SYSTEMATIC REVIEW

The Diagnostic Value of Biomarkers in Acute Mesenteric Ischaemia Is Insufficiently Substantiated: A Systematic Review

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WHAT THIS PAPER ADDS

This systematic review concludes that the diagnosis of arterial occlusive acute mesenteric ischaemia (AMI) cannot be rejected or determined solely based on (a combination of) biomarkers. To improve the timely diagnosis of AMI and thereby reduce mortality and prevent bowel resections, high quality research is needed using uniform diagnostic criteria for AMI and uniform normal and cut off values and units used in order to perform meta-analysis and validate biomarkers. Until then, the diagnosis of AMI can only be made based on a high index of clinical suspicion followed by one mm multiphase computer tomography angiography.

Objective: There is an urgent need for accurate biomarkers to support timely diagnosis of acute mesenteric ischaemia (AMI) and thereby improve clinical outcomes. With this systematic review, the aim was to substantiate the potential diagnostic value of biomarkers for arterial occlusive AMI.

Data Sources: The Pubmed, Embase, and the Cochrane Library electronic databases were searched.

Review Methods: A systematic review of the literature has been conducted to define the potential diagnostic value of biomarkers for arterial occlusive AMI. All studies including $\geq$ 10 patients describing biomarkers for macrovascular occlusive AMI between 1950 and 17 February 2023 were identified within the Pubmed, Embase, and the Cochrane Library electronic databases. There were no restrictions to any particular study design, but letters and editorials were excluded. The QUADAS-2 tool was used for the critical appraisal of quality. The study protocol was registered on Prospero (CRD42021254970).

Results: Fifty of 4334 studies were eligible for inclusion in this review. Ninety per cent of studies were of low quality. A total of 60 biomarkers were identified, with 24 in two or more studies and 15 in five or more studies. There was variation in reported units, normal range, and cut off values. Meta-analysis was not possible due to study heterogeneity. Biomarkers currently recommended by the European Journal of Vascular and Endovascular Surgery, European Society for Trauma and Emergency Surgery 2016, and World Society of Emergency Surgery 2017 guidelines also had heterogeneous low quality data for use in the diagnosis of AMI.

Conclusion: This systematic review demonstrates high heterogeneity and low quality of the available evidence on biomarkers for arterial occlusive AMI. No clinical conclusions can be drawn on a biomarker or combination of biomarkers for patients suspected of arterial occlusive AMI. Restraint is advised when rejecting or determining AMI solely based on biomarkers.

Keywords: Acute mesenteric ischaemia, Biomarker, Diagnostic value, Systemic review
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INTRODUCTION

The incidence of acute mesenteric ischaemia (AMI) is thought to be 7.3 — 12.9/100 000 person years, accounting for one in 1 000 patients presenting to emergency rooms and approximately 1% of acute abdomen hospitalisations.[1—5] Despite significant advances in imaging and treatment options over the past decades, AMI mortality rates remain high, at 60 — 80%.[1,6—12] The most important reason for this is a delay in diagnosis, because symptoms are non-specific and the diagnosis relies on a high index of clinical suspicion.[1,6,8,10,11,13—16]

Currently, the gold standard for patients suspected of AMI, is to undergo a 1 mm multiphase computer tomography angiography (CTA) scan. CTA has a sensitivity and specificity of 73 — 100% and 90 — 100% for detecting superior mesenteric artery (SMA) occlusion.[1] However, in nearly all studies that have focused on the diagnostic value of the CTA in AMI, the diagnosis was known in advance.[5] In real life, clinical suspicion is only mentioned in 31% of the CT referrals.[17,18] In fact, the critical point lies in the clinical suspicion. Without suspicion, the CT has significantly less diagnostic value (sensitivity of 94% with clinical suspicion *vs.* 81% without clinical suspicion, $p = .04$).[5,19] Accurate triage seems to be the key for timely diagnosis of AMI patients.[20] Lemma et al. showed important differences between presentation at surgical emergency departments (SERs) and non-surgical emergency departments (non-SERs).[20] Time to CTA, diagnosis, and operations (10 *vs.* 15 hours) were all shorter with SER presentation than non-SER presentation, which also led to shorter hospital stays (seven *vs.* 11 days), fewer bowel resections, and lower 90 day death rate (50% *vs.* 75%).[5,19,20] Considering that there is usually a 6 — 8 hour window before transmural ischaemia occurs, it is clear there is a high clinical need to facilitate AMI diagnosis in the early reversible stage.[21,22]

Much research has been focusing on biomarkers in the hope of finding a highly accurate, non-invasive, rapid, 24/7 available, and cost effective diagnostic marker that can solve the diagnostic dilemma and reduce the time to diagnosis.[6,15,16,23] Besides traditional biomarkers like lactate, C reactive protein, leucocytes, D dimer, phosphate and creatine kinase (CK), new biomarkers like intestinal fatty acid binding protein (I-FABP), ischaemia modified albumin (IMA), and D lactate are increasingly investigated. But the holy grail of a single or combination of markers has not yet been found.[1] Although a complete and thorough consideration of the evidence is lacking, diagnostic value in the clinical decision making of AMI has been given to different biomarkers.[6,10,16,24—26] With the present systematic review, the aim was to substantiate the evidence for biomarkers in the diagnostic process of arterial occlusive AMI. A meta-analysis could only be performed in case of low heterogeneity of the normal and cut off values used and patient cohorts.

MATERIALS AND METHODS

Search strategy

The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Supplementary Appendix 1).[27,28] A systematic search in Pubmed, Embase, and the Cochrane Library was performed to identify all relevant studies published (Supplementary Appendix 2). To avoid bias based on a language barrier, only studies written in English, Dutch, German, and French were included, due to language skills of the authors. Secondly, the references of the included studies were checked for additional citations using a snowballing approach. A librarian (F.E.-J.) performed the electronic searches. The complete literature search terms are shown in the Supplementary Appendices. The protocol for this systematic review was registered on PROSPERO (CRD42021254970). In order to give the most thorough representation of the literature, the closing date for inclusion was extended to just before submission, in contrast to the date stated in PROSPERO.

Study selection

Eligible studies describing a biomarker to determine arterial occlusive AMI in humans published between 1950 and 17 February 2023 were included. To improve the homogeneity of the study population, purely arterial occlusive mesenteric ischaemia was included, defined as significantly stenotic or occluded mesenteric arteries. Therefore, studies describing patients with non-occlusive mesenteric ischaemia, mesenteric ischaemia after major surgery or in intensive care unit (ICU) patients, and ischaemic bowel secondary to other diseases, such as strangulation and obstruction, have been excluded. If the results of patients with arterial occlusive AMI could be extracted separately from the other subgroups, the study was included. Study titles and abstracts were independently reviewed by two authors (J.B. and A.N. or F.M.). Studies were initially selected based on their titles and abstracts by using pre-defined inclusion and exclusion criteria (Table 1). Duplicates were removed.

By including all biomarkers, the aim was to give a complete overview of the current state of affairs. Next, full text articles were read to make a final selection, and consensus was reached for inclusion (F.M.M. and J.T.M.B.). A third screener (R.H.G.) resolved disagreements by adjudication. Full texts were obtained via PubMed, through national and international library requests, and, if necessary, by contacting the primary author three times and the journal administration once. If full texts could not be retrieved via these methods, the study was excluded.

Assessment of methodological quality

The QUADAS-2 tool was used by two authors (J.T.M.B. and F.M.M.) to independently appraise the selected studies for risk of bias and applicability.[29] The signalling questions were answered, after which each domain was appraised low, unclear, or high. The individual assessments were discussed (J.T.M.B., F.M.M., and R.H.G.) after which consensus was reached. Criteria used are available in Supplementary Appendix 3.

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Table 1. Inclusion and exclusion criteria.

Inclusion	Exclusion
Biomarkers in arterial occlusive AMI, defined as arterial atherosclerotic and or thromboembolic events	No arterial occlusive AMI
Adults	No data specific for the subgroup of AMI patients included
English, Dutch, German, French	NOMI, venous thrombosis, mesenteric ischaemia after major surgery or in intensive care unit patients and ischaemic bowel secondary to other diseases, such as strangulation and obstruction, secondarily to other diseases like strangulation
Between 1 January 1950 and 17 February 2023	No biomarkers or prognostic use of biomarkers
	Children, animals
	Duplicate
	No abstract or full text available
	Others than inclusion languages
	Microdialysis
	Comments, letter to editor or other forms of own opinions without scientific substantiation
	< 10 patients included

AMI = acute mesenteric ischaemia; NOMI = non-occlusive mesenteric ischaemia; RCT = randomised controlled trial.

Data extraction and statistical analysis

Two authors (J.T.M.B., F.M.M.) independently extracted data from the included studies. Data extraction included clinical setting, study design, study population, number of patients, reference standard employed, disease prevalence, properties of the respective diagnostic tests, and the cut off level used for each biomarker. Next to this, data on diagnostic accuracy (sensitivity, specificity, likelihood ratios, predictive values, diagnostic odds ratio, and area under the receiver operating characteristic curve) were extracted if available.

Continuous variables were presented as means with standard deviation or median with interquartile range for parametric and non-parametric data, respectively. Categorical variables were presented as numbers with percentages.

RESULTS

Search and selection criteria

The flowchart according to PRISMA is shown in Figure 1. A total of 4334 papers was identified, of which 203 were retrieved for full text review. Fifty papers were ultimately included for final critical appraisal. Table 2 shows the characteristics of the included articles, with prospective articles and retrospective articles identified. Two studies were excluded because the patient data were inconsistent.[30,31] For both studies, the outcomes presented in the text were conflicting with the outcomes presented in the tables. It is thought that the first study[30] has been cited three times so far, including two systematic reviews[26,32,33] and the second study[31] has been cited four times so far.[34–37] Also in these cases both the corresponding authors and the journals concerned were asked for a response, but the data could not be retrieved.

Critical appraisal

Results of the critical appraisal are shown in the last column of Table 2. The full QUADAS-2 data are shown in Supplementary Appendix 4. The overall quality of studies was low, because overall risk of bias is high and applicability is low. There was only one study[69] with low risk of bias and low concern regarding applicability. Three studies[38,49,51] were at risk of bias with a low concern of applicability. All other studies were at risk of bias and there were concerns regarding applicability.

Of the 50 studies, 35 (70%) were retrospective analyses. Moreover, there was a large variance in the inclusion and exclusion criteria used, leading to extensive differences in selected patients with AMI and control groups, possible exclusion of eligible patients, and risks of missing or questionable data. The exact intervals between the index test and the reference standard and whether the investigators were blinded to the outcomes were also not reported in the vast majority of studies.

Biomarkers

A total of 60 biomarkers was identified. Fifteen biomarkers were described in five or more studies and 21 biomarkers were described in two or more studies (data shown in Supplementary Appendix 5). Twenty-four biomarkers were described in only one study for which data are not shown. These 24 biomarkers were antithrombin,[39] antidiuretic hormone,[58] activated partial thromboplastin time,[39] bicarbonate,[45] bilirubin,[43] cell free DNA,[45] chloride,[43] creatine kinase isoenzymes MB (CK-MB),[57] complement factor 3,[74] elastase-a1 proteinase inhibitor complex,[74] endotoxin,[74] fibrinogen,[39] fibrinopeptide A,[74] ileal bile acid binding protein,[81] interleukin 6,[76] interleukin 8,[76] IMA,[60] liver type fatty acid binding protein,[81] mean cell haemoglobin,[65] mean cell volume,[65] net-CK BB,[57] neurotensin,[76] troponin,[40] and quick time.[55]

Table 3 presents the diagnostic accuracy of biomarkers on arterial occlusive AMI diagnosis. Table 4 presents the reported values of the individual AMI biomarkers: total cohort and subcohort analysis. These tables contain the data of the five most studied biomarkers and the three explicitly noted in the European Society for Vascular Surgery (ESVS) guideline (D dimer, I-FABP, and D lactate).[1] The data of the other 35 biomarkers are in the Supplementary material. Reviewing the individual biomarkers, a wide variety in units, normal values, and cut off values was observed. Furthermore, a great variety of included patient groups was observed, making it impossible to pool data into comparable subgroups. Although many studies presented

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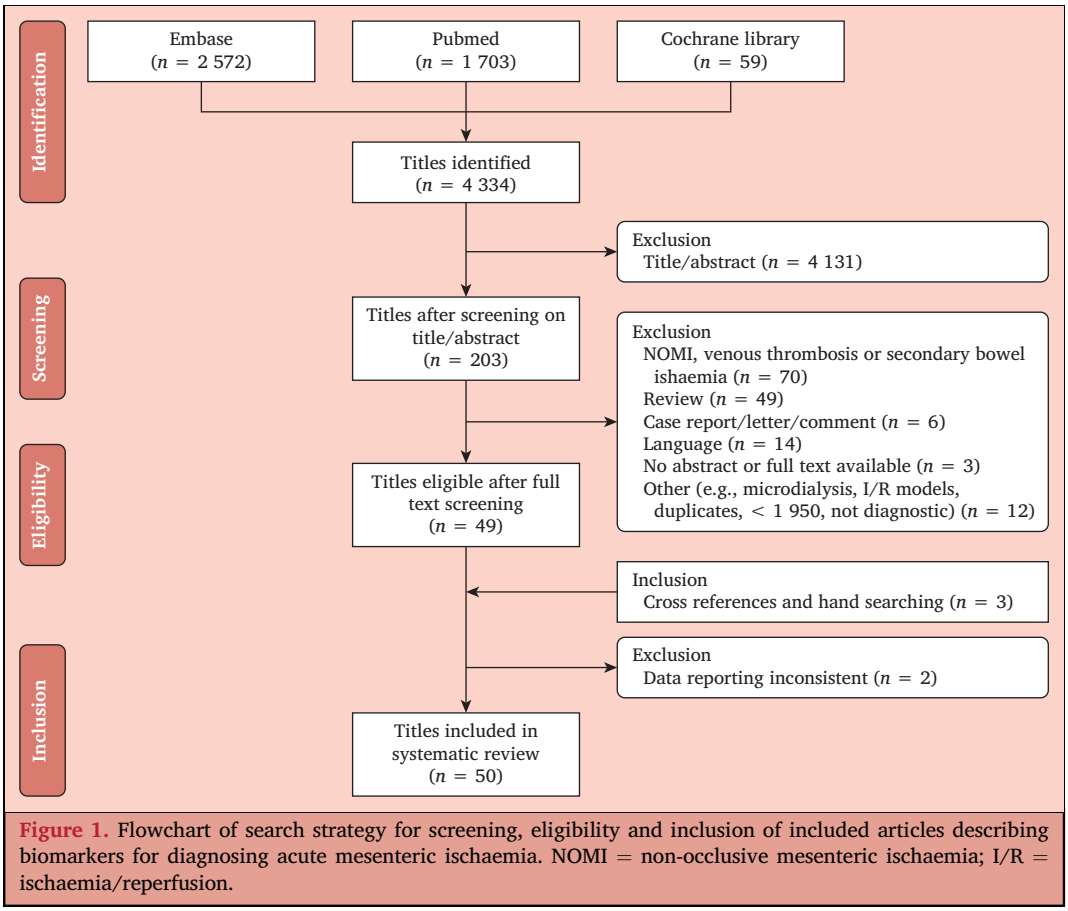

Figure 1. Flowchart of search strategy for screening, eligibility and inclusion of included articles describing biomarkers for diagnosing acute mesenteric ischaemia. NOMI = non-occlusive mesenteric ischaemia; I/R = ischaemia/reperfusion.

descriptive data on the researched biomarkers, there were only a few studies portraying diagnostic outcome parameters per individual biomarker.

DISCUSSION

With this systematic review, the results of 50 studies on the diagnostic value of 60 biomarkers in 2 057 patients with arterial occlusive AMI are presented. An extensive methodological variety in the studies was observed, and there was a substantial variation in the studied patient populations. Furthermore, there were large differences in terms of units used and applied normal values between the studies, if any are even given. Subsequently, different cut off values are used per study. It was concluded that the quality of the studies was low after risk of bias and applicability assessment using the QUADAS-2 tool, because only four studies were of moderate to high quality, but 92% of studies were of low quality. The main reasons for this are the high number of retrospective studies and the use of laparotomy as the reference test. Altogether, this makes it non-desirable to compare outcomes of individual studies and perform a meta-analysis.[88] Based on the data from the current systematic review, no clinical conclusions can be drawn on an individual biomarker or a combination of biomarkers in the diagnostic pathway of patients with arterial occlusive AMI.

After exploring the quality of the included studies, it was observed that the overall quality of the studies was low. The study populations were diverse and criteria for diagnosing AMI were diverse and often not described. The studies used different normal values and cut off values for the same biomarkers, which made it impossible to reliably pool the data. After discussion with multiple epidemiologists, it was therefore decided to perform a narrative description of the results without a formal meta-analysis, which would provide the reader with misleading data that should not be (mis)used in future reports.

There were three guidelines discussing the place of biomarkers in diagnosing acute mesenteric ischaemia.[1,13,14] Only D dimer was considered by the 2017 ESVS guideline as a biomarker that can be used to exclude the diagnosis of AMI due to its high sensitivity of 100% and therefore a negative predictive value (NPV) of 100%.[1] D dimer is suggested to aid in the diagnostic process of AMI alongside a clinical suspicion and the CTA.[39,42] This is true, but the added value of D dimer in the clinical decision making process in a patient with acute abdominal complaints is very low because the D dimer will rise with almost every acute abdominal pathology. Furthermore, although the quality of the studies that substantiate this recommendation is relatively good, again there is a wide variety in units used and normal and cut off values in these small patient groups (nine to 28 patients).[39,42,51,69] Based on the absence

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Table 2. Study design characteristics of included articles describing biomarkers for diagnosing acute mesenteric ischaemia (AMI).

Author	Marker	Period	Study population	AMI patients / total cohort – *n* (%)	Reference test	QUADAS-2 risk of bias
Acosta[38],*	D dimer	1999–2000	Clinical suspicion of AMI	6/14 (43)	Laparotomy	Moderate
Acosta[39],*	APTT, antithrombin, creatinine, CRP, D dimer, fibrinogen, Hb, PT, WBC	2000–2003	Acute abdominal pain	9/101 (9)	Clinical, ECG, endoscopy, lab, laparotomy, radiology, pathology	Moderate
Acosta[40],†	Amylase, ALT, AST, INR, lactate, troponin 1	2005–2009	Acute abdominal pain and vascular treatment of AMI referral	55 (100)	Laparotomy, radiology	High
Aktimur[41],†	MPV, NLR, RDW, WBC	2009–2014	AMI patients for laparotomy and or bowel resection	70/193 (36)	Laparotomy, pathology	High
Akyildiz[42],*	D dimer	2005–2007	Clinical suspicion of AMI	28/47 (60)	CT, laparotomy	High
Altintoprak[43],†	Albumin, ALP, ALT, amylase, AST, Ca, Cl, Creatinine, GGT, Hb, Ht, K, MPV, Na, bilirubin, PC, urea, WBC	2008–2012	Surgical intervention for AMI	30 (100)	Laparotomy	High
Ambe[44],†	L-lactate	2009–2014	Laparotomy for suspected AMI	64/75 (85)	Laparotomy	High
Arnalich[45],*	Amylase, bicarbonate, Cell free plasma DNA, creatinine, glucose, LDH	2004–2007	Laparotomy for suspected AMI	99/130 (76)	Laparotomy	High
BengFuh[46],†	Blood gas, lactate, WBC	1990- 1999	Acute abdomen with suspected AMI	62/116 (53)	Laparotomy, radiology	High
Bilgiç[47],†	LDH, RDW, urea, WBC	2008–2011	Laparotomy for suspected AMI	61 (100)	Laparotomy	High
Bilgiç[48],†	ALP, ALT, amylase, AST, creatinine, GGT, Hb, Ht, LDH, MPV, PC, urea, WBC	2005–2011	Patients operated with a diagnosis of AMI	61 (100)	Laparotomy	High
Brillantino[49],*	Lactate	2014–2015	Acute abdomen	48/284 (17)	CTA	Moderate
Canfora[50],†	CRP, lactate, LDH, WBC	2010–2016	Laparotomy for suspected ITIN	36/55 (65)	Laparotomy, radiology	High
Chiu[51],*	Amylase, D-dimer, lactate, WBC	2007–2009	Acute abdominal pain and clinical suspicion of AMI	23/67 (34)	CT	High
Czerny[52],†	Lactate	1970–1996	Diagnosis of AMI	145 (100)	Autopsy, clinic, laparotomy, radiology	High
Degerli[53],†	MPV, PC	2008–2014	Patients operated with a diagnosis of AMI and pathological confirmation	41/123 (33)	Laparotomy, pathology	High
Destek[54],†	Amylase, CRP, D dimer, L-lactate, NLR, WBC	2015–2019	Laparotomy for suspected AMI	44/51 (86)	CT, laparotomy or laparoscopy	High
Elthes[55],†	ALT, AST, CK, creatinine, glucose, INR, K, LDH, Na, QT, urea, WBC	2014–2016	Diagnosed with AMI	50 (100)	Laparotomy	High
Emile[56],*	Albumin, amylase, creatinine, electrolytes, Hb, lactate, pH, PT, WBC	2013–2017	Acute abdomen	101 (100)	Clinic, histology, laparotomy	High
Fried[57],†	CK-MB, CK-BB, total CK	NR	Acute abdomen, suspicion of intra-abdominal catastrophe or admitted with unexplained symptoms	8/50 (16)	Autopsy, laparotomy, radiology	High
Gaddam[58],†	ADH, GGT	NR	AMI	32/125 (26)		High

Continued

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Table 2-*continued*

Author	Marker	Period	Study population	AMI patients / total cohort – *n* (%)	Reference test	QUADAS-2 risk of bias
Gün[59,†]	CK, D dimer, WBC	2012	Abdominal pain, suspected of AMI	13/676 (2)	CT, laparotomy	High
Gunduz[60,†]	IMA	2006–2007	ED patients with thromboembolic SMA occlusion	7/14 (50)	Clinic, laparotomy, radiology	High
Güzel[61,*]	D dimer, I-FABP, WBC	2007–2008	AMI, Acute abdomen and controls	30/77 (39)	Clinic, laparotomy, radiology	High
Jamieson[62,†]	Phosphate	5 year period	Abdominal symptoms and massive gut ischaemia	20 (100)	Laparotomy	High
Janda[63,†]	Lactate	1979–1983	Acute abdomen, final diagnosis of AMI	18/132 (14)	Laparotomy	High
Kim[64,†]	CRP, WBC	2001–2016	Consecutive patients diagnosed with acute SMAE	66 (100)	Clinic, laparotomy, radiology	High
Kisaoglu[65,†]	Albumin, BUN, CBC, creatinine, glucose, LDH, RDW, WBC	2005–2013	Patients with AMI, AA patients without urgent surgery required	49/159 (31)	CTA, laparotomy	High
Lange[66,*]	Amylase, lactate	1985–1992	Acute abdomen	20/90 (22)	Clinic, laparotomy	High
Leo[67,†]	Phosphate	1990–1994	Acute abdomen, final diagnosis of AMI or infarction	23/50 (46)	Laparotomy	High
Lieberman[68,*]	I-FABP	NR	Clinical suspicion of AMI	7/19 (36)	Laparotomy	High
Matsumoto[69,*]	AST, base deficit, CK, CRP, D dimer, I-FABP, lactate, LDH, WBC	2009–2010	Acute abdomen	24/208 (12)	Autopsy, clinic, laparotomy	Low
Meyer[70,†]	Lactate, WBC	1988–1994	AMI	35 (100)	Clinic, laparotomy, radiology	High
Murray[71,*]	D lactate	NR	Laparotomy for acute abdominal emergencies including suspected AMI	9/41 (22)	Laparotomy	High
Rivera Nunez[72,†]	LDH, neutrophils, NLR, WBC	2013–2016	Acute abdomen	32/61 (52)	Radiology, pathology	High
Sachs[73,†]	CPK, LDH, SGOT, WBC	1965 -1980	Intestinal ischaemia treated in medical and surgical departments	49 (100)	Laparotomy	High
Schoeffel[74,*]	C3a, EarPI, endotoxin, FibA, lactate, PGE2, TNFa, WBC	NR	Ischaemic bowel wall damage during laparotomy	15/19 (79)	Laparotomy, angiography	High
Shrestha[75,†]	Lactate, pH, WBC	NR	Post-operative and or radiological diagnosis of mesenteric ischaemia	10 (100)	CTA, Laparotomy	High
Sgourakis[76,*]	ALP, ALT, AST, BUN, creatinine, GGT, IL-6, IL-8, lactic acidosis, neurotensin	2011–2012	Acute abdomen	8/53 (15)	Histology, laparotomy	High
Shi[77,†]	CPK, CRP, D lactate, I-FABP, LDH, WBC	2011–2014	Severe abdominal pain requiring surgery	7/272 (3)	Autopsy, endoscopy, laparotomy, CT	High
Struder[78,†]	CRP, lactate, pH, WBC	2006–2012	AMI	91 (100)	Histology, laparotomy	High
Takis[79,†]	Blood metabolic fingerprint	NR	Acute abdomen	9/64 (14)		High
Tanrıkulu[80,†]	CBC, CRP, MPV, NLR, RDW, WBC	2010–2015	Laparotomy or resection for AMI and NVBN patients	58/182 (32)	Laparotomy	High
Thuijls[81,†]	BE, lactate, plasma and urinary I-FABP, L-FABP, I-BABP, WBC	2007–2009	Consecutive patients with clinical suspicion of AMI	22/46 (48)	Autopsy, histology, laparotomy	High
Toptas[82,†]	CBC, CRP, lymphocytes, neutrophils, WBC	2009–2013	Patients with AMI	46/92 (50)		High

Table 2-*continued*

Author	Marker	Period	Study population	AMI patients / total cohort – *n* (%)	Reference test	QUADAS-2 risk of bias
Tsai[83,†]	Amylase, lactate, phosphate, WBC	1981–1988	Acute intestinal ischaemia	43 (100)	Angiography, histology, laparotomy	High
Türkoglu[84,†]	Hb, MPV, PC, WBC	2006–2011	Laparotomy for AMI	95/185 (51)	Clinic, laparotomy	High
Uzun[85,*]	I-FABP	2009–2010	Acute abdomen	7/171 (4)	Clinic, laparotomy, radiology	High
Wang[86,†]	NLR, PLR	2008–2015	Patients with AMEA or AMAT	137 (100)	Laparotomy, radiology	High
Yilmaz[87,†]	PLR	2014–2016	Operation for AMI	34 (100)	Laparotomy	High

If field is left blank, no data were available. NR = not reported; A = artery; AA = acute abdomen; AAA = acute abdominal aorta; ADH = alcohol dehydrogenase; AMEA = acute mesenteric arterial embolism; AMAT = acute mesenteric arterial thrombosis; AP = abdominal pain; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; BE = base excess; BUN = blood urea nitrogen; C3a = complement factor 3 split product; Ca = calcium; CBC = complete blood count; CK = creatine kinase; CK-BB = creatine kinase isoenzyme BB; Cl = chloride; CPK = creatine phosphokinase; CRP = C reactive Protein; CT = computed tomography; CTA = computed tomography angiography; CU = ulcerative colitis; DNA = deoxyribonucleic acid; EarPI = elastase-a1 proteinase inhibitor complex; ECG = electrocardiography; FibA = fibrinopeptide A; GGT = γ glutamyl transpeptidase; Hb = haemoglobin; Ht = haematocrit; ICU = intensive care unit; I-FABP = intestinal fatty acid binding protein; I-BABP = ileal bile acid binding protein; IBD = inflammatory bowel disease; IMA = ischaemia modified albumin; INR = international normalised ratio; K = potassium; LDH = lactate dehydrogenase; L-FABP = liver type fatty acid-binding protein; MPV = mean platelet volume; Na = sodium; NLR = neutrophil to lymphocyte ratio; NOMI = non-occlusive mesenteric ischaemia; NVBN = non-vascular bowel necrosis; NVI = non-vascular ischaemia; PC = platelet count; PGE2 = prostaglandin E2; PLR = platelet to lymphocyte ratio; PT = prothrombin time; Ptn. = patients; QT = quick time; RAAA = ruptured acute abdominal aorta; RDW = red cell distribution width; SBI = small bowel ischaemia; SGOT = serum glutamate oxaloacetate transaminase; SMA = superior mesenteric artery; SMAE = superior mesenteric artery embolus; SMV(T) = superior mesenteric venous thrombosis; TE = thrombo-embolic; TNFa = tumour necrosis factor alpha; WBC = white blood cell count.

* Prospective study.

† Retrospective study.

of clinical applicability and the fragile underlying scientific substantiation, current advice is not to use D dimer as an exclusion biomarker for arterial occlusive AMI.

The guideline of the World Society of Emergency Surgery, although briefly discussing D dimer, amylase, I-FABP, and IMA, concluded that more research was needed and that accuracy was not demonstrated.[14] In the European Society for Trauma and Emergency Surgery guideline, several biomarkers were briefly addressed, but they also concluded that biomarkers could be used to assess disease progression in AMI but were not suitable for diagnostic purposes.[13]

While nearly all systematic reviews on this topic have indicated that better quality research is needed to answer this question, many performed meta-analyses and assigned a diagnostic accuracy to various biomarkers despite the aforementioned methodological errors.[1,6,10,16,24–26] It is believed that by doing this, researchers uphold the clinical problem at hand. By giving an insufficiently substantiated qualitative measure to a certain biomarker, clinicians may be tempted to use such biomarkers in daily practice without knowing the full scope and limitations of the underlying data.[88]

A highly accurate, minimally invasive, rapid, 24/7 available and cost effective tool that can be deployed between presentation and the CTA to shorten the delay and eliminate the uncertainty of having a clinical suspicion on AMI is needed. The warning sign of elevated biomarkers has the potential to increase the index of clinical suspicion of AMI, which can lower the threshold for and speed up the deployment of additional diagnostic modalities. Ideally, the biomarker has both a high sensitivity and specificity to diagnose AMI. In the clinical setting, however, the positive predictive value (PPV) and NPV are more commonly used, which are influenced by the prevalence of the disease. In case of a high PPV, patients are more prone to actually have AMI and a targeted CTA can be performed with optimal use of its high sensitivity and specificity.[1] If a biomarker has a high NPV, it offers the possibility to rule out the diagnosis and a CTA can possibly be omitted.

High quality research is needed using uniform standards and pre-set thresholds, normal and cut off values, and units used, in order to perform meta-analysis and validate biomarkers. Diagnosing AMI needs to be established in a uniform way. Clearer frameworks need to be established for future studies performed through national and international collaborations instead of individual institutions to create a clearer overview on this topic and to prevent anymore blurring of data. As a result, outcomes can be reproduced and meta-analysis can be performed, finally giving statements and guidelines more depth, value, and content, with the patients ultimately benefitting the most. Furthermore, centralisation is both essential in improving patient outcomes and taking research quality to the next level. In The Netherlands these patients are treated in specialised centres

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Table 3. Diagnostic accuracy of biomarkers on acute mesenteric ischaemia (AMI) diagnosis.

Biomarker and design	Study	AMI / total patients − *n*	Cut off values	Sens − %	Spec − %	+LR	−LR	Positive predictive value − %	Negative predictive value − %	Odds ratio	AUC
WBC											
Prospective	Güzel[61]	30/77[39]	>11 042 mm^3	90	100			100	87		
	Matsumoto[69]	24/208[10]									0.54 (0.39–0.70)*
Retrospective	Aktimur[41]	70/193[36]	14.4/μL	57.1	69.3						0.623 (0.53–0.71)*
	BengFuh[46]	62/116[53]	>9 000/μL	93.6	26.2						
	Gün[59]	13/676[13]		92.3							
	Kisaoglu[65]	49/159[31]	10.05/μL	81.6	55.2	1.82	0.33				
			12.90/μL	71.4	81.2	3.80	0.35				
			15.05/μL	55.1	92.7	7.55	0.48				
	Shi[77]	7/272[14]	>8.50 × 10^9 /L	61.1 (50.6–78.4)*	36.5 (28.7–40.5)*	0.86 (0.71–1.17)*	1.12 (0.69–1.58)*	13.3 (9.1–17.8)*	79.8 (72.4–87.5)*		0.47
	Tanrıkulu[80]	58/182[32]	10.99 × 10^9/L	86.21	95.16			94.30	88.10		0.814
Lactate											
Prospective	Brillantino[49]	48/284[17]	≥2.050	64	90						0.85
	Lange[66]	20/90[22]	>2.4	100	42						
	Matsumoto[69]	24/208[10]									0.72 (0.58–0.86)*
Retrospective	BengFuh[46]	62/116[53]		92	42.9						
	Canfora[50]	36/55[65]	>2 mmol/L							49.66, $p < .001$	
LDH											
Prospective	Matsumoto[69]	24/208[10]	>211 U/L								0.78 (0.68–0.88)*
Retrospective	Kisaoglu[65]	49/159[31]	>249 U/L	91.8	49.0	1.80	0.17				
			>299.5 U/L	87.8	76.0	3.66	0.16				
			>407 U/L	71.4	88.5	6.21	0.32				
	Shi[77]	36/55[65]	>211 U/L	61.6 (49.3–72.1)*	77.3 (70.4–83.6)*	2.61 (2.04–3.81)*	0.54 (0.31–0.73)*	36.7 (23.2–42.7)*	72.3 (67.5–86.4)*		0.62
Amylase											
	No data available										
CRP											
Prospective	Matsumoto[69]	24/208[10]	<0.5 mg/dL								0.74 (0.64–0.84)*
Retrospective	Shi[77]	36/55[65]		68.9 (54.1–80.6)*	34.2 (28.8–47.2)*	1.21 (0.93–1.55)*	0.71 (0.44–1.08)*	13.8 (10.9–20.4)*	81.6 (79.5–91.3)*		0.53
	Tanrıkulu[42]	58/182[32]	2.10 mg/dL	100	100			100	100		1.00
D dimer											
Prospective	Acosta[38]	6/14[43]		100	35						
	Acosta[39]	9/101[7]	>0.3 mg/L	100	36	1.6		100	13		
			>0.8 mg/L			2.4					
			>1.5 mg/L			3.9					
	Akyildiz[42]	28/47[60]	>3.17 μg FEU/mL	95	79			75.0	95.7		0.93 (0.81–0.98)* $p < .001$
	Chiu[51]	23/67[34]	>1.0 μg FEU/mL	96	18	1.17	0.24				
	Güzel[61]	30/77[39]	>130 μg/L	93	100			100	91		
	Matsumoto[69]	24/208[10]									0.74 (0.63–0.85)*
Retrospective	Gün[59]	13/676[13]	>1 000 ng/mL	85	48						
I-FABP											
Prospective	Güzel[61]	30/77[39]	>90 pg/mL	90	100			100	87		
	Matsumoto[69]	24/208[10]	>9.1 ng/mL	83.3	89.1			97.6	50.0		0.88 (0.79–0.96)*
	Uzun[85]	7/171[2]	>145 pg/mL	71.4	94.6			41.7	98.4		0.755

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Table 3-*continued*

Biomarker and design	Study	AMI / total patients − *n*	Cut off values	Sens − %	Spec − %	+LR	−LR	Positive predictive value − %	Negative predictive value − %	Odds ratio	AUC
Retrospective	Shi[77]	7/272[14]	>82.4 ng/mL	76.2 (67.4–91.5)	74.8 (68.7–82.4)	3.25 (2.41–3.92)	0.24 (0.15–0.47)	32.1 (24.7–41.4)	96.3 (91.6–98.4)		0.85
	Thuijls[81]	22/46[48]	>268 pg/mL	68	71	2.34 (1.18–4.67)*	0.45 (0.23–0.87)*	68 (52–81)*	29 (18–45)*		0.70 (0.53–0.86)* $p = .02$
D lactate											
Prospective	Murray[71]	9/41[22]	>20 μg/mL	90	87			70	96		
Retrospective	Shi[77]	7/272[14]	>31.8 μg/mL	66.7 (52.8–84.2)*	85.9 (77.8–92.6)*	2.82 (2.07–3.61)*	0.31 (0.17–0.57)*	86.3 (79.8–90.7)*	72.6 (65.3–88.2)*		0.69

Amylase no data available. If field is left blank, no data were available. NR = not reported; AMI = acute mesenteric ischaemia; CRP = C reactive Protein; I-FABP = intestinal fatty acid binding protein normalised ratio; LDH = lactate dehydrogenase; WBC = white blood cell count. Sens = sensitivity; Spec = specificity; +LR = positive likelihood ratio; −LR = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value; OR = odds ratio; AUC = area under the receiver operating characteristic curve.
* Numbers in parentheses represent 95% confidence intervals.

with 24/7 expertise. For this review, there was a national and international collaboration with experts in the field, supported by the Dutch Mesenteric Ischaemia Study Group.[89]

In conclusion, this systematic review underlines the conclusion of the 2017 European Guideline on Treatment of Mesenteric Ischaemia that no individual biomarker or combination of biomarkers are yet suitable to aid in the diagnostic process of arterial occlusive AMI, based on the lack of high quality and homogeneic evidence.[1] In fact, it is believed that it is justifiable to argue that clinicians should stop ascribing any diagnostic value to any biomarker in daily practice, even leucocytes, lactate, and D dimer. The diagnosis of arterial occlusive AMI can currently only be made on the basis of a high index of clinical suspicion followed by a 1 mm multiphase CTA.[1] This index of clinical suspicion should be defined in more detail, and disease specific biomarkers may eventually aid in the process of earlier diagnosis. The importance of the establishment of clinical algorithms for the diagnosis and treatment of AMI is substantiated in a recent worldwide survey.[90] In the absence of

Table 4. Reported values of individual acute mesenteric ischaemia biomarkers; total cohort and subcohort analysis.

Biomarker and design	Study	AMI/total cohort − *n* (%)	Normal values in total cohort	Subcohort A/ Subcohort B (patients − *n*)	Reported value in subcohort A	Reported value in subcohort B	*p* value
WBC							
Prospective	Acosta[39]	9/101 (9)	4.0–10.0 × 10 g/L	SMA occl (9)/no SMA occl (92)	28.3 (9.6–60) × 10 g/L*	11.2 (1.3–98.0) × 10 g/L*	.001
	Chiu[51]	23/67 (34)	NR	AMI (23)/no-AMI (44)	15.2 ± 6.7 × 10^9 cells/L†	13.1 ± 7.4 × 10^9 cells/L†	.20
	Emile[56]	101 (100)	NR		18.4 ± 5.9† (4.8–35)¶¶ 10^3/μL		
	Güzel[61]	30/77 (39)	NR	AMI (30)/Control (20)	18.50 (3.73–40.89) mm^3‡	6.99 (3.55–11.04) mm^3‡	<.001
				AMI (30)/AA (27)		14.56 (4.44–32.00) mm^3‡	<.001
	Matsumoto[69]	24/208 (12)	3.50–8.50 × 10^9/L	AMI (24)/NID (122)	11.7 ± 7.7 × 10^9/L†	10.3 ± 4.8 × 10^9/L†	NS
				AMI (24)/non-vascular (62)		10.4 ± 3.7 × 10^9/L†	NS
				VII (19)/no VII (122)	13.0 ± 8.1 × 10^9/L†	10.3 ± 4.8 × 10^9/L†	NS
				VII (19)/non-VII (26)		11.1 ± 3.9 × 10^9/L†	NS
	Schoeffel[74]	15/19 (79)	NR	SMA occ (9)	17.4 ± 8.97 cells × 1000/μL†		

Continued

Table 4-*continued*

Biomarker and design	Study	AMI/total cohort − *n* (%)	Normal values in total cohort	Subcohort A/ Subcohort B (patients − *n*)	Reported value in subcohort A	Reported value in subcohort B	*p* value
Retrospective	Acosta[40]	55 (100)	3.5–8.8 × 10^9/L	Embolic (24)	Elevated in 1 of 24 (4%)		
					18.9 (14.8–24.1) × 10^9/L[§]		
				Thrombotic (27)	Elevated in 1 of 27 (2%)		
					14.5 (11.4–23.4) × 10^9/L[§]		
	Aktimur[41]	70/193 (36)	NR	AMI (70)/total (193)	15.2 (2.8–34.2)/ μL[*]	13.0 (2.8–39.9)/ μL[*]	.002
				AMI (70)/AA (62)		13.7 (3.7–24.5)/ μL[*]	.11
				AMI (70)/NA (61)		11 (3.4–39.9)/μL[*]	.001
	Altintoprak[43]	30 (100)	NR	Death (15)/ survival (15)	18.046/μL	14.040/μL	.05
	BengFuh[46]	62/116 (53)	4.0–9.0/μL	AMI (62)/no AMI (42)	Elevated in 58 of 62 (93.54%)	Elevated in 31 of 42 (73.81%)	
					19.40/μL[‖‖]	12.90/μL[‖‖]	
				Total necrosis = ?/vital bowel = ?	22.36/μL[‖‖]	18.10/μL[‖‖]	
				Partial necrosis = ?/vital bowel = ?	19.40/μL[‖‖]		
	Bilgiç[48]	61 (100)	NR	AMI (61)	16.47 (6.20–52.20) × 10^9/L[‡]		
	Canfora[50]	36/55 (65)	<10^4/mL	ITIN (36)/no ITIN (19)	Elevated in 28 of 36 (78%)	Elevated in 16 of 19 (84%)	.57
	Destek[54]	44/51 (86)	4.6–10.2 × 10^3/μL	SBI (37)/SLBI (7)	18.51 (4.21–50.67) × 10^3/μL[‖]	20 (10.80–42.10) × 10^3/μL[‖]	.73
				Embolic (14)	19.10 (6.75–42.10) × 10^3/μL[‖]		
				Thrombotic (13)	18.51 (7.51–50.67) × 10^3/μL[‖]		
	Elthes[55]	50 (100)	NR	Deceased (37)/ survivors (13)	16.69 × 1 000/μL[¶]	18.55 × 1 000/μL[¶]	.37
	Gün[59]	13/676 (2)	4.300–10.300/mm^3	AMI (13)/no AMI (629)	Elevated in 12 of 13 (92.3%)		<.05
					20.38 ± 7.18/mm^3[†]	10.28 ± 5.32/mm^3[†]	.001
	Kim[64]	66 (100)	NR	Acute SMAE (66)	16.83 (1.47–54.51) × 10^3/μL[**]		
				BR (31)/no BR (31)	17.91 (5.45–54.51) × 10^3/μL[**]	16.09 (1.47–42.39) × 10^3/μL[**]	.45
	Kisaoglu[65]	49/159 (31)	NR	AMI (49)/control (110)	16.63 ± 6.84/μL[†]	9.83 ± 3.46/μL[†]	<.001
	Meyer[70]	35/46 (75)	4000–10000 /mL	AMI (35)	Elevated in 32 (91.42%)		
					15 050 (9 300–32 000)/mL[*]		
	RiveraNunez[72]	32/61 (52)	NR	AMI (32)/control (29)	1.18 (0.54–2.07) × 10^9/L[§]	2.2 (7.95–2.01) × 10^9/L[§]	<.05
	Sachs[73]	49 (100)	NR	Arterial thrombosis (12)	21 200/mm^3[**]		
				Arterial embolisation (14)	22 100/mm^3[**]		
				Emboli secondary to angio (4)	18 500/mm^3[**]		
	Tanrıkulu[80]	58/182 (32)	4.0–10.0 × 10^9/L	AMI (58)/control (62)	16.38 (4.48–38.20) × 10^9/L[††]	8.28 (4.15–12.23) × 10^9/L[††]	.002
	Thuijls[81]	22/46 (48)	NR	AMI (22)/control (24)	13.9 (1.7–28.0) mg/L[††]	12.7 (3.3–33.7) mg/L[††]	.89
	Toptas[82]	46/92 (50)	NR	AMI (42)/control (42)	17.6 ± 7.8 × 10^9[†]	8.8 ± 4.6 × 10^9[†]	<.001

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Table 4-*continued*

Biomarker and design	Study	AMI/total cohort − *n* (%)	Normal values in total cohort	Subcohort A/ Subcohort B (patients − *n*)	Reported value in subcohort A	Reported value in subcohort B	*p* value
	Tsai[83]	43 (100)	NR	SMA occl (22)	Elevated in 22 of 22 (100%)		
	Türkoglu[84]	95/185 (51)	4.0−10.0 × 10^9/L	AMI (95)/control (90)	20.4 ± 8.3 × 10^9/L[††]	7.4 ± 2.1 × 10^9/L[††]	<.001
Lactate							
Prospective	Brillantino[49]	48/284 (17)	0.5−1.8 mmol/L	AMI (48)/NID (201)	2.3 (1.1−5.2) mmol/L[*]	1.2 (0.2−5.1) mmol/L[*]	<.001
	Chiu[51]	23/67 (34)	NR	AMI (23)/non-AMI (44)	3.56 (0.62−32.69) mg/dL[*]	3.66 (0.75−14.05) mg/dL[*]	.88
	Emile[56]	101 (100)	NR		19.2 ± 9[†] (11.3−44)[¶¶] mg/dL		
				Bowel necrosis (73)/VB (28)	27.8 ± 12.8 mg/dL[†]	15.5 ± 2.7 mg/dL[†]	<.001
	Lange[66]	20/90 (22)	0.6−2.4 mmol/L	AMI (20)	Elevated in 20 (100%)		
				AMI (20)/AA other (30)	5.4 ± 2.3 mmol/L[†]	1.5 ± 0.8 mmol/L[†]	
				Peritonitis (15)	Elevated in 15 (100%)		
					3.9 ± 0.8 mmol/L[†]		
				Intestinal obstruction (20)	Elevated in 10 of 20 (50%)		
					2.7 ± 1.6 mmol/L[†]		
	Matsumoto[69]	24/208 (12)	4−16 mg/dL	AMI (24)/NID (122)	38 (7−125) mg/dL[§]	17 (0−59) mg/dL[§]	<.010
				VII (19)/NID (122)	41 (7−125) mg/dL[§]	1.89 (0−6.55) mg/dL[§]	<.010
	Schoeffel[74]	15/19 (79)	NR	Bowel resections only, Lethal (5)/ Non-lethal (9)	3.0 (0.0−8.6) mmol/L[*]	1.8 (0.8−7.5) mmol/L[*]	.14
Retrospective	Acosta[40]	55 (100)	0.5−2.2 mmol/L	Only available in 27 AMI patients	Elevated in 14 of 27 (52%)		
					2.4 (1.6−4.5) mmol/L[§]		
	BengFuh[46]	62/116 (53)	<2.2 mmol/L	AMI (62)/No-AMI (42)	Elevated in 57 of 62 (91.93%)	Elevated in 24 of 42 (57.14%)	
					5.5 mmol/L[‖‖]	2.6 mmol/L[‖‖]	
				Total necrosis = ?/vital bowel = ?	7.6 mmol/L[‖‖]	3.8 mmol/L[‖‖]	
	Canfora[50]	36/55 (65)	<2.0	ITIN (36)/no ITIN (19)	Elevated in 30 of 36 (83%)	Elevated in 1 of 19 (5%)	<.001
	Czerny[52]	145 (100)	NR	Starting in 1984	Elevated in 56 of 69 (81.2%)		
					9.81 (3.21−22.3) mmol/L[*]		
	Janda[63]	18/132 (14)	1−2 mmol/L	AMI (18)/Occl a Fem (10)	7.45 ± 2.86 mmol/L[†]	1.72 ± 0.85 mmol/L[†]	α = .02
	Meyer[70]	35 (100)	5−20 U/L	Only available in 26 AMI patients	Elevated in 24 of 26 (92.30%)		
					53 (15 - 156) U/L[*]		
	Shrestha[75]	10 (100)	NR				
	Struder[78]	91 (100)	NR	Non-survivor (39)/survivor (52)	5.6 ± 4.8 mmol/L[†]	3.0 ± 2.2 mmol/L[†]	.024
	Thuijls[81]	22/46 (48)	NR	AMI (22)/control (24)	2.5 (0.4−23.1) mmol/L[††]	2.3 (1.0−5.2) mmol/L[††]	.56
	Tsai[83]	43 (100)	NR	SMA occl (21)/ total group (35)	Elevated in 9 of 21	Elevated in 31 of 35	
LDH							
Prospective	Arnalich[45]	99/130 (76)	NR	AMI (63)/no AMI (31)	414 (345−470) lU/L[§]	316 (278−372) lU/L[§]	NS
	Matsumoto[69]	24/208 (12)	106−211 U/L	VII (19)/NID (122)	398 (186−1048) U/L[§]	228 (138−613) U/L[§]	<.010

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Table 4-*continued*

Biomarker and design	Study	AMI/total cohort − *n* (%)	Normal values in total cohort	Subcohort A/ Subcohort B (patients − *n*)	Reported value in subcohort A	Reported value in subcohort B	*p* value
Retrospective	Bilgiç[47]	61 (100)	NR	AMI (61)	305 (210−433) U/L[§]		
	Bilgiç[48]	61 (100)	NR	AMI (61)	381.4 (124−1 779) U/L[‡]		
	Canfora[50]	36/55 (65)	NR	ITIN (36)/No ITIN (19)	Elevated in 33 of 36 (92%)	Elevated in 17 of 19 (89%)	.79
	Destek[54]	44/51 (86)	125−220 U/L	SBI (37)/SLBI (7)	263 (162−832) U/L[‖]	330 (223−400) U/L[‖]	.13
				Embolic (14)	277.50 (218−832) U/L[‖]		
				Thrombotic (13)	267 (175−524) U/L[‖]		
	Elthes[55]	50 (100)	NR	Deceased (37)/ survivors (13)	392.92 U/L[¶]	249.13 U/L[¶]	.044
	Kisaoglu[65]	49/159 (31)	NR	AMI (49)/control (110)	700 ± 450 U/L[†]	283 ± 120 U/L[†]	<.001
	RiveraNunez[72]	32/61 (52)	NR	AMI (32)/control (29)	311 (258−422) U/L[§]	213 (182.25−239) U/L[§]	<.05
	Sachs[73]	49 (100)	100−225 lU/L	Arterial embolus (3)	Elevated in 2 (67%)		
					257 lU/L[**]		
				Arterial thrombosis (5)	Elevated in 4 (80%)		
					334 lU/L[**]		
Amylase							
Prospective	Arnalich[45]	99/130 (76)	NR	AMI (63)/non-AMI (31)	258 (136−438) U/L[†]	148 (122−183) U/L[†]	<.05
	Chiu[51]	23/67 (34)	NR	AMI (23)/non-AMI (44)	215 (38−875) U/L[*]	109 (18−2850) U/L[*]	.078
	Emile[56]	101 (100)	NR		103.7 ± 133.5[†] (26−422)[¶¶] U/L		
				Bowel necrosis (73)/VB (28)	218.7 ± 191.5[†]	46.2 ± 20.7[†]	<.001
	Lange[66]	20/90 (22)	NR		Elevated in 3 of 10 (30%)		
Retrospective	Acosta[40]	55 (100)	0.15−1.10 mkat/L	Only available in 45 AMI patients	Elevated in 12 of 45 (27%)		
					0.69 (0.32−1.19) mkat/L[§]		
	Altintoprak[43]	30 (100)	NR	Death (15)/ survival (15)	214.0[§§]	73.0[§§]	.022
	Bilgiç[48]	61 (100)	NR	AMI (61)	133.0 (4−677) U/L[‡]		
				Death (35)/ survivor (26)	108 (4−471) U/L[‡]	57 (11−329) U/L[‡]	<.01
	Destek[54]	44/51 (86)	25−125 U/L	SBI (37)/SLBI (7)	96 (19−902) U/L[‖]	71 (22−464) U/L[‖]	.62
				Embolic	72.50 (22−593) U/L[‖]		
				Thrombotic	122 (41−902) U/L[‖]		
	Tsai[83]	43 (100)	NR	SMA occl (18)/ overall (32)	Elevated in 8 of 18 (44%)	Elevated in 15 of 32 (47%)	
CRP							
Prospective	Acosta[39]	9/101 (9)	<5 mg/L	SMA occl (9)/no SMA occl (92)	117 (5−446) mg/L[*]	23 (5−393) mg/L[*]	.015
	Matsumoto[69]	24/208 (12)	<0.5 mg/dL	AMI (24)/no AMI (122)	3.5 (1−37.0) mg/dL[§]	0.4 (0−34.5) mg/dL[§]	<.010
				VII (19)/NID (122)	7.5 (0.3−37.0) mg/dL[§]	0.4 (0−34.5) mg/dL[§]	<.010
Retrospective	Acosta[40]	55 (100)	≤5 mg/L	Embolic	Elevated in 7 of 28 (25%)		
					49 (3.8−167) mg/L[§]		

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Table 4-*continued*

Biomarker and design	Study	AMI/total cohort − *n* (%)	Normal values in total cohort	Subcohort A/ Subcohort B (patients − *n*)	Reported value in subcohort A	Reported value in subcohort B	*p* value
				Thrombotic	Elevated in 6 of 24 (25%)		
					123 (11.5−245.2) mg/L[§]		
	Canfora[50]	36/55 (65)	<50 (unit NR)	ITIN (36)/No-ITIN (19)	Elevated in 25 of 36 (69%)	Elevated in 15 of 19 (79%)	.45
	Destek[54]	44/51 (86)	<0.5 mg/L	SBI (37)/SLBI (7)	23 (1.9−412) mg/L[‖]	9 (1.1−22) mg/L[‖]	.018
				Embolic	30.29 (16−412) mg/L[‖]		
				Thrombotic	18.53 (1.1−50) mg/L[‖]		
	Kim[64]	66 (100)	NR	Acute SMAE (66)	7.32 (0.08−35.39) mg/dL[**]		
				BR (31)/no BR (31)	4.3 (0.2−22.9)[**]	11.6 (0.1−35.4)[**]	.010
	Tanrıkulu[42]	58/182 (32)	<0.5 mg/dL	AMI (58)/control (62)	16.60 (3.20−63.20) mg/dL[††]	0.20 (0−2.10) mg/dL[††]	<.001
	Toptas[82]	46/92 (50)	NR	AMI (42)/control (42)	2.1 ± 3.02[§§]	1.3 ± 1.22[§§]	.01
D dimer							
Prospective	Acosta[38]	6/14 (43)	<0.3 mg/L	AMI (6)/no AMI (8)	4.7 (3.3) mg/L	1.38 (1.7) mg/L	<.05
	Acosta[39]	9/101 (9)	<0.3 mg/L	SMA occl (9)/No SMA occl (92)	1.6 (0.4−5.6) mg/L*	0.5 (0.1−7.7) mg/L*	.009
						Elevated in 33 of 92 (36%)	
	Chiu[51]	23/67 (34)	NR	AMI (23)/no AMI (44)	6.24 (0.96 - 53.48) μg FEU/mL*	3.45 (0.50−44.69) μg FEU/mL*	.064
	Güzel[61]	30/77 (39)	NR	AMI (30)/AA (27)	675 (50−6 403) μg/L[‡]	435 (76−1 290)μg/L[‡]	<.001
	Matsumoto[69]	24/208 (12)	<1.0 μg/mL	VII (19)/NID (122)	11.0 (1.3−47.2) μg/mL[§]	2.0 (0.5−53.8) μg/mL[§]	<.010
Retrospective	Destek[54]	44/51 (86)	0−0.5 μg/mL FEU	SBI (37)/SLBI= 7	2.30 (0.30−7.80) μg/mL FEU[‖]	0.70 (0.20−2.80) μg/mL FEU[‖]	.029
				Embolic	2.90 (1.30−7.10) μg/mL FEU[‖]		
				Thrombotic	2.1 (0.4−5.9) μg/mL FEU[‖]		
	Gün[59]	13/676 (2)	<470 ng/mL	AMI (13)/No-AMI (217)	Elevated in 11/13 (84.6%)		<.05
					1 177.77 ± 710.4 ng/mL[†]	744.89 ± 1752.4 ng/mL[†]	.003
I-FABP							
Prospective	Güzel[61]	30/77 (39)	NR	AMI (30)/AA (27)	421 (40−5 000) pg/mL[‡]	80 (1−200) pg/mL[‡]	<.001
	Liebermann[68]	7/19 (36)	<1.87 ng/mL	AMI (7)/Control (12)	Elevated in 7 of 7 (100%)	Elevated in 1 of 12 (8.3%)	
					50 ± 72 (5.4 - 100) ng/mL[†]		
	Matsumoto[69]	24/208 (12)	1.1(0.9) ng/mL[†](range 0.1−5.5)	AMI (24)/NID (122)	31.0 (1.1−498.4) ng/mL[§]	2.5 (0.2−56.7) ng/mL[§]	<.010
				SBI (37)/SLBI= 7	2.30 (0.30−7.80) ng/mL[§]	0.70 (0.20−2.80) ng/mL[§]	.029
	Uzun[85]	7/171 (4)	NR	AMI (7)/control (130)	708.6 ± 669.1 pg/mL[†]	61.4 ± 47.4 pg/mL[†]	<.05
Retrospective	Shi[77]	7/272 (3)	8.33 ± 6.25 ng/mL	AMI (7)/control (37)	125.8 ± 39.8 ng/mL[†]	8.33 ± 6.25 ng/mL[†]	<.05
				Death (14)/survival (25)	108 ± 40.6 ng/mL[†]	104 ± 58.2 ng/mL[†]	>.05
	Thuijls[81]	22/46 (48)	NR	AMI (22)/control (24)	653 (40−74.711) pg/mL[‡‡]	109 (40−1.691) pg/mL[‡‡]	.02

Continued

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Table 4-*continued*

Biomarker and design	Study	AMI/total cohort − *n* (%)	Normal values in total cohort	Subcohort A/ Subcohort B (patients − *n*)	Reported value in subcohort A	Reported value in subcohort B	*p* value
D lactate							
Prospective	Murray[71]	9/41 (22)	<20 μg/mL	AMI (9)/control (10)	Elevated in 8 of 9	Elevated in 0 of 10	
					32.37 ± 4.0 μg/mL†	4.89 ± 0.9 μg/mL†	<.001
				AMI (9)/AA (17)	32.37 ± 4.0 μg/mL†	10.61 ± 3.2 μg/mL†	<.001
				AMI (9)/SBO (5)		10.65 ± 1.6 μg/mL†	<.001
Retrospective	Shi[77]	7/272 (3)	5.47 ± 1.64 g/mL	AMI (7)/control (37)	78.4 ± 27.6 μg/mL†	5.47 ± 3.64 μg/mL†	<.05
				Ischaemic deceased (14)/ ischaemic survived (25)	76.7 ± 34.5 μg/mL†	23.7 ± 14.3 μg/mL†	<.01
				Ischaemia (39)/no ischaemia (233)	59.7 ± 24.5 μg/mL†	13.2 ± 5.7 μg/mL†	<.001
				Ischaemia (39)/ control (37)	59.7 ± 24.5 μg/mL†	5.47 ± 3.64 μg/mL†	<.001

AA = acute abdomen; Angio = angiography; ITIN = irreversible transmural intestinal necrosis, II = intestinal ischaemia, VII = vascular irreversible ischaemia, BR = bowel resection; Occl = occlusion; NID = non-ischaemic disease; NR = not reported; NS = not significant; SBI = small bowel ischaemia; SBO = small bowel obstruction; SLBI = small and large bowel ischaemia; SMAE = superior mesenteric artery embolism; VB = viable bowel.
* Values are presented as median (range).
† Values are presented as mean ± standard deviation.
‡ Values are presented as mean (min−max).
§ Values are presented as median value and interquartile range.
‖ Values are presented as median (min−max).
¶ Values are presented as mean.
** Values are presented as mean (range).
†† Not reported how values are presented as.
‡‡ Values are presented as median (unknown reporting)
§§ Unit not reported and not reported how values are presented as.
‖‖ Values are presented as median.
¶¶ Range.

good quality evidence and reliable diagnostic tools, when clinical suspicion exists, clinicians, and especially vascular surgeons, should act fast.

CONFLICT OF INTEREST STATEMENT AND FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.08.059.

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