Biomarkers in Inflammatory Bowel Disease

DR. MAHMOUD MOSLI
MD FRCPC ABIM MSC (CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS)
ASSISTANT PROFESSOR, KING ABDULAZIZ UNIVERSITY
The diagnosis of Inflammatory Bowel Disease (IBD) is often delayed.

Endoscopic disease activity does not correlate well with symptoms of IBD, especially Crohn’s disease (CD).

Non-invasive biomarkers such as C-reactive protein (CRP), fecal calprotectin (CD) and stool lactoferrin (SL) might aid in diagnosing and monitoring patients with IBD.
Endoscopy

• Endoscopy (ileocolonoscopy) is the gold standard for diagnosing and assessing response to therapy in IBD

• Cost, availability, wait time, and risk of perforation limit routine endoscopic evaluations in clinical practice

• Surrogate biomarkers are desirable
Surrogates for Bowel Inflammation

• CRP: non-parametric distribution, large variances, non-production

• FC, SL: differential expression by disease and anatomical location

• Imaging: not ideal due to cost, time, availability, Ionizing radiation for CT, operator dependence for US, however MRE is probably most promising
FC and SL Applications

- Diagnosing IBD i.e. differentiating IBD from IBS
- Evaluating disease activity in IBD patients
- Predicting relapse in quiescent IBD patients
- Post operative surveillance in CD
- Monitoring response to therapy
Cochrane Review: Biomarkers for Assessing Disease Activity in Inflammatory Bowel Disease


• Meta-analysis on the diagnostic accuracy of C-reactive protein (CRP), fecal calprotectin (FC), and stool lactoferrin (SL) for assessment of endoscopically defined disease activity in IBD
Methods

- Databases were searched from inception to November 6, 2014 for relevant cohort and case-control
- Studies that evaluated the diagnostic accuracy of CRP, FC, or SL and studies that used endoscopy as a gold standard in patients with symptoms consistent with active IBD.
- Sensitivities and specificities were pooled to generate operating property estimates for each test using a bivariate diagnostic meta-analysis.
5431 records identified

9 records from other sources

2515 records identified

2515 records after duplicates removed

2515 records screened

2466 records excluded

29 full text articles assessed

10 records excluded with reasons

19 studies included in the qualitative synthesis
<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>AUC</th>
<th>Diagnostic OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-reactive protein</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.49 (0.34, 0.64)</td>
<td>0.92 (0.72, 0.98)</td>
<td>6.3 (1.9, 21.3)</td>
<td>0.56 (0.44, 0.71)</td>
<td>0.72 (0.68, 0.76)</td>
<td>11 (3, 38)</td>
</tr>
<tr>
<td>Fecal calprotectin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.88 (0.84, 0.90)</td>
<td>0.73 (0.66, 0.79)</td>
<td>3.2 (2.6, 4.1)</td>
<td>0.17 (0.14, 0.21)</td>
<td>0.89 (0.86, 0.91)</td>
<td>19 (13, 27)</td>
</tr>
<tr>
<td>CD</td>
<td>0.87 (0.82, 0.91)</td>
<td>0.67 (0.58, 0.75)</td>
<td>2.7 (2.1, 3.4)</td>
<td>0.19 (0.14, 0.27)</td>
<td>0.85 (0.82, 0.88)</td>
<td>14 (9, 22)</td>
</tr>
<tr>
<td>UC</td>
<td>0.88 (0.84, 0.92)</td>
<td>0.79 (0.68, 0.87)</td>
<td>4.2 (2.8, 6.4)</td>
<td>0.15 (0.11, 0.20)</td>
<td>0.91 (0.89, 0.94)</td>
<td>28 (18, 46)</td>
</tr>
<tr>
<td>Sensitivity analysis 1</td>
<td>0.87 (0.82, 0.90)</td>
<td>0.71 (0.62, 0.78)</td>
<td>3 (2.3, 3.8)</td>
<td>0.19 (0.14, 0.24)</td>
<td>0.87 (0.84, 0.90)</td>
<td>16 (11, 23)</td>
</tr>
<tr>
<td>Sensitivity analysis 2</td>
<td>0.87 (0.83, 0.91)</td>
<td>0.71 (0.63, 0.78)</td>
<td>3 (2.3, 3.9)</td>
<td>0.18 (0.13, 0.24)</td>
<td>0.88 (0.85, 0.91)</td>
<td>19 (14, 28)</td>
</tr>
<tr>
<td>Sensitivity analysis 3</td>
<td>0.88 (0.84, 0.91)</td>
<td>0.73 (0.66, 0.79)</td>
<td>3.2 (2.5, 4.1)</td>
<td>0.17 (0.13, 0.21)</td>
<td>0.89 (0.86, 0.92)</td>
<td>19 (14, 28)</td>
</tr>
<tr>
<td>Sensitivity analysis 4</td>
<td>0.87 (0.83, 0.90)</td>
<td>0.72 (0.65, 0.78)</td>
<td>3.1 (2.5, 3.9)</td>
<td>0.18 (0.14, 0.23)</td>
<td>0.88 (0.85, 0.91)</td>
<td>17 (12, 24)</td>
</tr>
<tr>
<td><strong>Stool lactoferrin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.82 (0.73, 0.88)</td>
<td>0.79 (0.62, 0.89)</td>
<td>3.8 (2.0, 7.5)</td>
<td>0.23 (0.14, 0.38)</td>
<td>0.87 (0.84, 0.90)</td>
<td>16 (6, 48)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CD, Crohn’s disease; IBD, inflammatory bowel disease; LR, likelihood ratio; OR, odds ratio; UC, ulcerative colitis.

*Sensitivity analysis 1: excluding studies that included healthy controls that did not undergo colonoscopy; sensitivity analysis 2: excluding studies that included any patient not known to have a diagnosis of inflammatory bowel disease; sensitivity analysis 3: excluding one study that examined patients presenting with lower gastrointestinal symptoms; and sensitivity analysis 4: excluding two studies that were published in abstract form.


<table>
<thead>
<tr>
<th>Test</th>
<th>Prevalence of endoscopically active IBD</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Weighed positive likelihood ratio</th>
<th>Weighed negative likelihood ratio</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fecal calprotectin</strong></td>
<td>0.25</td>
<td>0.88 (0.84, 0.90)</td>
<td>0.73 (0.66, 0.79)</td>
<td>1.09</td>
<td>0.05</td>
<td>0.52</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.88 (0.84, 0.90)</td>
<td>0.73 (0.66, 0.79)</td>
<td>3.26</td>
<td>0.16</td>
<td><strong>0.76</strong></td>
<td><strong>0.86</strong></td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.88 (0.84, 0.90)</td>
<td>0.73 (0.66, 0.79)</td>
<td>9.78</td>
<td>0.49</td>
<td>0.91</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Stool lactoferrin</strong></td>
<td>0.25</td>
<td>0.82 (0.73, 0.88)</td>
<td>0.79 (0.62, 0.89)</td>
<td>1.3</td>
<td>0.08</td>
<td>0.57</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.82 (0.73, 0.88)</td>
<td>0.79 (0.62, 0.89)</td>
<td>3.90</td>
<td>0.23</td>
<td><strong>0.80</strong></td>
<td><strong>0.82</strong></td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.82 (0.73, 0.88)</td>
<td>0.79 (0.62, 0.89)</td>
<td>11.7</td>
<td>0.68</td>
<td>0.92</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>C-reactive protein</strong></td>
<td>0.25</td>
<td>0.49 (0.34, 0.64)</td>
<td>0.92 (0.72, 0.98)</td>
<td>2.04</td>
<td>0.18</td>
<td>0.67</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.49 (0.34, 0.64)</td>
<td>0.92 (0.72, 0.98)</td>
<td>6.13</td>
<td>0.55</td>
<td><strong>0.86</strong></td>
<td><strong>0.64</strong></td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.49 (0.34, 0.64)</td>
<td>0.92 (0.72, 0.98)</td>
<td>18.3</td>
<td>1.66</td>
<td>0.95</td>
<td>0.38</td>
</tr>
</tbody>
</table>

CI, confidence interval; IBD, inflammatory bowel disease
Cochrane Review: Biomarkers for Evaluating Endoscopic Disease Activity in Asymptomatic Inflammatory Bowel Disease Patients


• Meta-analysis on the diagnostic accuracy of C-reactive protein (CRP), fecal calprotectin (FC), and stool lactoferrin (SL) for predicting endoscopically proven relapse in asymptomatic IBD patients
Methods

• Databases were searched from inception to December 18, 2015 for relevant cohort and case-control

• Studies that evaluated the diagnostic accuracy of CRP, FC, or SL, and used endoscopy as a gold standard to document future relapse, in patients with asymptomatic IBD.

• Sensitivities and specificities were pooled to generate operating property estimates for each test using a bivariate diagnostic meta-analysis.
5431 records identified

9 records from other sources

2515 records after duplicates removed

2515 records screened

2466 records excluded

29 full text articles assessed

10 records excluded with reasons

19 studies included in the qualitative synthesis
sensitivity

specificity
<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooiweer 2015</td>
<td>6</td>
<td>6</td>
<td>24</td>
<td>66</td>
<td>22.55</td>
<td>[1.22; 417.75]</td>
</tr>
<tr>
<td>Jauregui-Amezaga 2014</td>
<td>9</td>
<td>17</td>
<td>14</td>
<td>47</td>
<td>2.58</td>
<td>[0.85; 7.85]</td>
</tr>
<tr>
<td>Molander 2015</td>
<td>8</td>
<td>15</td>
<td>7</td>
<td>34</td>
<td>4.16</td>
<td>[1.17; 14.82]</td>
</tr>
<tr>
<td>Yamamoto 2014</td>
<td>14</td>
<td>21</td>
<td>19</td>
<td>59</td>
<td>4.02</td>
<td>[1.43; 11.29]</td>
</tr>
<tr>
<td>Jauregui-Amezaga 2014</td>
<td>7</td>
<td>17</td>
<td>8</td>
<td>47</td>
<td>3.32</td>
<td>[1.01; 10.96]</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>97</strong></td>
<td><strong>312</strong></td>
<td></td>
<td></td>
<td><strong>4.44</strong></td>
<td><strong>[2.69; 7.34]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: I-squared=0% [0%; 69.2%], tau-squared=0, Q=4.1, df=5, p=0.53
Conclusions

• CRP, FC, and SL can accurately identify symptomatic IBD patients that have endoscopically active disease

• FC is less accurate when used to predict relapse in asymptomatic IBD patients
Case 1 - Biomarkers

- 32 year old female
- Patchy Crohn’s colitis x 2 years
- Presenting symptoms:
  - Bloody diarrhea 8-10 / day
  - Abdominal pain
  - Mouth ulcers
  - Joint aches
  - Weight loss 10 kg
- Initial response to prednisone

- Intolerance to azathioprine
- adalimumab monitoring with clinical response
- In clinical remission after 1 year
  - 2 formed non-bloody bowel movements daily
  - No pain
  - Good appetite, stable weight
Case 1 - Biomarkers

- Clinical remission on adalimumab 40 mg q2 weeks
- Slight rise in fecal calprotectin and serum CRP

![Graph showing fecal calprotectin and CRP levels](image-url)