

Evaluation of the possible effects of the COVID-19 period on the clinical outcomes of acute mesenteric ischemia

Evaluación de los posibles efectos del periodo COVID-19 en los resultados clínicos de la isquemia mesentérica aguda

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Abstract

Objective: The objective of the study was to investigate the possible effects of the coronavirus disease 2019 (COVID-19) period on the frequency and clinical course of acute mesenteric ischemia (AMI) cases. **Material and methods:** A total of 35 patients who were treated and followed up with a diagnosis of AMI over 44 months were included. **Results:** The mean age of the patients was 69 ± 12 years. Of these patients, 22 were male (63%). The most common cause of AMI in the patients was arterial embolism/thrombosis (68.6%). Thirty-three (94%) of the patients underwent surgical intervention. The duration of the pre-COVID-19 and COVID-19 periods was equal as 22 months, and 18 (51%) of the patients were admitted during the pandemic period. The mortality rate of the patients admitted during the COVID-19 period was also significantly higher than that of the patients admitted during the pre-COVID-19 period (61% and 29%) ($p = 0.05$). **Conclusions:** Although the COVID-19 period did not cause a significant increase in the number of AMI cases when compared to the pre-COVID-19 period, the mortality rate was higher in this period. It is thought that further studies are required to investigate the cause of this increased mortality rate during the pandemic period.

Keywords: Acute mesenteric ischemia. Coronavirus. COVID-19. Mortality. Pandemic.

Resumen

Objetivo: Investigar los posibles efectos del periodo COVID-19 en la frecuencia y el curso clínico de los casos de isquemia mesentérica aguda (IAM). **Material y métodos:** Se incluyeron un total de 35 pacientes tratados y seguidos con diagnóstico de IAM durante 44 meses. **Resultados:** La edad media de los pacientes fue de 69 ± 12 años. De estos pacientes, 22 eran hombres (63%). La causa más frecuente de IAM en los pacientes fue la embolia/trombosis arterial (68.6%). Treinta y tres (94%) de los pacientes fueron intervenidos quirúrgicamente. La duración de los periodos pre-COVID-19 y COVID-19 fue igual a 22 meses, y 18 (51%) de los pacientes ingresaron durante el periodo pandémico. La tasa de mortalidad de los pacientes ingresados durante el periodo COVID-19 también fue significativamente mayor que la de los pacientes ingresados durante el periodo pre-COVID-19 (61% y 29%) ($p = 0.05$). **Conclusiones:** Si bien el periodo COVID-19 no provocó un aumento significativo en el número de casos de IAM en comparación con el periodo pre-COVID-19, la tasa de mortalidad fue mayor en este periodo. Se cree que se requieren más estudios para investigar la causa de este aumento en la tasa de mortalidad durante el periodo pandémico.

Palabras clave: Isquemia mesentérica aguda. Coronavirus. COVID-19. Mortalidad. Pandemia.

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Introduction

Acute mesenteric ischemia (AMI) is an important medical emergency caused by insufficient blood flow to the small intestine that can result in mortality. Late diagnosis and treatment negatively affect the prognosis of the disease. Despite advanced technological devices used in its diagnosis and various surgical and/or interventional treatment methods, AMI remains a condition with a high mortality rate^{1,2}.

Computed tomography (CT) angiography is the golden standard of imaging methods used for the diagnosis of AMI. The dilatation of the intestinal lumen, pneumatosis intestinalis, superior mesenteric vein thrombosis, intraperitoneal fluid, portal vein thrombosis, and splenic vein thrombosis seen on CT angiography results indicate intestinal necrosis³. The incidence rates of arterial embolism, arterial thrombosis, non-occlusive mesenteric ischemia (NOMI), and vein thrombosis in AMI have been reported as 50%, 15-25%, 20%, and 5-15%, respectively⁴.

The World Health Organization declared that coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was a pandemic on March 11th, 2020. It is known that COVID-19 not only affects the respiratory system but also can affect all the systems. It has been reported that two-thirds of the patients who have contracted COVID-19 also showed gastrointestinal system symptoms^{5,6}.

Coronavirus disease 2019 causes systemic inflammation, platelet activation, and endothelial damage and thus increases the tendency of thrombosis in both the venous and arterial systems⁵. Accordingly, it has been established that thromboembolic complications, such as pulmonary embolism, acute myocardial infarction, deep vein thrombosis, and AMI, can be observed in patients with COVID-19⁷. Intestinal necrosis due to thrombosis of small arterioles in the submucosal areas has been detected in histopathological examinations of the gastrointestinal tract of patients infected with the SARS-CoV-2 virus⁸. It has also been reported that AMI can manifest as an early or late complication of COVID-19⁹.

The indirect effects of COVID-19 pandemic cause delayed admission of non-COVID-19 emergency cases to the emergency department. It has been suggested that this situation may cause an increase in mortality and morbidity in these cases^{10,11}. In addition, Reschen et al. showed that in the first wave of the

COVID-19 pandemic, there was a significant decrease in the daily number of non-COVID-19 cases admitted to the emergency department compared to the pre-COVID-19 period. It is thought that this may increase the delay in diagnosis or the missed case rates in non-COVID-19 emergency cases¹². When the literature was examined, it was seen that studies on the clinical course of AMI, a serious medical emergency, during the COVID-19 pandemic period are limited⁷.

In this study, it was aimed to compare the incidence and clinical course of AMI cases during the COVID-19 pandemic period and the pre-COVID-19 period.

Materials and methods

Patients who were followed up with a diagnosis of AMI in the General Surgery Clinic of Bursa Yüksek İhtisas Training and Research Hospital, between 01 May 2018 and 31 December 2021 were included in this retrospective study. The pre-COVID-19 period group was composed of patients diagnosed with AMI over a total of 22 months, between May 2018 and February 2020 (n = 17). The COVID-19 period group was composed of patients diagnosed with AMI over an equal period of 22 months, between March 2020 and December 2021 (n = 18). The demographic (age and gender) and laboratory data (pH, lactate, C-reactive protein (CRP), platelet, ferritin, D-dimer, white blood cell, creatinine, transaminases, lactate dehydrogenase, total bilirubin, and neutrophil-to-lymphocyte ratio) of the patients were obtained from the patient files. In addition, the clinical data (intensive care Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, surgery types, comorbidities, COVID-19 vaccination status, Sars-CoV-2 virus positivity, mortality, length of hospital stay, and abdominal CT and/or CT angiography) of the patients were also recorded. The patients had been diagnosed with AMI according to a combination of clinical, laboratory, radiological, and histopathological findings. The patients were divided into two groups as those who died and those who survived. While the patients who died during their hospitalization were defined as the exitus group, the patients who were discharged as healthy were defined as the survivors group. Individuals aged 18 years and over who were diagnosed with AMI were included in the study. Patients who had prior cases of AMI, intravascular involvement, chronic mesenteric ischemia, inflammatory bowel disease or intestinal masses, were pregnant, or diagnosed with thrombophilia were excluded from the study. All of the patients

were checked for COVID-19 infection by real-time polymerase chain reaction (RT-PCR) tests on combined nasal and oropharyngeal swabs.

Ethical approval

Ethics committee approval for the study was obtained from the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, under decision number 2011-KAEK-25 2022/02-08, on February 9th, 2022. The study was carried out by the Declaration of Helsinki.

Statistical analysis

For statistical evaluation of data obtained in the study, IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used. The study population was checked for normal distribution with the Shapiro–Wilk test. Values were expressed as mean $\pm$ standard deviation (SD) for normally distributed variables, as median (min-max) for non-normally distributed variables, and count and percent for categorical variables. In the comparison of the data between the two groups, the independent samples t-test was used for the parametric data, and the Mann–Whitney *U*-test was used for the non-parametric data. The chi-square test was used to compare the categorical variables. For all analyses, a $p < 0.05$ was considered to be statistically significant.

Results

The mean age of the patients included in the study was 69 ± 12 years. Of the patients, 13 (37%) were female and 22 were male (63%). The duration of the pre-COVID-19 and COVID-19 periods was equal, as 22 months. The number of patients admitted during the COVID-19 period was 18 (51%). While small intestine resection was performed in 12 (34%) patients, colon resection was performed in 1 (3%) patient. Combined small intestine and colon resection were performed in 20 patients (57%). Two (6%) patients underwent no resection. A total of 16 (46%) patients were lost (Table 1). The COVID-19 RT-PCR tests performed during the hospitalization and follow-up of the patients were all negative.

When the demographic, clinical, and laboratory parameters of the AMI patients admitted during the pre-COVID-19 and COVID-19 periods were compared, no

Table 1. Clinical, demographic, and laboratory data of the patients (n = 35)

Variables	Value
Age, year*	69 $\pm$ 12 (range: 44-90)
Gender, F/M, n (%)	13/22 (37/63)
pH*	7.34 ($\pm$ 0.1)
Lactate*, mmol/L	4.8 $\pm$ 3.6
CRP*, mg/L	172 $\pm$ 130
APACHE II*	20 $\pm$ 9
Platelet*, ($\times 10^3$) (cells/mm ³)	283 $\pm$ 106
Ferritin†, ml/ng	147 (11-750)
D-dimer†, mg/dL	7 (1-66)
WBC†, ($\times 10^3$)	14 (3-24)
Creatinine†, mg/dl	1.4 (0.5-4.7)
AST†, (U/L)	37 (5-4113)
ALT†, (U/L)	20 (6-3717)
LDH†, (U/L)	302 (144-1303)
Total bilirubin†, mg/dl	0.8 (0.2-4)
N/L†	10 (1-57)
Total hospital stay†, days	10 (1-49)
Intensive care unit stay†, days	3 (0-35)
Pre-COVID-19/COVID-19 period, n (%)	17/18 (49/51)
Cause of mesenteric ischemia, n (%)	
Arterial embolism/thrombosis	24 (68.6)
Venous	3 (8.6)
Non-occlusive	8 (22.9)
Operation status, n (%)	
Small bowel resection	12 (34)
Colon resection	1 (3)
Small intestine + colon resection	20 (57)
No resection	2 (6)
Comorbid disease, n (%)	
AF	4 (11)
HT	8 (23)
DM	11 (31)
CAD	17 (49)
Mortality, n (%)	16 (46)

*mean ($\pm$ standard deviation).

†median (minimum-maximum).

F: female; M: male; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; N/L: neutrophil/lymphocyte; SMA: superior mesenteric artery; AF: atrial fibrillation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

significant differences were found in terms of age, gender, comorbidities, or etiology. However, patients admitted during the COVID-19 period had significantly

higher aminotransferase aspartate (AST) and lactate dehydrogenase (LDH) values ($p < 0.05$). While the total duration of hospital stay in both groups was similar, the median duration of intensive care unit (ICU) stay for the patients admitted during the COVID-19 period was significantly longer ($p = 0.02$). In addition, the mortality rate of the patients admitted during the COVID-19 period was significantly higher (61% and 29%) ($p = 0.05$) (Table 2).

When the demographic, clinical, and laboratory parameters of the patients who were lost and the patients who survived were compared, it was found that the patients who were lost had significantly higher arterial blood gas pH, lactate, ferritin, creatinine, ALT, and AST values when compared to the patients who survived ($p < 0.05$). It was found that the mean duration of hospital stay was significantly shorter in the patients who were lost when compared to the patients who survived ($p = 0.001$), but their duration of ICU stay was significantly longer ($p = 0.01$) (Table 3).

Discussion

The absence of a specific laboratory parameter that can be used in the diagnosis of AMI and the indefinite abdominal examination findings in AMI patients may cause a delay in the diagnosis. Moreover, AMI is more common in the elderly and patients with comorbid diseases. As a result, AMI has a high mortality rate. The COVID-19 pandemic, the effects of which are still ongoing, has caused an important public health problem that has given rise to medical and socioeconomic problems all over the world¹³. COVID-19 is a multisystemic disease with reported thromboembolic complications developing during and after its course¹⁴. During the course of COVID-19, it has been reported that the virus causes thrombosis in the microvascular system secondary to the colonization of the intestinal mucosa¹⁵.

The number of studies in the literature on the possible effect of COVID-19 infection on AMI is limited, and most of them have been presented in the form of case reports^{16,17}. Thus, it is thought that this study will make an important contribution to the literature.

AMI is a disease that affects the elderly and is observed at a higher rate in females¹⁸. Similar to the literature, in the present study, most of the patients were elderly. Unlike the results presented in the literature, however, most of the patients in this study were male. AMI most often develops secondary to thromboembolic events in the superior mesenteric artery.

Table 2. Comparison of clinical, demographic, and laboratory data of the patients diagnosed before and during the COVID-19 period

Variables	Pre-COVID-19 period (n = 17)	COVID-19 period (n = 18)	p
Age, year	72 ± 11	66 (± 12)	0.1
Gender, F/M, n (%)	6/11 (35/65)	7/11 (39/61)	0.8
pH*	7.33 (± 0.1)	7.35 (± 0.1)	0.6
Laktate*, mmol/L	4.7 ± 3.1	4.8 ± 4.1	0.9
CRP*, mg/L	156 ± 139	187 ± 124	0.5
APACHE II*	19 ± 8	21 ± 10	0.5
Platelet*, (× 10 ³)/mcL	285 ± 100	282 ± 113	0.9
Ferritin†, ml/ng	163 (17-405)	147 (11-750)	0.8
D-dimer†, mg/dL	9 (5-10)	7 (1-66)	0.7
WBC†, (× 10 ³)/mcL	15 (4-24)	15 (3-21)	0.6
Creatinine†, mg/dl	1.2 (0.5-2.7)	1.3 (0.6-4.7)	0.7
AST†, (U/L)	22 (5-1209)	48 (20-4113)	0.002
ALT†, (U/L)	16 (6-1664)	30 (10-3717)	0.1
LDH†, (U/L)	230 (144-653)	341 (182-1303)	0.02
Total bilirubin†, mg/dl	0.7 (0.2-2.8)	0.9 (0.4-4)	0.5
N/L†	11 (1-57)	10 (1-55)	0.9
Total hospital stay†, days	10 (1-30)	10 (1-49)	0.9
Intensive care unit stay†, days	2 (0-10)	4 (1-35)	0.02
Cause of mesenteric ischemia, n (%)			0.8
Arterial embolism/ thrombosis	12 (71)	12 (67)	
Venous	1 (6)	2 (11)	
Non-occlusive	4 (23)	4 (22)	
Operation status, n (%)			0.08
Small bowel resection	9 (53)	3 (17)	
Colon resection	0	1 (6)	
Small intestine + colon resection	8 (47)	12 (67)	
No resection	0	2 (11)	
Comorbid disease, n (%)			0.4
AF	2 (12)	2 (11)	
HT	6 (35)	2 (11)	
DM	6 (35)	5 (28)	
CAD	8 (47)	9 (50)	
Mortality, n (%)	5 (29)	11 (61)	0.05
Past COVID-19 infection, n (%)	-	4 (22)	-
Covid-19 vaccine status, n (%)	-	2 (11)	-

*mean (± standard deviation).

†median (minimum-maximum).

F: female; M: male; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; N/L: neutrophil/lymphocyte; SMA: superior mesenteric artery; AF: atrial fibrillation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

Table 3. Comparison of demographic, clinical, and laboratory data of the patients with and without exitus

Variables	Exitus (n = 16)	Survivors (n = 19)	p
Age, year	70 ± 11	68 (± 13)	0.7
Gender, F/M, n (%)	4/12 (25/75)	9/10 (47/53)	0.8
pH*	7.26 (± 0.1)	7.40 (± 0.1)	< 0.001
Laktate*, mmol/L	6.5 ± 3.9	3.3 ± 2.5	0.007
CRP*, mg/L	170 ± 139	173 ± 127	0.9
APACHE II*	26 ± 8	15 ± 5	< 0.001
Platelet*, (× 10 ³)/mcl	252 ± 83	309 ± 117	0.1
Ferritin†, ml/ng	269 (85-750)	118 (11-405)	0.05
D-dimer†, mg/dL	12 (4-66)	6 (1-19)	0.5
WBC†, (× 10 ³)/mcl	14 (3-24)	15 (9-21)	0.5
Creatinine†, mg/dl	1.8 (0.6-4.7)	1.1 (0.5-2.3)	0.03
AST†, (U/L)	102 (5-4113)	30 (8-81)	0.02
ALT†, (U/L)	47 (10-3717)	16 (6-88)	0.01
LDH†, (U/L)	335 (144-1303)	247 (171-653)	0.2
Total bilirubin†, mg/dl	0.8 (0.3-4)	0.5 (0.2-2.8)	0.9
N/L†	10 (1-57)	11 (1-26)	0.9
Total hospital stay†, days	6 (1-35)	11 (8-49)	0.001
Intensive care unit stay†, days	5 (1-35)	2 (0-7)	0.01
Patients in the COVID-19 period, n (%)	11 (69)	7 (37)	0.05
Cause of mesenteric ischemia, n (%)	12 (75)	12 (63)	0.7
Arterial embolism/thrombosis	1 (6)	2 (11)	
Venous	3 (19)	5 (26)	
Non-occlusive			
Operation status, n (%)	2 (13)	10 (52)	0.07
Small bowel resection	1 (6)	0	
Colon resection	12 (75)	8 (42)	
Small intestine + colon resection	1 (6)	1 (5)	
No resection			
Comorbid disease, n (%)			0.3
AF	0	4 (21)	
HT	3 (19)	5 (26)	
DM	6 (38)	5 (26)	
CAD	9 (56)	8 (42)	
Past COVID-19 infection, n (%)	1 (6)	3 (16)	0.4
COVID-19 vaccine status, n (%)	0	2 (11)	0.2

*mean (± standard deviation).

†median (minimum-maximum).

F: female; M: male; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; N/L: neutrophil/lymphocyte; SMA: superior mesenteric artery; AF: atrial fibrillation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

The incidence rates of arterial embolism/thrombosis, venous thrombosis, and NOMI in AMI have been reported in the literature as 65-75%, 5-15%, and 25%, respectively¹⁹. In this study, a result similar to that in the literature was obtained in terms of etiology.

AMI is an important medical emergency that may often require surgical resections involving the colon and/or small intestine for its treatment. It is seen that the small intestine is included in the resection in most cases¹³. In the present study, surgical intervention was

performed in 33 (94%) of the patients and small intestine resection was performed in 32 (91%) patients. Moreover, 2 (6%) patients who did not undergo resection were patients who were admitted during the COVID-19 period. One of them died. It was reported that AMI has a mortality rate of 26-97%²⁰. It is thought that the most important reasons for these high mortality rates are late diagnosis and the fact that this disease most often affects the elderly and individuals with comorbidities¹³. In this study, the overall mortality rate was 46%, which is consistent with the literature.

According to the current information, there are no studies on the possible effects of the COVID-19 period on the frequency and clinical course of AMI cases. When the number and demographic data of AMI patients admitted to our hospital during the pre-COVID-19 and COVID-19 pandemic periods were compared, it was found that the number of patients admitted to our hospital in both periods was similar (17 patients and 18 patients, respectively), and no significant differences were found between the mean age and gender distributions of the groups. However, the mortality rate in the COVID-19 period was significantly higher than in the pre-COVID-19 period (61% and 29%). The mortality rate of patients diagnosed with AMI during COVID-19 infection was reported as 62.5%. It was also reported that these patients had a worse prognosis¹⁶. When the literature searched, it was suggested that the COVID-19 pandemic may indirectly increase mortality and morbidity in emergency cases. It has been stated that the reason for this may be due to the delay in the admission of these patients to the emergency department during the COVID-19 period¹⁰⁻¹². In this study, the rate of patients who were vaccinated and had previous COVID-19 infection during the COVID-19 period was 33%. It is thought that the cause of the higher mortality rate, when compared to the pre-COVID-19 period, is not related to the direct effects of the virus, since the 2 patients who were vaccinated survived, only one of the 4 patients with prior COVID-19 infection was lost, and none of the patients were infected with COVID-19 during this treatment period. It is suggested that this increased mortality may have been caused by the late admission of these patients with AMI to the hospital during the COVID-19 period and delays in the treatment. However, multicentered studies with large patient populations are needed to confirm this hypothesis.

Leukocytosis and increased serum lactate values can be observed in 88-90% of patients with AMI²¹. Serum lactate values of > 2 mmol/L have been

associated with intestinal ischemia. In addition, a positive correlation was found between serum lactate values and mortality rate²². In the present study, increased lactate values and leukocytosis were also observed. CRP and ferritin are acute-phase reactants, and high serum levels of CRP and ferritin are observed in cases of inflammation and ischemia²³. It has also been reported that D-dimer values are increased in thromboembolic events and a high D-dimer value is an independent risk factor for intestinal ischemia^{24,25}. In this study, high serum CRP, D-dimer, and ferritin values were observed in the patients, similar to the literature. It has been reported that there is a positive correlation between the neutrophil-to-lymphocyte ratio (NLR) and mortality in AMI²⁶. The mean NLR has been reported to be quite high (19.5) in patients with AMI who had a prior COVID-19 infection¹⁶. In the present study, although it was observed that the NLR was increased in patients with AMI, no significant differences in the NLR were found between patients who were admitted in the different periods, and between patients who were lost and those who survived.

Lactic dehydrogenase and AST are laboratory parameters that increase during tissue ischemia and cell destruction. Serum levels of lactic dehydrogenase and AST also increase in systemic viral infections²⁷. In a study conducted during the pre-COVID-19 period, the mean LDH level in AMI patients was 365 U/L²⁸. LDH levels were found to have increased to 623 U/L in AMI patients in the COVID-19 period¹⁶. Serum AST values were found to be significantly higher in patients with intestinal ischemia when compared to those who did not have intestinal ischemia²⁹. It was also reported that serum AST levels were increased during the COVID-19 infection due to both increased viral load and tissue hypoperfusion³⁰. In the present study, the serum LDH and AST levels during the COVID-19 period were significantly higher than those during the pre-COVID period. Since patients admitted during the COVID-19 period were not infected with COVID-19 during their AMI clinic periods and only 22% had a prior COVID-19 infection, it is thought that these high LDH and AST levels could not be directly associated with the viral infection. In addition, there was no significant difference among the serum lactate, CRP, ferritin, D-dimer, and white blood cell levels of patients admitted in either period. There was also no significant difference between the two groups in terms of AMI etiologies, total duration of hospital stay, and comorbidities. However, the median duration of ICU stay for the patients admitted during the COVID-19

period was significantly higher than for the patients admitted during the pre-COVID-19 period. This is also an indirect indicator of high mortality during the COVID-19 period.

In the study, no significant differences were found between the patients who were lost and the patients who survived in terms of age, gender, comorbidities, causes of AMI, or surgical treatment methods. However, the blood pH, serum ferritin, and lactic acid levels were significantly higher in the patients who were lost. In addition, the median duration of hospital stay was significantly higher in the patients who survived, while the duration of ICU stay was significantly lower. It is thought that the increase in the duration of ICU stay negatively affects the mortality rates in AMI patients. Sepsis is a serious clinical condition that is frequently seen in the patients admitted to ICU and causes mortality. The risk of sepsis increases as the length of stay of the patient in the ICU is prolonged^{31,32}. In our cohort, the fact that the ICU stay was longer in the exitus group compared to the survivor group was found to be compatible with the literature. A high APACHE-II score is an important parameter that indicates mortality in AMI³³. In this study, the patients who were lost had a higher APACHE-II score when compared to the patients who survived, similar to the literature.

Limitations

The most important limitation of this study was its single centered and retrospective. Another limitation was the small number of our cohort.

Conclusion

AMI is an important condition affecting the elderly and patients with comorbidities and it still has high mortality rates. Although there has been no significant increase in the number of AMI cases during the COVID-19 period when compared to the pre-COVID-19 period, there has been a statistically significant increase in mortality in the COVID-19 period. It is thought that multicentered studies that include large patient populations are required to conclude the cause of increased mortality during the pandemic period in the patients with AMI.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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