Review

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Acute Mesenteric Ischemia in Critically Ill Patients. Possibilities of Laboratory Diagnostics. Systematic Literature Review and Meta-Analysis

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BACKGROUND Acute mesenteric ischemia (AMI) is diagnosed in 1 case per 5,000–15,000 operations associated with elective abdominal surgical intervention and in 1 case of 1,000 emergency laparotomies associated with the acute abdomen clinical features. Non-occlusive disorders account for 20-30% of all cases of AMI. The absence of pathognomonic symptoms and syndromes, as well as specific laboratory markers of AMI, determines significant difficulties in the early diagnosis of this disease, especially in critically ill patients.

AIM OF STUDY To identify the main laboratory markers of acute mesenteric ischemia applicable in the resuscitation and intensive care unit (RICU) based on a systematic literature review.

MATERIAL AND METHODS A systematic search and selection of publications was carried out in March-April 2021 in accordance with the PRISMA system checklist (PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyzes). The search used two databases: the Cochrane Library of Systematic Reviews (https://www.cochranelibrary.com) and the PubMed bibliographic database (https://pubmed.ncbi.nlm.nih.gov). Key terms in the search parameters were: acute mesenteric ischemia; bowel necrosis predictors; laboratory diagnostics of mesenteric ischemia. Search parameters were limited to the year of publication (not later than 2015). The main results of the review included patients with an established diagnosis of acute mesenteric ischemia, indicating the level of laboratory parameters (pH of mixed venous blood, lactate, D-dimer, white blood count, MPV, I-FABP, serum marker and alpha-glutathione-S-transferase, indicators of the coagulation and hemostasis). Case reports and editorial letters were excluded from the search.

RESULTS The threshold value for serum L-lactate ranged from 1.05 mmol/L to 5.6 mmol/L. The sensitivity of serum lactate for the diagnosis of AMI ranged from 34.7% (95% CI: 0.82–91.64%) to 89.51% (95.4% CI: 75.12–94.28%), and the specificity ranged from 47.3% (94.7% CI: 26.54–67.98%) to 94.5% (93.2% CI: 75.44–96.85%). The threshold level of D-dimer varied from 0.58 nmol/L to 7.84 nmol/L. The sensitivity of blood D-dimer for the diagnosis of AMI was 72.6% (94% CI: 56.1–92.4%) to 99.7% (94% CI: 69.15–100%); the specificity ranged from 69% (95% CI: 7.41–33.63%) to 97.89% (95% CI: 90.42–98.1%). Parameters such as transaminases (AST, ALT), MPV, LDH, D-lactate, serum amylase were not included in the review due to the lack of a sufficient number of studies.

CONCLUSION Today, there is no highly specific laboratory marker that could be considered the "gold standard" in the laboratory diagnosis of acute mesenteric ischemia. The most promising in predicting AMI are serum levels of L-lactate and D-dimer.

Keywords: acute mesenteric ischemia; intestinal necrosis; critical conditions; laboratory diagnostics

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ALV – artificial lung ventilation
AMI – acute mesenteric ischemia
CI – confidence interval
ICU – intensive care unit
MA – meta-analysis
SMA – superior mesenteric artery

INTRODUCTION

Acute mesenteric ischemia (AMI) is a disease that develops due to impairment of arterial and venous blood flow in the vessels of the mesenteric bed, characterized by violation of adequate perfusion of various parts of the intestine, leading to cellular damage, ischemia of a certain segment and, as a result, secondary inflammatory changes. In the absence of timely diagnosis and treatment, this process can result in intestinal necrosis, translocation of the intestinal flora, peritonitis, multiple organ failure syndrome, and death [1].

The most well-known risk factors for the development of AMI are atrial fibrillation, myocardial infarction with ventricular thrombosis, mitral stenosis, left ventricular aneurysm, infective endocarditis, history of arterial embolism, multifocal atherosclerosis, rapid weight loss [2].

Mesenteric venous thrombosis is diagnosed in 1 in 5000–15,000 operations associated with elective abdominal surgery and in 1 in 1000 emergency laparotomies associated with an "acute abdomen" clinic. In most cases, the etiology of venous thrombosis is explained by Virchow's triad: decreased blood flow velocity, hypercoagulability and inflammation of the vascular wall. In 1/5 of the observations 20% it can be idiopathic [3].

About 50% of all cases of AMI are due to mesenteric vascular embolism. The most vulnerable to embolic screenings is the superior mesenteric artery (SMA) due to its relatively large diameter and small angle of origin from the aorta, while in 1/5 of cases, SMA embolism may be accompanied by embolism of the renal and/or splenic arteries [4].

Non-occlusive disorders of the mesenteric circulation account for 20-30% of all cases of mesenteric ischemia. This type of pathology occurs with violations of central hemodynamics, a decrease in cardiac output, cardiac arrhythmias, long-term use of high doses of inotropes and catecholamines. As a result, there is a violation of local perfusion, a decrease in blood flow in certain segments of the intestine, arterial stenosis, angiopasm of the mesenteric vessels, which, like occlusive mechanisms, lead to ischemia and cellular damage [5].

Until recently, there were no approved clinical guidelines for the diagnosis and treatment of mesenteric thrombosis, both in Russia and abroad. Among all the medical literature relating to this pathology, it was possible to single out several systematic reviews and descriptions of individual clinical cases of acute mesenteric thrombosis, where experts present a personal vision of the problem.

The emergence of advanced endovascular methods of treatment and diagnostics, the development and implementation of new imaging techniques has led to a change in the strategy and tactics of treating AMI. The clinical guidelines prepared by the European Society for Trauma and Emergency Surgery (ESTES), as well as the conciliation commission of the World Society for Emergency Surgery on the diagnosis and treatment of mesenteric ischemia and published in 2016 and 2017, became in fact the first universal documents regulating the provision of care in this pathological process [3, 6].

Despite the existence of clinical recommendations, it should be recognized that at the moment there is no specific laboratory marker for the routine diagnosis of AMI. The absence of pathognomonic symptoms and syndromes, as well as specific laboratory markers of AMI, determines significant difficulties in diagnosing this disease, especially in critically ill patients on artificial lung ventilation (ALV), during prolonged analgosedation and myoplegia.

In this regard, we performed a systematic review of the literature on the possibilities of laboratory diagnosis of acute mesenteric ischemia in the intensive care unit (ICU).

MATERIAL AND METHODS

SEARCH. SELECTION OF PUBLICATIONS. INCLUSION CRITERIA

A systematic search and selection of publications was performed in March-April 2021 in accordance with the checklist of the PRISMA system (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [7]. Two databases were used in the search: the Cochrane Library of Systematic Reviews (https://www.cochranelibrary.com) and the PubMed bibliographic database (https://pubmed.ncbi.nlm.nih.gov).

The systematic review included the following steps: systematic search and selection of publications, assessment of the methodological quality of selected studies, meta-analysis (MA) and indirect comparison (assessment of the difference between laboratory criteria that were not previously compared with each other).

The key terms in the search parameters were: "acute mesenteric ischemia", "predictors of intestinal necrosis", "laboratory diagnosis of mesenteric thrombosis". Search parameters were limited to the year of publication – not later than 2015. The main findings of the review included patients diagnosed with acute mesenteric ischemia, indicating the level of laboratory parameters, such as mixed venous blood pH, lactate, D-dimer, blood leukocyte count, mean platelet volume (MPV), intestinal fatty acid binding protein (I-FABP), serum marker and alpha-glutathione-S-transferase, indicators of the coagulation link of hemostasis. Case reports and editorial letters were excluded from the search.

EVALUATION OF THE METHODOLOGICAL QUALITY OF PUBLICATIONS

When assessing the risks of bias in individual studies, the Newcastle–Ottawa scale (MINORS SCORE, methodological quality of non-randomized studies), AMSTAR criteria were used, for systematic reviews and MA a questionnaire to assess the risk of systematic bias in cross-sectional studies of QUADAS-2 diagnostic tests was used. (http://osdm.org/wp-content/uploads/2017/04/QUADAS_Rebrova-Fediaeva.pdf).

STATISTICAL ANALYSIS. DATA COLLECTION PROCESS. SYNTHESIS OF RESULTS

Testing of statistical hypotheses about the difference between groups in binary characteristics was performed using the two-tailed Fisher's exact test, implemented in the Statistica 10.0 package. The hypothesis about the presence of differences between the compared groups was accepted at the calculated $p < 0.05$. To select an MA model, the heterogeneity (statistical heterogeneity) of the results of the intervention effect in different studies was assessed using Pearson's chi-square test with the null hypothesis in an equal effect in all studies and with a significance level of 0.1 to increase the statistical power (sensitivity) of the test. Heterogeneity index I was also calculated. At its value of more than 50%, heterogeneity was considered high. During MA, the relative risk and its 95% confidence interval, CI, were calculated. A relative risk value of 1.0 corresponded to no difference in efficacy.

RESULTS

SELECTION AND CHARACTERIZATION OF STUDIES

The algorithm for systematic search and selection of publications with indication of reasons for exclusion is shown in Fig. 1.

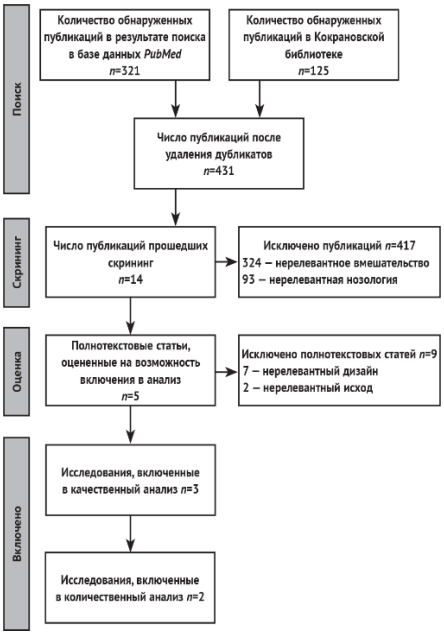

Fig. 1. The algorithm for conducting a systematic review

We selected 5 relevant studies: 2 MA and 3 multicenter cohort studies. In all MAs, lactate levels were analyzed in patients with AMI at the preoperative stage and in the first three days after surgery. In cohort studies, data were provided on the clinical picture depending on the location of the mesenteric thrombosis segment, as well as monitoring of laboratory parameters, which were followed up dynamically.

This systematic review included 5 articles, which included 754 patients with diagnosed acute mesenteric ischemia who underwent emergency surgery in the form of laparotomy. The mean age of the patients was 58 years. Irreversible intestinal necrosis was diagnosed in 328 people (43.5%). These articles and MA contain data on the laboratory diagnosis of intestinal ischemia. Most of the research was devoted to the relationship of lactate and D-dimer of blood serum with the degree of damage to the microvasculature of the mesenteric vessels.

The Wilcoxon T-test was used to compare the AMI 1 (preoperative indicator) group and the AMI 2 (4 hours after surgery) group. The data are presented in Table 1.

Table 1

Serum lactate and D-dimer levels in patients with acute mesenteric ischemia before and after surgery

Indicators	Average value in the group AMI 1	Average value in the AMI 2 group	Empirical value of the criterion	Level of statistical significance of differences
Lactate, mmol/l	3.213	6.453	5.5	0.002**
D-dimer, μg/ml FEU	1.687	2.220	20.0	0.136

Notes: ** — p<0.01; AMI - acute mesenteric ischemia

As can be seen from Table 1, there were significant differences in indicators of "lactate (mmol/l)" between the group AMI 1 (preoperative indicator) and the group AMI 2 (4 hours after surgery) (U=5.5, p <0.01). The mean value in the group AMI 1 (preoperative index) (X=3.213) was less than the mean value in the group AMI 2 (4 hours after surgery) (X=6.453).

Two studies (all retrospective) [8, 9] involving 623 patients presented data on the dynamics of serum D-dimer. Acute mesenteric thrombosis was diagnosed in 154 patients (24.7%). One study [10] found no significant difference in D dimer levels between the non-ischemic "acute abdomen" group and the AMI group. Both studies concluded that D-dimer is significantly increased in occlusive ischemia when compared with other causes of "acute abdomen". Mean D-dimer values ranged from 0.62 (95% CI, 0.50–0.78) to 0.91 (95% CI, 0.81–0.98). The threshold level of D-dimer varied from 0.58 to 7.84 nmol/L. Because the included studies used different thresholds, pooling data for analysis was not appropriate. The sensitivity of D-dimer for the diagnosis of AMI ranged from 72.6% (94% CI: 56.1–92.4%) to 99.7% (94% CI: 69.15–100%); specificity ranged from 69% (95% CI: 7.41–33.63%) to 97.89% (95% CI: 90.42–98.1%).

Three studies [11–13] involving 754 patients presented data on serum L-lactate. The diagnosis of AMI was confirmed in 321 patients (42.57%). Two studies found a significant difference in L-lactate concentration between ischemic and non-ischemic groups, while one study found a non-significant difference in L-lactate levels. A total of 26 patients with suspected AMI were retrospectively studied and the authors found no significant difference in lactate values between ischemic and non-ischemic bowel disease.

The threshold value of serum L-lactate ranged from 1.05 to 5.6 mmol/l. Due to the different thresholds included in the studies, data pooling was not considered appropriate. The sensitivity of serum lactate for the diagnosis of AMI ranged from 34.7% (95% CI: 0.82–91.64%) to 89.51% (95.4% CI: 75.12–94.28%); specificity ranged from 47.3% (94.7% CI: 26.54–67.98%) to 94.5% (93.2% CI: 75.44–96.85%).

Two studies [14, 15] in this review did not reveal a significant increase in the number of white blood cells in patients with AMI compared to the group without ischemic mesenteric vascular disease. One study found that white blood cell counts increased significantly in patients with AMI. The overall sensitivity and specificity of WBC as a marker of AMI showed a wide range of values from 54% to 94.7% and from 35% to 99.7%, respectively. However, a recent study by Emile S.H. et al. showed that an increase in the number of WBC above 18,000 mm^3 can be an important independent predictor of transmural intestinal necrosis in patients with occlusive AMI [16]. However, the authors note that it is impossible to focus only on counting the number of leukocytes and the leukocyte formula in order to determine the volume of intestinal damage and indications for surgical intervention. It is necessary to evaluate laboratory parameters in combination with the clinical picture.

In Table 2 the results of our meta-analysis on the summary data of the main laboratory parameters used to diagnose AMI are given. This MA showed that the L-fraction of lactate is more sensitive to disturbances in the microcirculation of the mesenteric vessels than the D-dimer. Cases of AMI in the form of segmental lesions of the intestine were analyzed. Total intestinal necrosis was not considered in this context.

Table 2

Meta-analysis of the significance of blood L-lactate and D-dimer in the diagnosis of acute mesenteric thrombosis

Subgroups	L-lactate		D-dimer		The weight	Risk RatioFixed, 95% CI	Risk Ratio Fixed, 95% CI
	Events	Total	Events	Total			
Wu W. et al ., 2020	12	28	5	24	16.20%	0.25 [0.04, 0.97]	
Emile S.H. et al ., 2021	9	25	4	3	16.40%	0.4 [0.08, 1.02]	
Koumarinov A. et al., 2020	15	32	7	21	24.30%	2.21 [0.79, 8.04	
Acosta S. et al., 2020	21	58	3	17	25.30%	0.7 [0.13, 1.64]	
Khan SM et al ., 2019	11	33	4	15	17,80%	0,45 [0,09, 2,74]	
Total (95% CI)		176		109	100%	0,74 [0,35, 0,98]	
Total events	68		23				
Heterogeneity Chi^2=7,52, df=4,28 (p=0,23); I^2=28%							0,03 0,1 1 10 50
Test for overall effect Z=2,1 (p=0,03)							Favours L-lactat Favours D-dimer

DISCUSSION

The analysis of the selected studies revealed significant clinical and methodological heterogeneity. Patient populations ranged from patients admitted with "acute abdomen" in the ICU to critically ill patients with long stays.

Also, in the presented works, differences were found in the diagnostic tests used to confirm or refute the diagnosis of AMI. One part of the patients underwent multispiral computed tomography in the angiography mode, the other part underwent diagnostic laparoscopy with subsequent expansion of the scope of the surgical intervention, and a group of patients was identified in which the diagnosis of AMI was established by chance after laparotomy and subsequent histopathological examination. Statistical analysis shows that D-dimer has the highest median sensitivity. An increase in the level of D-dimer during thrombosis, apparently, is associated with the activation of the fibrinolytic system after occlusion of the mesenteric vessels.

Most of the studies in this review presented a large proportion of patients with intestinal ischemia of occlusive etiology. However, ischemia of the intestinal wall and impaired microcirculation may have another etiological factor. The specificity and sensitivity of the D-dimer level in the medical innovation scientific community is not well defined. The high sensitivity of D-dimer in this review highlights its potential as a diagnostic test. But it should be borne in mind that the indicator can vary significantly depending on various comorbidities, which includes numerous conditions associated with the activation of the coagulation link of hemostasis. Based on the scales and studies presented in our work, we can conclude that the only significant marker of intestinal wall ischemia is lactate, or rather its L-fraction.

Taking into account the fact that lactate metabolism occurs in the liver, and acute intestinal ischemia and a full-scale AMI clinic, as a rule, represent a systemic inflammatory response syndrome and, as a result, reduce hepatic clearance, one can rely on the values of lactate in the blood serum, as marker of ischemia progression and development of systemic inflammatory response syndrome. Also, in the literature we analyzed, there are scattered data on the possible relationship between AMI and such laboratory parameters as transaminases (aspartate aminotransferase, alanine aminotransferase), MPV, lactate dehydrogenase, D-lactate, blood amylase. In this systematic review, they are not considered due to too little evidence base and the lack of a sufficient number of studies [7, 17].

LIMITS

The underlying pathology, which predisposes the occurrence of various variants of intestinal wall ischemia in patients due to occlusive or any other etiology, can in one way or another affect laboratory parameters at the stage of AMI diagnosis. Also, paroxysmal atrial fibrillation or previous thrombophlebitis can lead to an increase in serum D-dimer levels. Oncological diseases also lead to the breakdown of fibrin, and the activation of the coagulation link increases. Bleeding or hemorrhagic shock is known to cause a rise in lactate in diagnostic tests. This is due to the fact that, against the background of organ hypoperfusion, activation of redox reactions occurs, and anaerobic glycolysis reactions contribute to the formation of large amounts of lactate.

CONCLUSION

At the moment, there is no specific laboratory marker that could be classified as highly specific and considered the "gold standard" in the diagnosis of acute mesenteric ischemia in critically ill patients.

The most promising laboratory parameters should be considered serum levels of D-dimer and L-lactate. In the future, it is necessary to organize and conduct studies on the laboratory diagnosis of acute mesenteric ischemia in patients in intensive care units and intensive care units based on the principles of multivariate analysis.

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