ENHANCING THE UTILITY OF ANTRODUODENAL MANOMETRY IN PEDIATRIC INTESTINAL PSEUDO-OBSTRUCTION.

Atchariya Chanpong[1,2,4], Hannah Cronin[1], Dyanne Rampling[3], Michael Ashworth[3], Simon Eaton[4], Anna Rybak[1], Efstratios Saliakellis[1], Keith J. Lindley[1], Osvaldo Borrelli[1] and Nikhil Thapar[1,4,5]

[1]Neurogastroenterology & Motility Unit, Gastroenterology Department, Great Ormond Street Hospital for Children, London, UK

[2]Division of Gastroenterology and Hepatology, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[3]Histopathology Department, Great Ormond Street Hospital for Children, London, UK

[4]Stem Cells and Regenerative Medicine, UCL Great Ormond Street Institute of Child Health, London, UK

[5]Gastroenterology, Hepatology and Liver Transplant, Queensland Children's Hospital, Brisbane, Australia

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NT and OB contribute jointly as senior authors

Corresponding Author
Professor Nikhil Thapar
Professor of Paediatric Gastroenterology
Gastroenterology, Hepatology and Liver Transplant
Queensland Children's Hospital, Brisbane
Australia
Telephone: +61 (0)730684502
Email: Nikhil.Thapar@health.qld.gov.au

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NT - Guarantor of manuscript,

AC: design of the study and GLASS score, performed the experiment, preparation of synopsis data, analysis of results, drafting the article and approval of the final version of the paper. HC: performed the motility investigations, critical revision of the manuscript and approval of the final version of the paper. DR: performed the pathological evaluation, critical revision of the manuscript and approval of the final version of the paper. MA: performed the pathological evaluation, critical revision of the manuscript and approval of the final version of the paper. SE: preparation of synopsis data, analysis of results, critical revision of the manuscript and approval of the final version of the paper. ES: analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. AR: performance of motility studies; analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. KJL: performance of motility studies; analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. OB: design of the study and GLASS score, performance of motility studies, analysis and interpretation of data, critical revision of the manuscript and approval of the final version of the paper. NT: Conception and

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Abstract

Background:

Antroduodenal manometry (ADM) and histopathology are currently employed to aid the diagnosis of pediatric intestinal pseudo-obstruction (PIPO). Limited data are available on the reliability of ADM analysis and its correlation with histopathology. We aimed to develop a protocol for enhanced analysis of ADM contractile patterns, including a scoring system, and explore whether this provided better correlation with histopathology.

Methods:

Children referred with suspected PIPO between April 2012-December 2019 who underwent both ADM and full thickness biopsies were included. ADM tracings were analyzed using both standard (conventional ADM) and novel (enhanced ADM) motility parameters. A novel ADM score (GLASS score) was generated based on the enhanced ADM analysis. Conventional and enhanced ADM analyses were then correlated with histopathology.

Results:

Forty patients were included. Using conventional clinical criteria, 29 of these were diagnosed with PIPO and the other 11 with non-PIPO diagnoses. Twenty three of the PIPO patients had abnormal histopathology: 6 myopathy, 4 neuropathy, 3 neuro-myopathy, and 10 non-specific changes. No agreement in diagnosis was found between conventional ADM analysis and histopathology (κ=0.068; P=0.197), whereas the latter significantly correlated with enhanced ADM analysis (κ=0.191; P=0.003). The enhanced ADM score was significantly higher in PIPO vs non-PIPO (16.0 vs 8.0; P<0.001)..

Conclusions:

As opposed to conventional analysis protocols, the newly developed enhanced ADM analysis and associated score is not only able to discriminate between PIPO and non-PIPO patients, but also between distinct histopathological pathologies. Further studies are required to assess the utility of enhanced ADM analysis in larger populations.

Keywords: intestinal pseudo-obstruction; pediatric; antroduodenal manometry; histopathology; small intestine; gastrointestinal motility; scoring system

Abstract word count: 248 words

INTRODUCTION

Pediatric intestinal pseudo-obstruction (PIPO) is an uncommon, severe gastrointestinal (GI) motility disorder, with an incidence of 0.4-2.5 per 100,000 live births[1-3]. It is characterized by chronic (≥2 months from birth or ≥6 months thereafter), or recurrent episodes of symptoms mimicking intestinal obstruction in the absence of mechanical obstruction[4].

The diagnosis of PIPO has relied, predominantly, on clinical symptoms and signs together with radiological findings, such as the presence of air fluid levels within dilated small bowel loops. However, new diagnostic criteria[3] proposed by an international expert group have highlighted the relevance of acquiring objective evidence of small intestinal neuromuscular involvement. In this regard, histopathology and antroduodenal manometry (ADM) have been the most common diagnostic modalities advocated[3].

Histology has been used to diagnose GI neuromuscular diseases since the eighties[5]. However, it is only recently that an International Working Group[6] has established guidelines for the optimal histological assessment of GI neuromuscular diseases as well as defined the histopathological classification for such disorders. This classification has categorized enteric GI neuromuscular disorders, such as PIPO, into 3 main subtypes based on the neuromuscular component of the intestine predominantly affected: neuropathies with predominant neuronal involvement, myopathies with predominant involvement of smooth muscles, and mesenchymopathies resulting from abnormalities of interstitial cells of Cajal[6, 7].

ADM is a diagnostic tool that provides both qualitative and quantitative assessment of foregut motor function by recording intraluminal pressure changes within the stomach and the proximal small intestine. ADM is currently considered the

most discriminating investigation for confirming the diagnosis of PIPO as well as clarifying pathophysiology and directing clinical management[3, 8].

Although ADM and histopathology are commonly used for assessing patients with severe intestinal dysmotility there has been little validation on the performance of either test or how reliably each diagnostic modality relates to the other. A study in 14 PIPO patients, comparing the ADM patterns, histological findings, and feeding outcomes, found that while some manometric features, such as low contractile amplitude and motility index, might predict the presence of smooth muscle disease, the neuropathic manometric features did not parallel the enteric neuropathy reported from histology[9]. In adults with severe intestinal dysmotility, Malagelada et al showed that although abnormalities in both ADM and intestinal histopathology were commonly detected, there was no correlation between specific manometric patterns and abnormal neuromuscular histopathological findings[10]. With this in mind it is also important to note that the diagnosis of PIPO based on ADM in the published literature has relied on analysis protocols that have predominantly focused on very specific components of the whole repertoire of small intestinal contractile activity, namely phase III of the migrating motor complex (MMC) occurring during fasting and the post-prandial response[3, 11]. These phases, however, occupy a minority (<20%) of the small bowel contractile activity captured during an ADM study[8, 12-14], with the vast majority of the tracing comprising phase I and II activity. Therefore, in the present study we aimed to develop a protocol for enhanced analysis encompassing all phases of gastrointestinal contractile activity on prolonged ADM recordings, together with the development of a novel practical scoring system. We then assessed how well these enhanced analyses compared to conventional analysis with regards to correlation with

164 histopathology performed on small intestinal full-thickness biopsies from the same
165 PIPO patients.

MATERIAL AND METHODS

Patients

All children referred for suspected PIPO to Gastroenterology Department at Great Ormond Street Hospital for Children, London, UK between April 2012 and December 2019 were considered for the study. Only children who had undergone both an ADM recording of at least 8 hours duration and full-thickness small intestinal tissue biopsies were included. Patients in whom histopathology results of the small intestine were not available to be reviewed and those who had a manometric recording of <8 hours duration or without a test meal and postprandial recording were excluded. The diagnosis of PIPO was established using the new published criteria[3]. Eleven children, who underwent ADM assessment given the severity of their symptoms and in whom PIPO was excluded, were used as disease controls for the ADM tracing analysis (Control group). In these patients after a full hospital-based assessment both the clinical picture and conventional ADM analysis were not consistent with a diagnosis of PIPO. The patients were subsequently diagnosed with conditions that fell within the spectrum of functional GI disorders[15, 16].

Ethics

The study protocol was defined in accordance with the Declaration of Helsinki and was approved by the National Research Ethics Service Committee London - Brent (REC reference 19/LO/0854, protocol number 18DS19).

Antroduodenal manometry

All children referred with suspected PIPO underwent ADM using a low compliance water-perfused system (Solar GI HRM system, Medical Measurement Systems,

Enschede, The Netherlands). A water-perfused PVC manometric catheter with 20 recording ports at 2.5-cm intervals and 5 radiopaque markers 10 cm apart was used in each patient. Each recording port was perfused with air-free distilled water by a pneumo-hydraulic infusion pump at a constant flow rate (0.15 mL/min). Intraluminal pressures were transmitted to external transducers and the signals were amplified, digitized and analyzed using commercially available software (software v8.21, Medical Measurement System, Enschede, The Netherlands).

After a fasting period according to the hospital guidelines, the placement of the ADM catheter was performed via the child's nostril or gastrostomy under fluoroscopy guidance under general anesthesia. The ADM catheter was positioned to ensure an ideal final position with at least 2-3 of the distal recording ports in the small intestine beyond the ligament of Treitz and 1-2 of the most proximal recording ports in the gastric antrum[8]. The ADM recording was started when the patients were fully awake after general anesthesia, generally at least two hours after the placement of the catheter. The fasting period was recorded, thereafter, for at least six hours followed by a test meal with the aim to run the study for 8-24 hours. The type and size of test meal were defined according to the patient's age aiming to achieve at least 400 kcal or 10 kcal/kg either given orally over a maximum of 30 minutes, or via gastrostomy over 30-60 minutes depending on the symptoms, or via jejunostomy over 60 minutes[8, 17, 18].

Conventional ADM analysis

As per routine clinical practice, the ADM recordings were analysed and the official reports finalised by ≥2 consultant pediatric neurogastroenterologists with the aim to inform clinical management. This analysis was based on a defined number of

criteria (mainly qualitative characteristics), obtained from selected segments of the ADM tracing ('conventional ADM analysis'), mentioned previously[3, 8, 11].

Enhanced ADM analysis

Anonymized ADM tracings of all eligible patients were reviewed by one of the authors (AC) blinded to the patients' clinical condition. The ADM "enhanced analysis" was based on the qualitative and quantitative assessment of a number of contractile parameters across all phases (phases I, II, III and post-prandial period) of the entire ADM tracing. A scoring system (**G**reat Ormond Street Hospital **L**ondon **A**DM **S**coring **S**ystem; **GLASS**) was developed to allocate a 'functional severity score' for each characteristic of each parameter, where a score of 0 was allocated to 'normal' characteristics and increasing abnormalities reflected in sequentially higher numerical scores (1, 2, 3, 4). The final (GLASS) ADM scoring system (minimum total 0, maximum total 36) was formulated and agreed among the main authors (AC, NT, OB) **(Table1)**.

During the fasting period, the presence of phase III, phase I and phase II, together with the number and duration of each phase were noted. The number and length of migrating motor complexes (MMCs) were recorded. The quality of contractile activities was evaluated and scored according to the characteristics of each phase. Following administration of a test feed, the characteristics of the postprandial pattern were scored according to the presence/absence of phase III or phase III-like activity, an increase in the frequency or motility index of antral contractions and to the change in the motility index of the small intestine. The motility index was automatically calculated by the software, comparing 60-minute periods before and after meal completion. The assessment of the fed state included the 60 minutes after consumption of a test meal with adequate calories. If the test were run for >60 minutes

after the meal, the reappearance of phase III was continuously evaluated until the third hour after meal ingestion[8].

According to previously published criteria, the definitions of different contractile activities and the measurements of different phases were defined as follows:

a. **Valid contraction,** as a contraction with an amplitude of >10 mmHg[11].

b. **Artefact,** as the rise of pressure simultaneously in all channels with similar morphology, amplitude and duration; this occurs due to body movements or straining[19] **(Figure1A)**.

c. **Phase III,** as a band of regular repetitive pressure waves that contracted at a frequency of 10-14 cycle per minute in the proximal small intestine/duodenum[20]. The following characteristics of phase III were analyzed:

- **duration of phase III** was measured from the time when the longest period of regular repetitive contraction started, to the time of its ending **(Figure1B)**. Mostly, the longest phase III is located at the distal recording channel[21].
- **elevated baseline** or tonic contraction signifying the rise of the baseline >10 mmHg for ≥1 minute.
- **propagated pattern** was evidence of ordered proximal to distal propagation of contractile waveform confirmed by drawing an assumption line between the first phasic wave of phase III presented at the proximal channels to those located at distal channels **(Figure1B)**.
- **quiescent period** was counted as a period of absence of contractions between the last valid contraction of phase II to the first phasic wave of each phase III **(Figure1B and Suppl Figure1)**.

d. **Phase I,** defined as a quiescent period, located after phase III, containing less than three valid contractions every 10 minutes[12].

e. **Phase II,** defined as a period between phase I and phase III which contained irregular pressure waves. The following distinct motility patterns during the phase II were encountered:

- **discrete clustered contractions (DCC),** defined as a group of 3-10 pressure waves, occurring at a rate of less than 10 cycle per minute, with an amplitude of >10 mmHg, and both preceded and followed by ≥1 minute of absent motor activity[22, 23] **(Figure1C and 1D)**.
- **sustained burst contractions (SBC),** defined as a sequence of pressure waves with a tonic component lasting ≥10 minutes. It typically appears on only one recording site[11, 24] **(Figure1C)**.
- **single propagated contraction (SPC) during fed state,** defined as single (or double) pressure wave propagating aborally at a rapid rate[22] **(Figure1D)**.

f. **Length of MMC cycle** – the duration between the beginning of two consecutive phase IIIs, or the interval between phase III-episodes.

g. **Motility index** – the sum of amplitudes multiplied by the number of contractions.

The rationale behind the construction of GLASS score is described in the **Appendix.**

Finally, the sum of the GLASS score was calculated and correlated with histology findings. To classify the subtype of PIPO based on enhanced ADM analysis, the score of contractile amplitude during phase III MMC was interpreted separately from other

components of the GLASS score to indicate the myopathic component (a score of 2 represented myopathy). This is because a low amplitude of intestinal contractions (<20 mmHg) has been accepted as a feature of myopathy[8, 43, 44].

Histopathology

The analysis and reporting of full-thickness tissue samples were reviewed by histopathologists expert in assessing neuromuscular GI disorders (RD and MA) based on the guidelines of the International Working Group[6] and the London Classification[7]. The histologic results were classified into five groups as follows:

a. **Myopathy,** characterized by fibrotic replacement of smooth muscle, and/or infiltration of inflammatory cells into the muscular layer, and/or presence of inclusion bodies in smooth muscle, and/or missing or additional myofibres associated to muscle fibre changes such as abnormal staining or vacuolation.
b. **Neuropathy,** characterized by loss/reduction of ganglion cells, ganglionitis, ectopic ganglia, hamartomatous increase in neurons and glia, intraneuronal nuclear inclusion bodies, or abnormal ICC networks.
c. **Neuro-myopathy,** characterized by abnormal components of both the enteric nerves and muscles.
d. **Uncertain significant change,** defined as the presence of single abnormal myofibre change (abnormal immunostaining and/or vacuolation) without other features of muscular abnormalities, or secondary tissue changes e.g. fibrosis from unidentified causes, abnormal appearance or reduction of α-smooth muscle actin staining (SMA).
e. **Normal histopathology,** when no detectable abnormality of the intestinal neuro-musculature was identified.

Finally, patients' demographic data, clinical course including their conventional ADM reports were noted.

Statistical analysis

Given the fact that within the ADM tracing of any given patient many MMC cycles consisting of multiple phase III, phase I and phase II, can be recorded, the median value was used as a representative of multiple repeated variables. Descriptive analysis was used to evaluate the baseline characteristics of the patients. All continuous variables were reported as median with range or interquartile range (IQR). As the data were not normally distributed, non-parametric statistical methods were used for the analysis. The Kruskal-Wallis test was applied to compare the manometric GLASS scores between patients with different histological subtypes of PIPO. Additionally, the agreement between the previous ADM reports and histology was evaluated with Cohen's Kappa (κ) coefficient. Moreover, a receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic and predictive value of the GLASS score. Statistical analysis was done using SPSS 24.0 for Windows (IBM, USA) and $P<0.05$ was defined as the level of significance.

RESULTS

Demographic data

Over the 7-year study period, 76 children were diagnosed with PIPO: 70 underwent ADM monitoring (68 recorded for >8 hours), 40 had full thickness small intestinal biopsies. Only 29 patients (17 boys; age range 0.6-15.7 years) satisfied the inclusion

criteria, represented by ADM recording of at least 8 hours of duration performed with a test meal together with availability of full-thickness small intestinal tissue for histological review **(Figure2)**. Eleven children (4 boys, age range: 3.6-16.1 years), who underwent ADM assessment given the nature and severity of their symptoms and in whom PIPO was subsequently excluded, were used as disease controls for the ADM tracing analysis. The demographic characteristics of both patients and controls are summarized in **Table2 and Suppl Table1**, whilst the characteristics of ADM in both groups are reported in **Table3**.

Histopathological features in PIPO patients and the correlation with conventional ADM reports

Of 29 PIPO patients, 23 (79.3%) had abnormal histopathological features: 6 myopathy, 4 neuropathy, 3 neuro-myopathy, and 10 changes of uncertain clinical significance. Of the latter 10 patients, 4 had a variable intensity of smooth muscle actin (SMA) immunostaining (two in samples of jejunum, and two in ileum), whilst another 3 had a reduction in the expression of SMA (all identified in the ileum). The other 3 patient's histopathological results demonstrated either ischemic changes, an increase of macrophage in the muscularis propria or mild fibrosis with disorganized muscle coats near the stomal area. No histopathologic abnormalities were reported in six patients.

The original conventional ADM analyses suggested neuropathy in 22 patients, neuro-myopathy in 5; myopathy in 1 and one without definite abnormality. Of note, the latter patient had myopathic small bowel reported on histopathology at a later stage.

Comparing the results from both diagnostic methods, there was no significant agreement between the diagnostic labels from conventional ADM analyses and histopathology (κ=0.068; *P*=0.197) **(Table4)**.

Enhanced ADM analysis

The calculated GLASS score from enhanced ADM analysis was significantly higher in PIPO patients compared to controls (16 vs 8; *P*<0.001) **(Table3)**. The noticeable differences in the manometric patterns between the two groups related to the characteristics of phase III (amplitude, baseline, propagation, quiescence), number of phase I, percentage phase I to phase III, presence of SBC during phase II and the presence of postprandial DCC **(Table3)**. Of note, when the GLASS score was tested in a particular group of 15 patients (those with histological examinations and ADMs recorded for ≥20 hours), there was a significant difference in terms of postprandial response to the test meal (increased contractile activity of both the antrum and small intestine) between control and PIPO patients.

A GLASS score of ≥10 could discriminate between PIPO and control patients; this can be seen by the area under the ROC curve of 0.983 (95% confidence interval (CI) 0.948-1.000). All PIPO patients had enhanced GLASS scores ≥10, whilst two in the control group had a GLASS score of ≥10. This gave a sensitivity of 100.00%, specificity of 81.82%, positive predictive value of 88.24%, and a negative predictive value of 100.00%. The GLASS score did not only help differentiate PIPO patients, but also correlated with the requirement for parenteral nutrition (PN) at the time of the ADM study. From the ROC curve analysis, the total fasting score is the best model, giving the ROC curve of 0.725 (95% CI 0.561-0.889), followed by the GLASS score with ROC curve of 0.718 (95% CI 0.549-0.887). Whilst, the fasting score of ≥8.50

provided a sensitivity of 75.00% and specificity of 63.20%, a GLASS score of ≥13.50 gave a sensitivity and specificity of 70.00% and 73.70%, respectively.

Novel contractile parameters

Apart from abnormal characteristics of phase III (particularly its propagated pattern), children with neuropathic histological abnormalities showed abnormal findings of phase I, with fewer numbers of phase I per hour (0.00 vs 0.24 per hour; *P*=0.013) and tended to have a reduced percentage of phase I following phase III (0% vs 45.58%; *P*=0.070], as compared to the non-neuropathy group **(Table5)**. Additionally, patients with neuropathic histology were found to have a higher score of fed responses (score of 2.00 vs 1.00; *P*=0.032).

Moreover, comparing manometric parameters based on the amplitude of contractions, patients with a neuropathic ADM have a lower percentage of phase I to phase III, a lower percentage of pre-phase III motor quiescence, a higher score of phase II and phase I, shorter duration of phase I, and a higher score of fasting period (**Table 6**).

Correlation between enhanced ADM analyses components and scores with histology

For PIPO patients, enhanced ADM analyses showed a better correlation with histopathology, demonstrated by significant agreement between the two parameters (***κ***=0.191; *P*=0.003, **Table4**). Interestingly, the characteristics of contractile patterns in patients who had histopathology reported as normal and/or uncertain clinical significance were quite similar to the ones in the myopathy group. The number, and percentage, of phase I to phase III in the normal/unspecified group were higher than

413 in those patients with either neuropathy or neuro-myopathy, although the enhanced
414 ADM GLASS score was closer to those in the neuropathy group **(Suppl Table2)**.
415 When PIPO patients were re-classified into two main groups as either having
416 (neuropathic group) or not having (non-neuropathic group) neuropathic components
417 based on histopathology, we found differences in the number of phase I per hour and
418 the score of fed response. The ADM scores were not different between the two groups
419 **(Table5)**. Interestingly, when PIPO patients were classified based on the amplitude
420 score of phase III (the score of 2 represented myopathy), we found significant
421 differences in the manometric patterns and ADM score between the two groups **(Table**
422 **6)**.

DISCUSSION

The main aims of this study were to evaluate the correlation between two diagnostic methods for PIPO, ADM and histopathology, and assess whether the utility of ADM could be improved by enhancing the depth of the current analysis of the ADM tracing.

In this study, we considered assessing histopathological features from full-thickness biopsies as a 'gold standard' method for the diagnosis of PIPO, as this provided objective evidence of whether neurons or muscles are involved in the pathophysiology of the disease. However, a recent study[8] suggested that ADM is comparable to histopathology as an accurate diagnostic tool for PIPO, given it provides clinically relevant information regarding the pathophysiology and severity of actual intestinal function compared to histopathology.

Based on the original ADM reports of PIPO patients, produced by ≥2 experienced pediatric neurogastroenterologists using conventional protocols for analysis, we found a poor correlation between the generated PIPO diagnostic labels and abnormalities seen on histopathology. Our finding is comparable with published studies in adults[10, 43, 45].

Lindberg et al[43] compared manometric findings with histopathology in 72 adults with chronic intestinal pseudo-obstruction (CIPO) in Sweden during a 10-year period. They found that histopathology could not be predicted by ADM findings, except the features of myopathy that could be correlated with severe hypomotility on ADM. Of note, they classified ADM findings into five groups: abnormal propagated phase III, bursts of contraction, sustained burst contraction >30 minutes, failure to switch to fed pattern after a meal, and severe hypomotility [low-amplitude (<20 mmHg) of contraction or no contractions throughout the tracing]. These abnormality criteria on ADM were also applied to describe and classify subtypes of PIPO in our original

448 'conventional' ADM reports. Additionally, a recent study[10] evaluating the concordance
449 between ADM and histology for the diagnosis of CIPO in adults also revealed poor
450 agreement between these two diagnostic techniques by Cohen's κ analysis (κ=0.09,
451 *P*=0.54).

452 To our knowledge, there has been very limited data regarding the comparison
453 between ADM and histologic findings in children with PIPO. A single study, performed
454 in 14 PIPO patients at our center in 1996[9], illustrated that all five patients who had
455 myopathic histology displayed either low amplitude of phase III contractions or no
456 motor activity on the ADM, while the manometric features in the patients with
457 neuropathic histology showed either non-contractile activity or abnormal phase III
458 configuration and/or propagation.

459 Although more advanced histological techniques have been applied to increase
460 the diagnostic yield of histopathology and a standard protocol of performing ADM
461 studies has been developed over the past 20 years, the correlation between both
462 diagnostic methods has, thus far, not been addressed. We hypothesized that this
463 relates to the limitation of current protocols for ADM analysis and interpretation, where
464 only a minority (estimated in our experience to be <20%[8, 12-14]) of the tracing and
465 contractile parameters are practically utilized in the analysis. A possible reason for this
466 apparent shortcoming is that the original criteria were developed when clinicians were
467 not using high resolution manometry with manometric catheters with multiple
468 recording ports as is the case currently. Thus, given the low resolution and limited
469 recording channels, they chose to focus on elements of contractility that were easily
470 identifiable, such as phase III[11]. The 'high-resolution' tracings used in our study are a
471 function of the increased number and closer spacing of sensors placed in the intestine
472 allowing better visualization of all components of contractile activity. Therefore, in an

effort to improve the diagnostic value of ADM analysis, we developed an enhanced ADM analysis evaluating the entire tracing of ADM recordings and constructed a scoring system (GLASS score) based on previously reported abnormal gastrointestinal contractile patterns in PIPO to investigate whether these can improve the diagnosis of PIPO.

Enhanced ADM analysis

The characteristics of phase III, its baseline, amplitude, pattern of propagation, the presence of quiescence before the beginning of phase III along with the duration between phase IIIs were documented and scored according to previously reported evidence[11, 24, 25]. We have introduced a novel parameter based on our observations and propose that the beginning of phase III should be preceded by a quiescent period during which the irregular motor activity of phase II should stop to prepare for the new intense phasic activity of phase III. Although such quiescence is well described after phase III (called phase I) in the conventional analysis[9], there are almost no data regarding its presence prior to phase III activity. Such contractile quiescence has been well reported in the context of colonic motility patterns, where they manifest as periods that contains low or no contractile activity defined by the motility index[38]. Giorgio et al[38] found that the absence of this motor quiescence before and after colonic high amplitude propagating sequences was a specific biomarker of colonic neuropathy[38]. In our study, pre-phase III motor quiescence was found to be absent more often in the PIPO rather than in the control group with the percentage of having pre-phase III quiescence of 50% in PIPO vs 75% in non-PIPO patients. Some may argue that the motor quiescence was not completely absent in the whole PIPO group. This could be explained by the fact that the PIPO group is heterogeneous and comprised of both

myopathic and neuropathic phenotypes. The pre-phase III quiescence may still present in myopathic PIPO as they only have an overall low amplitude of contractile activity, but preservation of the normal configuration of phase III[20].

From the enhanced analysis, we highlighted that patients with neuropathic histology did not only have abnormal characteristics of phase III but also abnormal findings of phase I, such as less numbers of phase I per hour and less percentage of phase I following phase III, as compared to the non-neuropathy group **(Table5)**.

With conventional ADM analysis, phase II of the MMC, despite covering a majority of the overall ADM study[8, 12-14], is rarely used to assess for abnormal neuromuscular function. We, therefore, applied scores for DCC and SBC appearing during phase II period. We were unable to identify any differences between controls and PIPO patients in the number of patients displaying DCC during the fasting period, but the score of post-prandial DCC were significantly different **(Table3)**. In addition to DCC, SBC has also been known to be associated with intestinal pseudo-obstruction[11]. In our study, only PIPO patients (60%) demonstrated the presence of SBC on the ADM tracing, which was absent in the controls **(Table3)**. However, the presence of SBC was not significantly different across the subtypes of PIPO **(Suppl Table2)**.

Following a test meal, we scored the characteristics of fed response (presence/absence of phase III or phase III-like activity[40, 41], an increase in either frequency or motility index of antral contraction and the change in the motility index of the small bowel[8]), the findings of DCC and SPC, the contractile activities which can be seen in normal population[22, 24]. In this study, the score of the fed response was significantly different between patients with neuropathic and non-neuropathic histology. Likewise, higher GLASS score of ≥13.5 correlated with the need of

parenteral nutrition. Although Castedal et al[39] reported that postprandial duodenal activity in healthy volunteers appeared to occur in a retrograde fashion; their ADM catheters contained pressure ports at 1.5 cm spacing which was different to ours (2.5 cm spacing). Therefore, our GLASS score for postprandial DCC was based on the findings from Kerrigan et al (using 3 cm spacing catheter)[42]. In our study we did not find any difference in DCC score during both fasting and fed state between PIPO and controls, which parallels the findings of other studies showing the presence of DCC in both normal and (pseudo-) obstructive patients[22, 46].

With enhanced ADM analysis and scoring, we successfully demonstrated that our enhanced ADM (GLASS) score was significantly different between PIPO and control patients for both the fasting and postprandial periods. These novel scores provided a significantly better correlation with histopathology, suggesting the GLASS score presented some enhancement to conventional ADM analysis. Furthermore, we showed that not only abnormal characteristics of phase III and specific motor patterns of phase II, such as SBC, should be considered as features of neuropathic PIPO, but also abnormalities in phase I. We also showed that the enhanced ADM (GLASS) score was significantly higher in patients with either normal histology or categorized as “of uncertain clinical significance”, such as abnormalities in SMA staining, suggesting that some pathological abnormalities may not be detected with current histological techniques as well as that some *changes of unknown significance* may represent true pathological abnormalities. Moreover, we have found that the GLASS score of ≥13.50 was related to the requirement of parenteral nutrition. This finding may be consistent with a previous study in PIPO children, where they found that patients without a phase III during a 4-hr ADM recording were more likely to require parenteral nutrition[11].

This study is not without limitations. Firstly, the sample size in our study could have affected the power of the study and the differences found between PIPO and controls may represent a type II error. Although a larger number of patients would have been beneficial for the strength of the results, we do believe that the sample size is large enough to provide clinically relevant information. Secondly, for obvious ethical reasons the study lacks truly healthy pediatric controls and our “normal” values were derived from symptomatic children undergoing ADM. Although the presence of largely normal ADM in the ‘disease control group’ allowed comparison with the PIPO patient group, it could be argued whether the controls truly had normal histology given full thickness small intestinal biopsies were not indicated in this group.

In conclusion, our data suggested that PIPO diagnostic labels derived from currently applied ‘conventional’ analyses of ADM tracings do not correlate with abnormalities seen on histopathology and may reflect incomplete assessment of the contractile elements, whilst new scores derived from enhanced ADM analyses (GLASS score) show a better correlation with histopathology. However, further studies on a larger study population are needed to confirm our findings and assess the utility of enhanced ADM analysis on clinical decision-making.

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TABLE 1

Great Ormond Street Hospital London ADM scoring system (GLASS)

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

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 contraction (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 contraction (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

3 No phase III

- Interval between phase III

0 < two phase IIIs in 60 minutes

1 ≥ two phase IIIs in 60 minutes

2 No phase III

TABLE 2

Demographic data in paediatric intestinal pseudo-obstruction and control patients

Characteristics	PIPO (n=29)	Controls (n=11)	*P* value
Age at first symptom (months), median (IQR)	2.50 (0.00-16.50)	36.00 (24.00-147.40)	0.002
Age at diagnosis (yr), median (IQR)	4.30 (2.59-9.87)	10.40 (7.30-15.30)	0.009
Age at histology examination (yr), median (IQR)	3.82 (1.83-8.76)	9.96† (7.97-11.06)	0.127
Male, n (%)	17/29 (58.62)	4/29 (36.40)	0.183
Dominant symptoms, n (%)			0.297
- Abdominal distension	7/29 (24.14)	1/29 (9.09)	
- Constipation	7/29 (24.14)	1/29 (9.09)	
- Feeding intolerance	6/29 (20.69)	2/29 (18.18)	
- Vomiting	6/29 (20.69)	6/29 (54.55)	
- Abdominal pain	3/29 (10.34)	1/29 (9.09)	
Presence of history of preterm birth, n (%)	8/29 (27.59)	1/29 (9.09)	0.209
Presence of intestinal failure, n (%)	15/29 (51.72)	0/29 (0.00)	0.015
Involvement of other GI segments, n (%)	23/27 (85.19)	6/11 (54.55)	0.044
- Abnormal colonic manometry	13/21 (61.90)	3/8 (37.50)	0.223
- Delayed gastric emptying	14/25 (56.00)	5/9 (55.56)	0.640
Bladder involvement, n (%)	11/29 (37.93)	1/11 (9.09)	0.077
Genetic mutation, n (%)	5/10 (50.00)	-	
- ACTG2	4/10 (40.00)	-	
- RET	1/10 (10.00)	-	
Feeding type at presentation, n (%)			0.027
- oral feeding	5/28 (17.86)	2/11 (18.18)	
- full enteral feeding	5/28 (17.86)	7/11 (63.64)	
- combine enteral and parenteral nutrition	3/28 (10.71)	1/11 (9.09)	
- parenteral nutrition dependence	15/28 (53.57)	1/11 (9.09)	
Latest feeding type, n (%)			0.085
- oral feeding	5/28 (17.86)	5/11 (45.45)	
- full enteral feeding	5/28 (17.86)	3/11 (27.27)	
- combine enteral and parenteral nutrition	8/28 (28.57)	3/11 (27.27)	
- parenteral nutrition dependence	10/28 (35.71)	0/11 (0.00)	
Duration of follow-up (months), median (IQR)	35.23 (6.13-64.84)	15.00 (4.17-148.08)	0.765

PIPO: paediatric intestinal pseudo-obstruction, IQR: interquartile range; †n=3

TABLE 3

The characteristics of antroduodenal manometry in paediatric intestinal pseudo-obstruction and control patients

Parameters	**PIPO (n=29)**	**Controls (n=11)**	***P* value**
Type of test meal			
- Solid, n (%)	10 (34.48)	4 (40.0)	0.686
Duration of ADM (hr), median (IQR)	22.03 (20.26-23.96)	21.18 (20.45-23.32)	0.811
Duration of fasting period (hr), median (IQR)	20.48 (18.72-21.87)	19.32 (18.23-20.72)	0.124
Duration of test meal (min), median (IQR)	28.15 (20.99-36.03)	29.78 (21.52-33.47)	1.000
MMC duration (min), median (IQR)	73.82 (55.62-106.95)	75.18 (60.22-96.74)	0.856
Duration of phase III (min), median (IQR)	6.40 (4.71-11.29)	5.22 (4.14-7.28)	0.157
Duration of phase II (min), median (IQR)	63.05 (44.19-255.47)	64.47 (40.95-104.30)	0.654
Duration of phase I (min), median (IQR)	0.00 (0.00-14.590)	10.84 (8.59-12.73)	0.131
Number of phase III per hour (no/hr), median (IQR)	0.44 (0.08-0.60)	0.63 (0.41-0.68)	0.052
Number of phase I per hour (no/hr), median (IQR)	0.14 (0.00-0.29)	0.59 (0.38-0.74)	<0.001
Percentage phase I to phase III (%), median (IQR)	25.00 (0.00-81.75)	90.00 (84.62-94.12)	0.002
Phase III score (16), median (IQR)	6.00 (5.00-8.00)	2.00 (2.00-3.00)	<0.001
- Score of amplitude, median (IQR)	1.00 (0.00-2.00)	0	0.002
- Score of baseline, median (IQR)	1.00 (1.00-2.00)	0	0.002
- Score of propagation, median (IQR)	3.00 (2.00-3.00)	1.00 (0.00-1.00)	<0.001
- Normal baseline (%), median (IQR	15.38 (0.00-57.78)	70.59 (50.00-100.00)	0.002
- Anterograde propagation (%), median (IQR)	47.73 (0.00-80.00)	100.00 (87.50-100.00)	0.001
- Have quiescence prior to phase III (%), median (IQR)	50.00 (0.00-80.00)	75.00 (57.14-90.00)	0.041
Phase I score (5), median (IQR)	4.00 (1.00-5.00)	1.00 (1.00-1.00)	0.001
Phase II score (6), median (IQR)	3.00 (2.00-3.00)	1.00 (1.00-3.00)	0.038
- Presence of DCC, n (%)	24/29 (82.76)	8/11 (72.70)	0.381
- Preprandial score of DCC, median (IQR)	2.00 (1.00-2.00)	1.00 (1.00-3.00)	0.591
- Presence of SBC, n (%)	16/29 (60.0)	0	0.001

Fasting score (27), median (IQR)	12.00 (9.50-17.50)	5.00 (4.00-5.00)	<0.001
Postprandial score (9), median (IQR)	5.00 (3.00-6.00)	3.00 (2.00-4.00)	0.009
- Reappearance of phase III, n (%)	3/29 (10.34)	1/11 (9.09)	0.700
- Increased postprandial antral activity, n (%)	16/29 (55.17)	9/11 (81.81)	0.313
- Increased postprandial duodenal motility index, n (%)	12/29 (41.37)	7/11 (63.63)	0.183
- Postprandial score of DCC, median (IQR)	2.00 (1.00-3.00)	1.00 (1.00-1.00)	0.030
Total ADM (GLASS) score (36), median (IQR)	16.00 (12.50-22.00)	8.00 (7.00-9.00)	<0.001

Results are expressed as median (interquartile range; IQR). PIPO: paediatric intestinal pseudo-obstruction, ADM: Antroduodenal manometry, DCC: Discrete clustered contractions, SBC: Sustained burst contractions, GLASS: **G**reat Ormond Street Hospital **L**ondon **A**DM **S**coring **S**ystem

TABLE 4

The degree of agreement analyzed by Cohen's Kappa test between histopathology and antroduodenal manometry to classify subtypes of pediatric intestinal pseudo-obstruction

Histopathology / ADM	Normal/unspecified (No. of patients)	Myopathy (No. of patients)	Neuropathy (No. of patients)	Neuro-myopathy (No. of patients)	Cohen Kappa (κ)	*P* value
1. Original ADM reports					**0.068**	**0.197**
- Normal/unspecified	0	1	0	0		
- Myopathy	0	1	0	0		
- Neuropathy	12	4	4	2		
- Neuro-myopathy	4	0	0	1		
2. Enhanced ADM (GLASS) scores					**0.191**	**0.003**
- Normal/unspecified	0	1	0	0		
- Myopathy	1	2	0	0		
- Neuropathy	9	2	4	0		
- Neuro-myopathy	6	1	0	3		

ADM: antroduodenal manometry, GLASS: **G**reat Ormond Street Hospital **L**ondon **A**DM **S**coring **S**ystem

TABLE 5

The comparison of gastrointestinal contractile patterns and enhanced ADM (GLASS) score between patients with and without neuropathic histology.

Parameters	**No neuropathy (n=22)**	**neuropathy (n=7)**	***P* value**
Age at diagnosis (yr), median (IQR)	3.45 (2.24-8.12)	9.00 (2.90-11.80)	0.237
Number of phase I per hour (no/hr), median (IQR)	0.24 (0.03-0.33)	0.00 (0.00-0.11)	0.013
Percentage of phase I to phase III (%), median (IQR)	45.58 (4.17-87.20)	0.00 (0.00-21.43)	0.070
Phase III score (16), median (IQR)	6.00 (4.75-7.00)	6.00 (5.00-16.00)	0.328
- Score of baseline, median (IQR)	1.0 (0.75-1.25)	2.00 (1.00-4.00)	0.088
- Score of amplitude, median (IQR)	1.50 (0.00-2.00)	0.00 (0.00-3.00)	0.940
- Score of propagation, median (IQR)	2.00 (2.00-3.00)	3.00 (3.00-4.00)	0.048
- Score of quiescence, median (IQR)	1.00 (1.00-2.00)	2.00 (1.00-3.00)	0.354
Phase I score, median (IQR)	4.00 (1.00-5.00)	5.00 (4.00-5.00)	0.165
- Duration of phase I (min), median (IQR)	0.00 (0.00-14.89)	0.00 (0.00-0.00)	0.165
Phase II score, median (IQR)	3.00 (2.00-3.00)	2.00 (1.00-3.00)	0.533
Fasting score (27), median (IQR)	11.50 (8.00-14.75)	12.00 (10.00-24.00)	0.304
Postprandial score (9), median (IQR)	5.00 (3.00-5.25)	5.00 (5.00-6.00)	0.217
- Score of fed response (4), median (IQR)	1.00 (0.00-2.25)	2.00 (2.00-3.00)	0.032
Total ADM (GLASS) score (36), median (IQR)	15.50 (12.00-20.25)	19.00 (14.00-30.00)	0.181

Values reported as median (interquartile range; IQR). ADM: Antroduodenal manometry; GLASS: **G**reat Ormond Street Hospital **L**ondon **A**DM **S**coring **S**ystem

TABLE 6

The comparison of gastrointestinal contractile patterns between patients with and without neuropathic manometric component.

Parameters	**No neuropathy (n=4)**	**neuropathy (n=25)**	***P* value**
Age at diagnosis (yr), median (IQR)	3.66 (1.23-6.98)	4.30 (2.73-10.45)	0.310
Duration of MMC (min), median (IQR)	113.28 (100.35-127.58)	67.86 (54.69-77.54)	0.035
Number of phase I per hour (no/hr), median (IQR)	0.31 (0.25-0.35)	0.09 (0.00-0.27)	0.070
Percentage of phase I to phase III (%), median (IQR)	80.89 (71.95-100.00)	18.18 (0.00-64.59)	0.013
Phase III score, median (IQR) - Score of baseline, median (IQR) - Score of amplitude, median (IQR) - Score of propagation, median (IQR) - Score of quiescence, median (IQR) Have quiescence prior to phase III (%), median (IQR)	4.50 (3.25-5.75) 0.00 (0.00-0.75) 2.00 (1.25-2.00) 1.50 (0.25-2.75) 1.00 (1.00-1.00) 89.45 (82.22-97.50)	6.00 (5.00-9.00) 1.00 (1.00-3.00) 1.00 (0.00-2.50) 3.00 (2.00-3.50) 2.00 (1.00-2.50) 37.50 (0.00-66.67)	0.070 0.016 0.482 0.060 0.082 0.004
Phase I score, median (IQR) - Duration of phase I (min), median (IQR)	1.00 (1.00-1.00) 14.00 (12.55-19.72)	4.00 (1.75-5.00) 0.00 (0.00-13.75)	0.008 0.043
Phase II score, median (IQR) - Preprandial score of DCC, median (IQR)	1.00 (1.00-1.75)	3.00 (2.00-3.00)	0.006 0.013
Fasting score (27), median (IQR)	7.00 (5.50-8.50)	12.00 (10.00-20.50)	0.001
Postprandial score (9), median (IQR)	5.0 (3.0-6.0) 2.00 (1.00-3.00)	4.5 (3.5-6.3) 1.00 (0.00-2.00)	0.927 0.341

- Score of fed response (4), median (IQR)			
Total ADM (GLASS) score (36), median (IQR)	12.0 (10.5-12.00)	18.00 (14.00-26.00)	0.003

Values reported as median (interquartile range; IQR). ADM: Antroduodenal manometry; GLASS: **G**reat Ormond Street Hospital **L**ondon **A**DM **S**coring **S**ystem

SUPPLEMENT TABLE 1

Characteristics of 11 patients in the control group

No	Gender	Age at first symptoms (mo)	Diagnosis	Co-morbidity	Dominant symptoms	Lower GI symptoms	ADM score	Colonic manometry	Gastric emptying	Feeding type		Management	Duration of follow-up (mo)
										Pre-ADM	Post-ADM		
1	M	0.00	Gastroparesis	-	vomit	constipation	8	Normal	Delayed	Enteral	Oral	gastric pacing	148.08
2	F	6.00	Gastroparesis	POTS	vomit	constipation	7	Abnormal	Delayed	Enteral	enteral + oral	gastric pacing, Ileostomy†	189.67
3	F	117.43	Rumination	-	vomit	-	12	Abnormal	Rapid	Enteral	enteral + some oral	baclofen	65.75
4	F	147.40	Gastroparesis	POTS , EDS	abdominal pain	constipation	6	Normal	Delayed	Enteral +PN	Enteral +PN	psychologist	3.50
5	F	167.03	Rumination		vomiting	constipation	8	Normal	Normal	Enteral	Oral	psychologist	2.83
6	F	36.00	Gastroparesis and aerophagia	Post infectious	abdominal distension	constipation	9	Abnormal	Delayed	Oral	Oral	Ileostomy*	9.92
7	M	24.00	Colonic dysmotility	EDS COL5A2 gene	feeding intolerance	constipation	8	Abnormal	Not done	PN	Enteral +PN	Ileostomy†, plan reduce PN	205.25
8	M	24.53	Munchausen syndrome by proxy and constipation	Epilepsy	feeding intolerance	constipation	4	Normal	Normal	Enteral	Oral	Under child protection	92.25
9	F	36.00	Rumination	-	vomit	constipation	7	Not done	Normal	Oral	Enteral	nutrition rehabilitation	15.00
10	M	24.00	Gastroparesis	Pearson's syndrome	vomiting	-	9	Not done	Delayed	Enteral	Enteral +PN	PN required for quality of life	6.50
11	F	184.23	POTS	-	vomiting	constipation	10	Normal	Not done	Enteral	Oral	psychologist	4.17

GI: Gastrointestinal, mo: months, M: male, F: female, POTS: Postural orthostatic tachycardia syndrome, EDS: Ehlers-Danlos Syndrome, PN: Parenteral nutrition, †normal histology of the small bowel, *formed before referral (unavailable histology)

SUPPLEMENTARY TABLE 2

Comparison of gastrointestinal contractile patterns and enhanced ADM score among different PIPO subtypes classified by histopathology.

Parameters	**Normal/unspecified (n=16)**	**Myopathy (n=6)**	**Neuropathy (n=4)**	**Neuro-myopathy (n=3)**	***P* value**
Age at diagnosis (yr), median (IQR)	3.35 (2.48-7.31)	6.55 (1.37-15.29)	4.15 (2.68-8.70)	9.00 (7.15-10.40)	0.188
Number of phase III per hour (no/hr), median (IQR)	0.47 (0.19-0.55)	0.35 (0.17-0.78)	0.41 (0.12-0.79)	0.00 (0.00-0.00)	0.103
Number of phase I per hour (no/hr), median (IQR)	0.24 (0.01-0.34)	0.26 (0.04-0.40)	0.06 (0.00-0.13)	0.00 (0.00-0.00)	0.073
Percentage of phase I to phase III (%), median (IQR)	41.73 (2.08-75.00)	77.86 (4.17-100.00)	10.72 (0.00-80.36)	0.00 (0.00-0.00)	0.123
Phase III GLASS score (16), median (IQR) - Score of baseline, median (IQR) - Score of amplitude, median (IQR) - Score of propagation, median (IQR) - Score of quiescence, median (IQR)	6.00 (5.00-6.75) 1.00 (1.00-1.00) 1.50 (0.00-2.00) 2.50 (2.00-3.00) 1.25 (1.00-2.00) 8.47 (6.23-11.56)	4.50 (3.75-10.75) 1.00 (0.00-2.50) 1.50 (0.75-2.25) 2.00 (0.75-3.25) 1.00 (1.00-2.25) 4.71 (2.21-8.56)	5.00 (5.00-5.75) 1.50 (0.25-2.00) 0.00 (0.00-0.00) 3.00 (2.25-3.00) 1.00 (1.00-1.75) 9.42 (5.74-17.95)	16.00 (16.00-16.00) 4.00 (4.00-4.00) 3.00 (3.00-3.00) 4.00 (4.00-4.00) 3.00 (3.00-3.00) 0.00 (0.00-0.00)	0.041 0.073 0.011 0.051 0.046 0.022

Parameters	**Normal/unspecified (n=16)**	**Myopathy (n=6)**	**Neuropathy (n=4)**	**Neuro-myopathy (n=3)**	***P* value**
- Duration of phase III (min), median (IQR)					
Phase I GLASS score (5), median (IQR) - Duration of phase I (min), median (IQR)	4.00 (1.00-5.00) 0.00 (0.00-18.96)	1.00 (1.00-5.00) 12.74 (0.00-14.78)	4.00 (2.13-4.75) 0.00 (0.00-9.81)	5.00 (5.00-5.00) 0.00 (0.00-0.00)	0.190 0.365
Phase II GLASS score (6), median (IQR) - Score of DCC, median (IQR) - Score of SBC, median (IQR) - Duration of phase II (min), median (IQR)	3.00 (2.00-3.75) 2.00 (2.00-3.00) 1.00 (0.00-1.00) 52.68 (42.32-138.36)	2.00 (1.00-3.00) 1.50 (1.00-2.25) 0.00 (0.00-1.00) 91.23 (38.26-224.49)	1.50 (1.00-2.75) 1.00 (1.00-1.75) 0.00 (0.00-0.75) 60.70 (45.07-146.23)	3.0 (2.50-2.88) 2.00 (1.50-2.00) 1.00 (1.00-1.50) 1215.10 (1203.14-1236.04)	0.147 0.142 0.131 0.129
Have neuropathic component based on GLASS score (%), median (IQR)	15/16 (93.75)	3/6 (50.00)	4/4 (100.00)	3/3 (100.00)	0.037
Fasting GLASS score (27), median (IQR)	12.00 (10.00-14.00)	7.50 (6.50-18.75)	10.5 (10.00-11.75)	24.00 (23.50-24.50)	0.056
Postprandial GLASS score (9), median (IQR)	4.50 (3.00-5.75)	5.00 (3.75-5.25)	5.00 (3.50-7.25)	5.00 (4.50-5.50)	0.517

Parameters	**Normal/unspecified (n=16)**	**Myopathy (n=6)**	**Neuropathy (n=4)**	**Neuro-myopathy (n=3)**	***P* value**
Neuropathic score (33), median (IQR)	15.5 (12.50-19.50)	10.50 (9.75-21.50)	14.50 (13.25-18.00)	27.00 (26.50-27.00)	0.046
Total ADM (GLASS) score (36), median (IQR)	16.50 (13.25-19.75)	12.00 (10.75-23.00)	14.50 (13.25-18.00)	30.00 (29.50-30.00)	0.050

Values reported as median (interquartile range: IQR), DCC: Discrete clustered contractions, SBC: Sustained burst contractions, ADM: Antroduodenal manometry; GLASS: **G**reat Ormond Street Hospital **L**ondon **A**DM **S**coring **S**ystem

FIGURE LEGENDS

Figure1

Examples of different contractile activities analyzed in the study.

A. Artefact was detected in between the period of phase III.

B. Phase III in a studied patient comprised antral activity of 2 cycles per minute and small bowel activity of 10-14 cycle per minute.

C. A manometric recording showed discrete cluster contractions (arrows) and sustained burst contractions (arrow head).

D. Patterns of contractile activities showed; a) single propagated contraction, b) non-propagated clustered contractions, c) propagated contraction with a clustered contraction, d) Discrete clustered contractions.

Figure2

Study flow chart

Suppl Figure1

Examples of pre-phase III motor quiescence identified in non-PIPO **(A and B)** and PIPO **(C and D)** patients with simulated low resolution (conventional; line graph **A and C**) versus high resolution (HRM) antroduodenal manometry plots **(B and D)**

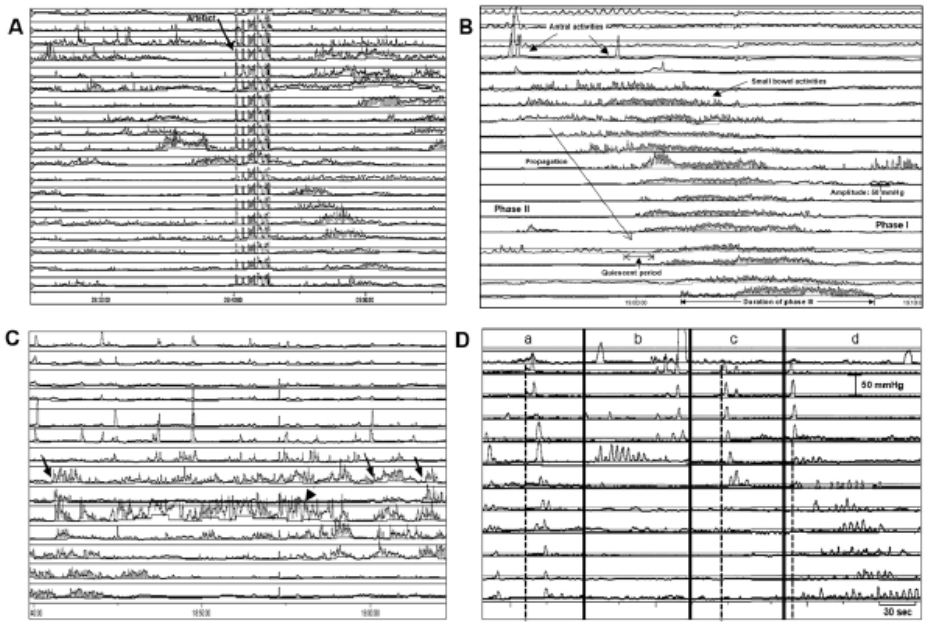


Figure 1 Examples of different contractile activities analyzed in the study. A. Artefact was detected in between the period of phase III. B. Phase III in a studied patient comprised antral activity of 2 cycles per minute and small bowel activity of 10-14 cycle per minute. C. A manometric recording showed discrete cluster contractions (arrows) and sustained burst contractions (arrow head). D. Patterns of contractile activities showed; a) single propagated contraction, b) non-propagated clustered contractions, c) propagated contraction with a clustered contraction, d) Discrete clustered contractions.

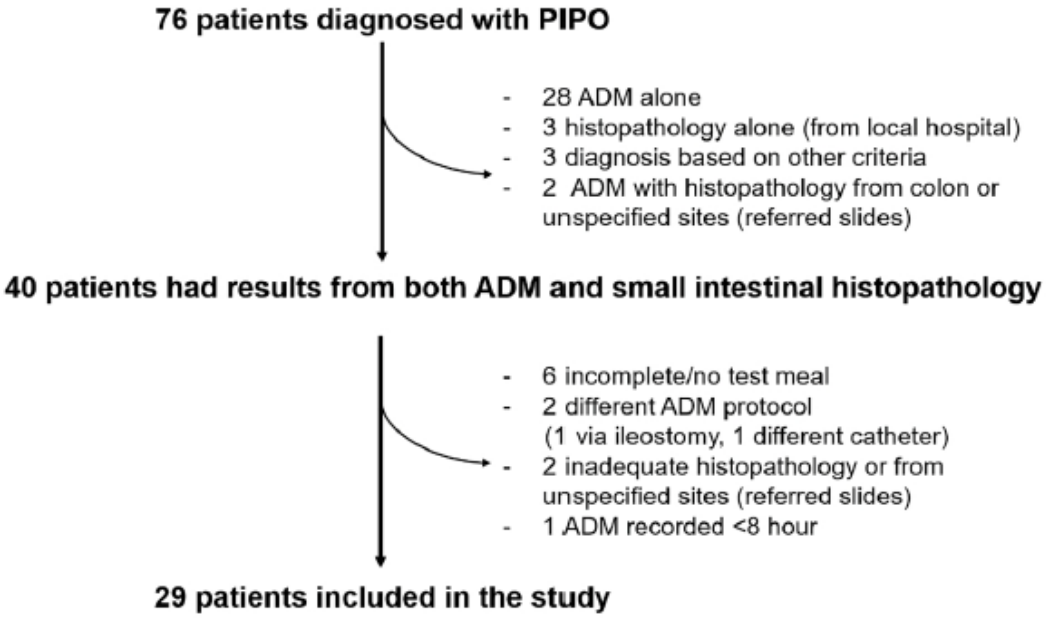
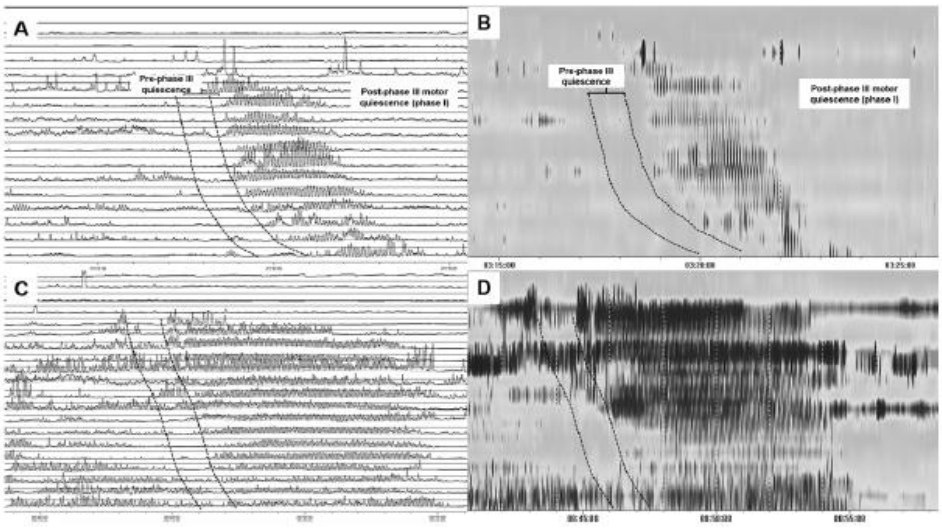


Figure2 Study flow chart



Caption : Suppl Figure1 Examples of pre-phase III motor quiescence identified in non-PIPO (A and B) and PIPO (C and D) patients with simulated low resolution (conventional; line graph A and C) versus high resolution (HRM) antroduodenal manometry plots (B and D)