PAPER DETAILS

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Diagnostic and prognostic value of the ratio of mean platelet volume to platelet count in acute mesenteric ischemia

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ABSTRACT

Introduction: Acute mesenteric ischemia (AMI) is a condition in which there is a sudden cessation of blood supply to a particular intestinal segment and consequent cellular damage. Although it has a low incidence of approximately 0.09-0.2% of all emergency surgery admissions, AMI is a severe condition that can cause high early mortality. A direct relationship between an increased mean platelet volume (MPV) and acute thrombotic events has been shown in recent years. we aimed to find out whether the diagnosis of mesenteric ischemia and the amount of bowel segment affected by ischemia will guide clinicians preoperatively with these markers

Material and Method: A total of 57 cases with bowel resection due to mesenteric ischemia were included in the study. The gender, age, serum platelet (PLT), MPV, white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), Albumin, CRP, neutrophil-lymphocyte ratio (NLR), MPV/Platelet Count, and CRP-albumin ratio (CAR) levels at the time of admission, operation time, length of resected bowel segment, length of hospital stay, presence of necrosis and perforation from pathology reports, and length of bowel segment leading to necrosis were scanned.

Results: A moderate (moderate) negative correlation was found between the length of resected bowel segment and PLT ($P<0.001$; $r=-0.685$). A moderate positive significant correlation was found between resection length and MPV ($P<0.001$; $r=0.565$). A high significant positive correlation was found between resection length and MPV/PC ($P<0.001$; $r=0.857$). PLT, WBC and MPV/PC values were statistically different between the perforated group and no-perforation group ($p=0.009$, $p=0.024$, $p=0.010$). WBC and MPV/PC values were significantly higher in the perforated group.

Conclusion: MPV/PC and PLT value at hospital admission is a reliable and simple predictive factor in determining perforation and the amount of bowel segment affected in patients with acute mesenteric ischemia.

Keywords: Acute mesenteric ischemia, mean platelet volume, platelet indices, bowel necrosis

INTRODUCTION

Acute mesenteric ischemia (AMI) is a condition in which there is a sudden cessation of blood supply to a particular intestinal segment and consequent cellular damage (1). Although it has a low incidence of approximately 0.09-0.2% of all emergency surgery admissions, AMI is a severe condition that can cause high early mortality. If early and effective intervention is not performed, the risk of mortality increases even more (2). Rapid, easily accessible, uncomplicated, person-independent methods are needed to diagnose AMI, usually due to non-specific clinical findings and diagnostic limitations. Early detection of AMI, particularly before signs of multi-organ failure or clinical peritonitis appear, reduces morbidity and mortality, improves patient outcomes, and reduces surgical complications (3,4).

Decreased mesenteric blood flow resulting from a sudden arterial occlusion results in reduced oxygen transport that cannot meet the metabolic needs of the visceral organs. However, the first response to this condition is vasodilation, the response changes in the direction of vasoconstriction in prolonged ischemia. Systemic inflammatory pathways are activated with mucosal and submucosal damage (5).

Although serum laboratory tests are predictive in diagnosing acute mesenteric ischemia, they are not helpful in the definitive diagnosis. There is a left shift in neutrophils in AMI, an increase in leukocytes and CRP. Still, these parameters are not specific as they are elevated in all inflammation and infectious diseases (6). Metabolic acidosis occurs in approximately half of the patients. In cases of necrosis, increased non-AMI-specific laboratory

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tests such as hyperamylasemia, prerenal azotemia, increased phosphate, and alkaline phosphatase levels are also seen (7). There are also studies evaluating the increase in lactate level as a marker showing ischemia (8). The number of studies focusing on investigating a specific biochemical and serological parameter in the early diagnosis of AMI has increased recently (9).

In AMI, excessive inflammation and infection have prompted researchers to investigate inflammation-related hemogram parameters. Among these, mean platelet volume (MPV) has been a parameter that has been emphasized in many studies (10). In the study of Türkoğlu A et al. (11), it was shown that a high MPV level was associated with AMI in patients who applied to the emergency department with abdominal pain. In addition, another study concluded that patients with high MPV had worse survival in mesenteric ischemia (12). MPV is an indicator of the size and activation of platelets, and high MPV levels reflect increased production and activation of platelets. An increase in MPV indicates increased production of large platelets. This is a harbinger of more enzymatic activity and high thrombogenic potential. These platelets are more active, and increased activity causes an increase in the expression of secreted molecules such as thromboxane A2 and p-selectin and adhesion molecules. This triggers binding to the endothelium (13). In light of this information, increased MPV rates in mesenteric ischemia patients are expected. A direct relationship has been shown between increased MPV and acute thrombotic events such as acute myocardial infarction, unstable angina, and stroke (14-16). In this study, we aimed to determine whether the diagnosis of mesenteric ischemia and the amount of bowel segment affected by ischemia will guide clinicians preoperatively with these markers. Ours is the first article investigating the relationship between biochemical markers and the intestinal segment affected in mesenteric ischemia to the best of our knowledge.

MATERIAL AND METHOD

Ethics committee approval of this study was received from Hitit University Non-interventional Researches Ethics Committee (Date: 27/09/2021, Decision No: 2021-78). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

For this study, a total of 317 cases were found by scanning all segmental and subtotal small bowel resections performed in Hitit University Department of General Surgery between 01.01.2016 and 15.05.2021. Among these cases, 81 patients remained after excluding cases that had resection due to oncological surgeries, incarcerated inguinal hernias, and other causes other than mesenteric ischemia. After examining the surgical notes and pathology reports of these 81 cases, it was observed that other intra-abdominal pathologies were found in 18 cases, and they were excluded from the study. Five more patients were excluded due to the presence of known hematological disease, and a total of 57 cases with bowel resection due to mesenteric ischemia were included in the study.

From the hospital information management system and patient files of 57 patients included in the study, the gender, age, serum platelet (PLT), MPV, white blood cell count(WBC), neutrophil count (NEU), lymphocyte count (LYM), Albumin, CRP, neutrophil-lymphocyte ratio (NLR), MPV/Platelet Count and CRP-albumin ratio (CAR) levels at the time of admission, operation time, length of resected bowel segment, length of hospital stay, presence of necrosis and perforation from pathology reports, and length of bowel segment leading to necrosis were scanned.

Statistical Analysis

Statistical analyzes of the data collected in our study were performed with the SPSS (SPSS Inc., Chicago, IL, USA) package program. Shapiro-Wilk test was used to determine whether the data obtained with the measurement were in accordance with the normal distribution. Descriptive statistics of continuous variables suitable for normal distribution were reported as mean ± standard deviation. Descriptive statistics for non-normally distributed data were presented as median ± interquartile range (IQR). Categorical variables were presented with frequency (n). Independent groups t-test for normally distributed data in comparison of patient age, operative time, hospital stay, platelet (PLT), MPV, white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), Albumin, CRP, neutrophil-lymphocyte ratio (NLR), MPV/Platelet Count and CRP-albumin ratio (CAR) values by perforation status, and for data not normally distributed Mann-Whitney U test was used. The data distribution analyzed the relationship between numerical variables using the Spearman correlation coefficient. ROC (Receiver Working Characteristic) analysis was used to determine whether PLT, MPV, WBC, NEU, LYM, Albumin, CRP, NLR, MPV/PC, and CAR values are prognostic indicators for perforation prediction. As a result of the ROC analysis, the area under the ROC curves (AUC) and the 95% confidence interval of this area were determined. The AUC values obtained from the analysis were 0.9-1: excellent, 0.8-0.9: good, 0.7-0.8: moderate, 0.6-0.7: poor, and 0.5-0, 6: evaluated as unsuccessful. The best cut-off point in the ROC analysis was determined by the Youden index (maximum sensitivity and selectivity). To determine the discriminating power of the parameters that can

be used to diagnose perforation, the cut-off points are determined after the ROC analysis. And the sensitivity, selectivity, positive-negative predictive values, and likelihood ratio (+) values were calculated. Univariate and Multivariate Binary Logistic Regression analyses were used to determine the risk factors in the formation of perforation. Odds ratios (OR) with 95% confidence intervals were calculated for each parameter found to be statistically significant in Logistic Regression analysis. Statistical significance level was accepted as p <0.05.

RESULTS

There were 57 patients in this study. Bowel perforation due to mesenteric ischemia was observed in 17.5% (n=10) of the cases, and perforation was not observed in 82.5% (n=47) of the patients. Twentythree (40.4%) patients were female, and 34 (59.6%) were male. The mean age of the patients in this study was 71.05±12.03 (48-97). The mean age of Group 1 (with bowel perforation) was 71.90±11.42 (50-91), and the mean age of Group 2 (without bowel perforation) was 70.87±12.26 (48-97). The age of the patients was not statistically different between the groups (p=0.809). The mean operation time of all patients was 110.42±27.96 (60-180). The operation times of Group 1 were 122.5±33.63 (75-180), and the operation times of Group 2 were 107.85±26.31 (60-169). Operation times were not statistically different between the groups (p=0.134). The mean hospital stay of all patients was 15.12±24.19 (1-181). The duration of hospitalization in the group with perforation was 17.20±15.82 (median±IQR: 8.5±30), and the duration of hospitalization in the group without perforation was 14.68±25.73 (median±IQR: 10±7). The patients' length of stay was not statistically different between the groups (p=0.760). The female-male ratios were not statistically different between the groups (p=0.178). In the perforated group, 20% (n=2) were female and 80% (n=8) male, 44.7% (n=21) female and 55.3% (n=26) male of the non-perforated group .

The correlation analysis results between the resected bowel segment length and PLT, MPV, WBC, NEU, LYM, Alb, CRP, NLR, MPV/PC, and CAR are given in Table 1. A moderate negative correlation was found between the length of resected bowel segment and PLT (P<0.001; r=-0.685). A moderate positive significant correlation was found between resection length and MPV (P<0.001; r=0.565). A high significant positive correlation was found between resection length and MPV/PC (P<0.001; r=0.857). A very weak (negligible) significant positive correlation was found between resection length and CAR (P=0.047; r=0.264). No significant correlation was found between the length of resected bowel segment and other blood values (P>0.05).

Table 1. Results of correlation analysis between resected bowel segment length and PLT, MPV, WBC, NEU, LYM, Alb, CRP, NLR, MPV/PC, and CAR (n=57)

		Length of resected bowel
PLT	r	-0.685**
	p	<0.001
MPV	r	0.565**
	p	<0.001
WBC	r	0.200
	p	0.136
NEU	r	0.133
	p	0.324
LYM	r	0.053
	p	0.696
Alb	r	-0.213
	p	0.112
CRP	r	0.231
	p	0.083
NLR	r	0.221
	p	0.099
MPV/PC	r	0.857**
	p	<0.001
CAR	r	0.264*
	p	0.047

Spearman correlation coefficient, PLT: platelets, MPV: Mean platelet volume, WBC: White blood cell count, NEU: Neutrophil, LYM: Lymphocyte, CRP: c-reactive protein, NLR: neutrophil to lymphocyte ratio, MPV/PC: Mean platelet volume to platelet count, CAR: c-reactive protein to albumin ratio

The comparison of PLT, MPV, WBC, NEU, LYM, Albumin, CRP, NLR, MPV/PC, CAR values of patients in Group 1 and Group 2 is presented in **Table 2**. PLT, WBC and MPV/PC values were statistically different between the groups (p=0.009, p=0.024, p=0.010 **Table 2**). WBC and MPV/PC values were significantly higher in the perforated group (**Table 2**). PLT values were significantly lower in the perforated group (**Table 2**). MPV, NEU, LYM, Albumin, CRP, NLR, and CAR values were not statistically different (P>0.05). Distribution is shown in **Figure 1.**

Table 2. Comparison of laboratory values, NLR, MPV/PC, and CAR values between groups

	Perforation		P values
	No (n=47)	Yes (n=10)	
PLT	254.6±64.80	192.6±70.23	0.009[a]
MPV	10.64±1.470	11.08±1.423	0.395[a]
WBC	12.86±6.460	18.23±7.55	0.024[a]
NEU	10±9.26	10.92±7.05	0.390[b]
LYM	0.99±1.03	1.32±0.81	0.450[b]
Albumin	3.14±0.717	2.82±0.763	0.215[a]
CRP	113±121.9	96±77.58	0.916[b]
NLR	10.23±12.52	9.82±10.99	0.629[b]
MPV/PC	0.042±0.018	0.068±0.030	0.010[b]
CAR	38.13±44.53	29.05±37.29	0.660[b]

a Student's t-test with mean ± standard deviation (SD), b Mann Whitney U test with median ± interquartile range (IQR), PLT: platelets, MPV: Mean platelet volume, WBC: White blood cell count, NEU: Neutrophil, LYM: Lymphocyte, CRP: c-reactive protein, NLR: neutrophil to lymphocyte ratio, MPV/PC: Mean platelet volume to platelet count, CAR: c-reactive protein to albumin ratio

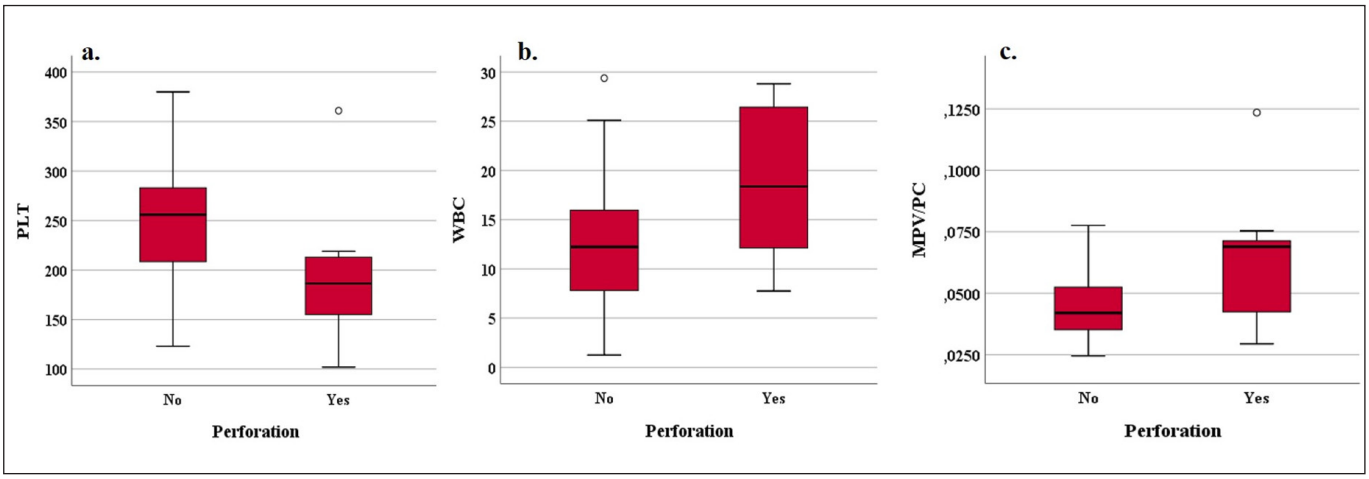

Figure 1. Boxplot of the distribution of (a.) PLT: platelets, (b.) WBC: White blood cell count and (c.) MPV/PC: Mean platelet volume to platelet count values among groups

As a result of blood parameters and ROC analysis for NLR, MPV/PC and CAR, MPV, WBC, NEU, LYM, Albumin, CRP, NLR and CAR parameters were insignificant in the differentiation of perforation (Respectively; AUC= 0.591; p=0.367, AUC=0.696; p=0.054, AUC=0.587; p=0.390, AUC=0.577; p=0.450, AUC=0.634; p=0.186, AUC=0.511; p=0.916, AUC= 0.549; p= 0.629, AUC=0.545; p= 0.660). As a result of ROC analysis, PLT and MPV/PC parameters were found to be significant in perforation discrimination (AUC=0.777 (0.606-0.947), p=0.006, AUC=0.762 (0.581-0.943), p=0.010 **Table 4**) The number of patients with successful categorization of the parameters in the prediction of perforation according to the cut-off values chosen as a result of the ROC analysis is shown in **Table 3** to determine the success of the PLT and MPV/PC values in the prediction of perforation.

In addition, the 95% confidence intervals were calculated as a result of the ROC analysis, together with the AUC values and the sensitivity, selectivity, positive-negative predictive values, and the likelihood ratio (+) values calculated using **Table 3** values, are presented in **Table 4.** The ROC curve is shown in **Figure 3**. The cut-off point for the PLT value was found to be 220.5. Classification success for this cut-off point; sensitivity was 90%, and selectivity was 72.3% (**Table 4**). The cut-off point for the MPV/PC value was found to be 0.066. Classification success for this cut-off point; sensitivity was 60%, and selectivity was 91.4% (**Table 4**).

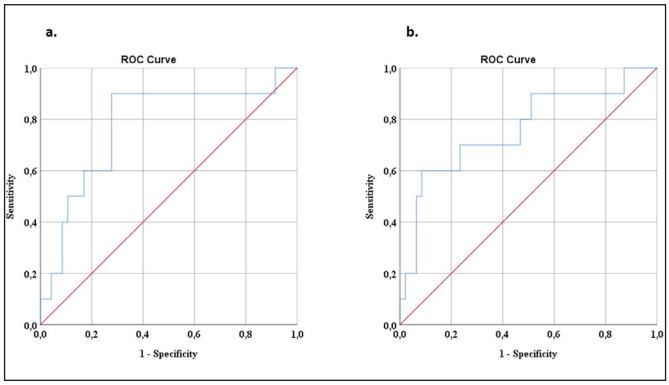

Figure 3. ROC curves for (a.) PLT: platelets, (b.) MPV/PC: Mean platelet volume to platelet count values in perforation prediction

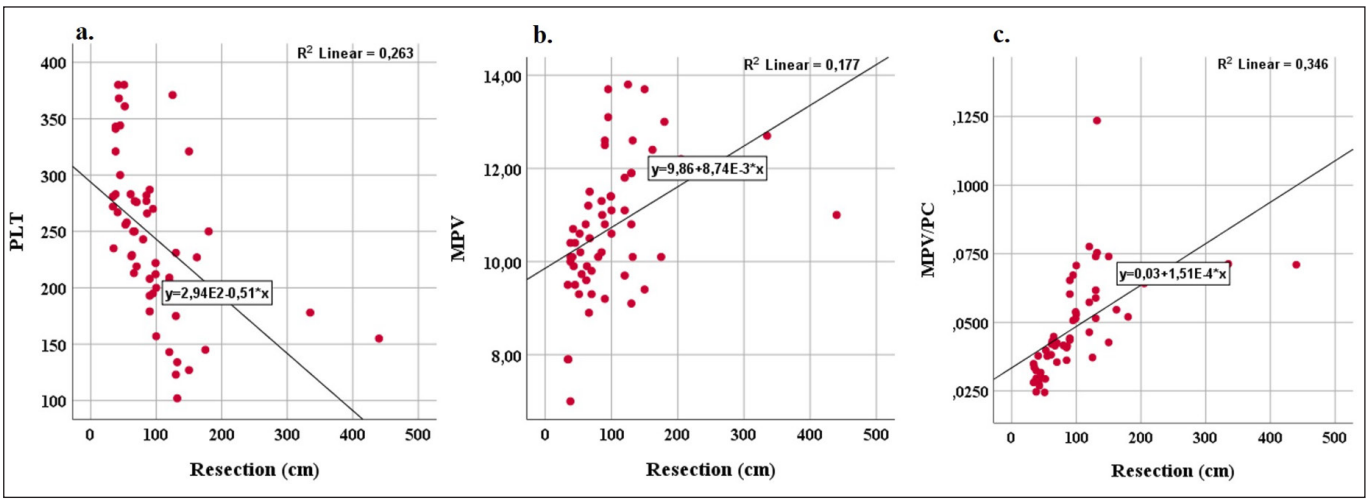

Figure 2. Scatter plot of the distribution of (a.) PLT: platelets, (b.) MPV: Mean platelet volume and (c.) MPV/PC: Mean platelet volume to platelet count values among resection

Table 3. The success of cut-off values determined by ROC analysis in perforation prediction

	Cut-off	Perforation		Total
		No	Yes	
PLT	> 220.5	34	1	35
	≤ 220.5	13	9	22
MPV/PC	< 0.066	43	4	47
	≥ 0.066	4	6	10
Total		47	10	57

PLT: platelets, MPV/PC: Mean platelet volume to platelet count

Table 4. Results of ROC analysis; and sensitivity, specificity, PPV, NPV, and likelihood ratio (+) values of PLT and MPV/PC values for prediction of perforation

	PLT	MPV/PC
AUC (95% CI)	0.777 (0.606-0.947)	0.762 (0.581-0.943)
P values	0.006	0.010
Cut off	≤ 220.5	≥ 0.066
Sensitivity (95% CI)	0.9 (0.541-0.994)	0.6 (0.273-0.863)
Specificity (95% CI)	0.723 (0.571-0.839)	0.914 (0.787-0.972)
PPV (95% CI)	0.409 (0.214-0.633)	0.6 (0.273-0.863)
NPV (95% CI)	0.971 (0.833-0.998)	0.914 (0.787-0.972)
LR+ (95% CI)	3.25 (1.96-5.39)	7.05 (2.42-20.45)

ROC: Receiver Operating Characteristic, PPV: positive predictive value, NPV: negative predictive value, AUC: Area under the curve, CI: Confidence interval
PLT: platelets, MPV/PC: Mean platelet volume to platelet count

Univariate and Multivariate Binary Logistic Regression analysis results were performed to determine the effective parameters in the formation of perforation, and the odds ratio (OR) and 95% confidence intervals for each statistically significant parameter are presented in **Table 5.** Gender and age were statistically insignificant in the univariate model (p=0.164, p=0.805, respectively; **Table 5**). The OR (95% CI) for PLT and MPV/PC were 23.53 (2.7-204.6) and 16.12 (3.16-82.1), respectively (p=0.004, p=0.001; **Table 5**). In the multivariate model, MPV/PC was statistically insignificant (p=0.105). The OR (95% CI) for the statistically significant PLT was 11.33 (1.04-122.3) (p=0.046; **Table 5**).

Table 5. Univariate and multivariate binary logistic regression analysis results

	Univariate		Multivariate	
	P values	OR (CI 95%)	P values	OR (CI 95%)
Gender	0.164	-	-	-
Age	0.805	-	-	-
PLT ≤ 220.5	0.004	23.53 (2.7-204.6)	0.046	11.33 (1.04-122.3)
MPV/PC ≥ 0.066	0.001	16.12 (3.16-82.1)	0.105	4.5 (0.73-27.73)
Multivariate model: Nagelkerke R Square=0.424, Classification accuracy: 86%				

OR: Odds ratio, CI: Confidence interval, PLT: platelets, MPV/PC: Mean platelet volume to platelet count, Reference value for PLT: > 220.5, Reference value for NLR: < 0.066

DISCUSSION

In our study, increased MPV and decreased platelet rates were found significant in the length of intestinal segment affected in mesenteric ischemia and acute mesenteric ischemia itself. However, according to this result, it would not be appropriate to think that "increased MPV proves to be a predictive value for perforation in acute mesenteric ischemia". Because AMI is not only a surgical but also a vascular disease, and high MPV can be found in atherosclerosis-related conditions. However, in addition to the values such as CRP, leukocytes, and CAR, which are routinely examined, we believe that the MPV/PC ratio is more significant than previous parameters in predicting perforation in mesenteric ischemia and in estimating the amount of affected bowel loop.

Many studies have investigated that NLR rate may be a precursor of acute mesenteric ischemia in patients with non-specific abdominal pain. In the Kısaoğlu A study (17), it was shown that NLR rates increased significantly when healthy individuals and AMI patients were compared, and it was argued that NLR is an independent prognostic factor in AMI patients. In our study, NLR parameters were insignificant in distinguishing perforation. This result was similar to WBC, NEU, LYM, Albumin, CRP, and CAR values. Although these values predict mesenteric ischemia, it seems more rational to use the MPV/PC ratio, which we also emphasized in our study, to predict perforation and can be used to estimate the length of a necrosed bowel segment.

In two separate studies with limb ischemia, low MPV values were found to be associated with critical lower limb ischemia and hepatic fibrosis(17-19). There are also studies that found decreased MPV levels in ulcerative colitis (20). These results are inconsistent with both ischemic cerebrovascular events, ischemic heart diseases, and high MPV results in mesenteric ischemic patients that we found in our study. Therefore, it was thought that this might be the severe systemic inflammatory response that occurs, especially in mesenteric ischemia.

In recent years, there has also been many researchs about platelet indices and cancer diagnosis, and cancer stage (21). Yang-Yang Wu et al. (22) found in their study about colorectal cancer MPV/PC was significantly different in subgroups between patients with stage I/II and stage III/IV cancer, and they believed that this ratio might be helpful in the differential diagnosis of early and advanced colorectal cancer.

Also, with the COVID-19 pandemic, coagulopathy-related diseases have been increased explicitly because there is growing evidence about SARS CoV-2 infection and hypercoagulability (23). Acute arterial obstruction of the small intestinal vessels and mesenteric ischemia may

appear due to hypercoagulability associated with SARS-CoV-2 infection, mucosal ischemia, viral dissemination, and endothelial cell invasion vis ACE-2 receptors (24). Serban D et al. (25) emphasized in their study that the diagnosis of an ischemic bowel should be one of the top differentials in critically ill patients with acute onset of abdominal pain and distension. So it is more than possible that we will encounter more patients with bowel ischemia than ever.

Our study concluded that the affected bowel length of patients who were operated on for mesenteric ischemia increased as the blood platelet value decreased and increased as the MPV, MPV/PC, and CAR values increased. Examination of these values, especially in patients before surgery, may help predict the amount of intestinal loop affected at the time of surgery.

This study has some limitations. Based on our results, several perspectives can be suggested. First, our study was a retrospective single-center study, and the cohort size may have limited the statistical power of the analysis. However, the number of patients per subgroup was sufficient to evaluate perforation discrimination and the amount of affected bowel loop according to laboratory parameters. Second, we investigated two parameters that influence the prognosis of mesenteric ischemia. It would be interesting to extend this study to larger cohorts and more extended follow-up periods. To the best of our knowledge, our study is the first to use laboratory data to predict perforation and the amount of affected bowel loop in case of mesenteric ischemia.

CONCLUSION

MPV/PC and PLT value at hospital admission is a simple and reliable predictive marker in determining perforation and the amount of bowel segment to be affected in patients with acute mesenteric ischemia. However, further studies are required to establish a causal link between MPV/PC and PLT values and patients' outcomes. It may be helpful as an inexpensive and non-invasive prognostic biomarker for centers without the possibility of computer tomography angiography, magnetic resonance angiography, etc.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval of this study was received from Hitit University Non-interventional Researches Ethics Committee (Date: 27/09/2021, Decision No: 2021-78).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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