



## Did Covid 19 disease increase mesenteric ischemia cases?

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### Research Article

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### ABSTRACT

**Background:** Covid 19 (C19) disease causes mortal complications due to both respiratory system involvement and extrapulmonary involvement. C19 patients may present with gastrointestinal symptoms such as nausea-vomiting, diarrhea and loss of appetite, as well as serious conditions such as acute mesenteric ischemia. C19 disease is a proinflammatory condition that causes thrombus formation.

**Methods:** The first group (G1) was treated with 21 mesenteric ischemia cases operated in the General Surgery Department of Aksaray Training and Research Hospital in approximately two years between March 2020 and February 2022, and the second group (G2), in a two-year period between 2018-2020 before the pandemic, in the same department. The information of 11 mesenteric ischemia cases who underwent surgery were analyzed from the hospital information system. Statistically, the predisposing diseases, demographic data, intestinal lengths removed during the operation, and survival of the patients in both groups were compared.

**Results:** When the number of patients who were operated on in G1 and G2 were compared, it was seen that more patients were operated in G1. The probability of mesenteric ischemia in a 24-month period was found to be 0.875 in G1 and 0.458 in G2. These rates were statistically different ( $p=0.002$ ). When the mean age, length of the removed bowel, and postoperative mortality of both groups were compared, no significant difference was found.

**Conclusion:** Although the exact mechanism by which the Covid 19 disease causes mesenteric ischemia is not understood, we observed a statistically significant increase in mesenteric ischemia cases during the pandemic period compared to the pre-pandemic return. Considering the Physiopathology of C19, it is known that the diseases in the body generally occur on the basis of vasculitis. When C19 infection is detected, we recommend anticoagulant treatment for at least 3 months during the infection and for the prevention of other complications related to vasculitis, especially mesenteric ischemia.

**Keywords:** Covid 19, mesenteric ischemia, pandemic, vasculitis

## COVID-19 hastalığı mezenterik iskemi vakalarını artırdı mı?

#### Süreç

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#### Öz

**Amaç:** Covid 19 (C19) hastalığı, hem solunum sistemi tutulumu hem de ekstrapulmoner tutulum nedeniyle ölümcül komplikasyonlara yol açar. C19 hastaları bulantı-kusma, ishal ve iştah kaybı gibi gastrointestinal semptomlarla birlikte akut mezenterik iskemi gibi ciddi durumlara da karşılaşılabılır. C19 hastalığı, trombus oluşumuna neden olan proinflatuar bir durumdur.

**Yöntemler:** İlk grup (G1), Aksaray Eğitim ve Araştırma Hastanesi Genel Cerrahi Bölümü'nde Mart 2020 ile Şubat 2022 arasında yaklaşık iki yıl süresince opere edilen 21 mezenterik iskemi vakası ile, ikinci grup (G2) ise pandemi öncesi 2018-2020 yılları arasında aynı bölümde opere edilen hastaları içermektedir. Hastane bilgi sistemi üzerinden cerrahi geçiren 11 mezenterik iskemi vakasının bilgileri analiz edildi. İki grup arasında yatkın hastalıklar, demografik veriler, operasyon sırasında çıkarılan bağırsak uzunlukları ve hastaların sağ kalımları istatistiksel olarak karşılaştırıldı.

**Bulgular:** G1 ve G2'de opere edilen hasta sayıları karşılaştırıldığında, G1'de daha fazla hasta opere edildiği görüldü. 24 aylık bir dönemde mezenterik iskemi olasılığı, G1'de 0,875 ve G2'de 0,458 olarak bulundu. Bu oranlar istatistiksel olarak farklıydı ( $p=0,002$ ). Her iki grup arasında ortalama yaş, çıkarılan bağırsak uzunluğu ve ameliyat sonrası mortalite karşılaştırıldığında anlamlı bir fark bulunmadı.

**Sonuç:** Covid 19 hastalığının mezenterik iskemiye nasıl yol açtığı tam olarak anlaşılmasa da, pandemi döneminde mezenterik iskemi vakalarında pandemi öncesi döneme göre istatistiksel olarak önemli bir artış gözlemledik. C19'nun Fizyopatolojisini düşünerek, vücuttaki hastalıkların genellikle vaskülit temelinde meydana geldiği bilinmektedir. C19 enfeksiyonu tespit edildiğinde, enfeksiyon süresince ve özellikle mezenterik iskemi ile ilişkili diğer komplikasyonların önlenmesi için en az 3 ay süreyle antikoagulan tedavi öneriyoruz.

**Anahtar sözcükler:** Covid 19, mezenterik iskemi, pandemi, vaskülit

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## Introduction

Although SARS-CoV-2 (Covid 19,C19) infection, which emerged in Wuhan, China in December 2019 and affected the whole world in a short time, was thought to be a respiratory disease at first, it was understood that it also caused complications in other organs due to coagulopathy. Venous thrombosis has been reported in 25% to 50% of patients[1]. In fact, most of the most fatal complications related to C-19 are pathologies related to coagulopathy[2]. The S-type protein found in the coronavirus envelope that causes C19 disease and bound by angiotensin-converting enzyme 2 (ACE-2) has been found to be associated with these thrombosis events. Similar to SARS-CoV and MERS-CoV infections, it has been determined that there is an increased risk of thrombosis in C19 infection, and SARS-CoV-2 is thought to create a prothrombotic environment in vascular structures. Pulmonary embolism is one of the most common thrombotic complications of C-19. In addition to clinical signs of hypercoagulability such as pulmonary embolism observed in C19 patients, increased D-dimer, fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF) and decreased antithrombin as well as thromboelastography (TEG) test results showed that the virus has the ability to create a prothrombotic environment. It has also been shown that this virus increases the expression of tissue factor and plasminogen activator type 1 inhibitor, as well as the production of Angiotensin II, interleukin 6, and the tendency to coagulation increases accordingly[3]. In C19 disease, thromboembolic events occur in veins rather than arteries. In the literature, mesenteric ischemia cases have been reported at a rate of 4% in C19 patients[4]. Therefore, anticoagulant drugs may be insufficient in patients with comorbidities and alternative or additional treatments may be needed[1]. Despite all this, the pathophysiology underlying this hypercoagulopathy observed in C19 infections is still not fully understood.

## Material Method

C19 infection in Turkey started to be seen for the first time on March 11, 2020 as a branch of the pandemic. In the first group (G1), 21 cases of Acute mesenteric ischemia (AMI) were operated in the General Surgery department of Aksaray Training and Research Hospital in approximately two years between March 2020 and February 2022, and the second group (G2) was divided into two-year

intervals between 2018-2020 before the pandemic. During this period, the information of 11 AMI cases operated in the same department was analyzed from the hospital information system. Our study was carried out with the approval of Aksaray University Clinical Research Ethics Committee, dated 13.01.2022, numbered 74-SBKAEK and numbered 2022/01-11. In our study, patient files were reviewed by two independent researchers. In addition to the factors that increase mesenteric ischemia, additional diseases (Diabetes mellitus (DM), Hypertension (HT), coronary heart disease (CD), atrial fibrillation (AF), cerebrovascular diseases (CVD), chronic renal failure (CRF), age, gender In addition, the patients in G1 were questioned whether they had C19, if they had the disease, how long ago they had the disease, their vaccination status against C19. The length of the necrosis bowel removed during the operation, and the reoperation information of the patients in both groups were recorded.

## Statistical analysis

We tried to determine whether the incidence of mesenteric ischemia increases due to the increased risk of thrombosis in the active phase of C-19 disease and in the post-disease period. SPSS 24.0 package program was used to evaluate the data obtained in the study. As a result of the examination of the relevant distribution charts as well as the normality tests such as Kolmogorov-Smirnov and Shapiro-Wilk, it was observed that the variables did not show normal distribution, and accordingly, appropriate test methods were selected. In the study, which is a descriptive study, the frequencies and percentages of the variables are given and they are summarized visually with the help of various graphs. Chi-square or Fisher's exact test was used to test the distribution of categorical variables in the groups, and Mann Whitney U test was used to investigate the differences in the groups in terms of continuous variables. Results; Mean±Standard Deviation and Median-Span for continuous variables and categorical variables were expressed by using frequency distributions and percentiles as descriptive statistics. In the study,  $p < 0.05$  was taken as the statistical significance limit.

## Results

The mean age of 21 patients in G1 (Table-1) was 66, 16 of them were male and 5 were female. In the first group, 2 of the patients were using varfarin, 2 of them were using acetylsalicylic acid + clopidogrel, and one of them was using only acetylsalicylic acid.

It was determined that 12 patients in G1 had C19 disease 60 days ago. Seven of the patients in G1 were vaccinated against C19 before they had AMI. 5 of these patients were vaccinated with sinovac and 2 with biontec. It was observed that mesenteric

ischemia developed in patients an average of 6.57 months after vaccination. The high number of people vaccinated with Sinovac is due to the fact that the first vaccine to be administered in our country is sinovac.

**Table 1: Mesenteric ischemia cases operated during the pandemic period (G1) (2020-2022)**

<u>PN</u>	<u>G</u>	<u>A</u>	<u>C-19</u> <u>T.</u>	<u>V</u>	<u>V.T</u>	<u>A</u> <u>C</u>	<u>DM</u>	<u>H</u> <u>T</u>	<u>C</u> <u>D</u>	<u>CRF</u>	<u>CVD</u>	<u>A</u> <u>F</u>	<u>Operation</u>	<u>RO</u>	<u>FU</u>
1	M	63	30	S	9	-	-	-	-	-	-	-	SIR+SIO-150		C
2	M	56	10	-		-	+	+	-	-	-	-	SIR+SIO-100	S.L	C
3	F	60	-	-		-	-	-	+	-	-	-	SIR+A-130		C
4	M	67	8	-		-	+	-	-	-	-	-	SIR+SIO-80		C
5	F	78	-	S	6	+	+	+	+	-	-	-	SIR+SIO-180	RCR+ TCR- 70	E
6	M	45	61	-		-	-	-	-	-	-	-	SIR+SIO-140		E
7	M	65	-	B	4	-	+	-	-	-	-	-	SIR+A-80	SIR- 50	C
8	M	82	15	-		+	+	-	+	-	-	+	SIR+RCR+SIO -240		E
9	F	76	33	-		-	-	+	-	-	-	-	SIR+SIO-180		E
10	M	38	-	-		-	-	-	-	-	-	-	SIR+SIO-120		C
11	F	54	-	-		-	-	+	-	-	-	-	SIR+A-110		C
12	M	53	203	S	9	-	-	-	-	-	-	-	SIR+A-170		C
13	M	58	65	-		-	+	+	-	-	-	-	SIR+A-160		C
14	F	52	-	-		-	-	-	+	-	+	-	SIR+SIO-220		C
15	M	72	73	S	7	-	+	+	+	-	-	-	SIR+A-80		E
16	M	63	-	B	2	-	-	-	+	-	-	+	SIR+SIO-70		C
17	M	51	123	-		-	-	-	-	+	+	-	SIR+SIO-200		E
18	M	73	-	-		+	+	+	+	-	-	-	SIR+SIO-150		C
19	M	61	35	-		-	-	-	+	-	-	-	SIR+RCR+SIO -260	TCR- 50	E
20	M	78	61	S	9	+	+	+	+	-	-	-	SIR+SIO-170		C
21	M	80	-	-		+	+	+	+	-	-	-	SIR+A-150		C

**PN:**Patient no, **G:**Gender, **A:**Age, **C-19 T.:**Covid 19 Time, **V:**Vacine, **V.T:**Vaccine Time, **AC:** Anticoagulant, **DM:**Diabetes mellitus, **HT:**Hypertension, **CD:**Cronary heart disease, **CRF:** Chronic renal failure, **CVD:** Cerabrovascular disease, **AF:** Atrial Fibrillation, **S:** Sinovac, **B:** Biontec, **SIR:** Small intestine resection, **SIO:** Small intestine ostomy, **A:** Anastomosis, **RCR:** Right colon res. **TCR:** Transverse colon rez. **SL:**Second look, **RO:** Reoperation, **C:**Contineu, **E:**Exitus, **FU:**Follow-up/ month

Small bowel resection was performed in all G1 patients, and right colon resection was performed in addition to two of them. Anastomosis was performed in 7 of the patients and ostomy was opened in 14 of them. While second look was performed in 4 of the patients in G1, the length of the removed bowel segment was found to be approximately 149 cm. Mesenteric venous ischemia operated in G1 is shown in figure-1.



**Figure 1** Venous Mesenteric Ischemia and intestinal edema due to stasis operated in G1

In G2 (table 2), the mean age of the patients was 63 years. When the mean age of both groups was compared, no significant difference was found. In this group, 9 of the patients were male and 2 were female, and 5 of the patients were using anticoagulants. 3 of these patients were using acetylsalicylic acid and 2 of them were using warfarin. Of the patients in G2, 3 had DM, 7 had HT, 6 had CD, 1 had CRF, 3 had CVD, and 1 had AF. Small bowel resection was performed in all of the patients in G2, and colon resection was required in addition to 2 of them.

Four patients underwent anastomosis during the operation, and ostomy was opened in the other 7 patients. A second look was performed on one patient, and the patient's anastomosis was disrupted, and an ostomy was opened after 60 cm more resection. The average amount of resection performed in patients in G2 is 158 cm. Arterial mesenteric ischemia operated in G2 is shown in figure-2.

**Table 2: Mesenteric Ischemia cases operated before the pandemic (G2) (2018-2020)**

<u>PN</u>	<u>G</u>	<u>A</u>	<u>AC</u>	<u>DM</u>	<u>H</u>	<u>CD</u>	<u>CRF</u>	<u>CVD</u>	<u>AF</u>	<u>Operatlon-cm</u>	<u>RO-cm</u>	<u>FU</u>
1	M	73	-	-	+	-	-	+	-	SIR+SIO-180		E
2	F	64	+	-	-	+	+	-	-	SIR+RCR+SIO-280		E
3	M	46	+	-	-	+	-	-	-	SIR+A-70	S.L SIR-60 +SIO	C
4	M	87	-	+	+	-	-	+	-	SIR+SIO-240		E
5	M	76	+	-	+	+	-	-	+	SIR+SIO-120		E
6		48	-	-	+	-	-	+	-	SIR+A-90		C
7	M	82	+	+	+	+	-	+	-	SIR+SIR+RCR-300		E
8	M	71	+	+	+	+	-	-	-	SIR+A-170		C
9	F	69	-	-	+	+	-	-	-	SIR+SIO-130		E
10	M	35	-	-	-	-	-	-	-	SIR+A-60		C
11	M	74	-	-	+	-	-	-	-	SIR+SIO-100		C

**PN:**Patient no, **G:**Gender, **A:**Age, **AC:** Anticoagulant, **DM:**Diabetes mellitus, **HT:**Hypertension, **CD:**Cronary heart disease , **CRF:** Chronic renal failure, **CVD:** Cerabrovascular disease, **AF:** Atrial Fibrillation, **SIR:** Small intestine resection, **SIO:** Small intestine ostomy, **A:** Anastomosis, **RCR:** Right colon res. **SL:**Second look, **RO:** Reoperation, **C:**Continueu, **E:**Exitus, **FU:**Follow-up/ month



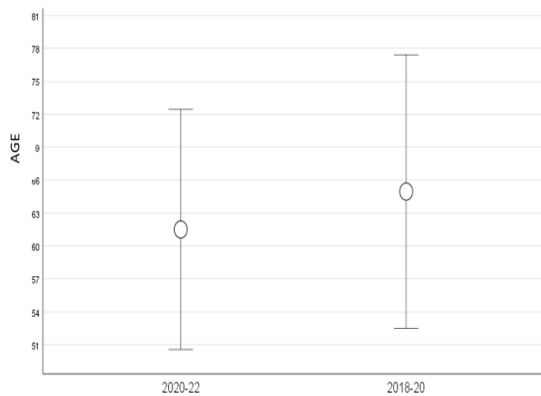
**Figure 2** Arterial Mesenteric Ischemia operated in G2

No perforation was observed in the operated patients in both groups. We started all postoperative patients with rivaroxaban at first 20 mg and then 15 mg. When the number of patients operated on in G1 (table 1) and G2 (table 2) were compared, it was seen that more patients were operated on in G1. The probability of encountering AMI within a 24-month period was found to be 0.875 in G1 and 0.458 in G2, this difference was statistically significant ( $p=0.002$ ). (Table 3).

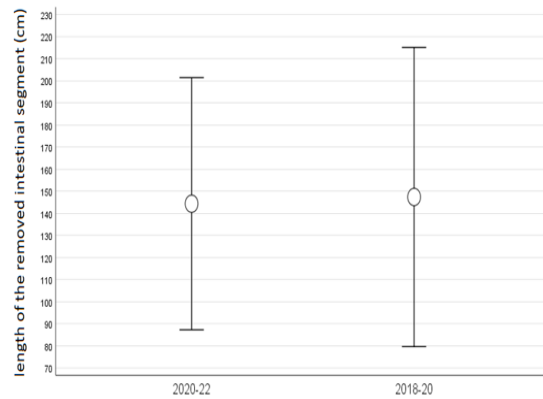
**Table 3** Comparison of the probability of mesenteric ischemia

			Grup		p	Total
			G1 (2020-22)	G2 (2018-20)		
Mesenteric Ischemia	(-)	n	3	13	<b>0,002</b>	16
		%	12,5	54,2		33,3
	(+)	n	21	11		32
		%	87,5	45,8		66,7

There was no significant difference between the two groups in terms of predisposing diseases (Table 3). When the age and length of the removed intestinal segment were compared, no statistically significant difference was observed in both groups (table 4, graph 1-2).



**Graph 1** Age distribution in G1 and G2



**Graph 2** Length of resected bowel distribution in G1 and G2

7 patients in G1 and 6 patients in G2 died after the operation, and there was no significant difference in mortality when the two groups were compared ( $p 0.283$ ) (table 5).

Venous occlusion was observed in 6 of the patients in G1 and venous occlusion was observed in 2 of the patients in G2, and there was no significant difference between the two groups.

**Table 4 Relationship between Age and Bowel Resections**

	G2 (2018-2020)		G1 (2020-2022)		p
	Mean±S.Dev.	Median-Range	Mean±S.Dev.	Median-Range	
Age	65,90±16,23	71,0-52,0	63,09±12,15	63,0-44,0	0,475
Bowel length	158,18±83,64	130,0-240,0	149,52±53,34	150,0-190,0	0,968

\*Mann Whitney U test p value

**Table 5 Comparison of Predisposing Factors and Comparison of Mortality**

		2018-2020	2020-2022	p
		Gender	F	
	M	9-81,82	16-76,19	
AC	-	6-54,55	16-76,19	0,252
	+	5-45,45	5-23,81	
DM	-	8-72,73	11-52,38	0,450
	+	3-27,27	10-47,62	
HT	-	4-36,36	12-57,14	0,458*
	+	7-63,64	9-42,86	
CD	-	5-45,45	11-52,38	1,000*
	+	6-54,55	10-47,62	
CRF	-	10-90,91	20-95,24	1,000
	+	1-9,09	1-4,76	
CVD	-	8-72,73	18-85,71	0,390
	+	3-27,27	3-14,29	
AF	-	10-90,91	19-90,48	1,000
	+	1-9,09	2-9,52	
FU	E	6-54,55	7-33,33	0,283
	C	5-45,45	14-66,67	

\*Kikare and others Fisher's exact test p values.

## Discussion

Acute mesenteric ischemia is a rare cause of abdominal pain and constitutes 0.09%-0.2% of patients presenting to the emergency department with abdominal pain [5]. Although acute mesenteric ischemia is rare, it is a life-threatening abdominal emergency that causes 60% to 80% mortality [6]. While C19 disease was initially thought to cause only respiratory problems, it was seen that it could affect all body organs with coagulopathy in a short time[7]. The relationship between C19 disease and AMI is not clearly known. It should be kept in mind that mortal diseases such as C19 and AMI may be present in all patients who present with nausea, vomiting, diarrhea, abdominal pain and abdominal distension or develop these symptoms during hospitalization[8].

The Virchow triad was investigated for the study of thrombosis in patient C19. The endothelial damage is primary element of the Virchow triad, it binds to the ACE-2 receptor on the endothelium, resulting in the endothelial damage. The hypotension, low oxygen saturation and direct injury of the intestinal mucosa through ACE-2 receptors seen in Covid infection may be responsible for the mechanism in non-occlusive mesenteric ischemia[9]. Reduction in stasis blood flow is the second element of the Virchow triad. Stasis, which develops as a result of slowing blood flow due to long-term immobilization of patients both at home and in a limited area such as the intensive care unit, facilitates the formation of thrombosis. Finally, thrombosis is completed with the development of hypercoagulopathy. During the course of this disease, many changes occur, such as vascular, elevated fibrinogen, prothrombotic factors such as factor VIII, extracellular neutrophil movement, and an increase

in the number of circulating prothrombotic microparticles. These changes cause the development of hypercoagulopathy, which can be detected by thromboelastography[8].

In the literature, the rate of abdominal symptoms caused by C19 disease has been found to be between 3% and 39%. The reported association of C19 and AMI is 1.9-4%. Activation of the lecithin pathway and direct endothelial damage cause arterial thrombosis. Again in the literature, it has been shown that C19-related venous thromboembolic events are more common than arterial events [4]. In another study in which 878 patients were examined, serious abdominal complications were reported in 5.1% of the patients. These are 1.1% bleeding, 0.1% acute pancreatitis, 0.2% acute cholecystitis, 0.1% intestinal obstruction, 0.2% Ogilvie syndrome, 0.2% mesenteric ischemia.

There are no studies on how AMI developing in COVID 19 patients changes mortality compared to AMI developing in non-C19 patients. However, it is thought that mortality will increase due to the increasing disease burden. Therefore, it is extremely important for clinicians to know that mesenteric ischemia can develop in C19 patients and to make a rapid diagnosis when typical symptoms of mesenteric ischemia occur in order to reduce the mortality curve. However, in our study, there was no significant difference in mortality when compared with those who had AMI after C19 and those who developed AMI without C19 (p 0.283).

Anticoagulant therapy, which is a fundamental part of the treatment of Covid19, is heparin prophylaxis that improves prognosis in patients with D-dimer>0.3 µg/mL and sepsis-induced coagulopathy index>4. The anticoagulant treatment dose is 40 mg (40 mg/0.4 ml/day) in the absence of renal insufficiency, and 30 mg in case of renal insufficiency. It is important to continue oral-type anticoagulant therapy for 3 months in patients with a previous co-morbidity predisposing to AMI [10,11]. Known risk factors for mesenteric ischemia are diseases such as arrhythmia, heart failure, atherosclerosis, pancreatitis, renal failure, diabetes, hypertension, and vasculitis[12]. In our study, we looked for additional predisposing diseases in both groups. We did not find any significant difference between G1 and G2 in terms of additional disease. In our series, the rate of anticoagulant use was 45.45% in G1 and 23.81% in G2, and there was no significant difference between the two groups.

CT angiography for mesenteric ischemia is the best diagnostic method with 89.4% sensitivity and 99.5% specificity[13]. We diagnosed all of our patients using CT angiography.(Figure 3)



Figure 3 Tomography image of mesenteric ischemia

Patients can be admitted to the emergency department with acute AMI clinic or mesenteric ischemia clinic may occur on the 7th day of hospitalization due to C19[1,3]. Balraj Singh and Parminder Kaur collected 14 cases of post-C19 mesenteric ischemia in the literature in 2021. While all of these cases emphasized that they developed within the first 14 days after C19 disease [14], in our series, the mean time to develop AMI after C19 disease was found to be 60 days.

In our study, we do not know the severity of the disease, how long it will take to recover, and how many times they were covid 19 positive.

## Conclusion

We have determined that the number of AMI-related operations performed in our clinic since March 2020, the beginning of the C19 pandemic, is higher than in the pre-pandemic period. In our study, we showed that C19 disease is a predisposing factor for the development of AMI. However, more research is needed to understand the exact mechanism by which C19 disease may cause mesenteric ischemia. We also recommend using long-term anticoagulant therapy for at least 3 months to prevent or reduce the development of AMI in patients with C19.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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