1. Introduction

Acute appendicitis (AA) is the most common abdominal surgical emergency in the pediatric and adult population, with an estimated lifetime risk of 9% in boys and 7% in girls, and the lifetime risk of appendectomy of 12% for males and 23% for females [1,2]. AA typically affects children and adolescents aged 10 to 20 years, but no age is exempt [2]. AA is uncommon in pre-school children and is often diagnosed at the perforated stage (perforated appendicitis, PA) [3]. Pediatric PA rates are ~30% but can be much higher for younger children [4,5]. Compared with non-perforated appendicitis (NPA), PA has a significant effect on the postoperative outcome, increasing the rate of complications (up to 39%) such as abdominal/pelvic abscess, bowel obstruction, and wound infections [6,7]. Increased morbidity in these patients also affected the hospital length and greater resource utilization [8]. Therefore, an accurate preoperative diagnosis of perforation is of utmost importance to enable earlier operative treatment and reduce the overall morbidity.

Previous studies have identified potential predictors of PA, including a delay in surgery [9-11], male gender [12], younger children [4,5], older adults [12], appendicoliths [13], comorbidities [14], neutrophil ratio [15], fever, anorexia, diarrhea, and imaging exams alterations [16]. However, prehospital or intrahospital factors that predict PA have been inconsistently identified, with the contradictory data in the current literature [17].
The present study aimed to identify factors predicting PA at admission in the pediatric emergency department (ED), comparing baseline demographic, clinical symptoms, and simple and readily available serum inflammatory markers of patients with PA and NPA.

2. Patients and methods

In this retrospective observational cohort study, consecutive medical records of children <18 years old with surgically and histopathologically confirmed AA over three years (2013–2015) were reviewed, including their medical histories, laboratory and diagnostic test results, physical examination, clinical and treatment notes.

All patients were classified into two groups as the PA group and the NPA group. The eligibility criteria were grossly positive and microscopically confirmed appendicitis. Patients were excluded when the removed appendix was not inflamed (n = 15).

Diagnoses were classified according to the World Health Organization International Classification of Diseases, version 9 and 10 (ICD-9 and ICD-10). The presence of fever was based on the history of fever and defined as the axillary temperature > 37.2 °C and rectal temperature > 38 °C. A C-reactive protein (CRP) level > 10 mg/dL was considered high [18]. A total white blood cell count (WBC) was considered elevated according to the age groups and cutoff values defined by Pediatric CBC Reference Values (LTR10211) (Table 1) [19].

Operative findings were classified as NPA and PA. PA was defined by a visible hole in the appendix or an appendicolith free within the abdominal cavity as well as the presence of purulent fluid (gross contamination) within the peritoneal cavity. Histological perforation was defined as a perforation confirmed by the microscopic analysis.

All patient medical records were de-identified and anonymized for the current study. This study was approved by the local institutional review board (Ethical Committee of the Clinical Center, University of Sarajevo, Number: 0901–27,723). However, the IRB waived the informed consent due to the retrospective nature of the study.

2.1. Statistical analysis

Univariate analysis was performed by comparing PA and NPA characteristics using the Mann-Whitney U test for numeric variables and the Fisher exact test for categorical variables. All variables in the univariate test were included in the multivariable analyses using multivariable logistic regression analysis to create a model to predict appendiceal perforation. For logistic regression analysis, the stepwise backward model was applied. P-values <0.05 were considered statistically significant for all statistical calculations. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) IBM Version 26 (SPSS) (UNICOM Systems, Inc.).

3. Results

During the study period, 295 patients underwent an appendectomy and had confirmatory appendicitis by histopathologic examination. Among them, 172 patients (58.3%) were male. The overall male-to-female ratio was 1.39:1. PA was found in 92 patients (31.2%). Male patients had PA significantly more frequently than females (p 0.001). Perforation was commonly seen in young children (<5 years) with a perforation rate of 50%. There was a significant difference in the number of PA patients per age group (Table 2).

Univariate analysis of variables that may serve as possible predictors of PA, conducted between the groups (PA and NPA), is shown in Table 2. We observed a significant difference between the two groups in gender presence, vomiting, diarrhea, fever, CRP count, and WBC (Table 3). Together with the variable age below five years, these variables were entered into the initial logistic regression model. The final model included male gender, age below five years, vomiting, diarrhea, fever, WBC, and CRP (Table 4) and was characterized by a Nagelkerke R-square value of 0.441 and Hosmer and Lemeshow goodness of fit with a Chi-square value of 8.128 and a P-value of 0.421. This model accurately classifies 78.2% of cases. Multivariate analysis revealed that the factors significantly associated with PA were male gender (odds ratio [OR]: 3.133; 95% confidence interval [CI]: 1.610–6.096); vomiting (OR: 2.346; 95% CI: 1.141–4.822); diarrhea (OR: 4.549; 95% CI: 1.850–11.181); fever (OR: 3.429; 95% CI: 1.765–6.663); elevated WBC (OR: 2.962; 95% CI: 1.491–5.884) and elevated CRP (OR: 3.061; 95% CI: 1.267–7.396).

4. Discussion

This study revealed that patients’ main demographic and clinical characteristics and commonly used laboratory tests might reliably distinguish between the NPA from PA in pediatric patients admitted to ED.

Due to the inadequate information flow with concerned parents about their children’s medical history, age-related communication difficulties with sick children, and often highly atypical and nonspecific clinical presentations, PA diagnosis in children is often very challenging on admission to pediatric ED. In contrast to the numerous studies that have focused on predictors of AA [20-22], there is a relative scarcity of studies exploring the differential diagnosis (PA vs. NPA) in children.

Consistent with the previous studies [2,23–25], we also found a slight male predominance among pediatric patients with AA. Additionally, our study’s PA rates were much higher in males (73.9%) (p 0.001). This finding is consistent with a study by Guss et al., who also reported that PA’s rate was significantly higher among males than females [26]. PA occurred was also substantially higher in children <5 years (50%). Our study’s overall PA incidence was in line with literature data [6,26,27]. Accurate diagnosis and timely treatment of AA in children <5 years is even more challenging due to the rarity of the disease, the variable clinical presentation, less ability to articulate the clinical symptoms, the rapid development, the immaturity of omentum, and defense mechanisms [28].

This study also explored the potential value of commonly utilized biomarkers, such as WBC and CRP, in predicting PA. It has been demonstrated that WBC can be within normal limits in more than 20% of pediatric patients with AA. Additionally, our study’s PA rates were much higher in males (73.9%) (p 0.001). This finding is consistent with a study by Guss et al., who also reported that PA’s rate was significantly higher among males than females [26]. PA occurred was also substantially higher in children <5 years (50%). Our study’s overall PA incidence was in line with literature data [6,26,27]. Accurate diagnosis and timely treatment of AA in children <5 years is even more challenging due to the rarity of the disease, the variable clinical presentation, less ability to articulate the clinical symptoms, the rapid development, the immaturity of omentum, and defense mechanisms [28].

The classic AA symptoms include anorexia, migration of pain, nausea, and vomiting [33]. The presence of fever with tachycardia is also a common finding in AA. Some of the mentioned symptoms in AA were especially emphasized by Rasmussen and Hoffmann, noting that the absence of nausea, vomiting, and anorexia called into question AA’s diagnosis [34]. Furthermore, sustained vomiting may occur due to generalized peritonitis, while diarrhea may result from irritation of the
**Table 2**

Incidence of acute appendicitis and perforated appendicitis in various pediatric age groups.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>All appendicitis</th>
<th>Perforated appendicitis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, in years (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>295 (13.6%)</td>
<td>92 (31.2%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>6–10 years</td>
<td>113 (38.3%)</td>
<td>27 (23.9%)</td>
<td></td>
</tr>
<tr>
<td>11–16 years</td>
<td>142 (48.1%)</td>
<td>45 (31.7%)</td>
<td></td>
</tr>
</tbody>
</table>

CI – Confidence interval.

**Table 3**

Univariate analysis of variables in non-perforated and perforated appendicitis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total NPA (1)</th>
<th>PA (2)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>295</td>
<td>203 (68.8%)</td>
<td>92 (31.2%)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>10 (8–13)</td>
<td>10 (7–13)</td>
<td>0.318⁴</td>
</tr>
<tr>
<td>Age &lt; 5 years</td>
<td>40 (13.5%)</td>
<td>20 (9.8%)</td>
<td>0.143⁴</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>172 (58.3%)</td>
<td>104 (51.2%)</td>
<td>95% CI (8.6%, 24.2%)</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>123 (41.7%)</td>
<td>99 (48.8%)</td>
<td>95% CI (63.7%, 82.5%)</td>
</tr>
<tr>
<td>Nausea (n, %)</td>
<td>56 (19%)</td>
<td>37 (18.2%)</td>
<td>95% CI (17.5%, 36.3%)</td>
</tr>
<tr>
<td>Vomiting (n)</td>
<td>118 (40%)</td>
<td>99 (48.3%)</td>
<td>95% CI (14.5%, 25.9%)</td>
</tr>
<tr>
<td>Diarrhea (n, %)</td>
<td>37 (12.5%)</td>
<td>12 (5.9%)</td>
<td>95% CI (7.8%, 23.5%)</td>
</tr>
<tr>
<td>Fever (n, %)</td>
<td>82 (27.3%)</td>
<td>33 (16.3%)</td>
<td>95% CI (11.5%, 22.1%)</td>
</tr>
<tr>
<td>Median leukocyte count (WBC) (x10⁹/L)</td>
<td>14.9 (5.8)</td>
<td>13.8 (5.3)</td>
<td>17.5 (6.2)</td>
</tr>
<tr>
<td>Median C-reactive protein (CRP) level (mg/L)²</td>
<td>28.4 (9.2–69.1)</td>
<td>18.7 (6.7–40.4)</td>
<td>71.1 (36.4–120)</td>
</tr>
</tbody>
</table>

NPA – Non-perforated appendicitis; PA – Perforated appendicitis; CI – Confidence interval.

Data were analyzed using a Fisher test³ and Mann-Whitney U-test⁴.

¹ Data are presented as numbers with the percentage between brackets.
² Data are presented as median with the interquartile range.
³ Data are presented as median with the P25 and P75 between brackets.
⁴ Data are presented as numbers with the percentage between brackets.

Distal ileum. However, these symptoms are common in many other diseases. Either way, the diagnosis of AA is predominantly a clinical one. It should be emphasized that signs and symptoms that presented with PA vary between studies. In our study, several clinical variables, including nausea, vomiting, diarrhea, and fever, along with readily available serum inflammatory markers and some demographic characteristics, can successfully distinguish PA from NPA at the admission in emergency department. These findings are in line with the previous studies [32].

The main limitation of our study is its retrospective nature and a single institution experience. Also, the duration of symptoms was not defined precisely enough through the documentation used, so this variable could not be included. Moreover, routine ultrasound examination at the ED was inconsistently used and reported, and therefore, it was excluded from the study. Furthermore, abdominal pain’s localization was not analyzed concerning the appendix’s position but was recorded in general. Thus, the possibility of monitoring the migration of pain, one of the characteristic clinical variables in patients with AA, was omitted. In addition, ultrasound examination of AA was inconsistently used and reported, and therefore, this essential variable was excluded from the study and statistical analysis. The study’s additional limitation was the lack of registration of patients’ prior visits to local clinics, making the clinical variable “time between the onset of symptoms to the presentation” to assess the real reason for the delayed diagnosis.

In conclusion, distinguishing PA from NPA is crucial for the decision-making process and surgical outcome. Several clinical and biochemical variables evaluated together can be helpful to distinguish between PA from NPA.

**Availability of data and materials**

The datasets presented in the current study are available by the corresponding author on reasonable request.

**Declaration of Competing Interest**

Una Glamoclija is an employee of the Bosnalijek d.d., Sarajevo, Bosnia and Herzegovina. The other authors declare no conflict of interest.
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