Small-bowel transit scintigraphy in children with paediatric intestinal pseudo-obstruction

Abstract

Introduction:

Objective evidence of small intestinal dysmotility is a key criterion for the diagnosis of paediatric intestinal pseudo-obstruction (PIPO). Small bowel scintigraphy (SBS) allows for objective measurement of small bowel transit (SBT), but limited data is available in children. We aimed to evaluate the utility of SBS in children suspected of GI dysmotility.

Methods:

Patients undergoing gastric emptying studies (GES) for suspected foregut dysmotility, including PIPO, from 2016 to 2022 at two tertiary children's hospitals were recruited to an extended protocol of GES to allow assessment of SBT. PIPO was classified based on antroduodenal manometry (ADM). SBT was compared between PIPO and non-PIPO patients. Scintigraphic parameters were assessed and correlated against ADM scores.

Results:

Fifty-nine patients (16 PIPO and 43 non-PIPO diagnoses) were included. SBS was performed with liquid and solid meals in 40 and 26 patients, respectively. As compared to the non-PIPO group, PIPO patients had a significantly lower median percentage of colonic filling at 6 hours, with both liquid (48% vs 83%) and solid tests (5% vs 65%). SBT in PIPO patients with myopathic involvement was significantly slower than in patients with neuropathic PIPO, both for liquid and solid meal. A significant correlation was found between solid-SBT and ADM scores (r=-0.638, *P*=0.036).

Discussion:

SBS provides a practically feasible assessment of small intestinal motility. It shows a potential utility to help diagnose and characterise PIPO. SBS appears most discriminative in PIPO patients with myopathic involvement. Studies in a larger paediatric population and across different ages are required.

Abstract word count: 248 words

WHAT IS KNOWN

- Small bowel scintigraphy (SBS) has potential utility to objectively measure small bowel transit (SBT) in adults.
- In adults, normal SBT is defined if ≥40% of radiotracer has reached the colon at 6 hours.
- SBS has not been validated in children.

WHAT IS NEW HERE

- SBS provides a well-tolerated and practically feasible assessment of small intestinal motility in children.
- The test can be performed by extending data acquisition from gastric emptying studies
- SBS shows a potential utility as an aid to diagnose and characterise PIPO, particularly in PIPO patients with myopathic involvement.

INTRODUCTION

Small bowel transit tests are less invasive methods for the assessment of small intestinal function, as compared to antroduodenal manometry (ADM) and histopathology from full-thickness intestinal biopsies. They are considered physiologic methods allowing readout of the time taken for the small bowel to propel its contents[1-4].

Currently, ADM has been used as a tool for assessing small intestinal dysmotility. Although this test has not been standardized in either children or adults, potential enhancements have been observed in the recent years. By using an increased breadth of analysis for various contractile parameters and developing an associated score (GLASS), the diagnosis and subtypes of PIPO appeared to better correlate with histological findings from full-thickness small-intestinal biopsies[5]. However, both the insertion of manometric catheter into the small bowel and small bowel full-thickness biopsies may be considered as invasive methods.

Scintigraphic assessment of small bowel transit time (SBTT) allows direct non-invasive quantitative readout of small intestinal propulsion by tracking the progression of an ingested radiopharmaceutical propelled through the intestine[4]. In recent recommendations[2], it is suggested as a potential tool to provide objective evidence of small intestinal neuromuscular involvement, one of the key criteria for the diagnosis of paediatric intestinal pseudo-obstruction (PIPO)[2]. Small bowel scintigraphy (SBS) is usually performed using either a single Technetium-99m-labelled liquid test feed alone or a combination of solid and liquid using both Technetium-99m (^{99m}Tc; 6-hour half-life) and Indium-111 Diethylenetriaminepentaacetic Acid (^{111}In-DTPA; 2.8-day half-life)[6, 7]. Following the ingestion of a standardized radiolabelled meal (orally or via gastrostomy), the percentage of gastric retention and the movement of radiotracer from the stomach to the cecum are obtained at different time intervals. This allows the determination of gastric emptying and SBTT.

To quantify small bowel transit (SBT), several methods have been utilised[6, 8]. The terminal ileum filling method is based on the observation that the proximal small bowel has

the most rapid transit, with a slower transit into the distal part and the terminal ileum serving as a reservoir[9]. Therefore, the activity filling the terminal ileum before it crosses the ileo-cecal valve into the colon has been suggested to represent SBT.

The simplest scintigraphic approach is to determine the oro-cecal transit by using the amount of colon filling at 6 hours as an index of SBT. This method has provided good correlation with the hydrogen breath test[10].

Generally, the reference scintigraphic values of the small bowel depend on the measurement method, the radioisotope used, and the type of meal. According to The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Association of Nuclear Medicine (EANM) Practice Guidelines, SBT is normal if at 6 hours more than 40% of administered ^{111}In-DTPA radioactivity has reached either the terminal ileum or colon[6]. This definition has been widely used as an index of normal SBT in several studies, particularly in the adult population [11-13].

Despite several studies and guidelines used in adults, there is a lack of normative data on small intestinal scintigraphy in children. Additionally, there is limited data on SBS in children with motility disorders, although several studies have been performed in adults[6, 7, 14]. Therefore, this study aimed to evaluate the utility of SBS to help diagnose small bowel dysmotility in children, to identify possible reference values for the diagnosis of PIPO and to correlate findings with ADM, a standard test for small intestinal motility.

METHODS

Patients

All patients included in the study were referred to Great Ormond Street Hospital (GOSH) between January 2016 and December 2022, or to Queensland Children's Hospital (QCH) between January 2019 and December 2022, for further management. The patients underwent investigations of the gastrointestinal (GI) tract for gastric and small intestinal functional or motility disorders as part of their routine clinical care. A detailed description of

patient selection, inclusion and exclusion criteria and diagnostic definition is reported in the appendix.

Ethical considerations

The study protocol was approved by the Institutional Review Board of Great Ormond Street Hospital and HRA HCRW for conduct in the NHS by the London-Brent Research Ethics Committee (REC Ref 19/LO/0854). It was also approved by the Human Research Ethics Committee, Children's Health Queensland Hospital and Health Service, Brisbane, Australia (HREC/21/QCHQ/72690).

Small bowel transit

For the GES, the progression of a radiolabelled meal was measured by obtaining sequential scans over 3-4 hours with a dual-head gamma camera. For the liquid test meal, a test feed based on milk or formula was labelled with ^{99m}Tc-nanocolloid; a solid test meal based on egg white on toast or melted cheese on toast or pasta, radiolabelled with ^{99m}Tc-nanocolloid, was ingested. The SBS was performed by acquiring additional images up to 6-8 hours after meal ingestion to follow the movement of the test feed through the small intestine.

To establish the oro-cecal transit, a ROI was manually drawn around the expected location of ileo-cecal valve and/or cecum, and any colonic activity measured at 6 hours (**Figure 1**). A detailed descrition of scintigraphic method is reported in the appendix.

Antroduodenal manometry

The ADM tracing were analyzed by paediatric neurogastroenterologists as part of stardard clinical care. The analysis was mainly based on qualitative characteristics obtained from selected segments of the ADM recording. The final reports from this conventional analysis were collected. Since the enhanced ADM analysis and GLASS score have recently been established, the ADM recordings were anonymised and re-analysed based on previously published method[5] **(Appendix)**. A GLASS score of ≥10 was used to discriminate between PIPO and control patients; myopathy was identified by the presence of low amplitude of overall phase III contraction (<10 mmHg)[5]. A detailed description of ADM method is presented in the appendix.

RESULTS

Over 6 years, 59 patients (42 from GOSH and 17 controls from QCH) undergoing SBS were included in the study. Based on clinical and/or manometric criteria, 16 children were diagnosed with PIPO (median age of 8.98 years; IQR 3.45-13.04) and 43 with non-PIPO diagnoses (median age of 11.13 years; IQR 4.44-16.09). There was no significant age difference between the two groups (*P*=0.213). SBS was performed with liquid and solid test meals in 40 and 26 patients, respectively. Only 7 patients underwent both liquid- and solid-SBS. Demographic data for all patients are presented in **Table 1**.

1. Liquid-small bowel scintigraphy

Forty patients had SBS performed with a liquid test feed. Based on clinical and/or manometric criteria, 15 were diagnosed with PIPO and the remaining 25 with non-PIPO. The diagnoses in the non-PIPO (control) group included lower GI motility and functional disorders (GIMD), and upper GIMD. Demographic data for patients having liquid-SBS are presented in **Table 2**.

With a liquid test meal, PIPO patients had a significantly lower percentage of radiotracer reaching the colon within 6 hours, as compared to non-PIPO patients (48% vs 83%, *P*=0.005; **Figure 2**).

From the receiver operating characteristic (ROC) analysis, colonic filling of <55% at 6 hours after liquid meal ingestion provided a sensitivity of 68% for the diagnosis of PIPO and specificity of 84%, with an area under the curve (AUC) of 0.765 (*P*=0.005). It also provided a positive and negative predictive value of 67% and 80%, respectively.

By using enhanced ADM analysis and the associated GLASS score[5], 15 PIPO patients were classified into 2 groups: neuropathy (n=12), and neuromyopathy (n=3). Among these different PIPO subtypes, neuromyopathy had slower SBT compared to neuropathic PIPO and non-PIPO patients (6% vs 52% vs 83%, *P*=0.005; **Figure 3**).

As mentioned earlier, the non-PIPO patients included those with both upper and lower GIMD. SBT was not significantly different between patients with and without lower GIMD (73% vs 89%; NS; **Supplementary Figure 1A**). Neuromyopathy had slower SBT compared to neuropathic PIPO and non-PIPO patients without lower GIMD (6% vs 52% vs 73%, *P*=0.016; **Supplementary Figure 1B**)

Correlation between liquid small bowel transit and ADM

Nine and 15 patients in the non-PIPO and PIPO groups respectively underwent both liquid-SBS and ADM monitoring. The median interval between liquid-SBS and ADM was 6 days (**Table 2**).

Among 9 non-PIPO patients, 4 had conventional ADM analysis reported as unspecified abnormalities with enhanced ADM scores ≥10. However, they did not fulfil the other criteria for the diagnosis of PIPO. None of the 4 patients had colonic filling of <55% at 6 hours after the liquid meal.

All 15 PIPO patients had enhanced GLASS scores of ≥10. SBT in these patients was slow (colonic filling of <55% at 6 hours) in 10 patients.

When comparing the percentage of colonic filling at 6 hours with enhanced ADM (GLASS) score in 24 patients, there was no significant correlation between SBT of liquid meal and ADM score of manometric abnormalities (Spearman r=-0.266; *P*=0.208).

2. Solid-small bowel scintigraphy

Twenty-six small bowel scintigraphies were performed with a solid test meal. Based on clinical and/or manometric criteria, 5 of 26 patients were diagnosed with PIPO, and the remaining 21 with non-PIPO. Demographic data for patients having solid-SBS are presented in **Table 3**.

With a solid test meal, PIPO patients had a significantly slower SBT with the median value of radiotracer accumulation in the cecum at 6 hours of 5% compared to 65% in the non-PIPO group (*P*<0.001; **Figure 4**).

The result from the ROC analysis showed that a colonic filling of ≤26% provided a sensitivity of 100% and specificity of 81% for the diagnosis of PIPO (AUC = 0.962; *P*=0.002). It also provided a positive and a negative predictive value of 56% and 100%, respectively.

Correlation between solid small bowel transit and ADM

Based on enhanced ADM analysis[5], 3 PIPO patients were classified as neuropathic, and 2 as neuromyopathic. SBT performed with a solid test meal in patients with neuromyopathic PIPO was slower than in those with neuropathic ADM, with a colonic filling of 1.50% (IQR 1-2) at 6 hours, as compared to 8% (IQR 5-26) in neuropathic PIPO (*P*=0.006; **Figure 5**). Nine patients had both solid-SBS and ADM. The median interval between solid-SBS and ADM was 34 days (IQR 4-258). When comparing the percentage of colonic filling at 6 hours with ADM (GLASS) score, there was a significant correlation between solid-SBT and ADM score (Spearman r=-0.638; *P*=0.036).

3. Solid and Liquid small bowel scintigraphy

Among 59 patients who underwent SBS, 7 patients had the test performed with both liquid and solid meals (3 non-PIPO and 4 PIPO patients). There was no significant correlation between liquid- and solid-SBT reported by either qualitative (*P*=1.000 by Fisher's Exact Test, **Supplementary Table 1**) or quantitative analysis (Spearman r=0.393, *P*=0.383).

When comparing parameters from ADM with SBT in 5 patients (**Supplementary Table 1**), no significant correlation was found between either ADM GLASS score, the ADM score of fasting or post-prandial period, and the parameters from liquid and solid SBS.

Discussion

Nuclear scintigraphy has been suggested as the most accurate and sensitive method for the physiological measurement of GI transit, as the test allows the observation and quantification of the physiological movement of liquid or solid foods labelled with radiotracer along the GI tract through images taken with a gamma camera.[2, 6].

Scintigraphy is recommended by the American Neurogastroenterology and Gastrointestinal Motility Society and the European Society of Neurogastroenterology and Motility to determine SBT in patients with suspected diffuse GI motility disorder[15]. However, the normal range is vaguely defined in adults, and the test has not been validated in children. Therefore, this study aimed to evaluate the utility of SBS in children suspected of GI dysmotility, including PIPO.

Given the radiation exposure of scintigraphy is related to the activity of the radioisotope ingested with the test feed rather than the imaging duration and considering the short half-life (6 hours) of the radioisotope used to label both the liquid and the solid test feed (^{99m}Tc), we opted to perform the SBS as a continuation of the standard protocol for GES. Hence, the children undergoing GES as part of normal clinical care could have small bowel scintigraphic examination at no additional radiation risk, albeit with modest additional imaging time. Since the stomach and small intestine work together, as per ADM studies, we thought that a combined GES-SBS would provide a better assessment of upper GI transit. For children with PIPO there is a significant potential utility in collecting data on both the intestinal contractile pattern as well as the bowel transit, to better understand the underlying pathophysiology and identify the treatment option that best targets the pathophysiologic mechanism of the clinical condition. Of note, in this study, the amount of colon filling at 6 hours was used as an index of SBT since the measure of duodenal bulb to cecal time would require a continuous scanning to identify and measure the amount of radiotracers in the duodenal bulb and significantly longer scanning time (>7-8 hours) to follow the tracers until reaching the cecum. This may not be practical for the patients included.

In the cohort of 59 patients, most patients underwent liquid small bowel scintigraphy, given they presented with vomiting and feeding intolerance to solids. Additionally, most PIPO patients were PN dependent; only ~10% were able to feed orally. Although SBS performed with liquids may be less physiologic than solids, it was the form of feed tolerated by all patients in the study and therefore provided the only means of a valid comparison between patients on oral feeds and those who were not tolerant to solid meals.

All 16 PIPO patients were diagnosed based on at least 2 out of the 4 recommended criteria for the diagnosis of PIPO[2]. All patients underwent ADM and their tracings were analysed using enhanced analysis and GLASS scores[5]. Our earlier study reported that GLASS scores of ≥10 could differentiate PIPO from non-PIPO patients and a higher score represented more severe neuropathic features. In keeping with this all PIPO patients in this study had GLASS scores of ≥10[5]. Interestingly, 5 of 43 non-PIPO patients had GLASS scores of ≥10, but did not meet criteria for PIPO diagnosis (3 with constipation from colonic dysmotility and 2 with gastroparesis). It is known that constipation and colonic dysmotility can affect small intestinal contractile patterns[16]. Furthermore, given the GLASS scores are based on different contractile parameters including the antral response to test feeds[5], patients with gastroparesis might have slightly elevated scores. There was, however, no significant differences in SBT between non-PIPO patients diagnosed with and without lower GIMD. This finding was consistent with previously reported results that constipation did not change the transit pattern of the small intestine[17, 18].

In the non-PIPO patients who had liquid SBS, the median percentage of the colonic filling (83%) was higher than the cut-off value (60-70%), defined in the adult population[6, 13]. However, this figure was reduced to 72% when excluding the non-PIPO patients with lower GIMD. Of the 20 patients diagnosed with upper GIMD, 25% had prolonged SBT with <55% of test feed reaching the cecum by 6 hours. This is in keeping with a previous study by Maurer et al., where 19% of patients presenting with symptoms of upper GIMD had delayed SBT[13].

We accept that patients presenting with symptoms suggestive of GI dysmotility may not be comparable to healthy children. It is well known that justification for research studies involving ionising radiations in healthy children is strictly regulated. Although GES and SBS are thought to be non-invasive procedures, there remains concern regarding the risk of ionising radiation exposure in medical investigations (0.2-0.3mSv). Also, the patients need to be scanned every hour for at least 6-8 hours to complete the study. Therefore, children diagnosed with GIMD, who required GES as part of their clinical care, were recruited in the study.

As compared to non-PIPO patients, SBT in the PIPO group was significantly prolonged, particularly in those who had myopathic involvement on ADM. The delayed SBT, particularly in PIPO patients with myopathic features, was consistent with findings from previous studies[19-21]. In addition, Greydanus et al noted different patterns of bolus transit through the small bowel and ileocolonic bolus transfer among the study groups. Patients with myopathic intestinal pseudo-obstruction showed impaired colonic filling or prolonged ileocolonic bolus transfer, while patients with neuropathic small bowel had a similar pattern of bolus transfer to healthy controls but delayed initial cecal arrival time for 10% of the radiotracer (T10%)[21].

For solid SBS, the percentage of solid meal reaching the colon at 6 hours was smaller than with the test performed with liquids. Within the non-PIPO group, the median colonic filling at 6 hours was slower than in those with a liquid feed. It is unclear why there was a difference in the percentage of tracer reaching the colon between the solid and liquid SBS in non-PIPO patients. There is a significant difference in age (median age of 15.79 vs 7.76 years) but why this would affect the results is not known. Moreover, when patients diagnosed with lower GIMD were excluded, the colonic filling at 6 hours in non-PIPO patients studied with solid and liquid test meals were quite similar, with a median colonic filling percentage of 65% and 73%, respectively. Therefore, a colonic filling of >65% at 6 hours could be used as a potential cut-off value for normal SBS with both solid and liquid test feeds.

This study found a significant negative correlation between solid SBT and the ADM GLASS score. This means a more severe abnormality on ADM is associated with a more prolonged SBT, if the SBS was performed with solids. It is worth noting that liquid GES may not be as specific as solid GES[22]. However, a previous study showed that liquid GES correlated well with solid GES and an additional assessment of liquid GES could help identify patients with delayed gastric emptying particularly those with normal solid GES[23]. In our cohort, most of patients underwent liquid GES since patients with suspected PIPO commonly had history of solid or even liquid food intolerance. Hence, the study is limited due to the lack of solid GES. Additionally, a lack of correlation between liquid SBT and ADM parameters could

be explained by the methods used to determine the amount of bolus transfer, and the variability of transit times in patients with neuropathic PIPO, particularly rapid small bowel transit in some neuropathic patients[21, 24]. Only a small number of patients had both SBS performed with liquid and solid meals and ADM. Hence it was challenging to draw any conclusions on the association between each pair of the tests. Additionally, liquid SBS may not be able to fully distinguish patients with neuropathic PIPO from non-PIPO patients since there is a considerable overlap of these two groups.

In summary, solid-SBS provided better diagnostic accuracy for the diagnosis of PIPO, with higher sensitivity, specificity and negative predictive values, as compared to liquid-SBS. However, the method may be limited by patient feed tolerance. Although not very sensitive, liquid-SBS could identify patients with abnormal small-intestinal transit, particularly in those who could not undergo or complete the protocol for ADM monitoring. Thus, we proposed the use of SBS as a screening tool prior to referring patients for special investigation and treatment in the tertiary centers **(Supplementary Figure 2)**

Conclusions

This study shows promise for the potential utility of SBS as an aid to the diagnosis and characterisation of PIPO. The percentage of colonic filling at 6 hours of <55% for liquid and ≤26% for solid SBS could be used as a potential cut-off value for delayed SBT. Patients with neuromyopathy had extremely slow small intestinal transit. Studies in a larger paediatric population and across different age groups are required. We propose that until the test is better validated in larger studies across centres SBS may have utility as a screening tool prior to referring patients for special investigation and treatment in the tertiary centers.

Acknowledgement

Author's Contribution

NT - Guarantor of manuscript

AC: preparation of synopsis data, analysis and interpretation of data, drafting the article, critical revision of the manuscript and approval of the final version of the paper. EM: preparation of synopsis data, critical revision of the manuscript and approval of the final version of the paper. LB: analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. ME: analysis and interpretation of data and approval of the final version of the paper. BG: analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. KJL: recruitment of the patients; analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. AR: recruitment of the patients; analysis and interpretation of data and approval of the final version of the paper. SE: analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. OB: recruitment of the patients, analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. NT: Conception and study design, analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper.

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Figure legends

Figure 1 Regions of interest (ROIs) manually drawn (both anterior and posterior view) around the stomach at 3 hours and around the cecum and entire abdomen between 2 and 6 hours

Figure 2 The percentage of colonic filling at 6 hours after liquid meal ingestion in 25 non-PIPO and 15 PIPO patients

Figure 3 The colonic filling at 6 hours after liquid meal ingestion in controls and patients with different subtypes of PIPO, identified by enhanced ADM analysis

Figure 4 The percentage of colonic filling at 6 hours after solid meal ingestion in 21 non-PIPO and 5 PIPO patients

Figure 5 The colonic filling at 6 hours after solid meal ingestion in non-PIPO and PIPO patients classified subtype by enhanced ADM analysis

Table legends

Table 1 Demographic data for all patients including in the study

Table 2 Demographic data for studied patients who had liquid-small bowel scintigraphy

Table 3 Demographic data for studied patients who had solid-small bowel scintigraphy.

Supplementary files

Supplementary Figure 1 Liquid-small bowel transit in PIPO and non-PIPO patients with upper and lower functional GI disorders (GIMD; **A**) and the comparison between non-PIPO patients with upper GIMD and those with different subtypes of PIPO **(B)**

Supplementary Figure 2 Proposed diagnostic pathway for PIPO

Supplementary Table 1 A comparison between liquid and solid small bowel transit assessed by qualitative and quantitative analyses in 8 patients

Table 1 Demographic data for all patients including in the study.

Characteristics	**Non-PIPO patients (n=43)**	**PIPO patients (n=16)**	***P*-value**
Gender, male (%)	18 (41.86)	9 (56.25)	1.000
Age, years (IQR)	11.13 (4.44-16.09)	8.98 (3.45-13.04)	0.213
Age onset, years (IQR)	2.00 (0.33-13.01)	1.00 (0.04-4.00)	0.113
Presenting symptoms, (%)			
-Vomiting	32 (74.42)	16 (100.00)	0.026
-Constipation	27 (62.79)	11 (68.75)	0.766
-Abdominal pain	27 (62.79)	11 (68.75)	0.766
-Feeding intolerance	23 (53.49)	12 (75.00)	0.233
-Nausea	22 (51.16)	2 (12.50)	0.008
-Weight loss or failure to thrive	15 (34.88)	9 (56.25)	0.152
-Abdominal distension	10 (23.26)	11 (68.75)	0.002
Comorbidity, (%)			
-Preterm	7 (16.28)	2 (12.5)	1.000
-History of malrotation	1 (2.33)	3 (18.18)	0.057
-Urinary involvement	7 (16.28)	2 (12.50)	1.000
-Bowel dilatation	1 (2.33)	4 (25.00)	0.017
Feeding type, (%)			<0.001
- Oral liquid/solid	23 (53.49)	2 (12.50)	
- Liquid enteral	17 (39.53)	5 (31.25)	
- Mixed enteral and parenteral nutrition	3 (6.98)	2 (12.5)	
- TPN	0 (0)	7 (43.75)	
Investigations, (%)			
-Liquid SBS	25 (58.14)	15 (93.75)	0.011
-Solid SBS	21 (48.84)	5 (31.25)	0.255
-Both liquid and solid SBS	3 (6.98)	4 (25.00)	0.078
-ADM	12 (27.90)	16 (100.00)	<0.001
-cine-MRI	4 (9.30)	4 (25.00)	0.194
-Colonic manometry	7 (16.28)	14 (87.50)	<0.001
Colonic dysmotility	4/7 (57.14)	9/14 (64.29)	1.000
-Pellet study	5 (11.63)	0 (0)	0.310
Slow transit	1/5 (20.00)	0 (0)	NA
-Anorectal manometry	8 (18.60)	12 (75.00)	<0.001
Abnormal ARM	1/8 (12.5)	1/12 (8.33)	1.000
-Full-thickness small intestinal biopsies	1 (2.33)	4 (25.00)	0.017

PIPO: paediatric intestinal pseudo-obstruction, IQR: Interquartile range, TPN: total parenteral nutrition, ADM: antroduodenal manometry, SBS: small bowel scintigraphy, NA: not applicable

Table 2 Demographic data for studied patients who had liquid-small bowel scintigraphy

Characteristics	**Non-PIPO patients (n=25)**	**PIPO patients (n=15)**	***P*-value**
Gender, male (%)	13 (52.00)	8 (53.33)	1.000
Age, years (IQR)	7.76 (3.82-14.15)	8.91 (3.18-13.27)	0.967
Age onset of symptoms, years (IQR)	0.75 (0.33-11.03)	0.75 (0.03-3.34)	0.387
Presenting symptoms and signs, (%)			
-Vomiting	21 (84.00)	15 (100.00)	0.278
-Constipation	16 (64.00)	10 (66.67)	1.000
-Abdominal pain	17 (68.00)	10 (66.67)	1.000
-Feeding intolerance	19 (76.00)	12 (80.00)	1.000
-Abdominal distension	8 (32.00)	10 (66.67)	0.050
-Nausea	8 (32.00)	2 (13.33)	0.269
-Weight loss or failure to thrive	5 (20.00)	8 (53.33)	0.041
-Bowel dilatation on radiography	1 (4.00)	3 (20.00)	0.139
Comorbidity, (%)			
-Preterm	4 (16.00)	2 (13.33)	1.000
-History of malrotation	1 (4.00)	3 (20.00)	0.139
-Urinary involvement	6 (24.00)	2 (13.33)	0.686
Diagnosis, (%)			<0.001
•PIPO	0 (0)	15 (100.00)	<0.001
•Lower GIMD	5 (15.63)	9 (60.00)	1.000
- Colonic dysmotility	4 (16.00)	9 (60.00)	1.000
•Upper GIMD	23 (92.00)	3 (20.00)	<0.001
- GORD	7 (28.00)	0 (0)	0.033
- Rumination	5 (20.00)	0 (0)	0.137
- Gastroparesis	8 (32.00)	3 (20.00)	0.486
- CVS	2 (8.00)	0 (0)	0.519
- Functional dyspepsia	2 (8.00)	0 (0)	0.519
- Functional nausea	1 (4.00)	0 (0)	1.000
Investigations			
•Gastric emptying, % (IQR)	9.00 (1.50-24.00)	15.00 (6.00-20.00)	0.378
•ADM, (%)	9 (36.00)	15 (100.00)	
Conventional ADM			<0.001
- Normal/unspecified	9/9 (100.00)	1/15 (6.67)	
- Neuropathy	0 (0)	12/15 (80.00)	
- Neuromyopathy	0 (0)	2/15 (13.33)	
Enhanced ADM			0.001
- Normal/unspecified	5/9 (55.56)	0 (0)	
- Neuropathy	1/9 (11.11)	12/15 (68.42)	
- Neuromyopathy	3/9 (33.33)	3/15 (31.58)	
ADM score	8.00 (6.50-15.00)	15.00 (13.00-16.00)	0.020
Day from SBS, days (IQR)	6.00 (1.50-12.00)	6.00 (2.00-28.00)	0.652
•cine-MRI, (%)	2 (8.00)	4 (26.67)	0.174

Characteristics	Non-PIPO patients (n=25)	PIPO patients (n=15)	*P*-value
- Normal/unspecified	2/2 (100.00)	0/4 (0)	0.050
- Bowel dilatation	0 (0)	1/4 (25.00)	
- Abnormal peristalsis	0 (0)	3/4 (75.00)	
Day from SBS, days (IQR)	40.00 (6.00-74.00)	66.00 (11.25-249.00)	0.355
•Full-thickness small intestinal biopsies, (%)	1 (4.00)	3 (20.00)	0.139
- Normal/unspecified	1/1 (100.00)	1/3 (33.33)	
- Abnormal	0 (0)	1/3 (33.33)	
- Not available	0 (0)	1/3 (33.33)	
Day from SBS, days (IQR)	1447.00	1086.00 (47.00-1247.00)	0.180
•Pellet study, (%)	2 (4.65)	0	0.519
- Slow transit	1 (2.33)	-	NA
Duration from SBS, days (IQR)	165.50 (8.00-323.00)	-	NA
•Colonic manometry, (%)	6 (13.95)	13 (81.25)	<0.001
- Colonic dysmotility	4 (9.30)	9 (56.25)	1.000
Duration from SBS, days (IQR)	4.00 (2.75-21.75)	10.00 (3.50-152.50)	0.233
•Anorectal manometry, (%)	6 (13.95)	11 (68.75)	0.003
- Abnormal	0	1 (6.25)	1.000
Duration from SBS, days (IQR)	4.50 (2.75-19.00)	10.00 (4.00-40.00)	0.363
Feeding type, (%)			0.005
- Oral liquid/solid	7 (28.00)	2 (13.33)	
- Liquid enteral	16 (64.00)	5 (33.33)	
- Mixed enteral and parenteral nutrition	2 (8.00)	2 (13.33)	
- TPN	0 (0)	6 (40.00)	

SBS: small bowel scintigraphy, IQR: interquartile range; PIPO: paediatric intestinal pseudo-obstruction, GIMD: gastrointestinal motility and functional disorders; GORD: gastro-oesophageal reflux disease, CVS: cyclic vomiting syndrome, IBS: irritable bowel syndrome, TPN, total parenteral nutrition; NA: not applicable

Table 3 Demographic data for studied patients who had solid-small bowel scintigraphy.

Characteristics	**Non-PIPO patients (n=21)**	**PIPO patients (n=5)**	***P*-value**
Gender, male (%)	6 (28.57)	2 (40.00)	0.628
Age, years (IQR)	15.79 (9.19-16.46)	7.74 (5.94-9.73)	0.029
Age onset of symptoms, years (IQR)	11.22 (0.94-14.47)	1.00 (0.25-5.03)	0.048
Diagnosis			
• PIPO	0 (0)	5 (100.00)	<0.001
• Lower GIMD			
- Colonic dysmotility	0 (0)	3 (60.00)	0.200
• Upper GIMD	21 (100.00)	1 (20.00)	<0.001
- GORD	4 (19.05)	0 (0)	0.555
- Rumination	3 (14.29)	0 (0)	1.000
- Gastroparesis	10 (47.62)	1 (20.00)	0.356
- Functional dyspepsia	3 (14.29)	0 (0)	1.000
- Functional nausea	2 (9.52)	0 (0)	1.000
- Others	3 (14.29)	0 (0)	1.000
Investigations			
• Gastric emptying, % (IQR)	6.00 (1.00-22.50)	4.00 (1.00-14.50)	0.530
• ADM	4 (19.05)	5 (100.00)	
Conventional ADM			0.008
- Normal/unspecified	4/4 (100.00)	0 (0)	
- Neuropathy	0 (0)	5/5 (100.00)	
Enhanced ADM			0.051
- Normal/unspecified	3/4 (75%)	0 (0)	
- Neuropathy	1/4 (25%)	3/5 (60.00)	
- Neuromyopathy	0 (0)	2/5 (40.00)	
ADM score	7.50 (6.25-10.25)	16.00 (14.00-23.50)	0.014
Day from SBS	118.00 (3.50-273.75)	34.00 (4.00-166.00)	0.806
• cine-MRI	3 (14.29)	2 (40.00)	0.236
- Normal/unspecified	3/3 (100.00)	0 (0)	
- Abnormal peristalsis	0 (0)	2/2 (100.00)	
Day from SBS	48.00 (48.00-314.00)	715.00 (289.00-1141.00)	0.236
• Full-thickness small intestinal biopsies	0 (0)	1 (20.00)	0.192
- Normal/unspecified	0 (0)	0 (0)	
- Abnormal	0 (0)	1/1 (100.00)	
Day from SBS	-	198.00	NA
- Pellet study, (%)	4 (19.05)	0 (0)	0.555
- Slow transit	0/4 (0)	-	NA
Duration from SBS, days (IQR)	304.50 (88.75-890.00)	-	NA
• Colonic manometry, (%)	2 (9.52)	4 (80.00)	0.005
- Colonic dysmotility	0 (0)	3/4 (75.00)	0.400

Characteristics	**Non-PIPO patients (n=21)**	**PIPO patients (n=5)**	***P*-value**
Duration from SBS, days (IQR)	37.00 (2.00-72.00)	6.50 (1.50-32.50)	0.643
• Anorectal manometry, (%)	3 (14.29)	4 (80.00)	0.010
- Abnormal	1 (4.76)	0 (0)	0.429
Duration from SBS, days (IQR)	10.00 (3.00-613.00)	10.00 (3.25-32.50)	0.714
Feeding type			0.011
- Oral liquid/solid	18 (85.71)	2 (40.00)	
- Liquid enteral	1 (0)	1 (20.00)	
- Mixed enteral and parenteral nutrition	2 (9.52)	0 (0)	
- TPN	0 (0)	2 (40.00)	

SBS: small bowel scintigraphy, IQR: Interquartile range; PIPO: paediatric intestinal pseudo-obstruction, GIMD: gastrointestinal motility and functional disorders; GORD: gastro-oesophageal reflux disease, CVS: cyclic vomiting syndrome, IBS: irritable bowel syndrome, TPN, total parenteral nutrition; NA: not applicable

FIGURE 1

Regions of interest (ROIs) manually drawn (both anterior and posterior view) around the stomach at 3 hours and around the cecum and entire abdomen between 2 and 6 hours

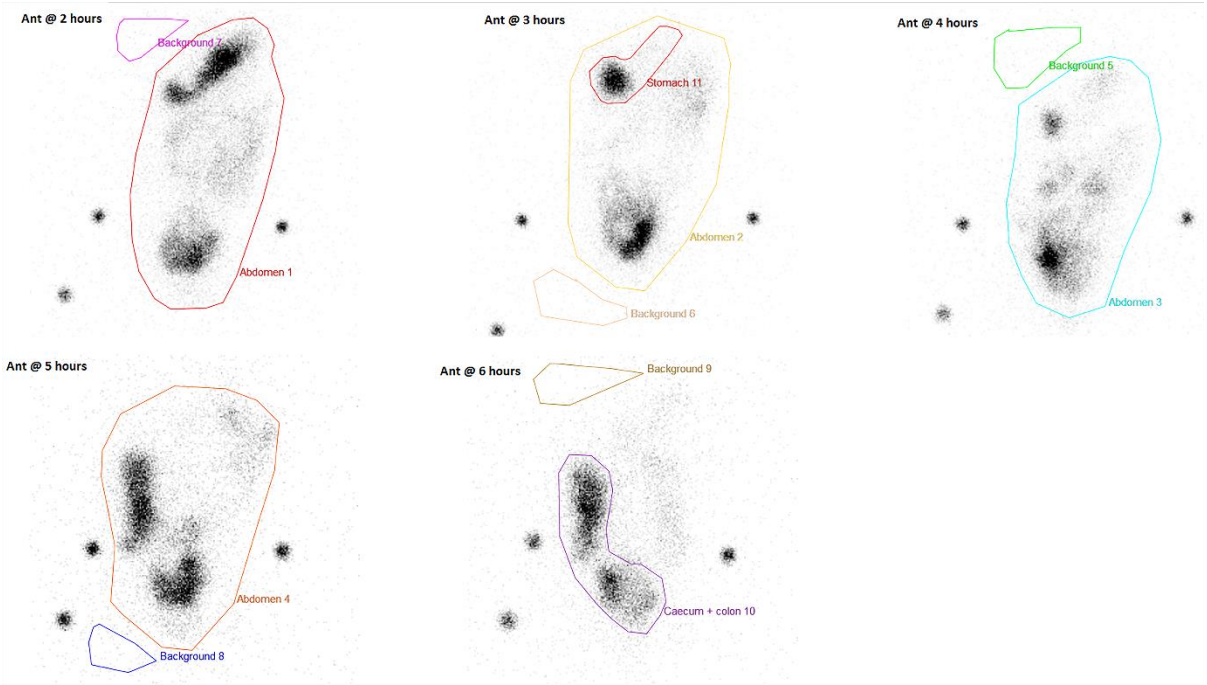


FIGURE 2

The percentage of colonic filling at 6 hours after liquid meal ingestion in 25 non-PIPO and 15 PIPO patients

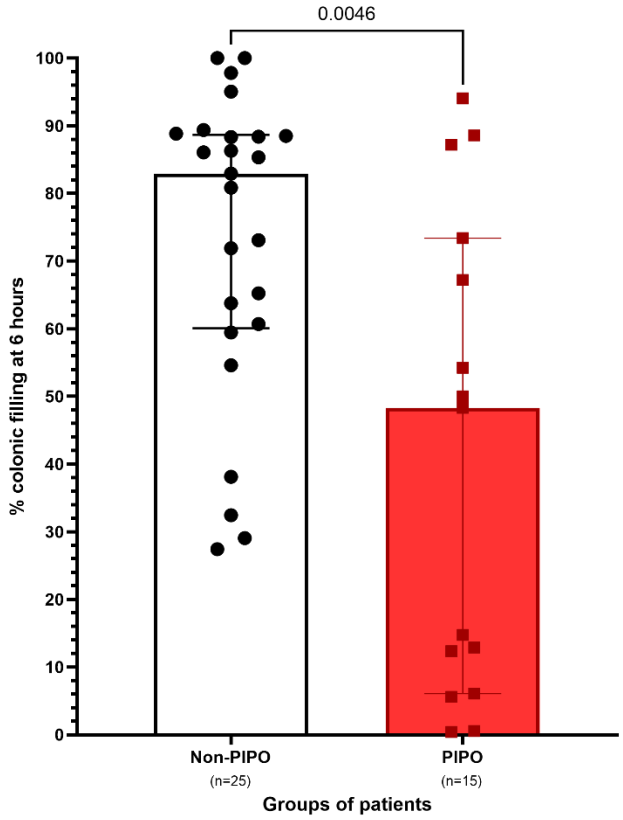


FIGURE 3

The colonic filling at 6 hours after liquid meal ingestion in controls and patients with different subtypes of PIPO, identified by enhanced ADM analysis.

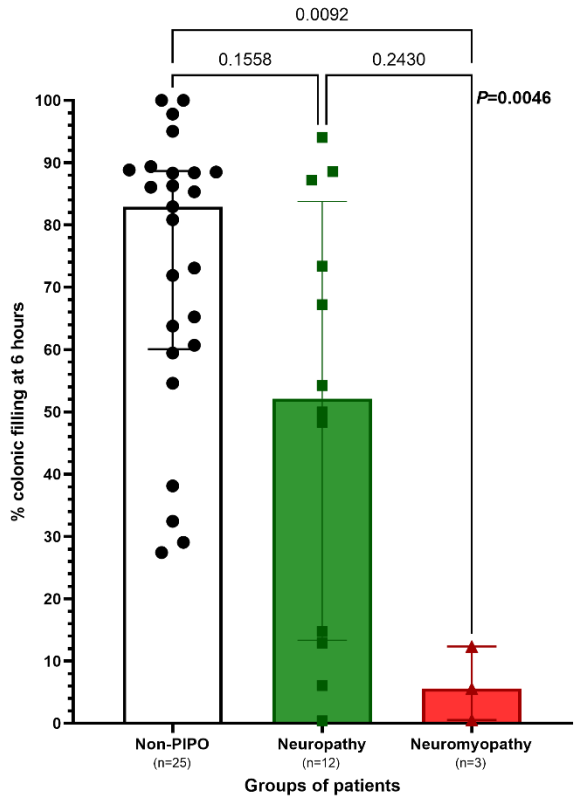


FIGURE 4

The percentage of colonic filling at 6 hours after solid meal ingestion in 21 non-PIPO and 5 PIPO patients.

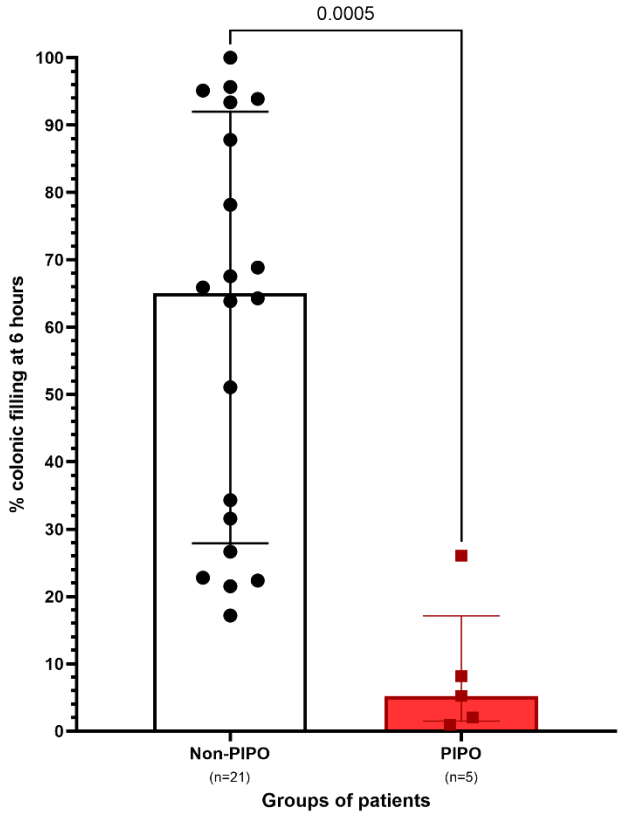
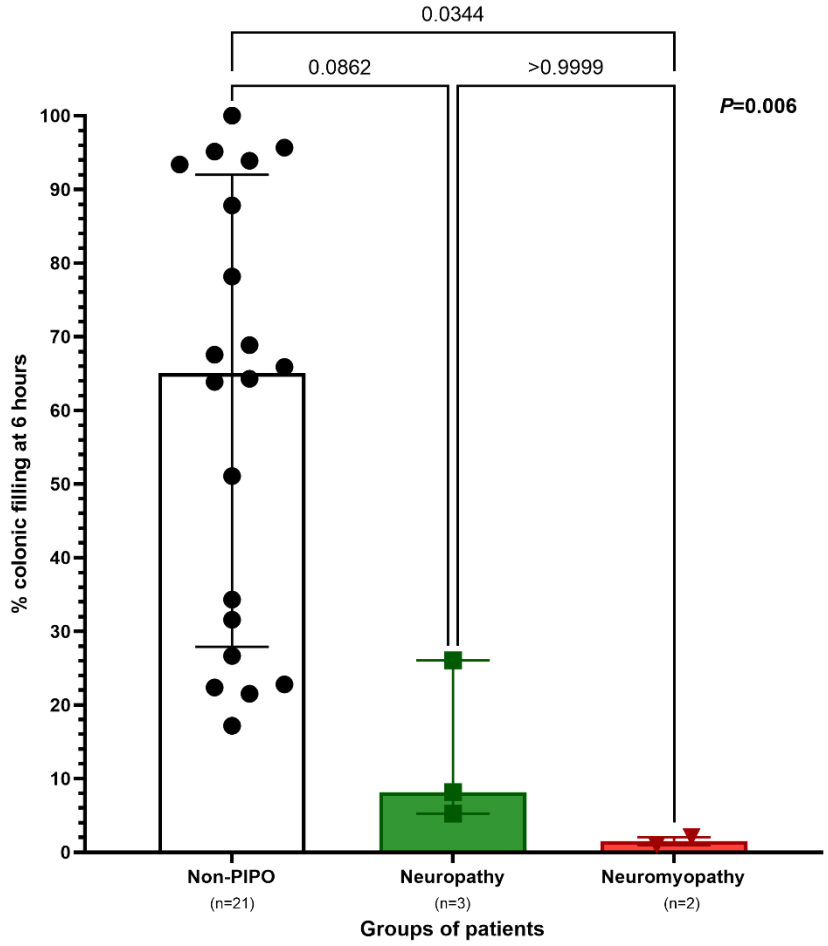


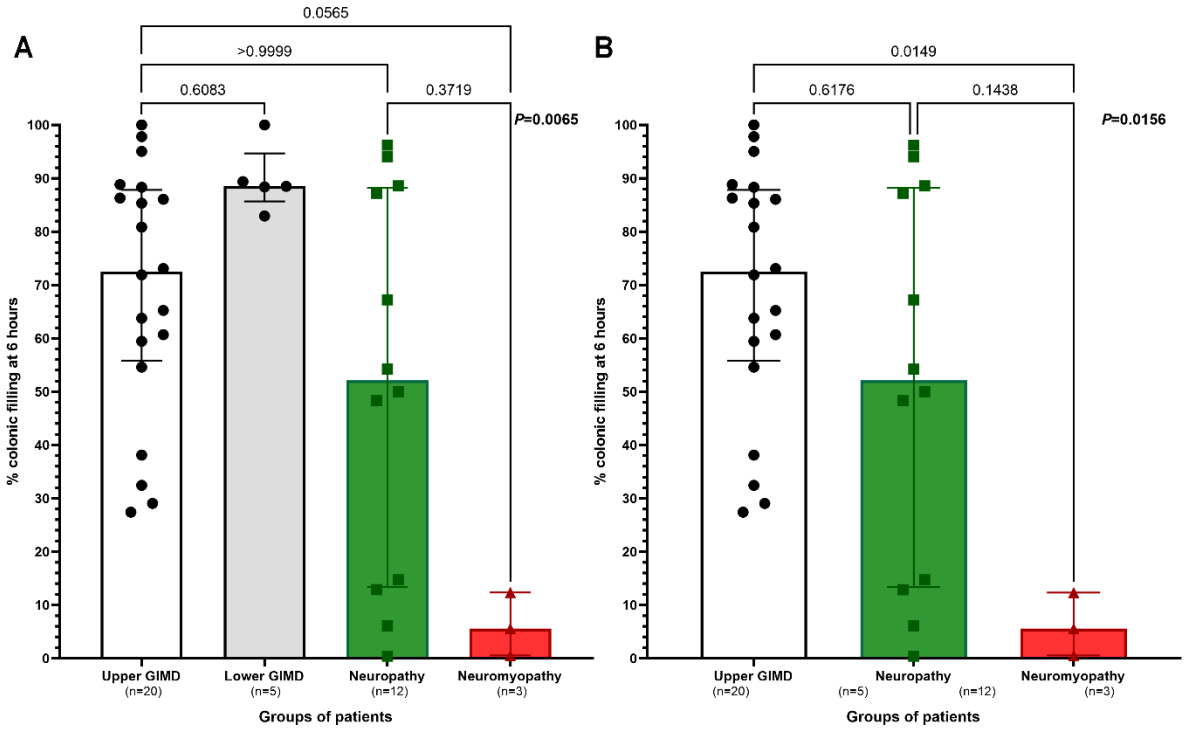
Figure 5

The colonic filling at 6 hours after solid meal ingestion in non-PIPO and PIPO patients classified subtype by enhanced ADM analysis



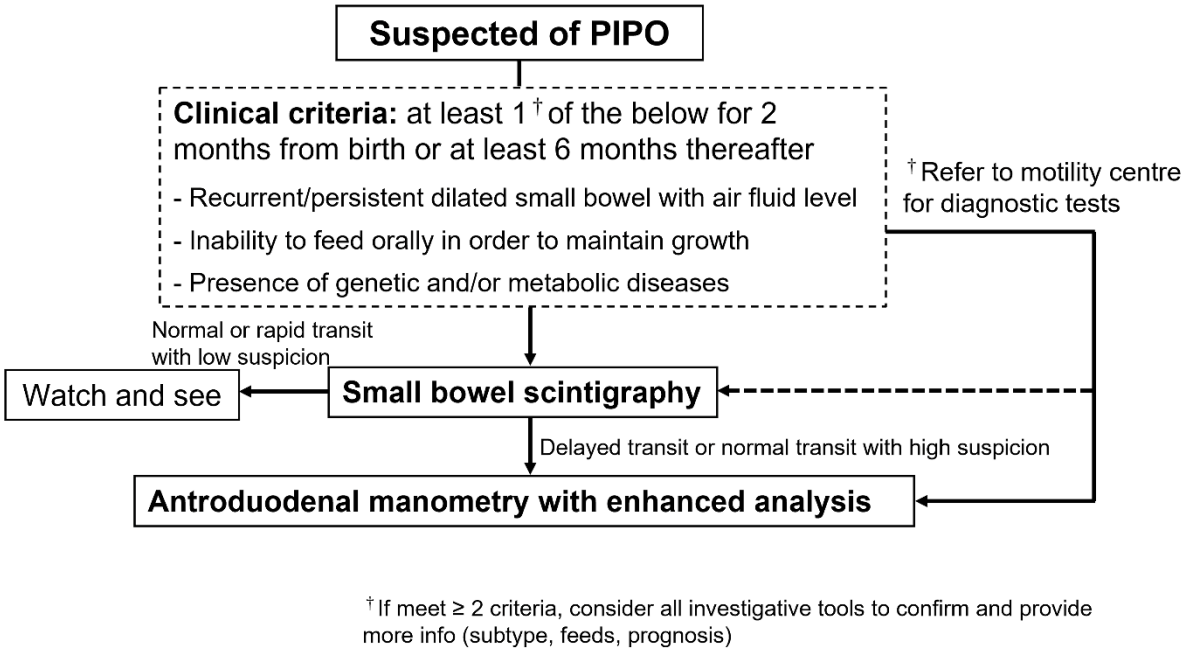
SUPPL FIGURE 1

Liquid-small bowel transit in PIPO and non-PIPO patients with upper and lower functional GI disorders (GIMD; **A**) and the comparison between non-PIPO patients with upper GIMD and those with different subtypes of PIPO **(B)**



SUPPL FIGURE 2

Proposed diagnostic pathway for PIPO



Supplementary Table 1 A comparison between liquid and solid small bowel transit assessed by qualitative and quantitative analyses in 7patients.

	Total ADM score	Fasting ADM score	Postprandial ADM score	Report from Liquid scintigraphy	Liquid (%colonic filling at 6h)	Report from Solid scintigraphy	Solid (%colonic filling at 6h)
1	-	-	-	delay	29.06	normal	78.16
2	13	9	4	delay	6.08	delay	5.24
3	-	-	-	delay	38.12	mild delay	65.9
4	16	12	4	delay	0.55	delay	0.94
5	15	11	4	normal	87.21	delay	8.18
6	17	12	5	delay	48.32	normal	26.07
7	-	-	-	delay	27.43	delay	31.57

Methods

Patients

All patients included in the study were referred to Great Ormond Street Hospital (GOSH) between January 2016 and December 2022, or to Queensland Children's Hospital (QCH) between January 2019 and December 2022, for further management. The patients underwent investigations of the gastrointestinal (GI) tract for gastric and small intestinal functional or motility disorders as part of their routine clinical care. The study was divided into two arms, a prospective recruitment, and retrospective review. For the retrospective arm, patients undergoing SBS as part of PIPO investigation at GOSH from January 2016 to December 2018 were also included. Prospectively, patients, aged 0-18 years, referred to the

Gastroenterology Department at GOSH and QCH from January 2019 to December 2022, who underwent gastric emptying scintigraphy with either a liquid or a solid meal, were included. Children with GI symptoms that were severe enough for considering specialist motility investigations but were not diagnosed with PIPO were used as surrogate 'controls' in this study.

Patients were excluded from the study if they were unable to complete the 6-hour SBS. Additionally, cases excluded from the non-PIPO group had any of the following 1) any disease that might affect the motility of the intestine (e.g. congenital myopathy, cerebral palsy); 2) a history of intestinal anatomical abnormalities (e.g. intestinal malrotation, pyloric stenosis); 3) a history of intestinal resection or anastomosis, including those who underwent ileostomy formation; 4) evidence or suspicion of mechanical intestinal obstruction.

According to the recommendation of the ESPGHAN-led expert group[2], PIPO was diagnosed based on at least two out of four criteria. These included (i) objective measure of small intestinal neuromuscular involvement, (ii) recurrent dilated loops of small intestine with air fluid levels, (iii) genetic and/or metabolic abnormalities, (iv) clinical history of feeding intolerance[2]. PIPO diagnosis was confirmed, and subtypes were classified based on ADM findings. Of note, PIPO patients who did not undergo ADM monitoring as part of the objective evidence of small intestinal neuromuscular involvement (criterion i) were excluded from this study.

Feeding intolerance was defined as the inability to maintain adequate nutrition and/or growth on oral feeding in combination with the presence of GI symptoms.

Small bowel transit

For the GES, the progression of a radiolabelled meal was measured by obtaining sequential scans over 3-4 hours with a dual-head gamma camera. For the liquid test meal, a test feed based on milk or formula was labelled with ^{99m}Tc-nanocolloid; a solid test meal based on egg white on toast or melted cheese on toast or pasta, radiolabelled with ^{99m}Tc-nanocolloid,

was ingested. The SBS was performed by acquiring additional images up to 6-8 hours after meal ingestion to follow the movement of the test feed through the small intestine.

All patients had a contrast barium fluoroscopy study or other radiological studies (e.g., cine-MRI, CT abdomen) performed prior to GES-SBS to exclude mechanical causes of intestinal obstruction. Medications that known to affect intestinal motility were stopped 48-72 hours before the start of the study[6].

Regions of interest (ROIs) were created for the whole abdomen, the stomach, and the caecum, based on visual assessment of sequential images at each of the hourly time points. The terminal ileum and/or caecum were localised by observing progressive accumulation of the radiolabelled test feed in the area near the right iliac crest where a position marker was placed as an anatomical reference point.

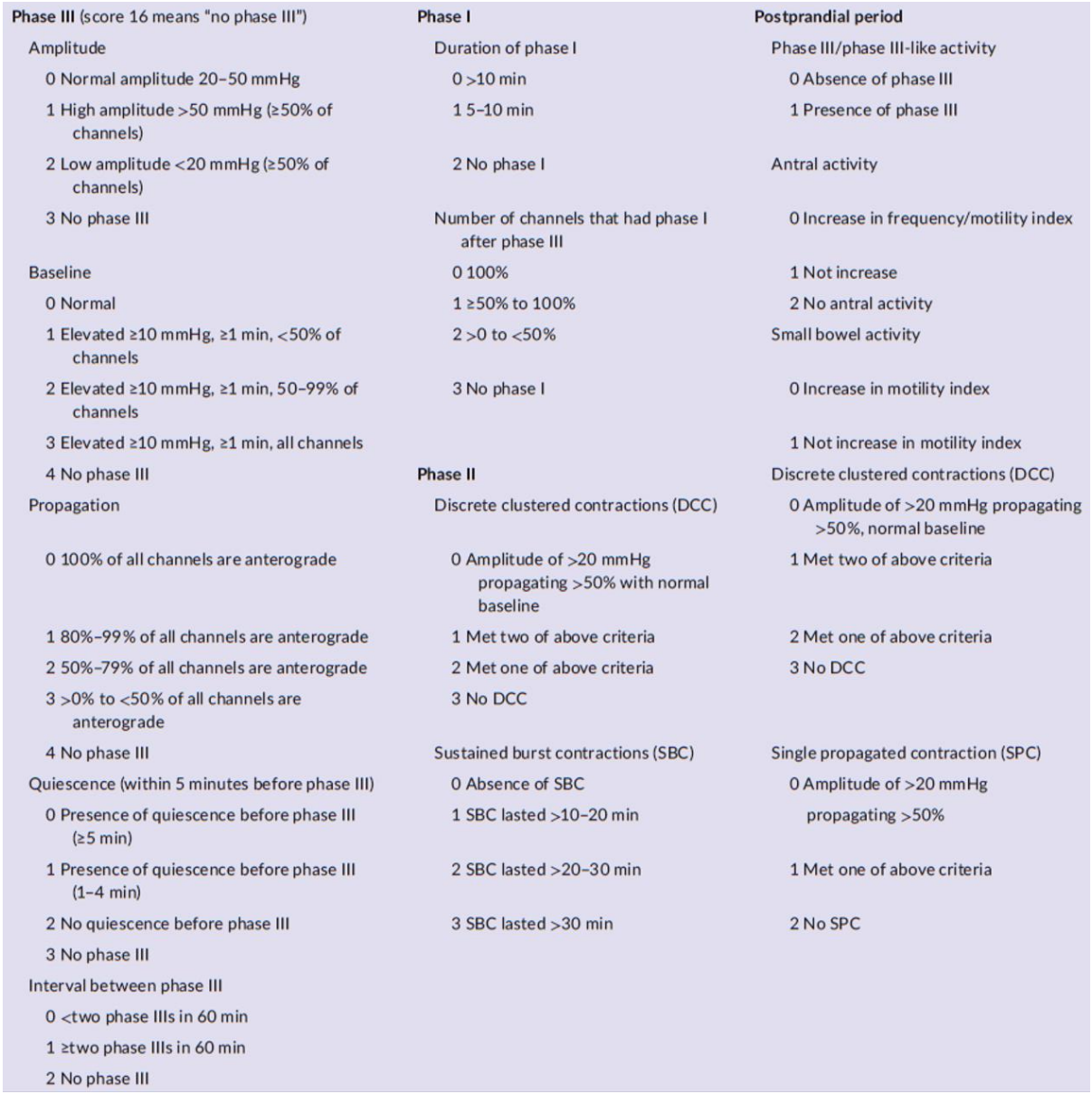
To determine the counts in the small bowel available to fill the terminal ileum, ROIs including the entire abdomen were drawn to calculate the average of total abdominal counts between 2 and 5 hours. To establish the oro-caecal transit, a ROI was manually drawn around the expected location of ileo-caecal valve and/or caecum, and any colonic activity measured at 6 hours (**Figure 1**). Calculations of test feed accumulation were performed using an Excel worksheet (Microsoft) with decay correction factors. The counts were not only decay-corrected but were also corrected for gastric counts if gastric emptying was delayed. SBT was calculated using the colon filling method, by dividing the total activity that had passed into the ileo-caecal valve/colonic area at 6 hours by the average 2- to 5-hour total abdominal activity[6].

Delayed gastric emptying was defined as gastric retention of >20% of tracer at 3 hours for a liquid and >10% at 4 hours for a solid test feed, respectively[13]. According to the previous definition, a rapid SBTT was defined as >70% colonic filling at 6 hours, or caecal arrival time of <90 minutes[15].

SBT was then compared between PIPO and non-PIPO patients. The correlation between parameters from the scintigraphic study and the ADM analysis was performed.

ADM

Enhanced ADM analysis has been proposed in 2021[5]. GLASS score is calculated based on the quantitative assessment of a number of contractile characteristics of all phases during the fasting (phase I, II and III) and postprandial periods across the entire ADM tracing. The score represents functional severity of the contractile activity, the higher score indicates a more severe abnormality. The maximum score for phase III is 16, phase II is 6 and phase I is 5, indicating that there is no cyclical contractile activity during fasting period. The postprandial score is calculated based on the presence of phase III-like activity, the antral and duodenal motility indexes (comparing 60 minutes pre- and post-meal) and other specific contractile parameters[5] **(Appendix Figure 1)**.



Phase III (score 16 means "no phase III")

Amplitude

0 Normal amplitude 20–50 mmHg

1 High amplitude >50 mmHg (≥50% of channels)

2 Low amplitude <20 mmHg (≥50% of channels)

3 No phase III

Baseline

0 Normal

1 Elevated ≥10 mmHg, ≥1 min, <50% of channels

2 Elevated ≥10 mmHg, ≥1 min, 50–99% of channels

3 Elevated ≥10 mmHg, ≥1 min, all channels

4 No phase III

Propagation

0 100% of all channels are anterograde

1 80%–99% of all channels are anterograde

2 50%–79% of all channels are anterograde

3 >0% to <50% of all channels are anterograde

4 No phase III

Quiescence (within 5 minutes before phase III)

0 Presence of quiescence before phase III (≥5 min)

1 Presence of quiescence before phase III (1–4 min)

2 No quiescence before phase III

3 No phase III

Interval between phase III

0 <two phase IIIs in 60 min

1 ≥two phase IIIs in 60 min

2 No phase III

Phase I

Duration of phase I

0 >10 min

1 5–10 min

2 No phase I

Number of channels that had phase I after phase III

0 100%

1 ≥50% to 100%

2 >0 to <50%

3 No phase I

Phase II

Discrete clustered contractions (DCC)

0 Amplitude of >20 mmHg propagating >50% with normal baseline

1 Met two of above criteria

2 Met one of above criteria

3 No DCC

Sustained burst contractions (SBC)

0 Absence of SBC

1 SBC lasted >10–20 min

2 SBC lasted >20–30 min

3 SBC lasted >30 min

Postprandial period

Phase III/phase III-like activity

0 Absence of phase III

1 Presence of phase III

Antral activity

0 Increase in frequency/motility index

1 Not increase

2 No antral activity

Small bowel activity

0 Increase in motility index

1 Not increase in motility index

Discrete clustered contractions (DCC)

0 Amplitude of >20 mmHg propagating >50%, normal baseline

1 Met two of above criteria

2 Met one of above criteria

3 No DCC

Single propagated contraction (SPC)

0 Amplitude of >20 mmHg propagating >50%

1 Met one of above criteria

2 No SPC

Appendix Figure 1 The calculation of ADM GLASS score[5] (with permission)

Statistical analysis

All data analysis was performed using SPSS software version 27. Baseline patients' characteristics were described as median (IQR) and percentage. Continuous data and categorical data were compared using Fisher's exact test and Mann-Whitney U test, respectively. SBT parameters were compared between PIPO and non-PIPO patients. Different parameters were correlated with the Spearman's rank correlation coefficient. The

agreement between diagnostic labels derived from two different diagnostic tests was evaluated with Cohen's Kappa (κ) analysis. $P < 0.05$ is defined as a level of significance.