

The predictive value of plasma sodium and other laboratory parameters in determining complicating appendicitis in children

Zlatan Zvizdic

Asmir Jonuzi

Una Glamoclija

Semir Vranic

semir.vranic@gmail.com

Research Article

Keywords: Complicated appendicitis, laboratory parameters, hyponatremia, prognosis, children

Posted Date: December 7th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-3716386/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at Medical Principles and Practice on April 9th, 2024. See the published version at <https://doi.org/10.1159/000538778>.

Abstract

Objectives

Finding a reliable preoperative predictor of complicated acute appendicitis (AA) has been a challenging diagnostic problem. The present study aimed to identify potential factors that may predict complicated AA in the pediatric emergency department (ED) based on routine, widely available laboratory tests on admission to the ED, including plasma sodium concentration.

Methods

We retrospectively reviewed clinical and laboratory data of pediatric patients with AA who underwent emergency surgery at our department between January 2020 and December 2022. The patients were divided into two groups: histopathologically proven complicated (n = 80), and non-complicated AA (n = 155).

Results

Complicated AA was associated with reduced plasma sodium and chloride concentrations ($p < 0.001$, both), decreased values of lymphocytes ($p = 0.002$), elevated C-reactive protein (CRP) ($p < 0.001$), elevated values of white blood cells (WBC) and neutrophils ($p = 0.012$ and 0.001 , respectively). In binomial logistic regression, increased CRP, WBC, and decreased sodium levels were predictors of complicated AA. The area under the ROC curve was 0.825 (95% CI 0.764, 0.886).

Conclusion

We identified mild hyponatremia and elevated CRP and WBC values as potential markers for distinguishing complicated from uncomplicated pediatric AA with implications for treatment approach, either surgical in complicated or conservative in uncomplicated disease.

Clinician's Capsule

- *What is known about the topic?*

Finding a reliable preoperative predictor of complicated acute appendicitis (AA) has been a challenging diagnostic problem in emergency departments worldwide.

- *What did this study ask?*

The present study explored potential factors that may predict complicated AA in the pediatric emergency department (ED) based on routine, widely available laboratory tests on admission to the ED, including plasma sodium concentration.

- *What did this study find?*

We identified mild hyponatremia and elevated CRP and WBC values as potential markers for distinguishing complicated from uncomplicated pediatric AA with implications for treatment approach, either surgical in complicated or conservative in uncomplicated disease.

- *Why does this study matter to clinicians?*

Routine blood tests can help emergency physicians discriminate between complicated and uncomplicated AA.

Introduction

Although acute appendicitis (AA) can develop at any age, it most commonly occurs in the second decade of life, with a rate of 23.3 cases per 10,000 per year (1). However, the diagnosis of AA remains challenging, and some controversies regarding its management are still present in different settings and practices worldwide, especially for the pediatric population (2). Consequently, the rate of appendiceal perforation is still high and varies from 16–40%, with a higher frequency occurring in preschool children (40–57%) and in patients > 50 years (55–70%) (3). Since managing complicated AA requires urgent intervention and intravenous broad-spectrum antibiotics, establishing its timely diagnosis through clinical examination, different clinical and imaging scoring systems, and laboratory markers is crucial (4–8). Otherwise, a delay in diagnosis can cause perforation, peritonitis, sepsis, and extended hospital stays (9).

In recent years, finding a reliable preoperative predictor of complicated AA has emerged as a prominent topic in clinical research, potentially improving diagnostic accuracy without invasive surgery or ionizing radiation. Among several laboratory parameters evaluated, serum sodium measurement has been proposed as valuable clinical data that may help delineate uncomplicated from complicated AA. Recent studies have investigated the possible association between preoperative hyponatremia (serum sodium level < 135 mEq/L) and complicated AA in both pediatric and adult populations (10–15). However, the results are contradictory, as several authors have found a positive association between preoperative hyponatremia and complicated appendicitis (10–15), while others have reported an insignificant association (16–18).

The present study aimed to identify reliable predictors of complicated AA in the pediatric emergency department (ED) based on routine, widely available laboratory tests and to clarify the potential association of pre-appendectomy hyponatremia with higher detection rates of complicated AA in the pediatric population of different ages. We hypothesized that preoperative serum sodium values in children with suspected AA would be helpful in early distinguishing complicated from uncomplicated appendicitis and more prompt treatment.

Methods

Study design and period

A retrospective chart review (RCR) of 264 consecutive pediatric patients (< 18 years old) who had undergone appendectomy (open or laparoscopic) due to AA (International Classification of Diseases Tenth Revision, code K35) was conducted. The study was performed at the Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina between January 2020 and December 2022. All surgeries were performed as emergency procedures.

Population

Patients were identified for inclusion in the study if they had received a histopathologic diagnosis of AA. All patients with negative (23/264, 8.7%) or interval appendectomies (1/264, 0.4%) were excluded from the study. Patients with missing or incomplete medical records were also excluded (5/264, 1.9%). Finally, 235 patients were selected for analysis. Based on intraoperative macroscopic appearance and postoperative histopathology, the patients were divided into two groups: those with simple AA (uncomplicated appendicitis group) and those with complicated AA (complicated appendicitis group). Uncomplicated AA was defined as simple (catarrhal and phlegmonous) or gangrenous without perforation, similar to American Association for the Surgery of Trauma (AAST) grades I and II (19). AA with perforation or abscess formation was defined as complicated AA (AAST grades III– V) (19).

Histopathologically, catarrhal AA was defined as the enlargement of lymphoid follicles in the appendiceal mucosa, and phlegmonous AA was defined as the presence of neutrophils in all appendiceal layers (20). Gangrenous AA was defined as neutrophil infiltration with smooth muscle layer necrosis, and perforated AA was defined as necrosis and perforation in all layers (20). From a surgeon's perspective, perforated AA was defined as a visual hole in the appendix, gross contamination in the abdomen during appendectomy, or the presence of an extraluminal appendicolith in the abdominal cavity.

The patients were categorized into five groups according to age: infancy (> 28 days - <1 year), toddlerhood (1–2 years), early childhood (3–5 years), middle childhood (6–11 years), and early adolescence (12–18 years) as per the *Eunice Kennedy Shriver*

National Institute of Child Health and Human Development in the United States (21). These subgroups were further subdivided into those with hyponatremia and eunatremia in the immediate preoperative setting. Hyponatremia was defined as a sodium level < 135 mmol/L and further classified into three categories by its severity: mild hyponatremia (130–134 mmol/L), moderate hyponatremia (125–129 mmol/L), and severe hyponatremia (< 125 mmol/L) (22). Eunatremia was defined as a sodium level between 135–145 mmol/L (22).

A C-reactive protein (CRP) level > 10 mg/dL was considered high (23). A total white blood cell count (WBC) was considered elevated according to the age groups and cutoff values defined by the Pediatric complete blood count (CBC) Reference Values (LTR10211) (24). Neutrophilia was defined as a percentage of neutrophils $> 70\%$ (13).

The length of postoperative hospital stay was counted as days from surgery until discharge.

All medical records were de-identified and anonymized for the current study. All modifications and analyses were performed via programming, a new database was created, and no changes were made to the original database. Ethical approval for this study was obtained by the local institutional review board (Ethical Committee of the Clinical Center, University of Sarajevo, number: 51-30-5-13298/23). The requirement for informed consent was waived due to the retrospective nature of the study.

Statistical analysis

The normality of data distribution and presence of outliers were evaluated visually by analyzing histograms, Q-Q, and box-plot graphs and numerically by calculating z-values for skewness and kurtosis and application of the Kolmogorov-Smirnov Test. For comparison of parameters between uncomplicated and complicated AA groups, an independent samples Student t-test with Welch-Satterthwaite solution (applied due to differences in sample size between groups) was used for the analysis of age at operation, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red blood cell distribution width (RDW), WBC and chloride since those variables had a normal distribution with no outliers. Mann-Whitney U test was used for the analysis of weight, height, hemoglobin, neutrophils, thrombocytes, mean platelet volume (MPV), potassium, and calcium since those variables had a normal distribution. Still, outliers were present, and distributions had similar shapes between the groups. Data with non-normal distribution were analyzed by Mann-Whitney U test [erythrocytes, CRP, mean corpuscular hemoglobin concentration (MCHC), lymphocytes, neutrophils lymphocytes ratio (NLR), sodium, and total bilirubin]. The chi-square test for homogeneity was used to analyze differences in proportions of sex, mild hyponatremia, elevated CRP, WBC, neutrophils, and decreased lymphocytes.

Binomial logistic regression was used to create a model for predicting patients' classification into complicated or noncomplicated AA. The missing data structure was analyzed by using the naniar package in R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) version 4.3.2 (25). Neutrophils, lymphocyte levels, and concentrations of calcium, chloride, and total bilirubin were not included in the model due to the large proportion of missing data for those variables. Age, sex, CRP, WBC, and sodium levels were included in the model. The linearity of continuous variables concerning dependent variable logit transformation was evaluated by the Box-Tidwell procedure (26). Multicollinearity was tested by linear regression. The odds ratio (OR) and 95% confidence interval (CI) were used for the presentation of outcome predictors. The Receiver Operating Characteristic (ROC) curve was prepared and analyzed.

All tests were two-tailed, with a p-value < 0.05 considered statistically significant. SPSS (Statistical Package for Social Sciences) program version 23.0 and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) version 4.3.2 were used for the analysis.

Results

The demographic and laboratory findings of the entire cohort are shown in Table 1. Of the 235 pediatric cases with confirmed AA, 155/235 (66%) had uncomplicated AA, and 80/235 (34%) presented with complicated AA.

Table 1
The demographic and laboratory data of patients included in the study.

Parameter	All patients (n = 235)	Uncomplicated AA (n = 155)	Complicated AA (n = 80)	p-values
Age (years)*	11 ± 4	12 ± 4	11 ± 4	0.135
Infancy (> 28 days - <1 year) n (%)†	0 (0)	0 (0)	0 (0)	0.013
Toddlerhood (1–2 years) n (%)†	1 (0.5)	1 (0.6)	0 (0)	
Early childhood (3–5 years) n (%)†	20 (8.5)	7 (4.5)	13 (16.3)	
Middle childhood (6–11 years) n (%)†	111 (47.2)	77 (49.7)	34 (42.5)	
Early adolescence (12–18 years) n (%)†	103 (43.8)	70 (45.2)	33 (41.3)	
Sex Male n (%)†	157 (67)	106 (68)	51 (64)	0.474
Weight (kg)*	46 ± 19	46 ± 18	45 ± 21	0.321
Height (cm)*	154 ± 21	155 ± 21	152 ± 22	0.189
CRP (mg/L)‡	39 (16–66)	31 (12–51)	63 (38–137)	< 0.001
CRP High n (%)†	192 (82)	118 (76)	74 (93)	0.002
Erythrocytes (x10 ⁹ /L)‡	4.8 (4.6–5.1)	4.8 (4.6–5.1)	4.8 (4.6–5.1)	0.372
Hemoglobin (g/L)*	136 ± 13	136 ± 13	136 ± 14	0.596
Hematocrit (%)*	0.39 ± 0.04	0.39 ± 0.04	0.39 ± 0.04	0.610
MCV (fL)*	80 ± 7	81 ± 5	79 ± 9	0.074
MCH (pg)*	28 ± 2	28 ± 2	28 ± 2	0.613
MCHC (g/L)‡	346 (332–361)	346 (331–361)	346 (332–363)	0.510
RDW (%)*	13 ± 1	13 ± 1	13 ± 2	0.582
WBC (x10 ⁹ /L)*	15.2 ± 5.3	14.6 ± 5.0	16.5 ± 5.6	0.012
WBC High n (%)†	138 (59)	86 (55)	52 (65)	0.128
Neutrophils (%)*	79 ± 13	76 ± 15	83 ± 8	0.001
Neutrophils High n (%)†	125 (53)	75 (48)	50 (63)	0.001
Lymphocytes (%)‡	10 (6–16)	11 (7–18)	8 (5–12)	0.002
Lymphocytes Low n (%)†	104 (44)	59 (38)	45 (56)	< 0.001
Data are presented as *mean ± standard deviation for normally distributed data, †absolute numbers (percentage of the total number in the column), or ‡median (interquartile range) for data that did not follow a normal distribution.				
Abbreviations: MCH – Mean corpuscular hemoglobin; MCHC – Mean corpuscular hemoglobin concentration; MCV – Mean corpuscular volume; MPV – Mean platelet volume; NLR – Neutrophils Lymphocytes Ratio; RDW – Red blood cell distribution width; WBC – White blood cells.				
Only significant p-values are bolded.				

Parameter	All patients (n = 235)	Uncomplicated AA (n = 155)	Complicated AA (n = 80)	p-values
NLR‡	8 (4–13)	6 (4–11)	10 (6–14)	0.178
Thrombocytes (x10 ⁹ /L)*	284 ± 78	279 ± 65	295 ± 97	0.488
MPV (fL)*	7.2 ± 1.1	7.2 ± 0.9	7.3 ± 1.5	0.964
Potassium (mmol/L)*	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.4	0.656
Sodium (mmol/L)‡	137 (135–139)	138 (136–139)	135 (134–138)	< 0.001
Mild hyponatremia n (%)†	46 (20)	11 (7)	35 (44)	< 0.001
Calcium (mmol/L)*	2.5 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	0.241
Chloride (mmol/L)*	101 ± 3	101 ± 3	100 ± 3	< 0.001
Bilirubin total (µmol/L)‡	14.3 (10.5–19.0)	13.1 (8.8–17.5)	16.2 (14.2–34.8)	0.055
Data are presented as *mean ± standard deviation for normally distributed data, †absolute numbers (percentage of the total number in the column), or ‡median (interquartile range) for data that did not follow a normal distribution.				
Abbreviations: MCH – Mean corpuscular hemoglobin; MCHC – Mean corpuscular hemoglobin concentration; MCV – Mean corpuscular volume; MPV – Mean platelet volume; NLR – Neutrophils Lymphocytes Ratio; RDW – Red blood cell distribution width; WBC – White blood cells.				
Only significant p-values are bolded.				

Sodium and chloride levels were significantly lower in complicated than uncomplicated AA (U = 3158.5, p < 0.001; 95% CI, 0.968, 3.005 p < 0.001). A significantly higher proportion of patients with mild hyponatremia was found in complicated compared with uncomplicated AA (p < 0.001) (Table 1, Fig. 1). There were no patients with moderate or severe hyponatremia.

Total bilirubin median concentration was 13.1 µmol/L [interquartile range (IQR) 8.8–17.5] in uncomplicated and 16.2 µmol/L (IQR 14.2–34.8) in complicated AA (U = 286.0, p = 0.055).

A significantly higher proportion of patients with elevated CRP was found in complicated compared with uncomplicated AA (93% vs. 76%, p = 0.002). We also found unsimilar distributions of CRP levels between the groups (U = 8933.5, p < 0.001) (Table 1).

Although the higher WBC level was found in the complicated (mean 16.5 ± SD 5.6 x10⁹/L) than in uncomplicated AA groups (mean 14.6 ± SD 5.0 x10⁹/L) (p = 0.012, 95% CI, -3.4, -0.4), there were similar proportions of patients with elevated WBC in both groups (p = 0.128) (Table 1). Neutrophils were significantly higher in the complicated AA (mean 83% ± SD 8%) than in uncomplicated AA (mean 76% ± SD 15%) (U = 3737.5, p = 0.001), with a higher proportion of patients with elevated neutrophils in the complicated AA group (p = 0.001). Significantly lower lymphocyte values were found in the complicated AA compared with the uncomplicated AA (median 8% vs. 11%, IQR 5–12%, and 7–18%, respectively) (U = 2010.5, p = 0.002) with a significantly higher proportion of lymphocytes below reference range in complicated AA (p < 0.001). However, no significant difference was observed in NLR between the groups (Table 1).

We performed binomial logistic regression to explore predictors of patients' classification into complicated or noncomplicated AA. The model included age, sex, CRP, WBC, and sodium. All continuous variables had a linear relation to the dependent variable logit. Eight standardized residuals with a value greater than 2.5 SD were included in the analysis. The model was statistically significant $\chi^2(4) = 78.29$, p < 0.001. The model explained 40.3% (Nagelkerke R²) of the variance in classification into complicated or noncomplicated AA and correctly classified 80.3% of cases. Of the five predictors, CRP, WBC, and sodium were statistically significant (Table 2). The area under the ROC curve was 0.825 (95% CI 0.764, 0.886), corresponding to excellent discrimination (27). Increased CRP, WBC, and decreased sodium levels were predictors of complicated AA in our study.

Table 2
 Logistic regression predicting the likelihood of complicated AA based on age, sex, white blood cells (WBC), C-reactive protein (CRP), and sodium.

Parameter	B	S.E.	Wald	df	Sig	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Sex	.135	.364	.137	1	0.712	1.144	.561	2.335
Age	.025	.047	.291	1	0.590	1.026	.935	1.125
CRP	.017	.003	23.329	1	0.000	1.017	1.010	1.024
WBC	.083	.036	5.267	1	0.022	1.087	1.012	1.167
Sodium	-.331	.071	21.466	1	0.000	.718	.625	.826
Constant	41.794	9.589	18.998	1	0.000	4.415E + 18		

S.E. – Standard error; CI – Confidence interval; CRP – C-reactive protein; WBC – White blood cells

Discussion

Interpretation of findings

In the current study, we explored the predictive utility of routine laboratory tests to discriminate between complicated and non-complicated AA in pediatric emergency settings. We found an association between preoperative hyponatremia and complicated AA. This finding could help emergency physicians, pediatricians, and pediatric surgeons resolve their diagnostic dilemmas in case of suspected complicated AA more quickly. The significance of this association lies in the fact that serum sodium level is routinely tested in all children presenting to the ED with suspected AA. The ability to predict complicated AA already at the initial evaluation of a pediatric patient in the ED could substantially reduce associated morbidity and the costs of additional diagnostic tests.

Comparison with previous studies

Several authors studied predictors of complicated AA, including CRP, leukocytosis, the length of symptoms, and fever, to assess the need for surgery (20, 28–30). However, the results of these studies were controversial and difficult to apply in clinical practice. The first study that reported hyponatremia as an independent predictor of complicated AA in children (n = 392) was published in 2016 when Pham et al. found hyponatremia in 63% of children with complicated AA and only 33% of those with uncomplicated AA (31). This finding has been confirmed by several recent studies (11–14, 32). However, several studies reporting no statistically significant association between hyponatremia and complicated AA in the pediatric population have also been published (18, 33). Such contradictory findings are probably due to inconsistencies in the definition of complicated AA, making the comparisons between the results difficult. The present study used the classification of complicated/uncomplicated AA based on the AAST grading system (19). Furthermore, the design of the previous studies varied (some were retrospective (11, 18, 33)) and others retrospective (13, 32). The definition of hyponatremia was also inconsistent, which could further affect the interpretation of the analyzed data.

Serum sodium level affects the cellular volume and determines tonicity, thus regulating fluid distribution among different body compartments (34). Hyponatremia is the most common electrolyte abnormality encountered in hospitalized patients, either as a complication of an underlying acute illness or as a consequence of therapeutic interventions (35). In the pediatric population, hyponatremia is associated with overall poor outcomes (36) in the case of central nervous system disorders, gastrointestinal disorders, and sepsis (37). Although the exact mechanism responsible for developing hyponatremia in severe infectious processes, including complicated AA, is not completely clear, the immuno-neuroendocrine pathway is believed to be behind it (38). Swart et al. pointed out the important role of interleukin 6, whose value increases during inflammation and mediates the cascade of non-osmotic secretion of vasopressin (antidiuretic hormone) with resulting hyponatremia (38).

Although appendectomy remains the standard of care in the treatment of AA at our institution, the results of the present study related to different sodium levels in uncomplicated and complicated AA could contribute to our additional rate of adoption of nonoperative management (NOM) by early prediction of patients with uncomplicated AA who would potentially benefit from this treatment modality. On the other hand, early prediction of complicated AA would enable more prompt treatment and reduce the morbidity rate, stay in the hospital, and reduce the exposure to unnecessary preoperative diagnostic procedures. The usefulness of hyponatremia as a promising marker for predicting the severity of AA is strengthened if changes in the values of other preoperative laboratory tests, especially inflammatory parameters, are observed. Ribeiro et al. in a retrospective cohort study of 841 adult patients who underwent emergency appendectomy emphasized the importance of basic laboratory parameters such as complete blood count (CBC) parameters and CRP and found that CRP proved to be a good independent predictor of complicated AA (39). Although in adult patients these basic laboratory parameters can be affected by various diseases (chronic, inflammatory, neoplastic, hematologic, and allergic) and drugs and therefore, be less reliable indicators of complicated AA (40). We believe that the use of basic preoperative biochemical laboratory parameters in determining complicated or uncomplicated AA in children can have an increased diagnostic value in achieving this goal, which was observed in our study.

Strengths and limitations

This study has some limitations. First, this study was retrospective, lacking the validation of prospective studies. Second, this study was a single-center study, and hence, further research would be needed to conduct with a large sample for the stronger association of hypothermia with complicated AA in children. Finally, there was a lack of certain laboratory tests for some patients, which could have led to a potential misinterpretation of the analyzed data.

Conclusions

In conclusion, our study supports the previous observations that preoperative hyponatremia along with elevated CRP and WBC levels could reliably predict complicated AA in pediatric patients. Further prospective and large-scale studies should confirm these observations.

Abbreviations

AA – Acute appendicitis

AAST – American Association for the Surgery of Trauma

CBC – Complete blood count

CI – Confidence interval

CRP – C-reactive protein

ED – Emergency department

IQR – Interquartile range

MCH – Mean corpuscular hemoglobin

MCHC – Mean corpuscular hemoglobin concentration

MCV – Mean corpuscular volume

MPV – Mean platelet volume

NOM – Nonoperative management

OR – Odds ratio

RCR – Retrospective chart review

RDW – Red blood cell distribution width

ROC – Receiver Operating Characteristic

WBC – White blood cells

Declarations

Acknowledgment

Qatar National Library (QNL) covered the article-processing fee of the manuscript.

Funding

None.

Conflict of Interest

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

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol.* 1990;132(5):910-25.
2. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg.* 2020;15(1):27.
3. Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. *Ann Surg.* 2007;245(6):886-92.
4. Gudjonsdottir J, Marklund E, Hagander L, Salo M. Clinical Prediction Scores for Pediatric Appendicitis. *Eur J Pediatr Surg.* 2021;31(3):252-60.
5. Gudjonsdottir J, Andersson RE. Validation of Clinical Prediction Scores for Pediatric Appendicitis: Update with New Cutoff Values for the AIR Score. *Eur J Pediatr Surg.* 2023;33(2):176-7.
6. Podda M, Pisanu A, Sartelli M, Coccolini F, Damaskos D, Augustin G, et al. Diagnosis of acute appendicitis based on clinical scores: is it a myth or reality? *Acta Biomed.* 2021;92(4):e2021231.
7. Zvizdic Z, Golos AD, Milisic E, Jonuzi A, Zvizdic D, Glamoclija U, et al. The predictors of perforated appendicitis in the pediatric emergency department: A retrospective observational cohort study. *Am J Emerg Med.* 2021;49:249-52.
8. Haider Kazmi SJ, Tabassum S, Asghar MS, Siddiqui MA, Avinash, Yasmin F, et al. Role of inflammatory and hematological markers in predicting the complicated and perforated acute appendicitis in pediatric population: A cohort study. *Ann Med Surg (Lond).* 2022;76:103524.
9. de Almeida Leite RM, de Souza AV, Bay CP, Cauley C, Bordeianou L, Goldstone R, et al. Delayed Operative Management in Complicated Acute Appendicitis-Is Avoiding Extended Resection Worth the Wait ? Results from a Global Cohort Study. *J Gastrointest Surg.* 2022;26(7):1482-9.
10. Poston LM, Leavitt T, Pope S, Hill H, Tollinche LE, Kaelber DC, et al. Pre-appendectomy hyponatremia is associated with increased rates of complicated appendicitis. *Surg Open Sci.* 2023;13:88-93.

11. Walsh A, Lala S, Wells C, Upadhyay V. Hyponatremia an indicator of complicated appendicitis in children: Starship experience. *ANZ J Surg.* 2022;92(4):747-52.
12. Anand S, Krishnan N, Birley JR, Tintor G, Bajpai M, Pogorelic Z. Hyponatremia-A New Diagnostic Marker for Complicated Acute Appendicitis in Children: A Systematic Review and Meta-Analysis. *Children (Basel).* 2022;9(7).
13. Pogorelic Z, Luksic B, Nincevic S, Luksic B, Polasek O. Hyponatremia as a predictor of perforated acute appendicitis in pediatric population: A prospective study. *J Pediatr Surg.* 2021;56(10):1816-21.
14. Giannis D, Matenoglou E, Moris D. Hyponatremia as a marker of complicated appendicitis: A systematic review. *Surgeon.* 2020;18(5):295-304.
15. Kim DY, Nassiri N, de Virgilio C, Ferebee MP, Kaji AH, Hamilton CE, et al. Association Between Hyponatremia and Complicated Appendicitis. *JAMA Surg.* 2015;150(9):911-2.
16. Wu HC, Yan MT, Lu KC, Chu P, Lin SH, Yu JC, et al. Clinical manifestations of acute appendicitis in hemodialysis patients. *Surg Today.* 2013;43(9):977-83.
17. Kaser SA, Furler R, Evequoz DC, Maurer CA. Hyponatremia is a specific marker of perforation in sigmoid diverticulitis or appendicitis in patients older than 50 years. *Gastroenterol Res Pract.* 2013;2013:462891.
18. Besli GE, Cetin M, Ulukaya Durakbasa C, Ozkanli S. Predictive Value of Serum Sodium Level in Determining Complicated Appendicitis Risk in Children. *Haydarpasa Numune Med J.* 2019;59(1):35-40.
19. Tominaga GT, Staudenmayer KL, Shafi S, Schuster KM, Savage SA, Ross S, et al. The American Association for the Surgery of Trauma grading scale for 16 emergency general surgery conditions: Disease-specific criteria characterizing anatomic severity grading. *J Trauma Acute Care Surg.* 2016;81(3):593-602.
20. Imaoka Y, Itamoto T, Takakura Y, Suzuki T, Ikeda S, Urushihara T. Validity of predictive factors of acute complicated appendicitis. *World J Emerg Surg.* 2016;11:48.
21. NICHD. Pediatric Terminology 2023 [Available from: <http://bioportal.bioontology.org/ontologies/45989?p=terms>.
22. Spasovski G, Vanholder R, Alolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med.* 2014;40(3):320-31.
23. Schlenz H, Intemann T, Wolters M, Gonzalez-Gil EM, Nappo A, Fraterman A, et al. C-reactive protein reference percentiles among pre-adolescent children in Europe based on the IDEFICS study population. *Int J Obes (Lond).* 2014;38 Suppl 2:S26-31.
24. Pediatric CBC Reference Values (LTR10211) [Available from: <https://www.dynalife.ca/portals/0/pdf/Lab%20procedure%20or%20protocol/Pediatric%20CBC%20reference%20values.pdf>.
25. Tierney N, Cook D. Expanding Tidy Data Principles to Facilitate Missing Data Exploration, Visualization and Assessment of Imputations. *Journal of Statistical Software.* 2023;105(7):1 - 31.
26. Box GEP, Tidwell PW. Transformation of the Independent Variables. *Technometrics.* 1962;4(4):531-50.
27. Hosmer DW Jr LS, Sturdivant RX. Applied logistic regression. 3rd ed. New York: Wiley; 2013.
28. Dayawansa NH, Segan JDS, Yao HHI, Chong HI, Sitzler PJ. Incidence of normal white cell count and C-reactive protein in adults with acute appendicitis. *ANZ J Surg.* 2018;88(6):E539-E43.
29. Beltran MA, Almonacid J, Vicencio A, Gutierrez J, Cruces KS, Cumsille MA. Predictive value of white blood cell count and C-reactive protein in children with appendicitis. *J Pediatr Surg.* 2007;42(7):1208-14.
30. Hansson LE, Laurell H, Gunnarsson U. Impact of time in the development of acute appendicitis. *Dig Surg.* 2008;25(5):394-9.
31. Pham XD, Sullins VF, Kim DY, Range B, Kaji AH, de Virgilio CM, et al. Factors predictive of complicated appendicitis in children. *J Surg Res.* 2016;206(1):62-6.
32. Lindestam U, Almstrom M, Jacks J, Malmquist P, Lonnqvist PA, Jensen BL, et al. Low Plasma Sodium Concentration Predicts Perforated Acute Appendicitis in Children: A Prospective Diagnostic Accuracy Study. *Eur J Pediatr Surg.* 2020;30(4):350-6.
33. Duman L, Karaibrahimoglu A, Buyukyavuz BI, Savas MC. Diagnostic Value of Monocyte-to-Lymphocyte Ratio Against Other Biomarkers in Children With Appendicitis. *Pediatr Emerg Care.* 2022;38(2):e739-e42.

34. Pintaldi S, Zago A, Pizzolon C, Magni E, Cozzi G, Andrade S, et al. Children with mild hyponatremia at the emergency department are at higher risk of hospitalization. *BMC Pediatr.* 2023;23(1):318.
35. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med.* 2006;119(7 Suppl 1):S30-5.
36. Elliman MG, Vongxay O, Soumphonphakdy B, Gray A. Hyponatraemia in a Lao paediatric intensive care unit: Prevalence, associations and intravenous fluid use. *J Paediatr Child Health.* 2019;55(6):695-700.
37. Al-Sofyani KA. Prevalence and Clinical Significance of Hyponatremia in Pediatric Intensive Care. *J Pediatr Intensive Care.* 2019;8(3):130-7.
38. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. *Nephron Physiol.* 2011;118(2):45-51.
39. Ribeiro AM, Romero I, Pereira CC, Soares F, Goncalves A, Costa S, et al. Inflammatory parameters as predictive factors for complicated appendicitis: A retrospective cohort study. *Ann Med Surg (Lond).* 2022;74:103266.
40. Peksoz R, Bayar B. The role of complete blood count parameters in diagnosing acute appendicitis and measuring the severity of inflammation. *Ulus Travma Acil Cerrahi Derg.* 2021;27(6):654-61.

Figures



Figure 1

Percentage and number of patients with uncomplicated and complicated acute appendicitis having eunatremia or mild hyponatremia.