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Original Article

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Pre-Coronavirus Disease 2019 Pediatric Acute Appendicitis: Risk Factors Model and Diagnosis Modality in a Developing Low-Income Country

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Pediatric acute appendicitis has a stable incidence rate in Western countries with an annual change of -0.36%. However, a sharp increase was observed in the Asian region. The Indonesian Health Department reveals appendicitis as the fourth most infectious disease, with more than 64,000 patients annually. Hence, there is an urgent need to identify and evaluate the risk factors and diagnostic modalities for accurate diagnosis and early treatment. This study also clarifies the usage of pediatric appendicitis score (PAS) for children <5 years of age.
Methods: The current study employed a cross-sectional design with purposive sampling through demographic and PAS questionnaires with ultrasound sonography (USG) results. The analysis was performed using the chi-square and Mann–Whitney tests and logistic regression.
Results: This study included 21 qualified patients with an average age of 6.76±4.679 years, weighing 21.72±10.437 kg, and who had been hospitalized for 4.24±1.513 days in Siloam Teaching Hospital. Compared to the surgical gold standard, PAS and USG have moderate sensitivity and specificity. Bodyweight and stay duration were significant for appendicitis ($p<0.05$); however, all were confounders in the multivariate regression analysis. Incidentally, a risk prediction model was generated with an area under the curve of 72.73%, sensitivity of 100.0%, specificity of 54.5%, and a cut-off value of 151.
Conclusion: PAS outperforms USG in the sensitivity of diagnosing appendicitis, whereas USG outperforms PAS in terms of specificity. This study demonstrates the use of PAS in children under 5 years old. Meanwhile, no risk factors were significant in multivariate pediatric acute appendicitis risk factors.

Keywords: Pediatric appendicitis score; Ultrasonography; Acute appendicitis; Pediatric; Risk factors

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INTRODUCTION

Appendicitis is the inflammation of the appendix due to obstruction or microorganism colonization. This disease currently has a stable incidence rate in Western countries with an annual change of −0.36%. However, a sharp increase has been observed in the Asian region [1].

Globally, appendicitis can reach up to 321 million cases each year with an incident rate of 84.2 per 100,000 population for all appendicitis and 64.9 per 100,000 population for the non-perforated subtype. Similarly, the incidence rate of appendicitis in Indonesia was 134 per 100,000 population [2]. The Indonesian Department of Health reveals appendicitis as the fourth most infectious disease in Indonesia with 28,949 inpatients and 34,386 outpatients [3]. Moreover, in 2009, appendicitis was one of the top 10 diseases, with 596,132 cases and mortality of at least 234 patients [3,4]. However, appendicitis cases increased by 3.53% the following year, with 621,435 cases [4].

Appendicitis lowers patients' quality of life due to its morbidity and mortality rates. A 2020 study reported that out of 89,935 pediatric appendicitis cases, 20.6% progress to peritonitis, 12% progress to a peritoneal abscess, and a mortality rate of 0.021% [5].

Therefore, appendicitis prevention, especially in pediatric patients, must be performed immediately. The initiation of prevention can start by identifying the most prevalent risk factors, and hence their demolition. The known contributing factors to pediatric acute appendicitis are age, sex, race, and ethnicity.

Sex and age can predispose people to inflammatory conditions, including appendicitis. Males and females show hormonal differences, especially in estrogen. Sex hormones found majorly in females can modulate the immune system through the regulation of T and B lymphocytes [6]. Simultaneously, age may provoke an imbalance of pro- and anti-inflammatory cytokines in the body, causing susceptibility for appendicitis [7].

Owing to the presented facts and arguments, the increasing incidence and prevalence rate of appendicitis both globally and within Indonesia raise an alarm of urgency to eradicate this disease. Similarly, the speed and accuracy of diagnosis are essential factors for more efficient and effective time and resources in appendicitis diagnosis as well as treatment. Consequently, aside from various risk factors, the current study examined the effectiveness of pediatric appendicitis score (PAS) and ultrasound sonography (USG) in diagnosing appendicitis in pediatric patients.

MATERIALS AND METHODS

Study design

The current study employed a cross-sectional design with purposive sampling in selecting respondents. The Pelita Harapan University Ethics Committee has approved the study with certification number 172/K-LKKJ/ETIK/IX/2018. The legal guardian of the respondents had understood, agreed, and signed an informed consent form before the study was commenced. In calculating the sample size, the author used an α of 5% and power of 20%, setting the $Z\alpha$ of 1.64 and $Z\beta$ of 0.84. Those coupled with the 95% prevalence rate in the diagnostic sample size equation, yield a minimum of 15.

Subject enrollment & data collection

From the selected 30 pediatric surgery patients from 2018 to 2019, nine were excluded due to incomplete data. The selected children were those who visited the emergency center of the hospital or outpatient department with symptoms of appendicitis. The research team medically assessed the children through exams and management, including surgical intervention, until the children were in the general or pediatric ward. Most data were collected in the emergency department and the rest after surgery.

Through a questionnaire and keen observation, the collected variables were appendicitis occurrence, age, duration of hospital stay, weight, PAS score, presence of appendicitis in USG, ethnicity, sex, and education. Furthermore, the classification of children's weight status was controlled by age using the weight-for-age growth chart by the World Health Organization and the Center for Disease Control.

Subject pre-operative workup

Preoperative workups may have some similarities and contrasts between children and adults, emergency cases, and non-emergency cases. The workups may have minor differences among healthcare centers, and the workup in the present study inquired about paranesthesia consultation, present illness, history of illness, routine medications, last meal and drink, family history, birth history, and allergies. For non-emergency cases, specialized consultation with the cardiologist and pulmonologist may be required; however, these can be nulled for urgent cases similar to acute appendicitis. The examination continued with physical screening for abnormalities in the body, such as cardiac murmurs, rashes, wheezing, and congenital malformations. Further assessment of laboratory findings, including blood typing and complete blood count, is required.

Statistical analysis

Data were tabulated using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA) and statistically analyzed using SPSS ver. 26 (IBM Co., Armonk, NY, USA). Categorical bivariate analysis was performed using chi-square or Fischer tests and numerical data using Mann–Whitney or *t*-test, while multivariate analysis was performed using logistic regression.

RESULTS

There were 21 qualified patients on Siloam Teaching Hospital with an average age of 6.76±4.679 years ranging from 1 to 15 years, weighing 21.72±10.437 kg, and who had been hospitalized for 4.24±1.513 days between 2018 and 2019. **Table 1** provides a unique observation that most respondents were male (71.43%) and Javanese (66.67%) and had not started school (61.90%). The mean PAS score from all respondents was 6.48±2.909. Furthermore, 10 respondents were confirmed to have acute appendicitis. However, USG only identified 60% of the cases, whereas the PAS score overestimated the positive cases by seven respondents.

Abdominal or appendix ultrasonography is usually chosen as a first-line appendicitis diagnostic approach in addition to routine clinical examinations, due to its portability and effectiveness. Nevertheless, complex appendix locations, other diseases, and financial limitations may obscure ultrasound-projected images. Thus, specific clinical examinations and scoring have been developed for an easier and more efficient diagnosis.

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Table 1. Demographic data of pediatric surgery patients at Siloam Teaching Hospital (n=21)

Feature	Value
Age (y)	6.76±4.679
Weight (kg)	21.72±10.437
Severely underweight	6 (28.6)
Underweight	1 (4.8)
Normal	13 (61.9)
Overweight	1 (4.8)
Stay duration (d)	4.24±1.513
Pediatric appendicitis score	6.48±2.909
Positive	17 (81.0)
Negative	4 (19.0)
Sex	
Male	15 (71.4)
Female	6 (28.6)
Ethnicity	
Javanese	14 (66.7)
Sundanese	7 (33.3)
Formal education	
Yes	8 (38.1)
No	13 (61.9)
Ultrasonography	
Appendicitis	9 (42.9)
Non-appendicitis	12 (57.1)
Appendicitis	
Yes, non-perforated	8 (38.1)
Yes, perforated	2 (9.5)
No	11 (52.4)

Values are presented as mean±standard deviation or number (%).

Table 2 shows that the appendix USG incorrectly determined three healthy patients of having appendicitis (27.27% false-positive rate) and four patients with appendicitis to be

Table 2. Stay duration, risk factors, and diagnosis modality for appendicitis

Factor	Appendicitis		OR (95% CI)	*p*-value	Sensitivity	Specificity
	Yes (n=10)	No (n=11)				
Age (y)	8.40±4.648	5.27±4.384		0.099		
Weight (kg)	25.21±7.512	18.55±11.996		0.043		
Severely underweight	4 (40.0)	2 (18.2)		0.208		
Underweight	1 (10.0)	0 (0.0)				
Normal	4 (40.0)	9 (81.8)				
Overweight	1 (10.0)	0 (0.0)				
Stay duration (d)	5.00±1.633	3.55±1.036		0.024		
Sex						
Male	8 (80.0)	7 (63.6)	2.286 (0.316–16.512)	0.367		
Female	2 (20.0)	4 (36.4)				
Ethnicity						
Javanese	6 (60.0)	8 (72.7)	0.536 (0.090–3.518)	0.438		
Sundanese	4 (40.0)	3 (27.3)				
Formal education						
Yes	6 (60.0)	2 (18.2)	6.750 (0.925–49.232)	0.063		
No	4 (40.0)	9 (81.8)				
Ultrasonography						
Positive	6 (60.0)	3 (27.3)		0.142	60.00%	72.73%
Negative	4 (40.0)	8 (72.7)				
PAS	7.80±1.619	5.27±3.349		0.043		
Positive	10 (100.0)	7 (63.6)		0.055	100.00%	47.99%
Negative	0 (0.0)	4 (36.4)				

Values are presented as mean±standard deviation or number (%).
OR: odds ratio, CI: confidence interval, PAS: pediatric appendicitis score.

Table 3. Diagnostic information of age-controlled PAS

Age	PAS	Appendicitis		Sensitivity	Specificity	PPV	NPV	Accuracy
		Yes	No					
<5	Positive	3 (100.0)	4 (57.14)	100.00%	42.86%	0.43	0.00	60.00%
	Negative	0 (0.0)	3 (42.86)					
≥5	Positive	7 (100.0)	3 (75.00)	100.00%	25.00%	0.70	0.00	72.73%
	Negative	0 (0.0)	1 (25.00)					

Values are presented as number (%) or number only.
PAS: pediatric appendicitis score, PPV: positive predictive value, NPV: negative predictive value.

healthy (40.00% false-negative rate), resulting in 60.00% sensitivity and 72.73% specificity. Meanwhile, PAS had 100.00% sensitivity and 47.99% specificity. Even after controlling for age, with 4 years as the cut-off, PAS procured adequate diagnostic capabilities (**Table 3**).

The respondents' sex and age were not essential for acute appendicitis (p=0.0367 and 0.099, respectively). Patients with appendicitis have a 4:1 sex ratio of male to female that comprised 8.40±4.648 year old respondents. In contrast, non-appendicitis respondents have a 7:4 sex ratio of male to female and a average age of 5.27±4.384 years.

Weight and appendicitis had a significant relationship in general (p=0.043). The average weight of respondents with appendicitis was 25.21±7.512 kg, while that of the controls was 18.55±11.996 kg. Nevertheless, we cannot directly compare the weight across individuals of different ages since weight is dependet on age. Hence, we stratified the sample by age prior to the comparison. After the subsequent age stratification, an equal prevalence of appendicitis was observed in the severely underweight and normal groups (40.0%), while the control group was mostly comprised of those with normal weight (81.8%). In addition, weight was found to be insignificant (p=0.208).

Duration of hospital stay was significantly associated with the occurrence of appendicitis (p=0.024). Patients with appendicitis tended to stay for 1.45 more days than patients without appendicitis. Likewise, the PAS score followed a similar trend (p=0.043), with a 2.53 higher mean score for the appendicitis group.

In contrast, the patients' ethnicity and education did not significantly contribute to the incidence of appendicitis (p=0.438; odds ratio [OR], 0.536; 95% confidence interval [CI], 0.090-3.518 and p=0.063; OR, 6.750; 95% CI, 0.925-49.232, respectively).

Multivariate logistic regression showed that no risk factors were significant (**Table 4**). Age, PAS score, and education are confounders. Nevertheless, the multivariate analysis regression developed to a pediatric acute appendicitis prediction model (**Table 5**) with area under the curve (AUC) of 72.73%, sensitivity of 100.0%, specificity of 54.5%, and a cut-off value of 151.

Meanwhile, several notable findings appeared during the surgery. First, the location of the appendix was mostly (>50%) in the retrocecal, subhepatic, or posteromedial quadrant.

Table 4. Regression of risk factors in pediatric acute appendicitis at Siloam Teaching Hospital

Risk factor	B	p-value	AOR (95% CI)	Score
Age	−0.071	0.770	0.932 (0.580–1.496)	1
PAS	0.370	0.142	1.447 (0.884–2.369)	25
Formal education	2.202	0.356	9.045 (0.084–970.454)	10

AOR: adjusted odds ratio, CI: confidence interval, PAS: pediatric appendicitis score.

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Table 5. Pediatric acute appendicitis risk factor modelling

Risk factor	Multiplier	Score
Age (y)	1	......
Pediatric appendicitis score	25	......
Formal education	10: yes | 0: no	......
Total	≥151: high risk <151: low risk	......

Perforated appendicitis occurred in 20.00% of patients in whom it had not been detected earlier using diagnostic measures. Lastly, several conditions mimicked the manifestation of appendicitis, such as invagination, Meckel's diverticulum, and malrotation.

DISCUSSION

The rate of appendicitis in the pediatric surgery setting of the Siloam Teaching Hospital from 2018 to 2019 was 47.62%. This finding is similar to the meta-analysis of acute appendicitis prevalence by Obsa et al. [8], with a 44.27% prevalence rate, which exceeded the prevalence rate of 7.0% in a 2018 surgical pathology study and 3.85% in a 2019 study by Mukendi [8-10]. The diagnosis of appendicitis has been a challenge for most physicians because of the various vermiform locations of appendicitis and its common signs and symptoms. In this study, USG outperforms PAS in terms of specificity in diagnosing acute appendicitis in children (72.73% vs. 47.99%), whereas PAS outperforms USG in terms of sensitivity (60.00% vs. 100.00%). The same dominance can be observed in the study by Sayed et al. [11] in Egypt, where the sensitivity and specificity for USG and PAS were 95% vs. 55.6% and 84% vs. 85%, respectively.

The varying sensitivity of USG has become a topic of debate in academia. Some studies have indicated high diagnostic capabilities of USG in appendicitis with sensitivity and specificity of 88.1-96.4% and 91.4-95.3%, respectively [11-13], while some studies have shown 38-67% sensitivity and 92-97% specificity [14-16]. The present study follows the latter trend with 60% sensitivity and 72.73% specificity for USG.

The diminishing diagnostic capabilities of USG in the current study are mainly due to anatomical, financial, and human lapses. Appendices located in in hard-to-reach areas, such as above the iliac crest, retrocecal, or posteromedial quadrant, are difficult to be visualized using 10 MHz USG. The amount of an appendix which lies in the hard to reach areas are significantly more than that expected by chance (p<0.00001), as seen in 62.4% of appendicitis patients [17]. Moreover, ordinary sonographers can have difficulties in locating the appendix of pediatric patients compared to trained, committed pediatric sonographers [18]. Subsequently, the current study employed non-pediatric sonographers, which may explain the disparity.

Furthermore, it is challenging to use the visualization technique for the appendix adequately in patients with suspected appendicitis, as compression in the abdominal area triggers excruciating pain. Even in an adequately graded compression, visualization failures can occur, especially in patients with severe pain or obesity [19]. Anxiety and uncooperative pediatric patients also contribute to unclear visualizations [20].

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Patients and their families disagreed on another examination with USG or alternative methods, such as computed tomography or magnetic resonance imaging, due to financial reasons, even though re-examining with compression USG or a better alternative may result in more satisfactory results [21,22]. All patients in the current study were financed through the *Badan Penyelenggara Jaminan Sosial Kesehatan*, a government-financed healthcare program in Indonesia with severe limitations on medical provisions and imaging modalities. After the deduction of government subsidies, the fee for re-examining using USG is USD 12, whereas that using magnetic resonance imaging is USD 39, which is high compared to the USD 85 average monthly income of Indonesians [23,24]. Such reasons, as observed in the present study, deteriorate the diagnostic measures for USG in pediatric appendicitis in developing countries, especially Indonesia.

The use of PAS in very young children is controversial. A prospective 19-months validation study of PAS in Canada with children ranging from 1 to 17 years of age procured satisfying results with an AUC of 0.95 along with 0.68 sensitivity and 0.73 specificity for a cut-off value of ≥2 [25]. Nonetheless, Salö et al. [26] found that children <4 years old had significantly lower PAS score although with more severe appendicitis (p=0.005 and 0.001). The inability to communicate and the parent-doctor delay are the proposed reasons. In contrast, in the present study, PAS was proven to be satisfactory, even between the age groups. PAS has only negligible difference of 0% in sensitivity and 17.68% in specificity across the age group. These findings corroborate the application of PAS in diagnosing acute appendicitis in patients, even in <5-year-old children. Nonetheless, although there is a discrepancy with the findings of other studies, the current study did not substantially contribute much since this is only a single study with normal power and cross-sectional design. The present study may act as a foundation for further studies to explore PAS in children <5 years of age.

Furthermore, a significant difference (p=0.043) was observed between the average weight of pediatric surgery patients with appendicitis and the control group. The weight difference between the two groups was 6.66 kg. Timmerman et al. [27] also reported that weight has a significant influence on the diagnosis of appendicitis in children, especially in those who were underweight (OR, 3.00; p=0.008). However, the difference was not significant after adjusting for age, as weight is heavily dependent on age. For instance, there is a relation of adiposity rebound and hence the weight and body mass index (BMI) with age in children [28]. Adiposity rebound is the increase in children's weight between 5 and 7 years of age, wherein a hormonal surge triggers rapid adipocyte development and adipokine secretion, leading to the increase in weight and BMI [29,30].

Weight difference affects the risk for appendicitis due to the waning of the immune system for abnormal weights (obesity or underweight). These impairments are caused by T-cell variance dysregulation, abnormal lymphocyte proliferation, excessive pro-inflammatory cytokine generation, anti-inflammatory cytokine production, hypertrophied adipose tissue hypoxia, and endoplasmic reticulum stress. These factors increase inflammatory responses, leading to appendicitis [31].

The proportion of pediatric surgery patients who contracted appendicitis was different in terms of the PAS score (p=0.043). In this study, the average score was 7.80±1.619 for patients and 5.27±3.349 for healthy individuals., which is similar to the findings of a Korean study that obtained significantly higher scores in patients with acute appendicitis (7.1±1.5) than those without appendicitis (3.8±2.0) (p<0.001) [32].

The change in proportion may occur due to the affinity of PAS components (anorexia, nausea, fever, pain migration, right lower quadrant tenderness, cough tenderness, leukocytosis, and left shift) to diagnose acute appendicitis. The aforementioned study from Korea also revealed a statistically essential relationship between most PAS components and acute appendicitis (p<0.001 for 6/8 components) [32].

On the other hand, the patient's sex did not contribute to the risk of appendicitis (p=0.367). A total of 53.3% of all males and 33.3% of all females had appendicitis with a 4:1 sex ratio. A study from USA in 2020 showed similar data with 59.4% vs. 40.6% of appendicitis prevalence in males and females, respectively [5]. Hormonal disparity between males and females can predispose to this dissonance. Estrogen through the ERα and ERβ receptors can induce secondary signaling to dysregulate leukocytes (neutrophils, macrophages, dendritic cells, T-helper cells, and B cells) and specific cytokines (interleukin I, interleukin 6, tumor necrosis factor α, and immunoglobulin), which cause a pro-inflammatory state in the host and hence heightened susceptibility to appendicitis [33]. Although substantially related, ethnicity and education are proven insignificant to the risk of appendicitis (p=0.438 and 0.063, respectively).

The observation of the patients also revealed significant differences in duration of hospital stay among patients with appendicitis and those without appendicitis. Discrepancies between the groups are causal for the management and treatment of appendicitis, not as a risk factor. The average length of hospital stay for the aforementioned patients' groups was 5.00±1.633 and 3.55±1.036 days, respectively. The significant increment of the duration of stay (p=0.024) was due to post-appendectomy or post-conservative treatment observation, presence of comorbidities, and the onset of symptoms to appendectomy. A multicentered large cohort study in Poland also showed that appendicitis (through the Alvarado score) has a significant relationship with the length of stay (OR, 1.10; p=0.008). Similar relations to the length of stay were also found on symptom onset before the surgery (OR, 1.72; p<0.001), diabetes (OR, 3.96; p<0.001), and old age (OR, 2.78; p<0.001) [34].

Multivariate analysis using logistic regression showed that no risk factors was truly significant. The risk factors served as confounders, including age (p=0.770), PAS score (p=0.142), and formal education (p=0.356). Thus, PAS and USG become the first-line approach in diagnosing pediatric acute appendicitis rather than the currently developed model.

Meanwhile, the present study observed that >50% of the appendices are located in the retrocecal, subhepatic, or posteromedial quadrant. This severely hinders visualization through USG and other imaging techniques, resulting in a lower diagnostic rate. Furthermore, this value is consistent with the study by Kuamr et al. [35] in India, where the incidence of retrocecal appendices is 78.20%. In addition, several conditions show similar measures to appendicitis, including invagination, Meckel's diverticulum, and malrotation. Monajemzadeh et al. [36] corroborated these findings, where 16.1% of their surgical findings belong to intra-abdominal pathologies that are similar to appendicitis. Furthermore, the health center observed a lower perforated appendicitis rate than its usual prevalence; there was 20.00% reported perforation rate in the center, while the usual rate can be at approximately 30% [37].

PAS outperforms USG in terms of sensitivity in diagnosing appendicitis, whereas USG outperforms PAS in terms of specificity. The study demonstrates the use of PAS in children

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<5 years of age. Meanwhile, no risk factors were significant in multivariate pediatric acute appendicitis risk factors.

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