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Clinical characteristics of COVID-19 patients with acute peripherial arterial occlusions

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ABSTRACT

Background: Even though arterial occlusions are not as frequent as venous thromboembolisms, they tend to be a serious manifestation of the COVID-19 disease followed with high mortality rate. The main aim of this article is to show that COVID-19 patients with a confirmed acute peripheral arterial occlusion have worse course of the disease and outcomes.

Methods: This study involved patients with acute peripheral arterial occlusion (n=90) treated in a time period from May, 16 2020 to April, 20 2023. The COVID-19 patients with confirmed acute peripheral and the control COVID-19 negative group. These two groups were compared according the course of acute peripheral arterial occlusion and treatment outcomes.

Main findings: In comparison with the COVID-19 negative group, the COVID-19 positive patients were significantly younger and showed significantly higher mortality rate, significantly greater incidence of rethrombosis events and significantly smaller incidence of cardiomyopathy and rhythm abnormalities. The full recovery rate was significantly higher in the control group. COVID patients were, prior to the verification of acute peripheral arterial occlusive events, taking significantly lower molecular weight heparin or some sort of an antithrombotic medication.

Principal conclusions: COVID positive patients have significantly higher rethrombosis rate, worse postoperative outcome and worse final outcome in comparison with the control group.

Key words: COVID-19, acute peripheral arterial occlusion, coagulopathy, thrombosis, thromboembolism

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INTRODUCTION

Virus SARS-CoV-2, which causes COVID-19, infects human cells by bounding with receptor-binding domain i.e. spike protein on human superficial cell receptor angiotensin converting enzyme 2 (ACE-2) (1). Except for respiratory epithelium, ACE-2 receptors are located at other cells like oesophageal cells, small bowel enterocytes, myocites, proximal tubules epithelium, urothelium and also endothelium of arteries and veins (2, 3). Inflammatory cells produce cytotoxic agents such as oxygen radicals which lead cells to death by destruction (4). During infection there is also activation of complement system, in which C3 component of complement has key role for developing acute distress syndrome (5). Altogether mortality of COVID-19 is about 5.6% and there is great variability of a mortality rate between different regions and states (6). Clinical features of COVID-19 are heterogeneous and can have spectrum from asymptomatic individuals to patients with multi organ failure. Incidence of asymptomatic individuals is about 11.9%, although incidence of severe form of disease, according to one other study, is 22.9% (6, 7). American National Institutes of Health recommends classification following severity of illness in categories, based on clinical signs and symptoms, laboratory parameters, radiographic findings, hemodynamic and whole organism function. Most important parameter which determines category of illness severity is arterial blood saturation with oxygen (SpO2) (8). COVID-19 is linked with procoagulation disorders, especially in severe forms of disease. Venous system is affected most commonly than arterial, but both localizations of disorder, far from now, are not usual for some respiratory virus (9). Activation of coagulation cascade and fibrinolytic system inhibition are consequence of extreme inflammation state in COVID-19. Hypoxia, which is part of COVID-19, could be also responsible for thrombosis onset via hypoxia-inducible transcription factors (HIFs) (10). Thromboembolic incidents noticed in COVID-19 patients are: multiorganic microthromboses with consequential organ failure (lungs, kidneys, liver), venous thromboembolisms, pulmonary thromboembolisms, deep venous thromboses, strokes, myocardial infarctions and appearance of thromboembolisms despite thromboprofilaxis (11, 12). One autopsy study on seven cadavers of patients which had COVID-19 and procoagulant state, showed that neither organ have not being spared from thromboembolisms (13). Elderly age is also proven unfavorable factor in the development of thrombosis and thromboembolism in this group of patients, different from pediatric population (14-16). In COVID 19 patients, it is proven thrombotic microangiopathy which includes microvascular thrombosis, microangiopathic hemolytic anemia and thrombocytopenia. Lowered hemoglobin, elevated bilirubin and LDH, lowered haptoglobin and appearance of schistocytes are constituent features of microangiopathy in the COVID-19 (17). Graduate fall of the fibrinogen level, which can be seen in the later phase of the disease, is in the correlation with increased mortality (18). It is great dissent about a question that considers frequency of thromboembolic events connected with COVID-19. Some studies show incidence about 20-30%, but some show incidence even 40-70% (19). Mortality of COVID-19 positive patients with verified arterial thrombosis is estimated about 20% (20). Acute limb ischemia is mainly presented in COVID-19 patients with low number of comorbidities (21). One study shows that COVID-19 patients with arterial thrombosis are older than those with deep venous thrombosis for about 16 years respectively (22). According to the Rutherford classification for ischemia, sources mostly claim that in COVID-19 patients there is IIa and IIb grade of limb ischemia (23,24). Regarding localization of occlusion, study of Goldman at all. show that COVID-19 patients are prone to develop arterial occlusions more proximal on the limb in comparison with COVID-19 negative patients (25). Mortality is higher if conservative therapy was applied, compared

with any kind of intervention, but also risk of amputation is same no matter which method of therapy used (21). Results of one metaanalysis show that appearance of acute limb ischemia is linked with high rate of rethrombosis, low rate of limb salvage and high mortality. Also, there was no difference in rate of limb salvage between COVID-19 positive and COVID-19 negative patients with arterial thrombosis. Final results were same in all patients, no matter of intervention (26). However, COVID positive patients have more serious level of ischemia compared to control group which confirms value of ABI that is 0.05 in COVID positive patients, compared with value of 0.35 in COVID negative group (27). Limited data from the literature is the reason of unknown optimal dosing of antithrombotic medications (28). There are still in the research period which exact factor or factors, influence on the appearance of procoagulant state in COVID-19 patients, thrombotic and thromboembolic incidents. Better knowledge of mechanism and risk factors would contribute in recognition of risk group as well as more effective therapy for those patients. Main aim of this research was to show that COVID-19 patients with proven acute peripheral arterial occlusion have less favorable course and outcome of disease. Additional aim was to contribute to introducing and better understanding COVID-19 and arterial occlusion to optimize therapeutic guidelines in treatment.

MATERIALS AND METHODS

The retrospective cohort study has been conducted Cat the Department of Surgery, Department of Infectiology, and Department of Radiology of the University Hospital in Mostar. The research was approved by the ethics committee of the Medical School University of Mostar.

Patients

The patients with acute peripheral arterial occlusion (n=90) treated in a time period from May, 16 2020 to April, 20 2023 were included in the study. Diagnosis of acute peripheral arterial occlusion was established using clinical, laboratory and radiologic findings. Exclusion criterion was incomplete medical documentation in the observed period. These patients were divided into COVID-19 positive and control COVID-19 negative group. These two groups were compared according the course of acute peripheral arterial occlusion and treatment outcomes.

Methods

Hospitalized patient medical history information and patient lists were used and the following input parameters were used: age, sex, COVID-19 status, COVID-19 disease severity, day of disease at the occurrence of acute peripheral arterial occlusion, date of patient admission, comorbidities and the number of comorbidities (atherosclerosis, arterial hypertension, diabetes mellitus, cardiac rhythm abnormalities, acute myocardial infarction, cardiomyopathy, valvular disease malignancy, COPD, thrombophilia), which were taken at the day of the verification of acute peripheral arterial occlusion. The output parameters were the arterial occlusion severity, determined by the input parameters, and the comparison between the two groups according to the input parameters.

Statistical analysis

Statistical analysis results were expressed with absolute and relative frequencies. The significance of the differences was tested with $\chi 2$ test (Fischer's exact test was used in the absence of anticipated frequencies) and the Student t – test. The statistical analysis results were interpreted with the significance rate of $p < 0.05$. If the p value could not have been expressed up to three decimals, they were expressed as $p < 0.001$. IBM SPSS statistics 21 for Windows (version 26.0, SPSS Inc, Chicago, Illinois, USA) was used for the statistical analysis of the given data.

RESULTS

There were total of 90 patients with acute peripheral arterial occlusion – 22 of them were

COVID-19 positive and 68 of them were COVID-19 negative.

The total sample consisted of more males (n=53) rather than females (n=37). There were significantly more males (n=19) in the COVID-19 positive group. COVID-19 negative patients with acute peripheral arterial occlusion significantly more often experienced complete recovery. COVID-19 positive patients significantly more often experienced rethrombosis. In the COVID-19 positive group, patient death was significantly more often. There were no more significant differences in the parameters between groups (Table 1).

The time of occurrence of the acute peripheral arterial occlusion in the COVID-19 positive group was 13.30 ± 1.91 days from the start of the COVID-19 disease. Patients with history of COVID-19 infection in the COVID-19 negative group experienced the acute peripheral arterial occlusion in 60.75 ± 61.13 days after their COVID-19 infection.

Table 1. Comparison of the clinical characteristics, atherosclerosis, sex distribution and used therapy in relationship with the COVID status

	Group				χ^2	p
	COVID +		COVID -			
	n	%	n	%		
Sex					7.639	0.006
Male	19	86.4	34	50.0		
Female	3	13.6	34	50.0		
Operation outcome					16.087	<0.001
Full recovery	3	13.6	38	55.9		
Amputation	3	13.6	12	17.6		
Other	16	72.7	18	26.5		
Previous atherosclerosis	15	68.2	55	80.9	0.903	0.342*
Type of occlusion					0.567	0.918*
Thromboembolism	12	54.5	34	50.0		
Thrombosis	10	45.5	31	45.6		
Trauma	0	0	3	4.4		
Therapy					7.844	0.058*
Embolectomy	11	50.0	48	70.6		
Conservative therapy with low molecular weight heparin	11	50.0	13	19.1		
Amputation	0	0	4	5.9		
Endovascular procedure	0	0	2	2.9		
By-pass	0	0	1	1.5		
Rethrombosis					24.533	<0.001
Rethrombosis positive	9	40.9	8	11.8		
Rethrombosis negative	6	27.3	57	83.8		
Unknown	7	31.8	3	4.4		
Localisation					0.578	0.447
Upper limb	8	36.4	17	25.0		
Lower limb	14	63.6	51	75.0		
Outcome					27.982	<0.001
Survival	4	18.2	56	82.4		
Death within 10 days	18	81.8	12	17.6		

*Fisher's exact test

Table 2. Differences in comorbidities and used drugs in relationship with the COVID status

	Group				χ^2	p
	COVID +		COVID -			
	n	%	n	%		
Arterial hypertension	14	63.6	57	83.8	2.946	0.069*
Diabetes mellitus	9	40.9	19	27.9	0.769	0.380
Cardiomyopathy					6.224	0.032*
Positive	3	13.6	28	41.2		
Negative	17	77.3	37	54.4		
Unknown	2	9.1	3	4.4		
Cardiac rhythm abnormalities					7.961	0.027*
Positive	2	9.1	23	33.8		
Electrostimulator present	1	4.5	0	0		
Negative	18	81.8	40	58.8		
Unknown	1	4.5	5	7.4		
Acute myocardial infarction	1	4.5	3	4.4	0	1*
Valvular diseases					4.104	0.138*
Positive	0	0	10	14.7		
Negative	22	100.0	56	82.4		
Unknown	0	0	2	2.9		
Malignancy	0	0	8	1.8	1.574	0.210*
COPD	3	13.6	6	8.8	0.060	0.806*
Thrombophilia	0	0	2	2.9	0	1*
Acetylsalicylic acid	8	36.4	22	32.4	0.008	0.931
Rivaroxaban	2	9.1	4	5.9	0.001	0.632*
Clopidogrel	0	0	3	4.4	0.102	0.750*
Low molecular weight heparin	14	63.6	7	10.3	23.541	<0.001

*Fisher's exact test

Cardiomyopathy and cardiac rhythm abnormalities were significantly less often in COVID-19 positive patients, however with the other comorbidities there was not any significant difference between groups. Low molecular weight heparin was significantly more used with the COVID-19 positive patients and generally any antithrombocitic agent before the verification of acute peripheral arterial occlusion (Table 2).

The highest incidence of acute peripheral arterial occlusions was in 2021 with significantly more often cases in the COVID-19 positive patient group (Figure 1).

The probability of death in COVID-19 positive patients with acute peripheral arterial occlusion was bigger than the COVID-19 negative patients (OR = 0.048; 95% CI = 0.014-0.166) (Table 3).

The probability of death in patients who previously used low molecular weight heparin is less than the patients who did not use low molecular weight heparin (OR = 0.080, 95% CI = 0.025-0.255) (Table 4).

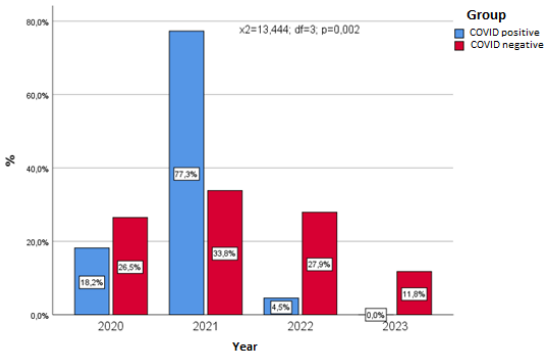

Figure 1. Timeline distribution of patients with acute peripheral arterial occlusion based on COVID status

Table 3. Risk ratio for outcome in relationship with COVID status

Outcome	Group			
	COVID +		COVID -	
	n	%	n	%
Survival	4	18.2	56	82.4
Death within 10 days	18	81.8	12	17.6

Table 4. Relation of outcome and previous therapy with low molecular weight heparin

Outcome	Low molecular weight heparin			
	used		not used	
	n	%	n	%
Survival	5	23.8	55	79.7
Death within 10 days	16	76.2	14	20.3

DISCUSSION

In this study, it was found that certain clinical characteristics of COVID-positive patients with acute peripheral arterial occlusion were less favorable compared to the control group, namely the outcome of surgery and the rate of thromboembolism. The final outcome of COVID-positive patients with acute peripheral arterial occlusion was worse compared with the control group, which was in accordance with the hypothesis.

As for demographic characteristics, some studies stated that there was no statistically significant difference in age and gender among the examined groups, which was not in accordance with my result (29,30). On the other hand, research showed that acute limb ischemia in the composition of COVID was more common in men with shares of 76-78.4% (21, 23, 31). It is possible that there are sex-specific clotting patterns that lead to a different distribution of occlusion between the sexes (32).

Galyfos et al stated that the median age of patients with acute limb occlusion in COVID-19 was 61.6, which is a slightly lower value compared to the result of this study (21). A more similar result to this research is shown by Pham and colleagues with a median age of 65 years in the COVID positive group, but without a significant difference between the groups (29).

Acute limb ischemia caused by thrombosis and thromboembolism appeared between 6.6. and 15.77 days of hospital treatment for COVID-19, which was consistent with the results of this study (22, 30, 31). However, post-COVID patients experienced an occlusion incident almost two months after the verification of COVID-19. It is still not clear why there is a time lag from the onset of infection to the verification of occlusion. The connection between the severity of the COVID infection and the moment of occurrence of the occlusion has also not been confirmed.

All found studies stated that occlusion is more common in the lower than in the upper extremities, regardless of whether it was a case of COVID patients or not, which is in accordance with the obtained results (21, 30, 33). Ilonzo et al cited the femoropopliteal segment as the most common region in COVID-positive patients with occlusion (24).

There was a large divergence in research regarding the frequency of comorbidities among COVID positive and negative patients with occlusion. Predenciuc et al showed that arterial hypertension, chronic ischemic heart disease, chronic obstructive pulmonary disease, and malignant diseases were more common in COVID-negative patients, and diabetes was more common in COVID-positive patients (29). De Athayde Soares et al showed that arrhythmias were less common in COVID-positive patients compared to the COVID-negative group with acute peripheral arterial occlusions, while there was no significant difference for other comorbidities (27). Predenciuc and colleagues also stated that COVID-positive patients with occlusion more often had diabetes, while atrial fibrillation is more common in COVID-negative patients. There was no difference between the two groups in the frequency of renal failure, ischemic heart disease, hypertension and anemia (30). From previous research, it can be concluded that diabetes occurred more often in COVID-positive patients, while rhythm disorders occurred more often in COVID-negative patients, but the results for arterial hypertension were contradictory. Compared to the above, the results of this study showed that rhythm disorders and cardiomyopathy were less common in COVID-positive patients. Rhythm disorders, as a rarer comorbidity in the COVID-positive group, would favor

thrombosis as the main type of occlusion; however, the results of this study showed that the majority of occlusions in both groups were caused by thromboembolism.

Research by de Athadye and colleagues showed that the most common type of occlusion was thrombosis in both observed groups, while Predenciuc et al showed that thromboembolism was the main type of occlusion in COVID-negative patients, and thrombosis in COVID-positive patients (27,30). In another meta-analysis, Jain et al., along with Predenciucic et al., stated that there was no difference in the rate of limb salvage between COVID-positive and negative patients with occlusion (26,30). The results of this research did not give a clear insight into how many patients experienced a complete recovery after revascularization, because a little more than half of those operated on in the COVID-negative group experienced a complete recovery of circulation, while we mostly had no insight into the state of circulation in the COVID-positive patients.

Jain et al showed that rethrombosis, as a complication of treatment, occurred more often in COVID-positive patients with occlusion, which was in line with our results (26). Zuin et al stated that the incidence of thrombotic and thromboembolic incidents remained elevated even months after being negative for COVID-19, although not to the same extent as in the phase of active disease (34).

As for the final outcome, all the found studies showed the same thing, namely that COVID patients with occlusion have a significantly higher mortality compared to COVID negative patients with occlusion, which is consistent with the results of this work (26, 27, 29, 30). The fact is that the COVID-19 pandemic disrupted the logistics of medical care as well as the speed of providing medical services, especially at the beginning of the pandemic. Sekar et al reported a significant time lag in providing medical treatment for COVID-positive patients with occlusion (35). However, Predenciuc showed that COVID-positive patients with occlusion were treated twice as quickly compared to the COVID-negative population with occlusion (30). A possible reason was that COVID patients were already hospitalized at the time of occlusion, so vascular treatment was more readily available. Certainly, the time span from the onset of the disease to the provision of treatment was one of the more important factors for the final outcome, and it would be important to consider this information when explaining the results of the final outcome of the patients in this research. However, this paper did not consider such data. Therefore, it would be useful in the future to compare the final outcome of patients with the speed of providing medical treatment depending on their COVID status. According to Predenciuc et al, the treatment modalities did not differ statistically significantly between the groups, which was in line with my result, but in that study, unfractionated heparin and low molecular weight heparin were used more often postoperatively than in COVID-negative patients with occlusion (30).

Regarding chronic therapy before the onset of the disease, Pham et al showed that COVID-negative patients were more often previously treated with aspirin, atorvastatin, ACE inhibitors and beta blockers (29). It is interesting to note that in our study, the COVID patients, who were more often on prophylactic therapy with low molecular weight heparin, which is indicated for these patients according to the guidelines, nevertheless developed a thrombotic incident. Research by Han et al shows that there is a significant lack of antithrombin in COVID-positive patients compared to the control group (36). As the mechanism of action of heparin requires antithrombin III to achieve an anticoagulant effect, such reduced values indicate the ineffectiveness of heparin in these patients and the occurrence of thrombotic incidents despite thromboprophylaxis (37).

This study showed a decline in acute limb ischemia incidence from 2021 to 2023 in COVID-19 positive patients which can be

explained by the gradual development of acquired immunity to the COVID-19 virus. Therefore, possible COVID-19 reinfections may be accompanied with a lower systemic inflammatory reaction, which acts as a catalyzer for clot formation, and consequently there may be a lower chance for acute arterial occlusions in the COVID-19 positive group, but this yet has to be proven.

This study had its limitations. There was no complete insight into the overall recovery of the patient. The most common reasons for this are early postoperative mortality and transport to another institution. The examined sample was not large, so the representativeness of the results can be questioned. We should not forget that in the overall population there were certainly those patients who were not diagnosed with arterial occlusion, for example in patients who refused hospitalization, terminal non-hospitalized patients and even asymptomatic COVID-positive individuals. At the time of writing this paper, a large amount of research has already been done on the topic of COVID-19 and its clinical features, but there are not so many meta-analyses and systematic reviews on the topic of rarer manifestations such as acute peripheral arterial occlusions. There are relatively few works that compare the characteristics of COVID-positive and negative patients with occlusion; therefore, it would be desirable to conduct quantitatively and qualitatively larger studies for a better understanding of the mentioned subject. It would also be possible to compare the vaccination status and subtype of SARS-CoV-2 to the frequency of occlusions and the outcome of treatment in the composition of the COVID-19 infection. As other sources show the inconsistency of accompanying comorbidities of the studied group, future research could focus on discovering the causes of such a distribution of comorbidities. Due to the significant mortality in the studied group, the focus should be on discovering and establishing more optimal therapy in these patients.

CONCLUSION

In conclusion, we can say that COVID-positive patients with acute peripheral arterial occlusion had less favorable clinical characteristics, the occurrence of thromboembolism and the outcome of surgery. Cardiomyopathy and rhythm disorders were less common in this group. Low-molecular-weight heparin was more often taken before the occlusive incident in COVID-positive patients. The final outcome of the disease was less favorable in COVID-19 positive patients compared to the control group.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS
DR: Conceptualization, Data curation, Investigation, Visualization, Writing – original draft. PR: Conceptualization, Methodology, Project administration, Supervision. MM: Validation, Writing – review & editing.

ETHICAL BACKGROUND

Institutional review board statement: This retrospective study was conducted according to all ethical principles at the University Clinical Hospital Mostar. This study was approved by the Ethics Committee of the School of Medicine, University of Mostar and valid documentation exists for this matter (number 01-I-894/23), from May, 26th 2023.
Informed consent statement: Informed consent was obtained from all subjects involved in the study.
Data availability statement: We deny any restrictions on the availability of data, materials and associated protocols.

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