



## ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# Thromboembolic complications in patients with COVID-19 – experiences of the General Surgery Department of Zemun Clinical Hospital Center

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## SUMMARY

**Introduction/Objective** More than three years have passed since the discovery of the new virus strain SARS-CoV-2, and the virus is still a challenge for all medical specialties. One of the most important characteristics is the tendency to develop thromboembolic complications, which are often lethal.

The aim of this paper is to present the experience of the General Surgery Department of the Zemun Clinical Hospital Center in the surgical treatment of patients with thromboembolic complications.

**Methods** The research was conceived as a retrospective study conducted in the period from March 2020 to March 2021. A total of 42 patients participated in the study and were divided into a group diagnosed with small and large bowel ischemia and a group diagnosed with acute limb ischemia.

**Results** In both groups, males were predominantly represented. The first group consisted of nine patients, all of whom had a clinical finding of acute abdomen and ileus, while seven of them also had a severe computed tomography image of bilateral pneumonia. In the second group, a smaller number of patients were initially candidates for thrombectomy, while in others, primary amputation treatment was approached. Mortality from the underlying disease in both groups was high.

**Conclusion** Moderate and severe forms of SARS-CoV-2 infection are associated with an inflammatory response leading to endothelial dysfunction accompanied by a high incidence of thromboembolic complications despite pharmacological prophylaxis. The current consensus supports the use of anticoagulants in all hospitalized patients with moderate to severe disease, as well as in critically ill patients.

**Keywords:** COVID-19; SARS-CoV-2; thromboembolic complications; thrombosis

## INTRODUCTION

More than three years have passed since the discovery of the new virus strain SARS-CoV-2 in Wuhan, People's Republic of China, and the virus is still present and poses a problem and challenge for all medical specialties. This disease is manifested by a different clinical manifestation, starting from asymptomatic cases, through symptoms and signs such as loss of taste and smell, fatigue, myalgia, gout, diarrhea and dry cough, which may or may not be accompanied by a fever. In addition to high transmissibility, the main feature of this disease is a significant tendency to develop complications at the level of various organ systems, which are often lethal. According to the data of the Institute of Public Health of the Republic of Serbia, over 200 million infected people are currently diagnosed in the world, with a fatal outcome in over 4 million patients. In our country there was 1,286,025 infected people until December 22, 2021, while the fatal outcome was confirmed in 12,488 patients.

One of the most significant complications of this disease is the dysfunction of the coagulation system. According to a study by Lazzaroni et al. [1] coagulation dysfunction itself can be observed through two main pathogenetic

pathways, i.e., through inflammation with a consequent cytokine storm and through virus-specific mechanisms. Excessive immune response, hypoxia, diffuse intravascular coagulation and prolonged resting in patients are thought to be the main triggers for venous and arterial thromboembolic complications. A study conducted by Klok et al. [2] showed that the incidence of thromboembolic complications in patients treated in the intensive care unit is as high as 31%. Due to the high potential for the development of thromboembolic complications, we have a higher frequency of pulmonary embolism, deep vein thrombosis, coronary infarction, acute limb ischemia, ischemia at the level of the gastrointestinal tract and cerebrovascular strokes. A study by Omar et al. [3], which referred to radiological findings, showed the presence of thromboembolic complications in 10% of patients, where 45% of patients had pulmonary embolism, 25% cerebrovascular event, 13.7% limb ischemia, while 15.3% of patients were diagnosed with gastrointestinal thromboembolic disease.

The aim of this study is to present the experience of the General Surgery Department of KBC Zemun in the surgical treatment of patients with thromboembolic complications of SARS-CoV-2 infection.

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## METHODS

Our research was conceived as a retrospective study, approved by the ethics committee of our Institution, and was conducted in the period from March 2020 to March 2021. The study involved a total of 42 patients hospitalized within the Department of General Surgery of KBC Zemun, who with their written consent underwent surgical treatment due to thromboembolic complications of SARS-CoV-2 infection.

We divided the patients into two groups. The first group consisted of nine patients with intraoperatively diagnosed ischemia of the small intestine and/or large intestine (Table 1), while the second group included 33 patients with diagnosed acute ischemia of the extremities (Table 2). In eight patients of the second group, acute arterial thromboembolism of the extremities was verified by clinical examination and via Color-Doppler, and they were operated on within six hours from the onset of the disease.

**Table 1.** Data on operated patients in COVID Zemun Clinical Hospital Center due to thromboembolic complications at the level of digestive tract

Gender	M = 6 (66.67%)	F = 3 (33.33%)
Age (years)	Youngest – 42	Oldest – 87
Pneumonia	(+) 9 (100%)	(-) 0 (0%)
PCR +/-	(+) 6 (66.67%)	(-) 0 (0%)
Ag +/-	(+) 7 (77.78%)	(-) 2 (22.22%)
Type of operation	Small bowel resection with primary anastomosis	6 (66.67%)
	Small bowel resection and right hemicolectomy	2 (22.22%)
	Hartmann procedure	1 (11.11%)
Mortality	6 (66.67%)	

**Table 2.** Data on operated patients in COVID Zemun Clinical Hospital Center due to thromboembolic complications at the level of extremities

Gender	M = 26 (78.79%)	F = 7 (21.21%)
Age (years)	Youngest – 49	Oldest – 81
Pneumonia	(+) 26 (78.79%)	(-) 7 (21.21%)
PCR +/-	(+) 28 (84.85%)	(-) 3 (9.1%)
Ag +/-	(+) 22 (66.67%)	(-) 11 (33.33%)
Type of operation	Thrombectomy/Embolectomy	8 (24.24%)
	Femoral amputation	18 (54.55%)
	Crural amputation	7 (21.21%)
Mortality	16 (48.48%)	

The inclusion criteria were: confirmed SARS-CoV-2 infection (polymerase chain reaction or antigen method), both sexes, age over 18 years and verified acute abdominal events or acute limb ischemia.

All patients who were included in the study were preoperatively prepared according to the emergency admission protocol of the Surgery Clinic of KBC Zemun. Among the additional diagnostic procedures, computed tomography (CT) examination of the target topographic region, Doppler examination of the main blood vessels of the extremities, X-ray and ultrasonographic examination of the abdomen

were applied. Consultative examinations of internists and anesthesiologists were also performed.

Methods of descriptive and analytical statistics were used in this study: absolute and relative numbers (n, %) and measures of central tendency (arithmetic mean, median). The necessary data were obtained by reviewing the protocol of surgical treatment, the patient's medical history, temperature list and anesthesia list, as well as by reviewing the histopathological findings.

## RESULTS

In the group of patients with small intestine and/or large intestine ischemia, there was a statistically significant difference between the sexes, where male patients were dominant, accounting for two thirds of those treated. Out of a total of nine patients, small bowel resection with primary anastomosis was performed in six of them, there were two small bowel resections with right hemicolectomy, while Hartmann procedure was performed on one patient due to descending colon ischemia. All patients had a clinical finding of acute abdomen and ileus with radiographically diagnosed hydroaerial levels. As many as seven patients in this group had severe bilateral pneumonia with a CT score of 17–23. Since CT angiography was not available for preoperative diagnosis, mesenteric venous thrombosis was verified intraoperatively in seven patients. Postoperatively, one patient had an operative wound infection, one had dehiscence of the operative wound - treated with re-suturing, while one had dehiscence of the anastomosis which was treated with reoperation and stoma. In six patients, a lethal outcome occurred within 48 hours due to complications of the underlying disease, while the remaining three were discharged for further home treatment.

In the second group, there was also a statistically significant difference between the sexes, with 78% being male. Thrombectomy was performed in eight patients, seven of which were lower limb thrombectomies, while one was thrombectomy of the upper limb. Despite the application of adequate antithrombotic therapy, after 48 hours the complication in terms of retrombosis occurred in six patients, and due to the progression of the ischemic finding, we had to perform femoral amputation in four patients. Due to the consequences of the underlying disease, six patients from this subgroup died. From the remaining 25 patients, in 18 cases femoral amputation had to be performed due to the irreversible ischemic process, while in seven patients crural amputation was performed. Mortality in this group was recorded in as many as 16 patients or 48.48%, who had numerous comorbidities, progression of ischemia and very poor general condition caused by SARS-CoV-2 infection. Complications in the form of surgical wound infection were present in a relatively small number of cases, which can be explained by the protracted use of antibiotics preoperatively, rapid and atraumatic surgical technique, as well as a fairly high rate of postoperative mortality due to cardiovascular complications. Complications in the form of hematoma of the amputation stump and prolonged drainage activity were

recorded in a very low percentage of only 0.9% in relation to the type of pathology, regardless of the perioperative application of high doses of anticoagulant therapy.

## DISCUSSION

The development of progressive endothelial thromboinflammatory syndrome, which leads to small blood vessel disease, is thought to be at the root of thromboembolic complications associated with SARS-CoV-2 infection [4]. A review of literature reveals that a large percentage of patients with a severe form of COVID-19 can develop venous and arterial complications [5].

COVID-19 is a multi-organ disease, causing acute complications through organ-specific pathogenesis followed by destruction of ACE2+ cells, including endothelium, cardiac microvasculature, alveolus and glomerulus. However, the fact that viral RNA is rarely detectable in patients' blood suggests that additional host-dependent factors may contribute to systemic endothelial dysfunction and vasculopathy in COVID-19, rather than just direct virus-dependent effects on endothelial cells [6].

The direct impact of Sars-Cov2 infection is achieved by binding the virus to endothelial cells. Endothelial cells are responsible for adequate hemostasis by maintaining the integrity of the blood vessel wall and maintaining the balance between fibrinolysis through the expression of coagulation inhibitors and blood clot enzymes, as well as maintaining the glycocalyx. SARS-CoV-2 alters vascular homeostasis by directly binding to endothelial cells via ACE2. Another piece of evidence is that *in vitro*, SARS-CoV-2 can successfully infect engineered organoids of human blood vessels, which further proves the tropism of SARS-CoV-2 for endothelial cells [7]. Binding to ACE2 results in internalization and down-regulation of ACE2, which further leads to reduced ACE2 expression and reduced angiotensin production. Angiotensin acts on the MAS receptor, and the consequent reduction of angiotensin leads to reduced activation of MAS, which promotes a local prothrombotic effect. In addition, the reduced expression of ACE2 can indirectly activate the kallikrein-kinin system and lead to an increase in vascular permeability [8].

On the other hand, the host's response can greatly affect endothelial dysfunction. As reviewed in a study by Perico et al. [9], hypercytokinemia and a massive proinflammatory host response may contribute to endothelial dysfunction in COVID-19 most likely through the action of IL-6 and TNF. The levels of these two cytokines are significantly increased in patients with severe forms of the disease [6]. In addition to the effect of cytokines, a number of studies have shown that reduced activity of endothelial nitric oxide synthase, decreased levels of nitric oxide and increased release of vascular endothelial growth factor due to hypoxia have also been suggested as key pathogenic processes [10]. Similarly, the complement system, as well as other components of the innate immune system, which helps control bacterial and viral infections, their unrestrained activation in prolonged SARS-CoV-2 infection can be harmful by causing direct

tissue damage to the host. Activation of the complement system leads to damage and apoptosis of endothelial cells with subsequent vascular denudation and exposure of the thrombogenic basement membrane, which initiates the activation of coagulation cascades. These events result in inflammation, microvascular thrombosis, vessel edema, and hemorrhagic sequelae [11]. In Northern Italy, in a large series of autopsied lungs, platelet-fibrin thrombi were found in the largest number of cases in both small and large blood vessels of the lungs. Indeed, patients with SARS-CoV-2 infection are at increased risk of widespread coagulation of small and large vessels [12].

The results of a systematic review of the literature by Keshavarz et al. [13], which included 22 studies with 31 patients, suggest that thrombosis at the level of mesenteric blood flow was demonstrated in approximately half of patients diagnosed with intestinal ischemia. Based on all of the above, we see that the pathogenesis of thromboembolic complications in the gastrointestinal system is very complex. At the base is microvascular thrombosis involving the submucosal vessels of the intestine resulting from a combination of direct injury to the endothelium due to severe acute respiratory syndrome SARS-CoV-2, hyperviscosity as a consequence of the inflammatory response, and increased expression of von Willebrand factor with vascular stasis [14]. The clinical presentation of acute mesenteric thrombosis in COVID-19 manifests itself most often as an acute abdomen, and sometimes it is accidentally detected by more sophisticated radiological methods [15].

Serban et al. [16] performed a systematic review of 89 patients with acute mesenteric ischemia due to COVID-19. The average age of the patients was  $59.3 \pm 12.7$  years with a slight predominance of men (61%), which is in accordance with our results. Among the clinical symptoms, abdominal pain was the most common symptom and was present in almost all patients. Fever was not differentially diagnostically significant because most hospitalized patients with COVID-19 either already have a fever or are receiving antipyretics. Other symptoms from the gastrointestinal tract such as nausea, anorexia, and vomiting are nonspecific and poorly sensitive and are present in only 30–40% of patients with mesenteric ischemia [16].

Our findings in terms of predominant venous thromboembolic events at the level of mesenteric blood flow coincide with the study by Omar et al. [3]. CT of the abdomen and pelvis with contrast is the method of choice for suspected mesenteric thrombosis. Ojha et al. [17] performed a systematic review of 75 patients with mesenteric thrombosis associated with COVID-19. It was shown that ischemia of the small intestine (46.7%) is more common than ischemia of the large intestine (37.3%). Arterial thrombosis was presented in about a quarter of patients, while venous thrombosis was verified in about 30% of patients [17]. In the case of the impossibility of CT diagnostics, native X-ray imaging can be of great help in the diagnosis of pneumatosis intestinalis and portal vein gas [18].

If we look at the study by Bhayan et al. [19], which included 412 patients with SARS-CoV-2 infection and was based on radiological diagnostic procedures performed



on the abdomen, we can note that abnormal findings at the level of the intestinal wall were verified in 31% of patients using CT imaging, by observing the presence of pneumatosis or gas at the level portal blood flow. Patients with this diagnostic finding underwent surgical treatment, where in two patients the finding was in favor of intestinal infarction, while the other findings were in favor of ischemic enteritis [19].

The surgical principles of treating acute abdomen in patients with COVID-19 infection are unchanged. By reviewing the literature, over 60% of patients with mesenteric thrombosis required surgical treatment. A smaller percentage of patients were treated conservatively or with endovascularly. The operative procedure that was carried out depended on the intraoperative findings, the time it took to diagnose mesenteric thrombosis, the location of the irreversible change on the intestines, but also the patient's general condition, as well as associated comorbidities. Hwabejire et al. [20] have described the undertaken surgical procedures. Based on their experience, over 85% of patients required bowel resection during the first exploratory laparotomy. Sometimes it is difficult to make a clear difference between an intestine with impending gangrene from a healthy intestine, so a second look is recommended. An individualization of the decision to perform an anastomosis or a stoma is required. According to their experience, about half of the patients could successfully undergo primary anastomosis [20].

The prognosis of mesenteric thrombosis in patients with COVID-19 is extremely poor. High mortality can be explained by the underlying disease but also by associated comorbidities [21]. A review of the literature by Kerawala et al. [22], which included 28 studies, indicated a high mortality rate in patients surgically treated for acute mesenteric ischemia, despite adequate follow-up, which agrees with our results. Numerous surgical series have reported a high mortality exceeding 50% [22].

As previously stated, the host's proinflammatory and procoagulant response, caused by virally induced vascular endothelial injury, can lead to arterial thrombosis and acute limb ischemia with a very poor prognosis [23]. This procoagulant condition significantly affects the veins, however, there is a large amount of evidence that indicates an increased risk of arterial thrombotic events in patients with COVID-19, especially for acute limb ischemia [24]. Galyfos et al. [25] performed a systematic review of data from multiple case studies to show that acute limb ischemia occurs more frequently in patients with COVID-19 and is associated with high mortality and amputation risk. Ischemic complications at the limb level were statistically significant in our study. Numerous retrospective studies have shown that the incidence of thrombotic events in SARS-CoV-2 patients ranges from 12% to 31%, as well as the fact that most are of venous origin. A study by Bozzani et al. [26] showed that arterial thromboembolic events are present in 4% of all thromboembolic complications. Al-Zoubi et al. [27] showed that the prevalence of acute limb ischemia is higher during SARS-CoV-2 infection than in the period before the pandemic. Of the seven patients

observed in that study, two patients with asymptomatic SARS-CoV-2 infection underwent successful thrombectomy without mortality, while the remaining five who had severe infection and who were admitted in the intensive care unit had a lethal outcome within 24 hours of diagnosis [27]. In a large study conducted in the United States, Pharm et al. [23] showed that patients with COVID-19 and acute limb ischemia face worse clinical outcomes compared to patients with acute limb ischemia but without COVID-19. They concluded that COVID-19 can not only cause acute limb ischemia, but can also be responsible for a worse outcome of the disease [23]. The study of Bellosta et al. [28], which included 20 patients with acute limb ischemia, also confirmed a higher number of patients during SARS-CoV-2 infection than before the pandemic. Seventeen patients were treated surgically, revascularization was successful in 12 patients (70%), while 40% of patients had lethal outcome. Two patients underwent reintervention due to retrombosis within 48 hours. Bellosta et al. [28] showed that the failure rate of revascularization is almost 30%, as a result of hypercoagulable state, early recurrent thrombosis, poor clinical condition of patients and frequent postoperative complications. In addition, studies in the United States have shown that by increasing the rate of revascularization, amputation treatment is significantly less common in cases of critical limb ischemia. Unfortunately, in the case of patients with COVID-19, amputation is often the best option due to the severe general condition of the patients, late presentation to the health facility and rapid deterioration of the underlying disease [29]. Timely recognition of ischemic thrombotic events in patients with COVID-19 with intensive anticoagulant, thrombolytic treatment as well as a timely decision on revascularization treatment can reduce unwanted events in patients with acute limb ischemia.

## CONCLUSION

Moderate and severe forms of SARS-CoV-2 infection are associated with an inflammatory response leading to an acute phase response and endothelial dysfunction, resulting in a procoagulant condition called COVID-19-associated coagulopathy. Incidence rates of thromboembolic complications in patients with SARS-CoV-2 infection are high despite pharmacological prophylaxis. Although most of the reports did not have a control group, as well as ours, the difference in incidence rates between those affected and those not affected is evident. Vulnerable groups, such as the elderly, pregnant women or people with multiple comorbidities, are at higher risk of hospitalization and even admission to the intensive care unit, which is a predisposition for the development of thromboembolic complications. The current consensus supports the use of anticoagulants in all hospitalized patients with SARS-CoV-2 infection who have moderate to severe disease, as well as in critically ill patients.

**Conflict of interest:** None declared.

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## Тромбоемболијске компликације код оболелих од ковида 19 – искуства службе опште хирургије Клиничко-болничког центра „Земун“

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### САЖЕТАК

**Увод/Циљ** Прошло је више од три године од откривања новог вирусног соја SARS-CoV-2, а вирус и даље представља изазов за све медицинске специјалности. Једна од најзначајнијих карактеристика је склоност ка развоју тромбоемболијских компликација, које су неретко леталне.

Циљ овог рада је приказ искуства Службе опште хирургије КБЦ Земун у хируршком лечењу оболелих од тромбоемболијских компликација.

**Методе** Истраживање је конципирано као ретроспективна студија која је спроведена у периоду од марта 2020. године до марта 2021. године. У студију су била укључена укупно 42 болесника и били су подељени у групу са дијагностикованом исхемијом танког и дебелог црева и групу са дијагностикованом акутном исхемијом екстремитета.

**Резултати** У обе групе доминантно је био заступљен мушки пол. Прву групу је чинило девет болесника. Сви су имали

клинички налаз акутног абдомена или илеуса, док је њих седам имало и тешку клиничку слику обостране пнеумоније. У другој групи мањи број болесника је у почетку био кандидат за тромбектомију, док се код осталих приступило примарно ампутационом лечењу. Смртност од основне болести у обе групе је била висока.

**Закључак** Умерене и озбиљне форме инфекције SARS-CoV-2 у спреси су са инфламаторним одговором који доводи до ендотелне дисфункције праћене високом стопом тромбоемболијских компликација упркос фармаколошкој профилакси. Тренутни консензус подржава примену антикоагуланаса код свих хоспитализованих болесника који имају умерену до тешку болест, као и код критично оболелих болесника.

**Кључне речи:** ковид 19; SARS-CoV-2; тромбоемболијске компликације; тромбоза