

## Can biological markers predict mortality in bowel ischemia

Biological markers in mesenteric ischemia

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### Abstract

**Aim:** High levels of fibrinogen and low levels of albumin are associated with ischemic vascular diseases. This study aims to investigate whether the levels of serum fibrinogen and albumin, FAO, and prognostic nutritional index (PNI) effectively predict prognosis in acute mesenteric ischemia.

**Material and Methods:** Patients treated in our clinic with the diagnosis of Acute mesenteric ischemia (AMI) between 2013 and 2023 were evaluated for inclusion. Patients were divided into two groups: those who were alive after the first month (group 1) and those who died within the first month (group 2). The investigated parameters were statistically compared between these groups.

**Results:** We included 39 patients in this study. Twenty-one of the patients (53.8%) were alive one month after the surgery (group 1), whereas 18 patients (46.2%) died (group 2). The difference in the mean ages of patients in both groups was not statistically significant (74.6±9.2 and 69.4±10.6, respectively;  $p=0.114$ ). Group 2 had higher fibrinogen levels compared with group 1 (524.0±165.7 mg/dL vs. 427.8±114.0 mg/dL;  $p=0.039$ ). Albumin levels were similar between the two groups (3.0±0.6 g/dL vs. 2.8±0.5 g/dL;  $p=0.179$ ). The mean FAR value was significantly higher in group 2 (198.5±76.9 vs. 149.8±56.9;  $p=0.029$ ). FAR in 71.8% of them with the optimal cut-off value >157.6 (AUC= 0.688,  $p= 0.033$ ). PNI was not successful in predicting mortality (AUC=0.605,  $p=0.189$ )

**Discussion:** The present study proposed that the FAO could be a new and valuable prognostic marker in patients with AMI, unlike PNI.

### Keywords

Far, Fibrinogen, Albumin, Ami, Prognosis

DOI: 10.4328/ACAM.22308 Received: 2024-06-15 Accepted: 2024-08-12 Published Online: 2024-08-23 Printed: 2024-11-01 Ann Clin Anal Med 2024;15(11):784-788

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This study was approved by the Ethics Committee of Sakarya University (Date: 2023-07-28, No: 245)

## Introduction

Acute mesenteric ischemia AMI represents a critical vascular condition occurring when blood supply to the intestine is compromised, resulting in tissue death due to ischemia caused by arterial or venous blockage, or constriction of mesenteric vessels, accompanied by subsequent tissue damage during blood flow restoration [1]. The frequency of its occurrence rises with advancing age, and prior studies have documented that the average age of onset falls toward the end of the seventh decade of life [1- 6]. Surgery for mesenteric ischemia accounts for 0.1-0.2% of acute surgical interventions in general hospital practice [5]. It represents approximately 1 patient out of every 1000 patients hospitalized with acute abdomen [4, 6]. The total occurrence rate of AMI is documented as 0.63 per 100,000 individuals in Europe, with an equal distribution between females and males [1, 4]. A recent Swedish study reported an incidence rate of 13 per 100,000 person-years over a 10-year period [7].

Common symptoms comprise abrupt onset of diffuse abdominal pain, accompanied by nausea, vomiting, diarrhea, and rectal bleeding. Despite advancements in diagnostic techniques and treatment options, mortality rates remain elevated [6]. Early diagnosis relies heavily on clinical suspicion. Suspected cases should undergo evaluation with computed tomography angiography (CTA) for accurate diagnosis [1, 2, 4, 6].

Various biomarkers, including white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), citrulline, and D-dimer, have been assessed for early detection of AMI. Nevertheless, there are currently no universally accepted biomarkers for such cases [8].

Elevated fibrinogen levels and decreased albumin levels have been linked to the systemic disorders. The fibrinogen-to-albumin ratio (FAR), a recently proposed parameter, has been investigated for its diagnostic and prognostic utility in various conditions characterized by inflammation and pro-coagulation, including coronary artery disease, cerebrovascular stroke, retinal venous occlusion, and cancers [9]. There are no studies investigating the predictive value of FAR in AMI prognosis. The aim of this study is to evaluate the predictive value of preoperative albumin, fibrinogen, and FAR levels in the prognosis of AMI.

## Material and Methods

The records of the patients who underwent surgery for AMI between 2014 and 2023 were analyzed retrospectively. Ethical approval was obtained from the Ethics Committee of the University. We collected the patient's data from the database of the general surgery department of our third-level hospital, which is the sole reference center for patients of acute mesenteric ischemia in our city. We derived the radiology, laboratory, clinical, and therapeutic data. Patients without laboratory data regarding the albumin and fibrinogen levels during the initial 48 hours of abdominal complaints were excluded.

AMI was identified by visualizing halted blood circulation on Computed Tomography Angiography or digital subtraction angiography (DSA), or by detecting ischemic alterations in the intestinal wall during surgical interventions.

The FAR was recorded within the first 48 hours after the onset

of abdominal complaints.

Demographics, primary diagnosis, medical history, laboratory results, imaging findings, and examination findings of the patients were obtained from the records of our hospital. Hemogram, FAR biochemistry, CRP, prothrombin time (PT), and the international normalized ratio (INR), which were tested concurrently within the first 48 hours after symptom onset were derived.

The population of the study is divided into two groups regarding the outcome described as exitus (death within the month without any other defined etiology) or alive (living at the end of the first month). In addition, the study population was categorized according to the extent of applied surgical procedure as patients with small intestine resection (SIR group) and patients with small intestine and colon resection (SICR group). The measured parameters were compared between these subgroups.

Statistical analysis was performed by using the Statistics Open For All package - SOFA stat (released with open source AGPL3 license 2009–2014; Paton Simpson and Associates Ltd, New Zealand). ROC curve analyses were done with MedCalc version 20.027 statistical software program (Ostend, Belgium). Descriptive statistics were expressed as mean±standard deviation (for normally distributed data), median and minimum–maximum (for not normally distributed data) or number of cases and percentage (%) (for Categorical variables). Normally distributed homogeneous data were compared with the Student's T-test. The data without normal distribution or not homogeneous were compared with the Mann-Whitney U test. Pearson linear correlation test or Spearman's Correlation Analysis was used for the correlation analysis. Less than 0.05 P values were considered significant. The receiver operating characteristic (ROC) curve was used to determine the predictive value of FAR according to the outcome and extent of ischemia. Youden J index was used to determine cut-off values.

## Ethical Approval

This study was approved by the Ethics Committee of Sakarya University, Faculty of Medicine (Date: 2023-07-28, No:245).

## Results

In total, 39 patients with AMI whose medical records were accessed from the archives of our hospital were included in this study. Thirty-three of them (84.6%) had arterial occlusive mesenteric ischemia, five of them (12.8%) had mesenteric venous thrombosis whereas one of them (2.6%) had a non-occlusive mesenteric ischemia. Eleven of the patients (28.2%) were treated medically after thrombectomy with DSA, one of the patients (2.6%) were treated with surgical thrombectomy without intestinal resection, 26 of the patients (66.7%) were treated with surgical resection, and one of the patients (2.6%) died just before the operation. Among the surgically treated patients, intestinal resection was applied in 11 of them with anastomosis, and in 13 of them with ostomies, and 2 of them who had total intestinal ischemia died during the surgery.

Twenty-one of the patients (53.8%) were alive one month after the surgery (group 1) whereas 18 patients (46.2%) died (group 2) two of them died during the operation and one of them died just before the surgery. The ischemia involved the

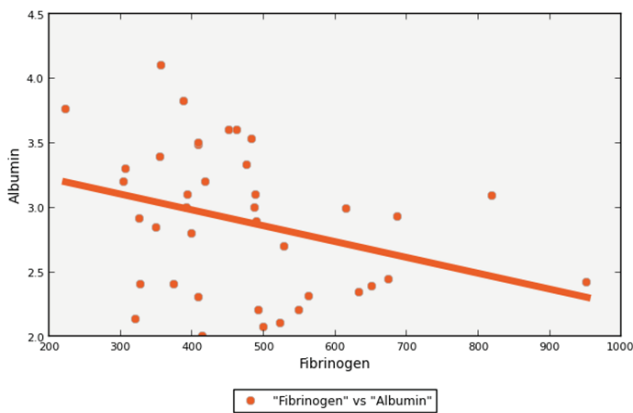
small intestine insole (small intestine ischemia- SII- group) in 29 (74.4%) of the patients, whereas the colon was also affected in 9 (23.1%) of the patients (small intestine and colon ischemia - SICI- group). In one patient (2.5%), the right colon and cecum were involved insole.

The mean ages of the surviving and dead patients were similar (74.6±9.2 and 69.4±10.6, respectively; p=0.114). Distributions of gender and laboratory parameters regarding inflammation were similar between the two groups. (Table 1) Albumin levels were similar between two groups (3.0±0.6 gr/dL vs. 2.8±0.5 gr/

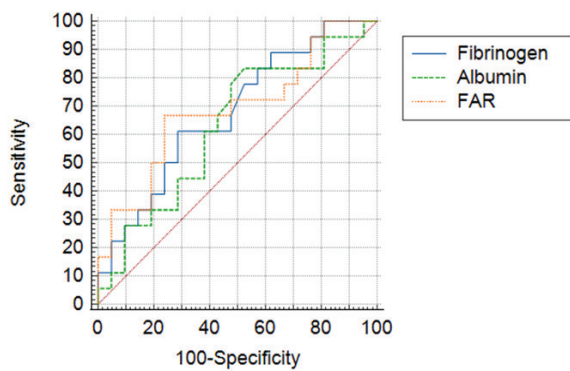
dL; p=0.179). Group 2 had higher fibrinogen levels compared with group 1 (524.0±165.7 mg/dL vs. 427.8±114.0 mg/dL; p=0.039). The mean FAR value was significantly higher in group 2 (198.5±76.9 vs. 149.8±56.9; p=0.029).

The mean ages of SII (73.4±8.9) and SICI (69.7±13.3) were similar. (p=0.139). Distributions of gender and laboratory parameters regarding inflammation were shown in Table 2. SII and SICI groups had similar fibrinogen, albumin and FAR values (p >0.05 for all comparisons)

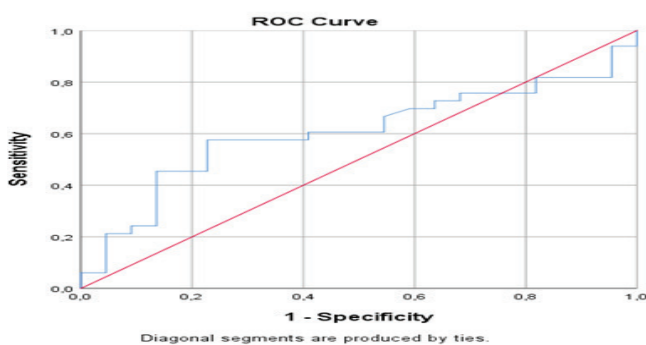
There was an inverse linear correlation between the serum fibrinogen and albumin levels in the study population (p=0.027). (Figure 1) ROC curves were plotted for albumin, FAR, and fibrinogen to identify non-survivors. (Figure 2) We also calculated the specificity, sensitivity, accuracy, negative likelihood ratio (-LR), and positive likelihood ratio (+LR) for optimal cut-off values in predicting mortality within one month (Table 3). Fibrinogen levels predicted the mortality in 66.7% of the patients accurately with the optimal cut-off value >476 mg/dL (AUC= 0.677, p= 0.041), albumin in 64.7% of them with the optimal cut-off value ≤3.1 g/dL (AUC= 0.630, p= 0.159) and FAR in 71.8% of them with the optimal cut-off value >157.6 (AUC= 0.688, p= 0.033). PNI was not successful in predicting mortality (AUC=0.605, p=0.189) (Figure 3)



**Figure 1.** Correlation between serum albumin and fibrinogen levels p=0.027 (R: -0.354, df: 37, Slope: -0.001, Intercept: 3.474



**Figure 2.** Receiver operating characteristic (ROC) curves for Fibrinogen, Albumin and FAR for predicting the ability of mortality



**Figure 3.** Receiver operating characteristic (ROC) curves for Prognostic Nutritional Index for predicting ability of mortality

**Discussion**

AMI is associated with high morbidity and mortality. Its etiology is primarily linked to in situ thrombosis in approximately 60% of patients. However, embolism due to atrial fibrillation is the underlying cause in 30% of patients and non-occlusive mesenteric ischemia in 10%. [10] Despite the increasing number of cases due to the aging population, diagnosis remains challenging with initial physical examination and diagnostic imaging [11]. In elderly patients presenting with sudden abdominal pain accompanied by minimal initial physical findings as well as vomiting and bloody diarrhea, especially if there is a history of atrial fibrillation, or metallic valve implantation, AMI should be suspected. Following the exclusion of other causes of abdominal pain, most patients undergo a computerized tomographic scan (CT) to visualize the anatomy of the mesenteric vessels. Traditional treatment has typically involved open surgical revascularization, which may include procedures such as embolectomy, bypass, and endarterectomy [12, 13]. Despite significant advancements in surgical and radiological techniques, the mortality rate associated with AMI remains high [8]. In our study population, the mortality rate was 46.2%. Our research focused on assessing the predictive value of traditional inflammatory parameters and a novel parameter, FAR, in patients with acute mesenteric occlusion. Our findings indicate that platelet, neutrophil, lymphocyte, white blood cell, hemoglobin, CRP, albumin counts, and NLR are not sensitive indicators for predicting the extent of ischemia and mortality. However, we observed that fibrinogen and FAR values may be valuable predictors of mortality. There are few studies in the literature investigating the role of serum biomarkers in predicting AMI prognosis. In a recent study by Wu and colleagues, they examined 77 patients with AMI who underwent laparotomy [14]. In their study, they reported a 30-day

postoperative mortality rate of 29.9%. Multivariate analysis revealed that time from admission to surgery, platelet count and arterial mesenteric occlusion were independent predictors of 30-day mortality after exploratory laparotomy. However, other traditional laboratory findings, such as elevated WBC, serum lactate level or CRP levels, are reported to have limited contribution in both diagnosing acute mesenteric occlusion and predicting prognosis [15]. In an animal study conducted by Ozcay and colleagues, it was observed that both partial and diffuse AMI resulted in a decrease in blood glucose levels, along with increases in AST, LDH, and fibrinogen levels in rats. However, the changes noted in ALT, CRP, BUN, and C3 levels were not statistically significant [16]. Our findings indicate that there were no significant differences in the levels of WBC, ALT, and CRP between patients who died and those who survived. However, the fibrinogen level was notably higher in the group of patients who died.

Albumin inhibits platelet aggregation and activation and plays a crucial role as a mediator for platelet-induced vasoconstriction [17]. In *in vitro* studies using human fibrinogen preparation, fibrinogen-induced platelet aggregation was reversed by adding human albumin. Decreases in serum albumin may elevate the viscosity of blood and impair endothelial function by increasing free lysophosphatidylcholine concentrations [18]. Some studies demonstrated that hypoalbuminemia increases morbidity and mortality in cardiovascular disease, cancer, and other conditions [19]. Serum albumin levels have been proposed to have predictive value in the occurrence and prognosis of vascular occlusions, such as acute myocardial infarction [19]. Serum albumin levels have been proposed to have predictive value in the occurrence and prognosis of vascular occlusions, such as acute myocardial infarction [20]. Although the relationship between elevated fibrinogen levels, hypoalbuminemia, and coronary artery disease was investigated in many studies, to our knowledge, none have addressed patients with AMI [8]. In our study, serum albumin levels were not associated with prognosis or the extent of ischemia. However, significantly high FAR values and fibrinogen levels have existed in patients who died within one month after surgery compared to survivors.

The association between serum CRP levels and the prognosis of patients with vascular accidents remains controversial. Winbeck and colleagues reported that elevated levels of CRP measured 12-24 hours after the onset of symptoms, rather than within the first 12 hours, in patients with first ischemic cerebrovascular stroke were associated with an unfavorable outcome and an increased recurrent cerebrovascular and cardiovascular events incidence [21].

Di Napoli et al. reported that CRP predicted the risk of ischemic stroke and that CRP levels at discharge were more closely associated with later outcomes [22]. In another report, Di Napoli and colleagues found that elevated serum CRP levels were more closely associated with new cardiovascular events risk after the first ischemic stroke compared to D-dimer and fibrinogen levels [23]. On the other hand, in a population-based study, Froyshov and colleagues found that fibrinogen and IL-6 were independent predictors of mortality in long-term stroke survivors, while elevated hs-CRP predicted mortality in stroke-free individuals [24].

In a recent report, Destek and colleagues found that CRP level could be used effectively preoperatively to diagnose AMI and to determine its clinical course. They also reported that NLR, D-dimer, L-lactate, and leukocyte levels were markers with no predictive value in the diagnosis of all AMI subtypes. We found that there were not any significant differences in terms of initial CRP and NLR levels between survived and non-survived patients within one month revealing that they are not valuable parameters in the prediction of mortality in patients of acute mesenteric ischaemia.

The previous reports showed that the D-dimer, one of the protein fragments produced during the degradation of fibrinogen, had a high sensitivity in the patients with acute mesenteric ischemia, although it did not get a satisfactory specificity [5]. Recently, Li and colleagues reported that fibrinogen levels in patients who developed necrosis due to strangulated intestinal obstruction were significantly higher than in patients in whom only ischemia was present without necrosis and in patients with intestinal obstruction without ischemia or necrosis [25]. As the occlusion of mesenteric vessels causes ischemia in intestinal tissues, the fibrinogen levels are expected to increase in these patients also. In this study, we aimed to determine the possible values of fibrinogen, albumin, and FAR in predicting the prognosis of acute mesenteric ischemia. Our results revealed that fibrinogen and FAR values were significantly higher in our patients who died within one month after the surgery than those who survived. Fibrinogen levels predicted mortality accurately in 66.7% of the patients within one month, albumin in 64.7% of them, and FAR in 71.8% of them.

#### **Limitation**

Our study has some limitations. One of them is the limited number of patients with venous occlusion, hampering the comparative statistics between the arterial and venous occlusion groups. Secondly, post-operative FAR values could not be evaluated as the fibrinogen and/or albumin measurements after the surgery were unavailable in some patients, and the time period between the surgery and the taken of serum specimens could not be standardized in others having postoperative fibrinogen and albumin measurements. Lack of lengths of ischemic bowel segments and D-dimer measurements could also be evaluated as other limitations.

#### **Conclusion**

In conclusion, we researched the possible predictive values of fibrinogen, albumin, and FAR, a new rational parameter of inflammation, in the prognosis of patients with AMI unlike PNI, and our results revealed that fibrinogen, which is widely available in emergency wards, and FAR could be valuable prognostic markers in these cases

#### **Scientific Responsibility Statement**

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

#### **Animal and Human Rights Statement**

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.*

**Funding:** None

**Conflict of Interest**

The authors declare that there is no conflict of interest.

This study was approved by the Ethics Committee of Sakarya University (Date: 2023-07-28, No: 245)

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**How to cite this article:**

Adem Senturk, Alp Omer Canturk, Fuldem Mutlu. Can biological markers predict mortality in bowel ischemia. *Ann Clin Anal Med* 2024;15(11):784-788