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Diagnostic yield of upper gastrointestinal endoscopy in patients attending a UK centre with symptoms compatible with Rome IV functional dyspepsia

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ABSTRACT

Background: Dyspeptic symptoms are common and mainly due to functional dyspepsia (FD). The Rome IV criteria mandate a normal upper gastrointestinal (UGI) endoscopy before diagnosing FD. However, endoscopies are costly, resource-intensive procedures that generate substantial waste. Hence, simpler means of diagnosing FD are desirable.

Objectives: To determine what proportion of UGI endoscopies are represented by patients with symptoms compatible with Rome IV FD, and the diagnostic yield in this cohort stratified according to alarm features.

Methods: Adult patients attending a UK centre for out-patient UGI endoscopy completed a pre-procedure questionnaire on demographics, medical history, alarm features, mood, somatisation, and gastrointestinal symptoms. Alarm features were defined as age ≥55 yrs, dysphagia, anaemia, unintentional weight loss, UGI bleed, or a family history of UGI cancer. Clinically significant endoscopic findings were cancers, barrett's oesophagus, erosive oesophagitis, peptic ulcers, or strictures.

Results: Of 387 patients attending for an out-patient non-surveillance diagnostic upper GI endoscopy, 221 had symptoms compatible with FD whereas 166 did not. Approximately 80% in both groups had alarm features, with a similar prevalence of clinically significant endoscopic findings at ~10%. Upper GI endoscopy was normal in a cohort of 9% (n=35) with symptoms compatible with FD and no alarm features, whilst benign peptic ulcer was noted in two of 29 cases without FD symptoms and no alarm features.

Conclusion: 1-in-10 UGI endoscopies are performed in patients with symptoms compatible with FD and no alarm features, in whom there is no diagnostic yield. We recommend such patients receive a positive diagnosis of FD without endoscopy.

SUMMARY BOX

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Chronic dyspeptic symptoms affect approximately 10% of the population, with functional dyspepsia (FD) being the most frequent cause.
- The Rome IV criteria require a normal upper gastrointestinal (UGI) endoscopy prior to diagnosing FD. However, endoscopies are expensive, labour-intensive, waste-generating procedures, and simpler means of diagnosing FD are preferable.
- There is a paucity of UK data evaluating the diagnostic yield of UGI endoscopy in patients with symptoms compatible with Rome IV FD, and the relative influence of alarm features in predicting FD.

WHAT THIS STUDY ADDS

- 1-in-10 non-surveillance UGI endoscopies are performed in patients with symptoms compatible with FD but no alarm features.
- The diagnostic yield of upper GI endoscopy in those without alarm features is negligible.

HOW MIGHT IT IMPACT ON CLINICAL PRACTISE IN THE FORESEEABLE FUTURE

- In the absence of alarm features, a positive diagnosis of FD without upper GI endoscopy should be recommended. The findings support the recommendations recently made by the BSG guidelines for FD, whilst challenging the diagnostic model proposed by the Rome IV criteria.
- The results might inform future diagnostic iterations of the Rome criteria, curb unnecessary endoscopic procedures, reduce waiting time pressures, and have downstream effects that lead to a greener endoscopy.

Introduction

Dyspepsia affects almost 10% of the population and refers to symptoms emanating from the gastro-duodenal region.[1,2] It is amongst the most frequent gastrointestinal conditions seen in clinical practice, and represents a significant societal burden, being associated with increased healthcare use, mood disturbances, reduced quality of life, and work absenteesim.[1-3] The cardinal symptoms of dyspepsia include epigastric pain or burning, postprandial fullness, and early satiety.[4] The vast majority of people in the community with dyspepsia (80-85%) do not have an organic disease to explain their symptoms, and can be diagnosed with functional dyspepsia (FD).[5,6] The pathophysiology of FD is not completely understood, but it is a disorder of gut-brain interaction as characterised by visceral hypersensitivity, altered sensorimotor function, impaired gastric accommodation, and altered central processing.[4]

The Rome IV diagnostic criteria states that for patients to be diagnosed with FD they must have had a normal upper gastrointestinal (GI) endoscopy.[4] However, upper GI endoscopies are expensive, labour intensive, invasive procedures that can be distressing to patients and have an appreciable risk profile. They also generate substantial environmental waste which impacts on climate change and, as healthcare professionals, we have a responsibility to implement quality improvement measures that allows for an environmentally sustainable clinical practise.[7,8] Hence, performing an upper GI endoscopy for a common condition with little diagnostic yield seems undesirable.

Moreover, the diagnostic model proposed by the Rome Foundation for FD contrasts with irritable bowel syndrome, another disorder of gut-brain interaction affecting 4.1% of the population,[2] where a symptom-based diagnosis without routine use of colonoscopy is encouraged.[9] Evidence to support the judicious use of investigations in irritable bowel syndrome comes from studies demonstrating the diagnostic yield of colonoscopy to be negligible in those without alarm features, and approximately 5-15% in those with alarm features.[10,11] Yet, regardless of the presence or absence of alarm features, this diagnostic construct does not currently apply to Rome IV FD (table 1).[4,9]

We performed a single centre UK-based study to determine what proportion of diagnostic upper GI endoscopies are represented by patients with symptoms compatible with FD, the diagnostic yield in this cohort, and the relative influence of alarm features in predicting FD. The results might help inform future iterations of the Rome criteria, curb unnecessary endoscopic procedures, help alleviate waiting time pressures, and have downstream effects that lead to a greener endoscopy.

Methods & Materials:

Study design and participants: This prospective cross-sectional study was ethically approved (STH ethics number 20572, IRAS project ID 253210) and undertaken at Sheffield Teaching Hospitals, UK, over a 6-month period between May to December 2021.

English speaking adults aged ≥18 years referred for a diagnostic out-patient upper GI endoscopy were invited to self-complete a questionnaire at home enquiring for basic demographics, past gastrointestinal and medical history, alarm symptoms, anxiety and depression, somatisation, and gastroduodenal symptoms compatible with FD according to the Rome IV diagnostic questionnaire.[12]

Patients were asked to return the questionnaire on the day of their procedure, where clinical chart review and laboratory-based alarm features that had been requested at the discretion of the referring physician were also entered into the questionnaire template. Alarm features were defined as age ≥ 55 yrs, dysphagia, anaemia, unintentional weight loss, UGI bleed, or a family history of UGI cancers. Endoscopists were blinded to the questionnaire data, with clinically significant endoscopic findings defined as malignancy, grade C/D erosive oesophagitis, barrett's oesophagus, strictures, and peptic ulcer disease.[5,6]

Statistical analysis: The primary analysis determined the proportion of people attending for UGI endoscopy who have symptoms compatible with FD, and the diagnostic yield of organic disease in this group, further divided according to the presence or absence of alarm features. In order to put these findings into context, we used those patients without symptoms compatible with FD as a comparative group.

Statistical analysis was carried out using SPSS version 27.0 software, with significance set at a p-value of <0.05. Categorical variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the chi-square test or exact fisher test. Continuous variables were summarized by mean and standard deviation, with difference between two independent groups performed using the unpaired student T-test.

Results

Study participants

As shown in figure 1 we sent out 1500 questionnaires of which 508 were returned (33% response rate). We subsequently excluded 121 patients as they either did not complete the questionnaire (n=6), reported a previous history of upper GI cancer (n=7), or were attending for a therapeutic procedure or enrolled within a dedicated surveillance program for varices/barrett's oesophagus (n=108). This left 387 patients eligible for analysis, of which almost 90% were of white race.

Patient characteristics, prevalence of alarm features, and the diagnostic yield of upper GI endoscopy

Of the 387 patients, 53% were direct open access referrals from primary care with the remaining 47% secondary-care referrals. Symptom criteria for FD was met by 221 (57%) patients whilst 166 (43%) did not. Recent testing for *Helicobacter pylori* was similar between groups (22% vs. 17%, p=0.23). However, patients who had symptoms compatible with FD, compared to those without, were significantly more likely to be female (62% vs. 46%), report reflux symptoms (38% vs. 27%, p=0.02) and have a higher use of acid-suppressive drugs (74% vs. 63%, p=0.02) but not neuromodulators (29% vs. 25%, p=0.30). They also had a significantly greater prevalence of fibromyalgia (10% vs. 2%), chronic fatigue syndrome (15% vs. 2.5%), and recorded higher mean PHQ-12 non-GI somatic scores (9.3 vs. 5.9), abnormal levels of anxiety (37% vs. 19%) and depression (27% vs. 11%); see table 2.

The presence of at least one alarm feature was similar across both groups (84% vs. 83%), although individuals with symptoms compatible with FD were significantly more likely to report unintentional weight loss (24% vs. 13%), likely as a consequence of restricted eating patterns secondary to dyspeptic symptoms. In contrast, those without FD symptoms had a higher prevalence of anaemia (23% vs. 15%) which is to be expected as asymptomatic patients are commonly triaged for endoscopies following incidental detection of anemia at routine annual medical review.

The presence of organic disease within the entire cohort of patients undergoing upper GI endoscopy was 10% (37/387), with no difference between those with and without symptoms compatible with FD; table 2.

The diagnostic yield of upper GI endoscopy stratified according to the presence or absence of alarm features

In the 221 patients with symptoms compatible with Rome IV FD, 186 had alarm features in whom the diagnostic yield of upper GI endoscopy was 11% (n=20/186). For the remaining 35 patients with symptoms compatible with FD but no alarm features - therefore 9% (35/387) of the entire cohort - there was no organic disease detected at upper GI endoscopy; table 3.

In the 166 patients without symptoms compatible with Rome IV FD, the presence of organic disease was 11% (n=15/137) in those with alarm features, and 7% (n=2/29) in those without alarm features; p=0.40. The findings noted in those without alarm features were peptic ulcers, with no cases of cancer; reasons for such patients undergoing endoscopy included reflux, nausea, vomiting, belching, or dyspeptic symptoms not meeting symptom frequency threshold for FD (data not shown).

Discussion

This UK study shows that approximately 1-in-10 out-patient non-surveillance endoscopies are performed in patients with symptoms compatible with Rome IV FD but no alarm features. This would be the equivalent to one case per standard upper GI endoscopy list. There is no appreciable diagnostic yield in those without alarm features, and arguably these patients would be better served by being diagnosed with FD without endoscopy.

The results are consistent with recent studies from the West (Canada, United States, Netherlands, and Sweden) which, having used a broader definition of dyspepsia, noted that almost a third to a half of upper GI endoscopies performed within GI clinics are in low risk dyspeptic patients without alarm features, in whom significant endoscopic findings were low, with malignancy rare.[13-16] To our knowledge, our study is the first evaluating this issue within the UK whilst using the Rome IV criteria. However, as ~90% of our studied population are British white race, and having used ≥55 years of age as one of the alarm features, our findings should not be extrapolated to other races or societies at higher risk of gastric cancer (e.g. those from the East Asia or South America) where, in the absence of associated alarm features, a lower age threshold to prompt referral for endoscopy is proposed.[17-19]

Reducing referrals for endoscopy would help ease departmental pressures and waiting times in over-stretched public healthcare systems, whilst facilitating quicker diagnosis and management. It would also have economic implications, with the cost of detecting one case of upper GI malignancy being estimated at over US $80,000.[20] Moreover, endoscopy is a major waste contributor which impacts on the environment and climate change; doing fewer procedures will undoubtedly lead towards a greener endoscopy and a more sustainable clinical practice.[7] A recently published national speciality report for gastroenterology, entitled Get It Right First Time, highlighted that in 2018 there were around 650,000 upper GI endoscopies performed in England, but only around 5,000 cases of gastric cancer (https://www.gettingitrightfirsttime.co.uk/medical-specialties/gastroenterology/). It also reported that in some trusts, over 40% of upper GI endoscopies were being performed in people under the age of 55 years where the diagnostic yield is likely to be minimal. Of interest, our study found limited testing for *H.pylori*, and a relatively low use of neuromodulators, which if addressed can be effective in treating FD.[21-23] In summary, there is a drive to curb unnecessary endoscopies and our data will help support such decision-making policies.

However, the Rome IV diagnostic criteria states that for patients to be diagnosed with FD they must have had a normal upper GI endoscopy.[4] We debate this diagnostic construct and believe that future diagnostic iterations (i.e. Rome V) should advice against a mandatory upper GI endoscopy in those without alarm features, but rather encourage a positive diagnosis of FD. This would then mirror the criteria the Rome Foundation already has in place for irritable bowel syndrome, where - in those without alarm features - a positive diagnosis without resorting to a colonoscopy is encouraged.[9] Further, given that FD and irritable bowel syndrome frequently co-exist in 30-50% of patients,[1] recommending endoscopies for upper but not lower GI symptoms (to confirm their respective diagnoses based on the Rome criteria) might arguably lead to confusion amongst patients and healthcare providers.

Of note, recent British, European, and North American guidelines do suggest that patients with dyspepsia can be managed without endoscopy if there are no alarm symptoms or risk factors.[21-23] They acknowledge that the diagnostic yield of upper GI endoscopy in this cohort is minimal and not cost-effective. In such instances, the British guidelines commit to a positive diagnosis of FD and recommend a clear explanation with patient-centred discussion followed by a step-wise treatment algorithm.[21] However, European and North American guidelines classify them as having uninvestigated dyspepsia, albeit propose treatments tailored to FD.[22,23] Arguably, using the term uninvestigated dyspepsia does not clearly inform the patient and could imply diagnostic uncertainty. Effective communication skills can improve the patient-provider relationship and health outcomes; an important aspect of treating patients with functional disorders of gut-brain interaction is to make a clear, confident diagnosis, and provide a brief explanation of the gut-brain axis.[24]

There is little justification in performing endoscopies simply to reassure patients, as such an effect is relatively short lived, with alternate methods being safer and cost effective.[25,26] A randomized controlled trial conducted in patients with dyspepsia without alarm symptoms compared a self-managed web-based educational intervention versus prompt endoscopy.[27] This demonstrated that educational intervention (explaining the diagnosis, gastric function, and the limited added value of endoscopy) is an effective tool in decreasing the need for endoscopies whilst leading to similar improvements in symptoms and quality of life, compared with prompt endoscopy alone.[27]

It is also worth highlighting that the diagnostic yield of upper GI endoscopy was minimal even in those with alarm features, which is consistent with the literature.[28] European guidelines on dyspepsia state

that, regardless of age, upper GI endoscopy is mandatory if there are alarm features or risk factors, although recognize their limited value.[22] British and North American guidelines recommend that in patients under 55 or 60 years, respectively, the presence of alarm features should not automatically precipitate endoscopy but considered on a case-by-case basis (e.g. associated family history, rapidly progressive weight loss, dysphagia).[21,23] Future studies are needed to better characterize which alarm features should prompt endoscopy, and this might be aided through the use of non-invasive biomarkers.[29,30]

The strengths of the study include its prospective design, the use of the Rome IV diagnostic criteria, and endoscopists being blinded to the questionnaire data. Limitations are that it was single centre, with a questionnaire response rate of 33%, although the findings of low diagnostic yield in those without alarm features is supported by other recent studies from the West.[13-16] Our study was performed in secondary care, with a mixed referral pattern, and the findings may not be applicable outside these clinical settings (e.g. in the community) where arguably the yield will be even lower.[5,6] As mentioned earlier, the results should not be extrapolated to societies at higher risk of gastric cancer, for example those from the Far East and South America.[17-19] Another limitation is that the presence of alarm features, such as anemia and unintentional weight loss, were collected as binary outcome data and it would have also been useful to collect data according to different threshold levels to help further optimize predicting organic disease at upper GI endoscopy.

In conclusion, 1-in-10 UGI endoscopies are performed in patients with symptoms compatible with FD and no alarm features, in whom there is no diagnostic yield. We recommend such patients receive a positive diagnosis of FD without endoscopy.

Table 1: Comparison between the Rome IV diagnostic criteria for functional dyspepsia and irritable bowel syndrome[4,9]

Functional dyspepsia (FD)	Irritable Bowel Syndrome
One or more of the following: - Bothersome epigastric pain (at least 1 day per week) - Bothersome epigastric burning (at least 1 day per week) - Bothersome postprandial fullness (at least 3 days per week) - Bothersome early satiation (at least 3 days per week) Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis *And no evidence of structural disease (including at upper endoscopy) likely to explain the symptoms*	Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more or the following: a. Related to defecation; b. Associated with a change in frequency of stool; c. Associated with a change in stool form. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Figure 1: Study flow chart

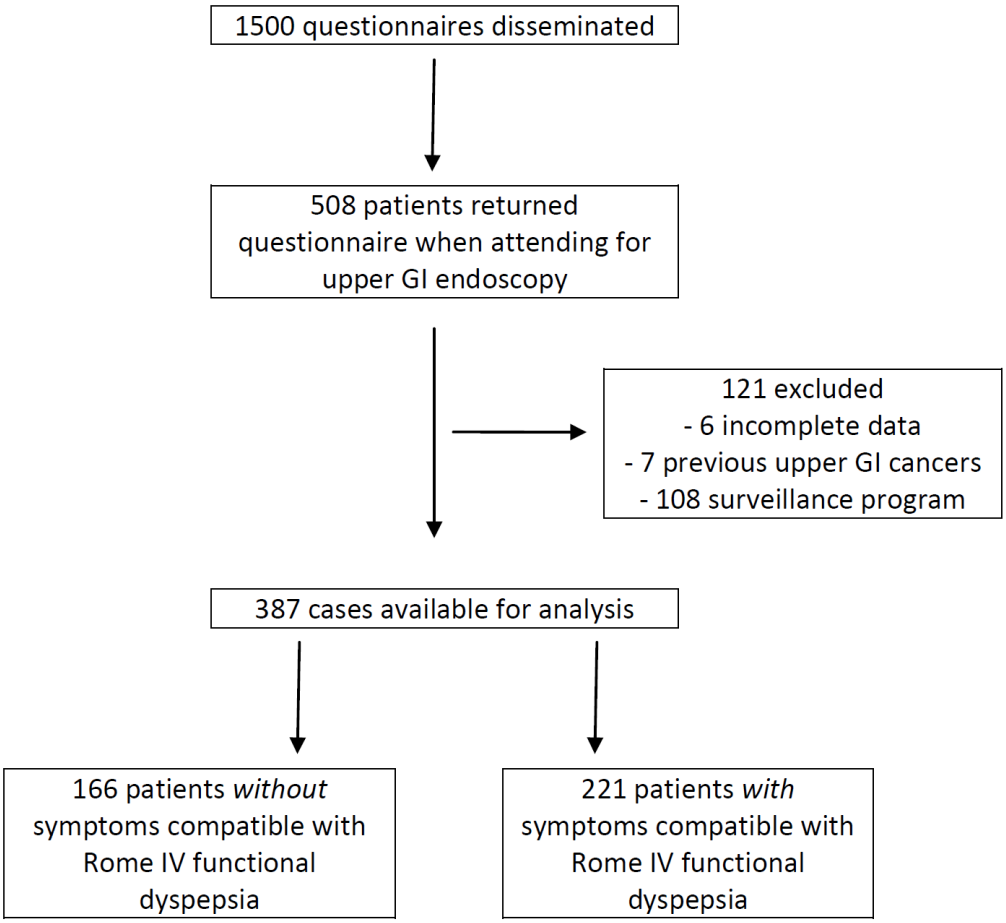

Table 2: Characteristics of those with and without symptoms compatible with Rome IV FD

	Symptoms not compatible with FD (n = 166, 43%)	Symptoms compatible with FD (n = 221, 57%)	P-value
Demographics			
Mean age, years (SD)	61 (17)	58 (17)	0.15
White race	149 (90%)	195 (88%)	0.28
Female	77 (46%)	136 (62%)	0.003
Body mass index (SD)	27 (6)	28 (6)	0.35
Past medical history			
Cholecystectomy	10 (6%)	25 (11%)	0.07
Appendectomy	26 (16%)	33 (15%)	0.84
Fibromyalgia	4 (2%)	21 (10%)	0.005
Chronic fatigue syndrome	6 (4%)	34 (15%)	<0.001
Alarm Features			
Age ≥ 55 years	118 (71%)	145 (66%)	0. 25
Dysphagia	42 (25%)	73 (33%)	0.10
Unintentional weight loss	21 (13%)	54 (24%)	0.004
Anaemia	38 (23%)	32 (15%)	0.03
Vomiting blood	3 (2%)	8 (4%)	0.29
Family history of upper GI cancer	14 (8%)	17 (8%)	0.79
Any of the above alarm features	137 (83%)	186 (84%)	0.67
Psychological distress and somatisation			
Anxiety (%, HADS score ≥ 11)	32 (19%)	82 (37%)	<0.001
Depression (%, HADS score ≥ 11)	19 (11%)	60 (27%)	<0.001
Total HADS score (SD)	11.2 (8.2)	16.6 (9.0)	<0.001

Total PHQ-12 score (SD)	5.9 (3.6)	9.3 (4.3)	<0.001
Clinically significant endoscopy findings			
Upper GI cancer	2 (1%)	3 (1%)	0.63
Barrett's oesophagus	8 (5%)	7 (3%)	0.41
Grade C/D oesophagitis	1 (0.6%)	2 (1%)	0.61
Strictures	3 (2%)	4 (2%)	0.65
Peptic ulcer disease	4 (2%)	5 (2%)	0.59
Any of the above	17 (10%)	20 (9%)	0.69

Table 3: Presence of clinically significant findings at upper GI endoscopy in patients with and without symptoms compatible with FD, stratified according to the presence or absence of alarm features

Symptoms compatible with FD (n=221)			
	No alarm features present (n = 35)	**Alarm features present (n = 186)**	**P-value**
Upper GI cancer	0 (0%)	3 (1.6%)	0.60
Barrett's esophagus	0 (0%)	7 (4%)	0.29
Grade C/D oesophagitis	0 (0%)	2 (1%)	0.71
Strictures	0 (0%)	4 (2%)	0.50
Peptic ulcer disease	0 (0%)	5 (3%)	0.42
Any of the above	0 (0%)	20 (11%)	0.03
Symptoms not compatible with FD (n=166)			
	No alarm features present (n =29)	**Alarm features present (n =137)**	**P-value**
Upper GI cancer	0 (0%)	2 (1.5%)	0.68
Barretts esophagus	0 (0%)	8 (6%)	0.21
Grade C/D oesophagitis	0 (0%)	1 (0.7%)	0.83
Strictures	0 (0%)	3 (2%)	0.56
Peptic ulcer disease	2 (7%)	2 (1.5%)	0.14
Any of the above	2 (7%)	15 (11%)	0.40

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