MEDDOCS Open Access Publisher

ISSN: 2637-9627

Annals of Pediatrics

Open Access | Research Article

Risk Factors Associated with Delayed Diagnosis of Acute Appendicitis in Children in a Single Tertiary Medical Center in South Texas

Akhila V[1]; Seunghwan K[1]; John R[2]; Arya K[1]; Adetomola B[1]; III Joel S[1]; Shang-Chen W[1]; Aarti K[1]; Yu-Hsun W[1]; Po-Yang T[1]; Stephen A[3]; Haroon P[3]; Mohammad E[3]; Marita R[4]; Subhankar B[4]*

[1]Department of Pediatrics, Driscoll Children's Hospital/Texas A&M College of Medicine, USA.

[2]School of Medicine, Texas Tech University Health Sciences Center, USA.

[3]Department of Surgery, Driscoll Children's Hospital/Texas A&M College of Medicine, USA.

[4]Department of Emergency Medicine, Driscoll Children's Hospital/Texas A&M College of Medicine, USA.

***Corresponding Author(s): Subhankar Bandyopadhyay**

Department of Emergency Medicine, Driscoll Children's Hospital/Texas A&M College of Medicine, Corpus Christi, TX 3533 S Alameda St Corpus Christi, TX, United States 78411.

Tel: 361-694-5000, Fax: 361-694-5449;

Mail: Subhankar.Bandyopadhyay@dchstx.org

Received: Oct 30, 2020

Accepted: Dec 04, 2020

Published Online: Dec 09, 2020

Journal: Annals of Pediatrics

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Appendicitis; Children; Delayed diagnosis; Risk factors; Retrospective cohort study.

Abstract

Introduction: Acute appendicitis is a common reason to visit the pediatric emergency department, the delayed diagnosis of which is associated with increased morbidity and mortality. The aim of this work is to investigate risk factors associated with delayed diagnosis of Acute Appendicitis (AA).

Materials and methods: We performed a retrospective cohort study consisting of children with pathologically confirmed diagnosis of AA hospitalized to a single center from 2015 to 2018. The primary outcome is delayed diagnosis of AA using the following definition: the diagnosis was made more than 48 hours but less than a week from the initial encounter at a healthcare institution. Multivariable regression models were used to fit the association between risk factors and primary outcomes.

Results: There were 517 children admitted for AA. The median age was 11.4 years (IQR: 8.6-14.5), 312 (60.3%) were male, 157 were obese (31.9%), 402 were Hispanic (77.8%) and 32 patients (6.18%) had the delayed diagnosis of AA. Compared to children without delayed diagnosis (n= 485), those with delayed diagnosis (n= 32) were younger (Median: 8.9, IQR: 5.7-13.4, p= 0.006) with higher initial CRP level (Median: 14.9, IQR: 8.2-21.5, p<0.001) and more likely to have pre-operative abscess (40.6%, p<0.001), percutaneous abscess drainage (12.5%, p<0.001), longer hospital stay (Median: 4.0, IQR: 2.5-7.0, p<0.001) and PICU admission (9.4%, p<0.001). Multivariable logistic regression indicated that CRP (adjusted OR, 1.11[95% CI 1.05-1.16], p<0.01) remained significantly associated with the outcome. Obesity, age, ethnicity, gender, or initial encounter site were not associated with the delayed diagnosis.

Cite this article: Akhila V, Seunghwan K, John R, Arya K, Adetomola B, et al. Risk Factors Associated with Delayed Diagnosis of Acute Appendicitis in Children in a Single Tertiary Medical Center in South Texas. Ann Pediatr. 2020; 3(1): 1042.

Conclusion: This work suggested that the initial CRP is a significant risk factor for delayed diagnosis for children presented with AA. This finding may help prompt identification of children with delayed diagnosis, as delayed diagnosis may be associated with longer LOS.

Introduction

Acute appendicitis is one of the most common causes of acute abdomen illness in children with an annual incidence ranging from 19 to 28 per 10,000 children younger than 14 years [1,2]. The estimated cost of pediatric appendectomies alone exceeds $600 million, not including incalculable costs in lost workforce productivity from parents, missed school days, hospital admissions and other aspects [3,4].

Even though it is a common diagnosis in the pediatric emergency department, nonspecific symptoms, varied clinical presentations, inexplicit history and difficult physical examination secondary to young age of children can make the diagnosis challenging. Laboratory testing and imaging modalities were incorporated into decision making to assist clinicians with diagnosis, but each has their own limitations and associated risks. While both White Blood Cell (WBC) count and Absolute Neutrophil Count (ANC) makes up part of the pediatric appendicitis score (PAS) and are elevated in almost all children who present with appendicitis [5,6]. These findings are nevertheless non-specific that mimic other diseases may hinder diagnosis [7,8]. Other inflammatory markers such as C-Reactive Protein (CRP) and Procalcitonin (PCT) have been accounted for in determining the diagnosis of acute appendicitis, but the diagnostic accuracies of them were suboptimal [9-11]. Abdominal Ultra Sound (US) is dependent on the operators' skill level and availability of sonographers; it may also be affected by the body habitus of patients [12]. On the other hand, Computed Tomography (CT) scan has high sensitivity (94-100%) and specificity (93-100%) for the diagnosis of acute appendicitis [13]. But results in significant exposure to radiation that is associated with adverse outcomes in the future [14].

Due to the difficulty of timely diagnosis of acute appendicitis in children, several clinical scoring systems have been developed to help early diagnosis of acute appendicitis [6]. Despite the use of these clinical tools, the rates of misdiagnosis remain high from 28% to 57% in children under 12 years of age [15]. Misdiagnosis or improper management not only can worsen outcomes but also increase cost burden; delayed treatment or surgery due to appendicitis has been significantly associated with higher hospital costs [16]. The suboptimal diagnostic accuracy for acute appendicitis and complications related to delayed diagnosis emphasize the need to investigate additional factors related to delayed diagnosis of acute appendicitis.

Previous studies have proposed several risk factors related to delayed diagnosis of acute appendicitis. However, it is unclear if the results found in previous studies are generalizable to the US populations with higher prevalence of obesity or of different ethnicities [17,18]. This study aims to investigate the risk factors associated with diagnostic delay of acute appendicitis among children in a single center in South Texas.

Materials and methods

Study design

A retrospective cohort study was conducted in children between the ages of 2 and 18 years with pathologically confirmed diagnosis of acute appendicitis at Driscoll Children's Hospital (DCH) from January 2015 to December 2018 using Electronic Medical Records (EMR). We retrospectively reviewed the EMR of eligible patients and documented the demographic, clinical, laboratory, imaging and outcome data. Exclusion criteria included children with chronic illness, prior history of abdominal anatomical anomalies, prior abdominal surgery, history of prophylactic appendectomy, negative pathological findings for appendicitis and patients that received appendectomy or initial management at outside facilities requiring further surgery or intervention. This study was approved by the Driscoll Children's Hospital Institutional Review Board.

Risk factors

The data collected included the patient's demographics (e.g., age, gender, ethnicity), overweight (less than 95 % but greater than or equal to 85 % of age and gender specific BMI) or obesity (≥95% of age and gender specific BMI), clinical characteristics (e.g., duration of symptoms), laboratory and radiologic findings (CRP, PCT, abdominal US and CT scan results), PASs on presentation, type of appendicitis, initial antibiotic regimen and type of intervention. Age were categorized into the following groups: toddlers/preschoolers (2-5 years of age), children (6-11 years of age) and adolescents (12-18 years of age). Significant elevated CRP was defined as level ≥10 mg/L.

Primary and secondary outcomes

The primary outcome of delayed diagnosis of appendicitis was based on the definition that the diagnosis was made more than 48 hours but less than a week from the initial encounter at a healthcare institution. The secondary outcome was the length of hospital stay (LOS).

Statistical analysis

Exploratory data analysis was conducted to describe the characteristics of children with delayed diagnosis of acute appendicitis and those without delayed diagnosis of acute appendicitis. Categorical variables are presented as frequency and percentage and were compared using the Chi-squared test. When frequency is less than 5 of a given variable, Fischer's exact test would be used instead of Chi-squared test. Continuous variables are presented as mean or median and were compared with the t test or Wilcoxon rank-sum test as appropriate for non-normally distributed continuous variables and normally distributed continuous variables. To explore the risk factors associated with delayed diagnosis of acute appendicitis, univariable and multivariable logistic regression analyses were used to determine the association between the identified risk factors and delayed diagnosis of acute appendicitis. The final logistic regression model investigating risk factors for delayed diagnosis of appendicitis was adjusted for the following variables: age category, obesity or overweight, gender, ethnicity, initial site of receiving medical care, presence of fever or migratory pain, duration of symptoms and types of imaging for diagnosis.

Covariates were initially determined based on the potential relevance reported in the literature and on their association with the outcome in the bivariate analysis at a significance level of P < 0.1. Similarly, for the secondary outcome, the Length of Hospital Stay (LOS), univariable and multivariable linear regression analyses were performed to explore the risk factors for prolonged stay. The final linear regression model exploring the risk factors for prolonged LOS among patients diagnosed with acute appendicitis was adjusted for the following variables: age category, obesity or overweight, gender, ethnicity, open appendectomy, presence of complications and the presence of abdominal drains and/or NG tube post-operatively. Covariates were initially determined based on the potential relevance reported in the literature. Complications consist of pre-operative abscess, perforated appendix and post-operative abscess. The level of significance of the association was set at 0.05 (p<0.05) a priori with statistical analysis calculated using STATA (Stata Corp, College Station, TX).

Results

Patient demographics and clinical characteristics

There were 517 children admitted for acute appendicitis. (Table 1) lists the demographics and clinical outcomes of the two groups. The median age was 11.4 years (Interquartile Range [IQR]: 8.6-14.5), 312 (60.3%) were male, 157 were obese (31.9%), 402 were Hispanic (77.8%) and 6.18 % (32/512) of patients had the delayed diagnosis of acute appendicitis. Compared to children without delayed diagnosis of appendicitis (n= 485), those with delayed diagnosis (n= 32) were significantly younger (Median: 8.9, [IQR: 5.7-13.4] vs. Median: 11.5 [IQR 8.7-14.6], p= 0.006) and were more likely to have perforated appendix (81.3% vs. 47.2%, p<0.001), pre-operative abscess (40.6% vs. 6.2%, p<0.001), percutaneous abscess drainage (12.5% vs 0.4%, p<0.001), post-operative nasogastric tube placement (53.1% vs. 16.2%, p<0.001), post-operative abdominal drain placement (75.0% vs. 22.4%, p<0.001), longer hospital stay level (Median: 4.0 [IQR: 2.5-7.0] vs. Median: 1.0, [IQR: 1.0-2.0], p<0.001), PICU admission (9.4% vs 1.0%, p<0.001) and post-operative abscess formation (6.3% vs 1.0%, p= 0.013). Differences in obesity (34.4% vs. 31.7%, p= 0.76) or overweight status (21.9% vs. 20.2%, p= 0.82), or gender (65.6% male vs. 60.0% male, p= 0.53) were not statistically different between the two groups.

Pediatric appendicitis score

(Table 2) lists the common signs and symptoms at presentation between the two groups. The PAS scores were not significantly different between the two groups (Median: 6.0 [IQR: 4.0-7.5] vs Median: 6.0, [IQR: 5.0-7.0], p=0.64). Compared to children without delayed diagnosis of appendicitis, however, those with delayed diagnosis had a statistically significant higher initial CRP level (Median: 14.9 [IQR: 8.2-21.5] vs Median: 3.2 [IQR: 1.0-8.1], p<0.001) and likelihood of CRP ≥ 10 mg/L (43.8% vs 9.3% p<0.001). Those with delayed diagnosis were also more likely to be febrile upon presentation (50.0% vs 30.5%, p<0.022). Patients with no delayed diagnosis presented with a shorter duration of symptoms (p<0.001) and higher likelihood of having migration of pain to the right lower quadrant (41.2% vs. 12.5%, p= 0.001). There were no significant differences between the likelihood of leukocytosis or neutrophilia between the two groups.

Risk factors for delayed diagnosis of acute appendicitis

Univariable logistic regression suggested initial significant elevated CRP (≥10 mg/L) (unadjusted Odds Ratio [OR], 7.60 [95% CI 3.55-16.31], p<0.001) was significantly associated with delayed diagnosis. Other significant risk factors include fever (unadjusted OR, 2.28 [95% CI 1.18-4.68], p= 0.025) and symptoms > 72 hours (unadjusted OR, 9.56 [95% CI 3.11-29.40], p<0.001). As compared with toddlers/preschoolers, children (unadjusted OR, 0.29 [95% CI 0.12-0.73], p= 0.008) and adolescents (unadjusted OR, 0.21 [95% CI 0.08-0.54], p<0.001) were less likely to have delayed diagnosis. Interestingly, obesity and/or overweight status (unadjusted OR, 1.19 [95% CI 0.58-2.45], p= 0.64), initial visit site to an urgent care (unadjusted OR, 1.47 [95% CI 0.33-6.64], p= 0.61) or clinic (unadjusted OR, 1.31 [95% CI 0.52-3.33], p= 0.56) and diagnosis of appendicitis via ultrasound (unadjusted OR, 0.44 [95%CI 0.15-1.35], p= 0.15), CT scan (unadjusted OR, 0.83 [95%CI 0.29-2.37], p= 0.73) were not significantly associated with the primary outcome.

Multivariable logistic regression showed elevated CRP (≥10 mg/L) (adjusted OR, 6.58 [95% CI 2.66-19.22], p<0.001) remained significantly associated with delayed diagnosis, while older age categories, children (adjusted OR, 0.38 [95% CI 0.11-1.37], p= 0.14) and adolescents (adjusted OR, 0.32 [95% CI 0.08-1.21], p= 0.09), became no longer significantly associated with delayed diagnosis. Interestingly, presence of migration of pain to RLQ remained associated with decreased odds of delayed diagnosis of appendicitis (adjusted OR, 0.28 [95% CI 0.08-0.91], p= 0.04) (Table 3 and Figure 1). Similar to the findings in univariable analyses, obesity and/or overweight status (adjusted OR, 1.06 [95% CI 0.42-2.69], p= 0.90), presence of fever (adjusted OR, 1.38 [95% CI 0.55-3.45], p= 0.49), initial visit site to an urgent care (adjusted OR, 0.80 [95% CI 0.12-5.21], p= 0.48) or clinic (adjusted OR, 0.93 [95% CI 0.27-3.19], p= 0.91) and diagnosis of appendicitis via ultrasound (adjusted OR, 0.26 [95% CI 0.06-1.10], p= 0.07) were not significantly associated with the delayed diagnosis of appendicitis.

Risk factors for prolonged Length of Hospital Stay (LOS)

Univariable linear regression suggested open appendectomy (unadjusted β, 0.92 [95% CI 0.22-1.62], p= 0.01), delayed diagnosis of acute appendicitis (unadjusted β, 2.98 [95% CI 2.30-3.66], p<0.01), presence of complications (unadjusted β, 1.82 [95% CI 1.51-2.13], p<0.01) and post-operative drain placement (unadjusted β, 3.22 [95% CI 2.94-3.50], p<0.01) were significantly associated with increased LOS, while older age categories were associated decreased LOS (Table 4). Multivariable linear regression indicated that open appendectomy (adjusted β, 0.80 [95% CI 0.27-1.33], p<0.01), delayed diagnosis of acute appendicitis (adjusted β, 1.36 [95% CI 0.27-1.33], p<0.01) and post-operative drain placement (adjusted β, 2.85 [95% CI 2.48-3.22], p<0.01) remained significantly associated with increased LOS. On the other hand, older age categories become non-significant risk factors for LOS in the multivariable regression model (Table 4).

Table 1: Demographics and clinical outcomes of patients with acute appendicitis stratified by delayed diagnosis.

	Total (n= 517)	No delay (n= 485)	Delay (n= 32)	p-value
Age, median (IQR)	11.4 (8.6, 14.5)	11.5 (8.7, 14.6)	8.9 (5.7, 13.4)	0.006
Age categories				
Toddler/preschool	52 (10.1)	43 (8.9)	9 (28.1)	0.002
Child	226 (43.7)	213 (43.9)	13 (40.6)	
Adolescent	239 (46.2)	229 (47.2)	10 (31.3)	
Male, n (%)	312 (60.3)	291 (60.0)	21 (65.6)	0.53
Obesity, n (%)	157 (31.9)	146 (31.7)	11 (34.4)	0.76
Overweight, n (%)	100 (20.3)	93 (20.2)	7 (21.9)	0.82
Race				
White, n (%)	468 (90.5)	439 (90.5)	29 (90.6)	0.90
Black, n (%)	14 (2.7)	13 (2.7)	1 (3.1)	
Others, n (%)	33 (6.4)	31 (6.4)	2 (6.3)	
American Indian/Eskimo/Aleut, n (%)	1 (0.2)	1 (0.2)	0 (0.0)	
Asian or pacific islander, n (%)	1 (0.2)	1 (0.2)	0 (0.0)	
Ethnicity				
Hispanic, n (%)	402 (77.8)	372 (76.7)	30 (93.8)	0.026
Non-Hispanic, n (%)	113 (21.9)	111 (22.9)	2 (6.3)	
History of surgery, n (%)	8 (1.6)	7 (1.4)	1 (3.1)	0.40
Immunocompromised status, n (%)	4 (0.8)	4 (0.8)	0 (0.0)	1.00
Method of diagnosis				
Clinical, n (%)	56 (10.8)	51 (10.5)	5 (15.6)	0.18
US, n (%)	240 (46.4)	230 (47.4)	10 (31.3)	
CT, n (%)	213 (41.2)	197 (40.6)	16 (50.0)	
Others, n (%)	8 (1.5)	7 (1.4)	1 (3.1)	
Antibiotics				
Piperacillin/Tazobactam, n (%)	384 (74.3)	363 (74.8)	21 (65.6)	0.39
Gentamicin and metronidazole, n (%)	109 (21.1)	100 (20.6)	9 (28.1)	
Others, n (%)	24 (4.6)	22 (4.5)	2 (6.3)	
Perforation, n (%)	255 (49.3)	229 (47.2)	26 (81.3)	<0.001
Pre-operative abscess, n (%)	43 (8.4)	30 (6.2)	13 (40.6)	<0.001
Types of interventions				
Open appendectomy, n (%)	33 (6.4)	33 (6.8)	0 (0.0)	<0.001
Laparoscopic appendectomy, n (%)	477 (92.3)	450 (92.8)	27 (84.4)	
Combined, n (%)	1 (0.2)	0 (0.0)	1 (3.1)	
Percutaneous drainage, n (%)	6 (1.2)	2 (0.4)	4 (12.5)	
Drain placement, n (%)	132 (25.6)	108 (22.4)	24 (75.0)	<0.001
NG placement, n (%)	95 (18.5)	78 (16.2)	17 (53.1)	<0.001
Length of stay (d), median (IQR)	1.0 (1.0, 3.0)	1.0 (1.0, 2.0)	4.0 (2.5, 7.0)	<0.001
PICU admission, n (%)	8 (1.5)	5 (1.0)	3 (9.4)	<0.001
Post-operative abscess, n (%)	7 (1.4)	5 (1.0)	2 (6.3)	0.013
ER revisit in 30 days, n (%)	18 (3.5)	17 (3.5)	1 (3.1)	0.91

Abbreviation: IQR: Interquartile Range; CRP: C-Reactive Protein; h: hour, d: day; ER: Emergency Room; US: Ultrasound; NG: Nasogastric; PICU: Intensive Care Unit.

Table 2: Clinical characteristics of patients with acute appendicitis stratified by delayed diagnosis.

	Total (n=517)	No delay (n=485)	Delay (n=32)	p-value
Duration of symptoms				<0.001
< 12h, n (%)	115 (22.2)	109 (22.5)	6 (18.8)	
12-24h, n (%)	209 (40.4)	207 (42.7)	2 (6.3)	
24-48h, n (%)	107 (20.7)	103 (21.2)	4 (12.5)	
48-72h, n (%)	57 (11.0)	47 (9.7)	10 (31.3)	
> 72h, n (%)	29 (5.6)	19 (3.9)	10 (31.3)	
Initial visit site				
ER, n (%)	413 (79.9)	389 (80.2)	24 (75.0)	0.77
Urgent care, n (%)	24 (4.6)	22 (4.5)	2 (6.3)	
Clinic, n (%)	80 (15.5)	74 (15.3)	6 (18.8)	
CRP, median (IQR)	3.7 (1.1, 9.6)	3.2 (1.0, 8.1)	14.9 (8.2, 21.5)	<0.001
CRP ≥ 10 mg/L, n (%)	59 (11.4)	45 (9.3)	14 (43.8)	<0.001
Pediatric Appendicitis Score, Median (IQR)	6.0 (5.0, 7.0)	6.0 (5.0, 7.0)	6.0 (4.0, 7.5)	0.64
Anorexia	391 (75.6%)	368 (75.9%)	23 (71.9%)	0.61
RLQ tenderness to cough, percussion, or hopping	274 (53.0%)	256 (52.8%)	18 (56.3%)	0.70
Fever (Temp ≥38.0ºC/100.4ºF)	164 (31.7%)	148 (30.5%)	16 (50.0%)	0.022
Nausea/Vomiting	444 (85.9%)	416 (85.8%)	28 (87.5%)	0.79
Tenderness over right iliac fossa	367 (71.0%)	348 (71.8%)	19 (59.4%)	0.14
Leukocytosis (WBC >10,000/µL)	311 (60.2%)	290 (59.8%)	21 (65.6%)	0.51
Neutrophilia (ANC >7,500/µL)	296 (57.3%)	276 (56.9%)	20 (62.5%)	0.54
Migration of pain to RLQ	204 (39.5%)	200 (41.2%)	4 (12.5%)	0.001

Abbreviation: IQR: Interquartile Range; CRP: C-Reactive Protein; H: Hour; D: Day; N: Sample Size; ER: Emergency Room; RLQ: Right Lower Quadrant; ANC: Absolute Neutrophil Count.

Table 3: Univariable and multivariable risk factor analyses for delayed diagnosis of appendicitis.

	Univariable analysis		Multivariable analysis	
Predictor	OR (95% CI)	*p*	OR (95% CI)	*p*
Obesity and/or overweight	1.19 (0.58-2.45)	0.64	1.06 (0.42-2.69)	0.90
Age categories				
Toddlers/preschoolers	Reference		Reference	
Children	0.29 (0.12-0.73)	0.008	0.38 (0.11-1.37)	0.14
Adolescents	0.21 (0.08-0.54)	0.001	0.32 (0.08-1.21)	0.09
Male	1.27 (0.60-2.70)	0.53	1.50 (0.59-3.80)	0.40
Hispanic	0.22 (0.05-0.93)	0.04	0.47 (0.10-2.23)	0.34
Initial visit site				
ER	Reference		Reference	
Urgent care	1.47 (0.33-6.64)	0.61	0.80 (0.12-5.21)	0.48
Clinic	1.31 (0.52-3.33)	0.56	0.93 (0.27-3.19)	0.91
Fever	2.28 (1.11-4.68)	0.025	1.38 (0.55-3.45)	0.49
Migration of pain	0.20 (0.07-0.59)	0.003	0.28 (0.08-0.91)	0.04
CRP≥10 mg/L	7.60 (3.55-16.31)	<0.001	6.58 (2.26-19.22)	<0.001
Method of diagnosis				
Clinical diagnosis	Reference			
US	0.44 (0.15-1.35)	0.15	0.26 (0.06-1.10)	0.07

CT	0.83 (0.29-2.37)	0.73	0.64 (0.18-2.31)	0.49
Others	1.46 (0.15-14.36)	0.75	0.80 (0.06-10.83)	0.87
Duration of symptoms				
< 12h				
12-24h	0.18 (0.03-0.88)	0.04	0.19 (0.03-1.04)	0.06
24-48h	0.71 (0.19-2.57)	0.60	0.55 (0.13-2.30)	0.42
48-72h	3.87 (1.33-11.25)	0.01	2.30 (0.62-8.61)	0.21
> 72h	9.56 (3.11-29.40)	3.11	10.08 (2.74-37.00)	0.001

Abbreviation: OR: Odds Ratio; CI: Confidence Interval; CRP: C-Reactive Protein; H: Hour; D: Day; N: Sample Size; ER: Emergency Room; RLQ: Right Lower Quadrant.

Table 4: Univariable and multivariable risk factor analyses for increased length of stay of children with acute appendicitis.

	Univariable analysis		**Multivariable analysis**	
Predictor	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Obesity and/or overweight	0.13 (-0.24-0.49)	0.49	0.19 (-0.07-0.44)	0.15
Age categories				
Toddlers/preschoolers	Reference		Reference	
Children	-1.40 (-1.99- -0.81)	<0.01	-0.39 (-0.84- -0.07)	0.10
Adolescents	-1.86 (-2.45- -1.27)	<0.01	-0.43 (-0.88- -0.03)	0.07
Male	0.26 (-0.10-0.62)	0.15	0.26 (0.01-0.51)	0.05
Hispanic	-0.45 (-0.87-0.03)	0.03	-0.17 (-0.47-0.14)	0.29
Open appendectomy	0.92 (0.22-1.62)	0.01	0.80 (0.27-1.33)	<0.01
Delayed diagnosis of appendicitis	2.98 (2.30-3.66)	<0.01	1.36 (0.83-1.89)	<0.01
Complications	1.82 (1.51-2.13)	<0.01	0.11 (-0.21-0.44)	0.49
Drain	3.22 (2.94-3.50)	<0.01	2.85 (2.48-3.22)	<0.01

Abbreviation: OR: Odds Ratio; CI: Confidence Interval; Complications: Perforated Appendix, Pre-Operative and Post-Operative Abscess Formation; Drain: Post-Operative Abdominal Drain and Nasogastric Tube Placement.

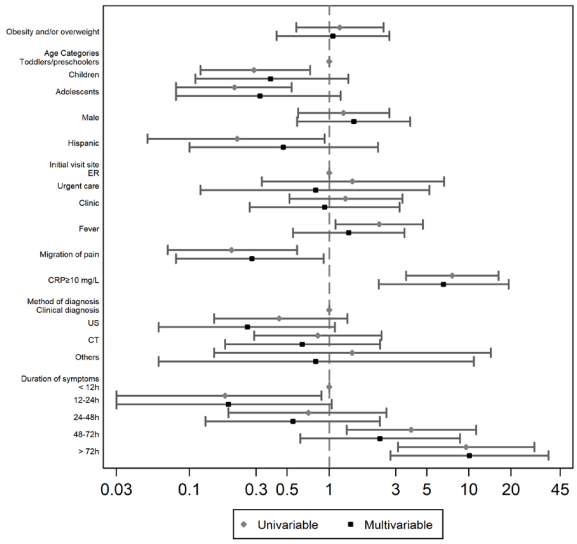

Figure 1: Summary of the univariable and multivariable logistic regression of the association between risk factors and delayed diagnosis of acute appendicitis.

Y-axis represents the risk factors under investigation and X-axis represents the odds ratio. A odds ratio of 1 is the reference point. Abbreviation: ER-Emergency Room, US- Ultrasound, CT-CT scan, h= hour.

Discussion

This study identified the risk factors associated with diagnostic delay of acute appendicitis among children in a single tertiary medical center in South Texas. Our finding suggested age and obesity were not significant risk factors associated with delayed diagnosis of acute appendicitis. It also demonstrated that elevated CRP level (≥10 mg/L) and prolonged symptoms are significantly risk factors for delayed diagnosis of acute appendicitis. Additionally, presence of migration of pain to the RLQ was associated with a decreased odds ratio of delayed diagnosis. These findings support the notion that a significantly elevated CRP in children suspected of acute appendicitis might be associated with a delayed diagnosis.

This study's results echoed previous studies exploring risk factors delaying appendicitis diagnosis. Similar to our findings, in a retrospective study conducted in South Korea, Choi, et al identified several factors associated with a delayed diagnosis appendicitis, including increased duration of symptoms, fever and CRP [15]. Furthermore, other risk factors not deemed significantly associated with delayed diagnosis in Choi et al, including age, sex, Body Mass Index (BMI), WBC and PAS, were also not risk factors in this study. An interesting difference between Choi et al.'s and ours studies was the absence in migrating pain as a risk factor for delayed diagnosis in Choi et al. The difference in these findings may be attributed to

the differences in the study populations and difference in medical practice. The study's location in Korea, where citizens are covered by a national health insurance system, may result in different ways of practicing medicine as compared to the physicians in the US. This may result in difference in accessibility to medical care and thresholds for ordering imaging studies (e.g. CT scan). Acute appendicitis typically begins with vague periumbilical pain resulting from the engorged appendix stimulating the surrounding visceral peritoneum [19,20]. The migration of pain to RLQ was a later presentation where the inflamed appendix caused localized irritation of the parietal peritoneum innervated by the same somatic nerve as the region of the abdominal wall [20]. Readily accessible medical care and imaging modalities (e.g. ultrasound, CT scan) help diagnose acute appendicitis at an early stage without the presence of RLQ pain. Additionally, the different definitions of delayed diagnosis of acute appendicitis between the two studies may be another contributing factor. This study defined delayed diagnosis as made more than 48 hours but less than a week from the initial encounter at a healthcare institution, while Choi et al defined delayed diagnosis as ≥24 hours from the initial visit to the final diagnosis and appendectomy. While our finite time window that is more specific in identifying children with delayed diagnosis may miss out a few significantly delayed diagnoses, Choi et al., lack of an upper limit for the time frame of delayed diagnosis of acute appendicitis may include cases with false positive cases. For example, a patient presented with an ER visit for acute gastroenteritis six weeks ago unrelated to the acute appendicitis might end up being labeled as delayed diagnosis of appendicitis. Consequently, this might introduce misclassification bias that subsequently skews the interpretation of the final result.

While the classic presentation of symptoms for acute appendicitis are well known [10]. Large variations in presentation may explain the pervasiveness of delayed diagnosis of acute appendicitis. Such cases warrant the use of other markers, including WBC, ANC and imaging that may facilitate the timely diagnosis of appendicitis. While CRP is not part of the PAS score criteria, our findings suggest significant elevation of CRP (≥10 mg/L) is associated with delayed diagnosis of acute appendicitis. This finding is pathophysiologically feasible as elevated CRP levels suggest a more prominent inflammatory process compatible with peritonitis and other complications (e.g., abscess formation) associated with severe inflammation caused by delayed diagnosis appendicitis. To test the hypothesis that significantly elevated CRP level is mediated by prominent inflammatory process secondary to the delayed diagnosis, we performed a mediation analysis. For the analysis of the secondary outcome, LOS (d), CRP was included in the model with or without inclusion of the variable delayed diagnosis of appendicitis. Before the introduction of the mediator, delayed diagnosis of appendicitis, a significantly elevated CRP level was significantly associated with the outcome (adjusted β, 0.51 [95% CI 0.81-0.94], p= 0.02); however, after the introduction of the mediator (adjusted β, 1.29 [95% CI 0.76-1.83], p<0.01), its association with the outcome became non-significant (adjusted β, 0.34 [95% CI -0.09-0.76], p= 0.12). The change of significance of the association between CRP and LOS suggested that delayed diagnosis of appendicitis and the prominent inflammatory process may be the mediator of significant elevation of CRP associated with a more severe hospital course. From the clinical perspective, a significant increase in CRP, presence of fever and the complaints of symptoms with several days should thus increase clinicians' suspicion of delayed presentation of acute appendicitis in children with equivocal history and physical findings.

Among the other clinical findings explored in this study, several noteworthy factors were not significantly associated with delayed diagnosis of acute appendicitis, age and obesity the most notable. It is believed that age could contribute to detection and diagnosis of appendicitis; patients lacking the verbal skills necessary to present their symptoms at the early stage of the disease may contribute to its misdiagnosis [21]. While descriptive statistics noted a lower median age for patients with delayed diagnosis, this association was no longer significant on multivariable logistic regression. This finding could be multifactorial. First, categorizing children into different age groups (e.g. toddlers, children and adolescents) may introduce residual confounding in the multivariable analyses. As a sensitivity analysis, age category was replaced with continuous age, but the association between age and delayed diagnosis still remains insignificant in the multivariable analyses. It could also result from inadequate statistical power. Interestingly, obesity and/or overweight status were not significant risk factors for the delayed diagnosis. This negative finding was also reported by Choi et al who did not find BMI to be a risk factor. It has been thought that increased BMI and higher body fat may affect the accuracy of physical examination and also hinder physicians diagnosing through US, as fat absorbs and diffuses the ultrasound beam [12]. This negative finding might be due to preferential use of abdominal CT instead of US for more obese patients by providers. This hypothesis is supported by our data that obese and/or overweight patients are less likely to receive US for the diagnosis of acute appendicitis than the patients with normal body habitus (59.53% vs 62.13%). However, as our dataset did not contain unique identifiers for healthcare providers, this hypothesis needs to be validated by future studies.

This study has several limitations. First, its retrospective nature and setting in a single, tertiary-care, non-profit pediatric hospital may limit the generalizability of the study's findings. Second, identifying factors associated with delayed diagnosis of appendicitis in this center may be hindered by non-standardized documentation of patient presentations in the hospital's Electronic Medical Records (EMR), introducing misclassification bias that confounds the final interpretation. There might be change of practice over the study period. For instance, as there is no structured protocol guiding when to use CT scan or US, it's based on providers' preference and experiences. Some may opt CT scan more frequent for overweight or obese patients, introducing bias to our results. Finally, the definition of delayed appendicitis, which sets an upper limit of delayed diagnosis to a week after the initial encounter, decreased its sensitivity in including all possible cases with longer sets of symptoms. However, this approach could provide us with more specific cases and preventing including false positive cases.

Conclusion

In conclusion, this study suggested that the initial elevated CRP levels (≥10 mg/L) is a significant risk factor for delayed diagnosis of appendicitis for children presented with acute appendicitis. Prompt diagnosis of acute appendicitis is crucial as the delayed diagnosis is associated with a more sever disease course and longer LOS.

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: 910-925.
2. Anderson JE, Bickler SW, Chang DC, Talamini MA. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. World J Surg. 2012; 36: 2787-2794.
3. Schmidt AS. Healthcare cost and utilization project (hcup). The SAGE encyclopedia of pharmacology and society. 2016; 1: 684-686.
4. Brennan GD. Pediatric appendicitis: pathophysiology and appropriate use of diagnostic imaging. CJEM. 2006; 8: 425-432.
5. Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med. 2000; 36: 39-51.
6. Samuel M. Pediatric appendicitis score. J Pediatr Surg. 2002; 37: 877-881.
7. Sack U, Biereder B, Elouahidi T, Bauer K, Keller T, et al. Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children. BMC Surg. 2006; 6: 15.
8. Williams R, Mackway-Jones K. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. White cell count and diagnosing appendicitis in children. Emerg Med J. 2002; 19: 428-429.
9. Kharbanda AB, Cosme Y, Liu K, Spitalnik SL, Dayan PS, et al. Discriminative accuracy of novel and traditional biomarkers in children with suspected appendicitis adjusted for duration of abdominal pain. Acad Emerg Med. 2011; 18: 567-574.
10. Bundy DG, Byerley JS, Liles EA, Perrin EM, Katznelson J, et al. Does this child have appendicitis? JAMA. 2007; 298: 438-451.
11. Kwan KY, Nager AL. Diagnosing pediatric appendicitis: usefulness of laboratory markers. Am J Emerg Med. 2010; 28: 1009-1015.
12. Aarssen MVd, Verhoef WA, Thijssen JM. Influence of absorbing and scattering media on the propagation of ultrasound. The Journal of the Acoustical Society of America. 1989; 85: 567-575.
13. Garcia Pena BM, Mandl KD, Kraus SJ, Fischer AC, Fleisher GR, et al. Ultrasonography and limited computed tomography in the diagnosis and management of appendicitis in children. JAMA. 1999; 282: 1041-1046.
14. Frush DP, , Rosen NS. Computed tomography and radiation risks: what pediatric health care providers should know. Pediatrics. 2003; 112: 951-957.
15. Choi JY, Ryoo E, Jo JH, Hann T, Kim SM, et al. Risk factors of delayed diagnosis of acute appendicitis in children: for early detection of acute appendicitis. Korean J Pediatr. 2016; 59: 368-373.
16. Myers AL, Williams RF, Giles K, Waters TM, Eubanks III JW, et al. Hospital Cost Analysis of a Prospective, Randomized Trial of Early vs Interval Appendectomy for Perforated Appendicitis in Children. Journal of the American College of Surgeons. 2012; 214: 427-434.
17. Foster BA, Maness TM, Aquino CA. Trends and Disparities in the Prevalence of Childhood Obesity in South Texas between 2009 and 2015. J Obes. 2017; 2017: 1424968.
18. (US) IoM. Childhood Obesity Prevention in Texas: Workshop Summary. Washington (DC): National Academies Press (US); 2009.
19. Birnbaum BA, Wilson SR. Appendicitis at the millennium. Radiology. 2000; 215: 337-348.
20. Mulholland MW LK, Doherty GM, Maier RV, Simeone DM, Upchurch GR. Greenfield's Surgery: Scientific Principles and Practice. 5 ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
21. Rothrock SG, Pagane J. Acute appendicitis in children: Emergency department diagnosis and management. Annals of Emergency Medicine. 2000; 36: 39-51.