Association of COVID-19 Infection and Acute Mesenteric Ischemia

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Abstract: COVID-19 is an infectious disease that is considered to be a thromboinflammatory disorder. The study was aimed to determine the prevalence of COVID-19 in patients with acute mesenteric ischemia (AMI) and the outcomes of surgical treatment in relation to COVID-19. A total of 140 patients were included in this multicentric study divided into two groups: the test group (n=65) consisted of cases of AMI detected during the COVID-19 pandemic and the control group (n=65) consisted of cases of AMI detected before the pandemic. Test group patients were classified as COVID-positive (COVID+), or COVID-negative (COVID–) if they tested positive, respectively negative test for COVID-19 on admission. Primary outcomes were: prevalence of COVID-19 infection among test group patients, association between COVID-19 infection and inoperability, and between COVID-19 and treatment outcome. Secondary outcomes were association between each blood parameter and inoperability and treatment outcome. There were no statistically significant differences between inoperability and COVID-19 positivity on admission, overall mortality between the control group and the test group and overall mortality between COVID+ and COVID– patients, as well as among those patients that have been surgically treated ($p>0.05$). There were statistically significant differences between serum amylase levels ($p=0.034$), and serum LDH levels ($p=0.0382$) and inoperability, between serum LDH levels and postoperative mortality ($p=0.0151$), and overall mortality ($p=0.00163$). High level of LDH and serum pancreatic amylase are associated with a higher rate of inoperability and a higher postoperative and overall mortality rate. COVID-19 does not seem to independently influence the treatment outcome of AMI.

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Introduction

Acute mesenteric ischemia (AMI) is a rare disease caused by insufficient intestinal blood flow, being involved in 0.1 to 1 per 1,000 hospital admissions, mostly affecting elderly patients. Early diagnosis and treatment are crucial to successful treatment and prevention of bowel necrosis as it has a high mortality of 60–80%. Thromboembolism of the superior mesenteric artery (SMA) is the most common cause of AMI (Clair and Beach, 2016). Patients with AMI present with acute abdominal pain as well as vomiting, diarrhoea, abdominal distension and blood in the stool, and abdominal tenderness which is minimal in the early stages but progresses to diffuse peritonitis as intestinal necrosis develops (Carver et al., 2016). Laboratory tests in AMI include white blood cell count, lactate, D-dimer and metabolic acidosis. Definitive diagnosis is achieved with CT (computed tomography) angiography. Treatment options include endovascular repair and open surgical therapy in the form of surgical embolectomy or bowel resection. COVID-19 is an infectious disease of the respiratory system caused by the SARS-nCoV2 virus, with significant vascular manifestations. The vascular endothelium plays an important role in the inflammatory response triggered by COVID-19 (Thomas and Scully, 2022). A complex interplay between the endothelium, the immune system and the coagulation cascade arises, which leads to the development of thrombosis. The endothelium is subject to several prothrombotic changes including glycocalyx shedding, loss of cytoprotective signalling and antithrombotic effectors. COVID-19 has been associated with a variety of events caused by abnormal coagulation, such as venous thromboembolism, pulmonary embolism, deep vein thrombosis, and arterial thromboses. COVID-19 is therefore considered to be a thromboinflammatory disorder (Mathieu et al., 2021).

In light of this evidence, the hypothesis of acute mesenterial ischemia as a complication of infection with the SARS-nCoV-2 virus is plausible.

The objective of this study was to evaluate the prevalence of COVID-19 in patients with AMI during the pandemic as well as the outcomes of surgical treatment in relation to COVID-19.

Material and Methods

This retrospective cohort multicentric study was done on patients treated in three public tertiary care hospitals in Skopje, North Macedonia. One hundred and forty patients admitted to hospital under suspicion of AMI were accepted in this study. Data was gathered anonymously using electronic medical records of the hospitals the patients were treated in. Inclusion criteria were patients with radiological and/or per operative evidence of AMI. Patients were excluded if AMI was excluded during treatment. They were divided into two groups with respect to the time period they were detected, either during or before the pandemic. The test group (n=65) consisted of cases detected during the COVID-19 pandemic. The first registered COVID-19 case in North Macedonia was detected on 26 February 2020 (Chen et al., 2022). Patient data was gathered until 30 November 2021, which amounts to

a time period of 644 days. The control group (n=65) consisted of cases detected during an equal time period of 644 days before the pandemic, i.e., between 28 April 2018 and 31 January 2020. Test group patients were classified as COVID-positive (COVID+) if they tested positive for COVID-19 on admission with a rapid antigen test and a subsequent PCR, or COVID-negative (COVID–) if they had a negative rapid antigen test on admission.

All patients were evaluated with respect to operability and treatment outcome. Patient operability was evaluated with two categories: operable, which designates patients that were subjected to intestinal resection of any kind; and inoperable, which designates patients that were not subjected to surgical treatment due to terminal disease stage. Treatment outcome was similarly evaluated: patients that were successfully treated and discharged were classified as survivors, and patients that were treated surgically without success or patients that were considered inoperable on admission were classified as non-survivors. Postoperative mortality is defined as the mortality rate of patients that have undergone surgery. Overall mortality is defined as the mortality rate of patients that have deceased both after surgery as well as due to terminal stage. The values of the following blood parameters on admission were noted: D-dimers, C-reactive protein (CRP), lactate dehydrogenase (LDH), and pancreatic amylase. Primary outcomes were: prevalence of COVID-19 infection among test group patients with AMI. Association between COVID-19 infection and inoperability, and between COVID-19 and treatment outcome. Secondary outcomes were: association between each blood parameter and inoperability, association between each blood parameter and treatment outcome.

Statistical analysis

Statistical analysis was performed by Mann Whitney U-test for continuous variables. Fisher's exact test and odds ratio with 95% confidence interval was used for frequencies. The level of statistical significance was $p<0.05$. RStudio was used for the statistical analysis.

Results

During both time periods, 140 patients were hospitalized under the suspicion of AMI. Ten patients were excluded due to exclusion of AMI as a diagnosis, which resulted in a final count of 130 patients. The control group and the test group contained 65 patients each. General patient characteristics can be found in Table 1. In the test group, 7 patients (10.78%) were COVID+. Five of them were surgically treated, of which 2 successfully recovered and 3 did not survive. Two patients were considered terminal. There were no statistically significant differences between inoperability on admission and COVID-19 positivity on admission ($p>0.05$). In the control group, 19 patients (29.23%) were considered inoperable. In the test group, 16 patients (24.62%) were considered inoperable. There was no difference between

Table 1 – General patient characteristics

	Control group (n=65)		Test group (n=65)
	COVID+ (n=7)	COVID– (n=58)	
Age	60.85 ± 8.13	68.64 ± 12.1	69.85 ± 13
Sex (m/f)	4/3	32/26	36/29
Inoperable	**2**	**14**	**19**
Treatable	**5**	**44**	**46**
Recovered	2	26	29
Deceased	3	18	17

m – male; f – female

the incidence of AMI during and before the pandemic due to the identical size of the control and the test groups. There were no statistically significant differences in overall mortality between the control group and the test group (56.9% vs. 61%; p>0.05). There was no statistically significant difference in overall mortality between COVID+ and COVID– patients (71.43% vs. 55.17%; p>0.05), as well as among those patients that have been surgically treated (40% vs. 59%; p>0.05). There were statistically significant differences between serum amylase levels on admission and inoperability on admission (p=0.034; Figure 1). There were statistically significant differences between serum LDH levels on admission and inoperability on admission (p=0.0382; Figure 1) as well as between serum LDH levels on admission and postoperative mortality (p=0.0151), as well as LDH levels on admission and overall mortality (p=0.00163). No statistically significant differences were noted between D-dimers and inoperability on admission (p>0.05; Figure 1), between D-dimers and overall (p>0.05) as well as postoperative mortality (p>0.05). Likewise, CRP influenced neither inoperability on admission (p>0.05; Figure 1) nor overall (p>0.05) nor postoperative mortality (p>0.05). Among the COVID+ patients, there were no statistically significant differences in CRP, D-dimer, LDH and amylase levels between the survivors, the patients that died after surgical treatment and the inoperable patients (p>0.05).

Discussion

AMI is a well-documented complication of COVID-19 (Helms et al., 2020; Serban et al., 2021; Chen et al., 2022; Gupta et al., 2022). Risk factors for AMI include conditions which favour thrombus formation such as atrial fibrillation, heart failure, recent myocardial infarction, cardiac thrombi, mitral valve disease, atherosclerosis, portal hypertension, and history of thromboembolic events (Bala et al., 2022). In addition to these factors, infection with the SARS-nCoV2 virus triggers a variety of mechanisms which promote thrombus formation in accordance with Virchow's triad, which consists of endothelial damage, turbulent blood flow and circulating

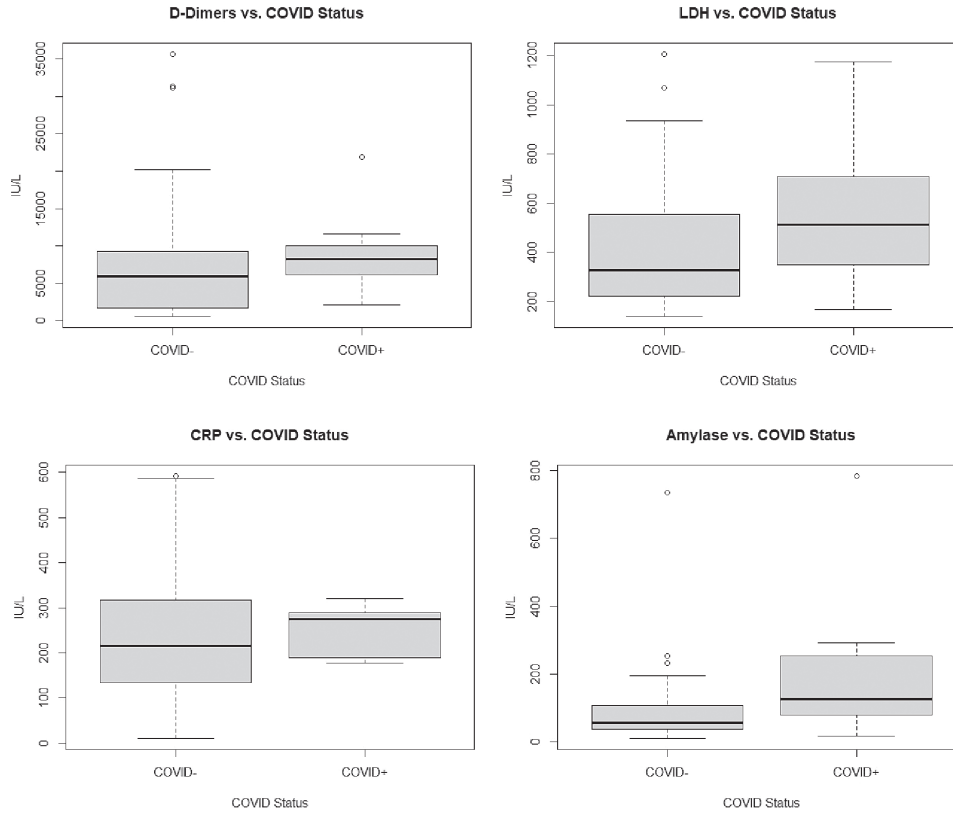

Figure 1 – Comparison of blood parameter levels.

factors that favour coagulation (Bobescu et al., 2021). There are multiple lines of evidence supporting the hypothesis of COVID-19-induced AMI. Platelet activation has been documented in COVID-19, in which the binding of SARS-nCoV2 to angiotensin-converting enzyme 2 (ACE2) has been implicated (Zhang et al., 2020). Endothelial dysfunction could be caused by viral entry in pericytes, where the expression of the ACE2 receptor is high (Becker, 2020). Endotheliosis is another mechanism of endothelial injury, given that viral particles and inclusion bodies as well as inflammatory cells within capillaries have been observed in patients with COVID-19. In one study was demonstrated endotheliosis of the submucosal vessels of the small intestine, providing evidence that COVID-19 coagulopathy may be directly implicated in the pathogenesis of AMI (Varga et al., 2020). Additionally, infection with SARS-nCoV2 can also lead to activation of the complement system, which can independently cause endothelial injury as well as induce exocytosis of P-selectin and von Willebrand factor multimers from endothelial cells that promote platelet adhesion (Noris et al., 2020). In our study, the prevalence of COVID-19

among patients with AMI is 10.78%. We believe this percentage in reality to be higher, considering that patients were classified as COVID+ only if they received positive COVID testing results on admission, without taking into account prior convalescence. Concerning the blood parameters, our results provided some curious findings. In patients with COVID-19, D-dimers have a good predictive value for the occurrence of arterial or venous thrombosis (Betoule et al., 2020) and also correlate with the severity of disease, development of acute respiratory distress syndrome (ARDS), and mortality (Nauka et al., 2020). In our study, D-dimer levels on their own did not seem to be indicative of a poorer prognosis of AMI in COVID+ patients. On the other hand, LDH levels on admission were associated with higher rate of inoperability on admission, higher postoperative and overall mortality; and amylase levels which were associated with higher rate of inoperability. Additionally, these blood parameters seemed to influence the treatment outcome independently of COVID-19. A study by Nachmias-Peiser et al. (2022) analysed mortality in patients with suspected AMI. In this study, LDH was found to be a significant risk factor for mortality in the AMI group as well as in the non-AMI group (Nachmias-Peiser et al., 2022). In our study, we think that the relation between LDH levels and both postoperative and overall mortality may be due to the delay in the procurement of medical care, with a possible correlation between LDH levels and the duration of ischemia, given that LDH is an indicator of injury severity (Guzmán-de la Garza et al., 2013). Evidence of increasing LDH levels in AMI over time has already been demonstrated in experimental models (Roth et al., 1989; Cakir et al., 2019). Of course, these findings require further confirmation in a prospective setting. COVID-19 can initially present with gastrointestinal symptoms (Redd et al., 2020). Given that the diagnosis of AMI requires a high degree of suspicion, we think that it is of utmost importance that COVID-19 patients do not be evaluated only for respiratory symptoms but also for symptoms hinting at potential involvement of the gastrointestinal system. El Moheb et al. (2020) reported a significant incidence of gastrointestinal complications in COVID-19 ARDS patients compared to non-COVID-19 ARDS patients, including bowel ischemia. A strength of this study is that it observes the incidence of AMI in relation to COVID-19 during a longer period of time. In this regard, our study expands the current body of research pertaining to AMI and COVID-19 which consists mostly of case reports. Another strength of this study is that it derives patients from all three public tertiary care hospitals in North Macedonia that treat this pathology. Tertiary health care in North Macedonia is highly centralized, which means that the overwhelming majority of patients evoking clinical suspicion of AMI would be transported to one of the three hospitals that have been included in this study. Consequently, the cases treated in these hospitals are an indicator of the incidence of AMI in the entire country. Limitations of this study include its retrospective design and the lack of prior COVID convalescence data. A more accurate estimate of the prevalence of COVID-19 in patients with AMI could be done with additional evaluation of prior convalescence. The strength of

the associations between COVID-19 and treatment outcomes, and the associations between the blood parameters and treatment outcomes could be more precisely determined with a case-control study.

Conclusion

COVID-19 prevalence in AMI is 10.78%. High level of LDH is associated with a higher rate of inoperability and a higher postoperative and overall mortality rate. High level of serum amylase is associated with a higher rate of inoperability. COVID-19 does not seem to independently influence the treatment outcome of AMI.

References

Bala, M., Catena, F., Kashuk, J., De Simone, B., Gomes, C. A., Weber, D., Sartelli, M., Coccolini, F., Kluger, Y., Abu-Zidan, F. M., Picetti, E., Ansaloni, L., Augustin, G., Biffl, W. L., Ceresoli, M., Chiara, O., Chiarugi, M., Coimbra, R., Cui, Y., Damaskos, D., Di Saverio, S., Galante, J. M., Khokha, V., Kirkpatrick, A. W., Inaba, K., Leppäniemi, A., Litvin, A., Peitzman, A. B., Shelat, V. G., Sugrue, M., Tolonen, M., Rizoli, S., Sall, I., Beka, S. G., Di Carlo, I., Ten Broek, R., Mircea, C., Tebala, G., Pisano, M., van Goor, H., Maier, R. V., Jeekel, H., Civil, I., Hecker, A., Tan, E., Soreide, K., Lee, M. J., Wani, I., Bonavina, L., Malangoni, M. A., Koike, K., Velmahos, G. C., Fraga, G. P., Fette, A., de'Angelis, N., Balogh, Z. J., Scalea, T. M., Sganga, G., Kelly, M. D., Khan, J., Stahel, P. F., Moore, E. E. (2022) Acute mesenteric ischemia: Updated guidelines of the World Society of Emergency Surgery. *World J. Emerg. Surg*. **17(1)**, 54.

Becker, R. C. (2020) COVID-19 update: Covid-19-associated coagulopathy. *J. Thromb. Thrombolysis* **50(1)**, 54–67.

Betoule, A., Martinet, C., Gasperini, G., Muller, P., Foucher, S., Benner, P., Renard, A. (2020) Diagnosis of venous and arterial thromboembolic events in COVID-19 virus-infected patients. *J. Thromb. Thrombolysis* **50(2)**, 302–304.

Bobescu, E., Marceanu, L. G., Covaciu, A., Vladau, L. A. (2021) Thrombosis, an important piece in the COVID-19 puzzle: From pathophysiology to therapy. *Anatol. J. Cardiol*. **9**, 601–608.

Cakir, M., Yildirim, D., Sarac, F., Donmez, T., Mirapoglu, S., Hut, A., Erozgen, F., Ozer, O. F., Gecer, M. O., Tigrel, L. Z., Tas, O. (2019) In the experimental model of acute mesenteric ischemia, the correlation of blood diagnostic parameters with the duration of ischemia and their effects on choice of treatment. *J. Invest. Surg*. **32(6)**, 507–514.

Carver, T. W., Vora, R. S., Taneja, A. (2016) Mesenteric ischemia. *Crit. Care Clin*. **32(2)**, 155–171.

Chen, C., Li, Y. W., Shi, P. F., Qian, S. X. (2022) Acute mesenteric ischemia in patients with COVID-19: Review of the literature. *J. Natl. Med. Assoc*. **114(1)**, 47–55.

Clair, D. G., Beach, J. M. (2016) Mesenteric ischemia. *N. Engl. J. Med*. **374(10)**, 959–968.

El Moheb, M., Naar, L., Christensen, M. A., Kapoen, C., Maurer, L. R., Farhat, M., Kaafarani, H. M. A. (2020) Gastrointestinal complications in critically ill patients with and without COVID-19. *JAMA* **324(18)**, 1899–1901.

Gupta, A., Sharma, O., Srikanth, K., Mishra, R., Tandon, A., Rajput, D. (2022) Review of mesenteric ischemia in COVID-19 patients. *Indian J. Surg*. **11**, 1–9.

Guzmán-de la Garza, F. J., Ibarra-Hernández, J. M., Cordero-Pérez, P., Villegas-Quintero, P., Villarreal-Ovalle, C. I., Torres-González, L., Oliva-Sosa, N. E., Alarcón-Galván, G., Fernández-Garza, N. E., Muñoz-Espinosa, L. E., Cámara-Lemarroy, C. R., Carrillo-Arriaga, J. G. (2013) Temporal relationship of

serum markers and tissue damage during acute intestinal ischemia/reperfusion. *Clinics (Sao Paulo)* **68(7)**, 1034–1038.

Helms, J., Tacquard, C., Severac, F., Leonard-Lorant, I., Ohana, M., Delabranche, X., Merdji, H., Clere-Jehl, R., Schenck, M., Fagot Gandet, F., Fafi-Kremer, S., Castelain, V., Schneider, F., Grunebaum, L., Anglés-Cano, E., Sattler, L., Mertes, P. M., Meziani, F. (2020) High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. *Intensive Care Med.* **46(6)**, 1089–1098.

Mathieu, E., Ritchie, H., Ortiz-Ospina, E., Roser, M., Hasell, J., Appel, C., Giattino, C., Rodés-Guirao, L. (2021) A global database of COVID-19 vaccinations. *Nat. Hum. Behav*. **5(7)**, 947–953.

Nachmias-Peiser, N., Soffer, S., Horesh, N., Zlotnick, G., Amitai, M. M., Klang, E. (2022) Mortality in patients who underwent computed tomography angiography for a suspected acute mesenteric ischemia as a final alternative diagnosis. *Isr. Med. Assoc. J*. **25(12)**, 828–833.

Nauka, P. C., Oran, E., Chekuri, S. (2020) Deep venous thrombosis in a non-critically ill patient with novel COVID-19 infection. *Thromb. Res*. **192**, 27–28.

Noris, M., Benigni, A., Remuzzi, G. (2020) The case of complement activation in COVID-19 multiorgan impact. *Kidney Int*. **98(2)**, 314–322.

Redd, W. D., Zhou, J. C., Hathorn, K. E., McCarty, T. R., Bazarbashi, A. N., Thompson, C. C., Shen, L., Chan, W. W. (2020) Prevalence and characteristics of gastrointestinal symptoms in patients with severe acute respiratory syndrome coronavirus 2 infection in the United States: A multicenter cohort study. *Gastroenterology* **159(2)**, 765–767.e2.

Roth, M., Jaquet, P. Y., Rohner, A. (1989) Increase of creatine kinase and lactate dehydrogenase in the serum of rats submitted to experimental intestinal infarction. *Clin. Chim. Acta* **183(1)**, 65–69.

Serban, D., Tribus, L. C., Vancea, G., Stoian, A. P., Dascalu, A. M., Suceveanu, A. I., Tanasescu, C., Costea, A. C., Tudosie, M. S., Tudor, C., Gangura, G. A., Duta, L., Costea, D. O. (2021) Acute mesenteric ischemia in COVID-19 patients. *J. Clin. Med*. **11(1)**, 200.

Thomas, M. R., Scully, M. (2022) Clinical features of thrombosis and bleeding in COVID-19. *Blood* **140(3)**, 184–195.

Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., Mehra, M. R., Schuepbach, R. A., Ruschitzka, F., Moch, H. (2020) Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **395(10234)**, 1417–1418.

Zhang, S., Liu, Y., Wang, X., Yang, L., Li, H., Wang, Y., Liu, M., Zhao, X., Xie, Y., Yang, Y., Zhang, S., Fan, Z., Dong, J., Yuan, Z., Ding, Z., Zhang, Y., Hu, L. (2020) SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *J. Hematol. Oncol*. **13(1)**, 120.