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ORIGINAL RESEARCH

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

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ABSTRACT

Purpose/Aim: Acute mesenteric ischemia is a syndrome characterized by sudden onset abdominal pain followed by intestinal necrosis. Morbidity and mortality increase with delayed diagnosis. Even with the latest radiological diagnostic methods, early diagnosis and initiation of treatment can be delayed. Using an experimental model, here we aim to determine the relationship between the laboratory parameters used to detect acute mesenteric ischemia and the duration of irreversible ischemia. *Materials and Methods*: A total of 30 male Wistar albino rats were divided into five groups, all of which underwent general anesthesia: (i) Superior mesenteric artery (SMA) dissection with laparotomy was performed, and blood samples and intestinal segment samples were taken after 2 hr (Sham group); (ii) volvulus of one-third of the small intestines was performed manually by laparotomy, and blood samples and intestinal segment samples were taken after 2 hr (Volvulus group); (iii) SMA was ligated with laparotomy, and blood samples and intestinal segment samples were taken after 2 hr (SMA+ligated 2-hr group); (iv) SMA was ligated with laparotomy, and blood samples and intestinal segment samples were taken after 4 hr (SMA+ligated 4-hr group); and (v) SMA was ligated with laparotomy, and blood samples and intestinal segment samples were taken after 6 hr (SMA+ligated 6-hr group). *Results*: The mean lactate dehydrogenase (LDH) activities of the SMA+ligated 2-hr and SMA+ligated 6-hr groups were statistically higher than the control group ($p = .004$). Compared to the Sham and Volvulus groups, the mean lactate level of the SMA+ligated 6-hr group was significantly higher ($p = .004$). Compared to the Sham and Volvulus groups, the mean D-dimer levels of the SMA+ligated 4-hr and SMA+ligated 6-hr groups were significantly higher ($p = .004$ and .003, respectively). By histopathological evaluation, we found that pathological damage increased as the ischemia lengthened. *Conclusions*: Mesenteric ischemia leads to an irreversible loss of intestinal perfusion and an increase in parameters of ischemia. Irreversible tissue damage occurs after 4 hr of ischemia and peaks after 6 hr, whereas parameters of ischemia (D-dimer, LDH, and L-Lactate levels) are highest at 2 hr after the onset of ischemia.

Keywords: acute mesenteric ischemia; D-dimer; LDH; L-lactate

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INTRODUCTION

Acute mesenteric ischemia (AMI) is the syndrome caused by occlusion of the superior mesenteric artery, which causes abdominal pain and intestinal ischemia. AMI requires early diagnosis and surgical intervention.[1] One percent of patients at emergency departments have sudden onset abdominal pain, of which 0.1% have AMI.[2]

AMI is frequently diagnosed in elderly patients with a history of cerebrovascular, cardiac or peripheral artery disease. These patients typically present with unspecific symptoms, such as abdominal pain, nausea, vomiting, and rectal bleeding. The prognosis worsens with delayed diagnosis. Even with the latest radiological diagnostic methods, mortality is 40%–70%.[2,3] The most important factors affecting intestinal damage are mesenteric artery occlusion level, the rate of collateral flow, and ischemia duration. Restoration of intestinal blood flow during the first 5–6 hr from the onset of ischemia improves prognosis.[4] There is no laboratory test specifically showing AMI, but in the literature there are a lot of studies investigating serum levels of amylase, aspartate aminotransferase, LDH, creatinin phosphokinase, alpha-glutathion-S transferase, D-lactate, L-lactate, intestinal fatty acid binding protein, alkaline phospotase, etc. The results are controversial. In the experimental model D-dimer, L-lactate, and LDH levels were studied because of their popularity in this type of mesenteric ischemia studies. Also, it must be kept in mind that important things are availability and utility.

When the body's coagulation balance is disturbed, the fibrinolytic system is activated.[5] Fibrin formed during coagulation is broken down by plasminogen into fibrin degradation products. D-dimer is the fibrin degradation product stabilized by factor XIII during wound healing and blood coagulation. The increase of D-dimer levels also predicts the stage of the thrombosis pathological coagulation processes. D-dimer is an important parameter in disseminated intravascular coagulation, deep venous thrombosis, pulmonary emboli, coronary heart disease, and venous thrombotic conditions.[6] In AMI, damage to the vital organs occurs due to hypoxia resulting from the interruption of blood flow in the mesenteric vessels.[7] L-lactate is produced from pyruvate via the enzyme LDH during anaerobic glycolysis. Although a variety of early AMI parameters are being investigated, a specific marker has not yet been found. Many studies have shown a correlation between mesenteric ischemia and blood D-dimer, LDH, and L-lactate levels. Here, using a rat model, we aimed to test whether there is a correlation between these three parameters and the duration of obstructive (SMA ligation) and non-obstructive (volvulus, strangulation) mesenteric ischemia.

MATERIALS AND METHODS

Our study was approved by the Bezmialem Foundation University Laboratory Animals Local Ethical Committee. Thirty male Wistar-Albino rats weighing between 220 and 240 g were used. Rats were kept in cages in groups of six and fed standard food and water. After 12 hr of fasting, the rats were randomly assigned into five groups: (i) a Sham group ($n = 6$), designed to assess the risk of operation and anesthetic agent and to standardize the study in terms of ischemia, in which superior mesenteric artery (SMA) dissection with laparotomy was performed, and blood samples and intestinal segment samples were taken after 2 hr; (ii) volvulus of one-third of the small intestines was performed manually by laparotomy, and blood samples and intestinal segment samples were taken after fixing the twist of volvulus at 2nd hour (Volvulus group, $n = 6$); (iii) SMA was ligated with laparotomy, and blood samples and intestinal segment samples were taken after 2 hr (SMA+ligated 2-hr group, $n = 6$); (iv) SMA was ligated with laparotomy, and blood samples and intestinal segment samples were taken after 4 hr (SMA+ligated 4-hr group, $n = 6$); and (v) SMA was ligated with laparotomy, and blood samples and intestinal segment samples were taken after 6 hr (SMA+ligated 6-hr group, $n = 6$).

Ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg) were administrated intraperitoneal for general anesthesia. Laparotomy was performed on rats with a 2.5-cm incision. The superior mesenteric artery was dissected only in the Sham group. In the Volvulus group, volvulus was formed by twisting 3 cm of the intestinal segment around the distal segment. In the remaining three groups, SMA was dissected and ligated with 3/0 silk, and mesenteric ischemia was formed. Mesenteric ischemia was identified by the change of the intestinal segment's color, lack of pulse, and verified with a Doppler ultrasound. To prevent fluid and heat loss, the rat's abdomens were closed. After dissection of the Sham group, and 2, 4, and 6 hr later for the remaining groups, a second laparotomy was performed, and 3 cc intracardiac blood was obtained. In the Volvulus group, the volvulus segment was sampled for histopathological examination. In all other groups, the intestinal segment was sampled and resected according to proximal and distal borders of the demarcation line. Intracardiac blood was drawn to create hypovolemic shock and rats were sacrificed.

For biochemical analyses, blood samples from all rats were centrifuged at 1,500 $\times$ g for 10 min (VWR mega star 1.6). The separated serums were stored at -80°C. D-dimer and lactate tests were performed on the Vet Test Chemistry Analyzer model (IDEXX brand). The LDH tests were performed using an Abbott Architect C 16000.

TABLE 1 LDH averages of groups.

	LDH (U/L)			
	Mean ± SD	Min–Max	Median	*p*
Control group	610.7 ± 77.0	510–736	588	.003
Volvulus group	898.0 ± 472.8	408–1628	785	
Mesenteric ischemia 2nd hour group	1389.2 ± 233.3	1,143–1,778	1,350	
Mesenteric ischemia 4th hour group	1533.7 ± 890.5	667–2,686	1,246	
Mesenteric ischemia 6th hour group	1679.5 ± 276.1	1,426–2,006	1,599	

There was a statistically significant difference in LDH averages among the groups ($p = .003$). The LDH averages of the mesenteric ischemia 2nd and 6th hour groups were statistically higher than the control group (both = $p = .004$).

For the histopathological examination, pathology materials were fixated with 10% formaldehyde. Sections prepared from paraffin blocks were stained with hemotoxylin-eosin by a pathologist who did not know from which groups the specimens were taken. After dyeing, sections were examined by light microscope. The level of ischemia was graded from 0 to 4 (Grade 0 = normal mucosa, Grade 4 = mucosal necrosis).

IBM SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics (mean, standard deviation, minimum, maximum for numerical variables, and percentages) were calculated. The Kruskal–Wallis test was used to compare the numerical variables in the independent, more than groups since normal distribution conditions were not provided. Subgroup analyses were done using the Mann–Whitney *U*-test and interpreted by Bonferroni correction. The ratios in groups were compared with chi-square analysis. Monte Carlo simulation was applied when conditions were not met. A statistical significance level of alpha was accepted as $p < .05$.

TABLE 2 Lactate averages of groups.

	Laktat (mmol/L)			
	Mean ± SD	Min–Max	Median	*p*
Control group	2.47 ± 0.53	1.88–3.3	2.575	<.001
Volvulus group	2.81 ± 0.70	2.04–3.64	2.83	
Mesenteric ischemia 2nd hour group	3.42 ± 0.47	2.59–3.9	3.57	
Mesenteric ischemia 4th hour group	4.60 ± 1.16	3.77–6.91	4.195	
Mesenteric ischemia 6th hour group	5.46 ± 1.39	3.3–7.33	5.36	

There was a statistically significant difference in the Lactate averages between the group ($p < .001$). Lactate averages of 6th hour mesenteric ischemia group were statistically higher than control group and Volvulus group (both $p = .004$).

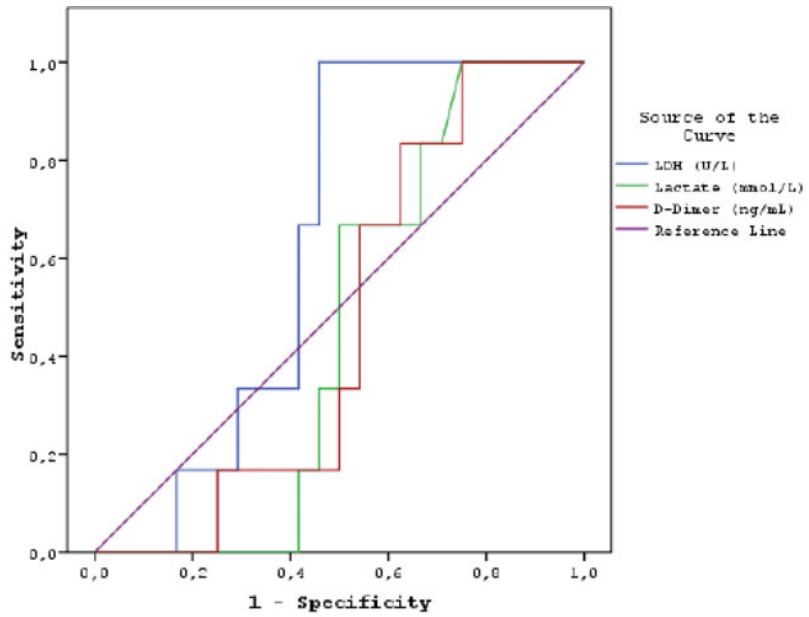
RESULTS

For the mean LDH values, we detected significant differences among the groups ($p = .003$). The mean lactate dehydrogenase (LDH) activities of the SMA+ligated 2-hr and SMA+ligated 6-hr groups were statistically higher than the control group ($p = .004$). We also detected significant differences among the groups for lactate levels ($p < .001$). The mean lactate value of the SMA+ligated 6-hr group was higher than the Sham and Volvulus groups (both $p = .004$). We also detected significant differences among the groups for D-dimer content ($p < .001$). The D-dimer values of the SMA+ligated 4-hr and SMA+ligated 6-hr groups were higher than the control (both $p = .003$) and the volvulus (both $p = .004$) groups (Tables 1–3). Sub-epithelial congestion increased as ischemia increased. The first change is dilated vascular structures in lamina propria (Picture 1). No congestion was detected in the Volvulus and SMA+ligated 2-hr groups, whereas 50% congestion was detected in the SMA+ligated 6-hr group. The ischemia at 2nd hour in volvulus and SMA + ligated 2 hr groups did not cause congestion detectable in pathological specimens because 2 hr was not enough for development of congestion. Massive epithelium dissociation and necrosis in the villi were observed in the Volvulus group. In the SMA+ligated 6-hr group, the epithelium was separated from the lamina propria

TABLE 3 D-dimer averages of groups.

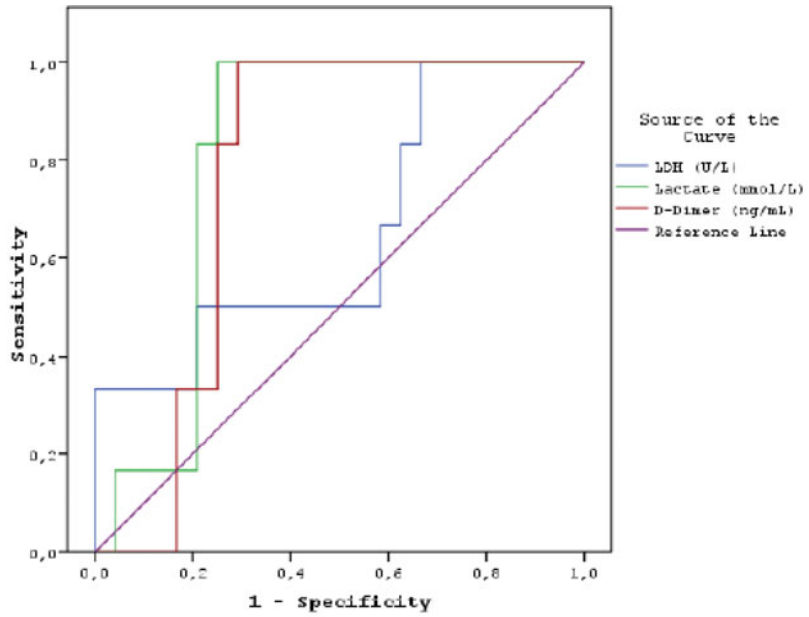
	D-Dimer (ng/mL)			
	Mean ± SD	Min–Max	Median	*p*
Control group	157.5 ± 36.0	140–230	140	<.001
Volvulus group	182.2 ± 56.6	140–284	159.5	
Mesenteric ischemia 2nd hour group	287.7 ± 146.7	147–564	258.5	
Mesenteric ischemia 4th hour group	472.8 ± 87.0	356–573	455.5	
Mesenteric ischemia 6th hour group	594.2 ± 132.6	379–780	592	

There was a statistically significant difference between the D-Dimer averages in the groups ($p < .001$). The mean D-dimer levels of the 4th and 6th hour mesenteric ischemia groups were statistically higher than the control group and the Volvulus Group (control group, both $p = .003$ and Volvulus group, both $p = .004$).



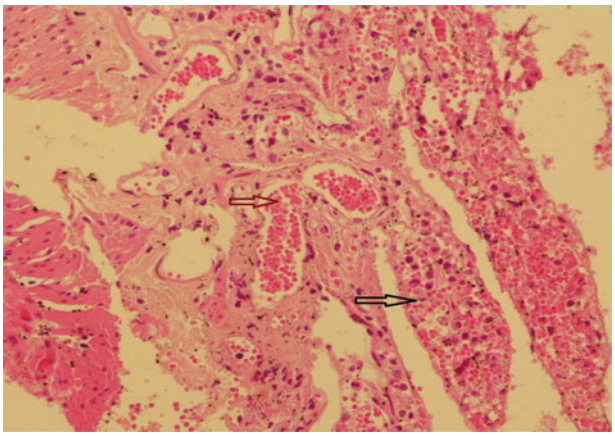
Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
LDH (U/L)	0,632	0,440	0,824
Lactate (mmol/L)	0,455	0,256	0,653
D-Dimer (ng/mL)	0,465	0,258	0,673

GRAPHIC 1 Mesenteric Ischemia 2nd hour group.



Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
LDH (U/L)	0,653	0,395	0,910
Lactate (mmol/L)	0,813	0,660	0,965
D-Dimer (ng/mL)	0,771	0,608	0,933

GRAPHIC 2 Mesenteric Ischemia 4th hour group.



PICTURE 1 Nude villi and dilated vascular structures in lamina propria.

TABLE 4 Subgroup analysis.

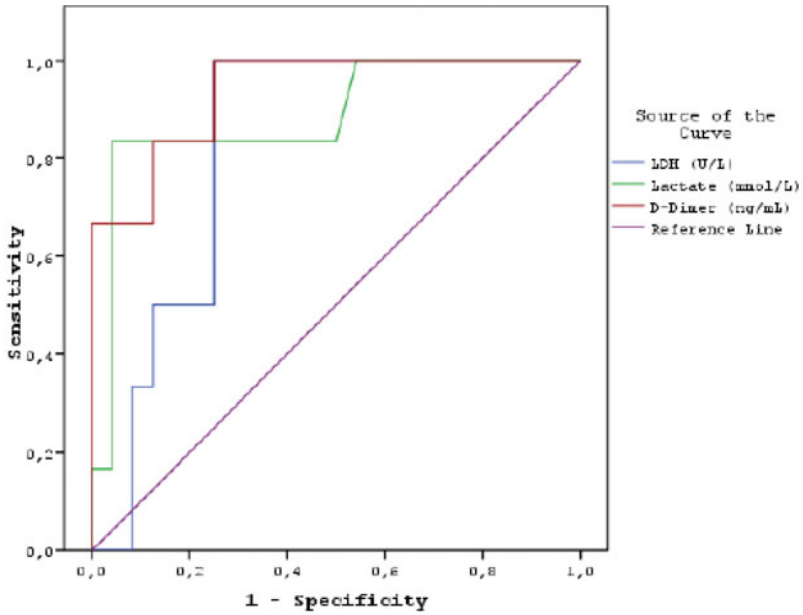
	LDH (U/L) p
Control vs. Volvulus	.423
Control vs. Mesenteric ischemia 2 hr	.004
Control vs. Mesenteric ischemia 4 hr	.006
Control vs. Mesenteric ischemia 6 hr	.004
Volvulus vs. Mesenteric ischemia 2 hr	.078
Volvulus vs. Mesenteric ischemia 4 hr	.150
Volvulus vs. Mesenteric ischemia 6 hr	.016
Mesenteric ischemia 2 hr vs. Mesenteric ischemia 4 hr	.873
Mesenteric ischemia 2 hr vs. Mesenteric ischemia 6 hr	.078
Mesenteric ischemia 4 hr vs. Mesenteric ischemia 6 hr	.631

Bonferroni correction $p < .005$. hr: hour.

due to bleeding. In conclusion, we found that pathological damage is positively correlated with the length of the ischemic period (Picture 2). According to the subgroup analysis with Bonferroni correction, mesenteric ischemia in 2 and 6 hr LDH levels were correlated with time when compared to control group. Other comparisons between volvulus and mesenteric ischemia and among mesenteric ischemia durations showed no correlation (Table 4). For this small sized experimental study definite cut off values were not detected. Sensitivity and specificity were analyzed. Related graphics showed specificity and sensitivity results for the parameters studied (Graphics 1–3). But, since this is an experimental study in a small number of rats, the results are controversial (Table 5).

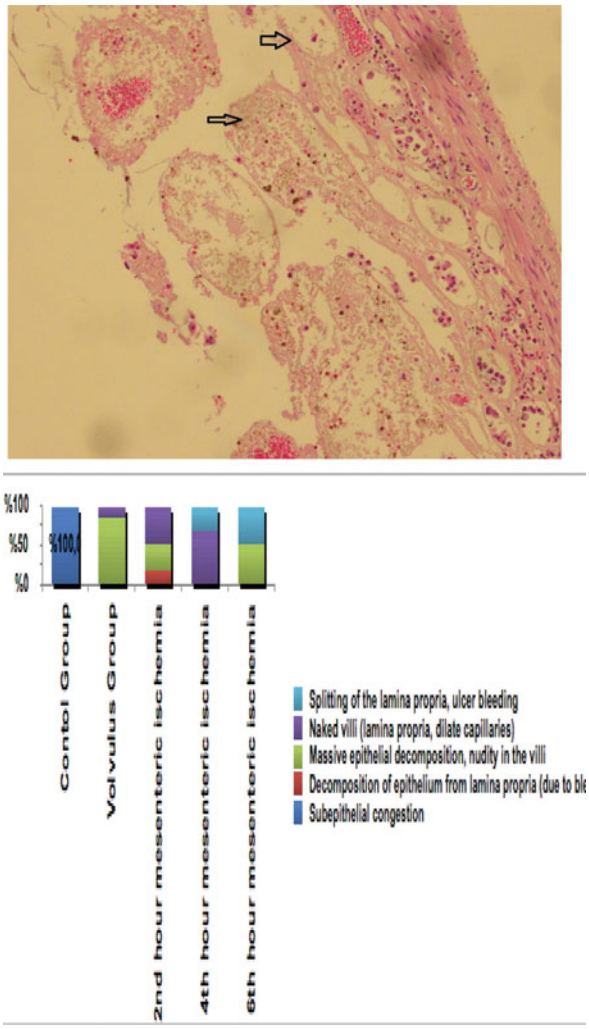
DISCUSSION

AMI is a life-threatening, acute abdominal disorder that results in sudden failure of the mesenteric blood supply.[7] Superior mesenteric artery (SMA) or its branches embolism are the most common clinical causes of AMI.[8] In 70%–80% of cases, arterial embolus or thrombosis within the SMA is the main cause



Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
LDH (U/L)	0,826	0,681	0,972
Lactate (mmol/L)	0,885	0,721	1,050
D-Dimer (ng/mL)	0,938	0,843	1,032

GRAPHIC 3 Mesenteric ischemia 6th hour group.



PICTURE 2 Splitting of laminar propria, ulcer, bleeding.

of AMI. Superior mesenteric vein (SMV) thrombosis (5%–10%) and non-occlusive mesenteric ischemia (NOMI, 20%) are other vascular and extravascular causes.[9,10] Vasculitis is a common cause of mesenteric ischemia in younger people with autoimmune disease.[10] Despite the differences in its etiology, intestinal gangrene and necrosis is the fatal end of AMI.[9,10] Volvulus is within the scope of this study since it is the ultimate cause of intestinal gangrene and necrosis. In this study, we compare the main vascular cause of AMI with other nonvascular causes, such as volvulus and strangulation. One-third of the small intestines of rats were experimentally manually strangulated, and AMI models were created. Intestinal intussusception, volvulus, strangulated hernias, and obstruction are rare extravascular causes of AMI. Although venous outflow seems impaired, it still causes increase in biomarker levels in this study, perhaps because of partial impairment. Volvulus was fixed before obtaining the blood sample; also we think that there is still somewhat venous circulation in the first 2 hr.

The most important factors determining intestinal injury are the level of mesenteric artery obstruction, the rate of collateral flow, and the duration of ischemia. Intestinal ischemia can be seen in a wide range of clinical and pathological conditions. Pathological findings can range from mild changes to total necrosis and gangrene. Also, biomarker levels are affected by the amount of ischemic bowel, the length was not measured because the experiment was based on total ligation of SMA for each group. It was seen that similar length ischemic segments were detected by the eye with varying degrees of color changes according to time passed. In experimental studies, structural changes in the mucosa begin within 10 min of SMA occlusion.[4] Although necrosis and edema in the submucosa can be regenerated, perforation or peritonitis can occur if the necrosis reaches the muscular and serosal layers.[4] Therefore, early diagnosis, vascular imaging methods, vascular surgery, and intensive care support can improve the prognosis of mesenteric ischemia.

TABLE 5 Sensitivity and specificity values of the parameters.

Test result variable (s)	Positive if greater than or equal to (a)	Sensitivity	Specificity
LDH (U/L)	1230.5	0.500	0.500
	1271	0.500	0.542
	1350	0.500	0,583
	1420.5	0.500	0.625
	1437.5	0.500	0.667
	1451	0.500	0.708
	1481.5	0.500	0.750
	1513	0.500	0.792
Lactate (mmol/L)	3.745	1.000	0.750
	3.835	0.833	0.750
	3.935	0.833	0.792
	4.045	0.667	0.792
D-Dimer (ng/mL)	329.5	1.000	0.708
	367.5	0.833	0.708
	402.5	0.833	0.750
	455.5	0.500	0.750

Differential diagnosis of AMI includes peptic ulcer disease, intestinal obstruction, complications of cholelithiasis, acute pancreatitis, acute appendicitis, and inflammatory bowel disease. The most important factors in the prognosis are early diagnosis and appropriate treatment before irreversible damage to the intestinal wall.[10,12] A variety of potential differential diagnoses can delay definitive diagnosis of AMI.[12] Serum phosphorus (P) level is the longest established parameter used in AMI diagnosis.[13] Jamieson et al. detected higher serum P levels in ischemia groups, but there were no significant findings of time-dependent elevation.[14] Therefore, the search for new markers of AMI is ongoing. D-dimer, whose value is increased by the activation of the coagulation system, is a candidate marker of AMI. D-dimer has long been recognized as a useful marker in the diagnosis of pulmonary embolism and deep vein thrombosis;[15,16] however,

there is a need for further work in arterial thrombotic conditions. Acosta et al. identified D-dimer as a useful marker of differential diagnosis of AMI in patients.[17] In a clinical trial with thrombus embolization and an experimental study with SMA ligation, D-dimer was elevated in the early period.[18,19] Conversely, there are studies showing that D-dimer levels do not increase with arterial occlusion. Elevated D-dimer values were detected following surgery, trauma, and intramuscular injection.[20,21] Yıldırım et al. reported an AMI mortality rate of 58% in 46 patients. D-dimer, white blood cell (WBC) count, and blood pH values were not statistically associated with mortality.[22] In a study by Chiu et al., 67 patients with D-dimer increase were investigated with AMI suspicion, of which 23 were diagnosed with AMI.[23] When the D-dimer values of these patients were compared, no significant difference was found between the AMI-diagnosed and non-AMI-diagnosed patients. In another clinical trial, it was reported that the plasma D-dimer concentration might be useful in the differential diagnosis of AMI from acute pancreatitis and acute cholecystitis.[11]

There is now need for further studies in which the threshold value of D-dimer is quantitatively determined, and differential disorders are involved as control groups. However, in studies by Acosta et al.[5,17] and Kurt et al.,[3] increased D-dimer levels were associated with AMI. In our study, D-dimer levels were higher in the ischemic group compared to the Sham group. Also, we detected a positive correlation between D-dimer level and duration of ischemia. By histopathological examination, we found that damage increased with prolonged ischemia. The D-dimer level in the control group was attributed to surgery-associated tissue damage. In our study, serum LDH and lactate levels were significantly higher in all ischemia groups compared to the Sham group. Furthermore, serum LDH and lactate levels increase with increasing ischemia time. The lactate increase can be accounted for by the high demand of the intestine for blood and oxygen and, thus, its high ischemic vulnerability.[24]

Based on our findings, we conclude that if D-dimer, lactate, and LDH values are evaluated, with further clinical and experimental studies, it may be possible to provide preliminary information with AMI duration. Thus, these parameters, together with radiological examinations, might help in the early diagnosis of AMI.

DECLARATION OF INTEREST

No potential conflicts of interest were disclosed.

FUNDING

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