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Colon ischemia: Right-sided colon involvement has a different presentation, etiology and worse outcome. A large retrospective cohort study in histology proven patients

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A B S T R A C T

Background: Colon ischemia (CI), is generally considered a non-occlusive mesenteric ischemia disorder that usually runs a benign course, but right-sided involvement (RCI) has been associated with worse outcome. The poor outcome of RCI has been associated with comorbidity, but more recently also with occlusions of the mesenteric arteries. We performed a retrospective analysis of a large cohort of CI-patients to assess differences in presentation, etiology, and comorbidity between right-sided colon ischemia (RCI) and non-right-sided colon ischemia (NRCI), and their relation to outcome.

Methods: We performed a retrospective cohort study in two centers from 2000 to 2011 for CI and analyzed clinical presentation, etiology, treatment and outcome. Diagnosis was based on full colonoscopy and/or surgical findings and confirmed by histopathology.

Results: 239 patients were included (mean age 69, 52% female). RCI was found in 48% and NRCI in 52%. Patients with NRCI presented more often with rectal bleeding (87% vs. 45%; $p < 0.001$). In RCI more nausea (58% vs. 39%; $p = 0.013$), weight loss (56% vs. 19%; $p < 0.001$), paralytic ileus (32% vs. 18%; $p = 0.018$) and peritoneal signs (27% vs. 7%; $p < 0.001$) was observed compared to NRCI. The cause of CI was more often idiopathic in NRCI (46% vs. 26%; $p = 0.002$); an occlusive cause was seen more often in RCI (26.3 vs 2.4%, $p < 0.0001$).

RCI patients had longer hospital stay (15 vs. 8 days, $p < 0.001$), need for surgery (61% vs. 34%, $p < 0.001$), and trend toward higher 30-day in-hospital mortality (20% vs. 12%, $p = 0.084$).

Conclusions: RCI ischemia has different etiology, presentation, and outcome. The series shows a high proportion of – treatable – vessel occlusion. It reinforces the advice to perform CT angiography in RCI as means to improve its poor outcome.

Background

Colon ischemia (CI) is considered a form of ischemia without vessel occlusion (non-occlusive ischemia), in contrast to mesenteric ischemia in the stomach and small bowel, with often an occlusive nature [1]. CI is however the most prevalent ischemic disease of the gastrointestinal tract with incidence rates ranging from 4.5 to 44 cases per 100.000 person years [2–5]. As in all mesenteric ischemia, the incidence rises with age, in recent study from Minnesota from 1:100.000 in those <40 years of age to 107:100.000 in octogenarians [5]. The cause is not always known but can vary widely from hypoperfusion (low-flow), to local bowel obstructions, infections [6–8], or mesenteric vascular occlusions [9]. Typical presenting symptoms are an abrupt onset of abdominal cramping pain, and passage of bloody stools [10,11]. Diagnosis is usually made by endoscopy or during laparotomy, the latter in patients with severe

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peritonitis; histopathological confirmation is highly recommended [6]. Urgent CT scanning has been advocated [12] especially in RCI [6,9], but still seems to be performed in a minority of cases. The outcome is generally good, and was associated largely on comorbidity and age [10,13], with large differences between general and tertiary centers [14].

It has been repeatedly shown RCI is an independent risk factor for adverse outcome [10,11,15]. In a meta-analysis of all published series in CI, right sided involvement was the most significant predictor of disease severity and adverse outcome, even when taking age and comorbidity into account [16]. The cause of this association between RCI and poor prognosis is unknown, but it has been noted that the clinical presentation is often unspecific with a lower incidence of rectal bleeding [14]. After a recent study that reported an association between acute mesenteric infarction and RCI [17], more attention to right-sided colon ischemia has been given [6]. It was especially noted that, although data on vascular imaging in these patients was sparse, early CTA should be considered in RCI [9].

The importance of RCI was repeatedly encountered in Medisch Spectrum Twente, a nation-wide referral center for analysis and treatment of gastrointestinal ischemia. In our series of over 600 patients diagnosed with chronic or acute-on-chronic mesenteric ischemia over the last 15 years, CI was part of the clinical presentation in 30 patients (data not yet published). Most of these had RCI, and often were treated for suspected Crohn's disease or non-occlusive ischemia. In most cases, the ischemic cause of the colon disorder was not suspected until peritonitis developed, or the so-called inflammation did not respond to anti-inflammatory drugs. An earlier diagnosis and treatment would have been helpful in these cases. This observation triggered us to perform a study in two large regional centers assessing all patients diagnosed with CI. Our main question was whether RCI differs from NRCI in clinical presentation, etiology, especially vascular anatomic information when available, and treatment outcome.

Methods

Study design & selection of patients

We included patients diagnosed with CI between January 2000 and December 2011 at Medical Spectrum Twente, Enschede, and at Isala Clinics, Zwolle, The Netherlands. To identify patients, we performed a search in the pathology, endoscopy, and vascular surgery database. The pathology database (PALGA) is a pathology registry that contains data of all histological, cytological and autopsy examinations in the Netherlands. The endoscopy data are stored in Endosoft, an endoscopy software data program. Search terms were 'ischemia' or 'ischemic' in all colonoscopy reports. We also searched the database of the department of vascular surgery. The search terms were: 'mesenterial', 'splanchnic', and 'ischemic' and 'colitis' or 'colon'. The medical records of all these patients were retrieved to decide whether the diagnosis was indeed CI. Criteria for diagnosis of CI for this study were: 1) a colonoscopy or surgical evaluation of the entire colon with description of ischemic findings confirmed by 2) a pathology report from biopsy or large bowel resection proven or compatible with CI. The main exclusion criteria were the presence of an alternative diagnosis, no large bowel involvement, incomplete colonoscopy, and absence of pathological confirmation of ischemia.

Data collection

We collected demographic findings, the onset of symptoms, whether it occurred in- or out-of hospital, the in-hospital diagnostic delay (time from admission or onset of symptoms − time of diagnostic procedure), clinical history and current medication. The symptoms and findings of physical examination at presentation, and during admission were also recorded as well as endoscopy, radiology, surgery and pathology reports.

A thorough search of all charts was performed to identify specific precipitating causes. They were classified according to the categories: low-flow, occlusive disease (arterial or venous), postoperative, infectious (positive stool culture), secondary to other colonic pathology and idiopathic. In some patients, more than one trigger factor could be identified, for example in patients that had a hypovolemic period after surgery.

For the subgroup analysis of mesenteric artery stenosis, all radiologic reports were reviewed and re-evaluated by an experienced radiologist when the initial report included no statement about the mesenteric vascularization.

Colon segment involvement

The involved colon segments were derived from colonoscopy and surgery reports. Patients were categorized as RCI and NRCI according to the classification proposed by Brandt et al. [10]. RCI is diagnosed if the most proximal ischemic lesion is located proximal to the hepatic flexure. When the most proximal lesion is seen distal from the hepatic flexure, patients are classified as NRCI. The rationale behind this distinction is that branches of the superior mesenteric artery uniformly perfuse the RCI-region and ischemia may then be accompanied by extensive small bowel ischemia.

Pathology

Using the histopathology reports, biopsy findings were graded as evident ischemia or suspect for ischemia based on the conclusion of the pathologist, which was based on the well-described features [18]. Recently, this has been summarized in large nation-wide Spanish study. Apart from mucosal infarction, early signs of CI are loss of mucus-containing glands, loss of superficial cells, ghost cells (presence of cellular outline without content), hemorrhage and edema, or fibrin thrombi in the capillaries and venules. The early inflammatory changes consists of neutrophils, and is usually moderate, and there is absence of chronic inflammation (no glandular distortion, branching or regeneration). Later abnormalities may show superficial ulceration, more diverse inflammatory infiltration (but no chronicity) and crypt abscesses. Pseudomembranes can be seen, as well as haemosiderin-laden macrophages [11].

Treatment and outcome

Types of treatment were: 1) medical treatment 2) revascularization of main mesenteric arteries and 3) acute laparotomy (with or without bowel resection). Medical therapy mainly consisted of intravenous resuscitation and analgesics and/or antibiotics. Revascularization consisted of percutaneous or open revascularization. Acute laparotomy was defined as laparotomy to assess bowel vitality, and may include bowel resection. All operative procedures and 30-day mortality were recorded. An unfavorable outcome was defined as the 1) need for acute laparotomy for suspected gangrene, 2) death, or a combination of both. Performance of open surgery to perform revascularization alone was not recorded as unfavorable outcome. Finally, the hospital stay was recorded as the difference between time of admission or symptom presentation (in case of in-hospital onset) and the time of hospital discharge or death.

Statistical analysis

Data were collected in a Microsoft Excel database. Data were analyzed using SPSS for Windows (version 17.0). Continuous baseline descriptive variables were displayed as mean with Standard Deviation (SD) for normal distributed variables and in case of non-parametric variables as median with interquartile range (IQR). Categorical variables were presented as numbers with percentages. Differences between groups were evaluated using Chi-square test and Fisher's exact test for categorical data as appropriate, and Student's *t* test and Mann Whitney-U test for continuous data, dependent on whether data were normally distributed. We estimated 30-day in-hospital survival by using the Kaplan–Meier method. All results were considered statistically significant with a p value < 0.05.

Results

Patient characteristics

Our wide ('high sensitive') search identified 1099 patients (see Fig. 1). In 474 a diagnosis of CI was likely of whom 161 were excluded for incomplete colon assessment, and another 72 for lack of histopathological confirmation, and two for double count (once in each center). This left 239 CI subjects with complete colon assessment and histopathological confirmation. The mean age was 69.3 yr; range 20–92, 52% was female. In 114 (48%) RCI was seen, in 125 (52%) NRCI. The patient characteristics including their co-morbidities are displayed in Table 1. Apart from a slightly higher age in NRCI patients, no differences between both groups were found. We found no difference in medication use at presentation between RCI and NRCI patients. The median in-hospital diagnostic delay from onset of symptoms until diagnosis was 27.5 hours (25.0 hours for RCI and 28.5 hours for NRCI, $p = 0.839$.)

Clinical presentation

The clinical presentation is summarized in Table 2. The common presentation was abdominal pain, diarrhea, and rectal blood loss.

Table 1
Patient characteristics for RCI (right-sided colon ischemia) and NRCI (non-right-sided colon ischemia).

	RCI ($n = 114$)	NRCI ($n = 125$)	p Value RCI vs NRCI
Females	47.4%	56.8%	0.145
Age in yr. mean (SD)	68 (13)	71 (12)	0.029
Onset out of hospital	59.6%	70.4%	0.081
During hospitalization	40.4%	29.6%	
Co-morbidities			
Coronary artery disease	38.1%	28.8%	0.130
Peripheral artery disease	21.2%	26.4%	0.352
Cerebrovascular disease	12.4%	16.8%	0.337
Congestive heart failure	12.4%	8.8%	0.367
Atrial fibrillation	15.0%	9.6%	0.200
Heart valve disease	13.3%	6.4%	0.073
Hypertension	40.8%	48.0%	0.447
Diabetes mellitus	18.6%	12.0%	0.157
Hyperlipidemia	21.2%	14.4%	0.167
COPD	18.6%	17.6%	0.844
Chronic renal disease	6.2%	4.0%	0.440
Dialysis	1.8%	2.4%	0.735

There was no difference in RCI and NRCI for abdominal pain or diarrhea. Rectal blood loss, however, was seen more in NRCI patients (87.4% vs. 44.9%, $p < 0.001$). Other differences included a medical history of weight loss, seen more in RCI (55.6% vs. 18.8%, $p < 0.001$), as well as nausea (57.6% vs. 39.4%, $p = 0.013$). At physical examination RCI patients more often had signs of progressed ischemia with the presence of paralytic ileus (31.5% vs. 17.9%, $p = 0.018$) and peritonitis (27.1% vs. 6.7%, $p < 0.001$).

Endoscopic, per-operative and histological findings

In 146 patients (61.1%) the diagnosis was made by colonoscopy. A diagnostic laparotomy, without preceding endoscopy, was performed in the remaining 93 patients (38.9%). The distribution of colonic lesions is depicted in Fig. 2. The main endoscopic findings of CI are showed in Table 3. In NRCI more erythema (42.7 vs 21.4%) and submucosal bleeding (18.3 vs 3.6%, both $p = 0.010$) was seen,

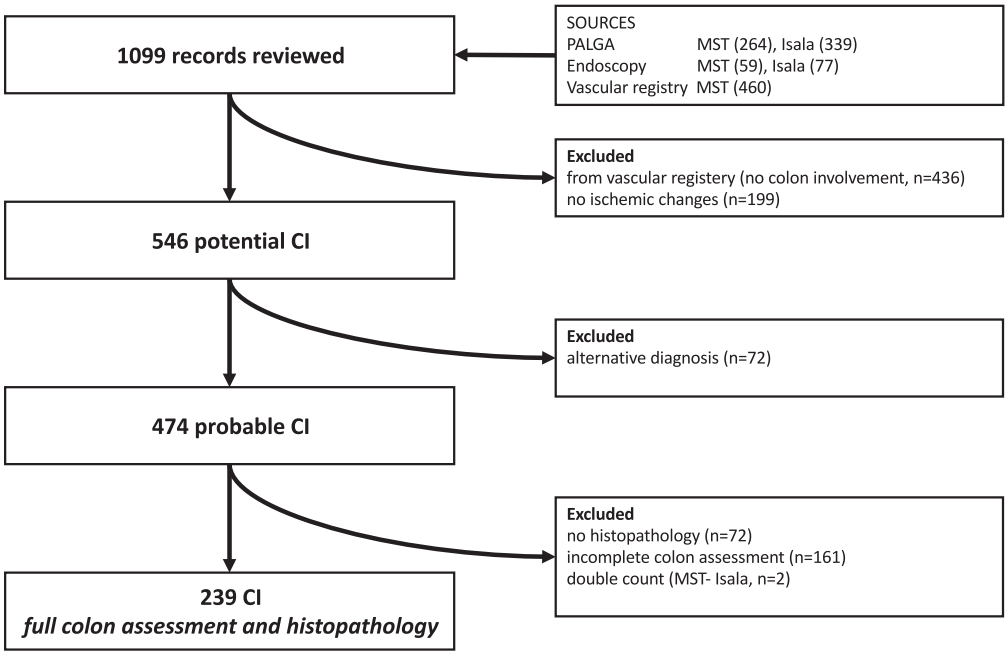

Fig. 1. Flow chart of patient selection for the study. PALGA: Nationwide pathology database. Because we decided to use only patients with complete colon assessment and histopathological confirmation of CI we included only 239 CI patients.

Table 2
Differences in clinical presentation and findings in RCI (right-sided colon ischemia) and NRCI (non-right-sided colon ischemia).

	RCI	NRCI	p Value
Symptoms			
Abdominal pain	78.6%	71.9%	0.266
Rectal bleeding	44.9%	87.4%	<0.001
Diarrhea	55.3%	45.5%	0.160
Nausea	57.6%	39.4%	0.013
Weight loss	55.6%	18.8%	<0.001
Physical examination			
Temperature ≥38°	22.3%	15.2%	0.178
Hypotension (<100 mmHg systolic pressure)	12.5%	15.9%	0.481
Tachycardia (>100/min)	33.0%	25.0%	0.207
Paralytic ileus	31.5%	17.9%	0.018
Peritoneal signs	27.1%	6.7%	<0.001

Table 3
Endoscopic findings in RCI (right-sided colon ischemia) and NRCI (non-right-sided colon ischemia).

	RCI ($n = 56$)	NRCI ($n = 82$)	p Value
Paleness	8.9%	11.0%	0.696
Cyanosis	3.6%	11.0%	0.115
Edema	35.7%	46.3%	0.214
Erythema	21.4%	42.7%	0.010
Vulnerability	8.9%	20.7%	0.063
Submucosal bleeding	3.6%	18.3%	0.010
Erosions	8.9%	15.9%	0.236
Ulcers	80.4%	65.9%	0.063
Necrosis	10.7%	8.5%	0.667

indicative of early ischemia. In both RCI and NRCI ulcerative abnormalities were observed (80.4 vs 65.9%, $p = 0.63$).

A pathology report was available in all 239 cases. Per the pathology report findings were evident for CI in 71.1% and suspect for CI in 28.9%.

Radiographic images and mesenteric artery stenosis

Radiographic images (CT, duplex imaging, Digital subtraction angiography (DSA)) to assess mesenteric artery stenoses, performed during diagnostic work-up were available in 85 patients (Table 4): 57 of 114 patients with RCI (50.0%) and 28 of 125 patients with NRCI (22.4%). In 66 patients, a CT scan was performed, in 30 patients a digital subtraction angiography and in 21 patients a duplex ultrasonography. Significant stenosis (>70%) of one or more mesenteric arteries was found more often in RCI (56.2% vs. 39.3%), although this difference was not significant, $p = 0.144$). In RCI more SMA stenosis (47.4% vs. 14.3%, $p < 0.001$) were found; IMA stenoses did not differ (10.5% vs. 17.9%, $p = 0.344$). Multi-vessel mesenteric artery stenoses was present in 28.1% of RCI, and 17.9% of NRCI patients in whom vessel anatomy was assessed ($p = 0.379$).

To evaluate for bias in selection of patients who underwent diagnostic imaging of mesenteric arteries, we compared the subgroups with and without radiologic imaging. This indeed revealed differences in baseline patient characteristics and symptoms. Patients with diagnostic imaging of mesenteric arteries had more often heart failure (60.0 % vs. 32.9%; $p = 0.001$), chronic kidney disease (66.7% vs. 34.1%; $p = 0.03$), RCI (50.0% vs. 22.4%; $p < 0.001$), abdominal pain (41.5% vs. 22.6%; $p = 0.014$) and weight loss (62.1% vs. 34.5%; $p = 0.016$). Patients with rectal bleeding were less likely to undergo vascular imaging (30.8% vs. 53.2%; $p = 0.003$). Thus, patients with more severe CI were overrepresented in this group.

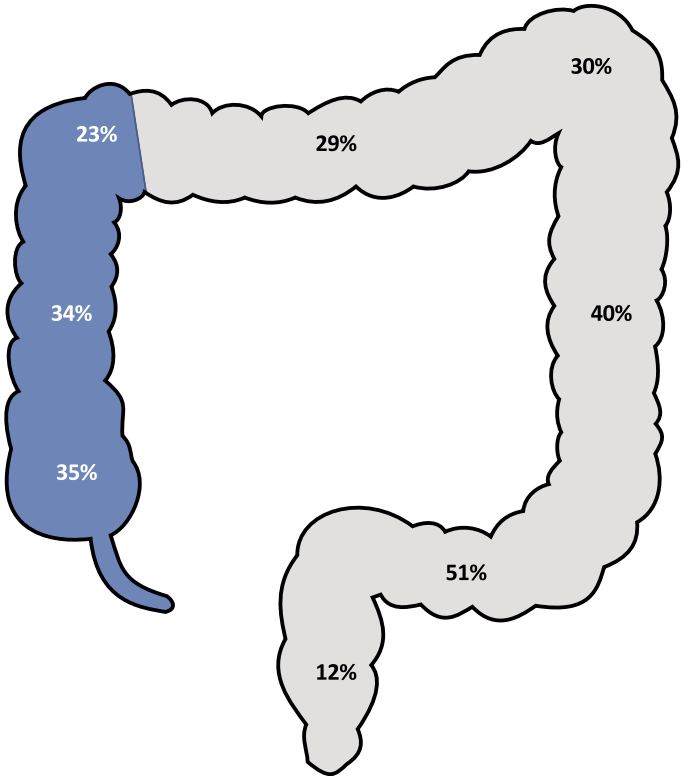

Fig. 2. Distribution of CI in the different colon segments. Of note, in 12% of CI patients the rectum was involved. Further, the classic watershed area, the splenic flexure was affected in only 30%. The sum >100% because often more segments are involved in CI.

Table 4
Mesenteric artery stenosis in RCI (right-sided colon ischemia) and NRCI (non-right-sided colon ischemia). CA: celiac artery, SMA superior mesenteric artery, IMA inferior mesenteric artery.

	RCI ($n = 57$)	NRCI ($n = 28$)	p Value
Single-vessel mesenteric artery stenosis	**16**	**6**	0.511
- Isolated CA	4	4	
- Isolated SMA	12	0	
- Isolated IMA	0	2	
Multi-vessel mesenteric artery stenosis	**16**	**5**	0.569
- CA + SMA	10	2	
- CA + IMA	1	1	
- SMA + IMA	0	1	
- CA + SMA + IMA	5	1	

Causation of colon ischemia

A cause of CI could be identified more often in RCI than in NRCI (73.7% vs. 54.0%, p = 0.002). Table 5 provides detailed information on all identified causative factors. The most prevalent cause was a low flow state (i.e. periods of hypotension or hypoperfusion before the onset of CI), which was similar for RCI and NRCI (33.3% vs. 32.3%; p = 0.868). Mesenteric vessel stenosis or occlusion as treatable cause of CI was identified in 26.3% of patients with RCI and in 2.4% of patients with NRCI (p < 0.0001). Of note, an isolated IMA occlusion / stenosis is in our opinion not a treatable cause of CI, in contrast to SMA stenoses. In 22 patients, more than one precipitating factor was identified: a combination of low-flow with surgery (77.2%) and low-flow with vascular occlusion (18.2%) was most common.

Treatment and outcome

In 122 patients (51.0%) treatment consisted of a conservative approach with intravenous fluid resuscitation and analgesics, antibiotics if needed. Revascularization was performed in 18 patients, more often in RCI (14.0% vs. 1.6%; p < 0.001) and consisted of an endovascular procedure in 14 and open repair in four patients. In five of these no further surgery was necessary. A laparotomy for suspected transmural ischemia was performed in 112 patients (46.9%), more often in RCI than NRCI (60.5% vs. 34.4%; p < 0.001). In 13 patients both a revascularization and resection was performed; in six the revascularization preceded the resection, in seven it was performed after resection; of these 13 patients eight survived and five died.

A colonic resection was performed in 108 of these patients (96.4%). In 4 (3.6%) cases no resection was performed. In three patients the ischemic changes were too mild to justify resection, and in one the concomitant massive small bowel involvement was deemed not compatible with sufficient quality of life. Overall, the outcome of RCI seemed worse than NRCI (Table 6) with a 30-day in-hospital mortality of 20.2% versus 12.0% (p = 0.084).

Table 5
Assessment of the etiology of RCI (right-sided colon ischemia) and NRCI (non-right-sided colon ischemia).

	RCI 114	NRCI 125 (124)	p Value
Low-flow state before/ at onset	33.3%	32.3%	0.868
Hypovolemic, dehydration, septic Gastroenteritis, cardiogenic, dialysis Anaphylactic, collapse			
Mesenteric occlusive ischemia	26.3%	2.4%	<0.0001
Mesenteric artery stenosis	24.6%	2.4%	
Venous thrombosis	1.7%	0.0%	
Postoperative states	16.7%	11.3%	0.231
Aortic surgery	3.5%	7.2%	
Thoracic surgery	11.3%	1.6%	
Hip surgery	0.9%	0.8%	
Secondary to other colonic pathology	7.0%	16.1%	0.029
Volvulus	0.0%	1.6%	
Proximal of structuring stenosis	5.2%	4.8%	
Adhesion ileus	0.9%	0.8%	
Diverticulitis	0.0%	8.0%	
Infectious[a]	1.8%	0.0%	0.228
No cause identified	26.3%	46.0%	0.002

[a] *Salmonella typhimurium.*

Discussion

The aims of this study were to establish the differences between right-sided (RCI) and non-right-sided colon ischemia (NRCI) with special focus on vascular imaging. Our study suggests that RCI and NRCI may be considered as two separate entities, with different etiology, clinical presentation, and outcome. RCI patients presented more often with nausea, weight loss, fever, paralytic ileus, peritoneal signs, and less often with rectal bleeding. In most RCI patients a cause was established; in contrast, 46.0% of NRCI remained unexplained despite careful analysis. It should be noted however, that in NRCI vascular imaging was done in only a minority of patients, and could have been missed. Also, we currently do not perform thrombophilia assessment in CI patients in line with current guidelines [6]. Mesenteric vessel stenosis resulting from arterial thrombosis, embolism or venous thrombosis was identified as cause for CI in 26.3% of RCI patients, and only in 2.4% of NRCI. This is more or less expected, as the right-colon is perfused by the SMA and stenoses in that artery may very well lead to ischemia, especially in those with multi-vessel involvement. This indicates that, of these patients who underwent vascular imaging, almost one in three RCI patients had mesenteric ischemia with 'end organ damage' and thus an indication for – urgent – revascularization. In most of our subjects this revascularization was done after salvage surgery, because the diagnosis was made during laparotomy. Finally, patients with RCI had a worse overall prognosis, with almost double the surgery and in-hospital mortality compared to those where the right-colon was not involved.

The exclusion of typical CI patients without histopathological proof is increasingly used as criterion for diagnosing CI [6,10,11,19]. The main argument to exclude those without histopathology is that CI may be difficult to distinguish from other colonic disorders, especially Crohn's disease, ulcerative colitis and infections [18]. Histopathology has serious limitations, with only two findings which are considered pathognomic: mucosal infarction and ghost cells. In a large nation-wide study by Montoro, mucosal infarction was seen in 8% of endoscopic and 64% of surgical specimens. Ghost cells, a sign of less severe ischemia were seen in 6% of endoscopic and 20% of surgical specimen [11]. Therefore, the mild signs of ischemia are difficult to recognize with histopathology, with subtle differences between inflammatory bowel disease and ischemia, with a very important role for the clinical setting. It is our experience that, in less-experienced hands or without asking the pathologist for potential CI, many of CI patients were initially

Table 6
Outcome and length of hospital stay.

Variable	RCI ($n = 114$)	NRCI ($n = 125$)	p Value
Laparotomy (%)	60.5%	34.4%	<0.001
30-day mortality (%)	20.2%	12.0%	0.084
Length of stay (days, median – IQR)	15 (8–30)	8 (4–21)	<0.001

diagnosed as non-specific inflammation. Two lessons may be drawn from these studies and observations: 1) for clinical purposes, histopathology may be less reliable than often assumed, and 2) the early, subtle changes should be actively looked for, or they will be missed with potentially grave consequences.

The proportion of patients with RCI of 48 % was higher than in other studies that ranged from 9.7% to 26% [10,11,15,17,19]. The two most likely factors to have influenced this difference are the RCI-definition and referral bias. Definitions for RCI and NRCI vary among studies [11,19]. We used the definition by Brandt et al. who defined RCI in those patients with lesions proximal to the hepatic flexure and the remaining as NRCI [10], although in more recent papers the proximal transverse colon was included in RCI, if in continuity with right colon [17]. This makes sense as the transverse colon is perfused by the SMA as well. Referral bias may also have played a role in the relative high proportion of RCI patients in this study, as has been noted before [14]. One of our two institutions is a nationwide referral center for gastrointestinal ischemia, including also patients with advanced ischemic disease.

The worse outcome of right-sided colon ischemia is in line with other studies, although the reasons have been poorly clarified [10,11,15,17,19–21].We expect that two interrelating factors play a role in the prognosis, and possibly could be targets to improve outcome: occlusive disease of the superior mesenteric artery, and diagnostic delay. An occlusive cause was identified in almost 29% of RCI patients, three times higher than in NRCI. In most occlusive CI patients, an occluded superior mesenteric artery was found. If in these cases the CI can, and often will, be accompanied by small bowel ischemia urgent treatment would be indicated. In that respect, the median diagnostic delay of 27.5 hours is quite long, even though it's shorter than currently published series [21,22]. To further put things in perspective: it may only take 6–8 hours to proceed from acute mesenteric occlusion to irreversible ischemia with concomitant small bowel involvement [18], and it is therefore advised to start treatment within 24 hours in suspected acute ischemia [23]. It is highly probable that more rapid diagnosis making could prevent development of gangrene, and thus reduce need for extensive surgery and related mortality. Our policy over the last years has therefore been to perform urgent CT-angiography and revascularization in all patients with RCI. We therefore strongly support the recent pleas for low-threshold CTA in these patients [6,9,24]. Future studies are needed to confirm if such measures could indeed improve survival.

Our study has limitations related to the retrospective design. First, we excluded patients with incomplete colonoscopies. In our first analysis, where we included 474 CI patients, including those with incomplete colonoscopy or histopathology [25] the mortality rate was higher. This was related to the high mortality in severely ill patients in the ICU in whom a sigmoidoscopy was clinically sufficient (data not shown). Because our main aim was to investigate right-sided as compared to non-right sided colon ischemia we had to exclude these patients. Second, as discussed above, we excluded patients in whom no histopathology was obtained. This included some of the worst RCI patients, for example those who were operated and in whom the resected specimen got lost, or in whom resection was deemed non-realistic. Taken together, the effect of restricting the inclusion to CI patients with complete colon assessment and histopathology, eliminated some of the worst RCI patients. This may explain the difference between the outcome if this study and a previous analysis of all 472 patients of this cohort, as presented at the Digestive Disease Week in 2013 [25]. When analyzing all 474 patients with CI as diagnosis, confirmed after chart revision, the in-hospital mortality of RCI was twice that of NRCI (31.0% vs. 16.1%). Restricting CI studies to include only those patients with complete colon assessment with histopathological proof, like all large recent [6,10,11,19], may underestimate the real difference between RCI and NRCI.

Third, the high percentage of RCI patients in our series may be explained by referral bias. Our center has a specialized working group on gastrointestinal ischemia with nation-wide referrals. Fourth, the decision to perform vascular imaging was made on clinical grounds, and information therefore was only available in a subset of patients. This may also explain why more patients with RCI underwent vascular imaging. It has been our experience that many of these patients with right-sided colon involvement have end-stage mesenteric ischemia and need urgent vascular imaging and intervention. The clinical significance of the high incidence of vessel stenosis in RCI was not influenced by this policy. This policy of vascular imaging in RCI patients may very well have underestimated vessel stenoses as factor even in NRCI. Whether patients with NRCI should also be evaluated for mesenteric artery stenosis, and whether this lack of vascular investigations explains the high number of 'unexplained' cases remains to be assessed.

Conclusions

In conclusion, this study suggests that RCI and NRCI are two different disease entities. RCI is characterized by a non-specific clinical presentation with abdominal pain, nausea, diarrhea, absence of rectal blood loss and more often peritonitis. The need for surgery and in-hospital mortality are two-fold higher, and vessel occlusions as cause were identified in almost 30% of RCI patients. These results reconfirm the advice to perform CTA in RCI patients to rule out, or detect and treat, occlusive disease, and thus improve the outcome. Future prospective studies are needed to test this hypothesis.

Practice points

- In patients with RCI a CTA is indicated because a significant proportion has – potentially treatable – mesenteric artery stenoses.
- The classic presentation of CI is abrupt onset of abdominal pain, blood loss and diarrhea. In RCI, blood loss is often absent, and the clinical picture is characterized by abdominal pain and nausea, often preceded by weight loss.
- The diagnostic delay in CI is long, ranging from one to three days (mean 25 hours in this study).
- Colonoscopy with biopsies is the most accurate diagnostic approach; CT scanning is useful, but less specific, but also less invasive.
- Histopathological proof if CI is difficult, in the early stages ghost-like cells, and limited inflammation are characteristic. Differentiation from Crohn's, or ulcerative colitis may often be difficult, and providing the pathologist with full clinical information is crucial.
- In almost one third of patients a period of low-flow precedes the onset of CI.
- In 26% of RCI patients a vascular event could be identified. In 46% of NRCI patients no cause could be identified.

Research points

1. It should be investigated whether early CTA in RCI could improve the outcome.
2. It should be established whether thrombophilic factors are increased in CI, and whether treatment could improver outcome or reduce recurrences.

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