Journal of Surgery
[Jurnalul de Chirurgie]

Original Paper Open Access

The Utility of Biomarkers in Diagnosing and Predicting Outcomes in Acute Mesenteric Ischemia

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Abstract

Background: Acute intestinal ischemia stands as the most lethal acute condition encountered by general surgeons and one of the deadliest pathologies in medicine triggered by thromboembolic events. The patients' survival decreases dramatically to a lower than 30% rate when diagnosed after 24 hours, thus early diagnosis with proper surgical or vascular intervention is mandatory. This study aims to determine the utility of biomarkers and routine blood tests in assessing the severity and mortality risk for patients with acute mesenteric ischemia. *Methods:* The study was developed on a prospective cross-sectional design over a period of five years, finding a total of 147 patients who underwent emergency surgery after a high suspicion of acute mesenteric ischemia. The available biomarkers used in our Clinic comprised a complete blood count, total bilirubin, CK, CK-MB, LDH, AST, ALT, amylase, and cholinesterase. *Results:* The leukocyte count (OR=1.105), hemoglobin (OR=3.912), LDH (OR=1.144), NLR (OR=1.154), and LLR (OR=1.286) were all independent and significant risk factors for AMI diagnosis. These covariates proved a good and reliable tool for diagnosing AMI with a 75.3% predicted probability. *Conclusion:* The prediction tool proved reliable, although it should only be considered in the clinical context where the surgeon suspects a case of acute mesenteric ischemia. The proposed model should be further investigated and validated in larger studies.

Keywords: bowel infarction, acute abdomen, intestinal ischemia, biomarkers, diagnostic tools

Introduction

Acute mesenteric ischemia (AMI) has the highest mortality rate in all surgical emergencies, where 60 to 80 percent of patients do not survive [1]. Despite the fact that surgeons benefit from a wide range of available investigations for diagnosis and the development of radio-interventional revascularization procedures, mortality has remained unchanged over the past 70 years [2]. The non-specific clinical presentation and the absence of biomarkers with proven diagnostic value lead to delayed diagnosis and treatment, which contributes significantly to the still high mortality. The realization of an early diagnosis method that would allow the rapid establishment of therapeutic modalities is consequently necessary. Although computed tomography with three-phase contrast media has high sensitivity and specificity [3], it claims a number of limitations. The relatively more difficult and delayed access to this type of investigation, respectively, the increased risk of acute kidney injury translated by oliguria [4] are just two reasons why this tool did not facilitate early diagnosis.

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Received April 20, 2021; **Accepted** Mayl 31, 2021**, Published** June 29, 2021

Citation: Pirvu C. A., Bratosin F., Nica C., Cârțu D., Patrascu Șt., Șurlin V, Sapalidis K.,Georgescu E., GeorgescuI.,Pantea S. The Utility of Biomarkers in Diagnosing and Predicting Outcomes in Acute Mesenteric Ischemia. Journal of Surgery [Jurnalul de chirurgie]. 2021; 17 (2): 119 – 126 .DOI: 10.7438/JSURG.2021.02.06

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There are four distinct etiological subtypes of AMI that must be recognized because of their treatment and prognostic differences [5]. These include embolism of the superior mesenteric artery, thrombosis of the SMA due to atherosclerosis, non-occlusive mesenteric ischemia, and venous mesenteric ischemia. SMA embolism and thrombosis are frequently referred to as arterial myocardial infarction (AMI) or occlusive myocardial infarction (AMI). The therapy of arterial occlusive AMI, which embolic or atherosclerotic etiologies can cause, attempts to restore blood supply to the SMA as quickly as possible using open or endovascular revascularization [6]. Non-occlusive mesenteric ischemia is defined as AMI that occurs in the absence of any hemodynamically significant obstruction in the mesenteric arteries and is typically caused by another underlying acute condition that results in decreased cardiac output or vasoconstriction of the mesenteric arteries. Finally, venous mesenteric ischemia is generally induced by venous thrombosis in the mesenteric veins.

Biomarkers are a relevant and potent tool for identifying a spectrum of illnesses. They are used in observational and analytic epidemiology, randomized clinical trials, screening, diagnosis, and prognosis [7]. These markers, which are defined as changes in the components of tissues or bodily fluids, enable the homogenous classification of diseases and risk factors, and they can supplement our existing knowledge of the underlying pathophysiology of an illness. Additionally, biomarkers can represent the full range of illness development, from its initial signs to its ultimate phases, but the validation of biomarkers is critical in relation to disease stage and severity. However, variability in biomarker measurement exists and can occur for a variety of reasons, ranging from human interaction and error to laboratory kits [8]. Therefore, issues affecting biomarker analysis should be reviewed and strategies for dealing with bias and confounding. Therefore, it is necessary to identify a biomarker with high specificity for intestinal ischemia that can be quickly analyzed, with values related to the extent and severity of ischemia and high sensitivity to exclude other pathologies. This study discusses the key applications of biomarkers in clinical use for the diagnosis and risk assessment of life-threatening diseases such as AMI. Also, we aim to evaluate a series of biomarkers that are quickly assessed in emergency situations with the purpose of developing an AMI risk score.

Materials and Methods

This multicentric study was spread between September 2015 and September 2020, taking place at the 3rd General Surgery Department from "Pius Brinzeu" Emergency Clinical Hospital in Timisoara, affiliated to the "Victor Babes" University of Medicine and Pharmacy, in partnership with the 1st General Surgery Department from the Emergency County Hospital Craiova. Our research was planned on a prospective, cross-sectional design, targeting cases of acute abdomen with high suspicion of AMI. The study subjects were selected from patients who presented to the hospital's emergency department with abdominal discomfort and evidence of acute abdomen. After signing an ethical approval form to participate in the current study, a total of 147 patients with acute abdomen but no obvious cause were included. The exclusion criteria comprised cases where the diagnosis was certified, for example, stabbed wounds, bowel obstruction, acute appendicitis, splenic rupture, etc. Cases of AMI diagnosed by angiography with aortic dissection obstructing the superior mesenteric artery (SMA) at its ostium, or post-traumatic occlusion of the SMA, were also excluded from the study. At the end of the study period, a cohort of 147 patients was formed after passing the exclusion criteria. These patients were clinically and paraclinical resembling AMI, having intense abdominal pain, sudden changes in intestinal transit, signs of intestinal bleeding, vomiting, tachycardia, and signs of shock [9]. All patients underwent exploratory laparotomy by performing a midline incision to explore the abdominal cavity and certify the diagnosis. The decision for intestinal resection was determined intra-operatively considering the aspect of the intestines [10]. We categorize our patients into two groups based on their diagnoses. There were 67 (44.4%) patients with the acute abdomen of unknown cause and 80 (65.5%) patients with intestinal infarction who were accurately identified and verified.

The biomarkers used in our study were analyzed in the laboratories affiliated to the "Pius Brinzeu" Emergency Clinical Hospital in Timisoara and the Emergency County Hospital Craiova, which shared the same tools for analysis and same normal ranges. The tested biomarkers included a complete blood count, creatinine, total bilirubin, CK, CK-MB, LDH, AST, ALT, NLR, LLR, lipase, and cholinesterase. Our laboratories considered the following normal ranges for the tested biomarkers: leukocyte count (4 – 9.5*10^3/mcL), neutrophil percentage (45 – 70%), lymphocyte percentage (20 – 40%), hemoglobin (13.6 – 17.2 g/dL), hematocrit (39 – 51%), platelets (150 – 400*10^3/mcL), ALT (0 – 50 U/L), AST (17 – 59 U/L), creatinine (0.8 – 1.5 mg/dL), CK (22 – 198 U/L), CK-MB (5 – 25 U/L), LDH (100 – 200 U/L), amylase (30 – 110 U/L), cholinesterase

(5000 – 11000 U/L), and total bilirubin (0.2 – 1.0 mg/dL).

Statistical data were analyzed using the IBM SPSS software version 26 (Statistical Package for the Social Sciences, Chicago, IL, USA). Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as evaluated by the Shapiro-Wilk test. Frequency counts represented qualitative data, and their associated percentages were computed from the total. To describe the characteristics of the study cohort, descriptive and inferential statistical analyses were performed. The Chi-square test was used to determine the significance of variations in clinical finding proportions across groups. The Student's t-test or the Mann-Whitney U-test were employed to compare continuous variables depending on their distribution. Correlation analysis involved the Spearman's and Person's correlation coefficients for categorical and continuous data, respectively. A multivariate logistic regression analysis of risk factors was implemented, and finally, the area under the receiver-operating characteristic curve (AUROC) was plotted to determine the reliability of the proposed diagnostic tool. The significance threshold was set for a p-value of less than 0.05.

Results

From the total number of 147 patients with high suspicion of AMI, there were 80 (65.5%) confirmed cases intraoperatively, leaving the other 67 (44.5%) patients with a different cause of acute abdomen, thus the accuracy of diagnosing AMI using the available resources was 54.4%. Comparing the two study groups, the patients suffering AMI were older men (p<0.001, respectively p=0.032) living in the rural regions of the country (p=0.015). Patients in the non-AMI group had a significantly longer hospital stay, which can be attributed to a significantly higher survival rate in this group (55.2% vs. 16.2%, p<0.001). Regarding comorbidities, atrial fibrillation and stroke were more common in patients with AMI (p=0.048 and p=0.038, respectively). Also, AMI patients showed more frequent signs of intestinal bleeding, hypotension, and dysuria (Table 1).

After evaluating the biomarkers from both groups of patients, we observed a significantly higher leukocyte and neutrophil count in the AMI group (p=0.023 and p=0.002, respectively); a higher eutrophils to leukocytes ratio (NLR), hemoglobin, hematocrit, and creatinine in the same group (Table 2).

A correlation analysis was performed to determine the biomarkers that are possibly associated with AMI, as well as with the outcome of surviving this condition (Table 3). Significant and positive correlations were observed between a patient being confirmed with AMI and the leukocyte count (r=0.190, p=0.021), neutrophil count (r=0.216, p=0.009), creatinine (r=0.215, p=0.010), NLR and LLR (r=0.428, p=0.065; r=0.488, p<0.001 respectively). Hemoglobin and hematocrit were also positively correlated to diagnosing AMI, although these values should be understood in the context of hemoconcentration in patients with AMI. On the other hand, the leukocyte and neutrophil count, NLR, LLR, creatinine, CK, CK-MB, LDH, amylase, total bilirubin, ALAT, and ASAT were all negatively correlated with patients' Survival (p<0.05).

A multinominal logistic regression model was built to assess risk factors for AMI. The statistically significant biomarkers that were found to be independent risk factors for AMI comprised the leukocyte count (OR=1.105, CI [1.066-1.264]), hemoglobin (OR=4.912, OR [2.735-7.683]), LDH (OR=1.144, CI [1.099-1.220], NLR (OR=1.154, CI[1.273-1.523]), and LLR (OR=1.286, CI[1.149-1.324]). They were all combined to compute the probability for diagnosis and to obtain the AUROC. The area under the ROC curve predicted a probability of 75.3% for the proposed model to diagnose AMI (Figure 1) correctly.

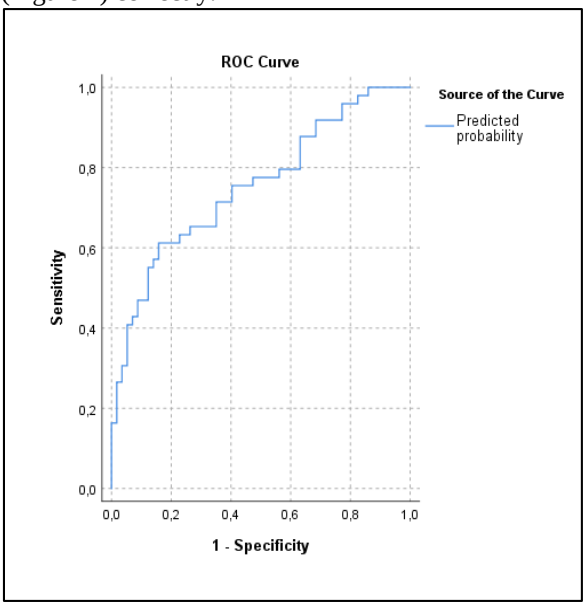

Figure 1. ROC curve

Table 1. General characteristics of the study population

Characteristic	Acute abdomen (n=67)	Mesenteric ischemia (n=80)	P-value
Generalities			
Age (years) [(a)]	65.19 ± 12.18	73.35 ± 10.56	<0.001**
Gender (male) [(b)]	46 (68.6%)	41 (51.2%)	0.032*
Length of hospital stay [(a)]	10 ± 8.89	5 ± 6.52	<0.001**
Place of origin (urban)	46 (68.7%)	39 (48.8%)	0.015*
Hours since onset [(a)]	49 ± 32.01	50 ± 35.31	0.801**
Outcome (survived) [(b)]	37 (55.2%)	13 (16.2%)	<0.001*
Comorbidities [(b)*]			
Atrial fibrilation	18 (26.9%)	34 (42.5%)	0.048*
Cardiovascular disease	30 (44.8%)	24 (30%)	0.064
Stroke	16 (23.9%)	32 (40%)	0.038*
Peripheral artery disease	12 (17.9%)	21 (26.3%)	0.227
Valvular disease	15 (22.3%)	26 (32.5%)	0.119
Obesity	23 (34.3%)	13 (16.5%)	0.032*
Neoplasia	19 (28.4%)	8 (10%)	0.004**
Recent surgery	58 (86.5%)	70 (87.5%)	0.867
Signs and Symptoms [(b)*]			
Abdominal pain	67 (100%)	80 (100%)	-
Absence of intestinal transit	44 (65.6%)	60 (75%)	0.216
Intestinal bleeding	3 (4.4%)	12 (15%)	0.036*
Shock	27 (40.2%)	38 (47.5%)	0.381
Hypotension	30 (44.7%)	54 (67.5%)	0.006*
Dysuria	37 (55.2%)	58 (72.5%)	0.029*

Legend: [(a)] mean ± SD; [(b)] observed frequency counts (percentage); statistically significant differences ($p < 0.05$; $p < 0.01$) for * Chi-square test and ** Student t-test; "-" abdominal pain is a constant value

Table 2. Biomarkers

Characteristic	Acute abdomen (n=67)	Mesenteric ischemia (n=80)	P-value
Leukocyte count [(a)] (10^3/mcL)	12.3 [6.63-11.69]	14.9 [9-22.8]	0.023*
Neutrophils (10^3/mcL)	9.9 [4.9-13.6]	19.6 [14.3-25.9]	0.002**
Neutrophils/Leukocytes ratio (%)	87.95 [77-92]	90.5 [86.8-62.5]	0.049*

Lymphocytes (10^3/mcL)	1.3 [0.8-1.97]	1.9 [1.4-2.5]	0.076
Lymphocytes/Leukocytes ratio (%)	10.8 [6.7-20.3]	8.5 [6.5-11.6]	0.059
Hemoglobin (g/dL) [(a)]	12.5 [9.9-14.5]	14 [11.9-15.3]	0.014*
Hematocrit (%) [(a)]	37.2 [29.7-42.2]	40.2 [34.4-45.2]	0.048*
Creatinine (mg/dL) [(c)]	0.99 [0.8-1.9]	1.49 [1.1-2.3]	0.011*
CK (U/L) [(c)]	111 [42-286]	173 [78-567]	0.059
CK-MB (U/L) [(c)]	20 [12-44]	29 [16-77]	0.097
LDH (U/L) [(c)]	359 [210-677]	555 [292-772]	0.096
Amylase (U/L) [(c)]	39 [14-111]	59 [20-108]	0.761
Cholinesterase (U/L) [(c)]	4130 [2291-5928]	4295 [1960-5748]	0.863
Total bilirubin (mg/dL) [(c)]	0.81 [0.6-1.3]	1 [0.67-1.37]	0.309
Platelets (10^3/mcL) [(a)]	221 [164-313]	221 [157-286]	0.480
ALAT (U/L) [(c)]	32 [17-49]	29 [21-45]	0.968
ASAT (U/L) [(c)]	34 [18-59]	36 [23-76]	0.214

Legend: [(a)] mean ± SD; [(b)] observed frequency counts (percentage); statistically significant differences ($p < 0.05$; $p < 0.01$) for * Chi-square test and ** Student t-test

Table 3. Correlation analysis

Characteristic	Diagnosis	P-value	Outcome	P-value
Leukocyte count (10^3/mcL)	0.190	0.021*	-0.067	0.422
Neutrophils (10^3/mcL)	0.216	0.009*	-0.187	0.023*
Neutrophils/Leukocytes ratio (%)	0.428	0.065	-0.331	0.012*
Lymphocytes (10^3/mcL)	-0.246	0.003*	0.183	0.026*
Lymphocytes/Leukocytes ratio (%)	0.488	<0.001*	-0.401	<0.001*
Hb (g/dL)	0.205	0.013*	-0.113	0.175
Ht (%)	0.164	0.047*	-0.101	0.226
Creatinine (mg/dL)	0.215	0.010*	-0.434	<0.001*
CK (U/L)	0.180	0.059	-0.342	<0.001*
CK-MB (U/L)	0.159	0.097	-0.373	<0.001*
LDH (U/L)	0.162	0.096	-0.457	<0.001*
Amylase (U/L)	0.027	0.762	-0.092	0.296
Cholinesterase (U/L)	-0.021	0.864	0.211	0.077
Total bilirubin (mg/dL)	0.088	0.303	-0.303	<0.001*
Platelets (10^3/mcL)	-0.059	0.482	0.139	0.096

ALAT (U/L)	0.003	0.968	-0.149	0.075
ASAT (U/L)	0.104	0.215	-0.394	<0.001*

Legend: Pearson's correlation coefficient for Diagnosis and Outcome; Outcome = patient survived; Diagnosis = AMI; * statistically significant differences ($p<0.05$; $p<0.01$); ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase CK – creatine kinase; CK-MB – creatine kinase MB; LDH – lactate dehydrogenase; NLR - neutrophil-lymphocyte ratio; LLR - lactic dehydrogenase-lymphocyte ratio

Table 4. Prediction model development

Characteristic	**Acute Mesenteric Ischemia**				
	Regression	P-value	OR	Lower Bound	Upper Bound
Leukocyte count (10^3/mcL)	0.117	0.044*	1.105	1.066	1.264
Neutrophils (10^3/mcL)	-0.018	0.866	0.982	0.798	1.209
Lymphocytes (10^3/mcL)	0.005	0.968	1.005	0.785	1.286
Hb (g/dL)	3.827	0.008*	3.912	2.735	7.683
Ht (%)	-1.163	0.015*	0.313	0.123	0.794
Platelets (10^3/mcL)	0.001	0.736	1.002	0.993	1.010
ALAT (U/L)	0.003	0.854	1.003	0.973	1.033
ASAT (U/L)	-0.007	0.575	0.993	0.970	1.017
Creatinine (mg/dL)	0.296	0.351	1.344	0.722	2.505
CK (U/L)	0.001	0.529	1.005	0.999	1.002
CK-MB (U/L)	0.001	0.860	1.001	0.991	1.011
LDH (U/L)	0.140	0.024*	1.144	1.099	1.220
Amylase (U/L)	-0.006	0.267	0.994	0.984	1.005
Cholinesterase (U/L)	0.001	0.829	1.037	1.017	1.020
Total bilirubin (mg/dL)	-0.054	0.912	0.947	0.363	2.470
NLR (%)	0.144	0.043*	1.154	1.273	1.523
LLR (%)	0.214	0.041*	1.286	1.149	1.324

Discussions

Review of literature

Considering the severity and the very high mortality that comes with it. AMI must be detected as soon as possible in order to prevent irreversible intestinal ischemia and the incapacity of general and vascular surgeons to intervene with favorable outcomes. Obtaining a clear early diagnosis was the main focus of the current research, and the same objective was set by other studies since the existing clinical, laboratory, and imaging tools are not efficient enough.

A recent study [11] reviewed the available biomarkers that promise to be reliable in determining an early onset of AMI, including the intestinal fatty acid-binding protein (I-FABP), procalcitonin,

citrulline, D-dimers, ischemia-modified albumin, a-glutathione S-transferase (a-GST), and the D- and L-isomers of lactic acid. In comparison to our unspecific biomarkers that were determined from a regular blood test and quantified together as a diagnostic tool, what changes to the aforementioned markers in making them possible candidates as independent diagnostic tools is their relation to the intestinal epithelial layer. Thus, the I-FABP released in urine from mature enterocytes when affected by early ischemia showed an average of 80% sensitivity and 85% specificity for AMI [12]. However, the cost and availability of detection instruments and kits do not make this an accessible tool in countries where healthcare budgets are limited. Another limitation of I-FABP is the insignificant difference in levels between mucosal and transmural intestinal infarction [13]. The a-GST is another biomarker released early from mature enterocytes in the event of ischemia but also increases in hypotension and multiple organ failure. Although, when compared to I-FABP, it has the same average specificity (85%) [14] but a lower average sensitivity (68%). The procalcitonin, citrulline, ischemia modified albumin, and the lactic acid isomers were all proven to be late-stage intestinal ischemia markers since they fail to accurately diagnose AMI at an early non-transmural stage [15]. Studying biomarkers at the molecular level that can identify early signs of intestinal infarction or determine the severity of the AMI has found the smooth muscle protein of 22 k Da (SM22) to significantly increase in concentration after being released in the circulation from the injured intestinal muscle layers [16].

Some of the biomarkers tested by the current research were also evaluated elsewhere; for example, Matsumoto et al. [17] analyzed the diagnostic ability of LDH, leukocytes, AST, and CK for AMI. The size of the study was comparable to ours, having 208 patients split into two groups based on the presence of intestinal ischemia in patients with high suspicion of AMI. After a ROC curve analysis, the results showed a 54% diagnostic probability for the leukocyte count, 61% for CK, 78% for LDH, and 80% for AST. I-FABP gave the best performance with an 88% probability for an optimal cut-off value of 9·1 ng/ml. In contradiction, Block et al. [18] analyzed the diagnostic accuracy of plasma biomarkers for intestinal ischemia and found that LDH has a diagnostic performance as low as 46%.

Limitations and future perspectives

One of the current study limitations is the absence of cut-off values that have the purpose of optimizing the reliability of the biomarkers under study. Instead, we have considered a combined increase over the laboratory's normal range for all the biomarkers found to be independent risk factors for AMI as a significant threshold. Also, including our diagnostic tool, there is currently no test or technique available that can distinguish a localized transmural infarction from broad non-transmural infarction that can determine different treatment approaches. Another limitation of this study is the lack of validation, as diagnostic tools must be verified before being used in a real setting in clinical practice. As the proposed diagnostic tool with biomarkers as covariates shows promising results, further research could test our results and validate them.

Conclusions

A positive patient outcome and a shift in decreasing mortality rates require early clinical suspicion of intestinal ischemia. Given that blood sample is conducted liberally or routinely in older patients with severe abdominal pain or acute abdomen which are hospitalized, a reliable plasma biomarker for intestinal ischemia is a necessary tool. Unfortunately, the biomarkers evaluated are insufficiently sensitive to detect intestinal ischemia early in its course, and a more developed study is necessary. To be detectable in peripheral blood, an optimum plasma biomarker should leak primarily from the intestinal mucosa and be able to bypass the liver's first-pass metabolism. Thus, our diagnostic tool comprising the regular blood tests performed in the ER for patients with high AMI suspicion should only be used following the surgeon's decision until further research can validate it, even though it shows a fairly performant prediction probability.

Funding:
This research received no external funding

Informed Consent Statement:
Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest:
The authors declare no conflict of interest.

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