Morpho-functional evaluation of small bowel using wireless motility capsule and video capsule endoscopy in patients with known or suspected Crohn's disease: pilot study

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Morpho-functional evaluation of small bowel using SmartPill® and Pillcam® combined in patients with known or suspected Crohn's disease; pilot study.

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Complete List of Authors:	Yung, Diana; Royal Infirmary of Edinburgh, Centre of Liver & Digestive Disorders Douglas, Sarah; Royal Infirmary of Edinburgh, Centre of Liver & Digestive Disorders Hobson, Anthony; The Functional Gut Clinic, The Functional Gut Clinic Giannakou, Andry; Open University of Cyprus, Faculty of Economics and Management Plevris, John N.; Royal Infirmary of Edinburgh, Centre of Liver & Digestive Disorders Koulaouzidis , Anastasios; Royal Infirmary of Edinburgh, Centre of Liver & Digestive Disorders
Keywords:	Endoscopy Small Bowel, Inflammatory bowel disease < Endoscopy Small Bowel, Capsule endoscopy < Endoscopy Small Bowel
Abstract:	Introduction: SmartPill® (Given Imaging Corp.,Yoqneam,Israel) is an ingestible, non-imaging capsule that records physiological data including contractions and pH throughout the gastrointestinal(GI) tract. There are scarce data looking at SmartPill® assessment of patients with known/suspected small-bowel Crohn's Disease (CD). This pilot study aims to investigate feasibility and safety of SmartPill® to assess gut motility in this group. Materials & methods: Over one year, patients with known/suspected CD, referred for small-bowel capsule endoscopy(SBCE), were invited. Patients underwent hydrogen breath test to exclude small-bowel bacterial overgrowth, patency capsule (Agile®), and provided stool samples for faecal calprotectin(FC). Patients ingested PillCam®SB2 and SmartPill® 4 hr apart. 33 healthy controls were obtained from unpublished data. P<0.05 was considered statistically significant. Results: 12 patients were recruited (7 female/5 male, mean age 44.2 ±16.6 years). 10 underwent complete Smartpill® examination (1 stomach retention, 1 dropout). Pillcam® was complete in 10 (1 dropout, 1 stomach retention). Mean faecal calprotectin was 340 ± 307.71 mcg/g. The study group had longer transit times and lower gut motility index versus controls. The difference in motility appears statistically significant (P<0.05). Longer transit times for SmartPill® (not statistically significant) were possibly due to different capsule specifications. Limitations included Smartpill® signal loss (5/10 studies). Discussion: This is the first pilot to attempt combining

	SBCE and SmartPill® to assess small-bowel CD. Data on motility in CD is scarce. Multimodal information can provide a clearer clinical picture. Despite concerns about capsule retention in CD patients, SmartPill® seems safe for use if a patency capsule is employed beforehand.

Title: Morpho-functional evaluation of small bowel using SmartPill® and Pillcam® combined in patients with known or suspected Crohn's disease; pilot study.

Authors and Institutions:

Dr Diana E Yung[1]
Ms Sarah Douglas[1]
Dr Anthony Hobson[2]
Dr Andry Giannakou[3]
Dr John N Plevris[1]
Dr Anastasios Koulaouzidis[1]

1 Royal Infirmary of Edinburgh, Centre of Liver & Digestive Disorders, Edinburgh, UK
2 The Functional Gut Clinic, London, UK
3 Open University of Cyprus, Faculty of Economics and Management, Nicoisia, Cyprus

Corresponding Author:

Dr Diana E Yung
Email: diana.e.yung@gmail.com
Mailing address: The Royal Infirmary of Edinburgh, Endoscopy Unit
51 Little France Crescent, Edinburgh, EH16 4SA
United Kingdom
Telephone: +44 7789588408

INTRODUCTION

The wireless motility capsule (WMC) (SmartPill®; Given Imaging Corp., Yoqneam, Israel) is a single use, ingestible device [1,2]. With dimensions 26.8 x 11.7mm, it is slightly bulkier than its imaging counterpart (PillCam®SB Medtronic, Minnesota, USA). SmartPill® records intraluminal pH, pressure and temperature as it is propelled through the gastrointestinal (GI) tract. Hence, the WMC is capable of providing gut motility parameters i.e. gastric transit time (GTT), small-bowel transit time (SBTT), colonic transit time (CTT) and whole gut transit time (WGTT) non-invasively. The American and European Neurogastroenterology & Motility Societies recommend the use of WMC to assess suspected gastroparesis, suspected small-bowel (SB) dysmotility and/or CTT in chronic constipation [3].

There are only scarce data on the motility patterns in patients with known or suspected Crohn's disease (CD). Furthermore, the use and clinical validity of the WMC has not been evaluated in this patient group. It is envisaged that future wireless investigation platforms for the digestive tract will be multimodal and versatile, thus able to incorporate imaging information with physiological or biochemistry data such as fecal calprotectin (FC), haemoglobin and gas constituents of the gastrointestinal tract. This combination data could be useful in the investigation and management of patients with CD. For instance, orocaecal transit time has been found to be prolonged in CD patients for various reasons including SB bacterial overgrowth (SBBO) whereas SBTT may conversely be shortened in CD patients following ileo-caecal resection; this would affect absorption of medications and should ideally be taken into account during drug design [4]. Therefore, we designed a pilot study to investigate whether WMC examination is feasible and safe in the assessment of gut motility in patients with known or suspected CD, and its utility compared to conventional video capsule endoscopy.

METHODS

Patient recruitment and study protocol

Consecutive patients with known or suspected CD (FC>200 µg/g), referred for SB evaluation with small-bowel capsule endoscopy (SBCE), were invited to participate in this study. The inclusion & exclusion criteria of the study are summarized in **Table 1**. Patients who accepted the invitation and consented to participate were invited for a lactulose hydrogen breath test for exclusion of SB bacterial overgrowth (SBBO) and were provided with a kit for stool sample collection and FC measurement [CALPROLAB™ ELISA (ALP), Calpro AS, Lysaker, Norway; reference range <50 µg/g]. Those with a positive breath test, indicating SBBO, were excluded. Patients with negative SBBO breath test were invited to return a stool specimen and attend for a SB patency check with the AGILE® capsule (Given Imaging Corp., Yoqneam, Israel).

The detailed flowchart of the study design is presented in **Figure 1**. Patients ingested consecutively the PillCam®SB followed, four h later, by the SmartPill®. The technical characteristics of the 2 capsules used (PillCam®SB and SmartPill®) are detailed in **Table 2**.

Data collection

Data were downloaded from the recorders to the relevant workstations and analysed using proprietary software, i.e. *RAPID*® for PillCam®SB and semi-automated pressure analysis software, MotiliGI® (Given®Imaging Corp) for SmartPill®. For the latter, results are presented in both graphical and statistical forms. PillCam® data include gut transit times and SB findings. The inflammation levels were quantified using the Lewis score (LS), which has been devised to objectively report SB inflammation in SBCE**.** SmartPill® data examined in this study were pH, transit times (GTT, SBTT, CTT and WGTT) and motility index (MI) per segment, where MI = Ln (sum of pressure amplitudes × number of contractions +1). The data acquired from the study group were compared to historical controls (healthy individuals with no known pathology obtained from unpublished data), used to establish the normal range for segmental and total gut transit times.

Statistical analysis

Microsoft Excel (© 2015 Microsoft) and StatsDirect (StatsDirect Ltd, Altrincham, UK) software were used for statistical analysis. Two-tailed Mann-Whitney U test was used for comparison of the study and control groups. Linear regression was used to establish any correlation between motility indices and FC or LS. *P* values < 0.05 were considered statistically significant.

The study was supported by a defined grant by Given®Imaging Ltd (ESGE- Given®Imaging Research grant 2011) and approved by the local ethics committee (ref. 12/SS/0013).

RESULTS

Over a 12 month period (2012), 19 patients were recruited. Three patients were excluded as their previous history included a known strong functional component to their symptoms which could affect gut motility independently of CD, including irritable bowel syndrome, chronic idiopathic intestinal pseudo-obstruction and cyclic vomiting. A further four patients, referred for SBCE on suspicion of CD, were also excluded as their FC levels were <200 µg/g. Twelve patients completed the study (7 female/5 male; mean age 44.2±16.6 years). **Figure 2** shows the number of patients recruited, dropouts, and complete/incomplete data sets obtained. Clinical characteristics and per patient study results are tabulated in detail in **Table 3**. The differences in the motility of the study group *vs.* the control group are depicted in **Table 4**. Patients in our study had longer transit times and significantly lower gut motility when compared to the control group, **Figures 3,4**.

The motility index (MI) in the stomach, SB and colon was significantly lower in patients with CD, as compared with controls, and this was statistically significant (*P*<0.05) for all motility indices measured throughout the gut. The total transit time for the WMC was longer compared with the SBCE; this could be attributed to the differences in the capsules' specifications as detailed in **Table 2** [1,5,6] and the difference in capsule density, **Figure 5** [7,8]**.** The distribution of WGTT, FC and LS for those study subjects for whom the data were available

is presented in **Figure 6a**. **Figures 6b and 6c** show the linear regression between MI/FC and MI/LS, respectively.

DISCUSSION

This pilot study is the first to attempt dual use of SBCE and WMC in the assessment of patients with known or suspected CD. Currently, diagnosing CD requires a clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations [9]. To date, the value of SBCE in the investigation of CD has already been established [10]. A previous study [11], in which cine magnetic resonance enterography (MRE) was employed in addition to the regular MRI protocol, found that imaging areas of altered gut motility helped to detect more CD-specific findings. Other studies have shown that CD is associated, possibly due to inflammation, with delayed gastric emptying [12].

Therefore, addition of motility data in this setting could be of use [2,13], especially when first-line investigations are inconclusive. Compared to the traditional method of assessing GI motility with scintigraphy/radio-opaque markers, WMC is not associated with any radiation exposure. The concurrent use of SBCE and WMC shows how multimodal information can provide information not only on the mucosal appearances of patients with CD but also physiological motility data. However, this needs to be balanced against the risk of capsule retention, a feared complication in patients with CD. There was one case of stomach retention of the capsule. This occurred after an incomplete patency check with follow-up abdominal x-ray (patency capsule seen within large bowel). Limited CT scanning post-patency may be more useful in these patients [14].

Our patient group had significantly longer transit times compared to the controls (P <0.05 for all parameters measured)**, Table 4**. However, statistical significance should be interpreted with caution due to the small sample size. Other limitations in this pilot study include potential selection bias, as patients with significant SB inflammation were excluded due to fear of capsule retention, and the SmartPill® signal loss (resulting in incomplete data sets in 5/10 completed WMC examinations). It is not clear if this is due to technological limitations or whether the concurrent use (4h apart) of two capsules caused some radiofrequency interference [1,5,6]. Furthermore, we experienced difficulty in correlating data obtained by the WMC with other parameters such as FC and LS. This can be seen in other studies that have tried to explore relationship between LS and FC in patients with SB CD [15].

Take home messages

- Physiological data obtained from the use of the SmartPill® could be of value in conjunction with 'conventional' SBCE to shed more light in the pathophysiology of CD and perhaps assist in patient management. However, to better help clinicians to understand and maximise use of the motility information, the development of a simplified interpretation system is necessary.

- Despite concerns about capsule retention in patients with CD, our study suggests that the SmartPill® seems generally safe for use in these patients, although use of a patency capsule is recommended beforehand.

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Legend for tables and figures

Table 1: Inclusion and exclusion criteria
Abbreviations: CD: Crohn's Disease; DM: Diabetes Mellitus; FC: Faecal Calprotectin; GI: gastrointestinal; ICD: Implantable Cardioverter Defibrillator; PC: Patency Capsule; SB: small-bowel; pts: patients

Table 2: Comparison between specifications of PillCam® SB2 and SmartPill®

Table 3: Summary of clinical characteristics and findings of patients in our study
Abbreviations: CD: Crohn's Disease; CR: Capsule retention; Duo: Duodenum; FC: Faecal Calprotectin; GTT: Gastric Transit Time; LS: Lewis Score; MI: Motility Index; MS: Montreal Score; PPI: Proton Pump Inhibitor; SB: Small Bowel; SBCE: Small-Bowel Capsule Endoscopy; SBTT: Small-Bowel Transit Time; TT: Transit Times; WBTT: Whole-bowel Transit Time; WMC: Wireless Motility Capsule
* In the case of patient 8, WBTT was taken as time to excretion of capsule in ileostomy.

Table 4: Comparison of results from our patients vs controls
For our patients, some results were not available for all patients, therefore N is given where N = number of patients for whom results were available.
Abbreviations: FC: faecal calprotectin; GTT: Gastric Transit Time; LS: Lewis Score; MI: Motility Index; SB: small bowel; SBTT: Small-Bowel Transit Time; WBTT: Whole-Bowel Transit Time

Figure 1: Summary of study protocol

Figure 2: Recruitment process for this study

Figure 3: Comparison of transit times between study group and controls
Abbreviations: Ctrl: controls; GTT: gastric transit time; SBTT: small-bowel transit time; WBTT: whole bowel transit time

Figure 4: Comparison of motility index between study group and controls
Abbreviations: Ctrl: controls; duo: duodenum; MI: Motility Index; SB: small-bowel

Figure 5: Floating characteristics of Pillcam SB2 (left) and Smartpill (right) submerged in 400ml sterile water for irrigation

Figure 6a: Distribution of WBTT, FC and LS for patients in our study for whom the relevant data sets were available. Each plot point represents a patient in our study with the numbers corresponding to patient numbers in Table 3.
Abbreviations: FC: faecal calprotectin; LS: Lewis Score; WBTT: whole bowel transit time

Figure 6b: Linear regression of FC against motility indices for patients in our study for whom the relevant data sets were available

Figure 6c: Linear regression of LS against motility indices for patients in our study for whom the relevant data sets were available

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
✓ age > 18 years ✓ Known diagnosis of CD, being referred for (re-) assessment of extent & severity of SB inflammation ✓ Suspected CD with FC>200 µg/g	× Pregnancy or lactation × Swallowing difficulties or frailty × Known SB strictures × Pacemaker/ICD in situ × Psychiatric history × Prior upper GI tract surgery (other than end-to-end anastomosis) × Known DM or other cause of metabolic gastroparesis × Pts on codeine/morphinoids unable or unwilling to stop them prior to the study × Lactose intolerance or egg allergy (for PC) × Positive hydrogen breath test × History of functional symptoms e.g. cyclical vomiting, irritable bowel syndrome

Abbreviations: CD: Crohn's Disease; DM: Diabetes Mellitus; FC: Faecal Calprotectin; GI: gastrointestinal; ICD: Implantable Cardioverter Defibrillator; PC: Patency Capsule; SB: small-bowel; pts: patients

Table 2: Comparison between specifications of PillCam® SB2 and SmartPill®

Specifications	**PillCam® SB2**	**SmartPill®**
Length (mm)	26	26
Diameter (mm)	11	13
Battery life	8 h	5 days
Mode of data transmission	Ultra-high frequency band radio telemetry	Radiofrequency-based

Table 3: Summary of clinical characteristics and findings of patients in our study

No.	Age (years)	Gender	Indication	MS (if known CD)	FC (µg/g)	SBCE findings Total time;GTT;SBTT (min) *Findings*	LS	MotilGI® report	TT (min) WBTT;GTT;SBTT	pH	MI (segmental)
1	49	M	Known CD	A2 L1 B1	60	546; 125; 205 Single aphtha, poor views	135	Signal loss, long GTT of SBCE but not WMCs	1667; 226; 141	n/a	n/a
2	37	M	Known CD	A1/2 L1 B1	-	516; 36; 242 Blood in stomach, no mucosal inflammation	0	Generally prolonged transit times, poor motility	6620; 2577; 288	Gastric 1.4 SB 7.2	Gastric 16.75 Duo 11.60 SB 15.18 Caecum 12.19
3	58	F	Known CD	A3 L1 B1	590	683; 28; 552 Gastric residue +++, lymphangiectasias, mucosal erythema, ?stenosis x 2	3810	Prolonged transit time	7161; 1096; 638	n/a	Gastric – Duo 12.51 SB – Caecum 14.17
4	34	F	Known CD	A2 L3 B1p	Insuff	n/a	n/a	High gastric pH, ?pt on PPI	2686; 867; 240	Gastric 5.4 SB 7.1	Gastric 16.3 Duo 9.89 SB 16.24 Caecum 14.72
5	72	F	Known CD	A? L1 B1	Insuff	857; 77; 252 Distortion of folds, Lymphangiectasias, mucosal erythema, multiple aphthae	5160	Generally low motility	1956; 798; 447	Gastric 1.1 SB 7.2	Gastric 14.65 Duo 9.19 SB 14.16 Caecum 12.00
6	51	M	Known CD	A2 L3 B1	80	436; 65; 342 aphtha x1, reticulonodular mucosal pattern	450	Signal loss	1609; n/a; n/a	n/a	n/a
7	37	F	Known CD	A2 L3	290	384; 19; n/a Normal to pouch	0	WMC not done –	n/a	n/a	n/a

			Colectomy + ileoanal pouch	B1				dropout			
8	40	F	Known CD Pancolectomy + ileostomy	A2 L3 B1	-	410; 10; 254 Gastritis, poor views	0	Signal loss, rapid transit time	808*; 233; n/a	n/a	n/a
9	66	F	?CD	NA	970	369; n/a; n/a Gastric retention, pyloric stenosis	n/a	Data loss, CR	n/a	n/a	n/a
10	58	M	?CD	-	320	517; 31; 169 Mucosal oedema & denudation, ? enteropathy	280	Low motility, acidic SB	1312; 167; 192	Gastric 1.2 SB 6.4	Gastric 11.58 Duo 11.41 SB 15.98 Caecum 14.61
11	36	M	?CD	-	110	234; 33; 188 Mucosal cobblestone, Several aphthae	450	Signal loss but normal transit of WMC	n/a	n/a	n/a
12	23	F	?CD	-	300	439; 14; 327 Aphthae x 2	450	High gastric pH, very long colon transit	6650; 142; 252	Gastric 3.7 SB 6.6	Gastric 10.26 Duo 11.31 SB 15.77 Caecum 11.97

Abbreviations: CD: Crohn's Disease; CR: Capsule retention; Duo: Duodenum; FC: Faecal Calprotectin; GTT: Gastric Transit Time; LS: Lewis Score; MI: Motility Index; MS: Montreal Score; PPI: Proton Pump Inhibitor; SB: Small Bowel; SBCE: Small-Bowel Capsule Endoscopy; SBTT: Small-Bowel Transit Time; TT: Transit Times; WBTT: Whole-bowel Transit Time; WMC: Wireless Motility Capsule

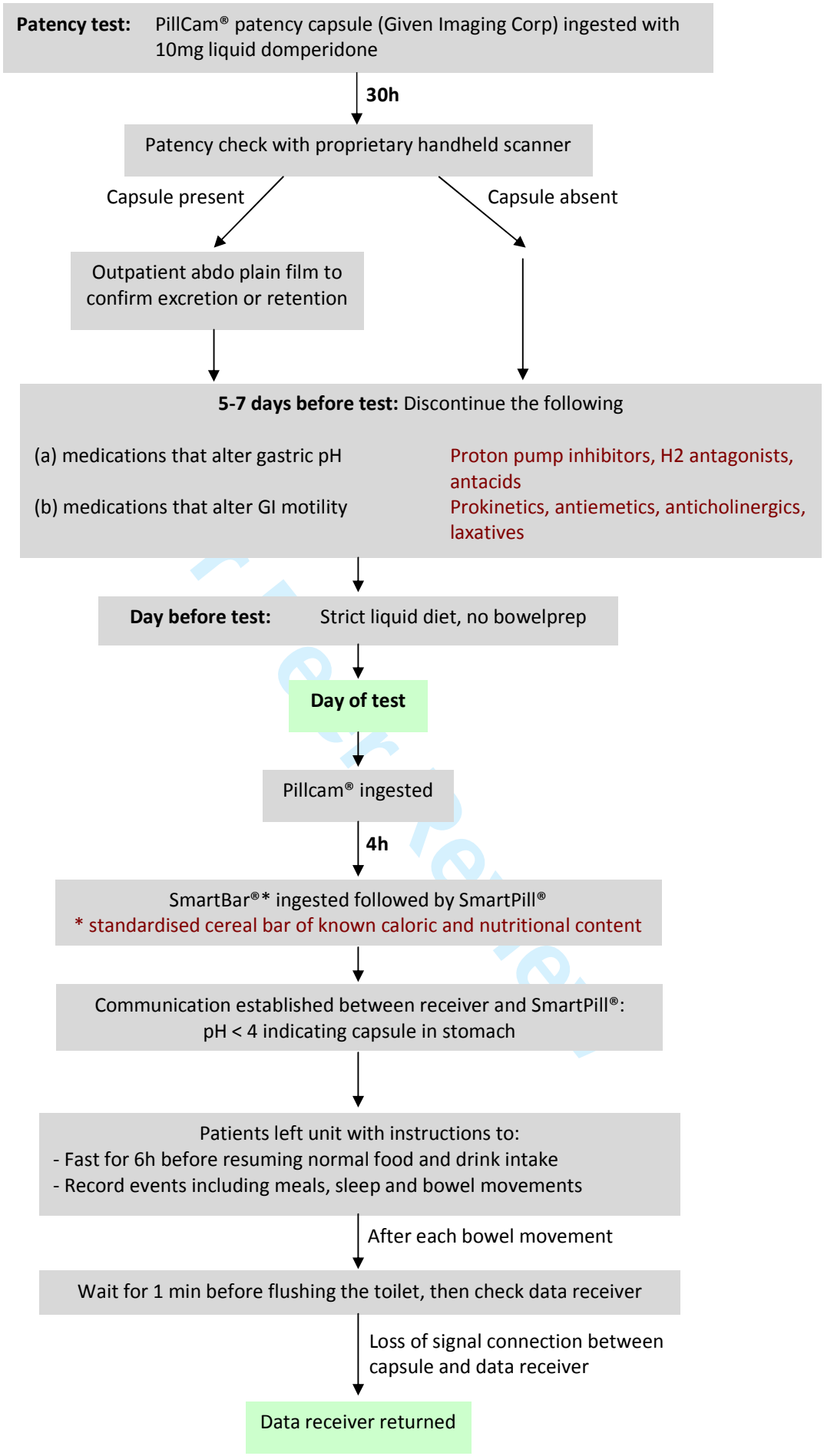
* In the case of patient 8, WBTT was taken as time to excretion of capsule in ileostomy.

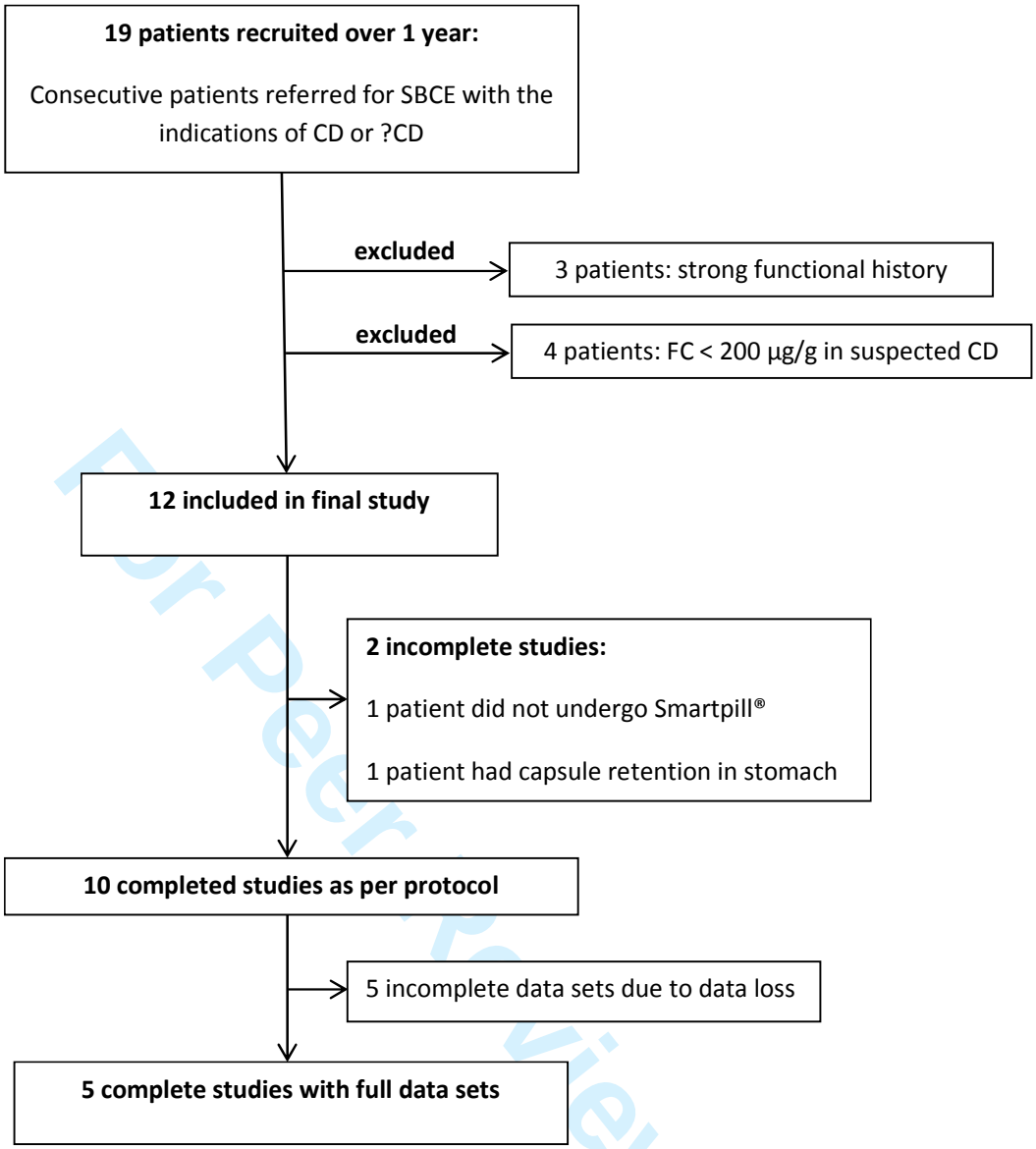
Table 4: Comparison of results from our patients vs controls

For our patients, some results were not available for all patients, therefore N is given where N = number of patients for whom results were available.

	Patients	**Controls**	***P*-values**
Number	12	33	
Gender	7 F, 5 M	15 F, 18 M	
Average Age ±SD	44.25 ±16.66 years	40.85 ±16.28 years	
FC (µg/g)	340 ±307.71 (N=8)	n/a	
LS	1073.5 ±1835.5 (N=10)	n/a	
GTT (min)	763.25 ±821.47 (N=8)	249.61 ±167.47	0.09
SBTT (min)	314 ±171.99 (N=7)	288.81 ±107.74	0.89
WBTT (min)	3385.44 ±2621.03 (N=9)	1988.67 ±972.99	0.82
Gastric pH	2.56 ±1.92 (N=5)	1.64 ±0.89	0.35
SB pH	6.9 ±0.37 (N=5)	7.16 ±0.45	0.17
Gastric MI	13.91 ±2.88 (N=5)	52.00 ±32.68	0.002
Duodenal MI	10.99 ±1.22 (N=6)	90.27 ±76.50	0.0001
SB MI	14.55 ±1.92 (N=5)	122.48 ±65.90	0.0004
Caecal MI	13.28 ±1.35 (N=6)	108.58 ±121.10	0.0006

Abbreviations: FC: faecal calprotectin; GTT: Gastric Transit Time; LS: Lewis Score; MI: Motility Index; SB: small bowel; SBTT: Small-Bowel Transit Time; WBTT: Whole-Bowel Transit Time


Patency test: PillCam® patency capsule (Given Imaging Corp) ingested with 10mg liquid domperidone
30h
Patency check with proprietary handheld scanner
Capsule present
Capsule absent
Outpatient abdo plain film to confirm excretion or retention
5-7 days before test: Discontinue the following
(a) medications that alter gastric pH
Proton pump inhibitors, H2 antagonists, antacids
(b) medications that alter GI motility
Prokinetics, antiemetics, anticholinergics, laxatives
Day before test: Strict liquid diet, no bowelprep
Day of test
Pillcam® ingested
4h
SmartBar®* ingested followed by SmartPill®
* standardised cereal bar of known caloric and nutritional content
Communication established between receiver and SmartPill®:
pH < 4 indicating capsule in stomach
Patients left unit with instructions to:
- Fast for 6h before resuming normal food and drink intake
- Record events including meals, sleep and bowel movements
After each bowel movement
Wait for 1 min before flushing the toilet, then check data receiver
Loss of signal connection between capsule and data receiver
Data receiver returned



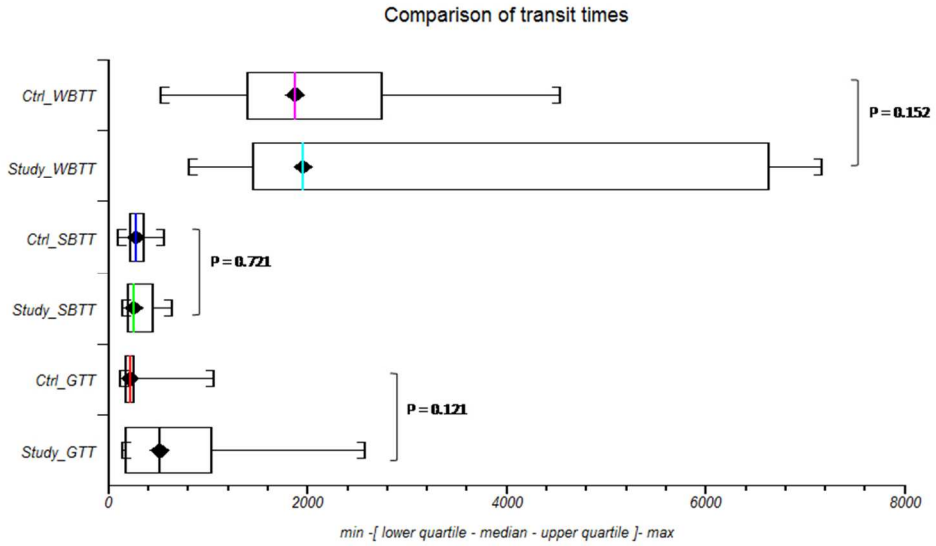


Figure 3: Comparison of transit times between study group and controls
Abbreviations: Ctrl: controls; GTT: gastric transit time; SBTT: small-bowel transit time; WBTT: whole bowel transit time
75x42mm (300 x 300 DPI)

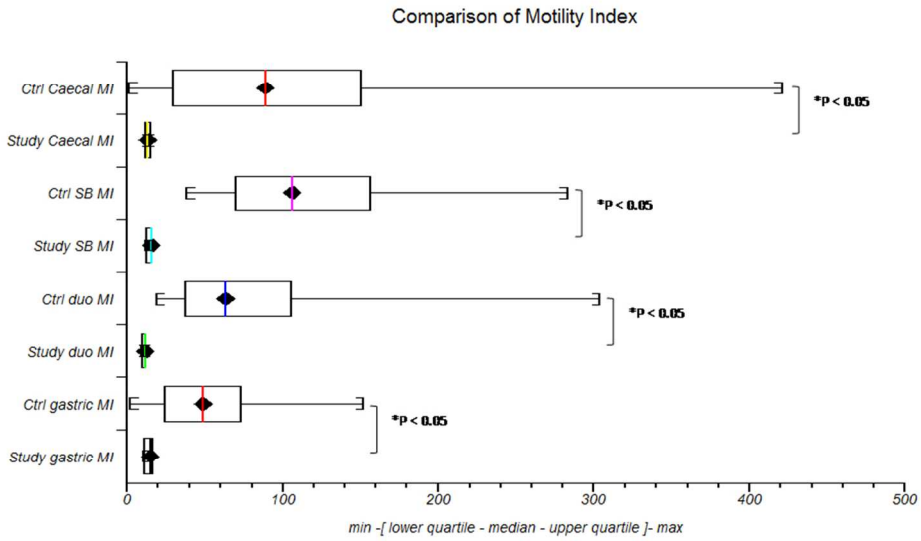


Figure 4: Comparison of motility index between study group and controls
Abbreviations: Ctrl: controls; duo: duodenum; MI: Motility Index; SB: small-bowel
82x46mm (300 x 300 DPI)

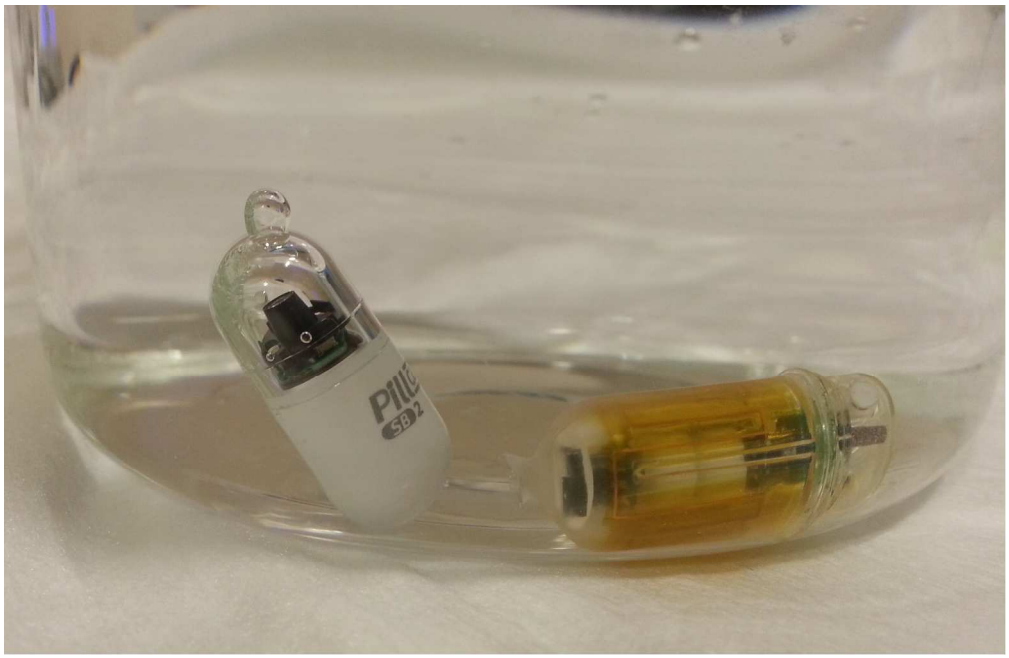


Figure 5: Floating characteristics of Pillcam SB2 (left) and Smartpill (right) submerged in 400ml sterile water for irrigation
243x157mm (300 x 300 DPI)

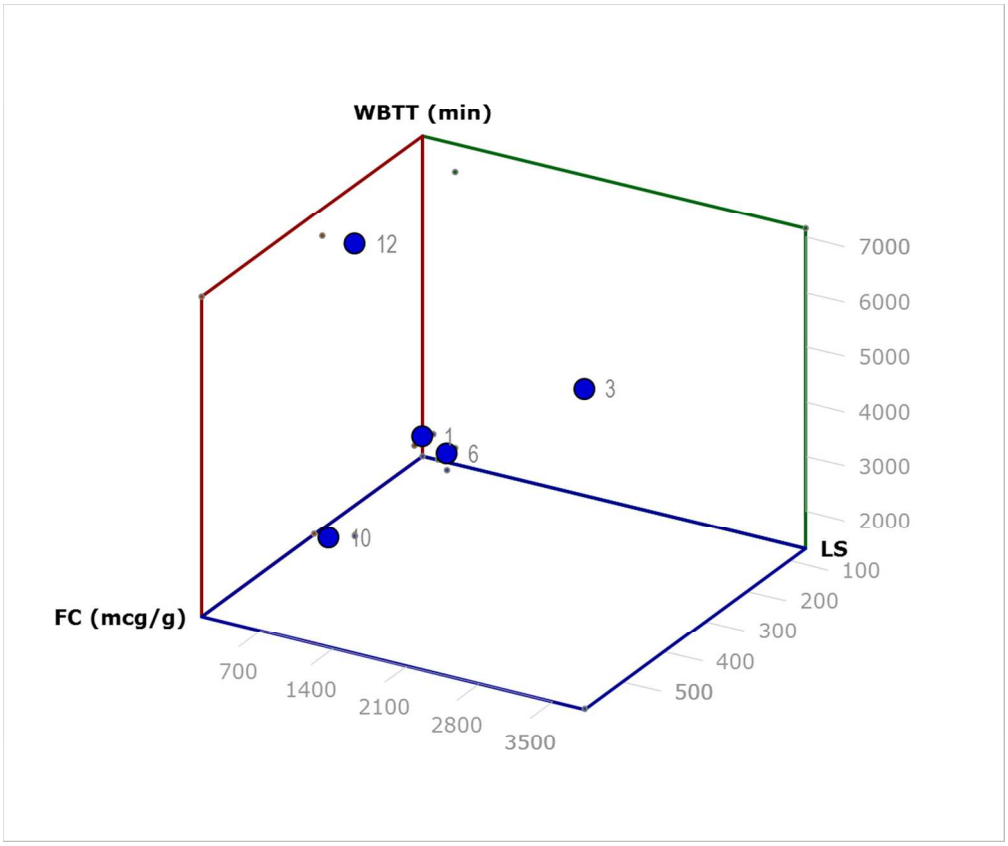


Figure 6a: Distribution of WBTT, FC and LS for patients in our study for whom the relevant data sets were available. Each plot point represents a patient in our study with the numbers corresponding to patient numbers in Table 3.
Abbreviations: FC: faecal calprotectin; LS: Lewis Score; WBTT: whole bowel transit time
104x87mm (300 x 300 DPI)

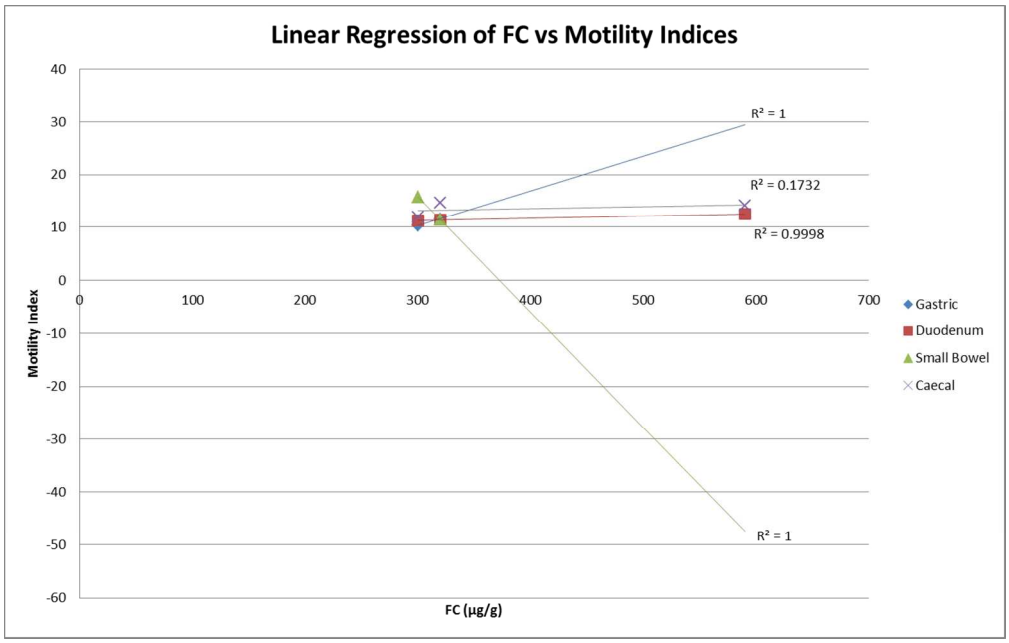


Figure 6b: Linear regression of FC against motility indices for patients in our study for whom the relevant data sets were available
118x74mm (300 x 300 DPI)

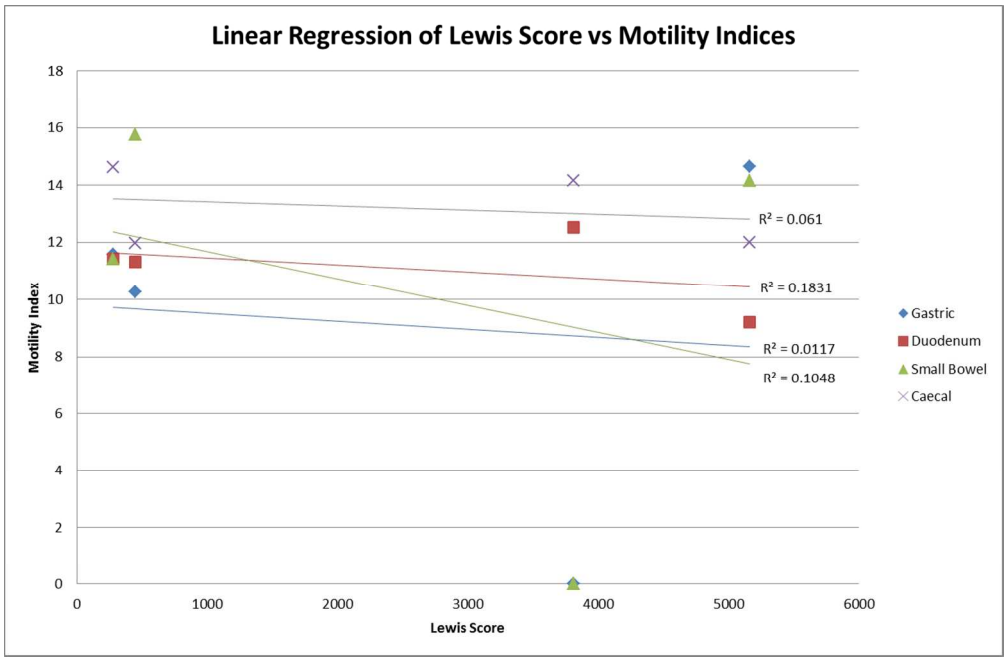


Figure 6c: Linear regression of LS against motility indices for patients in our study for whom the relevant data sets were available
114x74mm (300 x 300 DPI)