C-reactive protein estimation does not improve accuracy in the diagnosis of acute appendicitis in pediatric patients

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Abstract

Background: Appendectomy is the treatment of choice in acute appendicitis in children. Delayed diagnosis of acute appendicitis in children can lead to complications like perforation. Studies on the diagnostic value of WBC and CRP in establishing the diagnosis of appendicitis have contradictory results. Our study evaluates the role of CRP in diagnosing appendicitis in a pediatric population.

Methods: A retrospective chart study on 130 patients aged less than 19 years who had an appendectomy at Sparrow hospital during years 2002–2006 formed the basis for this report. Based on histology appendicitis was classified as simple or perforated (complicated).

Results: Patients (75 boys, 55 girls) were 6–18 years of age (median 14 years). The appendix was normal in 9/130 cases. Appendicitis was simple in 58/130 cases and perforated in 63/130 cases. Overall WBC count had the highest sensitivity in the prediction of (diagnosis) appendicitis at 88% whereas CRP was 69% and, WBC and CRP combined was 60%. PPV of WBC was highest at 0.81 (47/58) for simple appendicitis and 0.93 (51/58) for perforated appendicitis, when compared to CRP at 0.57 (33/58) and 0.75 (47/63); and CRP and WBC combined at 0.45 (26/58) and 0.75 (47/63).

Conclusion: The sensitivity and PPV of WBC were better than CRP alone, or in combination with WBC. We conclude that CRP does not aid in the diagnosis of appendicitis. Simple appendicitis was seen in spite of normal WBC and CRP.
Demographic data, preoperative WBC count and CRP levels obtained during diagnostic workup were tabulated and compared to the final surgical pathology report. WBC greater than $12.0 \times 10^3$ μL and a CRP of $>1.0$ mg/dL were deemed elevated. Based on histology appendicitis was divided into simple and perforated (including focal abscess, suppurative appendicitis and transmural necrosis).

### 3. Results

The age of patients ranged from 6 to 18 years with the median being 14 years. There were 46 children (4–11 years) and 84 adolescents (12–18 years). There were 75 boys and 55 girls. The appendix was normal in 9 instances; there was simple appendicitis in 58 cases and perforated appendicitis in 63 cases (Tables 1 and 2).

Continuous variables were expressed as mean ± standard deviation. Categorical variables were reported as percentage. The analysis was performed with Chi-square test and Fisher exact test for categorical variables and independent sample t-test was used for continuous variables. Binominal test was used for performing the statistical test on the number of patients.

WBC had the highest overall sensitivity of 88% in staging appendicitis when compared with that of CRP at 69% and WBC and CRP combined at 60%. PPV of WBC was highest at 0.81 (47/58) for simple appendicitis and 0.93 (59/63) for perforated appendicitis, when compared to CRP at 0.57 (33/58) and 0.81 (51/63); and CRP and WBC combined at 0.45 (26/58) and 0.75 (47/63) (Tables 3 and 4).

Specificity for WBC was lowest at 22% when compared with CRP at 56% and WBC and CRP combined at 67%. There was not much intergroup difference in the NPV. Low specificity of WBC can be explained by this study group which comprises patients who underwent appendectomy and not taking into consideration all the patients who presented with abdominal pain.

Normal CRP and WBC was seen in 7% (4/58) cases of simple appendicitis and in 11% (1/9) cases of normal appendix. CRP and WBC combined were not normal in any of the perforated appendicitis cases.

### 4. Discussion

Appendicitis is the most common condition requiring emergency abdominal operation in childhood. Diagnosis of acute appendicitis is best based on clinical judgement but additional laboratory and radiological confirmation may be needed. WBC, CT scan and ultrasonography, and urine examination aid in the diagnosis. Ultrasound is inaccurate especially in an uncooperative child, with sensitivities and specificities ranging from 71% to 92% and from 96% to 98%. CT scan has high sensitivity and specificity of 97% and 94% in acute appendicitis in adults, but the accuracy may only be 50% in children. Relative lack of body fat in children makes it difficult to identify fat streaking and to separate an inflamed appendix from bowel. Additional disadvantages of CT scan include cost, radiation exposure, and potential need for sedation and sensitivity reaction to contrast. The role of MR scan and diagnostic laparoscopy for diagnosing acute appendicitis in children is not well established.

Acute appendicitis follows a sequence of events starting with initial obstruction of the appendiceal lumen causing impaired blood flow with destruction of the mucosa, bacterial invasion, and leukocyte infiltration. These leukocytes migrate to their target tissues guided by a variety of soluble proteins such as CRP, cytokines, chemokines, adhesion molecules and proteases.

The laboratory tests chosen to aid the diagnosis of acute appendicitis are selected because of the wide availability, ease of performance, are minimally invasive, low costs and repeatable. WBC and CRP level estimations are the most widely used laboratory markers. Elevated WBC is found in the early phases of inflammation and CRP levels rise in more advanced appendicitis. The sensitivities and specificities for WBC for detecting acute appendicitis vary from 19% to 88% and from 53% to 100%. Adding the diff to the WBC increased the sensitivity from 67% to 80% in diagnosing appendicitis in pediatric patients. Up to 20% of pediatric patients with acute appendicitis can have a normal WBC with diff, WBC levels are insensitive and non-specific in distinguishing patients with and without appendicitis and to differentiate patients with perforated from those with simple appendicitis.

CRP, discovered in 1930 by Tillett and Francis in studies of serologic reactions that accompanied pneumonia, is an acute phase protein synthesized by hepatocytes. CRP synthesis increases within 4–6 h after the onset of inflammation or acute tissue injury and doubles every 8 h thereafter, peaking at ~36–50 h. Levels decline rapidly, because of a relatively short half-life of 4–7 h. Negative results may be of greater assistance than positive ones. CRP has a sensitivity and specificity ranging from 48% to 75% and from 57% to 82% in acute appendicitis, but is particularly insensitive for patients with symptoms less than 12 h. However, some studies suggest that CRP is better than WBC in detecting appendiceal

### Table 1

Results of 120 patients operated on for suspected appendicitis.

<table>
<thead>
<tr>
<th></th>
<th>Total patients (n = 130; 100%)</th>
<th>Normal appendix (n = 9; 6.9%)</th>
<th>Simple and perforated appendix (n = 121; 93.1%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>55 (42.3%)/75 (57.7%)</td>
<td>7 (77.8%)/2 (22.2%)</td>
<td>48 (39.7%)/73 (60.3%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Age (years)</td>
<td>131 ± 3.3 (6–18)</td>
<td>15.7 ± 1.4 (13–17)</td>
<td>12.9 ± 3.4 (8–18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (&gt; $10^3$) μL</td>
<td>17.4 ± 4.3 (10–21)</td>
<td>16.1 ± 4.2 (11–25)</td>
<td>17.4 ± 4.3 (10–31)</td>
<td>0.393</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.9 ± 0.9 (0.7–30.8)</td>
<td>1.3 ± 0.6 (0.9–2.5)</td>
<td>2.9 ± 3.9 (0.7–31)</td>
<td>0.220</td>
</tr>
<tr>
<td>Normal appendix</td>
<td>9 (6.9%)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Simple appendicitis</td>
<td>58 (44.6%)</td>
<td>–</td>
<td>58 (48%)</td>
<td></td>
</tr>
<tr>
<td>Perforated appendix</td>
<td>63 (48.5%)</td>
<td>–</td>
<td>63 (52%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

Results of 121 patients with simple and perforated appendicitis.

<table>
<thead>
<tr>
<th></th>
<th>Simple appendicitis</th>
<th>Perforated appendicitis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>58 (48%)</td>
<td>63 (52%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Female/male</td>
<td>21 (36.2%)/37 (63.8%)</td>
<td>27 (42.8%)/26 (57.2%)</td>
<td>0.465</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.9 ± 2.5 (8–18)</td>
<td>13.1 ± 2.2 (6–18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (&gt; $10^3$) μL</td>
<td>15.3 ± 3.0 (10.3–24.6)</td>
<td>19.4 ± 4.4 (10.8–31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.9 ± 1.6 (0.7–8.3)</td>
<td>3.9 ± 5.2 (0.9–30.8)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Normal appendix</th>
<th>Simple appendicitis</th>
<th>Perforated appendicitis</th>
<th>Simple and perforated appendicitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory markers</td>
<td>No WBC</td>
<td>E WBC</td>
<td>N CRP</td>
<td>E CRP</td>
</tr>
<tr>
<td>WBC</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>E WBC</td>
<td>31</td>
<td>47</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>N CRP</td>
<td>4</td>
<td>2</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>E CRP</td>
<td>4</td>
<td>33</td>
<td>51</td>
<td>84</td>
</tr>
</tbody>
</table>

N = elevated; N = normal.
perforation. Beltrán concluded that either CRP or WBC individually or in combination, was highly sensitive in differentiating simple and perforated appendicitis.21 In another study, clinical observation and serial measurement of WBC and CRP in suspected appendicitis with equivocal clinical findings showed a high sensitivity and specificity for serial WBC count and improved accuracy of diagnosis.3

Grönroos et al. found normal values of both WBC and CRP in 7 of 100 consecutive children with pathologically confirmed acute appendicitis but in none of the 200 adults, concluding that normal inflammatory markers exclude appendicitis in adults but not in children. All patients with complicated appendicitis had an increase of either CRP or both WCRP and B suggesting that, in those with normal inflammatory markers, complicated appendicitis can be excluded with accuracy when both are normal. Andersson et al. in a prospective study on 420 patients concluded that repeated clinical and laboratory examinations in patients with equivocal diagnosis of appendicitis are helpful.18

Our study had 4 patients with early acute appendicitis and normal WBC and CRP, but no patient with perforated appendicitis had both WBC and the CRP normal. Patients with abdominal pain who did not have operation were not included in our study, and thus, a precise estimate of negative predictive values of markers of inflammation could not be obtained.16 Studies on adult populations have shown that measurement of WBC and CRP could avoid up to one quarter of negative appendectomies.16,25 There has not been a study to look at the rates of avoiding negative appendectomy in pediatric patients.

In a report on 100 children with suspect appendicitis, the sensitivity of elevated WBC alone was 0.60, elevated CRP alone was 0.86 but elevation of both was 0.98.16 Similar results were seen in other studies, with sensitivity, specificity, positive and negative predictive values of WBC, diff and CRP combined being 86%, 90.7%, 93%, and 81.2%, respectively.17 In our study, sensitivity of WBC was greatest at 88%, only a modest 69% for CRP, and surprisingly 60% for WBC and CRP combination. Similarly, the positive predictive value of WBC was highest at 0.81 (47/58) for simple appendicitis and 0.93 (59/63) for perforated appendicitis, when compared to CRP at 0.57 (33/58) and 0.81 (51/63); and WBC and CRP in combination were 0.45 (26/58) and 0.75 (47/63). Thus, estimation of CRP in our pediatric patients with clinical suspicion of acute appendicitis did not enhance diagnostic accuracy.

Studies done on many mediators like IL8, IL10, granulocyte colony stimulating factor, interferon γ, soluble intercellular adhesion molecule-1, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinases-1 could not differentiate appendicitis in pediatric populations from other causes of abdominal pain.19 Further studies looking for a more reliable systemic inflammatory marker may have value.

In view of these results, further research with other inflammatory markers should be done prospectively. That study should note a surgeon’s decision to operate or not operate based on clinical judgement of the diagnosis of acute appendicitis in pediatric patients and then have the results of the laboratory to see how often that affects the decision to operate or not.

5. Conclusion

Appendicitis remains a sometimes difficult diagnosis. The diagnosis of acute appendicitis is primarily clinical and should be made on that basis. Due to a high rate of perforation in children acute appendicitis should be recognized and operated upon early but at the same time negative appendectomy should be avoided. Contrary to other studies in pediatric population on CRP we did not find any beneficial role in aiding the diagnosis of appendicitis in our pediatric patients. Further studies are needed with other systemic inflammatory markers to help in diagnosing appendicitis.

Conflict of interest

There are no personal conflicts of interest of any authors. There were no sources of outside support or funding.

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References


