ORIGINAL ARTICLE

Can laboratory and clinical parameters predict the occurrence of acute arterial occlusion in COVID-19 patients?

Kristian Karlović[1], Gojko Bogdan[1], Pejana Rastović[2], Martin Kajić[2]

[1]Department of Radiology, [2]Department of Surgery; University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina

ABSTRACT

Aim To determine radiologic, clinic and laboratory characteristics of COVID-19 positive patients with acute arterial occlusion and compare them with post COVID-19 and non-COVID-19 patients.

Methods In this retrospective study, 53 patients with acute occlusion of peripheral arteries admitted to the University Clinical Hospital Mostar in the period between 29 February 2020 and 30 September 2021 were involved. The first group was made of COVID-19 positive patients, the second group were post COVID-19 patients and a control group were non-COVID-19 patients.

Results Most patients were males, 37 (69.8%). The average age of COVID positive patients was 66.09±11.25 years, post COVID-19 patients 71.33±5.22 years and COVID-19 negative patients 69.82±1.99 years. Lower extremities were most affected, 38 (71.6%), without significant alteration in the coagulogram. Acute arterial occlusion occurred about 2 weeks after the beginning of COVID-19 or at the time of the first appearance of symptoms.

Conclusion We have to take special care about patients with risk factors for developing acute arterial occlusion due to thromboembolism or thrombosis 10 days after the beginning of the disease. We also recommend the use of low molecular weight heparin (LMWH) and monitoring coagulation state due to anti Xa and thromboelastometry.

Key words: angiography, coronavirus, heparin, thromboembolism

Corresponding author:
Kristian Karlović
[1]Department of Radiology,
University Clinical Hospital Mostar
Bijeli brijeg bb 88000 Mostar,
Bosnia and Herzegovina
Phone: +387 63 247 825;
Fax: +387 36 341 966;
E-mail: kristiankarlovic@live.com
ORCID ID: https://orcid.org/0000-0002-4149-6773

Original submission:
26 July 2022;
Revised submission:
11 August 2022;
Accepted:
10 December 2022
doi: 10.17392/1520-22

Med Glas (Zenica) 2023; 20(1): 32-37

INTRODUCTION

The clinical feature of the COVID-19 infection is dominated by bilateral pneumonia, often with a severe form and the development of respiratory failure, sometimes dependent on mechanical support (1). The disease has been named COVID-19 according to the World Health Organisation (WHO) (2). Except for pneumonia, SARS-CoV-2 has been associated with procoagulation incidents, especially in patients with severe COVID-19. The venous system is more frequently affected than arterial, but both systems are atypical for developing such complications after the infection with some respiratory virus (3). Most patients who died of COVID-19 had elevated D-dimers and fulfilled the criteria for diagnosing disseminated intravascular coagulopathy. Because of that, soon after the coagulation disorder had been noticed and connected with COVID-19, a need for some therapeutic solutions and diagnostic management occurred (4). COVID-19, among others, provokes inflammatory reaction which, along with complex mechanisms, affects blood coagulation, even due to prothrombotic state in some cases (5). This coagulopathy results in numerous pulmonary embolisms (PE), deep venous thromboses (DVT), and acute arterial occlusions because of thrombosis or thromboembolism (5,6). In the Klock et al. study among 184 patients with COVID-19 in the Intensive Care Unit (ICU), 57 (31%) had some thrombotic or thromboembolic incident, in which pulmonary embolism predominated; also, all patients were on high doses of heparin (6). A new entity has been described as COVID-19 associated coagulopathy (CAC), which is different from other kinds of coagulopathies, sepsis-induced coagulopathy (SIC) or disseminated intravascular coagulopathy (DIC); it is indicative by elevated D-dimers, while other parameters of coagulation are mildly disturbed (7). Understanding pathophysiology, monitoring and modification of coagulation is necessary for therapeutic purposes in order to maintain homeostasis (8). It has been shown that the use of low molecular weight heparin (LMWH) has positive impact in the treatment of COVID-19 patients, which significantly reduces mortality and thromboembolic incidents (9). In a study by Tang et al, severe clinical form patients with COVID-19 were examined and divided by sepsis-induced coagulopathy (SIC) score; further analysis showed that those who had received heparin in any form had lower mortality rates contrary to those who had not received heparin (9).

By identifying patients with COVID-19 who are at risk of thrombosis or thromboembolism, we could take timely diagnostic and therapeutic action, thereby reducing morbidity and mortality. The aim of this study was to determine clinical and laboratory characteristics of COVID-19 patients with arterial thrombosis or thromboembolism and to evaluate whether the obtained results can be used to predict the occurrence of such an incident.

PATIENTS AND METHODS

Patients and study design

In total, 53 patients from the University Hospital Centre (UHC) Mostar participated in this study. All patients were admitted in the period between 29 February 2020 and 30 September 2021, and all had acute occlusions of peripheral arteries caused by thrombosis or thromboembolism, confirmed with multi-slice computed tomography (MSCT) angiography.

An informed consent was obtained from all patients. The Ethical Committee of the UHC Mostar approved this study.

The patients were divided in three groups: COVID positive patients - those who had positive PCR test and active COVID-19, post COVID-19 patients - those who had overcome COVID-19 and COVID-19 negative patients – those without proof of active COVID-19.

Methods

Clinical data, general data, days since the start of the COVID-19 disease, when thromboembolism appeared and laboratory parameters were taken for every patient from the day when thromboembolism appeared. Laboratory results included a count of platelets (reference value 158-454x10^9/L), prothrombin time (PT) (reference value 7.7-9.7 s), thrombin time (TT) (reference value 14-21 s), activated thromboplastin time (aPTT) (reference value 23-32 s), international normalised ratio (INR) (reference value 0-1.1), fibrinogen concentration (reference value 1.8-3.5 g/L), and D-dimers concentration (reference value <0.50 mg/L). Blood tests were analysed in the Institute for Laboratory Diagnostics of UHC Mostar.

Statistical analysis

Data were presented as mean and standard deviation, mean and interquartile range, number and percentage. Student T test, $\chi 2$, ANOVA and Kruskal Wallis test were used. A $p<0.05$ was considered statistically significant.

RESULTS

Most patients were males, 37 (69.8%), and 16 (30.2%) were females (p=0.004).

Out of all 53 examined patients, 22 (41.5%) were SARS-CoV-2 positive and had active COVID-19, nine (17%) were post-COVID patients with overcoming disease, and 22 (41%) without proof of active COVID-19 considered as COVID-19 negative.

There were statistically more male than female patients in the group of COVID-19 positive patients, 20 (91%) versus two (9%), respectively (p=0.009).

The average age of COVID-19 positive patients was 66.09±11.25 years, post COVID-9 patients 71.33±5.22 years and COVID-19 negative patients 69.82±1.99 years (p=0.687).-Females in the COVID-19 positive group were slightly older than males (p=0.072).

The highest number of patients had thromboembolism of lower extremities, although in the group of COVID-19 positive there was a noticeable thromboembolism of upper extremities, but without statistical significance (p=0.343) (Table 1).

In the group of COVID-19 positive patients, thromboembolism occurred after 13±2 days of the disease (in average); the earliest incident was recorded 9 days after the disease and the latest one after 18 days.

In the group of post COVID-19 patients, thromboembolism occurred after 65 days (in average) with outstanding variability: the earliest incident happened after 19 days from the beginning of the disease and the latest one 180 days after the beginning of COVID-19.

Most patients had atherosclerosis according to the radiology diagnostic, 40 (75.5%) (p<0.001).

Regarding the therapy that affects blood clotting, patients with COVID-19 and post COVID-19 were mostly under therapy at the time of the thromboembolic incident for a longer period of time in contrast to patients without COVID-19 (Table 1).

Frequency of the intake of some medicines, which affect blood clotting and also the distribution and comparison regarding to the groups, showed that 14 (out of 22) COVID positive patients received LMWH in the therapy (p=0.000) (Table 3).

Table 1. Localization of thromboembolism and intake of drugs which affects blood clotting in the moment of thromboembolism with regard to group participation

Variable	No (%) of patients in the group			
	COVID positive	Post COVID	COVID negative	Total
Localization				
Upper limb	8 (15.09)	2 (3.77)	4 (7.54)	14 (26.41)
Lower limb	13 (24.52)	7 (13.2)	18 (33.96)	38 (71.69)
Visceral branch of aorta	1 (1.88)	0	0	1 (1.88)
Therapy				
YES	16 (30.18)	6 (11.32)	7 (13.2)	29 (54.7)
NO	6 (11.32)	3 (5.66)	15 (28.3)	22 (41.5)
Total	22 (41.5)	9 (16.9)	22 (41.5)	53 (100)

Table 2. Intake of some drugs which affect blood clotting in the moment of thromboembolism in standard doses once per day

Drug	YES/NO	No (%) of patients in the group			p
		COVID Positive (22)	Post COVID (9)	COVID Negative (22)	
Acetyl salicylic acid 100 mg	YES	8 (15.09)	2 (3.77)	6 (11.32)	0.685
	NO	14 (26.4)	7 (13.2)	16 (30.18)	
Rivaroxaban 20 mg	YES	1 (1.88)	3 (5.66)	0	0.005
	NO	21(39.62)	6 (11.32)	22 (41.5)	
Clopidogrel 75 mg	YES	0	1 (1.88)	0	0.083
	NO	22 (41.5)	8 (15.09)	22 (41.5)	
LMWH 0.6 mL	YES	14 (26.4)	3 (5.66)	1 (1.88)	0.000
	NO	8 (15.09)	6 (11.32)	21 (39.62)	

LMWH, Low molecule weight heparin;

Table 3. Average laboratory values of platelets, fibrinogen, D-dimers and coagulogram with regard to the group

Variable	Reference value	Mean±standard deviation			p
		COVID 19 positive	Post COVID 19	COVID 19 negative	
Platelet (x109 /L)	158-454	221.09±94.23	236.78±68.71	246.55±92.60	0.655
D-dimers mg/L	<0.50	3.39±1 56	2.82±1.46	3.27±1.20	0.428
Fibrinogen (g/L)	1.8-3.5	3.88±1.33	4.24±1.76	4.22±0.94	0.689
aPTT (seconds)	23-32	29.98±3.96	27.78±4.24	28.30±3.84	0.306
PT (seconds)	7.7-9.7	10.37±1.66	10.30±0.95	9.15±0.66	0.005
TT (seconds)	14-21	1787±6.34	17.48±2.08	20.09±15.63	0.799
INR (ratio)	0-1.1	1.21±0.19	1.19±0.10	1.07±0.08	0.010

aPTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; INR, international normalized ratio;

The lowest values of TT were in the group of COVID-19 negative, and highest were in the group of COVID-19 positive patients. The highest INR was in the group of COVID-19 positive patients, and the lowest in the group of COVID-19 negative patients (Table 4).

Table 4. Average values of coagulation parameters between the groups of COVID-19 positive and post COVID-19 according to the low molecular weight heparin (LMWH) intake

Variable (Reference value)	COVID status	Mean±standard deviation		p
		LMWH intake	Without LMWH intake	
Platelet (x109 /L) (158-454)	COVID positive	192.36±82.75	271.38±96.85	0.05
	Post COVID	185.67±73.11	262.33±55.37	0.11
D-dimers (mg/L) (<0.50)	COVID positive	3.07±1.83	3.85±1.02	0.32
	Post COVID	3.51±0.92	1.78±1.81	0.23
Fibrinogen (g/L) (1.8-3.5)	COVID positive	4.06±1.36	3.61±1.32	0.50
	Post COVID	3.43±2.88	4.65±1.51	0.36
aPTT (seconds) (23-32)	COVID positive	30.21±3.75	29.65±4.52	0.78
	Post COVID	27.86±3.65	27.75±4.85	0.97
PT (seconds) (7.7-9.7)	COVID positive	10.59±1.85	10.08±1.42	0.53
	Post COVID	10.60±1.01	10.15±0.98	0.54
TT (seconds) (14-21)	COVID positive	15.1±6.91	21.04±4.03	0.06
	Post COVID	18.76±3.26	16.72±0.59	0.20
INR (ratio)	COVID positive	1.22±0.21	1.19±0.16	0.73
	Post COVID	1.21±0.12	1.18±0.1	0.71

aPTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; INR, international normalized ratio,

DISCUSSION

According to this study, predomination of males is noticeable, especially in groups linked to COVID-19, while in the group without COVID-19 there was no difference in gender distribution. These results are similar with other studies (6, 10-12). Therefore, male gender can be considered a risk factor for developing procoagulation state in COVID-19 positive patients and consequent development of thromboembolism (10-12).

Although SARS-CoV-2 can infect people regardless of their age, the development of COVID-19, severity of clinical picture and presence of complications are linked to older age (12). In the context of thromboembolism, older age has shown to be an unfavourable factor (13). The main reasons are, among others, the weakness of the immune system, and often comorbidities such as atherosclerosis, hypertension, diabetes mellitus, etc. (12-14). The average age of our patients with active COVID-19 was 64.25 years, which is very close to the results of our neighbour Italy, where the average age was 66 years, and also male gender was more frequent (14).

Because of the appearance of procoagulation state in COVID-19 positive patients, acute thrombosis and thromboembolisms are very common despite of the use of different medicines that influence blood clot forming such as LMWH (15). Pulmonary emboli predominate as complications in up to 30% of cases, followed by venous thrombosis (16). Di Minno et al. reported the prevalence of venous thromboembolism 24.3-39.2%, whereas the prevalence of arterial thrombosis was 4.4% (16). The prevalence of patients with arterial incidents was low, but the total infected population was not negligible because of high mortality (15,16).

In the beginning, arterial thromboembolisms were presented as case reports, especially because of unusual localizations (17), but as time went on, they began to be considered as expected complication of COVID-19. The appearance of arterial thromboembolism in COVID-19 patients is, unfortunately, a sign predicting lethal outcome (17,18).

Perhaps the most significant result of our study is the identification of the period when thromboembolic incident most often occurred: in the group of COVID-19 positive patients, arterial thromboembolism occurred about 13 days from the beginning of the disease, and earliest at day 9. Gonzalez-Fajardo et al. (18) stated that arterial thromboembolism appears (in average) after 15.77 days of hospitalization, which is similar to our results. This fact implicates that one should be very alert in the period of 2 weeks from the beginning of COVID-19 and pay attention to clinical signs of circulatory insufficiency and according to the findings, make prompt diagnostics. The patients with COVID-19 in the intensive care unit (ICU) with impaired consciousness are the primary vulnerable group that happens due to the severity of the underlying disease, which is also due to the inability to communicate and be timely alert of the symptoms (18). Despite the recovery of COVID-19, the risk of thromboembolic incidents does not subside. Although not as high in incidence as during the disease, thromboembolic incidents threaten for up to several months after the negative test. They also occur despite the prophylaxis used (19).

Although more than half of the patients with COVID-19 and post COVID-19 from our study were taking a drug that affects blood clotting, in con-

trast to COVID-19 negative patients, thromboembolic incidents certainly occurred, and blood clotting monitoring parameters were not significantly altered (20).

Platelets were significantly lowered in the group of COVID-19 positive patients, and two-thirds of patients were on a therapeutic dose of LMWH for a long period. In this case, maybe we can talk about an impact of LMWH on platelets. However, if we want to discuss heparin induced thrombocytopenia (HIT) as an entity which can be responsible for paradox appearance of clots, we point out that literature adverts to such incidents in a low percentage (21). In addition, the occurrence of HIT has been associated with the use of unfractionated heparin, while in this study everyone received LWMH (22).

Only slightly modified values of PT and INR were found, which are known as measures of extrinsic pathway, and their elevated values should manifest reduced coagulability of blood. However, this finding is also possible because of the consumption of coagulation factors, and they were measured on the day when the thromboembolic incident happened (20). D-dimers were elevated in every of the three examined groups, in the group of COVID-19 positive patients, the lowest values were recorded in comparison with the other two. We have obtained similar results with fibrinogen, too. In a meta-analysis of Bao et al. who investigated differences in laboratory findings between severe and non-severe patients with COVID-19, there where disorders in coagulogram that were obvious in the first examined group; the author claimed that some disturbances in laboratory findings can predict the progress of COVID-19 (20).

Therefore, the coagulation findings obtained in this study, especially with the administration of therapy, do not indicate the risk of thromboembolic incidents. Administrated medicines, though, do not change the coagulogram significantly, so for monitoring of coagulation, measurements which can represent the effect of LMWH, such as anti-Xa or rotational thromboelastometry should be introduced (23,24).

In conclusion, attention should be paid to COVID-19 patients, especially hospitalized in the ICU about 10 days from the onset of the disease in terms of early detection and the treatment of thrombosis and thromboembolism. For this purpose, we suggest the use of thromboelastometry parameters, as well as faster radiological diagnostic tool, such as colour doppler ultrasound. Early diagnosis, as well as the treatment of these incidents, may increase the overall survival of COVID-19 positive patients.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506.
2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report– 26, February 15, 2020. https://www.who.int/docs/default-source/coronaviruse/ situation-reports/20200215-sitrep-26-covid-19.pdf? sfvrsn=a4cc6787_2. (28 March 2020).
3. Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis. Thromb Res 2020; 196:27-30.
4. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2020: a pooled analysis. ThrombHaemost 2020; 120:876-8.
5. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol 2021; 113:45-57.
6. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191:145-7.
7. Pawlowski C, Wagner T, Puranik A, Murugadoss K, Loscalzo L, Venkatakrishnan AJ, Pruthi RK, Houghton DE, O'Horo JC, Morice WG 2nd, Williams AW, Gores GJ, Halamka J, Badley AD, Barnathan ES, Makimura H, Khan N, Soundararajan V. Inference from longitudinal laboratory tests characterizes temporal evolution of COVID-19-associated coagulopathy (CAC). Elife 2020; 9:e59209.
8. Levy JH, Koster A, Quinones QJ, Milling TJ, Key NS. Antifibrinolytic therapy and perioperative considerations. Anesthesiology 2018; 128:657-70.

9. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 2020; 18:1094-9.
10. Naqvi IH, Alam MT, Rehan M, Mahmood K, Aurangzeb M, Talib A. COVID-19-associated coagulopathy and thromboembolism: determination of their patterns and risk factors as predictors of mortality among severe COVID-19 patients. Curr Vasc Pharmacol 2022; 20:77-86.
11. Su W, Qiu Z, Zhou L, Hou J, Wang Y, Huang F, Zhang Y, Jia Y, Zhou J, Liu D, Xia Z, Xia ZY, Lei S. Sex differences in clinical characteristics and risk factors for mortality among severe patients with COVID-19: a retrospective study. Aging (Albany NY) 2020; 12:18833-43.
12. Ya'qoub L, Elgendy IY, Pepine CJ. Sex and gender differences in COVID-19: More to be learned! Am Heart J Plus 2021; 3:100011.
13. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY) 2020; 12:9959-81.
14. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT, Barco S; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020; 191:9-14.
15. Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J, Ogeng'o J. Arterial Thrombosis in Coronavirus Disease 2019 Patients: A rapid systematic review. Ann Vasc Surg 2021; 70:273-81.
16. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. Semin Thromb Hemost 2020; 46:763-71.
17. Garg K, Barfield ME, Pezold ML, Sadek M, Cayne NS, Lugo J, Maldonado TS, Berland TL, Rockman CB, Jacobowitz GR. Arterial thromboembolism associated with COVID-19 and elevated D-dimer levels. J VascSurg Cases Innov Tech 2020; 6:348-51.
18. Gonzalez-Fajardo JA, Ansuategui M, Romero C, Comanges A, Gómez-Arbeláez D, Ibarra G, Garcia-Gutierrez A. Mortality of covid-19 patients with vascular thrombotic complications. Med Clin (Barc) 2021; 156:112-17.
19. Zuin M, Rigatelli G, Zuliani G, Roncon L. The risk of thrombosis after acute-COVID-19 infection. QJM 2021;114:619-20.
20. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clin Chim Acta 2020; 509:180-94.
21. Lovecchio F. Heparin-induced thrombocytopenia. ClinToxicol (Phila) 2014; 52:579-83.
22. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev 2017; 4:CD007557.
23. Brown W, Lunati M, Maceroli M, Ernst A, Staley C, Johnson R, Schenker M. Ability of thromboelastography to detect hypercoagulability: a systematic review and meta-analysis. J Orthop Trauma 2020; 34:278-86.
24. Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: a systematic review and meta-analysis. Thromb Res 2020; 196:27-30.