Diagnosis in acute abdominal pain and ongoing abdominal sepsis
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Chapter 5

A SYSTEMATIC REVIEW OF DIAGNOSTIC ACCURACY FOR EACH STEP IN THE COMMON WORK-UP OF SUSPECTED ACUTE INTESTINAL ISCHEMIA

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Submitted
ABSTRACT

Introduction: Patients presenting with acute abdominal pain at the emergency department that have intestinal ischemia are an essential different population than in-hospital patients that have intestinal ischemia after major surgery. The aim of this systematic review was to provide the diagnostic accuracy of commonly used diagnostic modalities in the work-up in this specific population.

Methods: A search was performed in MEDLINE and EMBASE up to July 2014 for studies reporting on the accuracy of clinical diagnosis, laboratory tests and imaging with explicit criteria for a positive test result, surgery and/or follow-up as the reference standard, and sufficient data to construct a 2 × 2 table. Studies evaluating in-hospital postoperative patients or patient with strangulated bowel were excluded. Bivariate random-effects modeling was used to obtain summary estimates of sensitivity and specificity.

Results: Two included studies evaluated D-lactate with a sensitivity of 90% (95%CI: 60% to 98%) and 89% (95%CI: 57% to 98%) at a specificity of 23% (95%CI: 14% to 35%) and 86% (95%CI: 67% to 95%), respectively. One included study evaluated i-FABP with a sensitivity of 83% (95%CI: 64% to 93%) at a specificity of 89% (95%CI: 83% to 93%). Four studies included evaluated D-dimer with a sensitivity ranging from 60% to 100% at a specificity ranging from 13% to 87%. Given the heterogeneity and the use of different cut-off values data were not pooled. Five included studies evaluated CT accuracy; mean sensitivity was 91% (95%CI: 80% to 98%) at a specificity of 94% (95%CI: 87% to 99%). No studies evaluated the diagnostic accuracy of a clinical diagnosis, L-lactate, MRI or angiography fulfilling the inclusion criteria could be identified.

Conclusion: Data from solid studies on the added value of each step of the common diagnostic work-up of suspected intestinal ischemia are lacking. CT with mesenteric CTA has a good accuracy in detecting acute intestinal ischemia in unselected patients presenting at the ED. Current laboratory tests are not accurate enough and lack adequate specificity.
INTRODUCTION

Acute intestinal ischemia is a relative rare condition in patients presenting at the emergency department (ED). The origin of intestinal ischemia can be related to a primary vascular disorder or can be secondary to a nonvascular condition such as a strangulated small bowel herniation. Intestinal ischemia is also seen after cardiac and aortic surgery. These patients are already admitted to the intensive care unit (ICU) or hospital ward and are an elementary different patient population than patients presenting to the ED with acute abdominal pain. About 1 in 1000 patients admitted with acute abdominal pain are assumed to develop acute intestinal ischemia; an annual incidence of 1 per 100,000 persons is frequently reported.\textsuperscript{1-3} Estimations of prevalence and incidence in original studies are limited and mostly based on a single study published in 1977.\textsuperscript{1} Incidence is reported to increase over the last decades without giving an indication on the magnitude of increase based on original studies.\textsuperscript{4-10} A systematic review has identified only four studies reporting general population based incidence, with estimates ranging from 4.5 to 44 cases per 100,000 person-years.\textsuperscript{11} Irrespective of the exact incidence of acute intestinal ischemia a 30% to 95% mortality is reported.\textsuperscript{2} An early therapeutic approach may increase survival making prompt diagnosis of intestinal ischemia pivotal.\textsuperscript{8,9,12} The diagnostic pathway in acute intestinal ischemia is comparable to the pathway commonly used for patients presenting with acute abdominal pain. The first diagnostic entity is clinical evaluation with history taking and physical examination. Laboratory tests comprise the second step in the diagnostic pathway. Serum lactate is frequently referred to as a marker for intestinal ischemia.\textsuperscript{8,13-16} The term lactate is widely used but the more routinely performed test is the measurement of L-lactate. D-lactate is the stereoisomer of human L-lactate and produced by bacterial fermentation. It needs separate testing which is not routinely done.\textsuperscript{17} For D-lactate and other laboratory tests such as intestinal fatty acid binding protein (i-FABP) and D-dimer promising results on discriminatory capacity have been reported.\textsuperscript{13,14,16,19-21} The third step in the diagnostic pathway is often imaging. The most frequently used imaging techniques to detect acute intestinal ischemia are computed tomography (CT), magnetic resonance imaging (MRI) and angiography. Diagnostic accuracy reviews of clinical characteristics, laboratory markers and CT have been published previously.\textsuperscript{7,22-24} These reviews did not differentiate between patients presenting at the ED with acute abdominal pain and those after major surgery. The reviews also did not evaluate the steps in an intestinal ischemia diagnostic work-up.
The aim of this systematic review was to give the diagnostic accuracy for each of the commonly used steps in the diagnostic work-up specifically for patients presenting with acute abdominal pain in the ED suspected of having intestinal ischemia.

METHODS

Search strategy

A search strategy was conducted to identify studies reporting on the diagnostic accuracy of each step in a commonly used stepwise approach in patients presenting with acute abdominal pain suspected of acute intestinal ischemia (Figure 1). In this review only acute intestinal ischemia with a primary vascular origin will be considered. Since patients already admitted to the hospital are an elementary different population this review does not include data on intestinal ischemia secondary to major surgery.

We searched the MEDLINE and EMBASE from inception up to July 2014, with indexed search terms combining intestinal ischemia with one of the following: clinical diagnosis, lactate (L-lactate or D-lactate), i-FABP, D-dimer, CT, MRI or angiography. We limited ourselves to studies reported in English.

Study selection

After excluding duplicates the titles and abstracts of identified titles were evaluated for potential eligibility by two reviewers (J.J.S.K. and S.L.G.) with 5 and 2 years of experience of systematic reviews, respectively. An article was considered potentially eligible if the diagnostic accuracy of clinical diagnosis, lactate (L-lactate or D-lactate), i-FABP, D-dimer, CT, MRI or angiography was reported in patients with acute abdominal pain and suspicion of intestinal ischemia. Full-text versions of potentially eligible articles were obtained for further evaluation.

Study reports were included if, in addition, all of the following inclusion criteria were met: (a) explicit criteria reported to define a positive result of the diagnostic modality; (b) surgery and/or clinical follow-up used as reference standard; (c) enough data to construct a contingency table with the number of true-positive, true-negative, false-positive, and false negative results. Studies were excluded when: a) strangulated bowel was the cause of bowel ischemia; b) patients included had already been admitted to the hospital after cardiac or aortic surgery. In case of disagreement between the two reviewers consensus was reached in a group discussion.
FIGURE 1. Steps in the diagnostic work-up of patients presented at the emergency department suspected of acute intestinal ischemia.

Step A
- **Clinical diagnosis**
  - History taking, physical examination

Step B
- **Laboratory findings**
  - D-lactate, L-lactate, i-FABP, D-dimer

Step C
- **Imaging**
  - CT, MRI, Angiography

Step D
- **Final diagnosis**

Critical appraisal

Baseline study characteristics were extracted including date of publication, country of origin, sample size, basic patient characteristics and prevalence of acute intestinal ischemia. The reference standard to establish the final diagnosis was recorded. Basic technical and procedural characteristics of laboratory testing and imaging modalities were extracted. Study quality was assessed using the QUADAS tool for diagnostic studies.\(^{25}\)
Data analysis
We recalculated study-specific estimates of sensitivity and specificity, based on the number of true and false positives and true and false negatives. Between studies that reported diagnostic accuracy of the same step or modality in the diagnostic pathway heterogeneity was explored. Heterogeneity was quantified with the $I^2$ test statistic including 95% confidence intervals. The $I^2$ statistic expresses the percentage of the total variation across studies that is due to heterogeneity rather than chance; a higher percentage indicates more heterogeneity. Summary estimates of diagnostic accuracy were calculated whenever three or more studies of the same step in the diagnostic work-up were included. We used a bivariate logitnormal random effects model to calculate the mean for sensitivity and specificity.26

RESULTS
Study selection
The search resulted in 3,290 hits of which 980 duplicates; 2,310 titles and abstracts were evaluated for potential eligibility, resulting in 150 potentially eligible studies. Based on reading the full text 11 studies13,14,18,20,21,27-32 could be included (Figure 2).

Study appraisal
Two studies evaluating the diagnostic accuracy of D-lactate in 71 patients and 31 patients, respectively were included.13,14 One study evaluated diagnostic accuracy of i-FABP in 208 patients.18 Five studies had evaluated a total of 300 patients for the accuracy of D-dimer13,20,21,27,29 of which one also studied D-lactate13, and another also evaluated CT.27 Overall CT accuracy had been evaluated in 5 studies including a total of 566 patients (range 47-291 patients)27,28,30-32 (Table 1). We did not identify any studies evaluating the diagnostic accuracy of the clinical diagnosis, L-lactate, MRI, or angiography in patients with suspicion of acute intestinal ischemia in the Emergency Department.

Two of the eleven studies did not include patients prospectively. Aschoff et al performed a retrospective chart review28 and Murray et al did not specifically report the study design.14 The proportion of patients with acute intestinal ischemia varied widely, from 8% to 60%, indicating different mechanisms for patient selection. Not all studies reported the exact gender distribution; among those who did the proportion of females ranged from 37% to 66%.

Eight of the included studies had selected patients based on clinical suspicion of acute intestinal ischemia18,20,21,27-31 (table 2). The remaining three studies included patients who presented...
with acute abdominal pain. Wiesner et al included all patients undergoing a CT scan. Murray et al included patients whenever a laparotomy was performed in the acute setting. Block et al included only patients with an intensity score of 5 or more on a visual analogue pain scale (VAS). Three studies did not report who the examiner was. In the other studies a surgical resident or surgeon had evaluated the patients. Operative findings being used as reference standard for the final diagnosis varied between 33% and 100% of patients. Again three studies did not specify the frequency of operative confirmation of diagnosis for their entire study population, but only in those patients with acute intestinal ischemia as a final diagnosis.
**TABLE 1. Study characteristics**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Modality</th>
<th>Sample size</th>
<th>Prevalence</th>
<th>Gender (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acosta²⁰</td>
<td>2001</td>
<td>Sweden</td>
<td>Prospective</td>
<td>serum D-dimer</td>
<td>14</td>
<td>43% (6/14)</td>
<td>6/8</td>
</tr>
<tr>
<td>Acosta²¹</td>
<td>2004</td>
<td>Sweden</td>
<td>Prospective</td>
<td>serum D-dimer</td>
<td>101</td>
<td>9% (9/101)</td>
<td>NA</td>
</tr>
<tr>
<td>Akyildiz²⁷</td>
<td>2009</td>
<td>Turkey</td>
<td>Prospective</td>
<td>serum D-dimer and CT (4 row MD, biphasic mesenteric CTA)</td>
<td>47</td>
<td>60% (28/47)</td>
<td>NA</td>
</tr>
<tr>
<td>Aschoff²⁸</td>
<td>2009</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>CT (16 or 40 row MD, biphasic mesenteric CTA)</td>
<td>75</td>
<td>37% (28/75)</td>
<td>47/32</td>
</tr>
<tr>
<td>Block¹³</td>
<td>2008</td>
<td>Sweden</td>
<td>Prospective</td>
<td>serum D-lactate and D-dimer</td>
<td>71</td>
<td>14% (10/71)</td>
<td>NA</td>
</tr>
<tr>
<td>Chui²⁹</td>
<td>2008</td>
<td>Taiwan</td>
<td>Prospective</td>
<td>D-dimer</td>
<td>67</td>
<td>34% (23/67)</td>
<td>48/19</td>
</tr>
<tr>
<td>Kirkpatrick³⁰</td>
<td>2003</td>
<td>Canada</td>
<td>Prospective</td>
<td>CT (4 row MD, biphasic mesenteric CTA)</td>
<td>62</td>
<td>42% (26/62)</td>
<td>21/41</td>
</tr>
<tr>
<td>Matsumoto¹⁸</td>
<td>2014</td>
<td>Japan</td>
<td>Prospective</td>
<td>serum i-FABP</td>
<td>208</td>
<td>12% (24/208)</td>
<td>132/76</td>
</tr>
<tr>
<td>Murray¹⁴</td>
<td>1994</td>
<td>USA</td>
<td>NA</td>
<td>serum D-Lactate</td>
<td>31</td>
<td>29% (9/31)</td>
<td>NA</td>
</tr>
<tr>
<td>Ofer³¹</td>
<td>2009</td>
<td>Israel</td>
<td>Prospective</td>
<td>CT (16 row MD, biphasic mesenteric CTA)</td>
<td>91</td>
<td>20% (18/92)</td>
<td>42/51</td>
</tr>
<tr>
<td>Wiesner³²</td>
<td>2004</td>
<td>Switzerland</td>
<td>Prospective</td>
<td>CT (4 row MD, biphasic mesenteric CTA in 4 patients suspected of intestinal ischemia)</td>
<td>291</td>
<td>8% (24/291)</td>
<td>11/13</td>
</tr>
</tbody>
</table>

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- a Not reported
- b Four patients were excluded, gender distribution was reported for the originally 79 included patients
- c 93 studies included in 91 patients, 1 study excluded because of technical problems, therefore analysis based on 92 studies
- d Only reported in patients with final diagnosis of acute intestinal ischemia
### TABLE 2. Patient selection and used reference standard

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient selection</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acosta(^{20})</td>
<td>Clinical suspicion of acute intestinal ischemia</td>
<td>Surgery/pathology (n=6)(^{a})</td>
</tr>
<tr>
<td>Acosta(^{21})</td>
<td>Acute abdominal pain with acute intestinal ischemia in differential diagnosis, sampling within 24 hours of onset of pain, over age of 50 and VAS score ≥5</td>
<td>Surgery/pathology (n=48), clinical follow up (n=53)</td>
</tr>
<tr>
<td>Akyildiz(^{27})</td>
<td>Clinical suspicion acute intestinal ischemia evaluated by a surgeon.</td>
<td>Surgery/pathology (n=40), clinical follow up (n=7)</td>
</tr>
<tr>
<td>Aschoff(^{28})</td>
<td>Clinical suspicion of acute intestinal ischemia presenting with acute abdominal pain evaluated by either an internist or a surgeon</td>
<td>Surgery/pathology (n=45), clinical follow up (n=34)</td>
</tr>
<tr>
<td>Block(^{13})</td>
<td>Acute abdominal pain, sampling within 24 hours of onset of pain and VAS score ≥5</td>
<td>Surgery/pathology (n=28), clinical follow up (n=43)</td>
</tr>
<tr>
<td>Chui(^{29})</td>
<td>Clinical suspicion of acute intestinal ischemia presenting with acute abdominal pain</td>
<td>Surgery/pathology (n=17), clinical follow up (n=5)(^{a})</td>
</tr>
<tr>
<td>Kirkpatrick(^{30})</td>
<td>Clinical suspicion of acute intestinal ischemia presenting with acute abdominal pain evaluated by a surgeon</td>
<td>Surgical/pathology (n=28), clinical follow up (n=34)</td>
</tr>
<tr>
<td>Matsumoto(^{18})</td>
<td>Clinical suspicion acute intestinal ischemia after abdominal CT scan</td>
<td>Surgery/pathology (n=116), clinical follow-up (n=92)</td>
</tr>
<tr>
<td>Murray(^{14})</td>
<td>Acute abdominal surgery including suspected acute intestinal ischemia</td>
<td>Surgery/pathology (n=31)</td>
</tr>
<tr>
<td>Ofer(^{31})</td>
<td>Clinical suspicion acute intestinal ischemia ischemia presenting with acute abdominal pain (76 emergency department, 26 hospital ward) evaluated by surgical resident or surgeon</td>
<td>Surgery/pathology (n=30), clinical follow up (n=61)</td>
</tr>
<tr>
<td>Wiesner(^{32})</td>
<td>Acute/subacute abdominal pain</td>
<td>Surgery/pathology (n=16), clinical follow up (n=8)(^{a})</td>
</tr>
</tbody>
</table>

\(^{a}\) Only reported for the patients with a final diagnosis of acute intestinal ischemia
Different cut-off values were used in the two studies that evaluated D-lactate. Murray et al used a cut-off value of >22.2 mmol/L (200mg/dl)\(^\text{14}\) and Block et al used cut-off of ≥0.20 mmol/L (1.8mg/dl)\(^\text{13}\) to construct a 2x2 table. Differences in cut-off values were also seen in the studies evaluating D-dimer. Acosta et al used a cut-off value of >0.3mg/L in his two studies\(^\text{20,21}\), Chui et al >1.0mg/L\(^\text{29}\), Akyildiz et al >3.17mg/L\(^\text{27}\) and Block et al calculated diagnostic accuracy for three different cut-off values >0.3mg/L, >0.6mg/L and ≥0.9mg/L\(^\text{13}\).

All CT studies used a multi-detector CT-scanner with between four and 40 detector rows. A standard mesenteric arterial phase was performed in four out of five studies\(^\text{27,28,30,31}\), whereas in the study by Wiesner et al only patients with clinical suspicion of acute intestinal ischemia underwent a mesenteric CTA\(^\text{32}\).

Figure 3 displays scores for each individual item of the QUADAS tool of the included studies. The studies showed a similar pattern in items that did not score well. No study reported the duration of the follow up period or the median time to surgical verification of the diagnosis, leaving item 4 to be scored as unclear in all cases. Most of the studies did not report if the index test result influenced the type of reference standard (item 6). No study explicitly reported that the reference standard was interpreted without knowledge of the index test (item 11). Finally, no study reported whether there were any uninterpretable or intermediate test results (item 13).

### Diagnostic accuracy

For D-lactate one study reported a sensitivity in detecting acute intestinal ischemia of 90% (95%CI: 60% to 98%) at a cut-off of ≥0.20 mmol/L.\(^\text{14}\) This is comparable to a sensitivity of 89% (95%CI: 57% to 98%) found by another study using a cut-off value of >22.2 mmol/L.\(^\text{13}\) Specificity differed between the two studies, 23% (95%CI: 14% to 35%) versus 86% (95%CI: 67% to 95%). Since there were only two studies, with different cut-off levels and substantial heterogeneity, we did not calculate summary estimates of sensitivity and specificity for D-lactate.

In one study i-FABP had an estimated sensitivity of 83% (95%CI: 64% to 93%) at a specificity of 89% (95%CI: 83% to 93%) with a cut-off value of 9.1 ng/ml. The original authors had based the optimal cut-off value from an receiver operating characteristics (ROC) curve.\(^\text{18}\)
TABLE 3. Diagnostic accuracy of individual studies evaluating D-dimer

<table>
<thead>
<tr>
<th>Author</th>
<th>Cut-off value (mg/L)</th>
<th>Ischemia/total patients (%)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV(^a) (95% CI)</th>
<th>NPV(^c) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acosta(^20)</td>
<td>&gt;0.3</td>
<td>6/14 (42%)</td>
<td>100% (61%-100%)</td>
<td>38% (14%-69%)</td>
<td>55% (28%-79%)</td>
<td>100% (44%-100%)</td>
</tr>
<tr>
<td>Acosta(^21)</td>
<td>&gt;0.3</td>
<td>9/101 (9%)</td>
<td>100% (70%-100%)</td>
<td>36% (27%-46%)</td>
<td>13% (7%-23%)</td>
<td>100% (90%-100%)</td>
</tr>
<tr>
<td>Akyildiz(^27)</td>
<td>&gt;3.17</td>
<td>28/47 (60%)</td>
<td>96% (82%-99%)</td>
<td>79% (57%-91%)</td>
<td>87% (71%-95%)</td>
<td>94% (72%-99%)</td>
</tr>
<tr>
<td>Block(^13)</td>
<td>&gt;0.3</td>
<td>10/71 (14%)</td>
<td>100% (72%-100%)</td>
<td>44% (33%-57%)</td>
<td>23% (13%-37%)</td>
<td>100% (88%-100%)</td>
</tr>
<tr>
<td>Block(^13)</td>
<td>&gt;0.6</td>
<td>10/71 (14%)</td>
<td>80% (49%-94%)</td>
<td>75% (63%-84%)</td>
<td>35% (19%-55%)</td>
<td>96% (86%-99%)</td>
</tr>
<tr>
<td>Block(^13)</td>
<td>≥0.9</td>
<td>10/71 (14%)</td>
<td>60% (31%-83%)</td>
<td>82% (71%-90%)</td>
<td>35% (17%-59%)</td>
<td>93% (82%-97%)</td>
</tr>
<tr>
<td>Chui(^29)</td>
<td>&gt;1.0</td>
<td>23/67 (34%)</td>
<td>96% (79%-99%)</td>
<td>18% (10%-32%)</td>
<td>38% (27%-51%)</td>
<td>89% (57%-98%)</td>
</tr>
</tbody>
</table>

\(^a\) 95% confidence interval (CI)  
\(^b\) Positive predictive value (PPV)  
\(^c\) Negative predictive value (NPV)
Table 4. Diagnostic accuracy of individual studies evaluating CT

<table>
<thead>
<tr>
<th>Author</th>
<th>Ischemia/total patients (%)</th>
<th>Sensitivity (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Specificity (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PPV&lt;sup&gt;b&lt;/sup&gt; (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NPV&lt;sup&gt;c&lt;/sup&gt; (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akyildiz&lt;sup&gt;27&lt;/sup&gt;</td>
<td>28/47 (60%)</td>
<td>93% (77%-98%)</td>
<td>89% (69%-97%)</td>
<td>93% (77%-98%)</td>
<td>89% (69%-97%)</td>
</tr>
<tr>
<td>Aschoff&lt;sup&gt;28&lt;/sup&gt;</td>
<td>28/75 (37%)</td>
<td>96% (82%-99%)</td>
<td>98% (89%-100%)</td>
<td>96% (82%-99%)</td>
<td>98% (89%-100%)</td>
</tr>
<tr>
<td>Kirkpatrick&lt;sup&gt;30&lt;/sup&gt;</td>
<td>26/62 (42%)</td>
<td>100% (87%-100%)</td>
<td>89% (75%-96%)</td>
<td>87% (70%-95%)</td>
<td>100% (89%-100%)</td>
</tr>
<tr>
<td>Ofer&lt;sup&gt;31&lt;/sup&gt;</td>
<td>18/92 (20%)</td>
<td>89% (67%-97%)</td>
<td>97% (91%-99%)</td>
<td>89% (67%-97%)</td>
<td>97% (91%-99%)</td>
</tr>
<tr>
<td>Wiesner&lt;sup&gt;32&lt;/sup&gt;</td>
<td>24/291 (8%)</td>
<td>79% (60%-91%)</td>
<td>99% (97%-100%)</td>
<td>90% (71%-97%)</td>
<td>98% (96%-99%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 95% confidence interval (CI)

<sup>b</sup> Positive predictive value (PPV)

<sup>c</sup> Negative predictive value (NPV)
FIGURE 3.

The grouped bar chart displays the cumulative score of the 11 included studies for each of the 14 QUADAS questions. The proportion of the bar that is white (■) represents that the answer to the question was ‘Yes’ (good quality), the grey bar (□) is ‘Unclear’ and the black bar (▲) is ‘No’ (low quality).

QUADAS Questions:
1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between surgery (histopathology) and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/intermediate test results reported?
14. Were withdrawals from the study explained?
Reported sensitivity of D-dimer ranged from 60% to 100% with a specificity between 18% and 79% in 5 studies, which had used different cut-off values (table 3). Because of these different cut-off values, we did not calculate summary estimates for D-dimer.

Mesenteric ischemia was found in 124 of 571 (22.%) patients in the studies that evaluated CT accuracy. Reported estimates of CT sensitivity ranged from 79% to 100%, and from 89% to 99% for specificity (table 4). We calculated a mean sensitivity of CT of 91% (95%CI: 80% to 98%) at a specificity of 94% (95%CI: 87% to 99%). The $I^2$ values for sensitivity and specificity were 24% (95%CI: 0% to 88%) and 76% (95%CI: 0% to 96%) respectively, demonstrating substantial heterogeneity for the specificity but not the sensitivity between included studies.

DISCUSSION

Based on a systematic review of the available evidence, CT is the most widely evaluated modality used in the work-up of patients presenting at the ED with suspicion of acute intestinal ischemia, with the best diagnostic accuracy. Five studies were included reporting the accuracy of D-dimer showing good sensitivity but at a wide range of specificity, probably also due to the different cut-off levels. The two studies evaluating D-lactate reported good sensitivity but varied in specificity. One study evaluated i-FABP having reasonable sensitivity at a reasonable to good specificity. For the other steps in the work-up limited data were available.

We did not identify studies that had resulted in estimates of the diagnostic accuracy of the clinical diagnosis, MRI or angiography. For angiography, for example, only outcomes of series of patients selected for angiography have been published, but not accuracy data from a population of patients suspected of intestinal ischemia. Therefore, test parameters such as sensitivity and specificity cannot be calculated for other diagnostic modalities than assessed in this systematic review.

Previous studies have evaluated diagnostic accuracy of components of the diagnostic work-up for intestinal ischemia. Three systematic reviews evaluated diagnostic accuracy of laboratory tests (L-lactate, D-lactate, i-FABP and D-dimer) in intestinal ischemia. In evaluating L-lactate one of the systematic reviews included four studies, while the other two reviews included two studies. If the included studies from these three published reviews are combined leaving out duplications, a total of five studies have evaluated diagnostic accuracy of L-lactate but none were included in present systematic review. Three of these five studies...
were not included in present review because the authors did not report a cut-off value at which they calculated the diagnostic accuracy.\textsuperscript{33-35} Another study only included patients with strangulated bowel.\textsuperscript{36} The fifth study constituted mainly of in-hospital patients after major surgery and the selection criteria of the remaining patients was not specified.\textsuperscript{37} Four studies evaluating D-lactate were included overall in the three published systematic reviews. We included only two of the four studies, similar to Acosta et al and Cudnik et al.\textsuperscript{13,14} Evenett et al included the two other studies also, which were excluded here because of solely including patients after aortic reconstruction.\textsuperscript{15,16} For i-FABP a total of four studies were included in the three previous reviews. None of these studies were included in this review because one of the studies only evaluated ICU patients\textsuperscript{38}, another evaluated a mixed patient population of in-hospital patients and patients presenting with acute abdominal pain whom could not be differentiated.\textsuperscript{19} The other two studies were not included because the patients had strangulated small bowel with ischemia\textsuperscript{36} and bowel obstruction with accompanying ischemia.\textsuperscript{39} We included a different study, published after the previous reviews had been published. Seven studies were included in the three previous reviews evaluating D-dimer. Five of those are also included in this review. One of the remaining two studies was not included because only patients with strangulated bowel had been included.\textsuperscript{40} The other study did not report enough data to construct a 2x2 contingency table.\textsuperscript{41} Evenett et al and Cudnik et al performed summary estimates of diagnostic accuracy of the laboratory tests.\textsuperscript{22,24} In our opinion pooling the results from studies with heterogeneous populations will not reflect the actual diagnostic accuracy that these serum markers have in the ED. Furthermore, the studies included in their reviews used different cut-off values making extrapolation to the summary results methodologically incorrect.

Summarized diagnostic accuracy of CT is comparable to two other studies evaluating CT but using different study selection criteria. Menke et al found a sensitivity of 93\% at a specificity of 96\% including six studies.\textsuperscript{7} The study that was not included in this review did not differentiate between patients with acute abdominal pain presenting to the ED and those in-hospital or post-operatively.\textsuperscript{42} This was also the reason not to include three studies that were included by Cudnik et al.\textsuperscript{43-45} They included eight studies evaluating CT with a summarized sensitivity of 94\% at a specificity of 95\%.

Since the aim of this review was to aid the clinician confronted with a patient suspected of acute intestinal ischemia in the ED we applied some specific selection criteria. Numerous studies evaluating diagnostic entities in acute intestinal ischemia mix outpatients with...
an acute presentation at the ED with groups of patients in a postoperative setting after cardiovascular operations. The presentation and pre-test probability differ substantially, which influences the diagnostic accuracy of the different steps in the diagnostic pathway. For example, many postoperative situations with decreased tissue oxygenation also result in increased lactate levels. Studies who might have evaluated patients presenting with acute abdominal complaints but who did not specify their patient selection process were excluded; potentially missing valuable scares data in meta-analysis of a rare condition. Studies evaluating diagnostic test accuracy in patients presenting with obstructed or strangulated bowel leading to ischemia of the intestine were also not included. We additionally excluded studies that did not allow reconstruction or extraction of a complete 2x2 contingency table. Since acute intestinal ischemia is a rare condition, numerous studies are designed retrospectively. A large proportion of studies that were excluded only evaluated patients with surgery or pathology proven acute intestinal ischemia. In these patients the diagnostic accuracy is evaluated by presenting sensitivity, whereas specificity is unknown, inherent to the patient selection. By excluding these studies we lose information about the characteristics of the diagnostic modality. However, in the ED the clinician is interested in how often, within the population of suspected (but not confirmed) patients, a patient with a positive test result indeed has acute intestinal ischemia (positive predictive value). In the case of acute intestinal ischemia it may be even more important for the clinician to know how many patients with a negative test result do have ischemia (missed cases or 1-negative predictive value). To calculate these test characteristics both sensitivity and specificity need to be reported. Unfortunately the lack of cut-off analysis made it impossible to construct 2x2 tables in several studies evaluating L-lactate. Therefore diagnostic accuracy could not be calculated in any study for L-lactate. In the past studies evaluating L-lactate in patients with acute abdominal pain suspected of acute intestinal ischemia show limited discriminatory capacity of serum levels to distinguish between intestinal ischemia and other diseases.18,19,46 Strength of this systematic review in comparison with other previously published reviews is that we differentiated between patient populations at risk for acute intestinal ischemia. For the clinician in the ED confronted with patients with acute abdominal this differentiation from post-operative patients is pivotal to interpret the reported diagnostic accuracy of each available step in the diagnostic work-up. D-lactate and D-dimer have promising sensitivity but poor to moderate sensitivity. Nevertheless, adoption of these results in difficult in practice because totally different cut-off values of D-lactate and D-dimer were used to calculate
sensitivity and specificity. Diagnostic accuracy of i-FABP also remains promising, based on the one study so far that has evaluated patients with acute abdominal pain presenting to the ED with suspected intestinal ischemia. Furthermore, as with D-lactate routine testing of i-FABP is not readily available in most emergency departments. Unfortunately the available evidence did not provide firm evidence for each routinely used step of the diagnostic work-up. For now, there is limited evidence that other diagnostic modalities than CT have additional value to improve diagnostic accuracy in the work-up of patients presenting at the ED suspected of acute intestinal ischemia. D-lactate, i-FABP and D-Dimer could turn out to be of adjunct, once properly studied.
REFERENCES

… in the common work-up of suspected acute intestinal ischemia.


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