Diagnostic accuracy of hyponatremia as a biomarker of perforated appendicitis in pediatrics in Dr. Soetomo General Hospital, Surabaya

Bela Mayvani Rachman¹, I Gusti Bagus Adria Hasriastawa², Ariandi Setiawan¹²

INTRODUCTION

Acute appendicitis is one of the common acute abdominal emergencies in pediatrics. There were 70,000 cases of acute appendicitis case diagnosed in the United States with a prevalence of 1:1000.¹² The clinical diagnosis of appendicitis in pediatrics is challenging due to various non-specific symptoms and characteristics of children who struggle to express pain. This condition can delay the diagnosis and, hence, can lead to complicated appendicitis.³⁴ According to a study by Nance et al., 2000 the incidence of perforated appendicitis in children is considerably high, 69% in children under 5 years old and 100% in children under 1-year-old.³ The misdiagnosed incidence was found in the range of 28% to 57%, particularly in children from 2 to 12 years old and almost 100% in children under 2 years old.⁵⁻⁷

The difficulties of clinically diagnosing appendicitis in pediatrics need further diagnostic tests to detect it early. Ultrasonography (USG) and Computerized Tomography Scans (CT-Scan) have been widely used to diagnose, but these tools still have drawbacks. USG is a non-invasive diagnostic tool that uses ultrasonic sound to evaluate the appendix. However, this tool is highly operator dependent and, hence, can fail to visualize the appendix with a percentage of approximately 55%.⁶ On the contrary, the CT-Scan abdomen offers high sensitivity and specificity to diagnose appendicitis. However, it is not recommended as a routine examination due to its high radiation, leading to increased malignancy risk in paediatrics. Moreover, the CT scan is considered a sophisticated examination that is expensive and has limited accessibility, in which not all hospitals can provide this facility.⁸

In the past decade, researchers have focused on developing a non-invasive technique, i.e., biomarker tests, for assessing appendicitis in pediatrics. The biomarker test can offer an affordable price with considerably high accuracy and does not depend on the operator. The most common biomarker test to diagnose appendicitis is leucocyte and C-Reactive Protein (CRP). According to Coleman et al., 1998, the leucocyte count is most likely to increase in cases of appendicitis.⁹ However, this value cannot be used to distinguish between acute and perforated appendicitis. A study conducted by Beltran et al., 2007, highlighted that an increase in the CRP value could be used as a predictor for acute appendicitis.¹⁰ Nevertheless, the change in the CRP value cannot be associated with perforated appendicitis due to its low sensitivity. Some studies
suggested that perforated appendicitis may be linked with the natrium level in patients. Kaser et al., 2013 observed that low natrium levels occurred in bowel and appendicitis perforation. Further studies by Giannis et al., 2020 highlighted that perforated appendicitis could stimulate proinflammatory cytokines, reducing the natrium level, particularly in pediatric patients.

Perforated appendicitis in pediatrics at Soetomo General Hospital is noticeably high. According to the medical records from 2017 to 2021, we found 245 pediatric patients diagnosed with appendicitis, of which 65% are perforated appendicitis. Accordingly, this study aimed to examine the accuracy of hyponatremia as a biomarker for cases of appendix perforation in pediatrics at Soetomo General Hospital.

METHODS

Study Design
Retrospective observational studies were used in this work by examining patients’ medical records at Soetomo General Hospital Surabaya for 5 years, from January 2017 to December 2021. It is important to note that patients with incomplete medical records were excluded from this study. Only pediatric patients diagnosed with acute and perforated appendicitis were considered. The Child Protection Law defines pediatric patients as children under 18 years old. Data from medical records used for analysis included the age, gender, duration of symptoms and fevers, laboratory tests, and diagnoses of appendicitis.

Data Collection
Note that abdominal pain and fever duration was estimated from the first time feeling the symptom until coming to the Emergency Room (ER). Symptoms of vomiting and diarrhea were taken from patient histories, whether present or absent. The natrium value was obtained from preoperative laboratory testing. The normal natrium value in our institution is in the range of 135-145 mmol/L. Accordingly, the term hyponatremia used thoroughly in this article, refers to the natrium value of less than 135 mmol/L. Diagnoses of acute and perforated appendicitis were identified from macroscopic intraoperative findings. In particular, acute appendicitis is when the appendix becomes inflamed with a length and diameter of at least 8 cm and 0.5 cm, respectively, showing hypernatreemia, edema, and fecalith without perforation. In contrast, perforated appendicitis refers to abscesses and perforation in the appendix or the appendix becoming gangrenous.

Data Analysis
The Chi-square and Mann-Whitney tests were used to examine the relevant data with the help of SPSS 23.0. Furthermore, The Receiver Operating Characteristic (ROC) curve is used to evaluate the accuracy of natrium in pediatric perforated appendicitis. Statistical significance was defined as a p-value ≤ 0.05.

RESULTS

Characteristics of the patients
A total of 102 samples consisting of 41 (40.2%) females and 61 (59.8%) males were obtained. From the total samples, the ratio of the patients diagnosed with acute appendicitis and perforated appendicitis is 32.70. Details of the characteristic of patients diagnosed with appendicitis are presented in Table 1. Note that the term ‘SD’ in Table 1 stands for Standard Deviation. It is seen that acute appendicitis is most likely to occur at the age of 12-14 years old, with a percentage of 40.6%, while the highest proportion of perforated appendicitis occurs at the age of 6-8 years old, with a percentage value of 27.1%. This demonstrates that perforated appendicitis tends to happen at a younger age than acute appendicitis. Furthermore, the p-value, estimated using the Mann-Whitney test with the help of SPSS 23.0, is considered significant if the p-value ≤ 0.05.

Table 1. Characteristics of pediatric patients with Appendicitis at Dr. Soetomo General Hospital

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acute Appendicitis</th>
<th>Perforated Appendicitis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 years</td>
<td>1 (3.1%)</td>
<td>3 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>3-5 years</td>
<td>1 (3.1%)</td>
<td>17 (24.2%)</td>
<td></td>
</tr>
<tr>
<td>6-8 years</td>
<td>5 (15.6%)</td>
<td>19 (27.1%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>9-11 years</td>
<td>11 (34.3%)</td>
<td>18 (25.7%)</td>
<td></td>
</tr>
<tr>
<td>12-14 years</td>
<td>13 (40.6%)</td>
<td>11 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>15-17 years</td>
<td>1 (3.1%)</td>
<td>2 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Duration of abdominal pain (Mean ± SD (days))</td>
<td>2.38 ± 1.12</td>
<td>3.99 ± 1.66</td>
<td>0.000*</td>
</tr>
<tr>
<td>Duration of fever (Mean ± SD (days))</td>
<td>1.28 ± 0.68</td>
<td>2.66 ± 1.66</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (93.8%)</td>
<td>69 (97.1%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (31.3%)</td>
<td>43 (61.4%)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Natrium Mean ± SD (mEq/L)</td>
<td>136.6 ± 3.9</td>
<td>131.1 ± 3.8</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Analysis was carried out using Chi-Square Test. The result was considered significant if the p-value ≤ 0.05.

Table 2. Frequency of hyponatremia in acute and perforated appendicitis

<table>
<thead>
<tr>
<th>Natrium</th>
<th>Acute Appendicitis n(%)</th>
<th>Perforated Appendicitis n(%)</th>
<th>p-value</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>11 (34.4%)</td>
<td>41 (58.6%)</td>
<td>0.04*</td>
<td>2.69</td>
</tr>
<tr>
<td>Normal natrium</td>
<td>21 (65.6%)</td>
<td>29 (41.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analysis was carried out using Chi-Square Test. The result was considered significant if the p-value ≤ 0.05.
falls below 0.05, indicating statistically significant evidence for the relationship between acute and perforated appendicitis and the age of patients.

From Table 1, the duration of abdominal pain in perforated appendicitis, 3.99 ± 1.66 days, was longer than acute appendicitis, 2.38 ± 1.12 days. The p-value from the Mann-Whitney test also shows a statistically significant correlation between appendicitis and duration of abdominal pain. The same phenomenon also occurs for the period of fevers where perforated appendicitis, 2.66 ± 1.66 days, takes longer than acute appendicitis, 1.28 ± 0.68 days, with the estimated p-value below 0.05. Over 90% of patients diagnosed with acute and perforated appendicitis experienced vomiting. Nevertheless, the p-value for vomiting and appendicitis assessed with the Chi-Square test does not have significant evidence that the variable follows the normal distribution. Symptoms of diarrhea are less frequent in acute appendicitis compared to perforated appendicitis. The p-value of the relationship between diarrhea and appendicitis is in the proximity of 0.009, which can be considered as having statistically significant evidence to reject the null hypothesis.

Further analysis of pediatric patients indicates that the mean serum natrium of perforated appendicitis, 131.1 ± 3.8 mEq/L, is lower than that of acute appendicitis, 136.6 ± 3.9 mEq/L. The results from the Mann-Whitney test also indicate that the p-value of the correlation between natrium and appendicitis fulfills the p-value<0.05. To extend the analysis, Table 2, presents the frequency of hyponatremia in acute and perforated appendicitis.

It can be seen that the frequency of hyponatremia in perforated appendicitis can reach about 58.6%. In contrast, 65.6% of acute appendicitis patients have normal natrium levels. Using the Chi-Square test to examine the connection between perforated appendicitis and hyponatremia, the estimated p-value is in the proximity of 0.04 with the sensitivity and specificity values of 58.5% and 65.6%, respectively, indicating a significant correlation between the two variables. Moreover, the prevalence risk of hyponatremia concerning perforated appendicitis is about 2.69.

The Receiver Operating Characteristic (ROC) curve is used to evaluate the accuracy of natrium in pediatric perforated appendicitis. Figure 1 displays the ROC curve of hyponatremia as a predictor of perforated appendicitis. The dotted brown (diagonal) and solid blue lines represent the random classifier and predictor, respectively. It is seen that the curve is above the arbitrary classifier line, indicating that the prediction method is better than a lucky guess. The area under the ROC curve (AUC) estimated using SPSS 23.0 is about 0.721, with a standard error of 5.41%. The 95% confidence interval (CI) ranges from 0.623 to 0.805, and the p-value is less than 0.001. Furthermore, with the cut-off value of natrium set to £ 133 mEq/L, the sensitivity and specificity values are 50% and 81.25%, respectively.

DISCUSSION

We demonstrated that the duration of symptoms in perforated appendicitis, which include abdominal pain, fever, vomiting and diarrhea, is longer than that of acute appendicitis. This agrees with the previous studies that there is an association between the duration of symptoms and the incidence of perforated appendicitis. Thus, the longer patients feel the signs, the higher the percentage of perforated appendicitis likely to occur.

We observed that 58.6% of patients with perforated appendicitis are hyponatremia. That percentage is similar to a study conducted by Roushan et al., 2021 which is 60% for hyponatremia and appendix perforation cases. In this study, the risk of perforated appendicitis patients being
hyponatremia is 3 times higher than that of acute appendicitis. Moreover, we noticed a significant correlation between diarrhea and perforated appendicitis which has yet to be mentioned in the previous studies.16 There needs to be a clear understanding of hyponatremia in perforated appendicitis. However, since perforated appendicitis can be linked to inflammation, Swartz et al.2010 reported that cytokines and inflammatory mediators contribute to hyponatremia. In particular, when inflammation occurs in the appendix, the endotoxin stimulates cytokines and inflammatory mediators such as TNF-α, IL-1α dan IL-6. In this case, IL-6 can pass through the brain-blood barrier, activating the supraoptic and paraventricular neurons and releasing vasopressin. Furthermore, vasopressin secretion increases the water and natrium reabsorption in ductus collectives in the renal, causing hyponatremia.17 It is important to note that this study was carried out in one institution or single center. Future work may consider performing this study in multi-institution research centers to gain more accurate results that can eventually be used as guidelines for the management therapy of pediatric appendicitis in Indonesia.

CONCLUSION
Our findings support that hyponatremia has a strong correlation with pediatric perforated appendicitis. Therefore, hyponatremia can be used as an alternative diagnostic tool for diagnosing perforated appendicitis, particularly in pediatrics. The advantage of this method is that the serum natrium is mostly affordable and available in most hospitals, making it easy to diagnose perforated appendicitis. Further studies are needed to validate these findings with more comprehensive design and larger sample size.

FUNDING
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CONFLICT OF INTEREST
No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION
Bela Mayvani Rachman: Conceptualisation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Visualization. I Gusti Bagus Adria Hasriastawa: Methodology, Supervision, Resources, Writing – review & editing. Ariandi Setiawan: Methodology, Supervision, Resources, Writing – review & editing

ETHICAL CONSIDERATION
This study was approved by the Ethics Committee of The Hospital with the Ethical Clearance number 0541/KEPK/XII/2022.

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REFERENCES