International Journal of Surgery 66 (2019) 18–27

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

Diagnostic accuracy of hematological parameters in Acute mesenteric ischemia-A systematic review

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ARTICLE INFO

Keywords:
Mesenteric ischemia
Sensitivity and specificity
Hematological parameters

ABSTRACT

Background: We conducted a systematic review on the diagnostic accuracy of classical and newly reported hematological parameters which are easily available in a resource limited setting in making a diagnosis of Acute Mesenteric Ischemia (AMI).

Methods: We searched the PubMed, Scopus, and Cochrane library from January 1940 to April 2018. The search was limited to studies published in English and those involving human subjects only. The diagnostic accuracy of conveniently available parameters: Mean Platelet Volume (MPV), Neutrophil to Lymphocyte Ratio (NLR), Red Cell Distribution Width (RDW), lactate, D-dimer, alkaline aminotransferase, aspartate amino transferase, white blood cell count, lactate dehydrogenase, and amylase were assessed in this review. Studies were only included if they provided sufficient information allowing us to make a diagnostic accuracy contingency table and define a gold standard test. We excluded letters, editorials, and case reports. There were no restrictions to any particular study design. The QUADAS 2 protocol was used for quality appraisal. This study protocol was registered on Prospero with ID CRD42018088953.

Results: Of 560 articles which were initially retrieved, 20 studies, comprising of 2043 participants, were eligible for this review. AMI was diagnosed in 518 patients. D-dimer had the highest median sensitivity of 93% while the median specificity of lactate and NLR were 85.9 and 85.8, respectively.

Conclusion: Observing the high heterogeneity among the studies, currently it is difficult to suggest any single marker for diagnosing AMI. Compared to the classical markers, RDW, NLR and MPV showed higher specificities. Using these new markers alongside with the classical markers in the context of a scoring system might help in making a diagnosis of AMI in emergency settings.

1. Introduction

Acute mesenteric ischemia (AMI) refers to the sudden onset of small intestinal hypoperfusion, which is secondary to reduction in arterial or venous inflow. Among the four etiological types that include arterial embolism, arterial thrombosis, venous thrombosis and NOMI (Non occlusive mesenteric ischemic), arterial embolism accounts for the majority of cases of AMI [1,2].

AMI can be regarded as a disease of the elderly. Acosta et al. reported a steep increase in incidence of AMI with age [3]. AMI is a medical emergency with high mortality rates (ranged from 30% to 90%) [4]. The pathophysiology of AMI is rather complex and the clinical manifestations diverse, thus making an early diagnosis difficult [2]. The mortality rate from AMI is closely linked to the extent of ischemic necrosis of the intestine, while transmural injury often results in inflammation, necrosis, sepsis and multiple organ failure [2,5]. It is evident from the literature that early diagnosis of the disease is correlated with a significant reduction in mortality rates [6].

Currently, the best diagnostic test for AMI, is CT angiography [7], but early CT findings in AMI are non-specific, especially in NOMI [8]. This approach is costly and is impractical when AMI occurs in a critical care setting. Furthermore, CT angiography is not widely available and utilizing it consumes time which is the most significant prognostic marker in AMI [9]. Thus, identifying a biomarker that has sufficient diagnostic accuracy could help clinicians in reaching a diagnosis promptly and in making a decision early.

Various novel biomarkers like I-FABP, although not widely available, have shown promising results, yet further research is needed to

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https://doi.org/10.1016/j.ijsu.2019.04.005
Received 10 January 2019; Received in revised form 21 February 2019; Accepted 10 April 2019
Available online 16 April 2019

fully establish their accuracy [10]. On the other hand, routine hematological markers like lactate and d-dimer have been shown to be non-specific [11]. Until recently, new hematological parameters such as mean platelet volume (MPV) and red cell distribution width (RDW) have been reported to be associated with reasonably high diagnostic accuracies.

To our knowledge there is no published review that assess the utility of these parameters (MPV, RDW, NLR) in AMI. The aim of this systematic review is to assess the diagnostic accuracies of the recently reported (RDW, NLR, MPV) and classical hematological markers (D-lactate, L-lactate, d-dimer, AST, and ALT, amylase, WBC count, LDH) in Acute mesenteric ischemia. We also discussed the possibility of a future scoring system.

2. Materials and methods

2.1. Search strategy

The protocol of this systematic review has been registered a priori in the PROSPERO registry under the special identifier [CRD42018088953].

The PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] and [12] (Supplementary file 1) and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines (supplementary file 3) were followed on reporting this review. An organized, systematic literature search was conducted on electronic databases in the period from January 1940 to April 2018. Two authors searched the PubMed/Medline and Scopus and one author searched the Cochrane library for all relevant articles. There were no restrictions to study design and population, Only English articles were included in the search. Using the “related articles” PubMed function, further publications were retrieved and screened. The reference section of the retrieved studies was screened for other potentially eligible studies.

The keywords used for the literature search were: “acute mesenteric ischemia”, “AMI”, “prognosis”, “biomarkers”, “diagnostic accuracy”, “red cell distribution width”, “RDW”, “Mean platelet volume”, “MPV”, “d-dimer”, “lactate”, “AST”, “ALT”, “neutrophil”, “lymphocyte”, “NLR”. In addition, medical subject headings (MeSH) terms including “mesenteric ischemia”, “mean platelet volume”, “red cell distribution width”, “d-dimer” and “lactate” were used in the search process (formal search strategy of PubMed is given in supplementary file 2).

3. Inclusion and exclusion criteria

All articles were identified by the above-mentioned strategies. After removing duplicates, articles were screened on the basis of pre-defined inclusion and exclusion criteria. We included studies that provided both the sensitivity and specificity of the concerned parameters for the diagnosis of AMI, or when they provided the data on individual study subjects, thus allowing us to derive the number of true positive, false positive, false negative, and true negative results. Only studies included in the review were those which evaluated patients with clinical suspicion of AMI.

An important prerequisite for inclusion to the review was confirmation of the final diagnosis of patients by either laparotomy, CT-Angiography, mesenteric angiography or histopathological examination of the resected surgical specimens or the final decision of the surgical team (reference standard).

We excluded case reports, editorial, letters to the editor, reviews and meta-analyses, and articles that did not report the main parameters of the present review clearly and completely. Studies examining plasma markers post laparotomy, and studies using healthy subjects as controls were excluded. Any study on a particular topic of ischemic colitis was also excluded.

Two authors (S.E. and S.K.) screened the articles by the title and abstract and then a full text screening was conducted. For any disagreement on an article, a final decision was made by mutual discussion.

4. Quality appraisal

Using the modified criteria based on the QUADAS-2 tool [13], two authors (S.E., S.K) critically appraised the selected articles for risk of bias (validity) and applicability in an independent manner. Decisions were made after a consensus was reached. We added one question in the flow and timing domain of the protocol (whether the article mentioned the time from initial presentation of patient to the department to the collection of samples for lab analysis). The risk of bias was considered high with a low score for ≥ 1 items, and was considered low when all the items were scored high.

5. Statistical analysis

Two authors (S.E., S.K) independently extracted the number of patients, clinical setting, study population, prevalence of intestinal ischemia, study design, and cut-off level for each marker. For each article the TP, FP, TN, FN were calculated and recorded.

Demographic and clinical study data were expressed as mean (SD), or median (range) for quantitative variables and as percentages for qualitative variables. We constructed the Two-by-two contingency tables for all markers, Sensitivity, specificity, +LR, -LR and 95% confidence interval (CI) were calculated based on the accuracy data (TP, TN, FP, and FN) extracted from each of the included studies. The cut off, sensitivity and specificity rates, +LR, and -LR from the individual studies were expressed as median with 95% confidence intervals (CI). The study heterogeneity was determined by the Cochrane's $\chi 2$ test and I^2 measures. Studies with an I^2 value below 25% were considered to have a low heterogeneity, 26–50% were considered to have a moderate heterogeneity, and above 75% were considered to have a high heterogeneity. The Spearman correlation test was used to assess the threshold effect. The Positive Spearman correlation coefficient and a $p < 0.05$ indicated a significant threshold effect. The Meta Disc® version 1.4 was used for calculation of heterogeneity and threshold effects.

6. Results

6.1. Study selection and description

Of 560 articles (380 from PubMed, 173 from Scopus, and 7 found by cross searching) which were initially retrieved after the initial literature search, 54 duplicate publications were removed. The remaining 506 articles were screened by titles and abstracts which led to the exclusion of 459 studies. The full text of the remaining studies was screened and 27 articles were excluded either because the sensitivity and specificity could not be calculated from the data, or because a contingency table could not be formed. Finally, 20 studies were included into the systematic review. The process of literature search and article selection is displayed in the PRISMA flow chart (Fig. 1).

The 20 studies included into this review comprised of 2043 patients. The publication time ranged from 1994 to 2018. Seven of the 20 studies were undertaken in Turkey. Four were retrospective and sixteen were prospective studies.

The characteristics of the included studies are shown in Table 1. The results of quality assessment are shown in Table 2. The heterogeneity among the studies is illustrated in Table 3. The diagnostic characteristics of the markers are shown in Table 4. The pathophysiology of elevation of the markers is summarized in Table 5.

6.2. RDW

Overall, three retrospective studies [14–16] comprising of 534 patients reported data on RDW. AMI was diagnosed in 177 (33.1%)

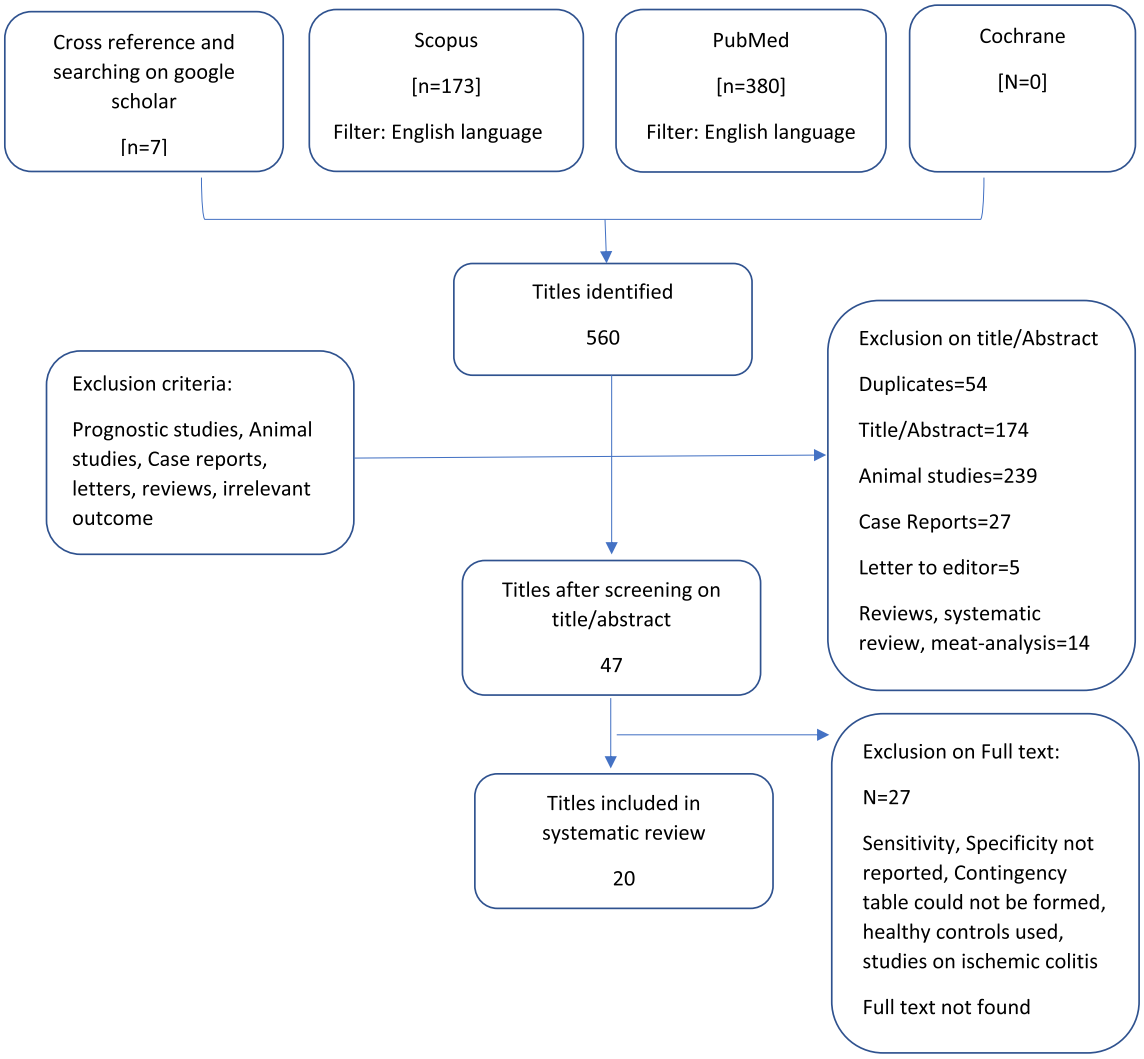

Fig. 1. Flow chart illustrating the process of literature Search.

patients. All studies reported a significantly higher RDW in AMI patients. The AUC of AMI ranged from 0.67 to 0.851 and the cut-off value of RDW varied from 13 to 14.7 fl. Because of the different cut-off values of the studies included, pooling of data was not feasible. The sensitivity of RDW for the diagnosis of AMI varied from 48.28% (95% CI: 34.95–61.78%) to 69.4% (95% CI: 54.58–81.75%); and the specificity varied from 62.7% (95% CI: 52.99%–71.76%) to 88.71% (95% CI: 78.11%–95.34%).

6.3. MPV

Overall, two retrospective studies [14,15] which included 313 patients reported data on MPV. AMI was confirmed in 128 (40.89%) patients.

Aktimur et al. showed a significant difference in MPV between AMI patients and those who required inflammation-related emergent surgery Interestingly, the study by Tanrikulu showed contradicting results, and the MPV was not significantly different among the study groups (AMI, Non-Vascular Bowel Necrosis and controls of acute abdomen, $p = 0.18$). Aktimur et al. reported the AUC to be 0.715 (95%CI, 0.642–0.788). The cut-off value of MPV varied from 8.3 fl to 10.5 fl. As different cut-off values were used in the included studies, pooling of data was not feasible. The sensitivity of MPV for the diagnosis of AMI varied from 46.55% (95% CI: 33.34%–60.13%) to 60% (95% CI: 62.71% to 79.31%and the specificity varied from 70.97% (95% CI: 58.05%–81.80%) to 71.54% (95% CI: 62.71%–79.31%).

6.4. Leukocyte count

Seven studies (5 retrospective and 2 prospective) [14–20] which included 952 patients reported data on leukocyte count. A diagnosis of AMI was confirmed in 289 (30.3%) patients.

Three studies (Gearhart, Delaney, Guzel) found no significant elevation in the WBC count in the AMI group, whereas another three studies (Tanrikulu, Akatimur, Kisaoglu) showed a significant elevation in the WBC count.

The AUC of WBC count varied from 0.674 to 0.799 and the cut-off value of leukocyte count varied from 10×10^9/L to 11.04×10^9/L. As different cut-off values were used in the included studies, pooling of data was not possible. The sensitivity of the leukocyte count in the diagnosis of AMI varied from 57.1% (95% CI: 44.75%–68.91%) to 90% (95% CI: 73.47%–97.89%); and the specificity varied from 36.5% (95% CI: 30.29%–43.02%) to 100% (95% CI: 91.59%–100%).

6.5. Lactate dehydrogenase

Three studies (2 prospective and one retrospective) [16,19,21] comprising of 502 patients with acute abdomen reported data on lactate dehydrogenase. AMI was diagnosed in 98 patients.

All studies reported significantly higher levels of LDH in the AMI

Table 1
Characteristics of the studies included to the review.

First author, year of publication	Country	Study design	Study population	Time of plasma tests	Patients with AMI	Prevalence of Intestinal Ischemia %	Reference test
Murray 1994 [29]	USA	Prospective	Acute abdomen	Pre-operative	9	29	Laparotomy
Delaney 1999 [17]	Ireland	Prospective	Acute abdomen	At initial presentation	12	46	Laparotomy/autopsy/return to full health
Gearhart 2003 [18]	USA	Prospective	Clinical suspicion of mesenteric ischemia	At initial presentation	31	65	angiography, or laparotomy.
Acosta 2003 [22]	Sweden	Prospective	Clinical suspicion of acute occlusive mesenteric ischemia due to thromboembolism of SMA	Preoperative	14	71	Laparotomy
Acosta 2004 [23]	Sweden	Prospective	Clinical suspicion of acute occlusive mesenteric ischemia due to thromboembolism of SMA	At initial presentation	9	9	Laparotomy with or without histopathology/laboratory/ radiology findings
Icoz 2006 [24]	Turkey	Prospective	Acute abdomen	Preoperative	3	21	Surgical intervention
Block 2008 [21]	Sweden	Prospective	Acute abdomen	At initial presentation	10	14.1	Findings at operation with or without histopathology/ laboratory/radiology findings or clinical evaluation
Akyildiz 2009 [57]	Turkey	Prospective	AMI patients	Preoperative	28	59.5	Multidetector CT scanner
Chiu 2009 [58]	Taiwan	Prospective	Acute abdominal pain	blood samples were taken Before CT	23	34.33	Biphasic CT with mesenteric CT angiography or non-enhanced CT
Gun 2014 [26]	Turkey	Prospective	Acute abdominal pain	Na	13	5.6	Multi-detector angio-CT
Guzel 2014 [20]	Turkey	Prospective	AMI	N/a	30	38.96	Laparotomy + histopathology
Kisaoglu et al., 2014 [16]	Turkey	Retrospective	Patients with AMI and Patients with abdominal pain who did not require urgent surgery	Preoperative	49	30.8	Computed tomography Angiography (CTA) and/or laparotomy
Van der voort 2014 [32]	Netherlands	Prospective	ICU patients	Considered at diagnostic workup at any time during intensive care stay.	23	52	Laparotomy, histopathology, endoscopy, CT scan
Shi 2015 [19]	China	Prospective	Acute abdomen	Before patients accepted treatment	39	14.3	CT angiography, and findings during surgery or autopsy and verified by histopathological examination
Aktimur et al., 2016 [15]	Turkey	Retrospective	Patients undergoing laparotomy for AMI, and patients undergoing inflammation-related emergent surgery	Preoperative	70	36.2	Laparotomy + histopathology or according to the Decision of the surgical team
Tanrikulu 2016 [14]	Turkey	Retrospective	AMI patients, non-vascular bowel necrosis, patients with acute abdomen	N/a	58	32	N. A
Kulu 2017 [27]	Turkey	Prospective	Clinical suspicion of ami	Preoperative	23	47.92	Surgical exploration.
Hong 2017 [30]	New zealand	Prospective pilot	Nomi after cardiac surgery	Preoperative	13	65	Laparotomy + histopathology
Salim 2017 [34]	Canada	Prospective	Clinical suspicion of ami	Preoperative	13	72	Pathological diagnosis of surgical resection
Zogheib 2018 [33]	France	Retrospective	Cardio-thoracic and Vascular ICU cardiac surgery	Preoperative	48	32.6	CT scan, endoscopy And/or laparotomy).

Table 2
Appraisal of the methodologic quality of the studies reviewed.

First author, year of publication	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference test	Patient flow and timing	Patient selection	Index test	Reference test
Murray 1994 [29]	High	High	High	High	Low	Low	Low
Delaney 1999 [17]	Low	Low	Low	High	Low	Low	Low
Gearhart 2003 [18]	Low	Low	Low	High	Low	Low	Low
Acosta 2003 [22]	High	High	High	High	Low	Low	Low
Acosta 2004 [23]	Low	Low	High	High	Low	Low	Low
Icoz 2006 [24]	Low	Low	High	High	Low	Low	Low
Block 2008 [21]	Low	Low	High	High	Low	Low	Low
Akyildiz 2009 [57]	Low	Low	High	High	Low	Low	Low
Chiu 2009 [58]	Low	Low	High	High	Low	Low	Low
Gun 2014 [26]	High	High	High	High	Low	Low	Low
Guzel 2014 [20]	High	High	High	High	Low	Low	Low
Kisaoglu et al., 2014 [16]	High	Low	High	High	Low	Low	Low
Van der voort 2014 [32]	Low	Low	Low	High	Low	Low	Low
Shi 2015 [19]	Low	Low	Low	High	Low	Low	Low
Aktimur 2016 [15]	High	Low	High	High	Low	Low	Low
Tanrikulu 2016 [14]	High	Low	High	High	Low	Low	Low
Kulu 2017 [27]	High	Low	High	High	Low	Low	Low
Hong 2017 [30]	Low	High	High	High	Low	Low	Low
Salim 2017 [34]	Low	Low	High	High	Low	Low	Low
Zogheib 2018 [33]	High	Low	High	High	Low	Low	Low

group. The cut-off value of lactate dehydrogenase varied from 4.16 μkat/L to 7.01 μkat/L and the AUC of LDH varied from 0.46 to 0.869 The sensitivity of lactate dehydrogenase for the diagnosis of AMI varied from 61.5% (95% CI: 44.62%–76.64%) to 91.8% (95% CI: 80.4%–97.73%); and the specificity varied from 43% (95% CI: 30.04%–55.94%) to 77.25% (95% CI: 72.01%–83.10%).

6.6. D-dimer

Nine studies (8 prospective and one retrospective) [22–24] [20,21,25-28] which included 819 patients reported data on D-dimer. AMI was diagnosed in 169 (22.9%) patients.

Two studies (Guzel, and Chiu) found no significant difference in the d-dimer levels between the non-ischemic acute abdomen group and the AMI group. In contrast, 4 studies (Kulu, Akyldz, Icoz, Block) reported significant elevations in the d-dimmer levels.

In both the studies by Acosta it was concluded that d-dimer had a significant elevation in occlusive ischemia compared with the other causes of acute abdomen. The AUC of d-dimer varied from 0.64 (95%CI, 0.50–0.78) to 0.93 (95%CI, 0.81–0.98). The cut-off value of d-dimer varied from 0.71 nmol/l to 11.61 nmol/L. As different cut-off values were used in the included studies we did not pool the data for analysis. The sensitivity of d-dimer for the diagnosis of AMI varied from 78.26% (95% CI: 56.3%–92.54%) to 100% (95% CI: 69.15%–100%); and the specificity varied from 18.18% (95% CI: 8.19%–32.71%) to 100% (95% CI: 91.59%–100%).

6.7. Serum D-lactate

Four studies using the prospective design [19,21,29,30] included 394 patients reported data on serum D lactate. Ultimately, 45 (11%) patients were diagnosed with AMI.

Murray et al. concluded that patients with AMI had significantly elevated D-lactate levels. Hong et al. who evaluated d lactate in 20 patients following cardiac surgery where there was sufficient clinical suspicion of intestinal infarction to warrant a laparotomy concluded that a positive laparotomy rate was not associated with any changes in D-lactate ($p = 0.95$). The study by Block et al. found no significant difference in d lactate levels.

The cut-off value of serum D lactate varied from 0.20 mmol/l to 0.44 mmol/l. The AUC ranged from 0.51 to 0.69. As different cut-off values were used in these included studies, we did not pool the data for further analysis. The sensitivity of serum D lactate for the diagnosis of AMI varied from 38.46% (95% CI: 13.86%–68.42%) to 90% (95% CI: 55.5%–99.75%); and the specificity varied from 23% (95% CI: 13.15%–35.5%) to 100% (95% CI: 59.04%–100%).

6.8. Serum L-lactate

Six studies [18,27,31–34] which comprised of 326 patients reported data on serum L-lactate. Diagnosis of AMI was confirmed in 145 (44.47%) patients.

Three studies (Gearhart, Kulu, Zogheib) found significant difference

Table 3
Assessment of heterogeneity across the studies.

parameter	Sensitivity		Specificity		+LR		-LR	
	I2	P-value	I2	p-value	I2	P-value	I2	P-value
RDW	69	0.04	89.3	0.000	80.4%	0.006	36.8%	0.206
MPV	56.8	0.128	0	0.935	0.0%	0.358	49.8%	0.02
NLR	0.0	0.985	10.6	0.29	1.0%	0.315	0.0%	0.84
amylase	53.2%	0.144	0.0%	0.667	27.2%	.241	40.6%	0.195
WBC count	75.8%	0.000	95.8%	0.000	90.0%	0.000	86.1%	0.000
LDH	84.0%	0.002	95.1%	0.000	75.0%	0.018	65%	0.057
AST	0.0	0.588	93.1%	0.000	95.4%	0.000	63.2%	0.099
D-dimer	36.4%	0.139	93.4%	0.000	91.9%	0.000	18.5%	0.283
D-lactate	69%	0.02	96.8	0.000	95.3%	0.000	52	0.1
L lactate	80.2%	0.000	87.2%	0.000	87.1%	0.000	84.3%	0.000

Table 4
Summary of the cut-off values, sensitivity and specificity of the parameters examined.

Marker	No. of studies	No. of patients with confirmed diagnosis	Median cut off (range)	Median sensitivity (range)	Median specificity (range)	Median + LR (range)	Median - LR (range	References
Newly reported parameters								
RDW (fl)	3	177	14.05 (13–14.7)	67.1 (48.28–69.4)	82.1 (62.5–88.71)	3.27 (1.85–4.28)	0.49 (0.4–0.58)	Kisaoglu [16], Aktimur [15] Tanrıkulu [14]
MPV (fl)	2	128	9.4 (8.3–10.5)	53.27 (46.55–60)	71.23 (70.95–71.5)	1.85 (1.6–2.11)	0.65 (0.56–0.75)	Aktimur [15] Tanrıkulu [14]
NLR	2	128	7.55 (5.21–9.9)	74.22 (74.14–74.3)	85.8 (82.9–88.71)	5.46 (4.35–6.57)	0.30 (0.29–0.31)	Aktimur [15] Tanrıkulu [14]
Classical parameters								
Serum amylase μkat/L	2	43	10.164	37.5 (25–50)	67.2 (63–71.4)	1.215 (0.68–1.75)	0.945 (0.7–1.19)	Delany[17] Gearhart [18]
Leukocyte count 10^9/l	7	289	11 (14.4–11.04)	81.6 (57.1to 90)	58 (36.5–100)	0.97to infinite	0.33 (0.1–1.05)	Delany [17] Gearhart [18] Guzel [20] Kisaoglu [16] Shi [19] Aktimur [15] Tanrikulu [14]
LDH μkat/L	3	98	5.59 (4.16–7.01)	70 (61.5–91.8)	49.1 43 to 77.25	1.8 (1.2–2.71)	0.5 (0.5–0.7)	Block [21] Kisaoglu [16] Shi [19]
ALT μkat/L	1	12	0.67	73	60	1.83	0.45	Delany [17]
AST μkat/L	2	60	0.67	69.5 (64–75)	72.91 (50–95.83)	9.64 (1.28–18)	0.515 (0.26–0.72)	Delany [17] Zogheib [33]
Alkaline phosphatase μkat/L	1	10	0.70	80	64	2.22	.31	Block [21]
D-dimer nmol/L	9	169	2.57 (0.71–11.61)	93 (78.26–100)	75 (18.18–100)	1.17 to infinite	0.24 (0–0.37)	Acosta [22] Acosta [23] Icoz [24] Chiu [58] Akldz [57] Guzel [20] Gün [59] Kulu [27] Block [21]
D-lactate mmol/l	4	45	0.29(0.20–0.44)	77.83 (38.46–90)	85.92 (23–100)	1.17 to infinite	0.415 (0.13–0.62)	Murray [29] Block [21] Shi [19] Hong [30]
L-lactate mmol/l	6	145	2.2 (0.00004–4)	69.27 (33–87.5)	76 (48–96)	2.36 (1.2–9.78)	0.47 (0.14–0.92)	Gearhart [18] Cronk [31] Van er Voort [32] Kulu [27] Zogheib [33] Salim(34)

in L-lactate between ischemic and non-ischemic groups, while one study (Van der voort) found non-significant difference in L-lactate levels Salim et al. studied 20 patients with suspected AMI and found no significant difference in d lactate between ischemic and non-ischemic group.

The cut-off value of serum L-lactate varied from 0.00004 mmol/l to 4 mmol/l. AUC ranged from 0.5 to 0.70. Because of the different cut-off values of included studies, we did not pool the data. The sensitivity of serum L-lactate for diagnosis of AMI varied from 33% (95% CI: 0.84%–90.57%) to 87.5% (95% CI: 74.75%–95.27%); and the specificity varied from 48% (95% CI: 25.71%–70.22%) to 96% (95% CI: 79.65%–99.90%).

Table 5
Summary of pathophysiology of studied markers.

Diagnostic Marker	Underlying pathophysiology
RDW	Severe inflammatory response to bone, RBC damage induced by hypoxia
NLR	severe inflammatory response of body to AMI, closely co-relates with degree of inflammatory response.
MPV	Reflecting hypoxic state and the effect of inflammatory markers on ploidy of megakaryocytes
d-dimer	Fibrinolysis in occlusive mesenteric ischemia
LDH	Marker of tissue damage
D-lactate	Bacterial product of fermentation, showing decreased mucosal integrity caused by intestinal ischemia
L-lactate	Human product of anaerobic metabolism
WBC count	Non-specific marker of inflammation
Liver enzymes	Showing concomitant liver damage in response to generalized hypoperfusion
amylase	Acute phase reactant of intra-abdominal inflammatory process

6.9. Serum amylase

Two studies (74 patients) reported data on serum amylase [17,18] and 47 (63.5%) patients were confirmed to have AMI.

Delaney studied 26 patients with acute abdominal pain, this study found no significant difference in amylase between ischemic and non-ischemic patients. Similar results were reported by Gearhart et al. Both studies reported a cut-off value of 10.16 μkat/L. The sensitivity of amylase for the diagnosis of AMI varied from 25% (95% CI: 5.49%–57.19%) to 50% (95% CI: 29.12%–70.88%); and the specificity varied from 63% (95% CI: 24.49%–91.48%) to 71.4% (95% CI: 41.9%–91.61%).

6.10. Neutrophil to lymphocyte ratio

Two retrospective studies [14,15] comprising of 313 patients reported data on neutrophil to lymphocyte ratio. AMI was diagnosed in 128 (40.8%) patients.

There was a wide variation in the patient population among the studies. The controls in the study of Tanrikulu consisted of patients who presented to the emergency department with non-specific abdominal pain, while in the study by Aktimur, patients with inflammation-related emergent surgery were used as controls.

The cut-off value of neutrophil to lymphocyte ratio varied from 5.21 to 9.9. As different cut-off values were used in the included studies, we did not pool the data for further analysis. The AUC ranged from 0.823 to 0.93. The sensitivity of neutrophil to lymphocyte ratio for diagnosis of AMI varied from 74.14% (95% CI: 60.96%–84.74%) to 74.29 (95% CI: 62.44%–83.99%); and the specificity varied from 82.93% (95% CI: 75.09%–89.11%) to 88.71% (95% CI: 78.11%–95.34%).

6.11. Aspartate aminotransferase

Two studies [17,33] which included 173 patients reported data on aspartate aminotransferase. Sixty (43.7%) patients were diagnosed with AMI.

Only the study by Delaney gave a specific cut off (0.67 μkat/L). The sensitivity of aspartate aminotransferase for the diagnosis of AMI varied from 64% (95% CI: 30.79%–89.07%) to 75% (95% CI: 60.40%–86.36%); and the specificity varied from 50% (95% CI: 18.71%–81.29%) to 95.83% (95% CI: 89.67%–98.85%).

6.12. Alanine aminotransferase

Only one study [17] which included 26 patients reported data on alanine aminotransferase with a cut off value of 0.67 μkat/L. The sensitivity and specificity of alanine aminotransferase for the diagnosis of AMI was 73% (95% CI: 39.03%–93.98%) and 60% (95% CI: 26.24%–87.84%), respectively.

6.13. Alkaline phosphatase

Only one study [21] which included 71 patients reported data on alkaline phosphatase with a cut off value of 0.70 μkat/L. The sensitivity and specificity of alkaline phosphatase for the diagnosis of AMI was 80% (95% CI: 44%–97.48%) and 64% (95% CI: 50.63%–75.84%), respectively.

7. Discussion

We found significant clinical and methodological heterogeneities. The patient populations varied from those presenting with acute abdomen in emergency departments to critically ill ICU patients. There was also a variation in the gold standard tests within and between studies which ranged from CT-Angiography, laparotomy, or laparotomy with histopathological examination.

Among the newly reported parameters, NLR showed the highest median sensitivity and specificity compared to RDW and MPV. The mechanism of increase in NLR is most probably linked to the underlying inflammation. During tissue injury, macrophages release pro-inflammatory cytokines which induces neutrophilia [35,36] whereas lymphopenia is related to the stress-induced cortisol release [37] and the apoptosis of lymphocytes induced by TNF-a [38]. Although NLR can be influenced by various diseases like acute cholecystitis [39], appendicitis [40], interestingly Aktimur et al. reported a significant difference between the NLR in AMI patients vs those who required inflammation related emergent surgery [15]. Similar results were reported by Tanrikulu et al. who showed that NLR could effectively differentiate AMI from other causes of acute abdomen [14]. The degree of elevation in NLR is closely linked to the magnitude of the underlying inflammatory state, with higher values signifying more severe inflammation. These observations signify the differentiating potential of NLR from other causes of acute abdomen. Based on the higher specificity of NLR in AMI, we recommend a high weighting for NLR in any scoring system for AMI.

The mechanism of increase in MPV in AMI is not clear. It is suggested that changes in platelet size are determined at thrombopoiesis in the megakaryocyte, and factors affecting ploidy of megakaryocytes such as interleukin 3, thrombopoietin, and interleukin 6 can increase platelet volume. Furthermore, chronic hypoxia can also increase MPV by increasing production and destruction of platelets [41–44]. Studies have linked MPV to coronary artery disease [45], hypertension [46], deep vein thrombosis [47]. It remains elusive whether the increase in MPV is due to the presence of comorbidities or to AMI per se. The effect of concomitant diseases on the diagnostic potential of MPV was shown by Degerli. They found no significant difference in the AMI patients vs the matched healthy controls with concomitant diseases [48]. The studies by Tanrikulu and Aktimur showed contradicting results. Based on these results, we consider a low weighting for MPV in the scoring of AMI.

RDW is the quantitative measure reflecting variability in RBCs size. Pro-inflammatory cytokines released as a consequence of AMI affects the bone marrow, and suppresses the red blood cells maturation, thus increasing RDW [49]. All the included studies showed a reasonably accuracy using RDW in distinguishing AMI from other causes of acute abdomen. Iron deficiency anemia is common among AMI patients, and can in theory effect RDW. Interestingly Kisaoglu [16] showed that the diagnostic accuracy of RDW was similar in AMI patients with and without anemia. Although various conditions like hepatic dysfunction, or bone marrow disease can affect RDW, it remains unclear whether the presence of these conditions has any significant impact on the accuracy of RDW in AMI. We recommend RDW should have a significant weighting in the scoring of AMI.

Three studies (Gearhart, Delaney, Guzel) in our review did not detect a significant elevation in WBC count in AMI patients compared to the control group. In contrast, another three studies (Tanrikulu, Alitimur, Kisaoglu) found WBC count to be significantly increased in patients with AMI. The overall sensitivity and specificity of WBC count as a marker of AMI showed a wide variation from 57 to 90% and from 36 to 100%, respectively. However, the recent study by Emile SH found elevations of WBC count beyond 18000 as a significant independent predictor for transmural bowel necrosis in patients with occlusive AMI, particularly AMI secondary to venous occlusion [50]. However WBC count cannot be used to differentiate between a small vs a large portion of bowel infarction, or to determine whether a patient is salvageable.

We have shown that D-dimer has the highest median sensitivity. Elevation in d-dimer in occlusive mesenteric ischemia is linked to the activation of the Fibrinolytic system after occlusion of the mesenteric vessels. Most studies in our review had a large proportion of patients with occlusive mesenteric ischemia. However, mesenteric ischemia can be caused by non-occlusive etiology as well. The accuracy and pathophysiology of d-dimer elevation in NOMI is not clearly defined in the literature. Compared to the review on d-dimer by Cudink [7] we added

five new studies. The high sensitivity of D-dimer highlights its potential ability as an exclusion test. We suggest considering it in any future scoring systems.

Along with NLR, we observed a high specificity of D-lactate which is the bacterial fermentation product and is fairly stable after liver clearance. In contrast to the D-lactate, elevation in L-lactate may not be appreciable in the early stages of ischemia, owing to the capacity of liver to clear it from the porto-mesenteric circulation [51]. Coherent with these observations we noticed a lower diagnostic accuracy of L-lactate when compared to D-lactate. A previous review on D-lactate by Treskes et al. [10] showed a pooled sensitivity of 71.7% and a pooled specificity of 74.2%. However most of the studies they pooled focused on occlusive mesenteric ischemia. Interestingly a recent study on NOMI by Hong et al. showed a high specificity of D-lactate in predicting a positive initial laparotomy (full thickness intestinal infarction). Thus D-lactate might be useful in predicting the occlusive sub-type of mesenteric ischemia but it might not predict the early stages of NOMI. We suggest using D-lactate rather than L-lactate in the scoring of AMI.

A meta-analysis by Evennett [52] in 2009 was the only study on the diagnostic accuracy of liver enzymes. We could not find any further studies on ALT, although a recent study by Zogheib evaluated the accuracy of AST. The heterogeneity of both the studies was zero for sensitivity. AST can offer a diagnostic advantage while considering NOMI, since both the studies evaluating AST included a high proportion of patients with NOMI [17,33].

All the studies on amylase showed a low diagnostic accuracy. We suggest to score amylase low to avoid confuse clinicians in diagnosing pancreatitis.

Studies evaluating LDH reported a significant elevation in the AMI group. However we found no study evaluating the accuracy of LDH in distinguishing AMI from other causes of acute abdomen LDH is a general marker of tissue damage and it can be expected to rise in a wide variety of conditions which mimicks AMI [53]. While most of studies in our review focused on occlusive AMI, a recent study by Bourcier [54] on NOMI found no significant elevation in NOMI in ICU patients. Based on these observations we would give a low weighting to LDH in any scoring systems for AMI.

The only significant markers of intestinal ischemia that could be affected by liver clearance appears to be L-lactate. D dimer is stable over liver clearance. Since the pathophysiology of elevation in RDW, MPV and NLR is severe systemic inflammatory response, so the impact of liver clearance should theoretically be minimal.

8. Limitations of this review

Due to the methodological and statistical heterogeneity between the studies, we could not analyze the data by a formal meta-analysis. The studies included in the review were reported from 1994 to 2018. The long duration of this review might have resulted in accumulation of some outdated studies on the classical markers of ischemia. During the period of literature review, the diagnosis of AMI was more likely to be made earlier in the more recent studies. For instance, measurement of L-lactate in the 90s were more likely to be performed late in the course of the disease (Lange et al.). The primary pathology that is predisposing the patient to the development of AMI can affect the diagnostic markers. Atrial fibrillation which can lead to embolization of the mesenteric artery can by itself affect the d-dimer levels. Similarly, circulatory shock can predispose to NOMI, and shock alone can raise the lactate levels, thus giving false results. SMA thrombosis is often associated with widespread atherosclerosis, and hypoperfusion of other organs from atherosclerosis can generate oxidative stress leading to a false elevation of parameters, even in absence of AMI. Most studies that were included in this review did not properly stratify this important confounding effect and better designed research is needed.

8.1. Implications of future research

Further research is needed to assess the effect of the primary pathology of AMI on the diagnostic markers.

Studies should focus on further evaluating the potential of NLR, MPV, and RDW in differentiating AMI from other causes of acute abdomen that may mimic AMI. It would be interesting to evaluate how early can these parameters predict AMI when compared to the classical markers.

Vitamin B12 deficiency, which is highly prevalent in elderly, was not tested in any of the studies that evaluated RDW and MPV. Both RDW [55] and MPV [56] can be influenced by a cobalamin deficiency.

Further research is also needed to assess the diagnostic potential of markers for NOMI.

9. Conclusion

The current review shows that due to the complex pathophysiology, AMI is still difficult to diagnose. Laboratory parameters can have varying degrees of diagnostic weighting. This review reinforces that currently there is no gold standard hematological tests available. Emergency surgeons should place lesser emphasis on the normal values of hematological parameters when AMI is suspected clinically. Aggressive and urgent surgery based on clinical suspicion is the key to improve outcomes. Given the heterogeneities among the studies, a scoring system is not possible.

Ethical approval

Not applicable, this is systematic review.

Sources of funding

None.

Author contribution

Sualeh Muslim Khan: literature search, study design, data collection, writing, figures, tables.

Sameh Hany Emile: literature search, data collection, reviewing and editing.

Zhen Wang: data analysis, data interpretation, reviewing and editing.

Muhammad Akbar Agha: data interpretation, writing, reviewing and editing.

Conflicts of interest

None.

Research registration number

Systematic review is registered on PROSPERO with ID [CRD42018088953].

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Data staement

Not applicable.

Acknowledgments

none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.04.005.

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