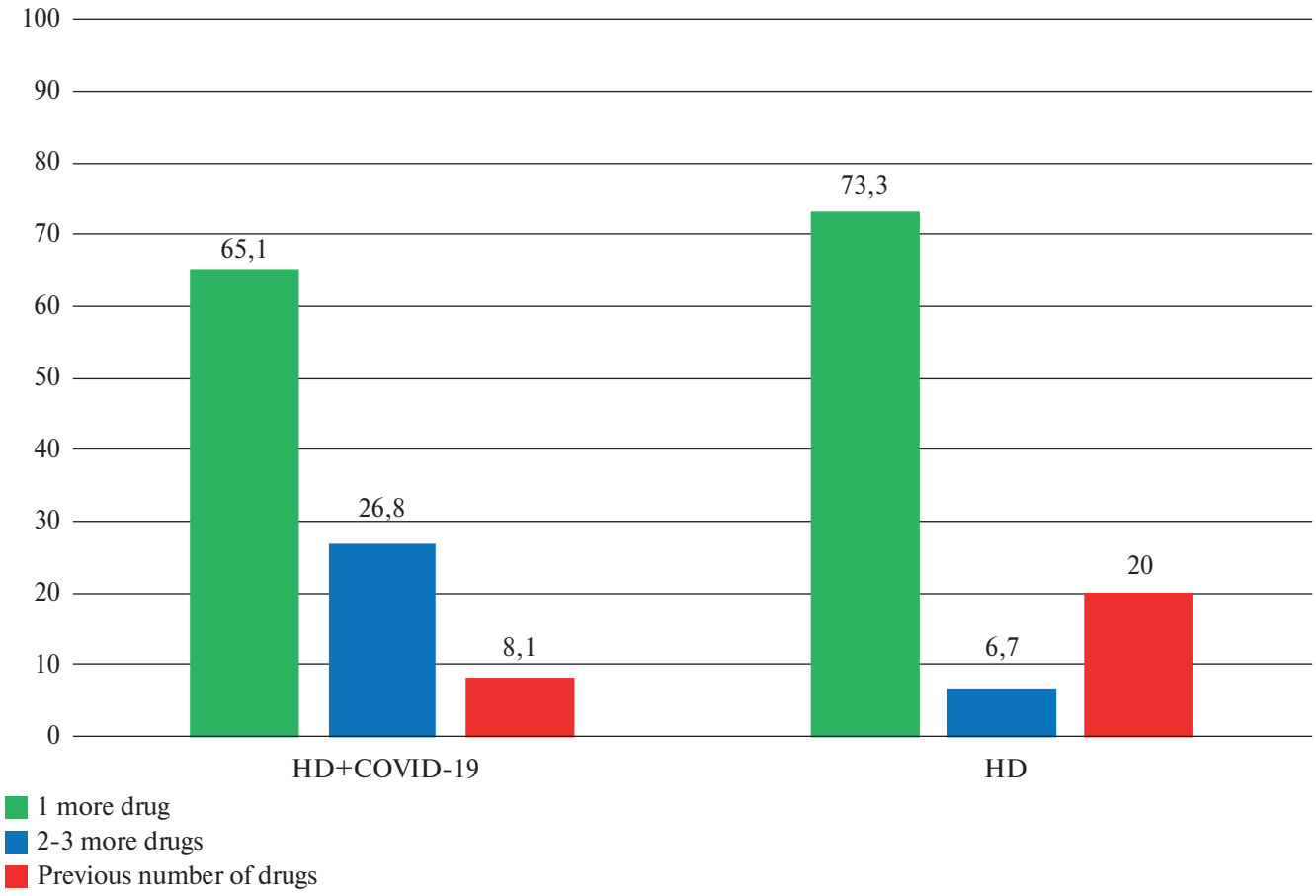

Figure 2. The comparison of the number of antihypertensive drugs (%) taken by patients before and 6 months after the inclusion into the study.
Abbreviations: HD — hypertensive disease, COVID-19 — novel coronavirus infection.

13,25±7,25 years, 20 patients had chronic ischemic heart disease — exertional angina pectoris, 6 of them previously suffered myocardial infarction, 14 patients suffered a different form of atrial fibrillation, 29 had different degree of obesity (mean body mass index was 31,9±4,4 kg/m^2), 8 patients had type 2 diabetes mellitus.

During the first examination in the clinic, 50% patients with HD and COVID-19 had a decrease in SpO_2 up to 87% minimum, 34% — increase in t° C from 37° C to 38,6° C; in 86% of the patients, systolic AP (SAP) was 100-138 mm Hg, and in 80% of the patients, diastolic AP (DAP) was 60-88 mm Hg. We noted the increased level of some laboratory parameters such as ferritin, glucose and potassium level in a significant number of the patients, while the level of ALB and total protein was decreased.

The main initial laboratory parameters are given in Table 1.

All patients in the group with HD and without COVID-19 had stable satisfactory condition, t° C and SpO_2 were normal; in almost half of them, SAP was ⩾140 mm Hg, and in a quarter — DAP was ⩾90 mm Hg. The analysis of the laboratory parameters showed that a significant number of the patients had an increased blood glucose level.

Most of the patients in the main and control groups took one hypotensive drug before the inclusion into the study — 76,5% and 83,3%, respectively, and 2-3 drugs — 17,7% and 16,6%. 5,9% patients of the group suffered COVID-19 did not take the drugs regularly immediately before hospitalization.

According to the results of the conducted survey, in six months after the discharge and outpatient treatment it was found that the mean value of emotional health in the patients with HD and COVID-19 corresponded to 41,7±6,5% based on SF-36, and in the patients without COVID-19 — 42,1±3,9%.

Emotional health in the group of the patients with HD and COVID-19 was improved during 6 months in 65% of respondents according to the assessment by the patients themselves, while in the comparison group, the improvement was noted in significantly larger number of the patients (80%).

The worsening of emotional state after the discharge was associated with relatively high SpO_2 (r=

-0,623), increased t° C (r=-0,371) and lower indicators of PEFR (r=0,423). As for the prognostic value of the laboratory data, emotional state worsened in initially relatively low values of GFR (r=0,339), total cholesterol (r=0,471) and platelet count (r=0,414). While in the group of the patients with HD and without COVID-19, emotional state worsened in initially relatively high values of total cholesterol (r=-0,294).

As for self-assessment of the physical state changes, most of the patients (60%) with HD and COVID-19 noted the worsening of the state in further 6 months after the discharge, while in the group without COVID-19 — just 20%, i.e. significantly less.

The testing of physical health using the SF-36 questionnaire showed the mean value of physical state in the group of the patients with HD and COVID-19 — 46,8±7,5%, and in the patients without COVID-19 — 42,1±3,9%.

The relative decrease in physical state in 6 months was noted in the group of the patients with COVID-19, who initially had the following changes of the laboratory parameters: lower level of ALB (r=0,512), relatively high value of lactate dehydrogenase (LDH) (r=0,342) and relatively increased red blood cell count (r=0,393).

The physical state in the group of the patients with HD and without COVID-19 worsened in relatively low values of the SpO_2 level (r=0,452) and higher values of DAP (r=-0,48).

After the discharge from the hospital during the follow-up period in the group with COVID-19 32% of the patients noted the development of non-complicated HC (p<0,05), that is 2 times larger than in the control group (16%).

SHEs were also a little more frequent (p>0,05) in the group of the patients with HD and COVID-19 (56%) than in the patients with HD and without COVID-19 (47%).

The assessment of the prognostic value of the laboratory parameters in the group with HD and COVID-19 showed that HC occurred more often in those patients who initially had lower platelet count (223,1±62,2*10*9/l) and higher level (450,8±198,5 μg/l) of ferritin than in the patients who did not develop HC (282,4±91,6*10*9/l and 353,7±117,4 μg/l, respectively).

In the group of the patients with HD and COVID-19 in 6 months after the discharge, 50% of the patients took two hypotensive drugs, and 47% had to take 3 drugs. Among the patients with HD and without COVID-19 — 77% took 2 antihypertensive drugs, and just 20% took 3 drugs, i.e. significantly less than after COVID-19. 3% in each group continued to take 1 drug (Figure 1). Compared to the period before the inclusion into the study, 28,6% of the patients of the group with COVID-19 began to take 2-3 more drugs, and 65,1% one more drug. In the control group — 6,7% and 73,3% patients, respectively. Other patients did not change the number of drugs (Figure 2). And almost all the patients said that during last 3 months the basic antihypertensive therapy was not corrected.

Discussion

The performed study was aimed to investigate the prognostic value of the levels of some clinical, laboratory and instrumental parameters in patients with HD after moderate COVID-19. Apart from that, while comparing the features of the clinical parameters in the selected groups after 6-month follow-up period, to a certain extent, we may judge the effect of moderate COVID-19 on the HD course. In general, the studies concerning the monitoring the patients with combination of HD and COVID-19 related to "strict" endpoints during and after the disease [3, 10, 11] or analyzed the problem within Long-COVID, while the present study emphasized the clinical characteristics of the course of HD itself after COVID-19.

In particular, in the group of the patients with HD and COVID-19, we revealed the increase in some laboratory parameters such as ferritin, glucose, potassium, and the decrease in ALB and total protein. The first AP measurement in the group of the patients with HD and COVID-19 showed lower mean value of AP compared to the AP level in the group of the patients without COVID-19 that is quite explainable by the different causes of hospitalization and consultations with doctor. For the main clinical parameters, the groups were comparable.

In six months after COVID-19, the patients with HD more often had the problems with emotional and physical state. We cannot exclude that the presence and absence of these deviations depended on the features of the reaction to COVID-19.

Probably, the disorders we revealed in emotional and physical sphere in 6 months after COVID-19 and associated with that changes in the level of some laboratory and instrumental parameters can be caused by the severity of systemic inflammation in the acute period of infection and its consequences. In particular, this can be indicated by the interrelationship between emotional state in 6 months after the discharge and the changes in such parameters as general level of t° C, PEFR, cholesterol, platelets, GFR in acute phase of the disease. They are the parameters with changes of which the negative tendencies in patients` emotional state were associated. It was described that these parameters react to the power release of pro-inflammatory cytokines in

COVID-19. It is also likely, the worsening of emotional state after COVID-19 during next 6 months is caused by the persistence of autoimmune-mediated dysfunction of the autonomic nervous system, which can play an important role in the disorders of psychoemotional status [10, 11]. We also cannot exclude the association of this with the development of anxiety and depressive disorders which probably may be regarded as the manifestations of Long-COVID, in particular, the changes in the brain work against the background of COVID-19 infection as well as unfavorable symptoms of HC and SHEs.

Besides, we can assume that the changes in physical state in the long-term period are associated with some signs of the liver lesion during COVID-19. [12, 13]. This was evidenced by the relative decrease in the level of ALB, and increase — LDH in patients who developed the worsening of physical state in 6 months after COVID-19.

More significant changes in the platelet count and ferritin level in patients with COVID-19 were subsequently associated with more frequent development of HC. As already noted, these changes in the laboratory parameters may indicate a more active inflammatory process in the acute period of COVID-19 in these patients and probably more severe lesion of significant for HD organs.

In general, the results of the analysis of the clinical characteristics allow us to assume that COVID-19 worsens the course of HD. For example, patients suffered COVID-19, against the background of more intensive therapy, more often developed HC and had a certain tendency to more frequent SHEs than patients who did not have COVID-19. And SHEs were more typical of the patients who developed the crises. Obviously, SHEs are associated with more significant disorder of autoregulation of bloodstream in the internal organs, in particular, brain [8, 14]. Probably, this results in the combination of SHEs and HC in the group of the patients with HD and COVID-19 [8, 15], i.e. these events have the same cause.

In 6 months, the patients with HD and COVID-19 significantly more often took a greater number of drugs. As known, during an acute infection period, the active systemic inflammation causes the lesion of many organs and systems, in particular due to microvascular injury, that aggravates imbalance between the pressor and depressor mechanisms. The latter worsens the course of HD, increases the frequency of HC and as a result requires the taking of greater number of antihypertensive drugs.

Conclusion

In 6 months after moderate COVID-19 patients with HD develop more severe disorders of emotional and physical state that patients after consultation with doctor for HD, who had no COVID-19. These events were revealed to be associated with the parameters reflecting the severity of systemic inflammation, the disorders of the liver function and the changes in the brain work in acute period of COVID-19, such as total cholesterol, platelet count, GFR, ALB, LDH. The latter makes perspective the use of these laboratory parameters as predictors.

The obtained data also indicated that moderate COVID-19 aggravates the course of HD. Among patients with HD during 6 months after COVID-19, the 2 times increase in the frequency of the development of non-complicated HC, a little more frequent SHEs and the requirement of greater number of antihypertensive drugs to control AP were revealed.

Relationships and Activities: none.

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