

# The role of immature granulocyte count and delta neutrophil index in the early prediction of mesenteric ischemia

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**Abstract. – OBJECTIVE:** Mesenteric ischemia is a fatal condition leading to ischemia and necrosis of the intestines following the interruption of blood flow in the vessels feeding the intestines. The present study investigated the significance of immature granulocyte count and delta neutrophil index in the early prediction of mesenteric ischemia.

**PATIENTS AND METHODS:** The study included 248 patients who applied to the hospital between 01.01.2020 and 01.04.2022 and underwent emergency and elective bowel resection in the general surgery clinic. The study population was divided into two groups as patients who underwent surgery for causes non-related to mesenteric ischemia (Group 1) and patients with findings of mesenteric ischemia who underwent laparotomy (Group 2). Preoperative immature granulocyte counts, and delta neutrophil index levels were compared between the groups with and without perioperative mesenteric ischemia.

**RESULTS:** No statistical difference was observed between the groups in terms of age or sex. Comparing the two groups regarding immature granulocyte count and delta neutrophil index revealed a statistically significant difference ( $p<0.001$ ). The median immature granulocyte count was 0.04 (0.02-0.06) in Group 1 and 1.83 (0.18-2.5) in Group 2, with a statistically significant difference ( $p<0.001$ ). Also, the comparison of delta neutrophil index levels revealed a median value of 0.4 (0.2-0.6) in Group 1 and 5.6 (0.7-8.1) in Group 2, with a statistically significant difference.

**CONCLUSIONS:** The results of this study have demonstrated that immature granulocyte counts, and delta neutrophil index levels are reliable markers that do not require any additional time or expense, can be easily measured in a complete blood count, and can be used for evaluating intestinal necrosis in mesenteric ischemia.

*Key Words:*

Mesenteric ischemia, Immature granulocyte, Delta neutrophil index, White blood cell, Creactive protein.

## Introduction

Acute mesenteric ischemia (AMI) is characterized by a significant reduction in mesenteric blood flow, which can cause irreversible changes in the intestinal mucosa and lead to intestinal necrosis, peritonitis, severe sepsis, and multiple organ failure<sup>1</sup>. AMI represents an uncommon cause of acute abdominal pain as it constitutes 0.09% to 0.2% of all acute surgical admissions<sup>2</sup>. Causes of AMI include embolism (50%), thrombosis (20%), non-occlusive factors (20%), and venous thrombosis (10%). Risk factors include age, myocardial infarction, arrhythmias (especially atrial fibrillation), atherosclerosis, heart failure, hypercoagulation, intra-abdominal trauma or infection, and malignancy<sup>3</sup>. Despite major diagnostic and treatment advances over the past decades, low clinical suspicion leads to persistently high mortality rates for acute mesenteric ischemia, ranging from 40 to 70% (AMI)<sup>4</sup>. It remains to be a challenging condition to diagnose. AMI generally presents with abdominal pain inconsistent with physical examination findings. Non-specific symptoms like diarrhea, bleeding in the lower gastrointestinal tract, intestinal obstruction, abdominal distension, and vomiting may be observed. Patients with mesenteric ischemia exhibit leukocytosis, metabolic acidosis, and elevated D-dimer and serum lactate levels<sup>5</sup>. Computed Tomographic Angiography (CTA) is the gold standard for diagnosis. However, even high-tech diagnostic equipment like CTA can sometimes miss acute occlusive intestinal ischemia, and radiological findings are often less specific<sup>6</sup>. In AMI, early diagnosis bears great importance as the duration of intestinal ischemia is considered a major prognostic factor<sup>7</sup>.

Immature granulocytes (IGs) in peripheral blood indicate increased bone marrow activity<sup>8</sup>. In healthy people, IGs, including promyelocytes, myelocytes, and metamyelocytes, are generally not released in peripheral blood and are thus undetectable. However, they can be detected in peripheral

blood in response to infection, inflammation, and other stimuli<sup>9</sup>. Recent studies show that IGs are more effective markers than white blood cells and C-reactive protein in determining the severity of inflammation<sup>10</sup>. Delta neutrophil index (DNI) is a novel inflammatory marker that measures the proportion of IGs in circulating blood<sup>11</sup>. Because infectious conditions are associated with elevated IG levels, several researchers have examined whether it can be used to predict the formation of sepsis<sup>12</sup>.

The present study investigated the significance of immature granulocyte count and delta neutrophil index in the early prediction of mesenteric ischemia.

## Patients and Methods

The study population consisted of patients who applied to the emergency service of Training and Research Hospital between 01.01.2020 and 01.04.2022, who were taken to emergency operation by the general surgery department upon consultation with the suspicion of mesenteric ischemia, and who underwent elective bowel resection. Data were recorded retrospectively from the hospital computer system. We included patients over the age of 18 who underwent surgery and bowel resection in the General Surgery Department and whose data could be accessed between the specified dates. Patients under the age of 18, those with a disease that may interfere with blood parameters (cirrhosis, chronic kidney failure, etc.), pregnant and lactating patients, patients with limitations (those with mental disorders, soldiers, convicts), and patients whose data could not be accessed were excluded. The Ethics Committee Approval was received from Hitit University Faculty of Medicine Clinical Research Ethics Committee in 2022 (Ethics Committee Decision Number: 2022-43).

The study population was divided into two groups as patients who underwent surgery for causes non-related to mesenteric ischemia (Group 1) and patients with findings of mesenteric ischemia who underwent laparotomy (Group 2). Group 1 consisted of patients who underwent emergency or elective bowel resection due to causes non-related to mesenteric ischemia. Group 2 consisted of patients who intraoperatively developed mesenteric ischemia and whose surgical data were retrospectively scanned from the records. The imaging methods were not evaluated due to limited data. Initial preoperative laboratory results were scanned from the hospital file system. IG counts,

DNI levels, white blood cell (WBC) counts, C-reactive protein (CRP) levels, and lactate dehydrogenase (LDH) levels were recorded. DNI is normally calculated with the formula (granulocyte count \* 1000)/leukocyte count. It is calculated as a standard procedure in our hospital's laboratory and routinely indicated in complete blood count tests. We compared preoperative IG counts, DNI levels, WBC counts, CRP levels, and LDH levels between groups with and without perioperative mesenteric ischemia. We then statistically evaluated the predictive values of these parameters for mesenteric ischemia.

## Statistical Analysis

Continuous variables are given as mean  $\pm$  standard deviation and categorical data as numbers and percentages. During the intergroup analysis of continuous variables, an analysis of normality was performed using the Kolmogorov-Smirnov Goodness of Fit Test. The *t*-test was used to analyze variables suitable for normal distribution and the Mann-Whitney U test was used for those that showed non-normal distribution. Categorical data analysis was performed using the Chi-squared Test. All analyses were performed using the IBM SPSS version 24.0 (IBM Corporation, Armonk, NY, USA). The threshold level for the presence of ischemia was determined using the receiver operating characteristic (ROC) test.  $p < 0.05$  was considered statistically significant.

## Results

248 patients who underwent bowel resection were included. Of these 248 patients, 157 were male (63.3%) and 91 were female (36.7%). The mean age of the patients was  $65.81 \pm 17.15$ . The mean age of the male patients was  $63.75 \pm 17.28$ , while the mean age of the female patients was  $69.35 \pm 16.41$ . Mesenteric ischemia was observed in 43 of 157 male patients and 42 of 91 female patients. No statistical difference was observed between the groups in terms of age or sex ( $p: 0.804$ ,  $p: 0.765$ , respectively).

The participants were divided into two groups as those without mesenteric ischemia (Group I) and those with mesenteric ischemia (Group II). The IG, DNI, WBC, CRP, and LDH levels were compared between the groups. Comparing IG and DNI levels between the two groups revealed a statistically significant difference ( $p < 0.001$ ). The

**Table I.** Group 1 and Group 2 comparison of hematological parameters.

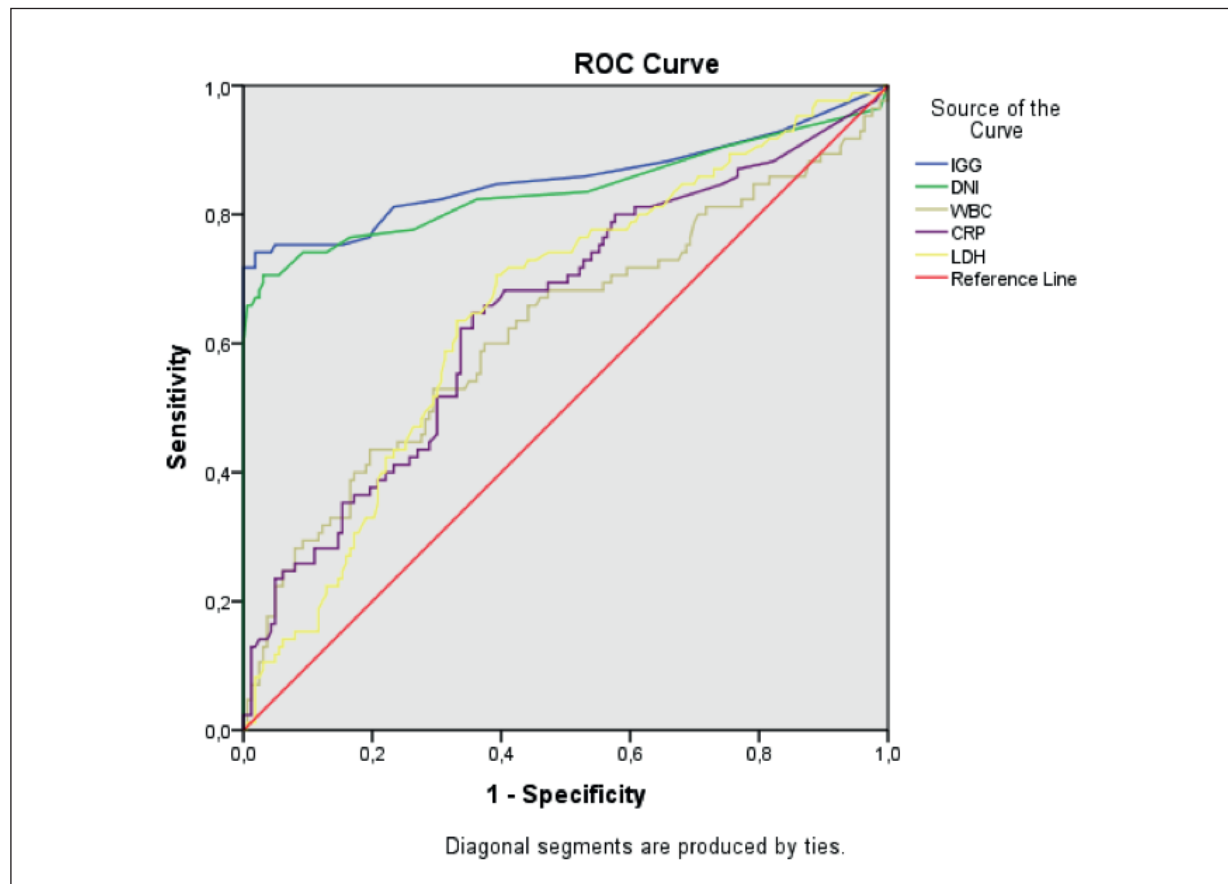
Hematological parameters	Group I	Group II	p-value
	Median (IQR 25-75)	Median (IQR 25-75)	
IG	0.04 (0.02-0.06)	1.83 (0.18-2.5)	<0.001
DNI	0.4 (0.2-0.6)	5.6 (0.7-8.1)	<0.001
WBC	7.46 (6.01-10.18)	9.49 (6.52-13.83)	0.002
CRP	7.56 (3.23-38.4)	22.7 (5.4-110)	<0.001
LDH	200 (167-267)	254 (199-312)	<0.001

\*Mann-Whitney U test

IG; immaturgranulocyte, DNI; delta neutrophil index, WBC: white blood cell, CRP; C-reactive Protein, LDH; lactate dehydrogenesis.

median IG count was 0.04 (0.02-0.06) in Group 1 and 1.83 (0.18-2.5) in Group 2, with a statistically significant difference ( $p < 0.001$ ). Also, the median DNI level was 0.4 (0.2-0.6) in Group 1 and 5.6 (0.7-8.1) in Group 2, again with a statistically significant difference ( $p < 0.001$ ). WBC, CRP, and LDH levels were statistically significantly higher in Group 2 ( $p = 0.002$ ;  $p < 0.001$ ;  $p < 0.001$ , respectively) (Table I).

We then performed a ROC analysis to investigate the predictive values of these parameters (Figure 1). The AUC value for IG counts was 0.856. At a cut-off value of 0.225, IG had a sensitivity of 74.1% and a specificity of 98.2%. The AUC value for DNI levels was 0.839. At a cut-off value of 1.4, DNI had a sensitivity of 70.6% and a specificity of 96.9%. For the other parameters, the cut-off values were 8.59 for WBC, 12.6 for CRP,



**Figure 1.** Roc curve for parameters. IG; immaturgranulocyte, DNI: delta neutrophil index, WBC: white blood cell, CRP: C-reactive Protein, LDH: lactate dehydrogenesis.

**Table II.** Cut-off points and diagnostic values of variables for distinction of mesenteric ischemia.

Hematological parameters	Area Under the Curve	Cut-off value	Sensitivity	Specificity	Odds ratio	(+) predictive value (%)	(-) predictive value (%)	Youden index	p-value
IGG	.856	0.225	74.1	98.2	152.7	95.5%	87.9%	0.723	.000
DNI	.839	1.4	70.6	96.9	75.8	92.3%	86.3%	0.675	.000
WBC	.621	8.59	60.0	62.6	2.3	44.3%	74.4%	0.226	.002
CRP	.649	12.6	64.7	64.4	1.6	35.8%	75%	0.291	.000
LDH	.654	214,000	70.6	60.7	3.7	48.4%	79.8%	0.313	.000

IG; immature granulocyte, DNI: delta neutrophil index, WBC: white blood cell, CRP: C-reactive Protein, LDH: lactate dehydrogenase.

and 214 for LDH. Accordingly, IG had the highest AUC value, sensitivity, and specificity (Table II).

## Discussion

The present study investigated the predictive value of immature granulocyte (IG) counts and delta neutrophil index (DNI) levels, which can be measured by hematological tests, in the early diagnosis of mesenteric ischemia. The study bears the significance of being the first to investigate mesenteric ischemia in the literature. Our findings showed that IG and DNI were statistically higher in mesenteric ischemia patients.

Mesenteric ischemia is a fatal condition leading to ischemia and necrosis of the intestines following the interruption of blood flow in the vessels feeding the intestines. Rapid diagnosis is vital as the condition is associated with high mortality rates when left untreated. Mesenteric ischemia can manifest with considerably varying clinical findings depending on its etiology. AMI mostly presents with abdominal pain, abdominal distension, and ileus, which are disproportionate to physical examination findings. Computed tomography is an important imaging method in the diagnosis of acute mesenteric ischemia. In a meta-analysis, tomography has been shown to have high sensitivity and specificity in the diagnosis of mesenteric ischemia<sup>13</sup>. Mesenteric ischemia is associated with an acute inflammatory response, and markers like WBC, CRP, serum lactic acid dehydrogenase, and D-dimer are studied to diagnose the disease<sup>14</sup>. Although elevated inflammatory markers are observed in AMI, these markers are nonspecific. Because of the insignificant and nonspecific clinical findings and limitations in diagnostic tests, diagnosis is the most important step in the course of AMI<sup>15</sup>.

IGs are inflammatory markers that increase in the event of infection and inflammation<sup>16</sup> and are easily

calculated using automatic hematological analyzers. Polymorphonuclear neutrophil granulocytes provide the first line of host defense against infective pathogens. They transform from progenitor cells into mature segmented neutrophils in the bone marrow within 7–10 days. Later, they migrate into the peripheral blood after full maturation. Therefore, IG formation in the blood indicates increased activation of the bone marrow found in sepsis<sup>17</sup>. Ayder et al<sup>18</sup> showed that the DNI could be used as a diagnostic marker of sepsis. Nierhaus et al<sup>19</sup> reported that DNI effectively discriminated between infected and non-infected patients. Unal et al<sup>10,20</sup> found that IG and DNI effectively helped diagnose necrotizing pancreatitis and differentiate between complicated appendicitis and normal appendicitis. Senlikci et al<sup>21</sup> reported significantly elevated IG levels in the diagnosis of intestinal necrosis due to irreducible hernia. Cha et al<sup>22</sup> determined that DNI was significantly elevated during intestinal ischemia due to strangulation. In the current study, IG was significantly elevated among all parameters that were analyzed to reveal intestinal necrosis associated with mesenteric ischemia. The cut-off value of IG for intestinal necrosis was 0.225, with a sensitivity of 71.1% and a specificity of 98.2%. DNI was another elevated parameter. The cut-off value of DNI for intestinal necrosis was 1.4, with a sensitivity of 70.6% and a specificity of 96.9%. Accordingly, IG and DNI are significant markers in diagnosing mesenteric ischemia.

Other markers of infection like white blood cell (WBC) and C-reactive protein (CRP) are also elevated in mesenteric ischemia. In a meta-analysis evaluating the performance of several biomarkers for intestinal ischemia, Evannett et al<sup>23</sup> calculated a 0.80 (95% CI: 0.66–0.91) sensitivity and a very modest 0.50 (95% CI: 0.31–0.69) specificity for WBC count for diagnosing intestinal ischemia. Matsumoto et al<sup>24</sup> studied 208 patients with a clinical suspicion of acute intestinal ischemia and reported a receiver operating char-



acteristic (ROC) curve of only 0.54 (95% CI: 0.39-0.70) for WBC count to distinguish intestinal ischemia from non-ischemic diseases. Thuijls et al<sup>25</sup> observed no significant difference between patients with and without bowel ischemia in terms of leukocyte count. In this study, mesenteric ischemia patients demonstrated a higher leukocyte count, consistent with the literature. However, it was not effective in discriminating mesenteric ischemia since leukocytosis occurs in all infections. CRP is a common inflammatory marker. Yildirim et al<sup>26</sup> found significantly elevated CRP levels among patients with intestinal ischemia. In the present study, CRP was significantly elevated in mesenteric ischemia patients, consistent with the literature. As per our findings, IG and DNI were determined to be superior diagnostic markers compared to WBC and CRP in diagnosing mesenteric ischemia.

As for the limitations of our research, the retrospective design may be considered a negative factor. D-dimer, which is used to diagnose mesenteric ischemia, was not included in this study due to the inaccessibility of the data. Former data could not be included as IG was studied in the hospital laboratory from 2020 onwards, so the number of parameters investigated was limited.

## Conclusions

The results of this study have demonstrated that IG and DNI are reliable markers that do not require any additional time or expense, can be easily measured in a complete blood count, and can be used to evaluate intestinal necrosis in mesenteric ischemia. In fact, they are more reliable than the routine WBC, CRP, and LDH parameters. Therefore, immature granulocyte counts, and delta neutrophil index levels should be considered when evaluating mesenteric ischemia.

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## Informed Consent

All participants in this study signed the informed consent.

## Ethical Approval

The Ethics Committee Approval was received from Hitit University Faculty of Medicine Clinical Research Ethics Committee in 2022 (Ethics Committee Decision Number: 2022-43).

## Conflict of Interest

The authors declare that they have no conflict of interest to declare.

## Authors' Contributions

Doğukan Durak: study design, data collection, analysis, and data interpretation; drafting the article, making critical revisions related to the relevant intellectual content of the manuscript. İbrahim Tayfun Şahiner: study design, making critical revisions related to the relevant intellectual content of the manuscript. Veysel Barış Turhan: data analysis and interpretation. Ertugul Gazi Alkurt: data collection. Mehmet Berksun Tutan: drafting the article.

## Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the Hospital Information Management System and the corresponding author, upon reasonable request.

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