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The Pattern of Nutritional and Inflammatory Parameters in Children with Acute Appendicitis

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Abstract

Background Surgical procedures in children with overweight and obesity have many difficulties due to the high incidence of postoperative complications. This impact on comorbidity has a great interest in various surgical pathologies, such as acute appendicitis, since it is the most frequent surgical emergency in all age and sex groups. However, there are few studies assessing the effect of body mass index (BMI) and other parameters like the Glasgow Prognostic Score (GPS) and C-reactive protein (CRP)/albumin ratio on the course of acute appendicitis in children.

Objectives Identify the impact of BMI and other biomarkers like CRP/albumin ratio and GPS on the clinical course of acute appendicitis in children.

Patients (Materials) and Methods This is a prospective study conducted on 90 pediatric patients of acute appendicitis (30 high BMI and 60 non-high BMI) admitted at Pediatric Surgery Department, Children Hospital Cairo University (CHCU) during the period from March 2022 to September 2022. All patients had preoperative laboratory tests, intraoperative assessment regarding the type of surgery, duration of surgery, and type of appendicitis, then the postoperative assessment.

Results Among the 90 patients, the mean age of participants was 8.74 (2.23) years and there was a male predominance. Frequencies of open surgeries were higher in overweight and obese children (children with high BMI). There was a significant positive correlation between the preoperative CRP/albumin ratio and GPS, and an inverse significant correlation of preoperative albumin with the postoperative hospital length of stay, duration of surgery (operation time), and duration of postoperative fever.

Conclusion There is a significant relationship between the preoperative inflammatory and nutritional markers and postoperative hospital length of stay, duration of surgery (operation time), and duration of postoperative fever.

Keywords
- pediatric
- appendicitis
- BMI
- hospital
- inflammatory
- markers

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Introduction

It is well known that being overweight and obese are major risk factors for poor surgical outcomes in the pediatric surgical field.[1,2]

Many studies have established a higher incidence of postoperative complications in obese patients, such as surgical wound infections and dehiscence,[3] as well as the increased postoperative length of hospital stay.[4] This effect on comorbidity has been investigated in different surgical pathologies, such as acute appendicitis, since it is the most frequent surgical emergency in all sex and age groups.[5]

However, the literature on overweight and obesity outcomes in pediatric abdominal surgery is rare compared with that of adult patients. Few reports have assessed the associations between body mass index (BMI) and postoperative complications in pediatric patients, sometimes with few conclusive results.[6] In addition, most studies are retrospective, with no prospective studies found in the literature reviewed up until now, which makes it difficult to generalize the results achieved. Furthermore, complication rates in children are low, so more extensive research is needed to note any potential difference.[7] Aslan et al[8] reported that complications were observed in 52.4% of appendicitis patients with high BMI compared with 21.6% in patients with normal BMI.

Of note, there are diagnostic and prognostic biomarkers that have been discussed in previous literature of reviews. Hyponatremia may have the potential to be applied as a biochemical nutritional marker in the diagnosis of pediatric complicated appendicitis.[9] To evaluate the landscape of inflammatory protein mediators, a precision medicine multiplex method identifies unique patterns of possible biomarkers that may be utilized to create a disease fingerprint in pediatric acute appendicitis.[10] In addition, it was found that there were significantly higher levels of capillary ketonemia in children with acute appendicitis and significantly higher levels were detected in children with complicated than in those with uncomplicated pediatric acute appendicitis.[11] Furthermore, another biomarker, Pentraxin-3, was found to be elevated in acute appendicitis. It is considered an acute-phase protein.[12] Besides, blood levels of neutrophil gelatinase-associated lipocalin (NGAL) were also studied. According to previous data, appendicitis patients' NGAL levels significantly differed between baseline and postoperative measures ($p = 0.05$). According to the receiver operating characteristic curve findings, NGAL is a promising new biomarker for differentiating acute appendicitis from abdominal discomfort.[13]

Because currently existing biomarkers may not be available and their delayed response limits emergency physicians' and pediatric surgeons' capacity to provide prompt and possibly successful treatments,[14] there is an urgent need for early, available, and accurate predictive biomarkers of appendicitis. Therefore, we studied other nutritional and inflammatory-based prognostic scores.

Nutritional and inflammatory-based prognostic scores, involving the Glasgow Prognostic Score (GPS; based on serum C-reactive protein [CRP] and albumin levels), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI; based on albumin and lymphocyte counts), have been documented as potential and significant prognostic biomarkers for several types of cancer.[7] However, no studies have investigated the relationship between them and the course of acute appendicitis in children. Therefore, our study was performed to outline this relation. The objective of this study is to investigate the impact of being overweight or obese on the clinical and laboratory profile of acute appendicitis in children. In addition, studying these biomarkers in the course of acute appendicitis was another objective.

Materials and Methods

This was a prospective study that was conducted on 90 pediatric patients with acute appendicitis: 30 with high BMI and 60 with non-high BMI, admitted at the Pediatric Surgery Department at Children's Hospital Cairo University from March 2022 to September 2022. *Inclusion criteria*: (1) children with acute appendicitis with different BMI, (2) age group from 5 to 12 years, (3) patients with acute appendicitis admitted for surgical intervention, and (4) open or laparoscopic appendectomy. *Exclusion criteria*: (1) children whose parents or caregivers did not agree to be enrolled in the study, (2) children with associated comorbidities other than obesity such as hypertension, diabetes mellitus, and sleep apnea, (3) children with previous abdominal exploration, and (4) children who were receiving immunosuppressants and steroids.

Data Collection

1. Preoperative assessment, including preoperative anthropometric assessment such as BMI, biochemical assessment including complete blood count (CBC), coagulation profile, albumin, and CRP, as well as measurement of NLR, PLR, PNI, and GPS, was performed. The assessment also included preoperative clinical assessment including presence of symptoms and signs such as fever. In general, the clinical presentations of appendicitis in the enrolled children included acute abdominal pain and tenderness in the right lower quadrant at McBurney's point (which is located at two-thirds the distance from the child's umbilicus to the right anterior superior iliac spine). Tenderness on this site is the most valuable clinical finding.[15]
2. Intraoperative surgical assessment included complicated (perforated with localized pus or peritonitis, appendicular abscess, appendicular mass) or not complicated, laparoscopic or open appendectomy, and the operation time (duration of surgery).
3. Postoperative assessment included postoperative biochemical assessment such as CBC, coagulation profile, albumin, and CRP, as well as measurement of NLR and PLR. The assessment also included the postoperative duration of hospital stay, duration of postoperative fever, surgical site infection, and postoperative complications such as adhesive intestinal obstruction.

Operational Definitions

1. BMI = weight (kg)/height^2 (m).
2. Overweight: When BMI is more than 85th centile for age or BMI *z*-score is more than 1 standard deviation (SD) of the World Health Organization (WHO) Child Standards for BMI (5–19 years).
3. Obesity: When BMI is more than 97th centile for age or BMI *z*-score is more than 2 SD of the WHO Child Standards for BMI (5–19 years).[16,17]
4. NLR was obtained and calculated as the absolute neutrophil count divided by the absolute lymphocyte count. A higher NLR might indicate a severe inflammatory progression in the patient. It is considered a prognostic biomarker.[18]
5. PNI was calculated as PNI = (10 × serum albumin [g/dL]) + (0.005 × lymphocytes/μL). A low PNI is an independent indicator of a worse prognosis.[19]
6. PLR: Higher ratios indicate severe inflammation with a possible hypercoagulable state; it is a prognostic biomarker.[20]
7. GPS was calculated based on CRP and albumin. Children with elevated CRP (> 0.3 mg/dL) and hypoalbuminemia (< 3.5 mg/dL) were assigned a score of 2. Children with either one of these two biochemical outliers were assigned a score of 1. Children with neither of these biochemical outliers were assigned a score of 0.[21]
8. Diagnosis of acute appendicitis was done according to Alvarado's score which depends on the clinical and laboratory data. In some cases, ultrasound was added to suspicious scores. Diagnosis in all cases was confirmed by operative findings and postoperative histopathological examination of removed appendix.[22]

Sample Size Estimation

The primary objective of the study was to assess the effect of obesity and overweight on the course of appendicitis in pediatrics. We would expect complications in the enrolled children with appendicitis to be nearly 50% in those with high BMI in comparison to children without where complicated appendicitis is expected to represent 20% of the enrolled children as previously reported.[8] G power software (version 3.1.9.2) was used to calculate the required sample size. Alpha was set as 0.05, power as 80%, and the allocation ratio of exposed patients to unexposed controls as 2:1. The total required sample size for the study was 90 patients (30 children with high BMI and 60 children without).

Sampling Technique

The patients were enrolled through consecutive sampling method, where every patient attending Pediatric Surgery Department, Children Hospital Cairo University (CHCU) and meeting the eligibility criteria was included in the study till reaching the required sample size

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics Version 25. Numerical data were presented as mean ± SD, median and interquartile range and frequencies (number of cases), and percentages in categorical data. Data were explored for normality by checking the data distribution using Kolmogorov–Smirnov and Shapiro–Wilk tests. Mann–Whitney test was used as almost all the data were nonparametric, and categorical data were analyzed using the Fisher's exact test. Correlation between numerical variables was done by Spearman's correlation. The significance level was set at $p \leq 0.05$.[23] Prediction of dependent variables was performed using the logistic regression analysis.

Ethical Approval

Approval from the local ethics committee of Pediatric Surgery Department, Children Hospital Cairo University (CHCU) was obtained. The ethical approval number of the Ethical Committee of Faculty of Medicine, Cairo University is MS-542–2021.

Consent to Participate and Consent to Publish

Written consents for participation and publication were obtained from the parents or caregivers.

Results

The present study was conducted on 90 pediatric patients with appendicitis (60 with nonhigh BMI and 30 with high BMI). These patients were enrolled in the pediatric surgery department at Pediatric Surgery Department, Children Hospital Cairo University (CHCU). There was a male predominance ($n = 48$; 53.3%), while females represented 46.7% of the study participants ($n = 42$). The mean age of participants was 8.74 ± 2.23 (minimum–maximum: 5–13). Notably, most of them were having complicated appendicitis at presentation (complicated appendicitis represented 58.8% of the study participants [$n = 53$] while noncomplicated appendicitis represented 41.2% [$n = 37$]).

It is known that being overweight and obese could have undesirable surgical circumstances. This is notable in our current study where open surgeries were required for them significantly (►**Table 1**).

Table 1 Comparison between children with high BMI and those without regard to the type of surgery needed

Type of surgery		High BMI		*p*-Value
		No	Yes	
Lap	*N*	57	23	0.014[a]
	%	95.0	76.7	
Open surgery	*N*	3	7	
	%	5.0	23.3	

Abbreviation: BMI, body mass index.
Note: Fisher's exact test.
[a]*p*-Value is considered significant if ≤ 0.05.

Table 2 Comparison between children with high BMI and those with no high BMI regards the preoperative markers

Preoperative data	High BMI	Non-high BMI	*p*-Value
CRP, median (IQR)	143 (119)	126.5 (73)	0.19
CRP/albumin ratio, median (IQR)	44.1 (40.8)	37.2 (24.2)	0.22
NLR, median (IQR)	2.82 (5.32)	3.5 (4.7)	0.44
PNI, median (IQR)	48.3 (14.8)	48 (20.6)	0.99
Platelets/lymphocytes ratio, median (IQR)	136 (107.4)	149.5 (147.2)	0.41
TLC, median (IQR)	15.53 (8.12)	16.35 (7.99)	0.990

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; TLC, total lymphocyte count.
Note: Mann–Whitney *U* test.

A comparison between groups of BMI (children with high BMI and those with nonhigh BM) and the preoperative nutritional and inflammatory markers was studied. No significant elevations in these markers were found in children with higher BMI at the time of presentation (►**Table 2**).

Preoperative laboratory results were investigated and their correlation with each other was studied. CRP and albumin showed a significant inverse correlation. Also, albumin showed a significant inverse correlation with total lymphocyte count (TLC). Besides, preoperative markers were correlated with the postoperative hospital length of stay (LOS), duration of surgery, and duration of postoperative fever and revealed a significant correlation with CRP/albumin ratio, CRP, albumin (an inverse correlation), TLC, and GPS (►**Table 3**).

Hospital LOS was further subdivided into short and long durations. Prolonged LOS in this study was defined as greater than the median LOS which was 5.5 days, so a duration of more than 5.5 days was set as a prolonged length of hospital stay (PLOS). The same was done to detect a longer duration of surgery (operation time) which was defined as greater than the median which was 2.5 hours. Logistic regression analyses were conducted for the prediction of PLOS, longer duration of surgery, and development of postoperative fever using the preoperative markers as possible predictors (►**Table 4**).

Table 3 Correlations between the preoperative markers with each other (albumin, CRP, and TLC) and the postoperative hospital stay, duration of surgery, and duration of postoperative fever

Preoperative data	Postoperative hospital length of stay		Duration of surgery (operation time)		Duration of postoperative fever	
	rs	*p*	rs	*p*	rs	*p*
CRP/albumin ratio	0.56	0.000[a]	0.57	0.000[a]	0.56	0.000[a]
Albumin	−0.4	0.000[a]	−0.41	0.000[a]	−0.31	0.003[a]
CRP	0.56	0.000[a]	0.55	0.000[a]	0.57	0.000[a]
PNI	−0.08	0.446	0.00	0.990	−0.00	0.94
GPS	0.31	0.003[a]	0.42	0.000[a]	0.35	0.001[a]
PLR	−0.11	0.28	0.02	0.792	0.01	0.87
NLR	0.11	0.28	0.06	0.537	0.06	0.55
TLC	0.25	0.01[a]	0.31	0.003[a]	0.31	0.003[a]
High BMI	0.09	0.36	0.09	0.36	0.15	0.14
Extended correlation between albumin, TLC, and CRP						
Albumin	CRP				TLC	
	rs		*p*-value		rs	*p*-value
	−0.45		< 0.001[a]		−0.29	0.004[a]

Abbreviations: BMI, body mass index; CRP, C-reactive protein; GPS, Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; TLC, total lymphocyte count.
Note: rs—Spearman's correlation coefficient.
[a]*p*-Value is considered significant if ≤ 0.05.

Table 4 Logistic regression analysis for prediction of prolonged length of hospital stay (PLOS), longer duration of surgery, and development of postoperative fever

Prolonged length of hospital stay (PLOS)						
Studied predictors	***B***	**Wald**	***p*-Value**	**Odds ratio**	**95% CI for the odds ratio**	
					Lower	**Upper**
Constant	−2.72	0.34	0.56	0.06		
Age	−0.23	3.48	0.06	0.79	0.61	1.01
Sex	0.66	1.39	0.23	1.94	0.64	5.83
Prognostic nutritional index (PNI)	−0.035	1.53	0.21	0.96	0.91	1.02
Glasgow Prognostic Score (GPS)	−0.017	0.00	0.98	0.98	0.15	6.34
Albumin	0.16	0.01	0.90	1.17	0.07	18.50
TLC	0.06	1.23	0.26	1.06	0.95	1.19
Neutrophils/lymphocytes ratio	−0.01	0.04	0.83	0.98	0.82	1.16
CRP/albumin ratio	0.06	9.84	0.002[a]	1.06	1.02	1.11
Platelets/lymphocyte ratio	0.001	0.11	0.73	1.00	0.99	1.00
Longer duration of surgery (operation time)						
Constant	−5.66	1.18	0.27	0.00		
Age	−0.10	0.63	0.42	0.90	0.69	1.16
Sex	0.10	0.03	0.85	1.11	0.35	3.48
Prognostic nutritional index (PNI)	−0.01	0.21	0.64	0.98	0.92	1.04
Glasgow Prognostic Score (GPS)	−0.89	0.72	0.39	0.40	0.05	3.21
TLC	0.11	2.99	0.08	1.12	0.98	1.27
Neutrophils/lymphocytes ratio	−0.17	3.23	0.07	0.83	0.69	1.01
CRP/albumin ratio	0.07	9.87	0.002[a]	1.07	1.02	1.12
Platelets/lymphocyte ratio	0.004	1.89	0.16	1.00	0.99	1.00
Albumin	0.61	0.14	0.70	1.84	0.08	41.85
Development of postoperative fever						
Constant	−5.00	0.96	0.32	0.00		
Age	−0.14	1.42	0.23	0.86	0.67	1.10
Sex	−0.15	0.07	0.78	0.85	0.28	2.54
Prognostic nutritional index (PNI)	−0.007	0.05	0.81	0.99	0.93	1.05
Glasgow Prognostic Score (GPS)	−0.76	0.57	0.44	0.46	0.06	3.36
TLC	0.07	1.30	0.25	1.07	0.95	1.21
Neutrophils/lymphocytes ratio	−0.04	0.22	0.63	0.95	0.80	1.14
CRP/albumin ratio	0.06	6.84	0.009[a]	1.06	1.01	1.12
Platelets/lymphocyte ratio	0.00	0.08	0.77	1.00	0.99	1.00
Albumin	0.82	0.29	0.58	2.29	0.11	46.30

Abbreviations: CI, confidence interval; CRP, C-reactive protein; TLC, total lymphocyte count.
[a]*p*-Value is considered significant if ≤ 0.05.

CRP/albumin ratio was a significant predictor for PLOS, longer duration of surgery, and development of postoperative fever.

Besides, the development of postoperative complications was noticed in some patients. Children with postoperative complications had significantly higher preoperative CRP and CRP/albumin ratios than those without (►**Table 5**). The preoperative CRP/albumin ratio also showed a significant increase in children with complicated appendicitis at presentation (►**Table 6**).

Table 5 Preoperative CRP, albumin, and CRP/albumin ratio regards the development of postoperative complications

Preoperative data	Postoperative complications Yes ($N = 16$)	Postoperative complications No ($N = 74$)	*p*-Value
CRP, median (IQR)	172.5 (85)	123 (75)	0.006[a]
Albumin, median (IQR)	3.2 (0.7)	3.5 (0.5)	0.399
CRP/albumin ratio, median (IQR)	50.2 (31.1)	35.4 (26.7)	0.009[a]

Abbreviations: CRP, C-reactive protein; IQR, interquartile range.
Note: Mann–Whitney test.
[a]*p*-Value is considered significant if ≤ 0.05.

Table 6 CRP/albumin ratio among studied cases at presentation

Studied variable	Noncomplicated appendicitis $N = 37$	Complicated appendicitis $N = 53$	*p*-Value
CRP/albumin ratio, median (IQR)	28.1 (9.6)	52.1 (30.4)	0.000[a]

Abbreviations: CRP, C-reactive protein; IQR, interquartile range.
Note: Mann–Whitney test.
[a]*p*-Value is considered significant if ≤ 0.05.

Discussion

Acute appendicitis in the first 5 years of life is unusual to exist. This is why one of our inclusion criteria was the inclusion of children more than 5 years. The mean age of appendicitis in our study was 8.74 years. A timely diagnosis of acute appendicitis in young children is difficult owing to the varied presentation, and the rapid development of complications. The higher occurrence of early perforation in younger patients could lead to frequent indications for abdominal surgery.[24,25] This was evident in our study as complicated appendicitis represented the greatest proportion at the time of presentation. In addition, the study location is a tertiary care center. This may contribute to the higher group of complicated appendicitis at the time of presentation or intervention in our study as most of them were referred from lower care centers.

Being overweight or obese in children is known to be linked to a low grade of systemic inflammation.[26,27] It was noted previously that there was a tendency toward perforation of appendicitis which was observed in obese children with subsequent higher needs for open surgeries.[28–30] This finding is in line with ours as children with high BMI showed significantly higher needs for open surgery. This may reveal the burden of high BMI on children in the field of acute appendicitis.

Of the many markers applied to detect the inflammatory state in overweight and obese children, CRP emerged as the analyte of choice.[31] This was not noticeable in our study in which there was not a significant elevation of CRP in children with high BMI. This finding was not consistent with a former one which yielded that levels of CRP were significantly elevated in overweight and obese children in comparison to normal ones.[32] The absence of the agreement may be justified that CRP normalization occurs usually within 12 hours after the onset of symptoms of appendicitis in children.[33] Therefore, different times for assessment of CRP may influence the value of CRP with regards to BMI in children with high BMI in our study. This may also explain why GPS was not significantly higher in children with high BMI as CRP is an integral part of GPS assessment. Another explanation may be that the study was performed in a tertiary center where many children with appendicitis are referred from different remote locations, so CRP may be normalized during this period of referral.

An extended value of CRP as an inflammatory marker is to be linked to albumin as a nutritional marker. The CRP/albumin ratio is a new inflammation-based prognostic score and it is linked to the inflammation severity and mortality. It represents an interplay between inflammation and nutrition.[34,35] The preoperative CRP/albumin ratio did not only have a significant correlation with duration of hospital LOS, duration of surgery, and duration of postoperative fever, but it also was a significant predictor for PLOS, longer duration of surgery, and development of postoperative fever.

It was found that CRP can be applied as a marker for the development of postoperative complications in a former study. This result agrees with our detection regarding the higher preoperative CRP and CRP/albumin ratio in children who had postoperative complications. Besides, CRP/albumin ratio was significantly higher in children who presented with complicated appendicitis, a result that was similar to another detected in a previous study.[35–37]

Evaluation of the protein and energy nutritional status is a complex and broad topic. A clinically meaningful evaluation of the nutritional status should be capable of identifying and stratifying children with protein energy malnutrition. In most previous clinical cohorts, low albumin levels are the consequence of the combined effects of both inflammation and inadequate caloric supply.[38] Although the significance of albumin as a prognostic marker for clinical outcomes in

surgical children is well established, its significance as a parameter for nutritional status is still a matter of debate.

Additionally, although albumin is well-known to be an acute-phase protein, there is deficient evidence on how albumin levels could change in the setting of increasing inflammation and postoperative complications.[39] This fact may disclose why there was a significant inverse correlation between the preoperative serum albumin and the postoperative hospital LOS, duration of surgery, and duration of postoperative fever in the enrolled children. This finding is close to a prior report which concluded that hypoalbuminemia in children undergoing abdominal surgery is linked to the increased risk of postoperative longer hospital LOS.[40] Additionally, preoperative serum albumin showed inverse significant correlations with both preoperative TLC and CRP, a relation which is close to a previous report which yielded that there was a persistent elevation of systemic inflammatory blood-borne markers (TLC and CRP) with a continued persistent reduction in albumin in patients who had undergone esophageal resections.[41]

Additionally, the role of GPS was also investigated in infections. GPS was significantly higher in children with higher postoperative hospital LOS in our study. A former study found a similar result that patients with higher GPS suffered longer postoperative stays.[42] Moreover, GPS showed a significant correlation with the duration of surgery (operation time) and the duration of postoperative fever in our study.

Strength of the Study

To the best of our knowledge, our study is considered to be one of the first studies to incorporate CRP/albumin ratio and GPS as prognostic nutritional and inflammatory biomarkers in the course of acute appendicitis and their relation with the outcomes as hospital LOS, operation time, and development of postoperative fever.

Study Limitations

A smaller sample size was one of our limitations as larger sample sizes may make the study more representative. In addition, prealbumin is a stronger nutritional biomarker than albumin due to its shorter half-life span. However, prealbumin was not available in emergency situations at the appendicitis diagnosis.

Conclusion

The nutritional status of children can affect the clinical course of acute appendicitis. Open surgeries may be required more for children with high BMI. Children with a higher preoperative CRP/albumin ratio showed longer postoperative hospital LOS, longer operation time, and longer duration of postoperative fever. CRP and CRP/albumin ratio may be markers for both complicated acute appendicitis at presentation and development of postoperative complications.

What is Known?

- Overweight and obese children may experience undesirable surgical outcomes.

What is New?

- The incorporation of new nutritional and inflammatory markers in the course of acute appendicitis like CRP/albumin ratio and GPS which could be considered new markers for the prognosis of appendicitis in children.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by H.A.A.I. and M.M. The first draft of the manuscript was written by H.A.A.I. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Recommendation

Health priorities should be directed toward children with higher CRP, CRP/albumin ratio, and GPS in cases of acute appendicitis as they may have higher risks for postoperative hospital length of stay.

Availability of Data and Materials

The data are available with the corresponding author upon a reasonable request

Conflict of Interest

None declared.

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