ORIGINAL ARTICLE

SURGICAL ISCHEMIC ASPECTS OF COVID-19: MANAGEMENT OF PATIENTS WITH COVID TOES AND FINGERS

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Oleksandr Yu. Ioffe[1], Stepan L. Kindzer[1], Mykola S. Kryvopustov[1], Yuri A. Dibrova[1], Yuri P. Tsiura[1], Mykhailo O. Havrylchenko[2], Oleg V. Lobanov[2]

[1] BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

[2] KYIV CITY CLINICAL HOSPITAL №3, KYIV, UKRAINE

ABSTRACT

The aim: Study of clinical manifestations and management of patients with COVID toes and fingers.

Materials and methods: 1,841 patients with laboratory-confirmed SARS-CoV-2 infection were hospitalized. All patients were divided into two groups: without surgical pathology – 1,693 (91.96%) and with surgical pathology (patients with COVID toes and fingers and abdominal syndrome) - 148 (8.04%). The diagnosis of COVID-19 was made on the basis of clinical data, laboratory test results (PCR test for SARS-CoV-2) and computed tomography of the chest. On admission, in addition to the general laboratory tests, mandatory special methods of examination included determination of D-dimer, procalcitonin (PCT), C-reactive protein, and interleukin-6 (IL-6).

Results: Surgical ischemic manifestations were observed in 8.04% of all patients with COVID-19, of which 86.48% presented with ischemic abdominal syndrome and 13.52% with COVID toes and fingers. C-reactive protein and procalcitonin are the markers that may indicate the development of ischemic surgical problems. A direct statistically significant linear correlation was found between the severity of the underlying disease and the mean D-dimer ($r = 0.815$; $p = 0.01$).

Conclusions: The confirmed phenomenon of COVID toes and fingers does not require active surgical tactics. It is necessary to conduct pathogenetic treatment of COVID-19 and dynamic monitoring of its clinical course.

KEY WORDS: COVID-19, phenomenon of COVID toes and fingers

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious condition first diagnosed in humans in December, 2019 in Wuhan (Central China) [1]. The disease began to spread rapidly in China and beyond and very quickly became a pandemic. As of February 14, 2022, 412,213,783 cases of COVID-19 were registered worldwide, including 5,818,108 deaths (COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University) [2].

The actual number of cases undoubtedly far exceeds official statistics. In particular, it can be explained by the asymptomatic course of the disease, inconsistent health-care-seeking behaviour in clinically mild cases, specific characteristics of diagnostic testing in different countries, false-negative virological test results, and incomplete data on COVID-19 cases [3-6].

Signs and symptoms of COVID-19 are quite diverse, but during the course of the disease many people with COVID-19 report fever or chills, cough, shortness of breath, difficulty breathing, fatigue, muscle pain throughout the body, headache, loss of taste and smell, sore throat, nasal congestion or runny nose, nausea or vomiting, and diarrhoea [4].

Dermatological manifestations may also be associated with COVID-19. Their frequency ranges from 0.2% to 20.4%. The clinical picture is diverse, although in a study of 171 patients with laboratory-confirmed COVID-19 (mild to severe), the most common skin manifestations reported were maculopapular rash (22%), discoloration of the fingers and toes (18%), and urticaria (16%). About 60% of all patients with COVID-19 and with any skin manifestations reported fever and / or cough. Assessment of skin manifestations in COVID-19 patients remains difficult because the symptoms may be linked to a variety of other diseases [4].

Some comorbid conditions can cause severe COVID-19. Hypertension and disorders of lipid metabolism are the most common, while obesity, complicated diabetes mellitus and anxiety disorders are the major risk factors for severe COVID-19 [7].

THE AIM

The aim of the work is the study of clinical manifestations and management of patients with COVID toes and fingers.

MATERIALS AND METHODS

On September 1, 2020, a medical center for the treatment of patients with SARS-CoV-2 was opened at the Kyiv

Table I. Distribution of patients with surgical pathology by gender, age and concomitant pathology

	Abdominal syndrome (n=128)	COVID toes and fingers (without concomitant pathology) (n=17)	COVID toes and fingers (with concomitant pathology) (n=3)	Total
Age (min-max)	55,4 ± 6,43 (45 - 67)	31,47 ± 7,21 (22 - 45)	59 ± 7,21 (53 - 67)	52,72 ± 10,07 (22 - 67)
Gender (male/female), abs, %	63 (49,22%) / 65 (50,78%)	8 (47,06%) / 9 (52,94%)	2 (66,67%) / 1 (33,33%)	73 (49,32%) / 75 (50,68%)
Ischemic heart disease, abs, %	111 (86,72%)	0 (0%)	3 (2,34%)	114 (89,06%)
Type 2 diabetes mellitus, abs, %	87 (67,97%)	0 (0%)	3 (2,34%)	90 (70,31%)
Hypertension, abs, %	100 (78,13%)	0 (0%)	1 (0,78%)	101 (78,91%)
Respiratory diseases, abs, %	8 (6,25%)	0 (0%)	0 (0%)	8 (6,25%)
Overweight, abs, %	79 (61,72%)	10 (7,81%)	2 (1,56%)	91 (71,09%)

Table II. Comparison of mean values of specific markers in groups with and without surgical pathology

	Mean value in the group with surgical pathology (excluding severity) (n=148)	Mean value in the group without surgical pathology (excluding severity) (n=1693)	P
Lymphocytes, %	7,02 ± 2,35 (0 - 10)	7,17 ± 2,24 (0 - 11)	0,528
Thrombocytes, x10^9	155,5 ± 16,28 (90 - 170)	156,54 ± 14,72 (92 - 171)	0,637
C-reactive protein, mg / l	48,32 ± 30,93 (6 - 187)	36,72 ± 19,37 (5 - 90)	< 0,001
D-dimer, µg / ml	3,24 ± 2,25 (1 - 8)	3,18 ± 2,22 (1 - 8)	0,787
Procalcitonin, ng / mg	1,15 ± 0,42 (0,5 - 2,1)	0,9 ± 0,49 (0,11 - 1,7)	< 0,001
Interleukin-6, pg / ml	75,99 ± 56,71 (7 - 200)	75,24 ± 61,46 (7 - 203)	0,641

City Clinical Hospital #3. Between September, 2020 and February, 2021, 1,841 patients with laboratory-confirmed SARS-CoV-2 infection were hospitalized. All patients were divided into two groups: without surgical pathology – 1,693 (91.96%) and with surgical pathology (patients with COVID toes and fingers and abdominal syndrome) - 148 (8.04%). Subsequently, these patients were divided into 3 groups: Group I - patients with ischemic syndrome of the upper and lower extremities (COVID toes and fingers) without concomitant pathology - 17 (11.49%), Group II - patients with COVID toes and fingers and with concomitant pathology - 3 (2.03%) and group III - patients with abdominal syndrome - 128 (86.48%), which was clinically manifested by nausea and loose stools, aching pain in the abdomen that was sometimes described as cramping and without clear localization.

Among patients with COVID toes and fingers, 12 patients developed chilblain-like lesions on their toes, whereas 8 patients on their fingers. In our observations, there were no patients with simultaneous affection of their toes and fingers.

For the study of changes in the capillary bed, patients underwent digital computer capillaroscopy using a digital optical capillaroscope "MICROPOTOK" manufactured by CJSC "Engineering Enterprise" POTOK" (Ukraine). Arterial and venous blood flow was investigated by dopplerography of the vessels of the upper and lower extremities using an ultrasound machine MyLab ™ X6 manufactured by Esaote (Italy).

The diagnosis of COVID-19 was made on the basis of clinical data, laboratory test results (PCR test for SARS-CoV-2) and computed tomography of the chest.

On admission, patients complained of severe weakness, difficulty breathing, shortness of breath, fever, loss of taste and smell, muscle aches, severe headache, unexplained anxiety, chest pain, nausea, and abdominal discomfort. In addition to the general laboratory tests, mandatory special methods of examination included determination of D-dimer, procalcitonin (PCT), C-reactive protein, and interleukin-6 (IL-6).

RESULTS

The data in Table I show that patients with surgical pathology could suffer from a very severe concomitant pathology, in particular chronic coronary heart disease, hypertension, type 2 diabetes mellitus, and respiratory diseases. These conditions could be frequently diagnosed simultaneously in one patient. In this case, the frequency of comorbidities did not depend on gender characteristics. The largest group with ischemic syndrome of the upper and lower extremities (COVID fingers and toes) consisted of patients of young age and without concomitant pathology. Patients with abdominal syndrome were not divided into groups depending

Table III. Changes in laboratory findings in COVID-19 patients with surgical pathology depending on the severity of the underlying condition

	Mean value in the group with surgical pathology (moderate condition) (n=74)	Mean value in the group with surgical pathology (severe condition) (n=74)	P
Lymphocytes, %	7,7 ± 1,75 (5 - 10)	6,34 ± 2,67 (0 - 10)	0,021
Thrombocytes, x10^9	160,27 ± 5,79 (150 - 170)	150,73 ± 21,31 (90 - 170)	0,070
C-reactive protein, mg / l	41,09 ± 22,85 (6 - 79)	55,55 ± 36,03 (7 - 187)	0,250
D-dimer, µg / ml	1,53 ± 0,5 (1 - 2)	4,96 ± 2 (2 - 8)	< 0,001
Procalcitonin, ng / mg	0,98 ± 0,4 (0,5 - 1,7)	1,32 ± 0,37 (0,58 - 2,1)	< 0,001
Interleukin-6, pg / ml	27,8 ± 11,9 (7 - 49)	124,18 ± 40,32 (50 - 200)	< 0,001

Table IV. Stages of the development of COVID toes and fingers and their duration

Stages	Onset time (a day)	Average duration (days)
I	1-3	2 ± 0,86
II	4-5	4,5 ± 0,51
III	6 - 17	12,1 ± 3,91
IV	18 - 23	20,9 ± 1,92

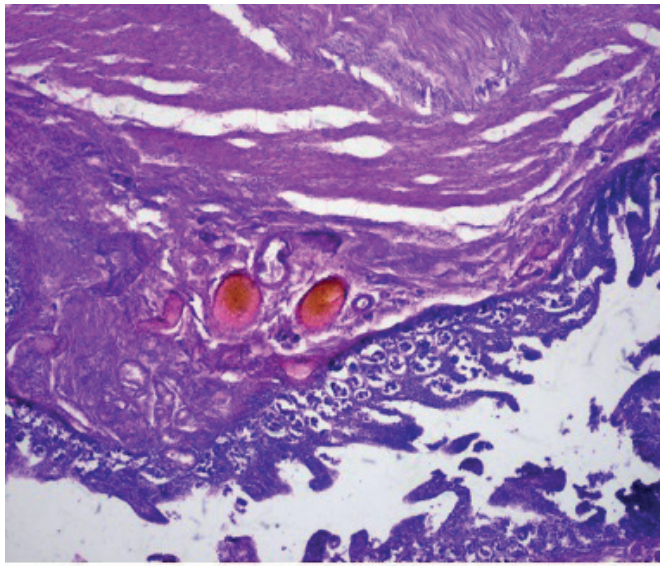

Fig. 1. Patient B., age 67, small intestinal micropreparation, hematoxylin staining with eosin, Leica DM LS2 microscope

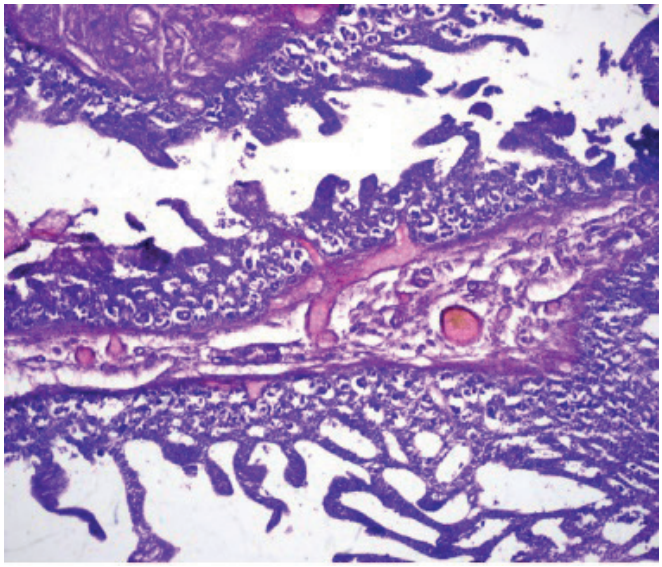

Fig. 2. Patient B., age 67, small intestinal micropreparation, hematoxylin staining with eosin, Leica DM LS2 microscope

on the presence or absence of concomitant pathology, as the latter occurred with the same frequency in all patients with COVID-19 regardless of their age and gender.

For the study of specific markers of surgical pathology in COVID-19 patients, the following quantitative indicators were analyzed: lymphocytes, platelets, C-reactive protein, D-dimer, procalcitonin, and interleukin-6. The mean values of these indicators were compared in groups with and without surgical pathology, without taking into account the severity of the underlying disease (Table II).

For the study of changes in the count of lymphocytes, platelets, C-reactive protein, D-dimer, procalcitonin, and IL-6 in COVID-19 patients with surgical pathology, depending on the severity of the underlying condition, patients were divided into two groups: moderate (n = 74) and severe disease (n = 74). The data are shown in Table III.

The severity of COVID-19 was determined in accordance with the protocol "Provision of medical care for the treatment of coronavirus disease (COVID-19)", approved by the order of the Ministry of Health of Ukraine as of April 2, 2020, №762 (as amended by the Ministry of Health of Ukraine as of September 20, 2021, №1979) [18].

The study of laboratory findings in a group of COVID-19 patients with surgical pathology allowed establishing correlations using Spearman's rank correlation coefficient, given that the distribution of data differed from normal. A direct statistically significant linear correlation between age and severity of the underlying disease (r = 0.495; p = 0.01) was observed. Therefore, age was an important factor

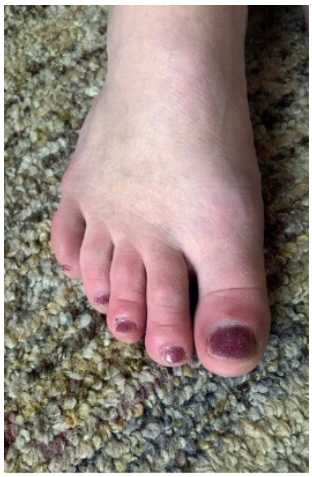

Fig. 3. Patient V., age 47, COVID toes, stage II - "hyperaemia".

Fig. 4. Patient T., age 34, COVID toes of the right foot, stage III - "ischemia".

Fig. 5. Patient T., age 41, COVID fingers of the right hand, stage III - "ischemia".

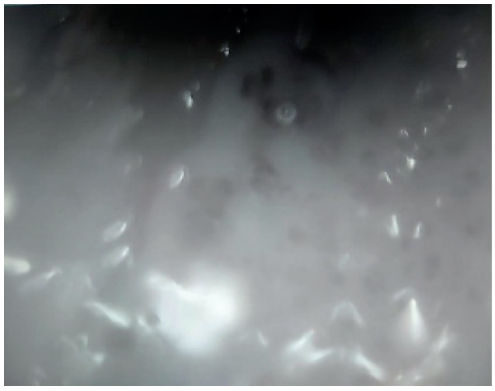

Fig. 6. Patient T., age 34, COVID toes of the right foot, stage IV - reversible changes

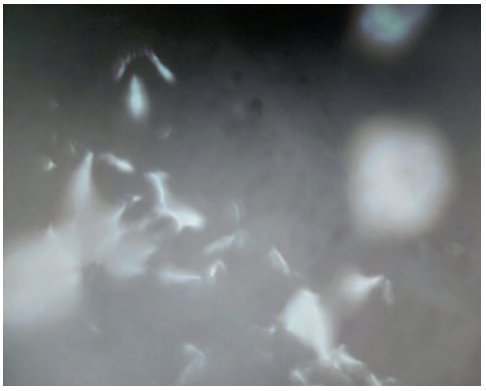

Fig. 7. Patient S., age 38, COVID fingers of the right hand, stage II – "ischemia". Capillaroscopy of the fingers of the hand.

Fig. 8. Patient O., age 31, COVID toes of both feet, stage III - "ischemia". Capillaroscopy of the toes.

contributing to the severity of COVID-19 in this group. A direct statistically significant linear correlation between age and mean D-dimer ($r = 0.475$; $p = 0.01$) was also noted. This correlation appears probably due to the predisposition of elderly patients to increased thrombosis.

The investigation of the relationship between the number of comorbidities and other factors revealed direct statistically significant linear correlations with the severity of the disease ($r = 0.491$; $p = 0.01$), the level of D-dimer ($r = 0.471$; $p = 0.01$), and interleukin-6 ($r = 0.423$; $p = 0.01$). Thus, the more comorbidities were seen the higher those indicators were, as each of them had its negative impact on the course of COVID-19.

The study of the factors associated with the course of COVID-19 in the group of patients with surgical pathology revealed a direct statistically significant linear correlation of the strong relationship between the severity of the underlying disease and the mean value of D-dimer ($r = 0.815$; $p = 0.01$), which could be due to the severity of the inflammatory process, vascular endothelium, including intestinal vessels and the development of thrombosis in them.

Severe inflammatory infiltration of the mucous layer and the presence of focal erosive defects were revealed on histological slides of the small intestinal wall (samples taken during autopsy, the cause of death - respiratory failure) (Fig. 1 and Fig. 2). Swelling and focal growth of connective tissue were also noted along the submucosal layer of the small intestinal wall. Endothelial thickening and vascular thrombosis were observed in a number of fields of view.

In addition, a direct statistically significant linear correlation was found between the severity of the underlying disease and the increase in the mean value of procalcitonin ($r = 0.395$; $p = 0.01$). The latter was due to the development of secondary bacterial infection, which in turn aggravated the course of COVID-19. There was also a statistically significant linear correlation between the severity of the underlying disease and the increased mean value of IL-6 ($r = 0.866$; $p = 0.01$), due to the body's protective response to SARS-CoV-2 and the onset of secondary bacterial infection.

An inverse statistically significant linear correlation was found between the average count of lymphocytes and C-reactive protein ($r = -0.315$; $p = 0.01$). The latter can be explained by the fact that the level of lymphocytes under viral load is reduced, the body's immune response

to inflammation is enhanced and thus increases the rate of C-reactive protein.

The group of COVID-19 patients with COVID toes and fingers included 20 patients (13.5%) without visible hemodynamic disorders of the main blood flow, without concomitant pathology - 17 patients, and with concomitant pathology - 3 patients. According to Doppler data, the main type of blood flow was preserved in all patients.

In our observations of the development of COVID toes and fingers, we identified four stages: I - stage of initial manifestations, II - stage of hyperaemia, III - stage of ischemia, IV - stage of reversible changes (Table IV).

At onset, chilblain-like lesions on the fingers and toes were detected on the 3rd - 5th day after the initial clinical manifestations of COVID-19.

At the first stage, patients noted the appearance of itchy skin on the toes or fingers, burning and tingling sensations in the fingertips. However, there were no visible skin manifestations.

In stage II, burning sensations disappeared, whereas noticeable redness of the skin appeared and the pain was described as persistent, aching or tangling (Fig. 3).

In stage III, bluish discoloration of the skin on the toes or fingers occurred on the dorsal and plantar surfaces of the foot, and some patients presented with skin cyanosis in patches involving the lower third of the shin bone or the forearm (Fig. 4 and Fig. 5).

Loss of skin colour and the disappearance of pain in the fingers and toes were typical for stage IV (Fig. 6). The skin acquired a normal body colour with time.

The analysis of the capillary bed allowed registering the mesotype of the capillary loops on the fingers (n = 8). The study revealed tortuous capillary loops of small caliber with signs of spasm as well as capillary loops of medium caliber that had slightly expanded length and showed tortuosity with "paragraphs" and spiral shapes. The proportion of the capillaries was not reduced. The density of capillary loops was 12-18 capillaries per 1mm^2. Capillary blood flow rate was moderately reduced; the index of capillary tortuosity was 28-32%. Patients had a normocirculatory type of blood flow with elements of deceleration and spastic type of microcirculation (Fig. 7).

The mesotype of capillary loops was registered on the toes (n = 12). Tortuosity of capillaries in the form of paragraphs with signs of a spasm and venular stagnation was also noted. The index of tortuosity of capillaries was 47-48%, and the density of capillary loops was 8-11 capillaries per 1mm^2. Patients had a spastic type of blood flow with signs of stagnation in the microcirculatory tract (Fig. 8).

COVID-19 treatment was administered according to the accepted protocols and depending on the severity of the disease and the presence of concomitant pathology [18].

Identical treatment was prescribed to patients with COVID fingers in both groups (n = 20). Given the nonspecificity of symptoms, the absence of visible skin manifestations in the first stage of the disease, no specific treatment was provided to these patients, except for subcutaneous administration of nadroparin or enoxiparin sodium according to the treatment protocol for COVID-19 [18].

In stage II characterized by the appearance of clinical manifestations of COVID toes and fingers, pentoxifylline infusion at a dose of 600 mg for the group without concomitant pathology (n = 17) and 300 mg for the group with concomitant pathology (n = 3) was administered intravenously daily. Due to its pharmacodynamics and pharmacokinetics, it inhibits the aggregation of platelets and erythrocytes, increases their elasticity, reduces the increased concentration of fibrinogen in blood plasma and enhances fibrinolysis, which reduces its viscosity and improves rheological properties. In addition, pentoxifylline has a myotropic vasodilating effect and reduces the total peripheral vascular resistance and thus improves microcirculation and tissue oxygen supply. The observation of the patients showed that on the 4th or 5th day of the therapy administration, they experienced less pain in their fingers and toes and had less severe skin cyanosis at rest. The course of vascular infusion therapy lasted from 10 to 20 days, depending on the positive response to treatment, which was characterized by less intensive pain on exertion and marbled skin with vague signs of cyanosis. After a course of infusion therapy, patients were transferred to tablet forms of the drug, discharged from the hospital after complete recovery from the underlying disease, and provided with further outpatient follow-up. It should be noted that in the group of patients without concomitant pathology (n = 17) the response to specific treatment was better, the duration of stage III and IV was reduced. In all patients with concomitant pathology, the duration of infusion therapy was 20 days.

In one patient with diabetes mellitus, despite specific treatment, on day 14 (stage III of COVID toes and fingers) the process turned into wet gangrene of the distal part of the foot, which necessitated an amputation of the upper third of the right shin bone. The patient was discharged on the 7th day after surgery with a negative PCR test SARS-CoV-2 and in satisfactory condition for outpatient treatment.

In the group, 1 patient with abdominal syndrome died. The cause of death was the underlying disease.

Therefore, in patients with confirmed COVID-19 and ischemic manifestations on the fingers or toes, it is necessary to use a differentiated approach in view of COVID-19 chilblain-like lesions, which do not require active surgical tactics.

DISCUSSION

In both groups (Table II), there were changes in the leukocyte formula, which were mainly manifested by a sharp decrease in the number of platelets and lymphocytes. This could most likely be due to the viral etiology of the disease and it is consistent with the literature [8, 9, 10, 11, 12]. No statistically significant difference was found (P> 0.05). Both groups demonstrated a significant increase in C-reactive protein, which is characteristic of patients with SARS-CoV-2. In the group of patients with surgical pathology, it was statistically significantly higher than

in the group without surgical pathology (P <0.001). The data obtained are typical for the inflammatory process. In both groups, there was an increase in D-dimer, in some cases up to 8 μg / ml, due to vascular endothelial damage, blood clotting and thrombosis and it is consistent with the literature [13, 14]. No statistically significant difference was found (P> 0.05). In both groups, there was also an increase in procalcitonin, and in the group with surgical pathology, this result was statistically significantly higher (P <0.001), indicating a high risk of the development of secondary bacterial infection concomitant to the underlying condition. The patients had elevated levels of interleukin-6 (IL-6), which may be due to the bodily response to the SARS-CoV-2 virus and it is consistent with the literature [15-17]. No statistically significant difference was found (P> 0.05).

Changes in laboratory findings in COVID-19 patients with surgical pathology depending on the severity of the underlying condition were more significant (Table III). Both groups were characterized by lymphopenia, but it was more pronounced in the group of patients with severe course of the disease and reached proper statistical significance. The obtained data are comparable with the literature data. Thrombocytopenia was observed in both groups of patients, but had no significant statistical differences [8-12]. C-reactive protein was significantly elevated in both groups, despite a higher mean value in the group of patients with severe COVID-19. When compared, its level was not statistically significant, which may be due to insufficient sample of patients. According to other authors, C-reactive protein levels were elevated and correlated with the severity of the disease [19, 20]. The D-dimer index was elevated in both groups, reaching 8 μg / ml in the group with the severe course of the disease, and was statistically significantly different from the group with the moderate course of the underlying disease. We believe that it can be explained by an intensive inflammatory process associated with a massive viral attack of the macroorganism. Elevated levels of procalcitonin in both groups indicated the development of the bacterial infection, and in patients with the severe course of the disease, this parameter was statistically significantly higher.

CONCLUSIONS

1. Surgical ischemic manifestations were observed in 8.04% of all patients with COVID-19, of which 86.48% presented with ischemic abdominal syndrome and 13.52% with COVID toes and fingers.
2. C-reactive protein and procalcitonin are the markers that may indicate the development of ischemic surgical problems. A direct statistically significant linear correlation was found between the severity of the underlying disease and the mean D-dimer (r = 0.815; p = 0.01).
3. The confirmed phenomenon of COVID toes and fingers does not require active surgical tactics. It is necessary to conduct pathogenetic treatment of COVID-19 and dynamic monitoring of its clinical course.

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ORCID and contributionship:
Oleksandr Yu. Ioffe: 0000-0002-1306-7920 [A, F]
Stepan L. Kindzer: 0000-0002-4136-9299 [D]
Mykola S. Kryvopustov: 0000-0003-4978-4873 [C, D]
Yuri A. Dibrova: 0000-0002-2833-1667 [A,E]
Yuri P. Tsiura: 0000-0001-6651-8564 [B]
Mykhailo O. Havrylchenko: 0000-0003-4564-0303 [B]
Oleg V. Lobanov: 0000-0003-1056-0709 [B]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Mykola S. Kryvopustov
Bogomolets National Medical University
13 Taras Shevchenko Boulevard, 01601 Kyiv, Ukraine
tel: +38(066)3916946
e-mail: mykola.kryvopustov@gmail.com

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