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TITLE PAGE

Title: Derivation and Validation of a Diagnostic Test for Irritable Bowel Syndrome Using Latent Class Analysis.

Short “running” head: Latent Class Analysis as a Diagnostic test for IBS.

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Abbreviations: AUC area under the curve

BMI	body mass index
CI	confidence interval
GI	gastrointestinal
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhoea
LR	likelihood ratio
PHQ-15	patient health questionnaire-15
ROC	receiver operating characteristic
SD	standard deviation
UK	United Kingdom

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SUMMARY

Background: The accuracy of symptom-based diagnostic criteria for irritable bowel syndrome (IBS) is modest.

Aims: To derive and validate a new test that utilises latent class analysis.

Methods: Symptom, colonoscopy, and histology data were collected from 1981 patients and 360 patients in two cohorts referred to secondary care for investigation of their gastrointestinal symptoms in Canada and the UK respectively. Latent class analysis was used to identify naturally occurring clusters in patient-reported symptoms in the Canadian dataset, and the latent class model derived from this was then applied to the UK dataset in order to validate it. Sensitivity, specificity, and positive and negative likelihood ratios (LRs) were calculated for the latent class models.

Results: In the Canadian cohort, the model had a sensitivity of 44.7% (95% CI 40.0%-50.0%) and a specificity of 85.3% (95% CI 83.4%-87.0%). Positive and negative LRs were 3.03 (95% CI 2.57-3.56) and 0.65 (95% CI 0.59-0.71) respectively. A maximum positive LR of 3.93 was achieved following construction of an ROC curve. The performance in the UK cohort was similar, with a sensitivity and specificity of 52.5% (95% CI 42.2%-62.7%) and 84.3% (95% CI 79.3%-88.6%) respectively. Positive and negative LRs were 3.35 (95% CI 2.38-4.70) and 0.56 (95% CI 0.45-0.68) respectively, with a maximum positive LR of 4.15.

Conclusions: A diagnostic test for IBS utilising patient-reported symptoms incorporated in to a latent class model performs as accurately as symptom-based criteria. It has potential for improvement via addition of clinical markers, such as coeliac serology and faecal calprotectin.

INTRODUCTION

Irritable bowel syndrome (IBS) is a complex and multifactorial disorder characterised by lower abdominal pain associated with a change in stool form and/or frequency. (1) Partly as a consequence of its likely multifactorial aetiology, (2–5) as well as overlap of symptoms with organic disease such as inflammatory bowel disease, (6) coeliac disease, (7) microscopic colitis, (8) and bile acid malabsorption, (9,10) diagnosing IBS without performing extensive, and frequently invasive, investigations remains challenging.

The current preferred approach to making a diagnosis of IBS is via symptom-based criteria, of which the Rome IV criteria are the gold-standard, (1) although their accuracy has yet to be assessed independently. (11) Their predecessor, the Rome III criteria, (12) were rarely used in routine clinical care, partly as a consequence of their perceived complexity, but also because they performed only modestly in diagnosing IBS. (13–15) Proposed biomarkers for IBS do not perform any better than symptom-based criteria, or are considered too invasive or too complex to be used beyond a research setting or a tertiary care centre. (16,17) A non-invasive test that could accurately diagnose IBS, and which is also administrable at the time of clinic consultation, would therefore be highly desirable.

Latent class analysis is a statistical method that hypothesises the existence of one or more unobserved groups (latent classes) among a set of observed categorical variables, such as patient-reported symptoms. For example, symptoms that are reported by patients with IBS, or are known to be associated with IBS, could be incorporated in to a latent class model, and it could then be observed how individuals naturally cluster in to IBS or non-IBS groups, based on these variables. Individuals are classified according to their most likely latent class membership probabilities, that is the probability for a randomly selected member of a given latent class, a given response pattern will be observed. Although this method may initially

appear overly complex for a diagnostic test, in the modern era of smartphones an easy to use application (app) could be developed, in which symptoms are inputted by the patient in the outpatient waiting room, with any relevant physical findings and results of blood tests added during the clinician's assessment, in order to give a probability of the patient having IBS.

(18)

Although there are very few examples of latent class analysis being used in the diagnosis of functional gastrointestinal (GI) disorders,(19) this statistical technique has been used successfully in other medical conditions where, as is the case in IBS, a gold-standard diagnostic test is lacking. (20–23) We applied latent class analysis to two separate patient cohorts referred to secondary care services for investigation of their GI symptoms in Canada and the United Kingdom (UK), with the aim of deriving and then validating a novel diagnostic test for IBS.

MATERIALS AND METHODS

Participants and Settings

In both studies, patients ≥ 16 years of age referred from primary care to secondary care for investigation of lower GI symptoms were eligible. There were no exclusion criteria, other than the inability to understand written English, as the questionnaires were self-administered. Potentially eligible participants were approached at their first clinic visit, and those agreeing to participate provided written informed consent at that visit. All questionnaires were completed prior to the patient's consultation with a gastroenterologist. The questionnaires used in both studies collected the same demographic and symptom data. We also used the validated patient health questionnaire-15 (PHQ-15) to assess for evidence of somatisation-type behaviour. (24)

Canada

Patients were recruited at the outpatient clinics of McMaster University Medical Center or St Joseph's Healthcare, two hospitals in Hamilton, Ontario, serving a local population of more than 500,000. The Hamilton Health Sciences and McMaster University research ethics board approved the study in January 2008 and recruitment continued until December 2012. The methodology and study population used has been described in detail elsewhere. (14,25–32) We used these patients to derive a latent class model to predict the presence of IBS.

UK

Patients were recruited at the outpatient clinics of Leeds Teaching Hospitals NHS Trust, West Yorkshire. The trust is situated in the north of England, and provides secondary care services for a population of approximately 800,000. The local ethics committee approved the study, with recruitment commencing in January 2014, and continuing through to December 2015. Again, the methodology and study population used have been described in detail elsewhere. (15,33) We used these patients to validate the latent class model derived from the patients contained in the Canadian dataset.

Data Collection and Synthesis

Demographic and Symptom Data

All demographic and symptom data were collected prospectively from the questionnaire at the initial clinic visit. Questionnaire data were entered into a database by trained researchers who were not involved in the clinical care of the patient, therefore ensuring assessors were blinded to symptom status. Demographic data of interest included age, height (in metres), and weight (in kilograms), from which body mass index (BMI) were calculated, gender, tobacco and alcohol use, marital status, educational level, and ethnicity.

Colonoscopic and Histopathological Data

In both studies, all patients underwent colonoscopy to the caecum or terminal ileum. All endoscopists performing colonoscopic examinations were blinded to the questionnaire data of the patient. Biopsy specimens were obtained at the discretion of the endoscopist

performing the colonoscopy, and were interpreted by experienced GI histopathologists, who were again blinded to the questionnaire data of the patient. Findings classified as being consistent with organic disease at colonoscopy, or after histopathological examination of biopsy specimens, are provided in Supplementary Table 1.

Data Incorporated in to the Latent Class Model

We used symptoms to identify naturally occurring clusters in the data. We considered all intestinal symptoms that can be associated with IBS, such as upper and lower abdominal pain or discomfort, (34) change in stool form or frequency, (35) abdominal bloating, (36) dyspepsia, (37,38) gastro-oesophageal reflux, (39) and post-prandial symptoms and nausea. (40) We also considered individual items from the PHQ-15 questionnaire. A recent study showed that mean somatisation scores and number of somatic symptoms were higher in patients with IBS, when compared with individuals with GI symptoms who did not meet criteria for IBS. (30) In particular, nine of the twelve extra-intestinal symptoms that are incorporated in to the PHQ-15 were found to be statistically significantly higher in patients with IBS. These nine items were therefore included in the latent class model. All variables incorporated in to the model are shown in Supplementary Table 2.

Reference Standard to Define the Presence of True IBS

The reference standard used to define the presence of true IBS in both study populations was lower abdominal pain or discomfort occurring at least once a week, in association with a change in bowel habit, and in the absence of organic lower GI disease after colonoscopy and histopathological examination of colonic biopsies, if obtained, which would

explain these symptoms. Exclusion of coeliac disease with distal duodenal biopsy was also undertaken in both studies, if coeliac serology was positive.

Statistical Analyses

We used the statistical program LatentGOLD version 4.5 (Vermunt and Magidson, 2005, Statistical Innovations, Inc., Belmont, MA, USA) to perform the latent class analyses. The latent class model was derived using the Canadian dataset, and an identical model was then applied to the UK dataset in order to validate it. In order to determine the optimum number of classes that best fit the data, we included up to six classes, and the number of classes that best fit the data was determined using the likelihood ratio chi-squared statistic, and parsimony indices, which help in maintaining a balance between goodness-of-fit and model complexity. The parsimony indices used were the number of parameters, the Akaike information criterion and the Bayesian information criterion. In general, smaller values correspond to more parsimonious models.

We used the modal assignment, which places individuals in the latent class in which they have the highest membership probability. Once individual membership to a latent class was derived, and the IBS and non-IBS latent classes determined based on their characteristics, correct latent class membership for each individual was calculated by comparing against the reference standard for IBS. From this we calculated the sensitivity, specificity, positive predictive value and negative predictive value, and positive and negative likelihood ratios (LRs), along with 95% confidence intervals (CIs), of the latent class model when compared with the reference standard, using a Microsoft Excel spreadsheet (2013 Edition; Microsoft Corp, Redmond, WA). The positive LR can be calculated from the formula: positive LR = sensitivity / (1-specificity). The negative LR is derived from the

formula: negative LR = (1-sensitivity) / specificity. LRs are a useful method for assessing the accuracy of a diagnostic test, as they vary to a lesser degree than predictive values when the prevalence of a disease changes. (41)

As latent class analysis was used to calculate the probability of having IBS, this meant it was possible to vary the discrimination threshold utilised in the model. In a diagnostic test for IBS, it is important that the risk of missing organic disease is minimised. We therefore constructed receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC), in order to maximise specificity over sensitivity, and calculate the maximum positive LR available for the test. These analyses were performed using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Demographics

There were 4224 consecutive patients recruited into the Canadian study between January 2008 and December 2012. Of these, 1981 (46.9%) underwent colonoscopy for investigation of their symptoms and provided their data for the derivation of the latent class model. Mean age of those undergoing colonoscopy was 49.3 years (standard deviation (SD) 17.1 years), 1251 (63.1%) were female and 1787 (90.2%) were White Caucasian. The prevalence of IBS in the study population as defined by the reference standard was 19.9% (n = 394). Compared with the 2243 subjects who did not undergo colonoscopy, the 1981 patients undergoing colonoscopy were slightly older, of higher BMI, and were more likely to be White Caucasian, but there were no other significant differences in demographics between groups, (14) including the number of patients who had IBS according to the latent class model (412 (20.8%) of 1981 patients colonoscoped, vs. 448 (20.0%) of 2243 not colonoscoped, $P = 0.53$).

Of the 1002 consecutive patients recruited to the UK study between January 2014 and December 2015, 360 (35.9%) underwent colonoscopic investigation for their symptoms, and therefore provided data to validate the latent class model. The mean age of those who underwent colonoscopy was 53.9 years (SD 16.5 years), 236 (65.6%) were female and 329 (91.4%) were White Caucasian. The prevalence of IBS in the UK study, as defined by the reference standard, was 27.5% (n = 99). Compared with those who did not undergo colonoscopy, patients undergoing colonoscopy had a higher BMI, but there were no other significant differences between the two groups, (15) including the number of patients who

had IBS according to the latent class model (94 (26.1%) of 360 patients colonoscoped, vs. 147 (22.9%) of 642 not colonoscoped, $P = 0.29$).

Demographics of those undergoing colonoscopic examination in the Canadian and UK studies are shown in Supplementary Table 3. Those in the UK study were older, and the prevalence of IBS was higher, but there were no other significant differences between the two cohorts. The prevalence of organic GI disease in the Canadian study was 20.6%, compared with 16.7% in the UK study. The breakdown of organic disease type in the two cohorts is detailed in Table 1.

Assessment of Model Fit

Using trends in the likelihood ratio chi-squared statistic, Bayesian information criterion, and Akaike information criterion, it was determined that a four-class solution best fitted the Canadian dataset, and maintained the optimum balance between goodness-of-fit and model complexity (Supplementary Table 4).

Description of Model Clusters

The clinical characteristics of each class in the model in the Canadian and UK studies are shown in Supplementary Table 5 and Supplementary Table 6 respectively. In the Canadian study, the latent class that was predominantly IBS represented 20.8% of the population ($n = 412$), and in the UK study, 26.1% of the study population ($n = 94$). In the Canadian study, in the preceding 3 months, the IBS class were more likely to experience the following symptoms: heartburn, feeling uncomfortably full after a meal, inability to finish a regular sized meal, pain or burning in the upper abdomen, bothersome nausea, and

bothersome belching, all at a frequency of every day, as well as bloating or distension occurring most of the time, than when compared with the non-IBS classes, as well as experiencing many of the extra-intestinal somatisation symptoms at a greater severity. However, although the IBS class was more likely to experience discomfort or pain in the lower abdominal pain once a week or more, non-IBS class 3 was more likely to experience the symptom of frequent loose, mushy, or watery stools at a frequency of $\geq 75\%$, and to report always having ≥ 4 bowel movements per day, than when compared with the IBS class.

In the UK study, in the previous 3 months, the IBS class were more likely to experience: feeling uncomfortably full after a meal, inability to finish a regular sized meal, bothersome nausea, and discomfort or pain in the lower abdomen every day, loose, mushy, or watery stools, ≥ 4 bowel movements per day, and bloating and distension occurring always, or 100% of the time. The majority of somatisation symptoms were also more severe. The IBS class experienced similar levels of heartburn, pain or burning in the upper abdomen, and bothersome belching as non-IBS class 2, who also experienced frequent somatisation symptoms, although to a lesser severity than the IBS class.

Accuracy of the Two Models

In the Canadian cohort, the latent class model was able to predict a diagnosis of IBS with a sensitivity of 44.7% (95% CI 40.0% to 50.0%) and specificity of 85.3% (95% CI 83.4% to 87.0%). Positive and negative LRs were 3.03 (95% CI 2.57 to 3.56) and 0.65 (95% CI 0.59 to 0.71) respectively (Table 2). Following construction of a ROC curve (Figure 1), sensitivity and specificity were calculated at 28.7% and 92.7% respectively, resulting in a maximum positive LR of 3.93 and a negative LR of 0.77. The AUC was 0.77.

Performance of the latent class model using the UK cohort was similar, with a sensitivity of 52.5% (95% CI 42.2% to 62.7%) and specificity of 84.3% (95% CI 79.3% to 88.6%). Positive and negative LR were 3.35 (95% CI 2.38 to 4.70) and 0.56 (95% CI 0.45 to 0.68) respectively (Table 2). Following construction of a ROC curve (Figure 2), a sensitivity of 29.3% and specificity of 93.0% resulted in a maximum positive LR of 4.15 and negative LR of 0.76, with an AUC of 0.79.

DISCUSSION

This study derived a diagnostic test for IBS in patients referred to a secondary care hospital in Canada. The same test was then validated in a separate cohort of patients referred to a secondary care hospital in the UK. We used latent class analysis to identify naturally occurring clusters in the data incorporated in to the model, and then determined if correct latent class membership was obtained by comparing against the reference standard for IBS used in this study. In both cohorts of patients, the IBS class was more likely to experience post-prandial symptoms, nausea, lower abdominal discomfort or pain, and somatisation symptoms, compared with the non-IBS classes. In the Canadian study, following construction of an ROC curve, the model had a positive LR approaching 4, whilst in the UK study the positive LR was 4.15. The discriminatory accuracy of the two models, as measured by the AUC, were good at 0.77 and 0.79 for the Canadian and UK models respectively. This compares with positive LRs of 3.35 to 3.87 in two previous validation studies of the Rome III criteria, (14,15) which was enhanced to over 7 by incorporating various combinations of levels of somatic symptom reporting, absence of nocturnal stool passage, and normal blood results in one of these studies. (15)

This is the first study that has used latent class analysis to develop a diagnostic test for IBS. To date, only one other study has utilised this approach in functional GI disorders. In a postal questionnaire conducted by Koloski et al., (19) the Rome III criteria for IBS with constipation (IBS-C) and functional constipation were included in a latent class model, in order to identify clinical and lifestyle factors that could be used to differentiate the two disorders. In this study, the latent class model was unable to reproduce the differentiation of individuals with IBS-C and functional constipation according to the Rome III criteria. However, the model derived and validated in the current study compares favourably to available approaches to diagnosing IBS. Although the Rome IV criteria have yet to be

validated independently, the previous iteration, Rome III, have been validated in one large study that included 1848 participants who provided complete symptom, colonoscopy, and histology data. (14) They performed modestly well in differentiating IBS from organic disease, with a sensitivity and specificity of 68.8% and specificity of 79.5%. Positive and negative LR were 3.35 and 0.39 respectively.

Biomarkers for IBS, individually or in combination, have either yielded disappointing results, despite being validated predominantly in IBS-enriched populations, (42–45) or have not progressed beyond a research setting. (17,46) There is currently one commercially available biomarker test for IBS which encompasses antibodies to cytolethal distending toxin B, a bacterial toxin produced by *Campylobacter jejuni*, and vinculin, a host cell adhesion protein known to cross react with cytolethal distending toxin B. (47) In a validation study, the two biomarkers were able to differentiate IBS with diarrhoea (IBS-D) from organic disease with positive LR of 5.2 and 2.0 for cytolethal distending toxin B and vinculin respectively. However, >80% of study subjects had IBS, so the results may not be reproducible in an unselected population, or among patients with IBS who do not have diarrhoea as their predominant symptom.

In a recently published systematic review, “medical certainty” was assumed for a novel biomarker in diagnosing IBS at a post-test probability (which is derived from the pre-test probability and positive LR) of $\geq 80\%$. (48) At this threshold, in a secondary or tertiary care setting with a prevalence of IBS of approximately 50%, a diagnostic test with a positive LR of ≥ 5 would identify IBS with a post-test probability of 86.5%. The latent class model has a positive LR of 3.93 and 4.15 in the Canadian and UK cohorts respectively. However, the study was conducted in a population referred to secondary care, with a combined prevalence of IBS of only 23.7% among the two cohorts. This suggests that the performance of the model should be seen as at least comparable to that of the only commercial biomarker for

IBS, which demonstrated a maximum positive LR of 5.2 when validated in an IBS-enriched population. (47) Furthermore, the latent class model has the potential for improvement in its accuracy. The addition of relevant clinical tests to the model, such as faecal calprotectin and coeliac serology, may result in a reduction in the number of false positive tests, and therefore improvement in the ability of the model to differentiate IBS from organic disease.

The idea of using statistical modelling to diagnose IBS is not novel, and was first described over 30 years ago. (49) Kruis and colleagues used logistic regression analysis to develop a diagnostic scoring system that incorporated symptoms, physical examination findings, and relevant blood test results, including haemoglobin level, leucocyte count, and erythrocyte sedimentation rate. The performance of this model has been found to be superior to any other available diagnostic test for IBS described to date, with pooled positive and negative LRs of 8.63 (95% CI: 2.89–25.8) and 0.26 (95% CI: 0.17–0.41) respectively, in the studies that have evaluated it. (13,17) Combining symptoms and biomarkers in this manner does seem more intuitive, as this approach is more likely to take in to account the probable composite nature of IBS, although this does result in a more complex test, and is perhaps the reason why the Kruis model has never been used widely. However, in the era of smartphone apps, data could be inputted in to an online statistical model that uses techniques such as latent class analysis, to give an accurate probability of IBS, which can then be used to aid the physician consulting in routine clinical care.

The study has a number of strengths. It used two large populations referred to secondary care to derive and then validate a diagnostic test for IBS. Furthermore, the test performed similarly, despite demographic differences between the two populations, suggesting that it is reliable. As the study was conducted in patient cohorts in secondary care, it means that the results are likely to be generalisable to gastroenterologists consulting with patients who have symptoms suggestive of IBS in usual clinical care. Furthermore, the test

developed from this study is inexpensive, and should be considered at least as accurate as other potentially more expensive biomarkers, which have only been validated in IBS-enriched populations.

The study also has limitations. The reference standard that we used to compare the accuracy of the latent class model included some of the symptoms that were also used in the model itself. This may have resulted in overestimation of its accuracy. In addition, due to our use of a negative colonoscopy as part of the gold-standard for IBS, not all patients who met criteria for IBS in these two cohorts provided data for analysis. The performance of the latent class model in these patients with presumed IBS who did not undergo colonoscopy may therefore be different from that observed in the patients who provided data for this study. In both populations, the majority of the participants were White Caucasian, so our findings may not be applicable to other ethnicities. Furthermore, the two patient cohorts were recruited by the same investigators, and therefore independent validation of the model in other cohorts will be required. Lastly, as we have previously discussed, our study only used symptom data to differentiate between IBS and non-IBS. It would be interesting to note if the addition of clinical tests, such as faecal calprotectin and coeliac serology, resulted in improved accuracy of the test.

The Rome IV criteria for IBS have only recently been described, (1) and are very similar to the previous iteration published over 10 years ago. (12) Data from our study provide some interesting insights into possible directions for the development of such symptom-based diagnostic criteria in the future. Our observation that patients in the latent class of IBS in both cohorts were more likely to report upper GI symptoms consistent with functional dyspepsia, such as early satiety and postprandial fullness, suggest that rather than making functional GI disorders discrete entities the presence of these co-existent symptoms are likely to be supportive of a diagnosis of IBS. In addition, in our study bloating or

distension seemed to be a key feature of IBS, present in over 80% of patients. This was first proposed as part of the diagnostic criteria for IBS by Manning et al. in 1978, (50) but is no longer required in the Rome criteria, and should perhaps be re-incorporated into the list of required symptoms for future iterations.

In conclusion, we have derived and validated a diagnostic test for IBS using a latent class model. We have shown that the test performs as accurately as current symptom-based diagnostic criteria, as well as available biomarkers. However, it did not perform better than the modifications to the Rome III criteria, which we have previously reported. (15)

Importantly, the test has the potential for improvement in its performance, and future studies should consider the addition of clinical test results when assessing its accuracy.

AUTHORSHIP

Guarantor of the article: RS is guarantor.

Author contributions: RS, ACF, and GRL conceived and drafted the study. RS, MIPS, MJG, NT, and ACF collected all data. RS, ACF, and GRL analysed and interpreted the data. RS, ACF, and GRL drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

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FIGURE LEGENDS

Figure 1. Receiver Operating Characteristic Curve for the Canadian Latent Class Model.

Figure 2. Receiver Operating Characteristic Curve for the UK Latent Class Model.