

REVIEW

Accuracy of Routine Endoscopy Diagnosing Colonic Ischaemia After Abdominal Aortic Aneurysm Repair: A Meta-analysis

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WHAT THIS PAPER ADDS

This paper presents a comprehensive overview of the diagnostic value of endoscopy in colonic ischaemia (CI) after aneurysm surgery. The 12 prospective studies included in this review showed that endoscopy is an accurate tool in ruling out CI rather than diagnosing the presence of the clinically relevant transmural CI. Endoscopy is a **safe** diagnostic test as none of the studies reported adverse events. The decision whether an exploratory laparotomy is necessary should also include the presence of pre- and post-operative risk factors of patients suspected of CI.

Background: Colonic ischaemia (CI) is a devastating complication after abdominal aortic aneurysm (AAA) surgery. The aim of this review was to evaluate the diagnostic test accuracy of routine endoscopy in diagnosing CI after treatment for elective and acute AAA.

Patients and methods: The Pubmed and Embase database searches resulted in **1188 articles**. Prospective studies describing routine post-operative colonoscopy or sigmoidoscopy after elective or emergency AAA repair were included. The study quality was assessed with the QUADAS-2 tool. Sensitivity and specificity forest plots were drawn. Diagnostic odds ratios were calculated by a random effect model.

Results: Twelve articles were included consisting of **718 AAA patients** of whom **44%** were treated **electively**, 56% ruptured and, 6% by endovascular repair. Of all patients, 20.8% were identified with CI (all grades), and **6.5%** of patients had **Grade 3 CI**. The pooled diagnostic odds ratio for all grades of CI on endoscopy was 26.60 (95% CI 8.86–79.88). The **sensitivity and specificity of endoscopy** for **detection of Grade 3 CI after AAA repair** was **0.52** (95% CI, 0.31–0.73) and **0.97** (95% CI 0.95–0.99) respectively. The **positive post-test probability is up to 60%** in all kinds of AAA patients and 68% in ruptured AAA patients.

Conclusion: **Routine endoscopy is highly accurate** for **ruling out** CI after AAA repair. Clinicians should be aware that endoscopy is **less accurate** in diagnosing the presence of the **clinically relevant transmural** CI. Endoscopy is a **safe** diagnostic test to use **routinely** as none of the studies reported adverse events.

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Article history: Received 30 August 2017, Accepted 8 February 2018, Available online 17 March 2018

Keywords: Abdominal aortic aneurysm, Aortic rupture, Colonic ischaemia, Colonoscopy, Laparotomy, Endovascular procedures

INTRODUCTION

Colonic ischaemia (CI) is a rare but severe and potentially fatal complication after abdominal aortic aneurysm (AAA) repair. Recent reports have shown an **incidence** of clinically significant CI of **1.4–2.8%** after **elective** repair of an **AAA**

and even **higher** after **ruptured AAA**.^{1–4} CI can raise the mortality more than sevenfold after emergency repair compared with elective repair.⁵ Open repair, emergency repair, peri-operative hypotension, abdominal compartment syndrome, and female sex are known risk factors for developing CI after AAA repair.

To lower the mortality after AAA repair, the **early diagnosis of CI is important** to allow for prompt and timely treatment of CI.⁶ Different tests have been studied to determine the presence of CI but most lack specificity.^{7–10} **Bloody diarrhoea** or **early** passage of **stool** occurred only in just over **half** of patients with transmural CI which makes

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<https://doi.org/10.1016/j.ejvs.2018.02.008>

clinical assessment very challenging. Moreover, measuring intra-abdominal pressure or sigmoid intramural pH did not correlate sufficiently with the occurrence of CI.

The **diagnostic test most frequently used** for diagnosing CI is **sigmoidoscopy** or **colonoscopy**. The majority of CI diagnosed on endoscopy will not involve transmural CI and will resolve with supportive care. However, **full thickness CI** may lead to colonic perforation and associated increased mortality and thus **necessitates immediate diagnosis and treatment**.

The aim of this review was to evaluate the diagnostic test accuracy of routine endoscopy in diagnosing CI after treatment for AAA, in both the elective and emergency setting.

METHODS

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹¹ and the Cochrane handbook for diagnostic test accuracy reviews.¹²

Objective

The study objective was divided in three key questions to improve full clinical comprehension.

Key question 1: What is the value of endoscopy (all grades) to diagnose CI confirmed at positive laparotomy or CI related death in AAA patients?

Key question 2: What is the value of Grade 3 CI (transmural) at first post-operative endoscopy confirmed at positive laparotomy or confirmation of CI on post-mortem in AAA patients?

Key question 3: What is the value of Grade 3 CI (transmural) at first post-operative endoscopy confirmed at positive laparotomy or confirmation of CI on post-mortem in ruptured AAA patients?

Data sources

PubMed and Embase were searched up to March 1, 2017, identifying eligible studies. The search strategy was formulated with the assistance of a clinical librarian (see [Supplementary material 1](#)). Medical subject heading¹³ terms and additional free entry terms for the patient groups (patients with an AAA, ruptured or elective, treated endovascular or with open surgery), the diagnostic test and result (endoscopy with CI), the reference standard (laparotomy), and outcome (sensitivity and specificity) were used. The references of the selected papers were reviewed for the completion of the list of articles eligible for full text assessment.

Study selection

Two investigators (G.v.M. and G.M.) individually reviewed 1188 titles and abstracts. Discrepancies were resolved through consensus and consultation with the last author. Pre-specified inclusion and exclusion criteria in the research protocol were used to select potentially eligible studies for

full text analysis. Inclusion of a study followed if the study used prospective data and performed at least one mandatory (routine) endoscopy after AAA repair. Acute and electively treated AAA patients were included as well as open and endovascular treated AAA patients. Both colonoscopy and sigmoidoscopy based studies were included. The endoscopies had to be done in the same admission as the initial treatment of the AAA. The studies needed to include at least 10 patients. There was no restriction in the year of publication or language of the study. The process of study inclusion was summarised in a flow diagram with explanation of exclusion of studies mentioned.

Data extraction

The two investigators (G.v.M. and G.M.) independently extracted the necessary information from the eligible articles. The data were cross-checked, and any discrepancies were resolved by discussion between the two investigators. Some of the studies also reported on the grade of CI: Grade 1 was defined as mucosal ischaemia; Grade 2 was defined as mucosal ischaemia and involvement of the muscularis layer; and Grade 3 was defined as transmural ischaemia, gangrene, and perforations.¹⁴ If any of the main variables were missing or not reported separately for AAA patients and aortic occlusive disease the authors of that particular study were contacted.

Quality assessment

The methodological quality of the included studies was independently assessed by two investigators (G.v.M. and G.M.). The quality assessment tool for diagnostic accuracy studies guidelines (QUADAS-2)¹⁵ was used to judge the risk of bias and applicability of the studies for the research question. Patient selection, the index test, the reference standard, and flow and timing were included in this assessment.

Data synthesis and analysis

Sensitivity and specificity forest plots were drawn using RevMan version 5.3.3¹⁶ per key question. Pooled sensitivities and specificities were calculated using 2×2 contingency tables and reported to show an estimation of the direction of the trend. Heterogeneity was investigated using the I^2 statistic and interpreted as follows: 0–40% was considered not to be important, 30–60% represented moderate heterogeneity, 50–90% represented substantial heterogeneity, 75–100% indicated considerable heterogeneity.¹⁷ The heterogeneity of the included studies was also visually drawn for all analyses in hierarchical summary receiver operating characteristics (HSROC). Publication bias was tested using the linear regression method and funnel plot of Deeks et al.¹⁸ A p value $< .05$ in this linear regression model indicated potential publication bias.

For the three key questions the pooled odds ratios were calculated using a random effect model because there was moderate heterogeneity between studies. Weighted estimates for each study were calculated and illustrated in a

forest plot. To evaluate the meaning of a positive or negative test result the pre-test probability, and positive and negative post-test probability were calculated and shown in a bar chart. All tests were two sided with a $p < .05$ indicating statistical significance. Meta-analyses were performed using STATA version 13.0 (StataCorp, College Station, TX, USA).

RESULTS

The search strategy identified 1188 potential studies after excluding duplicate records. Twelve prospective cohort studies met the inclusion criteria for the final analysis (Fig. 1).^{6,10,14,19–27} The studies included a total of 845 aortic surgery patients of which 718 were aneurysm patients (elective 44%, ruptured 56%). No randomised controlled trials were identified. The full overview of study variables is shown in Table 1. Included patients were 86.6% male with a mean age of 69.5 years. Only one study included patients treated exclusively endovascularly (44 patients). All patients underwent a routine sigmoidoscopy or colonoscopy post-operatively (median time 3 days, range 1–13 days). At endoscopy 20.8% patients were identified with CI (all grades); 6.5% of patients had Grade 3 CI. Sixty-eight percent of patients with Grade 3 CI underwent a laparotomy. A resection or confirmation of transmural CI was reported in

74% of all laparotomies performed. The reported CI related death rate was 3.7% (20/546, 9 studies). This accounts for 24.2% of the total 30 day mortality (16/66, 6 studies).

Quality assessment, heterogeneity, and publication bias

The quality assessment of all included studies is shown in Fig. 2. Some studies included not only patients with an aneurysm but also occlusive aortic disease, which accounts for the higher risk of bias assessment in patient selection. However, the results were mostly reported separately for both types of patients in these studies. The general risk of bias and applicability was deemed to be low in the included studies. The heterogeneity chi square statistic was 3.70 ($p = .079$) and the I^2 statistic was 46% (95% CI 0–100), which indicate moderate heterogeneity that is to be expected in a diagnostic accuracy test review.¹² In Fig. 3 the HSROC per key question is shown to visually interpret the heterogeneity as well. Significant evidence of publication bias was found ($p = .001$, Supplementary material 2) by using the linear regression method of Deeks et al.¹⁸

Key questions

In Fig. 4 the forest plots of sensitivities and specificities related to the three key questions is shown. These forest

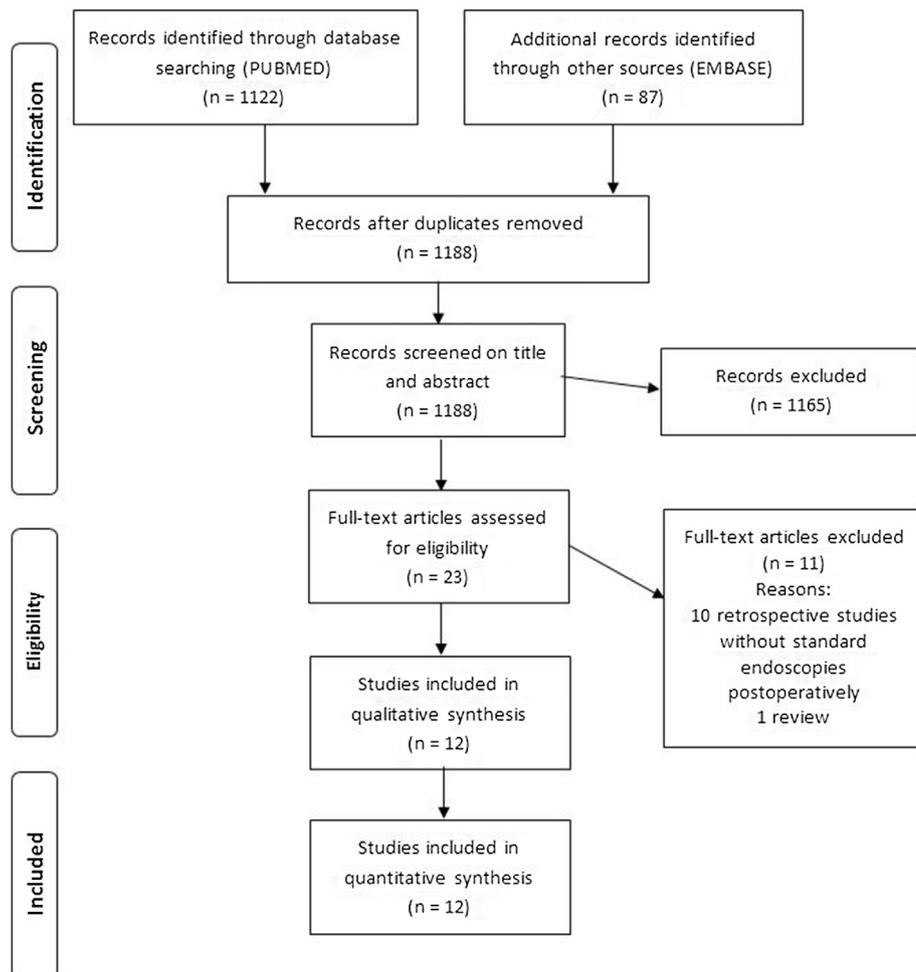


Figure 1. PRISMA flow diagram of study selection.

Table 1. Study characteristics and outcomes of the included studies.

Variables studies	Study duration	Number of patients	AAA surgery			Colonoscopy AAA patients			Time after surgery	Laparotomy AAA patients	30 day mortality AAA patients
			Total AAA surgery	Non-ruptured	Ruptured	N (%)	CI (n) with grades ^a	N			
Assadian 2008	Jan 1999–Dec 2003	100	100	N/A	N/A	100 (100%)	13 9 Gr 1–2 4 Gr 3	3–6 days	1	1	N/A
Bast 1990 ^e	Jan 1986–Jul 1987	107	107	69	38	100 (100%) ^b	9 6 Gr 1–2 3 Gr 3	Days 2 and 4	3	1	N/A
Champagne 2004	Jul 1995–Sep 2002	88	88	0	88	62 (86%) ^b	24 18 Gr 1–2 6 Gr 3	<48 h	9	9	24% (21/88)
Champagne 2007	Jan 2002–Jan 2006	44	44 (all EVAR)	0	44	36 (92%) ^b	8 6 Gr 1–2 2 Gr 3	<24 h	3	3	N/A
Ernst 1976	N/A	50	27	25	2	27 (100%)	2	<4 days	0	0	3.7% (1/27)
Fanti 1997	May 1991–May 1994	105	105	88	17	105 (100%)	12	<3 days	0	0	N/A
Megalopoulos 2008	Mar 1999–Dec 2005	62	59	0	59	59 (100%)	19 16 Gr 1–2 3 Gr 3	<48 h + every 12 h	11	9	29.0% (18/62)
Scherpenisse and van Hees 1989 ^e	'2 years'	48	48 (4 TAAA)	25 (2 TAAA)	23 (2 TAAA)	48 (100%)	24 15 Gr 1–2 9 Gr 3	<4 days	4	1	14.6% (7/48)
Schiedler 1987	May 1985–Feb 1986	34	20	16	4	20 (100%)	9	<13 days mean 3.2 days	3	3	N/A
Tottrup 2013	Jan 2010–Sep 2011	51	41	0	41	41 (100%)	9 5 Gr 1–2 4 Gr 3	<24 h	2	2	33.3% (17/51)
Welch 1998	N/A	56	28	28	0	28 (100%)	16 ^d	<7 days	0	0	34% (19/56)
Zelenock 1989	1983–1986	100	58	N/A	N/A	58 (100%)	3	<48 h	3 ^c	0 ^c	2% (2/100)
Total	1976–2011	845 (12 studies)	718 (12 studies)	248/560 (44%, 10 studies)	312/560 (56%, 10 studies)	718 (12 studies)	148/718 (20.8%, 12 studies) Grade 3: 31/480 (6.5%, 7 studies)	Median 3 days (12 studies)	39/718 (5.4%, 12 studies)	29/718 (4.0%, 9 studies) 74.4% positive laparotomies	85/432 (19.7%, 7 studies)

AAA = abdominal aortic aneurysm; CI = colonic ischaemia; EVAR = endovascular aortic repair; TAAA = thoraco-abdominal aortic aneurysm.

^a Grades of CI; Grade 1 was defined as mucosal ischaemia; Grade 2 was defined as mucosal ischaemia and involvement of the muscularis layers; and Grade 3 was defined as transmural ischaemia, gangrene, and perforations.

^b Percentage of patients who survived long enough to be offered a colonoscopy, were not lost to follow up for other reasons.

^c Data according to all patients included in the study not only AAA patients.

^d The diagnosis of ischaemic colitis was determined by colonoscopy and histology.

^e Studies from the same hospital in which the included patients might have overlapped.

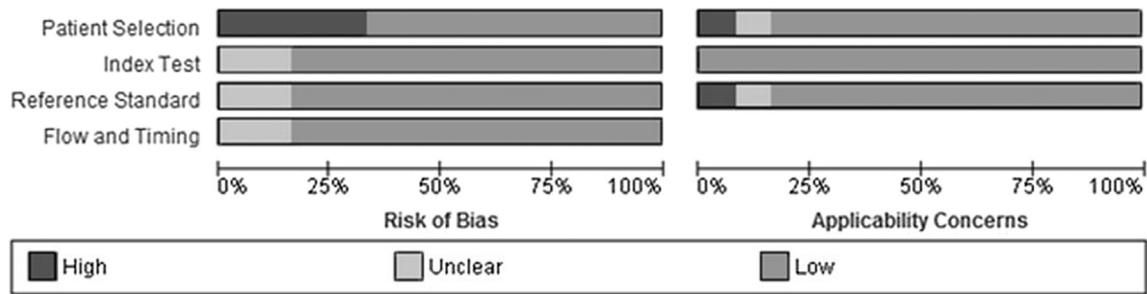


Figure 2. QUADAS-2 tool for quality assessment of the included studies for risk of bias and applicability concerns.

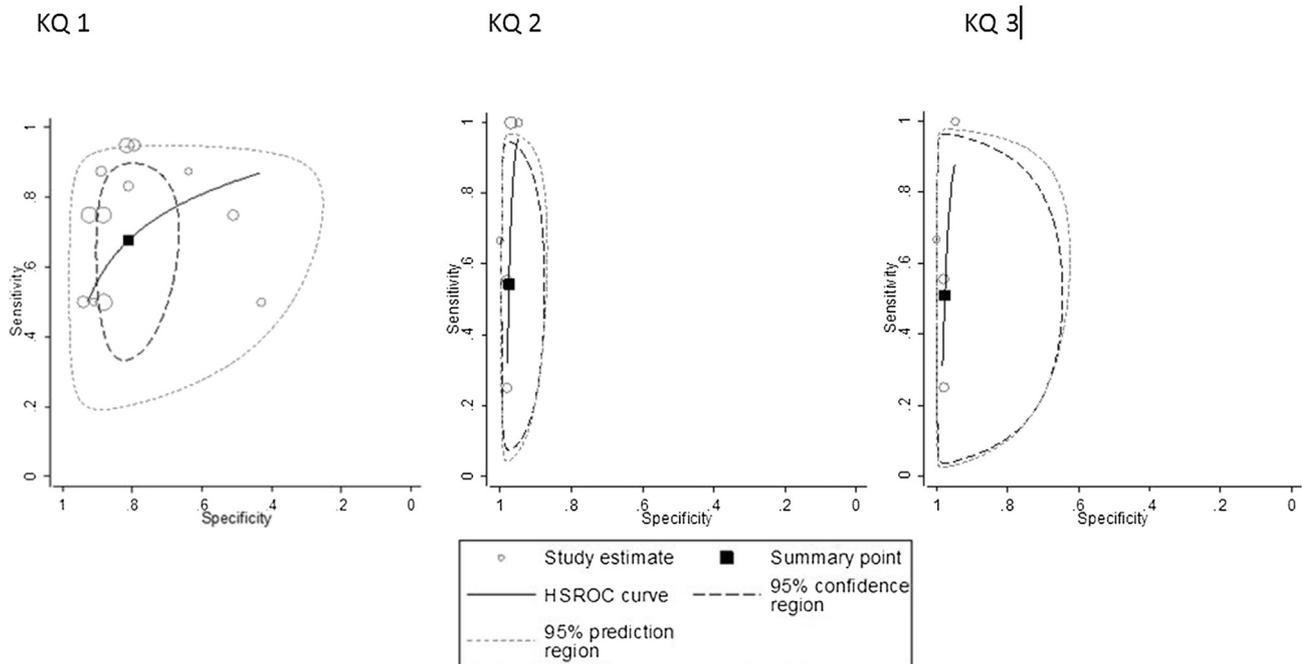


Figure 3. Hierarchical summary receiver operating characteristics (HSROC) per Key Question (KQ1–3). KQ1: all grades of CI on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in all AAA patients. KQ2: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in all AAA patients. KQ3: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in ruptured AAA patients. AAA = abdominal aortic aneurysm; CI = colonic ischaemia; HSROC = hierarchical summary receiver operating characteristics.

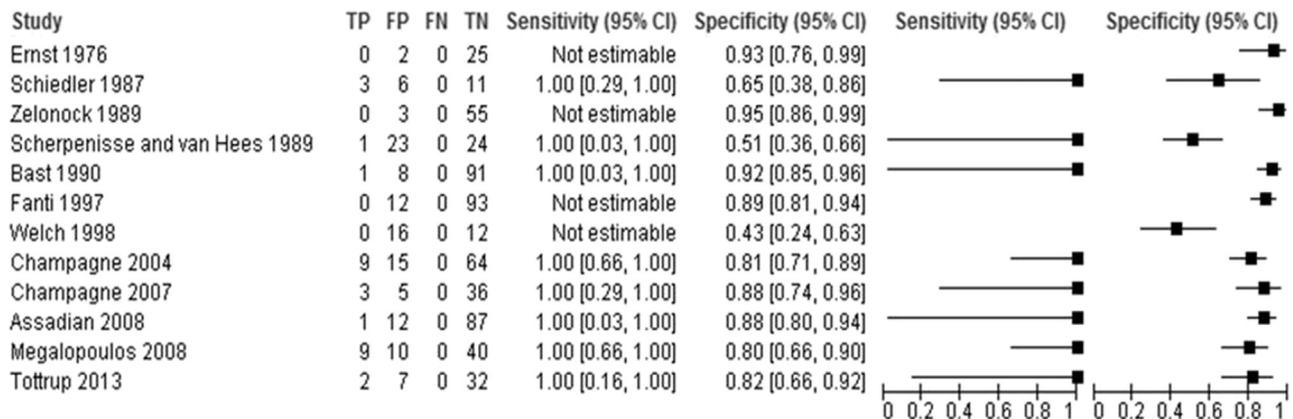
plots graphically show the differences in the sensitivities and specificities of the studies.

Key question 1: All grades of CI on colonoscopy confirmed at positive laparotomy or confirmation of CI on post-mortem in all AAA patients. To answer the first key question the estimated pooled sensitivity was 1.00 (95% CI 0.88–1.00) because no false negative test results were reported and the specificity was 0.83 (95% CI 0.80–0.86) (Fig. 4). The positive predictive value (PPV) for this test was 0.20 (95% CI 0.17–0.22) and the negative predictive value was 1.00. Some of the studies included only the final results of endoscopy since the endoscopy was repeated post-operatively. The pooled diagnostic odds ratio for all grades of CI on endoscopy was 26.60 (95% CI 8.86–79.88) as shown in Fig. 5. The diagnostic odds ratio reflects the diagnostic test accuracy of the index test and describes how many times higher the odds are of obtaining a positive test result in a diseased rather than a non-diseased person.¹²

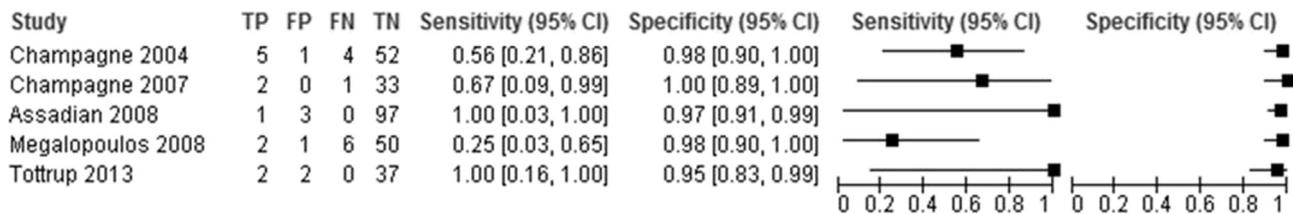
Key question 2: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on post-mortem in all AAA patients. The clinically more important second key question, to diagnose Grade 3 CI by endoscopy, showed an estimated pooled sensitivity of 0.52 (95% CI 0.31–0.73) and specificity of 0.97 (95% CI 0.95–0.99) (Fig. 4). The PPV was 0.63 (95% CI 0.43–0.80) and the NPV 0.96 (0.94–0.97). This corresponds with endoscopy being able to exclude CI reliably but in contrast, having a positive test result does not mean CI is definitely present in all cases. The pooled diagnostic odds ratio for Grade 3 CI on the first endoscopy was 50.40 (95% CI 13.89–182.89), which suggests good discriminative power of the test.

Key question 3: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on post-mortem in ruptured AAA patients. For ruptured AAA patients (KQ3) the estimated pooled sensitivity of the first endoscopy after repair was 0.50 (95% CI 0.28–0.72) with a

KQ1



KQ2



KQ3

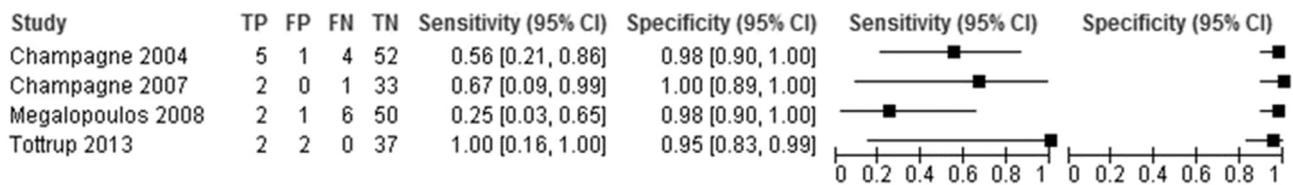


Figure 4. Forest plots of the sensitivities and specificities of the different key questions. KQ1: all grades of CI on colonoscopy confirmed at positive laparotomy or confirmation of CI on post-mortem in all AAA patients. KQ2: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in all AAA patients. KQ3: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in ruptured AAA patients. TP = true positives; FP = false positives; FN = false negatives; TN = true negatives.

specificity of 0.97 (95% CI 0.92–0.99) (Fig. 4). The PPV was 0.73 (95% CI 0.49–0.89) and the NPV 0.92 (95% CI 0.88–0.94). These results are quite similar to KQ2 as most studies included ruptured aneurysm patients. The pooled diagnostic odds ratio for Grade 3 CI on the first endoscopy in ruptured AAA patients was 47.78 (95% CI 12.09–188.81). There was no significant difference in the incidence of CI between patients treated endovascularly and those treated by open surgery for ruptured aneurysms (6.8% vs. 10.6% resp. $p = .58$). This non-significant difference could be explained by the small EVAR group that could be included in this review.

Pre- and post-test probabilities

To interpret the results of a positive or negative endoscopy after aneurysm repair the pre- and post-test probabilities were calculated (Fig. 6). This shows that having a positive endoscopy with any grade of CI, the chances of truly developing clinically relevant CI increase up to 22%. This is much higher if only Grade 3 is analysed, in which the

positive post-test probability goes up to 60% in both elective and ruptured AAA patients and 68% in ruptured AAA patients. The chance of developing Grade 3 CI when the first endoscopy was negative, decreases to 5% post-endoscopy for all types of AAA patients, and to 7% for ruptured AAA patients.

DISCUSSION

This review evaluated the diagnostic accuracy of routine post-operative endoscopy in diagnosing CI after AAA repair. Endoscopy shows a high negative predictive value for diagnosing CI but a less sufficient positive predictive value. Therefore endoscopy has a place in clinical practice ruling out CI when the suspicion arises but does not necessarily allow the clinician to link a positive result to immediate laparotomy. The most ideal timing for the first endoscopy appears to be between days 2 and 3 after initial treatment as most patients were diagnosed around this time in the included studies. Particularly for patients treated for a ruptured AAA, in whom the incidence is highest (10% in this

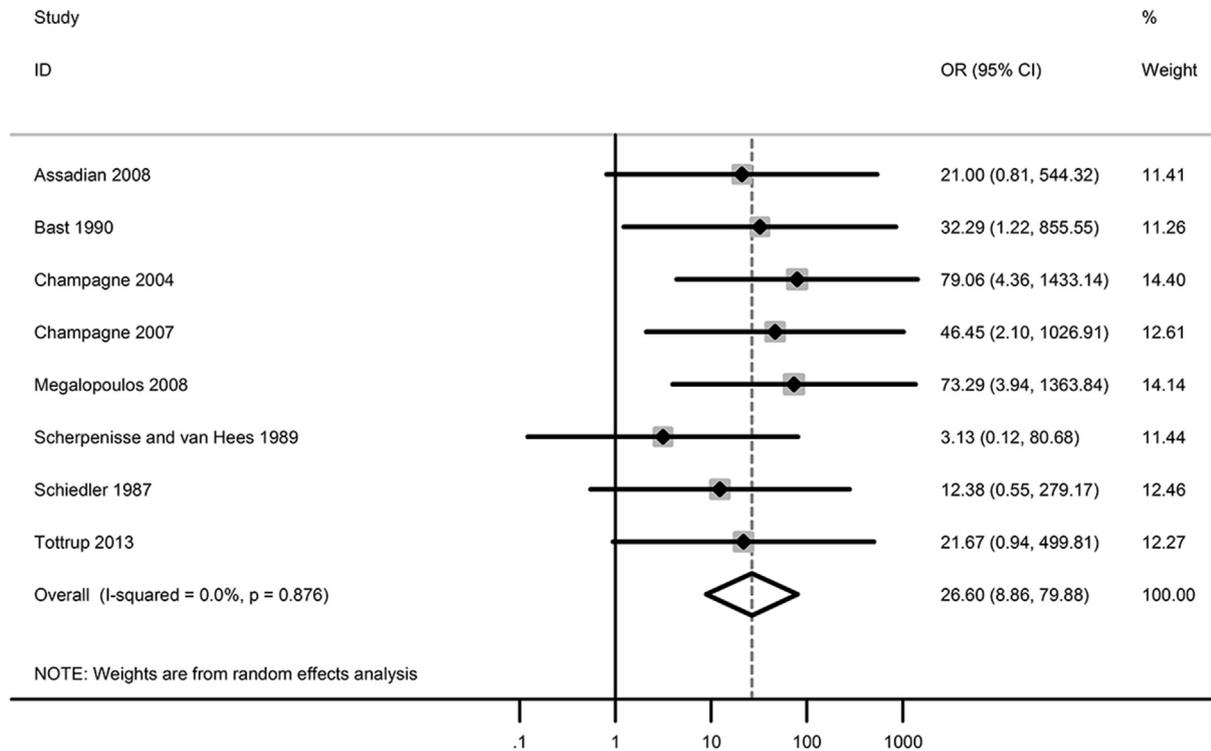


Figure 5. Pooled diagnostic odds ratios (OR) for Key Question 1: all grades of CI on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in all AAA patients. AAA = abdominal aortic aneurysm; CI = colonic ischaemia.

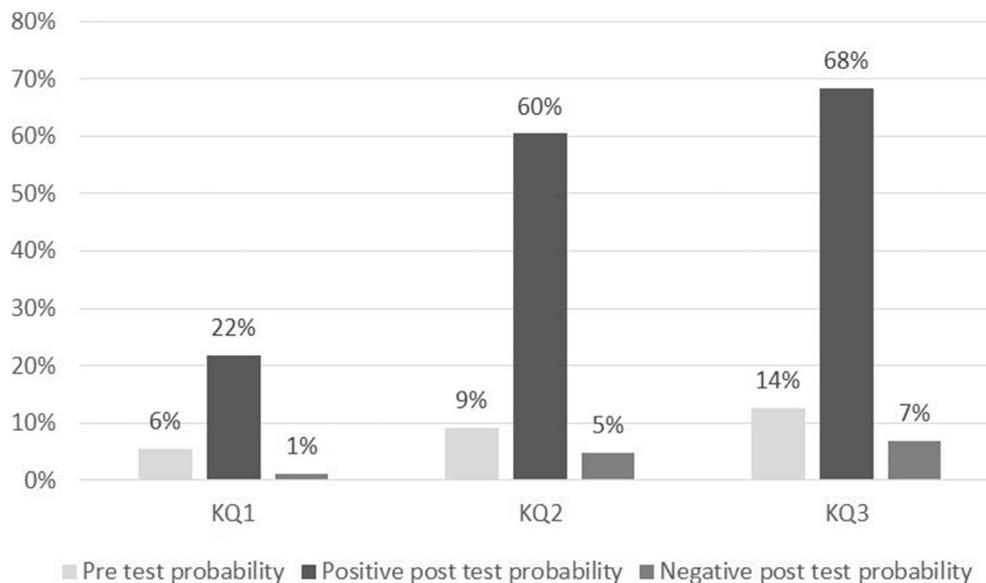


Figure 6. Pre- and post-test probabilities of the different Key Questions (KQ1–3). KQ1: all grades of CI on colonoscopy confirmed at laparotomy or confirmation of CI on postmortem in all AAA patients. KQ2: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in all AAA patients. KQ3: Grade 3 CI (transmural) on colonoscopy confirmed at positive laparotomy or confirmation of CI on postmortem in ruptured AAA patients. AAA = abdominal aortic aneurysm; CI = colonic ischaemia.

review), endoscopy has additional value to screen for CI. Additionally, none of the studies reported any adverse events due to the endoscopy. Therefore, the use of **routine endoscopy, especially in ruptured AAA patients, could be a safe method to screen for CI after repair as presenting symptoms of CI are frequently unreliable and non specific.**⁷

The reported overall pre-test probability in this review of 7% for CI is the combined incidence for elective and

emergency AAA repair and therefore higher compared with most elective AAA studies.⁴ Additionally, this reported incidence might be slightly higher than previously published cohorts because of the mandatory endoscopy protocol resulting in an overestimation of the clinically relevant transmural CI in whom intervention is necessary. Unfortunately, not enough data from the included studies were present to distinguish the value of endoscopy between

open and endovascularly treated patients reliably. Champagne et al.¹⁴ was the only study including endovascularly treated AAAs and showed an incidence of CI of 6.8% in ruptured AAA patients against 10.6% in the ruptured AAA patients treated by open surgery but this was not significantly different. Previous cohorts did show that the incidence of CI was significantly higher in patients treated by open repair than endovascular repair. No difference in CI incidence was shown in the AJAX or IMPROVE trial between the two treatment modalities for ruptured AAAs^{28,29} or elective endovascular and open AAA repair (DREAM trial; $n = 2$ after open vs. $n = 1$ after endo).³⁰

As endoscopy also identifies clinically less important ischaemic lesions the sensitivity is relatively low. **Endoscopy is insufficient to differentiate between severe mucosal ischaemia and clinically relevant transmural ischaemia.**³¹ Only a subsequent laparotomy can definitively confirm the presence of transmural ischaemia. A **quarter** of patients who underwent a **laparotomy** in this review had a **negative** laparotomy but it is unclear how this affected the morbidity and mortality in these patients.

It is important to realise the **mechanism** of developing CI after AAA repair is **multifactorial** and it is **suggested** to be caused by **ligation** of the inferior mesenteric artery (IMA) with **occluded** or **stenotic** internal iliac arteries,^{9,22} **hypoperfusion** in the acute setting and during aortic clamping,^{6,14,32} and abdominal **compartment syndrome**.⁸ Endoscopy might cause an extra risk of increased intra-abdominal pressure (IAP) due to insufflation. If the patient has a borderline IAP, CI may develop as a complication of the investigation, although this cannot be corroborated with data.

Other means to identify patients with CI or who are likely to develop it have previously been studied. Variables such as age, hypotension, ligation of hypogastric artery, aortic clamping time, open repair, and many more have been described as potential risk factors.^{4,6,9,27} A recent review including risk factors for CI could only identify open surgery and emergency repair as definite risk factors for CI.⁵ Champagne et al.¹⁴ showed that lactate was a good marker for CI, although this is contradicted by others.³² Furthermore, there is evidence that if lactate is used, plasma **D-lactate** is more reliable than total blood lactate.^{33,34} D-lactate is produced by colonic bacteria rather than the non specific L-lactate. The use of modalities like intramucosal pH and IMA stump pressure have not proven their additional worth.¹⁰

Diagnostic accuracy test reviews are generally affected by high heterogeneity and bias. In this review heterogeneity was attributable to different types of endoscopy, timing of the endoscopy after initial treatment (e.g., up to 13 days after AAA repair in the study of Schiedler et al.¹⁰) and the different thresholds for performing laparotomy. In addition to this, the publication date of the included studies was diverse. Also, according to the reported significant publication bias, studies that were not published due to negative results or other reasons could not be included in this review.¹⁵ From two of the included studies it remains unclear

if study cohorts overlap as they are from the same hospital. This would mean patients might have been included twice in this review.

As the incidence of CI is low, a large number of patients is necessary to reach sufficient statistical power. None of the included prospective studies mentioned a thorough power calculation to address this issue.

In conclusion, **routine endoscopy has a high accuracy to rule out CI after AAA repair and is safe.** Clinicians should be aware that endoscopy is less accurate in diagnosing the presence of clinically relevant transmural CI. The chance of truly having transmural CI after the diagnosis Grade 3 CI on endoscopy is 60% in contrast to only 5% when Grade 3 is not present on endoscopy. Endoscopy is a safe diagnostic test to use routinely as none of the studies reported adverse events. In future research a risk score might be developed to decide which patients would benefit most from endoscopy post-repair based on peri-operative risk factors. The decision whether a laparotomy is necessary should also include the presence of pre- and post-operative risk factors and comorbidities of patients suspected of CI.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejvs.2018.02.008>.

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