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Original Research

Investigating the diagnostic utility of high-resolution oesophageal manometry in patients with refractory respiratory symptoms

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A B S T R A C T

Background: The interaction between the respiratory and gastrointestinal systems, and the role of the latter in the development of respiratory pathology, has been examined with a focus on gastro-oesophageal reflux disease (GORD). However, little data exists examining the link between oesophageal motility and respiratory disease.

Aims and objectives: In this study, we examined patterns in oesophageal motility using high-resolution oesophageal manometry (HROM) in patients with refractory respiratory symptoms.

Methods: Data were collected retrospectively for all patients that were investigated using HROM at a single centre for refractory respiratory symptoms between January 1st, 2011–December 1st, 2021. Patients were selected for investigation based on airway reflux symptoms, measured by the Hull Airways Reflux Questionnaire (HARQ).

Results: 441 patients were investigated with HROM (64% female, mean age = 56.5 [SD = 13.9]). The commonest diagnoses of these patients were Chronic Cough (77%, n = 339), Asthma (10%, n = 44), and Interstitial Lung Disease (7%, n = 29). The prevalence of oesophageal dysmotility was 66% in our cohort. Those with oesophageal dysmotility had significantly higher HARQ scores than those with normal motility (40.6 vs 35.3, $p < 0.001$) and there was a significant inverse correlation between HARQ scores and distal contractile integral (DCI), a measure of oesophageal contractility.

Conclusions: Two-thirds of patients with refractory respiratory symptoms were found to have oesophageal dysmotility on HROM. These findings suggest motility disorders of the oesophagus may contribute to the development and progression of respiratory disease. This study highlights the need for further prospective study of the relationship between oesophageal dysmotility and respiratory disease.

Take home message

In a cohort of 441 patients with respiratory disease, 66% were found to have oesophageal dysmotility when investigated with high-resolution oesophageal manometry. Therapeutic agents that improve gastrointestinal motility may be of benefit in such patients.

1. Introduction

Respiratory symptoms such as cough, wheeze, and breathlessness are amongst the commonest reasons for presentation to healthcare in the United Kingdom, accounting for up to 22% of total patient contacts [1]. Chronic respiratory diseases also account for more than 10% of productive life lost secondary to medical issues, and are known to cause great detriment to the physical, psychological, and socioeconomic wellbeing of patients [2–4]. Unfortunately, many patients with respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and chronic cough (CC) may report persistent symptoms despite being treated with optimal medical therapy [5,6]. For patients and clinicians alike, the cause for these refractory respiratory symptoms and exacerbations is often frustratingly unclear and traditional investigations and treatments for pulmonary diseases may prove unhelpful in elucidating the aetiology.

In recent years the interaction between the respiratory and gastrointestinal systems, and the role of the latter in the development of respiratory pathology, has been examined [7–9]. Indeed, much of the current literature is focused on the link between gastroesophageal reflux disease (GORD) and conditions such as, COPD, asthma, CC and interstitial lung diseases (ILD) [10–13]. However, there is precious little work examining the link between oesophageal motility and respiratory disease in adults.

In this study, we collected data from patients with chronic

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respiratory diseases that experienced persistent symptoms despite optimal medical therapy who were being investigated with High-Resolution Oesophageal Manometry (HROM). Patients in this cohort were undergoing this procedure as part of routine clinical care to assess the suitability of surgical management of their respiratory disease. We assessed the utility of HROM in the investigation of this cohort of patients.

2. Methods

In this retrospective, single-centre observational study, data were collected for all patients that were investigated using HROM for refractory respiratory symptoms between January 1st, 2011 and December 1st, 2021. Refractory respiratory symptoms were defined as persistent symptoms such as cough and breathlessness despite optimal medical management for the patients' primary respiratory diagnosis. Therefore, all patients included in this study were investigated with HROM to decipher whether oesophageal dysmotility and/or gastro-esophageal reflux were associated with their symptoms. This procedure was carried out to assess the potential benefit and safety of anti-reflux surgery, which has been shown to improve symptoms in patients with CC, ILD, and asthma [14–16]. Patients who were selected for this investigation had reported a clear history of reflux-related symptoms.

All data included were recorded as part of routine clinical care and their inclusion in this study was ratified by the Hull University Teaching Hospitals NHS Trust clinical governance committee.

2.1. High resolution oesophageal manometry

HROM testing was carried out using a 36-channel solid-state unidirectional manometric catheter which was placed transnasally. Patients were asked to discontinue Proton-pump inhibitor (PPI) therapy 7 days prior to the procedure. Patients were asked to swallow boluses of water 10 times at intervals of 20–30 s, this would then be followed by solid bolus swallows for which the patient swallowed a small piece of bread.

Manometric measurements were then reported and analysed using the Laborie Investigation and Diagnostic Software and the quality of each swallow was assessed and stratified into 6 categories of peristalsis: normal, ineffective, failed contraction, premature, hypercontractile, and fragmented. Data from the quality of the swallows as well as measurements of the distal contractile integral (DCI), integrated relaxation pressure (IRP), distal latency (DL), and lower oesophageal sphincter resting pressure (LOSRP) were analysed and patients were given a manometric diagnosis as per the contemporaneous Chicago Classification [17]. All manometric diagnoses were made from the measurements of the 10 water swallows. Examples of each of these diagnoses can be seen in Fig. 1.

2.2. 24-Hour pH and impedance monitoring

The 24-h pH ambulatory and impedance study were carried out using the Laborie Investigation and Diagnostic Software. A pH sensor was placed 5 cm above the proximal border of the lower oesophageal sphincter, with 6 impedance-measuring electrodes positioned at

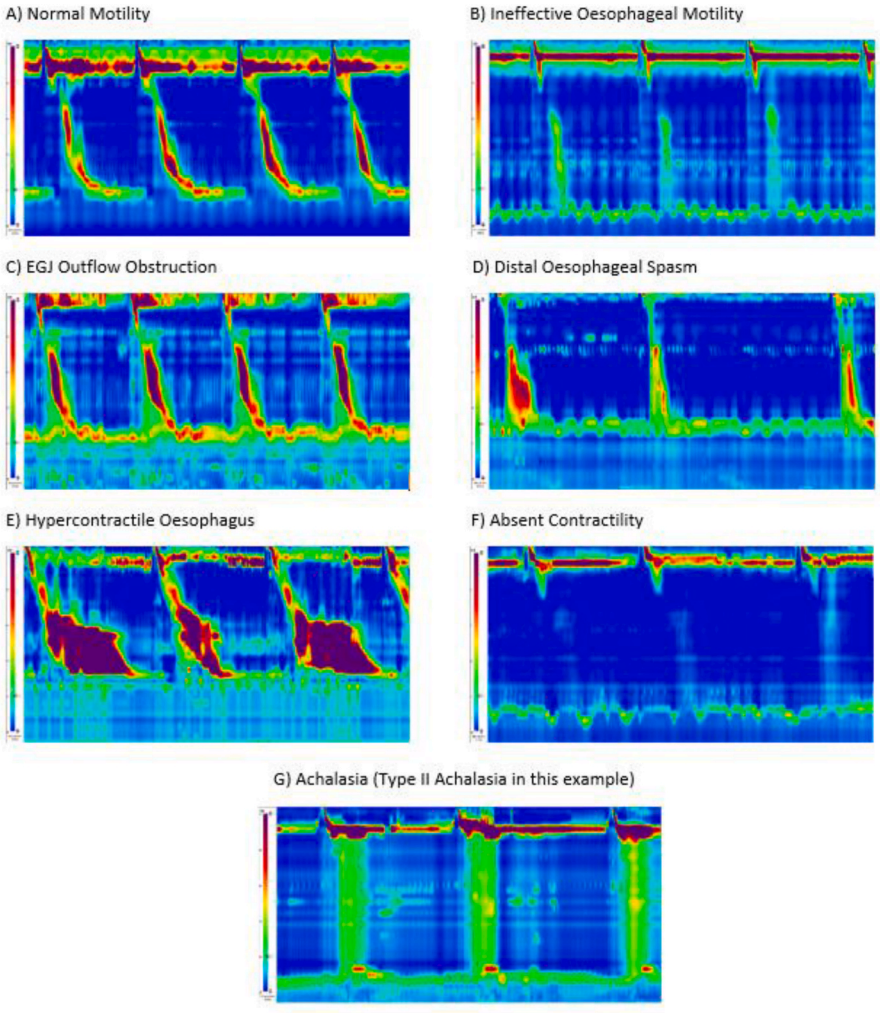

Fig. 1. Data acquired using HROM is visualised in the images above, converting manometric information and displaying the data as a topographic plot that represents both anatomy and physiology. Pressure is represented by colour; the lowest pressures are represented as blue, graduating to the higher pressures represented in purple. Sensor location is on the y-axis, and time ison the x-axis. The two horizontal bands of pressure correspond to the resting upper oesophageal sphincter (UOS) pressure (located at the top of the images), and the lower oesophageal sphincter (LOS) pressure (located at the bottom of the images). The pattern of colour in-between these two distinct bands of pressure represent the pressure profile within the oesophagus. Images A-G illustrate the manometric profile of the seven main categories of diagnosis from the Chicago Classification. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

intervals of 3 cm, 5 cm, 7 cm, 9 cm, 15 cm and 17 cm above the proximal border of the lower oesophageal sphincter. Patients were asked to carry out their normal activities of daily living for 24 h before returning the equipment.

Measurements were recorded to determine total duration of distal oesophageal acid exposure (Acid Exposure Time) [18], patient reported symptoms (using an event marker device), number of reflux events, and the character of the reflux event (whether it was gas/liquid and acidic/non-acidic). For the purposes of analysis, an arbitrary cut off of 50 reflux events was considered abnormal by the authors. This was based on current clinical practice and previous HROM studies of healthy subjects in the literature [19,20].

Data collected were analysed by the Laborie Investigation and Diagnostic Software to determine the DeMeester score and identify potential reflux events. The DeMeester score is a composite score of parameters that measure acid exposure, throughout this study it is used as an indicator of acid exposure time. These metrics were then manually analysed by a Specialist Clinical Scientist in GI Physiology.

2.3. Patient demographics

Demographic information including age, sex, smoking status, and primary respiratory diagnosis were collected for all patients through examination of electronic patient records. Previous clinical care event records were also examined to determine whether patients' symptoms have been assessed using the Hull Airway Reflux Questionnaire (HARQ) tool [21], a validated questionnaire which assess the symptoms and physiological features of extraoesophageal reflux into the respiratory tract, and scores were recorded.

2.4. Statistical analysis

All demographic data are presented descriptively. Comparison of means was performed using independent t-tests, comparison of medians was performed using Mann-Whitney U testing, and comparison of proportions was performed using Chi-squared testing. Comparison of the relationship between any two variables was performed using simple linear regression analysis. All data were analysed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA).

3. Results

Between the period January 1st, 2011 to December 1st, 2021, 441 patients with chronic respiratory disease were investigated with HROM. Of such patients, 64% were female and the mean age was 56.5 years old (SD = 13.9). The common primary diagnoses of the patients investigated included Chronic Cough (77%, n = 339), Asthma (10%, n = 44), Interstitial Lung Disease (7%, n = 29), Cystic Fibrosis (3%, n = 12), and COPD (2%, n = 10). Twenty-four percent of patients reported being a current or ex-smoker.

3.1. Manometry results and diagnoses

All patients had sufficient manometric assessment adequate to diagnose oesophageal disorders as per the contemporary Chicago Classification. Of all 441 patients, 34.5% (n = 152) demonstrated normal motility on HROM, 54% (n = 238) had Ineffective Oesophageal Motility (IOM), 7.3% (n = 32) had Absent Contractility, 3.2% (n = 14) had Oesophageal-gastric Junction Outflow Obstruction (EGJOO), 0.5% (n = 2) had Distal Oesophageal Spasm (DOS), 0.5% (n = 2) had Achalasia, and a single patient met the criteria for Hypercontractile Oesophagus. The overall prevalence of disorders of oesophageal motility (i.e. any diagnosis other than normal motility) was 66% (n = 290). There were no statistically significant differences between males and females in the prevalence of any of these manometric diagnoses. Furthermore, the proportion of patients with any disorder of oesophageal motility was not different between males and females (63% vs 67%, p = 0.414). All data regarding the manometric findings of all patients can be found in Table 1. The prevalence of each manometric diagnosis stratified by respiratory diagnosis can be seen in Fig. 2.

In addition to examination of oesophageal motility, patients were also assessed for the presence of a hiatus hernia. Of all patients, 41% (n = 181) were found to have a hiatus hernia on HROM testing. The proportion of females who were found to have a hiatus hernia was significantly higher than that of males (45% vs 34%, p = 0.029).

Table 1
Baseline demographics, HARQ scores, HROM and 24-h pH study findings for patients included in this study.

	All patients (n = 441)	Males (n = 158)	Females (n = 283)	p-value*
Mean Age (SD)	56.5 (13.9)	55.0 (16.6)	56.4 (12.7)	0.328
Female (%)	283 (64)	–	–	
Mean HARQ score (SD)	38.8 (13.2)	38.0 (12.5)	39.3 (13.6)	0.313
Smoking History (%)	106 (24)	29 (18)	77 (27)	0.062
Diagnosis (%)				
Chronic Cough	339 (77)	113 (72)	226 (80)	–
Interstitial Lung Disease	29 (7)	14 (9)	15 (5)	–
Cystic Fibrosis	12 (3)	8 (5)	4 (1)	–
Asthma	44 (10)	16 (10)	28 (10)	–
COPD	10 (2)	4 (3)	6 (2)	–
Median Oesophageal Manometry Metrics (range)				
Integrated Relaxation Pressure (mmHg)	11.6 (−3.5–104)	10.35 (−2.3–104)	11.95 (−3.5-30.5)	0.003
Distal Contractile Integral (mmHg/sec/cm)	570 (0–5890)	553 (0–3411)	572 (0–5890)	0.703
Distal Latency (sec)	6.7 (3.8–11.9)	6.6(3.8–10)	6.7 (4.6–11.9)	0.891
Lower Oesophageal Resting Pressure (mmHg)	26.2 (2.1–105)	24.5 (5.5–88.1)	25.9 (2.1–105)	0.310
Chicago Classification (%)				
Normal Motility	152 (34)	58 (37)	53 (39)	0.459
Ineffective Oesophageal Motility	238 (54)	84 (53)	154 (54)	0.800
EGJ Outflow Obstruction	14 (3)	2 (1)	12 (5)	0.088
Distal Oesophageal Spasm	2 (1)	2 (1)	0 (0)	–
Hypercontractile Oesophagus	1 (1)	1 (1)	0 (0)	–
Absent Contractility	32 (7)	10 (6)	22 (9)	0.575
Achalasia	2 (1)	1 (1)	1 (1)	0.675
Manometric Findings				
Any Oesophageal Dysmotility (%)	290 (66)	100 (63)	190 (67)	0.414
Hiatus Hernia (%)	181 (41)	54 (34)	127 (45)	0.029
Dysmotility or Hiatus Hernia (%)	360 (82)	119 (75)	241 (85)	0.010
Median 24-h pH Study Findings (range)				
DeMeester Score	8.49 (0.2–167.81)	10.65 (0.2–167.81)	7.48 (0.2–144.14)	0.064
Number of Reflux Events	64 (1–1050)	74 (4–1050)	59.5 (1–332)	0.997
% of Reflux Events Acidic	35 (0–87)	38 (0–87)	31.5 (0–84)	0.483
% of Reflux Events Gaseous	41 (0–100)	43 (0–91)	40 (0–100)	0.969

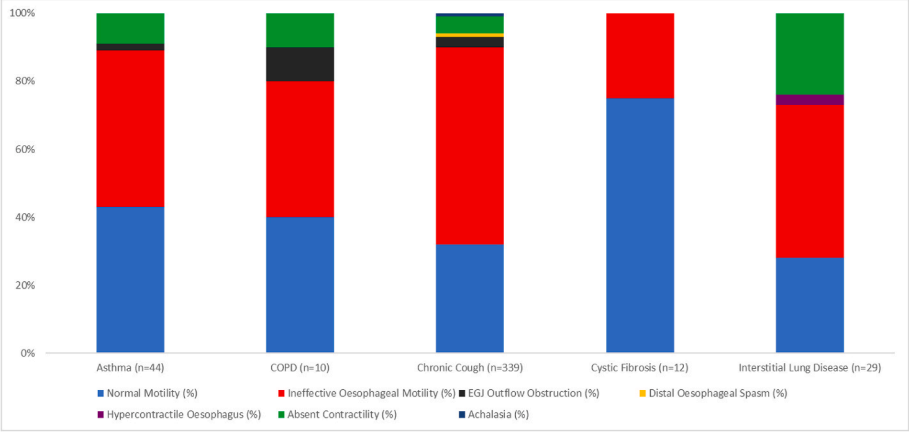

Fig. 2. Proportion of patients with each manometric diagnosis, stratified by the respiratory diagnoses frequently observed in this study.

3.2. 24-Hour pH testing

The results of 24-h pH testing were available for 87% (n = 383) of all patients. Of these patients the median DeMeester score was 8.49 (range = 0.2–167.81) and 38% (n = 144) of patients who underwent pH testing had a positive DeMeester score (defined as higher than 14.72), indicating acidic gastro-oesophageal reflux disease.

The median number of reflux events in 24 h in those who underwent testing was 64 (range = 1–1050). We were able to further characterise of each reflux event in 42% (n = 161) of the patients who had pH testing into acid/non-acid and gaseous/liquid reflux. The median proportion of reflux events that was characterised as acidic in all patients was 35% (range = 0–87) and the median proportion of reflux events characterised as gaseous was 41% (range = 0–100).

3.3. Correlation of oesophageal studies and clinical assessment with the HARQ

HARQ scores were available for 83% (n = 366) of all patients, with the mean score being 38.8 (SD = 13.2), the upper limit of normal in patients without airway reflux is a score of 14(21). The mean HARQ score was significantly higher in those with any diagnosis of oesophageal dysmotility when compared to those with normal manometric studies (40.6 vs 35.3, $p < 0.001$). Using linear regression analysis, there were no significant relationships identified between the HARQ and DCI, IRP, DL, and LOSRP.

There were no significant relationships identified between the HARQ score and DeMeester scores or number of reflux events in 24 h. There was no difference in the mean HARQ score between patients with ≥50 reflux events in 24 h and those with <50 reflux events in 24 h (39.2 vs 38.5, $p = 0.318$). Furthermore, there was no difference in the mean HARQ score between those who met the diagnostic criteria for GORD (i.e. a positive DeMeester score) and those who did not (37.9 vs 39.2, $p = 0.231$).

4. Discussion

In this study, we report that 66% of patients with refractory respiratory symptoms demonstrate disorders of oesophageal motility. The proportion of patients with oesophageal dysmotility is consistently high over a range of respiratory diseases, including interstitial lung disease (72%), airways disease (57%), and CC (68%). The median DCI (the measure of the peristaltic vigour of the oesophagus) in our study was 570 mmHg/s/cm, less than half of the average DCI in a study of healthy, albeit slightly younger, individuals [20]. Subsequent 24-h pH testing in our cohort of patients showed a lower prevalence of traditional GORD, with only 38% of patients exhibiting a positive DeMeester score. These findings suggest that in patients with respiratory symptoms persisting despite traditional medical management, oesophageal disease may have a role in the aetiology of their condition. Furthermore, the (relatively) lower prevalence of traditional GORD may suggest that the issue is not acidic reflux from the stomach, as has been historically suspected [11,12,22]. Indeed, other studies report a weak association with acidic reflux and coughing epsiodes in patients with CC, with volume of refluxate strongly associated with the timing of cough [23]. We hypothesise that impaired peristaltic activity of the oesophagus, leading to aspiration of gaseous non-acidic refluxate into the airways, may be a contributor in the development and progression of respiratory disease.

The concept of the gut-lung axis is one that has been previously recognised in systemic diseases that cause severely impaired oesophageal function such as systemic sclerosis. This latter has been closely linked with the development of ILD and airways disease [24,25]. Indeed, one study showed that patients with absent contractility on HROM demonstrated a significantly lower forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) than those with normal motility [26]. Furthermore, it has been shown that patients with idiopathic pulmonary fibrosis (IPF) there is a high incidence of oesophageal dysmotility and in this group of patients there are high levels of pepsin found in bronchoalveolar lavage fluid, suggesting aspiration of gastric contents [27]. Such findings suggest that the use of HROM may represent an investigation strategy for patients with whom conventional approaches have failed. However, it is important to recognise that not all those with refractory respiratory symptoms will have a degree of oesophageal dysfunction, thus careful patient selection for an invasive procedure such as HROM is essential.

In all patients in this study, investigation with HROM was deemed appropriate as they reported reflux-related symptoms as evidenced by their HARQ score. This validated tool evaluates the likelihood that a patient's respiratory symptoms could be attributed to airway reflux [28]. Indeed, our data shows that those with oesophageal dysmotility had a significantly higher HARQ score than those with normal motility. We believe the HARQ offers a useful screening tool for determining the appropriateness of oesophageal study in such patients.

The current therapeutic options to tackle the dysfunctional oesophagus in respiratory disease are limited. There is precedent of gastrointestinal intervention in diseases such as CC and ILD, as anti-reflux surgery has been utilised to improve symptoms in the former and prevent progression of disease in the latter [16,29]. Surgical intervention, however, may be contraindicated for those with poor peristaltic activity of the oesophagus as peristalsis may be worsened by the correction of lower oesophageal sphincter anatomy [30]. Therefore, we believe that HROM is a necessary examination for clinicians to perform before considering any patient for anti-reflux surgery, and a multidisciplinary approach between respiratory physicians and gastrointestinal surgeons

is paramount.

Macrolide antibiotics, drugs commonly used in the management of a number of chronic respiratory diseases [31], have been shown to promote gastrointestinal motility through agonist activity at the motilin receptor. Use of macrolides have demonstrated a reduction of the rate of reflux events in patients with GORD and in patients who have undergone lung transplantation [32–34]. There is a requirement for studies aiming to examine the effect of macrolides and other prokinetic agents on oesophageal motility in patients with respiratory disease. In patients reporting disproportionate respiratory symptoms and a high HARQ score, a potential 'treatable trait' may be identified, and therapeutic strategies aimed at improving oesophageal motility may be employed. Confirmation of dysmotility may be observed using HROM.

Our study has limitations, including the absence of lung function data for patients with airways disease and ILD to examine the relationship between oesophageal function and respiratory physiology. Furthermore, we cannot assume causation between oesophageal dysmotility and refractory respiratory symptoms. Our data cannot be used to estimate prevalence of oeosphageal dysmotility in all patients with respiratory disease, as our cohort were selected for investigation with HROM due to the clinical suspicion of airway reflux. One may also argue that the association between oesophageal dysfunction and the patients' symptoms may not be casual but rather shared vagal dysfunction as this has been described in those presenting with cough and dyspnoea [35, 36]. As this data was collected retrospectively, we were unable to collect any data on severity of symptoms using validated symptom questionnaires or visual analogue scales to examine the impact of oesophageal dysfunction on patient reported outcomes. We do, however, report a significant proportion of patients with oesophageal dysmotility in a large cohort of patients with chronic respiratory disease.

5. Conclusions

In this study, we have observed oesophageal dysmotility in two-thirds of patients with refractory respiratory symptoms that were investigated with HROM. We also observe a low prevalence of traditional GORD in the same population. These findings suggest that motility disorders of the oesophagus, rather than acidic reflux, may contribute to persistent symptoms in chronic respiratory diseases. This study provides a rationale for further prospective study examining the relationship between oesophageal dysmotility, lung function, and symptom burden in patients with chronic respiratory disease. This may help to inform studies investigating therapeutic targets.

CRediT authorship contribution statement

Dominic L. Sykes: were involved in the conception and design of the study, Conceptualization, performed all statistical analysis and created the manuscript, All authors reviewed the final manuscript, Formal analysis. **Michael G. Crooks:** were involved in the conception and design of the study, Conceptualization, All authors reviewed the final manuscript. **Simon P. Hart:** were involved in the conception and design of the study, Conceptualization, All authors reviewed the final manuscript. **Warren Jackson:** were included in the analysis of the findings and reviewing the manuscript, Formal analysis, Writing – review &; editing, All authors reviewed the final manuscript. **John Gallagher:** were included in the analysis of the findings and reviewing the manuscript, Formal analysis, Writing – review &; editing, All authors reviewed the final manuscript. **Alyn H. Morice:** were involved in the conception and design of the study, Conceptualization, All authors reviewed the final manuscript.

Declaration of competing interest

All authors declare no conflict of interest pertaining to the generation of this manuscript.

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