CME

The Diagnosis of Acute Mesenteric Ischemia: A Systematic Review and Meta-analysis

Michael T. Cudnik, MD, Subrahmanyam Darbha, MSc, Janice Jones, MD, Julian Macedo, MD, Sherrill W. Stockton, MD, PhD, and Brian C. Hiestand, MD, MPH

Abstract

Objectives: Acute mesenteric ischemia is an infrequent cause of abdominal pain in emergency department (ED) patients; however, mortality for this condition is high. Rapid diagnosis and surgery are key to survival, but presenting signs are often vague or variable, and there is no pathognomonic laboratory screening test. A systematic review and meta-analysis of the available literature was performed to determine diagnostic test characteristics of patient symptoms, objective signs, laboratory studies, and diagnostic modalities to help rule in or out the diagnosis of acute mesenteric ischemia in the ED.

Methods: In concordance with published guidelines for systematic reviews, the medical literature was searched for relevant articles. The Quality Assessment Tool for Diagnostic Accuracy Studies-2 (QUADAS-2) for systematic reviews was used to evaluate the overall quality of the trials included. Summary estimates of diagnostic accuracy were computed by using a random-effects model to combine studies. Those studies without data to fully complete a two-by-two table were not included in the meta-analysis portion of the project.

Results: The literature search identified 1,149 potentially relevant studies, of which 23 were included in the final analysis. The quality of the diagnostic studies was highly variable. A total of 1,970 patients were included in the combined population of all included studies. The prevalence of acute mesenteric ischemia ranged from 8% to 60%. There was a pooled sensitivity for L-lactate of 86% (95% confidence interval [CI] = 73% to 94%) and a pooled specificity of 44% (95% CI = 32% to 55%). There was a pooled sensitivity for D-dimer of 96% (95% CI = 89% to 99%) and a pooled specificity of 40% (95% CI = 33% to 47%). For computed tomography (CT), we found a pooled sensitivity of 94% (95% CI = 90% to 97%) and specificity of 95% (95% CI = 93% to 97%). The positive likelihood ratio (+LR) for a positive CT was 17.5 (95% CI = 5.99 to 51.29), and the negative likelihood ratio (–LR) was 0.09 (95% CI = 0.05 to 0.17). The pooled operative mortality rate for mesenteric ischemia was 47% (95% CI = 40% to 54%). Given these findings, the test threshold of 2.1% (below this pretest probability, do not test further) and a treatment threshold of 74% (above this pretest probability, proceed to surgical management) were calculated.

Conclusions: The quality of the overall literature base for mesenteric ischemia is varied. Signs, symptoms, and laboratory testing are insufficiently diagnostic for the condition. Only CT angiography had adequate accuracy to establish the diagnosis of acute mesenteric ischemia in lieu of laparotomy.

ACADEMIC EMERGENCY MEDICINE 2013; 20:1088–1100

Acute mesenteric ischemia is a rare disease, with an annual incidence of 0.09% to 0.2% per patient year, although the disease is thought to be underreported.[1–3] Accordingly, acute mesenteric ischemia is an infrequent cause of abdominal pain in emergency department (ED) patients; however, mortality for this condition is high.[4–7] Rapid diagnosis and surgical intervention are paramount to limiting mortality, but

From the Departments of Emergency Medicine, The Ohio State University (MC, SD, JJ, JM), Columbus, OH; and Wake Forest University Health Sciences (SWS, BCH), Winston-Salem, NC.

Dr. Cudnik is currently with Cape Coral Emergency Physicians, Cape Coral, FL. Dr. Stockton is currently with the Department of Emergency Medicine, Virginia Tech Carilion School of Medicine, Roanoke, VA.

Received October 25, 2012; revisions received February 13, June 10, and July 15, 2013; accepted July 20, 2013.

Presented at the Scientific Assembly, American College of Emergency Physicians, Denver, CO, October 2012.

The authors have no financial disclosures or conflicts of interest to report. Dr. Hiestand, an Associate Editor for this journal, had no role in the peer review process or decision publication for this paper.

Supervising Editor: Alan E. Jones, MD.

Address for correspondence and reprints: Brian C. Hiestand, MD, MPH; bhiestan@wakehealth.edu.

ISSN 1069-6563
PII ISSN 1069-6563583

doi: 10.1111/acem.12254

presenting signs are often vague or variable, and there is no pathognomonic laboratory screening test.[8–11] Even after the clinical suspicion for mesenteric ischemia is acknowledged, definitive diagnosis has traditionally required invasive and time-consuming subtraction angiography or specialized computed tomography (CT) techniques in conjunction with expert radiologic interpretation.[12–14] Accordingly, despite a growing clinical awareness and a rapid advancement of laboratory assays and radiologic techniques generally, the timely diagnosis of acute mesenteric ischemia remains challenging.[9,15,16]

Mortality rates vary in different published series, with a range of roughly 50% to 100%, likely secondary to varying disease etiologies (location of infarct, venous vs. arterial blockage, etc.).[17–19] Mesenteric ischemia is typically caused by arterial thrombi to the celiac axis, the superior mesenteric artery, or the inferior mesenteric artery, leading to decreased intestinal blood flow and direct ischemic and secondary reperfusion cellular damage.[20] This is occlusive mesenteric arterial ischemia, which accounts for approximately half of all reported cases.[21] Roughly one-third of cases are nonocclusive mesenteric arterial ischemia and result from vasoconstriction, low output states, or both.[21] Most of the remaining cases of mesenteric ischemia are the result of mesenteric venous thrombosis.[21] Although mortality after intervention may vary depending on the precise etiology, ranging from a reported 32% for mesenteric venous thrombosis to 77% for arterial thrombosis,[19] the emergency physician must be tasked with considering the global condition of "acute mesenteric ischemia" as a cause for the patient's presentation, rather than specific subtypes.

Acute mesenteric ischemia is a different clinical entity than chronic mesenteric ischemia or ischemic colitis. Chronic mesenteric ischemia occurs due to gradual stenosis, usually secondary to atherosclerotic disease, of the arterial supply to the viscera.[22,23] Pain, characterized as intestinal angina, is generally postprandial. Although debilitating due to pain and weight loss, chronic mesenteric ischemia is not acutely fatal and is not considered further within this review. Likewise, colonic ischemia refers to a heterogeneous collection of presentations that manifest as transmural colonic ischemia, usually due to a nonocclusive but low blood flow state insufficient to meet the metabolic demands of the colonic tissues. This may be due to vasospasm or systemic hypotension, frequently in the setting of an atherosclerotic arterial supply.[24] This is a distinct clinical entity from acute mesenteric ischemia as well and is not the topic of this review.

Regardless of the specific etiology, early diagnosis is central to successful management of mesenteric ischemia. The intestine does enjoy significant collateral circulation throughout its course, and it can tolerate a 75% reduction in blood flow for up to 12 hours.[25] This is clearly demonstrated in the mesenteric ischemia literature where the relationship between early diagnosis and intervention and decreased mortality is well established.[9,26,27]

Despite the acknowledged importance of early diagnosis of mesenteric ischemia, the goal remains difficult to achieve, which may contribute to the fact that mortality rates for acute mesenteric ischemia have remained consistently poor over time.[4,6] A major challenge in the diagnosis of mesenteric ischemia is the wide spectrum of patient presentations. Symptoms vary from the classic "pain out of proportion to physical exam," to vague or insidious abdominal symptoms, to absent abdominal pain.[1,28,29] Another diagnostic challenge is the lack of adequate laboratory markers. Numerous candidate plasma markers have been studied, among them serum lactic acid dehydrogenase, D-dimer, ischemia-modified albumin, and urinary and plasma fatty acid–binding proteins (FABPs).[16,30–34] Another diagnostic difficulty involves imaging techniques. At many centers, direct angiography has been supplanted by multidetector row CT as the initial imaging technique of choice for the diagnosis of suspected mesenteric ischemia.

In short, there remains no laboratory test, imaging technique, or risk stratification tool with adequate sensitivity and specificity to effectively rule out or rule in patients in whom mesenteric ischemia is a concern. The primary objective of this meta-analysis was to assess the diagnostic test characteristics for acute mesenteric ischemia from elements of patient symptoms, objective signs, laboratory studies, or imaging studies in ED patients. A secondary objective was to define mesenteric ischemia imaging test and treatment thresholds using the Pauker-Kassirer method based on best estimates of sensitivity, specificity, diagnostic risks, and treatment risks and benefits that were derived from this systematic literature review.[35]

METHODS

Search Strategy

The design and structure of this systematic review followed the recommendations from the Meta-analysis of Observational Studies in Epidemiology.[36] Three investigators (SWS, JJ, JM) searched the medical literature from 1966 through December 2011 using PUBMED and EMBASE using the search term *acute mesenteric ischemia*. The results from this search were combined with the MeSH terms *diagnosis, labs, emergency department, computed tomography*, and *angiography*. To identify the risks of intravenous (IV) dye for CT and IV dye from angiography for determination of the test threshold analysis, a PUBMED search was done using the terms *angiography* and *risk*, *angiography* and *complications*, *CT* and *risk*, and *CT* and *complications*. To identify the risks and benefits of operative or nonoperative management of acute mesenteric ischemia, a PUBMED clinical query under "therapy" was done. All search results were limited to studies of humans and English language. Two authors (MTC, BCH) reviewed the titles of the abstracts to identify potential articles for inclusion and reviewed the full manuscripts. These two authors independently reviewed each of the articles for potential inclusion. Consensus was achieved via discussion if there was a difference of opinion between authors regarding article inclusion. The references for selected articles were also reviewed to identify other potential articles for inclusion. Finally, one author (JJ) searched online for abstracts and articles in *Academic Emergency Medicine* and *Annals of Emergency Medicine* from 1990 to 2011.

Studies were included if they included adult patients (≥18 years old) who presented to the hospital or ED with suspicion of acute mesenteric ischemia and if they reported sufficient data on diagnostic tests and criterion standard results to reconstruct two-by-two tables in whole or in part. Case reports, narrative reviews, and studies focusing on therapy alone were excluded.

Individual Evidence Quality Appraisal

Two authors (MTC, BCH) used the Quality Assessment Tool for Diagnostic Accuracy Studies-2 (QUADAS-2) for systematic reviews to evaluate the overall quality of the trials included in the meta-analysis.[37] Any discrepancies of the quality assessments were resolved by discussion. Statistical agreement between the two reviewers was assessed via kappa analysis using Online Kappa Calculator.[38] A priori, the authors considered potential areas of concern with the assessment of the articles. Both ED and hospital-based populations were included in the study. If a trial did not explicitly state that investigators were blinded to the index test and/or the reference standard, then these portions of the QUADAS-2 were marked as "high bias." For those articles with relevant cohort information regarding symptom or physical examination prevalence (i.e., only disease-positive patients were studied), formal bias assessment with QUADAS-2 was not performed. In the absence of disease-negative patients, true diagnostic accuracy cannot be assessed, and we did not intend to include these studies in the diagnostic meta-analysis or test–treatment threshold calculations. They are included for descriptive purposes only.

Data Analysis

Two authors (MTC, BCH) independently abstracted the data from the included studies. Data abstracted included setting, patient population, study inclusion criteria, reference standard employed, disease prevalence, and properties of the respective diagnostic tests. A priori, we defined disease as acute mesenteric ischemia, as proven by operative findings or autopsy findings. We defined no disease as the absence of acute mesenteric ischemia as evidenced by clinical resolution of symptoms without intervention or negative operative findings. We then computed summary estimates by combining study patients with and without diagnoses of mesenteric ischemia using Meta-DiSc[39] (Hospital Universitario Ramon y Cajal, Madrid, Spain) using the Der-Simonian random-effects model.[40] Meta-DiSc was also used to generate summary receiver operator characteristic (SROC) curves. SROC curves provide graphical summaries of diagnostic data performance in meta-analyses, providing a summary overall diagnostic odds ratio as well as incorporating interstudy heterogeneity in the graphical output.[41]

Those studies without data to fully complete a two-by-two table were not included in the calculation of diagnostic test characteristics (sensitivity, specificity, likelihood ratios), although they could contribute to prevalence analysis via simple pooling of results. Statistical heterogeneity was assessed for pooled estimates via the Cochrane's χ^2 and I^2 statistic with 25, 50, and 75% representing low, moderate, and high heterogeneity, respectively.[42]

RESULTS

The PUBMED search identified 1,037 citations, while the EMBASE search identified 382 (Figure 1). No additional studies were obtained after reviewing abstracts and articles from the two emergency medicine journals. After initial screening, 87 unique manuscripts were selected for potential inclusion. After full manuscript review, a total of 23 studies were included in the final meta-analysis on diagnostic testing.[1,21,28–30,32–34,43–57] These 23 studies consisted of 17 prospective studies[1,21,30,32,34,43–45,47–49,51,53–57] and six retrospective studies.[28,29,33,46,50,52] In terms of history and physical examination findings, 19 studies were able to contribute prevalence data and estimates of test sensitivity.[1,4–7,9,10,28,29,50,58–66] A summary of all studies contributing data can be reviewed in Data Supplement S1 (available as supporting information in the online version of this paper).

The studies included a variety of patients in both the hospital and the ED settings with a wide range of inclusion criteria and diagnostic modalities including elements of the history and physical examination, laboratory tests, and radiographic imaging. A large number of the studies only included those patients with diagnoses of mesenteric ischemia, therefore lacking a control or comparator group. Only one study[34] acknowledged the STARD criteria[67] for diagnostic studies; however, several studies included in this analysis were published prior to the release of the STARD criteria in 2003.

The reliability for the authors' QUADAS-2 assessments of quality ranged from kappas of 0.52 to 0.88. The quality of the diagnostic studies was highly variable (Table 1). Only five studies explicitly stated that they included ED patients.[29,34,47,54,57] Many studies did not describe the inclusion criteria in detail. Additionally, the vast majority of studies did not report the precise intervals between the index test and reference standard. Most of the studies reporting laboratory test results

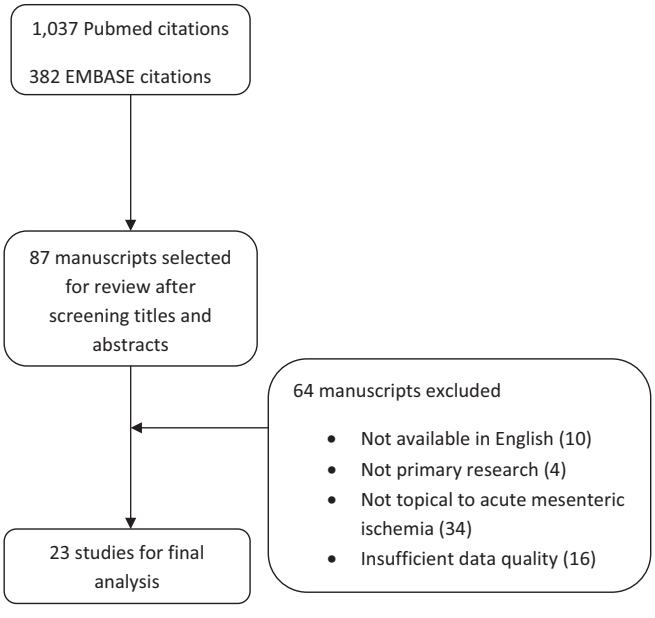

Figure 1. Article selection.

Table 1
Consensus Bias Evaluation Using QUADAS-2 Methodology

	Risk of Bias				Applicability Concerns		
First Author, Year (Reference)	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Clinical characteristics							
Batellier, 1990 (28)	HIGH	HIGH	LOW	HIGH	HIGH	LOW	LOW
Howard, 1996 (50)	HIGH	LOW	LOW	HIGH	HIGH	LOW	LOW
Acosta, 2003 (1)	HIGH	HIGH	LOW	LOW	LOW	LOW	LOW
Huang, 2005 (29)	HIGH	LOW	LOW	LOW	LOW	LOW	LOW
Laboratory studies							
Lange, 1994 (52)	LOW	LOW	?	LOW	?	LOW	LOW
Murray, 1994 (53)	HIGH	HIGH	LOW	LOW	LOW	LOW	LOW
Kanda, 1996 (33)	HIGH	HIGH	LOW	LOW	LOW	LOW	LOW
Delaney, 1999 (48)	?	LOW	LOW	LOW	LOW	LOW	LOW
Acosta, 2001 (43)	?	LOW	?	LOW	?	LOW	LOW
Gearhart, 2003 (49)	?	?	LOW	HIGH	LOW	LOW	LOW
Acosta, 2004 (30)	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW
Block, 2008 (32)	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW
Polk, 2008 (55)	LOW	?	?	LOW	LOW	LOW	LOW
Akyildiz, 2009 (44)	LOW	LOW	LOW	HIGH	LOW	LOW	LOW
Chiu, 2009 (47)	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Thuijls, 2011 (34)	LOW	?	LOW	HIGH	?	LOW	LOW
Imaging							
Kirkpatrick, 2003 (51)	LOW	LOW	HIGH	LOW	LOW	LOW	LOW
Wiesner, 2004 (56)	LOW	HIGH	HIGH	HIGH	LOW	LOW	LOW
Aschoff, 2009 (21)	LOW	LOW	HIGH	LOW	LOW	LOW	LOW
Ofer, 2009 (54)	LOW	LOW	HIGH	LOW	LOW	LOW	LOW
Barmase, 2011 (45)	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Blachar, 2011 (46)	HIGH	LOW	LOW	LOW	LOW	LOW	LOW
Yikilmaz, 2011 (57)	LOW	LOW	LOW	LOW	LOW	LOW	LOW

HIGH and LOW indicate high and low potential for bias, whereas ? indicates that the data presented in the study was insufficient to gauge risk of bias.
QUADAS-2 = Quality Assessment Tool for Diagnostic Accuracy Studies-2.

used dichotomous cutoff values for continuous variables of diagnostic tests (lactate, D-dimer).

Prevalence

A total of 1,970 patients were included in the combined population of all included studies. The prevalence of mesenteric ischemia ranged from 8%[56] to 60%[44,49] in those studies that included patients with and without mesenteric ischemia. The summary median age of patients was 67 years (interquartile range = 63 to 70 years).

History and Presentation

Risk factors and corresponding sensitivity ranges from the history, clinical presentation, and physical examination are listed in Table 2. Given the lack of a comparator group without mesenteric ischemia in the studies included, no data on the specificity or the likelihood ratios could be calculated, limiting the diagnostic utility of these historical features. A history of atrial fibrillation was frequently present in the setting of mesenteric ischemia (sensitivity range = 7.7% to 79.3%). Abdominal pain was also frequently present in patients with mesenteric ischemia, ranging from 60% to 100% prevalence in the case series.

Physical Examination

Physical examination findings suggestive of mesenteric ischemia were diffuse abdominal tenderness (sensitivity

Table 2
Prevalence Ranges of History, Signs, and Symptoms in Acute Mesenteric Ischemia Patients

Risk Factors	Sensitivity Range	References
Medical history		
Atrial fibrillation	7.7–79	1, 4–6, 28, 29, 50, 58–60, 66
Coronary artery disease	13–75	1, 4, 5, 9, 29, 30, 58–63, 66
Heart failure	5.6–58	5, 7, 29, 50, 60, 61, 65, 66
Hypercoagulable state	2.4–29	4, 5, 29, 58, 60, 64
Valvulopathy	3.3–11	29, 58, 59
Presentation characteristics		
Acute abdominal pain	60–100	1, 4–6, 9, 29, 50, 58–64, 66
Nausea/vomiting	39–93	1, 4–6, 29, 50, 58–60, 62, 64, 66
Pain out of proportion	45–54	1, 59
Diarrhea	18–48	1, 4–6, 29, 50, 59, 60, 62, 64, 66
Rectal bleeding	12–48	1, 4, 6, 29, 58–60, 64, 66
Physical examination		
Diffuse tenderness	54–90	9, 29, 50, 59
Peritoneal signs	13–65	5, 29, 50, 59, 60, 61, 64
Tachycardia	31	5
Distention	18–54	50, 59, 64
Hypotension	5.2–54	5, 29, 50, 61, 66
Guaiac-positive stool	5.9–23	9, 59

range = 54% to 90%), the presence of peritoneal signs (sensitivity range = 13% to 65%), and abdominal distention (sensitivity range = 18% to 54%). However, none of the studies reported findings on all patients with suspected mesenteric ischemia to calculate specificity or likelihood ratios, again limiting the diagnostic utility of these findings.

Serum Tests

Four studies evaluated the diagnostic accuracy of elevated lactate levels in patients with suspected mesenteric ischemia. The studies used varying cutoffs, which are reported with each study. Murray et al.[53] (D-lactate ≥ 2.0 μg/mL) reported a sensitivity of 89% and a specificity of 86%, while Block et al.[32] (D-lactate ≥ 0.20 mmol/L) reported a sensitivity of 90% with a specificity of 23%. This led to a pooled sensitivity for D-lactate of 90% (95% confidence interval [CI] = 67% to 99%) and a pooled specificity of 40% (95% CI = 29% to 51%). The heterogeneity was low for sensitivity (I^2 = 0%, Cochran's Q χ^2_1 = 0.01, p = 0.937) but quite high for specificity (I^2 = 96.5%, Cochran's Q χ^2_1 = 28.3, p < 0.001). It should be noted that the D-lactate isomer is a product of bacterial metabolism, as opposed to L-lactate, which is a product of human anaerobic metabolism. Both isomers will contribute to metabolic acidosis; however, a specific assay is required for the detection of D-lactate. Gearhart et al.[49] (L-lactate ≥ 2.2 mmol/L) reported sensitivity and specificity of 78 and 53% respectively, while data from Lange and Jackel[52] demonstrated a sensitivity of 100% (but with a lower limit of the 95% CI of 83%) and a specificity of 42%, using a cutoff of 2.4 mmol/L. These studies led to a pooled sensitivity for L-lactate of 86% (95% CI = 73% to 94%) and a pooled specificity of 44% (95% CI = 32% to 55%). With regard to L-lactate, high heterogeneity was noted between trials for sensitivity (I^2 = 87.5%, Cochran's Q χ^2_1 = 7.99, p = 0.005) and low heterogeneity for specificity (I^2 = 0%, Cochran's Q χ^2_1 = 0.66, p = 0.416). Data Supplement S2 provides forest plots for D-lactate, and Data Supplement S3 provides forest plots for L-lactate. SROC curves were not calculated for D- or L-lactate due to too few studies.

Five studies evaluated the diagnostic accuracy of elevated D-dimers in mesenteric ischemia patients.[30,32,43,44,47] The studies used varying cutoffs for defining an elevated D-dimer. All reported sensitivities of ≥95%, with three reporting sensitivities of 100%. The overall specificity of an elevated D-dimer ranged from 18% to 79%. All of the studies reported significantly higher D-dimer levels in patients with mesenteric ischemia compared to those without mesenteric ischemia. These studies led to a pooled sensitivity of 96% (95% CI = 89% to 99%) and a pooled specificity of 40% (95% CI = 33% to 47%). As seen in Table 3, the positive likelihood ratio (+LR) for an elevated d-dimer was 1.76 (95% CI = 1.20 to 2.57), and the negative likelihood ratio (–LR) was 0.12 (95% CI = 0.05 to 0.30). Little heterogeneity was noted between trials for sensitivity (I^2 = 0%, Cochran's Q χ^2_4 = 0.66, p = 0.96), but significant heterogeneity was observed between trials for specificity (I^2 = 86%, Cochran's Q χ^2_4 = 29.02, p < 0.001). Data Supplement S4 provides forest plots for D-dimer, and Data Supplement S5 provides the SROC curve.

Alpha-glutathione *S*-transferase (GST) and intestinal FABPs, two tests not readily available in most EDs, were also evaluated. The sensitivity of GST ranged from 20% to 100% in the three studies evaluating it.[32,48,49] Additionally, the sensitivity of FABP ranged from 64% to 100% depending on the study and which isomer of FABP was used.[33,34] Data Supplement S6 provides forest plots for GST, while Data Supplement S7 provides the SROC curve. Data Supplement S8 presents forest plots for FABP. An SROC could not be calculated for FABP due to too few studies.

Radiographic Tests

The most common test used for diagnosis of mesenteric ischemia was CT angiography. No studies meeting our inclusion criteria were found that assessed magnetic resonance imaging. Overall, there were eight studies that investigated the sensitivity and specificity of CT for the diagnosis of mesenteric ischemia.[21,45,46,51,54,56,57,66] The studies used different types of scanners in their studies (4-row to 64-row scanners), with one study[46] using three different types of scanners (16, 40, and 64 rows) on their study population. Sensitivity ranged from 83% to 100% with a pooled sensitivity of 94% (95% CI = 90% to 97%), while specificity ranged from 67% to 100% with a pooled specificity of 95% (95% CI = 93% to 97%).

As seen in Table 3, the +LR for a positive CT was 17.5 (95% CI = 5.99 to 51.29) and the –LR for a negative CT scan was 0.09 (95% CI = 0.05 to 0.17). Moderate heterogeneity was noted between trials for sensitivity (I^2 = 59.5%, Cochran's Q χ^2_7 = 17.29, p = 0.016) and high levels of heterogeneity were noted in terms of

Table 3
Pooled Test Performance Characteristics for Laboratory and Imaging Modalities for the Detection of Acute Mesenteric Ischemia

Diagnostic Study	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	–LR (95% CI)	Reference Numbers
D-Lactate	90 (67–99)	40 (29–51)	2.64 (0.27–25.5)	0.23 (0.06–0.88)	32, 53
L-Lactate	86 (73–94)	44 (32–55)	1.67 (1.37–2.05)	0.20 (0.01–2.86)	49, 52
D-dimer	96 (89–99)	40 (33–47)	1.76 (1.12–2.57)	0.12 (0.05–0.30)	30, 32, 42, 44, 47
GST	68 (55–80)	85 (76–92)	3.39 (1.77–6.48)	0.40 (0.11–1.48)	32, 48, 49
FABP	70 (50–86)	93 (87–97)	8.84 (0.67–116)	0.28 (0.04–2.15)	33, 34
MDCT	94 (90–97)	95 (93–97)	17.50 (5.99–51.29)	0.09 (0.05–0.17)	21, 45, 46, 51, 54, 56, 57, 66

FABP = fatty acid–binding protein; GST = alpha-glutathione *S*-transferase; +LR = positive likelihood ratio; –LR = negative likelihood ratio; MDCT = multidetector computed tomography.

specificity (I^2 = 87.6%, Cochran's Q χ^2_7 = 56.27, p < 0.001). Data Supplement S9 presents forest plots for CT imaging, and Data Supplement S10 provides the SROC curve.

Surgical Mortality

The most common management option of acute mesenteric ischemia is surgical exploration and intervention. There is a substantial degree of heterogeneity in the literature with regard to reported postoperative mortality after surgical intervention for suspected acute mesenteric ischemia. The operative mortality of mesenteric ischemia ranged from 26% to 72% with a pooled mortality rate of 47% (95% CI = 40% to 54%). Operative repair of mesenteric ischemia was associated with significant morbidity and adverse event rates in survivors, ranging from 39% to 64%. However, the mortality rate for missed mesenteric ischemia that is not operated on is considered to approach 100%

DISCUSSION

Acute mesenteric ischemia remains a difficult diagnosis to establish on a clinical basis. There are no presenting characteristics, historical features, or findings on physical examination that definitively establish the diagnosis. Rather, the pretest probability of disease must be gradually informed by the accumulation of mild shifts in likelihood provided by the presence or absence of various elements in the history and physical. As of yet, there are no laboratory tests readily available in the ED that possess enough diagnostic accuracy to establish mesenteric ischemia definitively. An ideal screening test would have a very low –LR. In general, a –LR less than 0.1 is considered an adequate "proof of absence of disease," as the posttest odds of disease would be decreased by a factor of 10.[68] A negative D-dimer has a strong –LR, although the 95% CI was high enough that we cannot recommend that it is a satisfactorily accurate screening test to preclude further testing as a standalone result. Serum lactate, the diagnostic test most frequently associated with mesenteric ischemia, had a lower pooled sensitivity than D-dimer and a higher –LR. Studies of these two tests did not consistently establish the interval between specimen acquisition and the final diagnosis of mesenteric ischemia. As well, neither test was substantially specific. This is in evidence by the wide CIs about the SROC (Data Supplement S5). It may also be that there are different degrees of predictive ability from different degrees of abnormality of the laboratory assay. In other words, a patient with a very elevated lactate may carry a higher probability of acute mesenteric ischemia than a patient who is just over the upper limit of normal. The heterogeneity of the source data precluded our ability to investigate this further; future prospective work may find incremental value in calculating interval likelihood ratios to evaluate this possibility.

We found substantially less variability with regard to CT imaging. However, there were outliers in terms of both sensitivity and specificity. Wiesner et al.[56] performed a retrospective review of abdominal CT interpretations performed for a variety of indications and with a variety of protocols on a four-slice multidetector CT, which may have contributed to their substantially lower sensitivity than the rest of the field. Likewise, Blachar et al.[46] performed a retrospective review of images that were reinterpreted for study purposes in a case–control format, allowing CT images that were acquired up to 3 days prior to the diagnosis of mesenteric ischemia. CT scans were performed on a variety of multidetector scanners (ranging from 10-to 64-slice) throughout the study. The most likely reason for the lower specificity noted in this study was their use of a diagnostic standard that stratified "possibly present" as a positive result for data interpretation, leading to potential overcalls.

With all studies of diagnostic methods, there is the potential for systematic bias that would affect the validity of the reported results. Newman and Kohn[69] provide an excellent discussion on the topic in their text, *Evidence-Based Diagnosis,* for those readers who wish to pursue a more in-depth discussion. Interested readers are also referred to the relevant chapter in *Evidence-Based Emergency Care: Diagnostic Testing and Clinical Decision Rules (Evidence-Based Medicine)* by Pines et al.[70] Several potential sources of bias are directly relevant to this collection of studies and are briefly summarized; an article by Kohn et al.,[71] elsewhere in this issue, provides additional details.

- Double criterion standard bias. This exists when patients suspected to have the disease receive one diagnostic standard (such as surgical exploration for mesenteric ischemia), and the remainder undergo simple clinical follow-up. We noted this in several studies; however, from an ethical standpoint this is simply unavoidable.
- Incorporation bias exists when the test being studied affects the likelihood of the final diagnosis being made. This is quite prevalent in the radiology studies, which examined retrospectively the performance of CT in diagnosing acute mesenteric ischemia. Incorporation bias has the potential to increase the reported accuracy of the index test.
- Verification bias occurs when the sample under study consists only of patients who got the diagnostic standard and the index test was used to make the decision to proceed to the diagnostic standard; for example, a study of CT scan accuracy in patients undergoing laparotomy for suspected mesenteric ischemia. This is modestly different than incorporation bias in the construct of the study sample—incorporation bias occurs when the index test helps define the reference standard, and verification bias occurs when the study sample is made up only of patients receiving the reference test. This bias will also tend to inflate the diagnostic performance of the index test or the prevalence of a baseline condition.

Implications and Test–Treatment Thresholds

Given that the surgical outcomes literature is composed predominantly of retrospective studies, it is critically important to understand how cases were selected to judge bias and applicability. Studies reporting surgical outcomes may specify patients by procedure (bowel resection,[10] revascularization[7]), type of vascular

occlusion (mesenteric venous thrombosis,[64] superior mesenteric artery[1,30,59]), or final diagnosis (ICD-9 codes, autopsy reports). Studies reporting diagnostic modalities (laboratory or imaging) may report on patient outcomes stratified by surgical intervention and diagnosis, but this is unfortunately not universal. In addition, among the things we do not know with any degree of certainty is the effect of a false-positive test.

Laparotomy is intuitively a nonbenign process. Multiple studies derived from the blunt and penetrating trauma populations suggest that undergoing a negative laparotomy does not result in an increase in morbidity or short-term complication rate[72,73]; however, the trauma population is a substantially different one than the suspected mesenteric ischemia population in that the latter are generally older, more frail, with higher comorbid illness burdens. All but a handful of studies examining surgical outcomes are based in cohorts consisting only of patients with known mesenteric ischemia. Woo et al.[74] reported outcomes on patients taken to the operating room with suspected mesenteric ischemia—the difference in mortality between those with mesenteric ischemia (48.8% mortality) and without mesenteric ischemia (39.3%) did not meet statistical significance, although the retrospective analysis was limited by sample size. Thuijls et al.,[34] in their study of FABP as a diagnostic marker for mesenteric ischemia, noted a mortality rate of seven of 21 patients operated on for confirmed mesenteric ischemia, compared to zero of 24 patients with other diagnoses. Eighteen of the 24 patients went to the operating room, with only five having nontherapeutic laparotomies. In other words, 13 of 24 patients in the study by Thuijls et al. without mesenteric ischemia still needed to go to the operating room. Again, sample size is obviously an issue, but this brings up the point that many patients in this at-risk population will have surgical causes for their acute abdominal pain, even if they do not have mesenteric ischemia. The current literature base is insufficient to definitively delineate the rate and risk of true negative laparotomy in this population.

Within these limitations, therefore, the calculation of test versus treat thresholds for diagnostic imaging is best conceptually approached as a sensitivity analysis, dependent upon the assumptions used. The concept of the test threshold incorporates the risk of harm induced by false-positive testing (the risk of which is 1 – specificity) combined with the risk of undergoing the test itself, over a denominator that consists of the risk of a false-positive plus the benefit of a true-positive test (sensitivity × benefit of the intervention). In this setting, this would include the risk of an unnecessary laparotomy combined with the risk of mortality due to contrast-induced nephropathy due to the CT itself, versus the benefit of accurately diagnosing mesenteric ischemia. It can be summarized by the following construct:

$$T_{test} = [(\text{false-postive}) \times (R_{surgery}) + R_{CT}]/[(\text{false-postive}) \times (R_{surgery}) + (\text{true-positive} \times B_{surgery})].$$

The treatment threshold accounts for the risk of a false-negative diagnostic test and the loss of benefit to the patient for undergoing a needed procedure. The risk of undergoing the diagnostic test is also incorporated in this calculus and is summarized thus:

$$T_{treat} = [(\text{specificity} \times R_{surgery}) - R_{CT})/[(\text{specificity} \times R_{surgery}) + (1 - \text{sensitivity} \times B_{surgery})].$$

Using the pooled sensitivity and specificity for abdominal CT scanning of 94 and 95%, we must then calculate a benefit of surgery. Assuming a mortality of 100% in untreated mesenteric ischemia,[75] and using the pooled operative mortality of 47% as previously stated, the benefit of surgery is 53%. Next to be considered is the risk of the diagnostic CT itself, which is predominantly related to renal insufficiency attributed to contrast exposure. There is an increasing body of literature that suggests that the risk of renal insufficiency in acutely ill patients is independent of contrast exposure.[8,76–78] The issue remains far from settled, but in these studies the range of renal insufficiency in patients exposed to contrast ranges from 0 to 6%, and the pooled estimate is 3%. Using an approximation of mortality attributable to renal insufficiency of 15%,[79] we obtain a mortality risk due to renal insufficiency of frequency × mortality = 3% × 15% = 0.45%. As stated previously, the area of greatest uncertainty becomes the risk of a false-positive study or attributable mortality risk due to an unnecessary laparotomy. Several manipulations of these variables, and the resultant test–treat thresholds, are presented in Table 4. Using the pooled

Table 4
The Effect of Varying Assumptions on the Test Threshold (Perform CT Scan) and Treatment Threshold (Go to the Operating Room) Parameters

	CT						
	Sensitivity	Specificity	Surgery Benefit	CT Risk	Surgery Risk	Test Threshold	Treat Threshold
Pooled test performance	94	95	53	0.45	10	1.9	74
Low test performance	90*	93*	53	0.45	10	2.4	61
High test performance	97*	97*	53	0.45	10	1.5	82
High test risk	94	95	53	4.5*	10	10	41
Medium negative surgery risk	94	95	53	0.45	20*	3.2	86
High negative surgery risk	94	95	53	0.45	50*	6.5	94

Data are reported as percentages
*Those assumptions that were altered from the pooled test results.

test characteristic of CT scanning (sensitivity of 94%, specificity of 95%), a risk to CT scanning of 0.45%, a surgery benefit of 53%, and an assumed mortality risk of a negative laparotomy of 10%, we can derive a test threshold of 2.1% and a treatment threshold of 74%. In other words, if the pretest probability of mesenteric ischemia is below 2.1%, then proceeding to CT scanning may harm more patients than it helps. Additionally, with these assumptions, if the pretest probability of mesenteric ischemia is above 74%, operative treatment should be initiated instead of additional diagnostic testing, or patients may experience more harm than good. This is consistent with studies that demonstrate a differential survival rate with early intervention compared to delayed intervention.[9,26]

This study adds breadth to the previous meta-analysis of the use of CT in the diagnosis of acute mesenteric ischemia. Menke[13] completed a meta-analysis in 2010 that included only studies of newer generation multislice CT scanners. Six studies met criteria.[21,44,51,54,56,80] Three studies were prospective, and three were retrospective. All studies were of high quality using QUADAS criteria. The meta-analysis by Menke[13] included 619 cases. The meta-analysis showed that CT scan had a pooled sensitivity of 93.3% (95% CI = 82.8% to 97.6%) for the diagnosis of acute mesenteric ischemia and a pooled specificity of 95.9% (95% CI = 91.2% to 98.2%). Our meta-analysis, with regard to imaging, added three additional studies to Menke's meta-analysis.[45,46,57] Our study added an additional 261 patients for analysis, which represents a 42% increase over Menke's 619 case analysis. Despite the substantial increase in the number of cases, we found a very similar pooled sensitivity for the diagnosis for acute mesenteric ischemia at 94% (95% CI = 90% to 97%), corroborating Menke's findings with a more robust case set.

To our knowledge, this study also represents the first meta-analysis of the sensitivity and specificity of D-dimer, lactate, GST, and FABP in the diagnosis of acute mesenteric ischemia. Acosta and Nilsson[31] summarized two papers exploring the utility of both L- and D-lactate,[11,12] four papers summarizing the results of D-dimer,[30,32,43,47] two papers addressing GST,[48,49] and three papers concerning FABP.[33,34,81] However, Acosta and Nilsson made no attempt to calculate pooled sensitivities or specificities of any of the markers, and they also considered animal studies in the review. Our analysis—with greater power than previous single studies—suggests that neither D-dimer nor lactate have adequate sensitivity to rule out disease.

The current study also provides specific testing and treatment thresholds. The thresholds have the potential to change management of suspected acute mesenteric ischemia in individual cases. For the clinician with less experience with acute mesenteric ischemia, or experienced clinicians with varying testing strategies, these numbers suggest discrete decision points for the testing and treatment of presumed acute mesenteric ischemia. Until the development of a validated risk stratification or criteria rule to calculate a discrete pretest probability for acute mesenteric ischemia, clinicians can benefit from data-driven thresholds to apply to their own "clinical gestalt" calculations of pretest probability.

Our analysis adds value in that there is scant guideline-based guidance available in the literature. Two major medical societies touch lightly on the topic of acute mesenteric ischemia in guidelines. In 2012, the Italian Society of Endoscopic Surgery released guidelines for the use of laparoscopic surgery in the acute abdomen.[82] In the setting of mesenteric ischemia, this guideline does not recommend laparoscopy for acute diagnosis over the use of CT scanning, although it suggests that there may be a role for "second-look" procedures for laparoscopy. Likewise, the American College of Cardiology, in conjunction with the American Heart Association and multiple other specialty societies, issued a guideline in 2006 relating to the management of peripheral arterial disease, to include acute mesenteric ischemia.[83] With regard to acute mesenteric ischemia, the recommendations from the guideline consist solely of reminders to keep acute mesenteric ischemia in the differential diagnosis for a patient with abdominal pain out of proportion to examination and a history of cardiovascular disease or one with recent aortic catheter–based procedures. The guideline also recommends against using duplex sonography for evaluating for acute mesenteric ischemia.[83] The same societies issued a joint focused update on the management of peripheral arterial disease in 2011; however, mesenteric ischemia was not addressed at all in the focused update.[84]

IMPLICATIONS FOR FUTURE RESEARCH

Clearly, the current state of the literature leaves substantial room for further investigations in the field of acute mesenteric ischemia. We still lack a screening test with sufficient sensitivity to forgo further testing in all but patients with very low pretest probability. Our diagnostic test of choice requires the administration of IV contrast and ionizing radiation. Many studies characterizing history and physical examination findings report data only on patients proven to have the disease, without comparator control groups.

Unfortunately, the low incidence of this condition, albeit one with high morbidity and mortality, has made it difficult to perform high-quality research and will continue to hinder future research efforts. Careful research design and adherence to publication standards such as the STARD criteria[67] will improve the quality of data returned from future investigations. Future studies should include comparable well-defined counterfactual controls, so as to be able to clearly establish whether differential findings are due to the disease state itself or due to bias within groups. Laboratory screening studies should be specific as to the intervals between symptom onset, specimen procurement, and final diagnosis. In addition to reporting strict dichotomous cutoff values for laboratory studies, future studies should consider evaluating ranges of results, so as to determine whether there is increasing risk of disease with increasing variance from the normal values. Interval LRs may be a helpful analytic maneuver for these studies. There may be value in establishing structured decision rules to concretely establish the pretest probability of disease; however, any such structured decision rule should be tested against overall physician gestalt to gauge comparative accuracy.

Alternate diagnostic modalities may need to be explored. Magnetic resonance angiography has not, at the time of this writing, been tested in a prospective fashion. Although not as widely available, and not without its own set of risks, as magnetic resonance technology spreads, it may prove a feasible alternative to CT scanning. The pooled sensitivity of CT scanning (94%, 95% CI = 90% to 97%) was very close to the pooled sensitivity of D-dimer testing (96%, 95% CI = 89% to 99%), although the specificity of CT was substantially higher. Therefore, missed cases are still going to occur, leading to the question of whether further refinement of test utility (as represented by interval LRs, examining the change in likelihood of disease using a "moving target" cut point) or improved imaging modalities will clarify the ideal diagnostic strategy.

LIMITATIONS

We only included studies in English. Although most international publications provide abstracts in English, the level of detail required to accurately ascertain potential sources of bias is generally not present in the abstract format. Most outcomes studies reported only on those patients who had confirmed diagnoses of mesenteric ischemia. Therefore, we cannot address the specificity of the history or physical examination findings, and it is conceivable that the prevalence of findings in these samples is biased upward.[85] The reference standard for a positive diagnosis of mesenteric ischemia, as established by the source studies, consisted of findings of ischemia in the operating room or at autopsy, without explicit definitions of what that consisted of. The reference standard for a negative diagnosis was much less rigorous. In those studies that included patients who did not go to the operating room, survival was considered proof of the absence of mesenteric ischemia. In addition, we encountered difficulty in estimating the risk of negative laparotomy in acutely ill elderly patients who may not have mesenteric ischemia, but may have other reasons to benefit from laparotomy. The heterogeneity of populations and outcomes was substantial—cohort characteristics from inpatients may differ substantially from patients presenting primarily to the ED with abdominal pain. Likewise, our estimates do not incorporate end-of-life and other care preferences. Most surgical series explicitly excluded those patients with existing do-not-resuscitate orders or those who opted for comfort measures only. Even with operative intervention, the mortality rate for mesenteric ischemia remains high, and patients and their surrogates may decide that the suffering engendered from surgery and recovery would not be of substantive value when viewed in terms of potential benefit.

During the review process, a concern was raised whether the lack of a medical librarian was a limitation. We do not feel that the lack of a medical librarian represents a substantive limitation. The consensus standards for systematic reviews and meta-analyses do not specify the use of particular personnel for the conduct of literature reviews.[36,86] This is bolstered by the fact that our literature search strategy identified further studies than previous works, as detailed above.

We did not apply the test–treatment threshold paradigm to laboratory tests. No laboratory test holds enough specificity to establish the diagnosis of acute mesenteric ischemia. Rather, the utility of laboratory findings, in concert with findings on history and physical examination, is to help shape the clinician's pretest probability of disease, which then can inform the decision to proceed with imaging or immediate surgical consultation.

We did not stratify pooled results by a variety of possible factors, such as the format of the CT imaging or various cutoff thresholds of laboratory testing. Different laboratory assays will have different ranges of normal versus abnormal by manufacturer, and the evaluation of interassay agreement is well beyond the scope of this article. For generalizability, we elected to recognize the cutoff reported in each study as a valid dichotomous endpoint. Likewise, the clinician evaluating a patient for potential acute mesenteric ischemia will not have a range of choices in terms of which CT scanner he or she will send the patient to. The heterogeneity of CT formats in the reviewed literature is certainly a limitation in discerning exact test characteristics. It would be desirable from an academic standpoint to have substantial numbers of trials and patients evaluated by different CT scanners of differing quality to know with precision the diagnostic accuracy of disparate protocols; however, the practical effect to the clinician needing to make decisions based on the equipment immediately available is unknown. Certainly, as the quality of CT scanners improves, the sensitivity for mesenteric ischemia will likely improve. It will be interesting to see if the epidemiology of diagnosed mesenteric ischemia and subsequent outcomes shift due to this secular trend. Finally, multiple studies evaluated different etiologies of acute mesenteric ischemia; while mortality after intervention may vary depending on the precise etiology, the emergency physician must evaluate the global condition of "acute mesenteric ischemia" as a cause for the patient's presentation, rather than specific subtypes. Therefore, we did not stratify results by the ultimate etiology of the mesenteric ischemia.

Given the amount of heterogeneity in the literature, what is the clinician to do with the results of this analysis? Mesenteric ischemia is a heterogeneous condition, with several potential etiologies, but frequently poor outcomes. Given the range of pooled test performance, however, the testing threshold remains relatively low when the disease is suspected. Laboratory tests, as well as findings on history and physical examination, may help inform the pretest probability, but are generally insufficient as stand-alone results to preclude further testing. The concept of the test–treatment threshold, applied with the results of our meta-analysis, will hopefully encourage appropriate testing and decrease time-to-diagnosis for these patients.

CONCLUSIONS

Acute mesenteric ischemia remains a highly mortal condition. Medical history and the characteristics of presenting complaints are not strongly helpful in ruling in or ruling out the disease. A negative D-dimer may be

helpful in ruling out acute mesenteric ischemia, but the data are insufficiently strong and the confidence intervals remain too wide at this time to recommend full exclusion of disease based on this test.

Computed tomography angiography of the abdomen has excellent test characteristics and likely low attributable risk when compared to the mortality of suspected mesenteric ischemia. In all but the lowest pretest probability patients, computed tomography is likely indicated to clarify the diagnostic picture. However, when the pretest probability is quite high (70% or higher), the patient may benefit from immediate surgical consultation and consideration of laparotomy. Physicians should be aware of the protean manifestations of mesenteric ischemia and maintain a low threshold for entertaining the diagnosis, as the morbidity and mortality for undiagnosed mesenteric ischemia is substantial.

References

1. Acosta S, Bjorck M. Acute thrombo-embolic occlusion of the superior mesenteric artery: a prospective study in a well defined population. Eur Soc Vasc Surg. 2003; 26:179–83.
2. Cooke M, Sande MA. Diagnosis and outcome of bowel infarction on an acute medical service. Am J Med. 1983; 75:984–92.
3. Liavåg I. Acute mesenteric vascular insufficiency. A five-year material, including a case of successful superior mesenteric artery embolectomy. Acta Chir Scand. 1967; 133:631–9.
4. Kassahun WT, Schulz T, Richter O, Hauss J. Unchanged high mortality rates from acute occlusive intestinal ischemia: six year review. Langenbeck's Arch Surg. 2008; 393:163–71.
5. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007; 46:467–74.
6. Mamode N, Pickford I, Leiberman P. Failure to improve outcome in acute mesenteric ischaemia: seven-year review. Eur J Surg. 1999; 165:203–8.
7. Newton WB III, Sagransky MJ, Andrews JS, et al. Outcomes of revascularized acute mesenteric ischemia in the American College of Surgeons National Surgical Quality Improvement Program database. Am Surg. 2011; 77:832–8.
8. Acosta S, Bjornsson S, Ekberg O, Resch T. CT angiography followed by endovascular intervention for acute superior mesenteric artery occlusion does not increase risk of contrast-induced renal failure. Eur J Vasc Endovasc Surg. 2010; 39:726–30.
9. Eltarawy IG, Etman YM, Zenati M, Simmons RL, Rosengart MR. Acute mesenteric ischemia: the importance of early surgical consultation. Am Surg. 2009; 75:212–9.
10. Gupta PK, Natarajan B, Gupta H, Fang X, Fitzgibbons RJ Jr. Morbidity and mortality after bowel resection for acute mesenteric ischemia. Surgery. 2011; 150:779–87.
11. Stamatakos M, Stefanaki C, Mastrokalos D, et al. Mesenteric ischemia: still a deadly puzzle for the medical community. Tohoku J Exp Med. 2008; 216:197–204.
12. Hellinger JC. Evaluating mesenteric ischemia with multidetector-row CT angiography. Tech Vasc Interv Radiol. 2004; 7:160–6.
13. Menke J. Diagnostic accuracy of multidetector CT in acute mesenteric ischemia: systematic review and meta-analysis. Radiology. 2010; 256:93–101.
14. Taourel PG, Deneuville M, Pradel JA, Regent D, Bruel JM. Acute mesenteric ischemia: diagnosis with contrast-enhanced CT. Radiology. 1996; 199:632–6.
15. Berland T, Oldenburg WA. Acute mesenteric ischemia. Curr Gastroenterol Rep. 2008; 10:341–6.
16. Gunduz A, Turkmen S, Turedi S, et al. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. Acad Emerg Med. 2009; 16:539–43.
17. Chang RW, Chang JB, Longo WE. Update in management of mesenteric ischemia. World J Gastroenterol. 2006; 12:3243–7.
18. Horton KM, Fishman EK. Multidetector CT angiography in the diagnosis of mesenteric ischemia. Radiol Clin North Am. 2007; 45:275–88.
19. Schoots IG, Koffeman GI, Legemate DA, Levi M, van Gulik TM. Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. Br J Surg. 2004; 91:17–27.
20. Patel A, Kaleya RN, Sammartano RJ. Pathophysiology of mesenteric ischemia. Surg Clin North Am. 1992; 72:31–41.
21. Aschoff AJ, Stuber G, Becker BW, et al. Evaluation of acute mesenteric ischemia: accuracy of biphasic mesenteric multi-detector CT angiography. Abdom Imaging. 2009; 34:345–57.
22. Korotinski S, Katz A, Malnick SD. Chronic ischaemic bowel diseases in the aged–go with the flow. Age Ageing. 2005; 34:10–16.
23. Pecoraro F, Rancic Z, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013; 27:113–22.
24. MacDonald PH. Ischaemic colitis. Best Pract Res Clin Gastroenterol. 2002; 16:51–61.
25. Boley SJ, Sprayregan S, Siegelman SS, Veith FJ. Initial results from an aggressive roentgenological and surgical approach to acute mesenteric ischemia. Surgery. 1977; 82:848–55.
26. Alvi AR, Khan S, Niazi SK, Ghulam M, Bibi S. Acute mesenteric venous thrombosis: improved outcome with early diagnosis and prompt anticoagulation therapy. Int J Surg. 2009; 7:210–3.
27. Mitsuyoshi A, Obama K, Shinkura N, Ito T, Zaima M. Survival in nonocclusive mesenteric ischemia: early diagnosis by multidetector row computed tomography and early treatment with continuous intravenous high-dose prostaglandin E(1). Ann Surg. 2007; 246:229–35.
28. Batellier J, Kieny R. Superior mesenteric artery embolism: eighty-two cases. Ann Vasc Surg. 1990; 4:112–6.
29. Huang HH, Chang YC, Yen DH, et al. Clinical factors and outcomes in patients with acute mesenteric

ischemia in the emergency department. J Chin Med Assoc. 2005; 68:299–306.
30. Acosta S, Nilsson TK, Bjorck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. Br J Surg. 2004; 91:991–4.
31. Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. J Thromb Thrombolysis. 2012; 33:355–61.
32. Block T, Nilsson TK, Bjorck M, Acosta S. Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. Scand J Clin Lab Invest. 2008; 68:242–8.
33. Kanda T, Fujii H, Tani T, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology. 1996; 110:339–43.
34. Thuijls G, van Wijck K, Grootjans J, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011; 253:303–8.
35. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med. 1980; 302:1109–17.
36. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283:2008–12.
37. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155:529–36.
38. Randolph J. Online Kappa Calculator. Available at: http://justus.randolph.name/kappa. Accessed Aug 8, 2013.
39. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006; 6:31.
40. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials. 2007; 28:105–14.
41. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med. 2002; 21:1237–56.
42. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J. 2003; 327:557–60.
43. Acosta S, Nilsson TK, Bjorck M. Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. Br J Surg. 2001; 88:385–8.
44. Akyildiz H, Akcan A, Oztürk A, Sozuer E, Kucuk C, Karahan I. The correlation of the D-dimer test and biphasic computed tomography with mesenteric computed tomography angiography in the diagnosis of acute mesenteric ischemia. Am J Surg. 2009; 197:429–33.
45. Barmase M, Kang M, Wig J, Kochhar R, Gupta R, Khandelwal N. Role of multidetector CT angiography in the evaluation of suspected mesenteric ischemia. Eur J Radiol. 2011; 80:e582–7.
46. Blachar A, Barnes S, Adam SZ, et al. Radiologists' performance in the diagnosis of acute intestinal ischemia, using MDCT and specific CT findings, using a variety of CT protocols. Emerg Radiol. 2011; 18:385–94.
47. Chiu YH, Huang MK, How CK, et al. D-dimer in patients with suspected acute mesenteric ischemia. Am J Emerg Med. 2009; 27:975–9.
48. Delaney CP, O'Neill S, Manning F, Fitzpatrick JM, Gorey TF. Plasma concentrations of glutathione S-transferase isoenzyme are raised in patients with intestinal ischaemia. Br J Surg. 1999; 86:1349–53.
49. Gearhart SL, Delaney CP, Senagore AJ, et al. Prospective assessment of the predictive value of alpha-glutathione S-transferase for intestinal ischemia. Am Surg. 2003; 69:324–9.
50. Howard TJ, Plaskon LA, Wiebke EA, Wilcox MG, Madura JA. Nonocclusive mesenteric ischemia remains a diagnostic dilemma. Am J Surg. 1996; 171:405–8.
51. Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: initial experience. Radiology. 2003; 229:91–8.
52. Lange H, Jackel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg. 1994; 160:381–4.
53. Murray MJ, Gonze MD, Nowak LR, Cobb CF. Serum D(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. Am J Surg. 1994; 167:575–8.
54. Ofer A, Abadi S, Nitecki S, et al. Multidetector CT angiography in the evaluation of acute mesenteric ischemia. Eur Radiol. 2009; 19:24–30.
55. Polk JD, Rael LT, Craun ML, Mains CW, vis-Merritt D, Bar-Or D. Clinical utility of the cobalt-albumin binding assay in the diagnosis of intestinal ischemia. J Trauma. 2008;64:42–5.
56. Wiesner W, Hauser A, Steinbrich W. Accuracy of multidetector row computed tomography for the diagnosis of acute bowel ischemia in a non-selected study population. Eur Radiol. 2004; 14:2347–56.
57. Yikilmaz A, Karahan OI, Senol S, Tuna IS, Akyildiz HY. Value of multislice computed tomography in the diagnosis of acute mesenteric ischemia. Eur J Radiol. 2011; 80:297–302.
58. Arthurs ZM, Titus J, Bannazadeh M, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. J Vasc Surg. 2011; 53:698–704.
59. Bjorck M, Acosta S, Lindberg F, Troeng T, Bergqvist D. Revascularization of the superior mesenteric artery after acute thromboembolic occlusion. Br J Surg. 2002; 89:923–7.
60. Dahlke MH, Asshoff L, Popp FC, et al. Mesenteric ischemia–outcome after surgical therapy in 83 patients. Dig Surg. 2008; 25:213–9.
61. Edwards MS, Cherr GS, Craven TE, et al. Acute occlusive mesenteric ischemia: surgical management and outcomes. Ann Vasc Surg. 2003; 17:72–9.
62. Endean ED, Barnes SL, Kwolek CJ, Minion DJ, Schwarcz TH, Mentzer RM Jr. Surgical management of thrombotic acute intestinal ischemia. Ann Surg. 2001; 233:801–8.

63. Hawkins BM, Khan Z, bu-Fadel MS, Exaire JE, Saucedo JF, Hennebry TA. Endovascular treatment of mesenteric ischemia. Cath Cardiovasc Interven. 2011;78:948–52.
64. Hedayati N, Riha GM, Kougias P, et al. Prognostic factors and treatment outcome in mesenteric vein thrombosis. Vasc Endovasc Surg. 2008; 42:217–24.
65. Marchena-Gomez J, Costa-Merida MA, Hemmersbach-Miller M, Conde-Martel A, Roque-Castellano C, Hernandez-Romero J. The age-adjusted Charlson Comorbidity Index as an outcome predictor of patients with acute mesenteric ischemia. Ann Vasc Surg. 2009;23:458–64.
66. Park WM, Gloviczki P, Cherry KJ Jr, et al. Contemporary management of acute mesenteric ischemia: factors associated with survival. J Vasc Surg. 2002; 35:445–52.
67. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Br Med J. 2003; 326:41–4.
68. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ. 2004; 329:168–9.
69. Newman TB, Kohn MA. Critical Appraisal of Diagnostic Tests. New York, NY: Cambridge University Press, 2009.
70. Pines JM, Carpenter CR, Raja AS, Schuur JD. Evidence-Based Emergency Care: Diagnostic Testing and Clinical Decision Rules (Evidence-Based Medicine). Oxford, UK: John Wiley & Sons, 2013.
71. Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy. Acad Emerg Med. 2013;20:1194–1206.
72. Crookes BA, Shackford SR, Gratton J, Khaleel M, Ratliff J, Osler T. "Never be wrong": the morbidity of negative and delayed laparotomies after blunt trauma. J Trauma. 2010; 69:1386–91.
73. Morrison JE, Wisner DH, Bodai BI. Complications after negative laparotomy for trauma: long-term follow-up in a health maintenance organization. J Trauma. 1996; 41:509–13.
74. Woo K, Major K, Kohanzadeh S, Allins AD. Laparotomy for visceral ischemia and gangrene. Am Surg. 2007; 73:1006–8.
75. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004; 164:1054–62.
76. Lima FO, Lev MH, Levy RA, et al. Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. Am J Neuroradiol. 2010; 31:817–21.
77. McGillicuddy EA, Schuster KM, Kaplan LJ, et al. Contrast-induced nephropathy in elderly trauma patients. J Trauma. 2010; 68:294–7.
78. Sinert R, Brandler E, Subramanian RA, Miller AC. Does the current definition of contrast-induced acute kidney injury reflect a true clinical entity? Acad Emerg Med. 2012; 19:1261–7.
79. From AM, Bartholmai BJ, Williams AW, Cha SS, McDonald FS. Mortality associated with nephropathy after radiographic contrast exposure. Mayo Clin Proceed. 2008; 83:1095–100.
80. Zandrino F, Musante F, Gallesio I, Benzi L. Assessment of patients with acute mesenteric ischemia: multislice computed tomography signs and clinical performance in a group of patients with surgical correlation. Minerva Gastroenterol Dietol. 2006; 52:317–25.
81. Lieberman JM, Sacchettini J, Marks C, Marks WH. Human intestinal fatty acid binding protein: report of an assay with studies in normal volunteers and intestinal ischemia. Surgery. 1997; 121:335–42.
82. Agresta F, Ansaloni L, Baiocchi GL, et al. Laparoscopic approach to acute abdomen from the Consensus Development Conference of the Societa Italiana di Chirurgia Endoscopica e nuove tecnologie (SICE), Associazione Chirurghi Ospedalieri Italiani (ACOI), Societa Italiana di Chirurgia (SIC), Societa Italiana di Chirurgia d'Urgenza e del Trauma (SICUT), Societa Italiana di Chirurgia nell'Ospedalita Privata (SICOP), and the European Association for Endoscopic Surgery (EAES). Surg Endosc. 2012; 26:2134–64.
83. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006; 113:e463–654.
84. 2011 ACCF/AHA Focused Update of the Guideline for the Management of patients with peripheral artery disease (Updating the 2005 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;124:2020–45.
85. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA. 1999; 282:1061–6.
86. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Br Med J. 2009; 339:b2700.

Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Summary characteristics of the literature base for this article.

Data Supplement S2. Forest plots for sensitivity and specificity of D-lactate.

Data Supplement S3. Forest plots for sensitivity and specificity of L-lactate.

Data Supplement S4. Forest plots for sensitivity and specificity of D-dimer.

Data Supplement S5. Summary receiver operator characteristic curve for D-dimer.

Data Supplement S6. Forest plots for sensitivity and specificity of alpha glutathione *S*-transferase.

Data Supplement S7. Summary receiver operator characteristic curve for alpha glutathione *S*-transferase.

Data Supplement S8. Forest plots for the sensitivity and specificity of fatty acid–binding protein.

Data Supplement S9. Forest plots for the sensitivity and specificity of CT scanning.

Data Supplement S10. Summary receiver operator characteristic curve for CT.

DR JEREMY BROWN TO DIRECT NIH OFFICE OF EMERGENCY CARE RESEARCH

The National Institutes of Health has announced in a press release that Jeremy Brown, MD, has been chosen to be the first permanent director of its Office of Emergency Care Research (OECR). Established in 2012 under NIH's National Institute of General Medical Sciences, OECR is a focal point for basic, clinical and translational emergency care research and training across NIH. It coordinates, catalyzes, and communicates about NIH funding opportunities in emergency care research and fosters the training of future researchers in this field. Dr. Brown is currently an associate professor of emergency medicine and chief of the clinical research section in the Department of Emergency Medicine at The George Washington University (GWU). He works clinically as an attending physician at the Washington D.C. VA Medical Center. His NIH appointment will begin in July. Dr. Brown will also represent NIH in government wide efforts to improve the nation's emergency care system. Alan E. Jones, MD, president of the Society for Academic Emergency Medicine, expressed the satisfaction of the emergency medicine community at the establishment of OECR and at Dr. Brown's selection as its first permanent director. "SAEM, along with other emergency medicine organizations, has been very involved in efforts to create a dedicated centralized national office for emergency care research. We are delighted at the progress that has been made since the announcement of OECR's creation last year, and congratulate Dr. Jeremy Brown on his well-deserved appointment as its first director." Dr. Brown is ready for the challenge of heading OECR. "I am excited to join this world-class institution and lead its efforts to improve emergency care in the U.S.," he says. "To pursue this goal, I look forward to partnering with all of the NIH institutes and centers, other government agencies, and a wide range of researchers and clinicians." Dr. Brown replaces Walter J. Koroshetz, M.D., deputy director of the National Institute of Neurological Disorders and Stroke, who had served as OECR's acting director since its inception.