

ORIGINAL ARTICLE

Performance of blood tests in diagnosis of inflammatory bowel disease in a specialist clinic

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Aims: To determine the reliability of a panel of blood tests in screening for ulcerative colitis and Crohn's disease.**Methods:** The subjects were 153 children referred to a paediatric gastroenterology department with possible inflammatory bowel disease (IBD). Of these, 103 were found to have IBD (Crohn's disease 60, ulcerative colitis 37, indeterminate colitis 6). The 50 without IBD formed the controls. Blood tests evaluated included haemoglobin, platelet count, ESR, CRP, and albumin. Receiver operating characteristic curves were used where possible to determine optimal threshold values. Binary logistic regression analysis was used to investigate the five screening tests in combination, and a stepwise method was used to find the best test combination.**Results:** The optimal screening strategy used a combination of haemoglobin and platelet count and "1 of 2 abnormal" as the criterion for positivity. This was associated with a sensitivity of 90.8% (95% CI 83.3 to 95.7%), a specificity of 80.0% (95% CI 65.7 to 89.8%), and positive and negative predictive values of 94.4% and 75.9% respectively.**Conclusions:** Haemoglobin and platelet count provide a useful screening test combination for patients with suspected IBD. These tests are not completely reliable however. If clinical suspicion is high further investigations are required.

Conventional investigations for inflammatory bowel disease (IBD) include small bowel barium contrast radiology, upper gastrointestinal endoscopy (UGIE), and colonoscopy. These diagnostic techniques are unpleasant and are potentially hazardous for young patients. Barium contrast radiology is associated with exposure to ionising radiation. Gastrointestinal endoscopic procedures are invasive and require the use of sedation or general anaesthesia. Paediatricians and paediatric gastroenterologists often see children with non-specific symptoms such as lethargy, weight loss, abdominal pain, or diarrhoea. Although such symptoms may point to a diagnosis of IBD, in many cases no such disorder is present. It may be difficult, therefore, to decide which children require extensive investigation.

Various laboratory blood tests including haemoglobin, platelet count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and albumin are widely used as preliminary screening tests for IBD. There are clinical reports suggesting that they can be helpful in identifying those likely to have IBD, thus avoiding unnecessary investigations. However, there are no published systematic studies aimed at determining the quantitative reliability of these tests in clinical practice. We examined their reliability in the setting of a paediatric gastroenterology department.

PATIENTS AND METHODS

The study included 153 children referred to the paediatric gastroenterology department outpatient clinic at Birmingham Children's Hospital. This department serves as a secondary and tertiary referral centre for children with gastrointestinal disorders. They presented with various gastrointestinal and nutritional symptoms compatible with IBD. Investigations routinely performed included the following: haemoglobin, platelet count, ESR, serum CRP, and serum albumin. ESR was estimated by the Westergen method. CRP was measured using the dry chemistry immunological method and a Vitros 250 analyser (Ortho

Clinical Diagnostics, Johnson & Johnson, USA). These five widely used screening tests for IBD were subjected to a systematic evaluation.

Further investigations such as small bowel barium contrast radiology, upper gastrointestinal endoscopy, and colonoscopy were undertaken at the discretion of a paediatric gastroenterologist, being governed by the specific clinical presentation in each case. Diagnoses of Crohn's disease and ulcerative colitis were based on conventional clinical, radiological, endoscopic, and histological criteria.

In total 103 children were found to have IBD (age range 1–17.6 years, median 11.6). Of these, 60 had Crohn's disease, 37 had ulcerative colitis, and six indeterminate colitis. Amongst those with Crohn's disease presenting clinical features included: anorexia and weight loss (n = 53), abdominal pain (n = 50), diarrhoea without blood (n = 24), bloody diarrhoea (n = 13), passage of blood without diarrhoea (n = 1), perianal Crohn's disease (n = 27), finger clubbing (n = 15), short stature (n = 11), arthralgia (n = 8), and erythema nodosum (n = 3). Those with ulcerative colitis presented with bloody diarrhoea (n = 28), diarrhoea without blood (n = 6), passage of blood without diarrhoea (n = 3), abdominal pain (n = 23), anorexia and weight loss (n = 21), short stature (n = 2), and arthralgia (n = 1).

The 50 children who did not have IBD (age range 2–17 years, median 9) acted as the control group. They included 30 with recurrent abdominal pain (29 functional abdominal pain, one abdominal migraine), 11 with diarrhoea (five coeliac disease, one gastroenteritis, five no identified disorder), three with vomiting (one gastro-oesophageal reflux,

Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; NPV, negative predictive value; ROC, receiver operating characteristic; PPV, positive predictive value; UGIE, upper gastrointestinal endoscopy

two no identified disorder), and one with unexplained intermittent rectal bleeding.

Data analysis

Receiver operating characteristic (ROC) curves were obtained for platelet count, ESR, CRP, and albumin concentrations to explore the sensitivity and specificity of these tests using varying threshold values. Based on these analyses threshold values could be determined for both platelet count and ESR that were associated with optimal sensitivities and specificities. The optimal platelet count threshold level was $>350 \times 10^9/l$, giving a sensitivity of 85% and a specificity of 85%. For ESR the optimal threshold level was >10 mm/h with a sensitivity of 82% and a specificity of 78%. ROC curves for CRP and albumin showed poor sensitivities with values of 60% or worse for plausible thresholds. For further statistical analysis, cut-off values were taken from the published literature (albumin <35 g/l; CRP >5 mg/l).¹ For haemoglobin, ROC curve analysis was not employed because the normal reference ranges are age specific. The selected cut-off values for haemoglobin corresponded to the lower limits of established age related reference ranges (1–3 y, <110 g/l; >3 to 6 y, <117 g/l; >6 to 18 y, <120 g/l).

Binary logistic regression analysis was used to investigate how the occurrence of IBD depended on the five screening tests in combination, and a stepwise method was used to find the combination of tests that best discriminated between the presence and absence of IBD. These analyses were done using both original test measurements as predictors and also using binary indicator variables showing when a test crossed the selected threshold from the ROC analysis above.

RESULTS

Logistic regression analysis

Binary logistic regression analysis using the selected cut-off values as binary indicators for each test proved to be more effective in discriminating between IBD patients and controls than using the actual test values, so only the former results are presented. Table 1 presents the results of this analysis. Tests with good discriminatory power show a combination of a high odds ratio together with a low p value (that is, a significant difference between the groups). Platelets and haemoglobin were the tests that best differentiated between the control and IBD groups. Albumin and CRP did not show significant discriminatory power either individually or in conjunction with the other tests, and were thus not included in further data analysis. This approach did not result in any patient with IBD being missed. For ESR, the conclusion derived from the ROC curve and binary logistic regression analysis was that this test was an inessential predictor of IBD when used in conjunction with platelets and haemoglobin. However, if ESR analysis were to be dropped, three patients with IBD might have gone without further investigations. Subsequent analysis therefore focused on the reliability of haemoglobin, platelet count, and ESR in screening for IBD.

Table 1 Logistic regression analysis

Test	p value	Odds ratio	95% CI
Platelets	0.002	6.39	1.96 to 20.88
ESR	0.489	1.55	0.45 to 5.42
CRP	0.159	6.32	0.48 to 82.28
Albumin	0.504	2.34	0.19 to 28.42
Haemoglobin	0.007	10.55	1.93 to 57.63

Comparison of accuracy indices

Finally, diagnostic accuracy indices were calculated using the above cut-off values for the combination of haemoglobin, platelets, and ESR. The logistic regression function as a predictor of IBD had a sensitivity of 89.5% and a specificity of 77.6%. As this is a very similar predictive performance to simpler, easily implemented rules using the same tests, we detail only the latter. By using a rule of “any two or three positive tests out of three predict IBD”, 85.7% sensitivity (95% CI 77.2 to 92.0%), and 89.8% specificity (95% CI 77.8 to 96.6%) was obtained. For platelets and haemoglobin only and using a rule of “any one or two positive tests out of two predict IBD”, 90.8% sensitivity (95% CI 83.3 to 95.7%) and 80.0% specificity (95% CI 65.7 to 89.8%) was achieved. This confirms the result of logistic regression that ESR is an inessential predictor of IBD when used in conjunction with platelets and haemoglobin. Diagnostic accuracy indices for Crohn’s disease and ulcerative colitis were calculated separately (table 2). Using “at least two of the triple test combination abnormal”, and “at least one of the dual test combination abnormal” gave comparably good reliability indices both for Crohn’s disease and ulcerative colitis.

DISCUSSION

There are a number of published descriptive studies on the value of haemoglobin, platelet count, ESR, CRP, and albumin as screening tests for IBD.^{1,2} In this study, however, a rigorous analysis was performed to determine the reliability of these blood tests both individually and in various combinations. Parameters of test reliability including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Both sensitivity and specificity are affected by sample size, and so 95% confidence intervals were determined for these estimates.

This study found that in children attending a paediatric gastroenterology department, combined measurement of haemoglobin and platelet count is an appropriate screening strategy for ulcerative colitis and Crohn’s disease. In patients presenting with gastrointestinal symptoms or nutritional concerns, the presence of anaemia or thrombocytosis was associated with a diagnostic sensitivity of 90.8% (95% CI 83.3 to 95.7%), a specificity of 80% (95% CI 65.7 to 89.8%), a PPV of 90%, and NPV of 81% for IBD. Similarly values were obtained for both Crohn’s disease and ulcerative colitis.

Beattie *et al* reported haemoglobin, platelet count, ESR, CRP, and albumin results in 39 children with IBD (26 with Crohn’s disease and 13 with ulcerative colitis) and 37 controls.¹ All children with Crohn’s disease had at least one test abnormality, but in 8% with ulcerative colitis all of the tests were normal. In that study all with Crohn’s disease and 60% with ulcerative colitis had an increased CRP. Hypoalbuminaemia was found in 35% with Crohn’s disease and 15% with ulcerative colitis. However, our study found that although increased CRP and hypoalbuminaemia were common in IBD, these did not contribute significantly to the reliability of the blood test panel.

The association between thrombocytosis and both Crohn’s disease and ulcerative colitis has been recognised for many years.^{2–6} Beattie *et al* also reported that the platelet count was increased in 88% with Crohn’s disease and 70% with ulcerative colitis.¹ This is in keeping with our study, and our analysis confirmed that platelet count was an important constituent in the test panel.

Another study reported the use of serum CRP, α_1 acid glycoprotein, α_1 antitrypsin, complement factor 9, factor B, and ESR in 18 children with IBD and 12 controls.⁷ Although the results were significantly different between the groups,

Table 2 Comparison of screening test combinations and criteria

Diagnosis	Combination and criteria	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
IBD	Hb, platelets, and ESR ≥2 abnormal	85.7 (77.2 to 92.0)	89.8 (77.8 to 96.6)	94.4	75.9
	≥1 abnormal	93.9 (87.1 to 97.7)	63.3 (48.3 to 76.6)	83.6	83.8
Crohn's disease	Hb and platelets ≥1 abnormal	90.8 (83.3 to 95.7)	80.0 (65.7 to 89.8)	89.9	81.3
	Hb, platelets, and ESR ≥2 abnormal	87.3 (76.0 to 93.7)	89.8 (78.2 to 95.6)	90.6	86.3
Ulcerative colitis	≥1 abnormal	94.5 (85.1 to 98.1)	63.3 (49.3 to 75.3)	74.3	91.2
	Hb and platelets ≥1 abnormal	90.9 (80.0 to 97.0)	80.0 (65.7 to 89.8)	83.3	88.6
	Hb, platelets, and ESR ≥2 abnormal	83.8 (68.9 to 92.3)	89.8 (78.2 to 95.6)	86.1	88.0
	≥1 abnormal	94.6 (82.3 to 98.5)	63.3 (49.3 to 75.3)	66.0	93.9
	Hb and platelets ≥1 abnormal	91.9 (78.1 to 98.3)	80.0 (65.7 to 89.8)	77.3	92.9

there was an overlap and no single test was reliable for diagnosis.

Other laboratory tests that have been used in this context have included interleukin-1 receptor antagonist,⁸ eotaxin,⁹ anti-neutrophil cytoplasmic and anti-saccharomyces cerevisiae antibodies,¹⁰ tumour necrosis factor α ,¹¹ and thrombopoietin.¹² Increased levels of these have been found in IBD but the reliability of these markers has not been studied adequately.

In conclusion, the simple combination of haemoglobin and platelet count provides a useful test panel for children with suspected IBD. However, it should not be relied on completely as both false positive and false negative results may occur. If clinical suspicion is high, further investigations are required.

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REFERENCES

- 1 **Beattie RM**, Walker-Smith JA, Murch SH. Indications for investigation of chronic gastrointestinal symptoms. *Arch Dis Child* 1995;**73**:354-5.
- 2 **Harries AD**, Beeching SJ, Rogerson SJ, *et al*. The platelet count as a simple measure to distinguish inflammatory bowel disease from infective diarrhoea. *J Infect* 1991;**22**:247-50.
- 3 **Morowitz DA**, Allen LW, Kirsner JB. Thrombocytosis in chronic inflammatory bowel disease. *Ann Intern Med* 1967;**68**:1013-21.
- 4 **Talstad I**, Rootwelt K, Gjone E. Thrombocytosis in ulcerative colitis and Crohn's disease. *Scand J Gastroenterol* 1973;**8**:135-8.
- 5 **Lam A**, Borda TT, Inwood MJ, *et al*. Coagulation studies in ulcerative colitis and Crohn's disease. *Gastroenterology* 1975;**68**:245-51.
- 6 **Harries AD**, Fitzsimons E, Fifield R, *et al*. Platelet count: a simple measure of activity in Crohn's disease. *BMJ* 1983;**286**:1476.
- 7 **Campbell CA**, Walker-Smith JA, Hindocha P, *et al*. Acute phase proteins in chronic inflammatory bowel disease in childhood. *J Pediatr Gastroenterol Nutr* 1982;**1**:193-200.
- 8 **Propst A**, Propst T, Herald M, *et al*. Interleukin-1 receptor antagonist in the differential diagnosis of inflammatory bowel diseases. *Eur J Gastroenterol Hepatol* 1995;**7**:1031-6.
- 9 **Chen W**, Paulus B, Shu D, *et al*. Increased serum levels of eotaxin in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2001;**36**:515-20.
- 10 **Papadakis KA**, Targan SR. Serologic testing of inflammatory bowel disease: its value in indeterminate colitis. *Curr Gastroenterol Rep* 1999;**1**:482-5.
- 11 **Komatsu M**, Kobayashi D, Saito K, *et al*. Tumor necrosis factor-alpha in serum of patients with inflammatory bowel disease as measured by a highly sensitive immuno-PCR. *Clin Chem* 2001;**47**:1297-301.
- 12 **Kapsoritakis AN**, Potamianos SP, Sfiridaki AI, *et al*. Elevated thrombopoietin serum levels in patients with inflammatory bowel disease. *Am J Gastroenterol* 2000;**95**:3478-81.