SUB-10 MINUTE HIGH QUALITY DIAGNOSTIC ILEO-COLONOSCOPY INCLUDING TERMINAL ILEAL INTUBATION IN CHILDREN IS FEASIBLE AND SAFE BUT COMPROMISED BY POOR BOWEL PREPARATION

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ABSTRACT

Objectives: To critically appraise ileocolonoscopy practice in a large tertiary center, where ileocolonoscopy is exclusively performed by experienced pediatric colonoscopists, particularly focusing on: indications for the procedure; bowel preparation efficacy; IC completion rates and timings; diagnostic yield; and complications.

Patients and methods: We prospectively evaluated all patients referred to our clinic between July 2015 and June 2016. Data on age, height and weight, gender, surgical history, indications for colonoscopy, bowel preparation given, bowel cleansing efficacy were collected. The following were calculated: percentage of terminal ileal intubation; time to terminal ileum; total duration of each procedure. Additionally, we evaluated the number and the type of complications encountered and the number of patients readmitted within 30 days from the elective procedure. Endoscopic diagnostic yield, stratified for indication, was calculated.

Results: A total of 1392 patients were referred; 181 required an endoscopic evaluation of the lower GI tract (Outpatient Department conversion rate: 13%). Main indications for IC were: recurrent abdominal pain 38.1%; unexplained chronic diarrhea 16%; suspected IBD 24.9%; isolated rectal bleeding 13.2%; occult GI bleeding 1.6%; unexplained faltering growth 1.6%; IBD restaging 2.6%; miscellaneous 1.6%. Terminal ileum was reached in all the patients (TI intubation rate = 100%). Median time to TI was 9.8 minutes (1 to 50 minutes). Time to TI was lower in younger patients compared to older ones (p = 0.005). Bowel-cleansing was judged as: Grade 1 in 49.2%; Grade 2 in 33.7%; Grade 3 in 13.3%; and Grade 4 in 3.9%. A significant statistical correlation was recorded between bowel-cleansing and time to TI. The positive diagnostic yield was: 11.6% in patients with abdominal pain; 37.9% in patients with chronic diarrhea; 51.1% in patients with suspected IBD; 29.2% in patients with isolated rectal bleeding; 33.3% in patients with occult GI bleeding; 0% in patients with faltering growth; and 33% in the miscellaneous group.

Conclusions: In conclusion, appropriately targeted IC in the management of children with GI symptoms, is a safe, fast and useful investigation. TI intubation rates of 100% are achievable and desirable and can be conducted quickly. Poor bowel preparation impacts negatively on this and IC duration may be faster in younger children. High diagnostic yields have been recorded in patients with a clinical suspicion of IBD. Diagnostic yield in isolated recurrent abdominal pain is low. Training to excellence in pediatric IC should be a persistent goal.

What is Known:

- Several markers of ileo-colonoscopy (IC) quality have been recognized in adults, such as adenoma detection rate and cecal intubation.
- Quality measures suitable in the pediatric population includes: diagnostic efficacy, safety, timeliness and patient focus.

What is New:

- Appropriately targeted IC in the management of children with gastrointestinal symptoms, is a safe, fast and useful investigation.
- Terminal ileum intubation rates of 100% are achievable and desirable and can be conducted quickly.
- Ileal intubation should be considered a quality indicator for pediatric colonoscopy.
- Diagnostic yield in isolated recurrent abdominal pain is low, therefore IC should be discouraged in those children.

INTRODUCTION

Ileo-colonoscopy (IC) is the most important diagnostic tool in detecting lower gastrointestinal tract pathology in both adult and pediatric patients. It is a safe and effective procedure (1-6) and now routinely performed by most pediatric gastroenterologists. Several markers of colonoscopy quality have been recognized in adults (1, 2), such as cecal intubation rate and adenoma detection rate. Such adult endoscopic quality markers are not applicable to the pediatric population due to significant differences in indications, possible diagnoses, biopsy distribution and number amongst others. However, Thakkar and colleagues recently proposed a list of candidate quality measures suitable in the pediatric population including: diagnostic efficacy; safety; timeliness; and patient focus (7). These measures were further ratified in the recent ESPGHAN/ESGE pediatric endoscopy Guidelines (8,9). Appropriate indications for IC in children have received recent attention (9-11) as has what constitutes an optimum diagnostic yield with emphasis on terminal ileal examination as part of full IC (11).

In our study the aims were to critically appraise the IC practice in a large tertiary center, where IC is exclusively performed by experienced pediatric colonoscopists, particularly focusing on: indications of the procedure; bowel preparation efficacy; IC completion rates and timings; diagnostic yield; and complications.

PATIENTS AND METHODS

We prospectively evaluated all patients referred to the pediatric gastroenterology clinic of the Portland Hospital, between 1st July 2015 and 30th June 2016. Data on age, height and weight, gender, surgical history, indications for colonoscopy, bowel preparation and bowel cleansing efficacy were collected. Procedures were performed by 6 experienced endoscopists: each of them performed more than 1000 ICs before the beginning of the study; all presented with more than 10 years of endoscopic practice (a mean of 19 years). All the procedures were conducted under general anesthesia and using carbon dioxide (CO_2) for insufflation. Starting position was on the back for all the patients.

The bowel cleansing protocol was sodium picosulfate-magnesium citrate and senna, administered approximately 18-24 and 6-12 hours pre-procedure (sodium picosulfate/magnesium oxide/citric acid anhidrous 10 mg/3.5 g/12 g sachet, dose 1 to 2 years: quarter sachet, 2 to 4 years: half sachet, 4 to 9 years: 1 sachet; senna dose: 1 mg/kg body

weight, max dose 30 mg). Nasogastric administration of bowel cleansing was not required. Enemas were reserved for those who found it difficult to ingest the prescribed doses of picosulfate-magnesium citrate and for those who still had residual fecal matter even after the additional dose (*Sodium citrate*/sodium lauryl sulfoacetate/glycerol 450 mg/45 mg/625 mg per 5 ml enemas were used: ¼ below 2 years, ½ 2-4 years and 1 full enema over 4 years). To assess the cleansing quality of the bowel preparations, a four-grade scale, recorded on the endoscopic examination reports, was used. Grade 1: no endoscopic cleansing suction is required (small amount of clear liquid, no residue). Grade 2: requiring slight cleansing suction (moderate amount of clear liquid with small amount of residue). Grade 3: requiring frequent cleansing suction (sludgy feces, large amount of residue). Grade 4: poor bowel cleansing (unable to suction, solid feces). The following were calculated: percentage of terminal ileal (TI) intubation; time to TI; and the total duration of each procedure. Procedural duration was measured as actual endoscopy time not including time for anesthesia. All the endoscopists used the biopsy forceps as "Seldinger" type technique to intubate the terminal ileum (23). Scopes were generally advanced for 20-30 cm into the TI, or as far as safely possible. Additionally, we evaluated the number and the type of complications encountered and the number of patients readmitted within 30 days from the elective procedure. Endoscopic diagnostic yield, stratified for indication, was calculated. TI intubation was confirmed by ileal histology and images obtained at endoscopy. According to main indication of the procedure, patients were divided into following groups: recurrent abdominal pain, unexplained chronic diarrhea, suspected IBD, isolated rectal bleeding, unexplained faltering growth, IBD restaging/follow up and miscellaneous. Suspected IBD was defined by the presence of both abdominal pain and rectal bleeding and/or anemia and/or chronic diarrhea and/or raised fecal calprotectin. All the patients with isolated rectal bleeding with a history of constipation were treated with laxatives prior to having a colonoscopy. The miscellaneous group included patients with altered bowel habit with a raised fecal calprotectin, investigation of anemia or a family history of FAP. Patients were allocated to the 'normal' category if the IC was macroscopically and histologically normal, even if simultaneous upper GI endoscopy revealed a diagnosis.

This prospective clinical audit was approved by the Audit and Compliance Committee of HCA Healthcare.

Statistical analysis

Data were described as numerosity and percentage for categoric variables and mean ± standard deviation (SD), median and range for numeric ones. Inferential analyses were conducted using linear regression models of age, bowel-cleansing and interaction between them, on time to TI and total procedure time. Age was categorized into age groups before use as a predictor in the models, in order to account for non-linearity in the effect. Age categories have been chosen statistically, in order to improve the correlation with the outcome, with the following procedure: we performed repeated linear regression between age and the outcomes (time to ileum and time to total procedure), dichotomizing the variable at subsequent age thresholds; then we chose the thresholds which provided the most predictive models and we used them to create the age groups. Consequently, age groups were (0, 3], (3 - 5], (5 - 13], (13 - 15], (15 - 20], for time to ileum and (0 - 5], (5 - 13], (13 - 15], (15 - 20], for time to total procedure (round brackets imply exclusion, square brackets inclusion of the values). Age groups were used either as linear predictors or for group to group comparisons. Inferential results are presented as differences in minutes, 95% confidence intervals (95% CI) and p values. Analyses and plots were produced using R 3.4.0 (28).

RESULTS

Patients and main indications

Total of 1392 patients were referred to the pediatric gastroenterology center between 1st July 2015 and 30th June 2016, of whom it was determined 181 required an endoscopic evaluation of the lower GI tract. The Outpatient Department (OPD) conversion rate was therefore approximately 13%. No statistically significant difference was observed in the case distribution among the 6 endoscopists, as concern number of procedures and age group belonging. The main indications for IC were: recurrent abdominal pain 69 (38.1%); unexplained chronic diarrhea 29 (16%); suspected IBD 45 (24.9%); isolated rectal bleeding 24 (13.2%); occult GI bleeding 3 (1.6%); unexplained faltering growth (with simultaneous upper GI endoscopy) 3 (1.6%); IBD restaging 5 (2.6%); and miscellaneous 3 (1.6%). There were 99 males (54.7%). The median age was 11.2 years (range 6 months to 18 years). None had a history of previous abdominal surgery. Patients' characteristics according to age group are described in Table 1.

TI intubation rate and bowel-cleansing

Terminal ileum was reached in all the patients (TI intubation rate = 100%).

Bowel preparation was as described above, with 32 (17%) requiring an enema. Bowel-cleansing was judged as: Grade 1 in 89 (49.2%); Grade 2 in 61 (33.7%); Grade 3 in 24 (13.3%); and Grade 4 in 7 (3.9%).

Time to TI and its relation to bowel-cleansing and patient age

Median time to TI was 9.8 minutes (1 to 50 minutes). Time to TI was found to increase with age (1.16 minutes between each group age, p = 0.005, 95% CI [0.359, 1.95]), and in particular mean time to TI was 7.1 minutes (SD: 3.7) in patients younger than 3 years, 9.1 minutes (SD: 5.9) in 3 to 5 year old patients, 9.6 minutes (SD: 5) in 5 to 13 years old patients, 10.1 minutes (SD: 4.9) in 13 to 15 years old patients, and 9.6 minutes (SD: 9.5) in patients older than 15 (Figure 1).

A significant statistical correlation was recorded between bowel-cleansing and time to TI, and in particular the mean time to TI was: 8.4 minutes (SD: 4.75) in patients with a grade 1 bowel cleansing score, 10.1 minutes (SD: 4.8) in patient with a grade 2 score, 11 minutes (SD: 4) in patients with a grade 3 score, 21.8 minutes (SD: 14.8) in patients with a grade 4 score. A statistical difference in time to TI was recorded between procedures carried out with a fair bowel preparation (judged as grade 3) and those with poor bowel preparation (grade 4) (p < 0.001, 95% CI [6.26, 15.3]), and a trend of statistical significance between procedures carried out with an excellent bowel preparation (grade 1) and those with good bowel preparation (grade 2) (p = 0.052, 95% CI [-0.0028, 3.5]). An increasing in time to TI was seen in patients with fair bowel preparation compared to those with good bowel preparation, though it was not statistically significant (p = 0.48, 95% CI [-1.65, 3.43]).

By analyzing the interaction between age group and bowel-cleansing, we can see that the effect of age in prolonging the procedure is particularly relevant in patients with poor bowel preparation (p = 0.012, 95% CI [1.57, 12.2]) (Figure 2).

Total procedure time and its relation to bowel-cleansing and patient age

Median time of total procedure including biopsies, from scope insertion until complete withdrawal, was 14.1 minutes (4 to 55 minutes). A statistical significant difference in total procedure length according to age group was found (p = 0.034, 95% CI [0.11, 2.54]).

By analyzing the interaction between age groups and bowel-cleansing, we noticed that the effect of age in prolonging the total procedure time is particularly relevant in patients with poor bowel preparation (grade 4) when compared to fair bowel preparation (grade 3) (p = 0.035, 95% CI [0.496, 12.7]). No statistical significant differences were recorded when comparing the remaining bowel-cleansing groups according to age. By running an adjusted regression with the difference in time between the total procedure and the time to TI we concluded the effect of age interferes only in the time to TI, especially in patients with poor bowel preparation (grade 4) if compared to fair bowel preparation (grade 3) (p = 0.026, 95% CI [0.447, 6.24]); no statistical significant differences were recorded when comparing the remaining bowel-cleansing groups according to age.

IC diagnostic yield

Biopsies were routinely taken during all procedures, whether macroscopically normal or not, from terminal ileum, cecum, transverse colon, descending colon, sigmoid colon and rectum. The positive diagnostic yield, defined as the percentage of patients in which the procedures led to a positive diagnosis determined histologically, according to clinical indication, was: 11.6% in patients with abdominal pain; 37.9% in patients with chronic diarrhea; 51.1% in patients with suspected IBD; 29.2% in patients with isolated rectal bleeding; 33.3% in patients with occult GI bleeding; 0% in patients with faltering growth; and 33% in the miscellaneous group (Figure 3). In the abdominal pain group, 2 patients were diagnosed with ulcerative colitis (UC), 2 eosinophilic enteritis and 4 with TI lymphoid hyperplasia. In the chronic diarrhea group, 5 were diagnosed with eosinophilic colitis and 3 with eosinophilic enterocolitis, 1 with eosinophilic procto-sigmoiditis, 1 with Crohn's disease and 1 with TI lymphoid hyperplasia. In the group of patients with suspected IBD: diagnosis was confirmed in 14 (31.1%) (9 Crohn's disease, 4 UC and 1 IBD-Unclassified (IBD-U)); a single polyp was found in 1; eosinophilic enteritis in 3; eosinophilic enterocolitis in 1; eosinophilic procto-sigmoiditis in 3; and TI lymphoid hyperplasia in 1. In the group with isolated rectal bleeding, findings included: isolated polyps in 2; UC in 1; eosinophilic enteritis in 1; eosinophilic

colitis in 1; and pan-colonic lymphoid hyperplasia in 1. In the group with occult GI bleeding 1 patient was diagnosed with a vasculitic disorder affecting the TI. In the miscellaneous group 1 diagnosis of eosinophilic colitis was made.

Among 176 IC (5 patients already diagnosed with IBD were excluded from the analysis), additional ileal intubation after achieving cecal intubation, altered the diagnosis in 21 patients (11.9%), and in particular: 6/69 (8.7%) with recurrent abdominal pain, 5/29 (17.2%) with chronic diarrhea, 8/45 (17.7%) with suspected IBD, 1/24 (4.1%) with isolated rectal bleeding, 1/3 (33.3%) with occult GI bleeding, 0/3 (0%) with unexplained faltering growth, 0/3 (0%) in the miscellaneous group.

No complications, nor emergency admissions within 30 days post-procedure, were encountered.

DISCUSSION

IC plays a pivotal role in investigation of children with lower GI symptoms, and modern practice allows a safe, easily accessible and diagnostically sensitive procedure (3-5, 7-10). The diagnostic yield of IC must always be critically scrutinized (11). A number of popular misconceptions surround the area of IC in children. The first is that the trade-off for an invasive investigation in a child (for example, IC, which usually requires general anesthetic) should be a high yield of positive findings. This point can be countered by the argument that a significant negative finding might be equally helpful in contributing to the positive outcome of a health episode for a child and their family, for example, confirmation of the absence of polyps in a child with rectal bleeding and a family history of polyp syndromes (3,10). The second misconception is that colonoscopy performed to any standard is sufficient to exclude significant pathology. The Porto criteria of the IBD Working Group of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has contributed significantly in standardizing the use of esophago-gastro-duodenoscopy (EGD) and IC in the diagnosis of IBD in children, stressing the importance of TI intubation and biopsy as an integral part of the complete work-up (13). Without terminal ileal intubation an IC is an incomplete investigation, falling short of the diagnostic rigor required especially when IBD is suspected. Isolated ileal inflammation is reported to occur in approximately 9% to 17% of patients with Crohn's disease and several studies demonstrate that TI intubation in children can significantly improve the sensitivity of IC (6, 7). However, recently, a study published by Kawada et al (12) details a 52% cecal intubation rate (only some of them with terminal ileal

intubation) and they quote a diagnostic yield in suspected IBD of 63%, that is higher than that of our study conducted with a 100% TI intubation rate (51,1%). We can explain this result supposing that in Kawada's study ileal intubation was performed only after a negative colonic examination in those patients with a high suspicion of Crohn's disease. Nevertheless, we would like to underline that overall additional ileal intubation after achieving cecal intubation, altered the diagnosis in 1/10 of our patients, and in particular in 17.7% of those with an IBD suspect. We believe that we found a high rate of normal colonoscopy, that probably could have been reduced by pre-procedure screening with faecal calprotectin, that was performed only in a minority (about 10%). It could be argued that any test being performed on children should have a 100% efficacy in aiming to eliminate or confirm pathology. Performance of lower gastrointestinal endoscopy below this level of accuracy should not be tolerated. Hence, an aspiration to 100% TI intubation, including multiple site biopsies at IC, in pediatric patients should be actively sought and training should reflect this aim (14-16). In addition, the experience of the operator is likely to be related to TI intubation success. In our study TI intubation rate was 100%, with all procedures performed by experienced endoscopists (> 1000 ICs performed before). We confirm that high rates of ileal intubation are feasible in children, and we strongly agree with the concept that ileal intubation should be considered a quality indicator for pediatric colonoscopy (32). There are few pediatric studies evaluating the performance of IC, such as the TI intubation rate and the procedural length, with TI intubation rate in children variously reported as between 50% to 96% (16-18, 32). Israel et al reported a TI intubation rate of 87-95% in 40 consecutive IC in children, with an average total procedural time of 38 min (31 minutes when performed by pediatric gastroenterology attending physician and 37 min when performed by a fellow in training) (17). In the same study the average time taken to reach the cecum was 19 min if performed by the attending physician and 25 min if performed by the fellow and the average time spent from cecum to terminal ileum was 3 min for all, with ranges of 1-12 min for the attending physician and 1-23 min for the fellow. Conversely, in a recent study by Singh et al, presence of trainee was not statistically significant on TI intubation success, that was overall 92.4%; only poor bowel preparation and age less than 5 years were inversely related to success (32). In another study, Mamula et al reported an 83% TI intubation rate, with an average time of 12.61 min (7.3 SD) to reach the caecum, and additional 3.67 min (3.62 SD) to enter the TI (18). In a larger multi-centric pediatric study, based on the analysis of 21,807 ileo-colonoscopies and including 104 pediatric gastroenterologists, Thakkar et al reported an overall TI intubation rate of 69.4%(4). However, TI intubation rate increased to 84.0% if

procedures without intention to reach the ileum were excluded. Considering the completed ICs only, Thakkar et al reported an overall mean total procedural duration of 32.0 minutes (SD = 13.9 minutes). If the procedure was carried out by a fellow or if poor bowel preparation was noted, then a longer procedure time ensued (4). Adult studies report lower median cecal intubation time, of about 9 to 15.8 minutes (to our knowledge no data on ileum intubation time has been reported so far) (19, 20). Several theories have been postulated on why pediatric IC may take longer than adult colonoscopy, although not in our study, including, in children, putative increased colonic elasticity, less adipose tissue and less developed abdominal musculature potentially leading to more frequent looping during colonoscopy in children (21). Countering this argument are such issues as diverticulosis and post-pelvic surgery in adults, amongst others. In our cohort, time spent to reach the terminal ileum was comparable to those quoted in large adult series i.e. 9.8 minutes. No special technique, apart from Seldinger thechnique for TI intubation, were used during the colonoscopy in our centre. Abdominal compressions maneuvers and patient position change were performed as required by the operator, and they were not analyzed in the study because considered as part of the procedure. The "Seldinger" type technique was used by all the endoscopist for ileocecal valve intubation as follows: ileocecal valve is identified and positioned inferiorly (6 o'clock position) by manipulating the colonoscope, the tip of the biopsy forceps is then pulled out, and the instrument is advanced above and beyond the valve and slowly withdrawn with the tip flexed downward until the orifice of the TI is exposed; hence, the colonoscope is advanced forward to intubate the ileum. The advantage of this technique is that it can actually allow the endoscopist to see where he is going, with almost no chance of adverse events. According to age, time to TI was shorter in younger patients compared to older ones. A significant difference in time to TI was recorded between procedures carried out with an excellent bowel preparation and those with good bowel preparation, and between fair bowel preparation and poor bowel preparation. Furthermore, by analyzing the interaction between age group and bowel-cleansing, we observed an effect of the age in prolonging the procedure, which was particularly relevant in patients with poor bowel preparation (Figure 2). Total procedural time in our patients was on average 14.1 minutes (4 to 55 minutes). In adults, much importance is given to withdrawal time, due to the fact that longer withdrawal time ($\geq$ 6 min) is associated with higher polyp detection rate (22). Conversely, in children withdrawal time plays a secondary role as a quality indicator, unless a polyp is suspected. If a polyp is suspected, an optimal bowel preparation should be sought in order to increase the detection rate as well as shorten the procedural time.

Nevertheless, the application of an investigation should not be predicated on by the availability of such an investigation, in either direction. According to available data, our OPD conversion rate of 13%, is somewhat lower than that of comparable services in the UK (17-32% in other large centers) (3, 24). In line with previously published evidences (12, 29), low diagnostic yield was recorded when the sole indication was recurrent abdominal pain alone (11.6%); a previous report figured out that a reassuringly negative investigation has not been shown to improve outcomes in children with functional abdominal pain (30). The diagnostic positive yield in patients with suspected IBD compares favorably with the published literature of between 51% and 96% (3, 12, 18, 24). Even if we treated with laxatives all the patients with isolated rectal bleeding prior to having a colonoscopy, we observed a low positive diagnostic yield in this group (29.2%), in accordance to one previously published study (25). This is possibly due to the fact that rectal bleeding is a worrying symptom for families, and doctors as well; furthermore, this might reflect the difficulty in detecting minor abnormalities, such as anal fissures, in the clinic setting. However, other studies reported higher positive finding of 60-80% in patients with rectal bleeding (26, 27). In line with previously published report, no diagnostic benefit was found in performing an IC in patients with faltering growth, even if the number of patients belonging to this group in our study was small (31). Excluding patients who had an IC for IBD restaging/follow up, in our series 67% of ICs were histologically normal. The higher diagnostic yield of a colonoscopy in appropriate indications suggests that the use of appropriateness criteria may enhance the efficient use of a colonoscopy in children. Main limitations of the study are the relatively small number of case presented, all belonging to a single centre, that could have underestimated the rate of complications; moreover, considering that this is a prospective study, there may have been a greater effort by the endoscopists to perform a complete IC, which would have influenced the TI intubation rate, and the procedure length. Furthermore, there may be some confounding factors, such as abdominal compression maneuvers used and body position change that might have affected the results.

In conclusion, appropriately targeted IC in the management of children with GI symptoms, is a safe, fast and useful investigation. Ileal intubation is desirable in order to perform a high quality IC in children. TI intubation rates of 100% are achievable and can be conducted quickly. Poor bowel preparation impacts negatively on this, and IC duration may be faster in younger children. Diagnostic yield in isolated recurrent abdominal pain is low, therefore IC should be discouraged in those children. Lastly, training to excellence in pediatric IC should be a persistent goal.

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Table 1 Patients' characteristics according to age group

Age group*	Patients, N (%)	Gender (M/F)
(0, 3]	16 (8.8 %)	(9/7)
(3, 5]	13 (7.2%)	(7/6)
(5, 13]	93 (51.4%)	(56/37)
(13, 15]	33 (18.2%)	(13/20)
(15, 20]	26 (14.4%)	(14/12)

* Round brackets imply exclusion, square brackets inclusion of the values

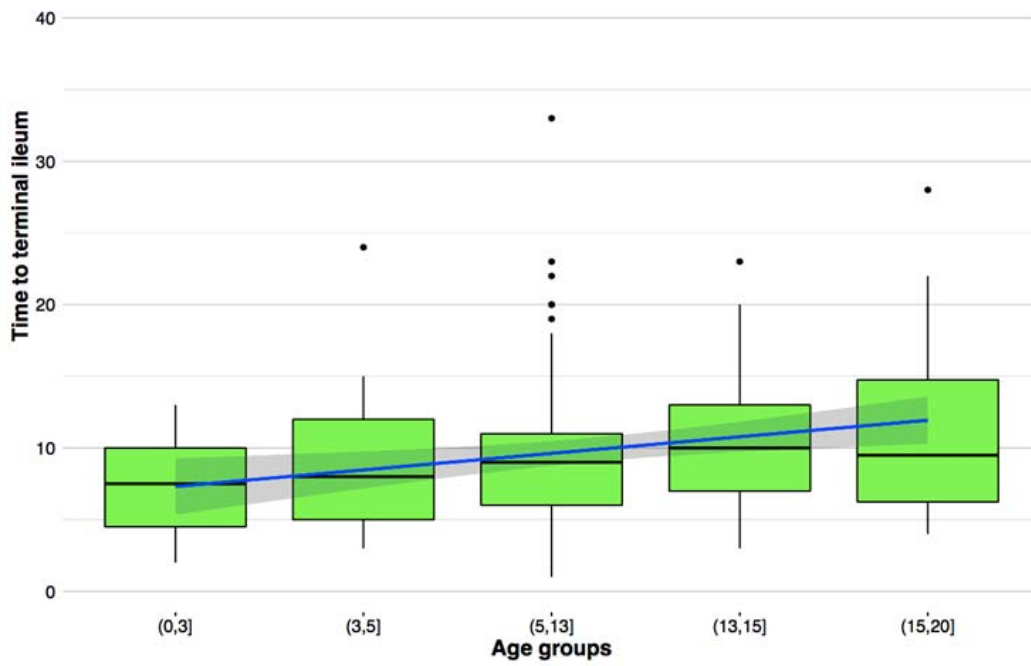Figure 1. Correlation between age groups and time to terminal ileum (minutes)
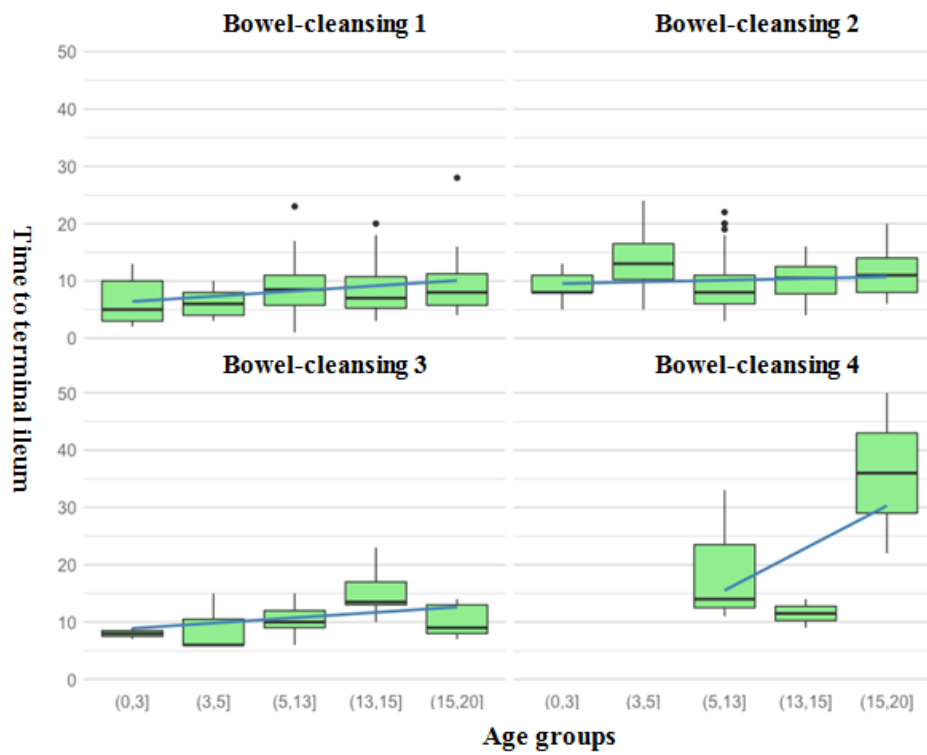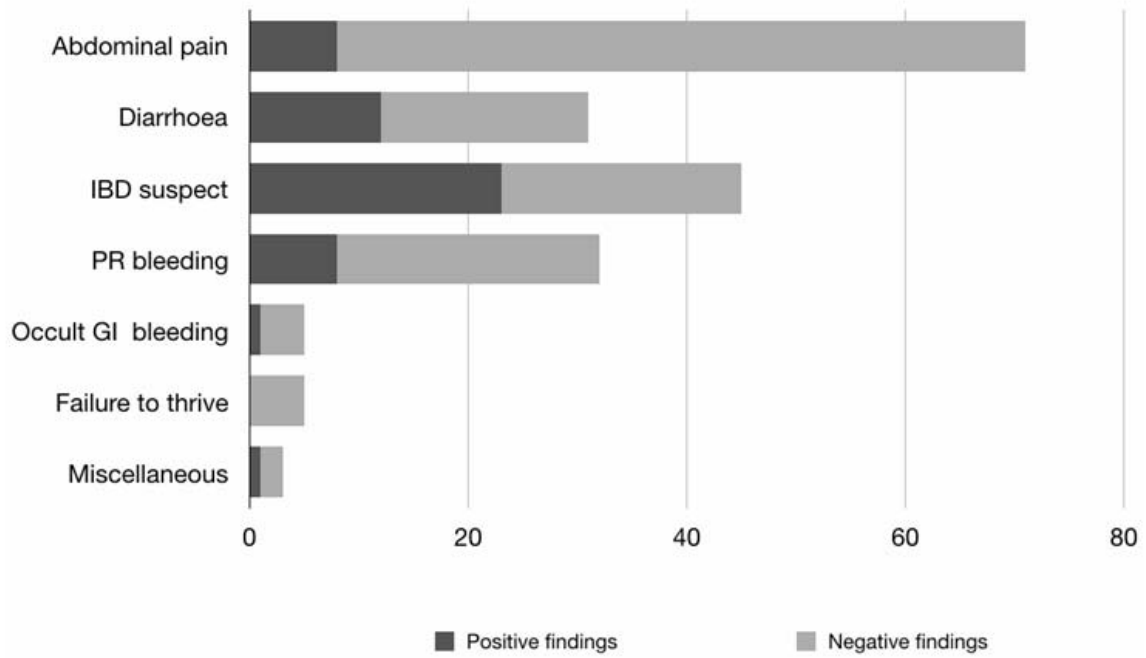
Figure 2. Correlation between bowel-cleansing and time to TI (minutes) stratified by age

Figure 3. Ileo-colonoscopy diagnostic yield stratified for indication

IBD: Inflammatory Bowel Disease; PR: per rectum; GI: gastrointestinal