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Young children with perforated appendicitis benefit from prompt appendectomy☆,☆☆

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ABSTRACT

Background/Purpose: To identify factors associated with nonoperative treatment failure in pediatric perforated appendicitis compared to immediate appendectomy.
Methods: After IRB approval, between September 2016 and August 2017, prospective data were recorded for children (age: 1–18 years) with completed appendectomies and pathologist-confirmed perforations. Children were treated according to clinician-designated preference. Nonoperative treatment was considered failed if a nonresolving obstruction developed or any return of symptoms before the planned interval. The median time from pain onset to treatment initiation was 3 days (range: 1–14). Presentation on days 1 or 2 (early) was compared to day 3 or after(late). The nonoperatives were compared to appendectomies stratified by presentation time. Variables were compared by chi-square, Fisher exact or t-tests. Logistic regression evaluated for independence.
Results: Of 201 suspected perforations, 176 were included, 101 (57%) immediate appendectomies and 75 (43%) nonoperatives. Of 75, 24 (32%) failed; 6 (25%) in hospital, 18 (75%) after discharge. In 51 (68%), nonoperative treatment succeeded. Significantly younger children failed nonoperative treatment ($p = 0.03$). Failure was independently associated with treatment initiation within 2.75 days from pain onset (OR: 0.07, 95% CI: 0.57–0.98) ($p = 0.010$) and lower WBC at presentation (OR: 0.03, 95% CI: 0.81–0.98) ($p = 0.014$). When compared to immediate appendectomy, nonoperatives had more morbidity.
Conclusion: Younger children fail nonoperative treatment, perforate rapidly and have a significantly lower WBC, but benefit from immediate appendectomy.
Level of evidence: Treatment Study Level II.

More than 30% of children with pediatric appendicitis present with perforation [1]. Younger children often have a diagnostic delay, which contributes to a complex clinical course [2]. For acute nonperforated appendicitis, the literature is extensive, but the management of perforated appendicitis remains controversial.

In the past two decades, initial antibiotic administration and interval appendectomy emerged as a frequent approach to pediatric perforated appendicitis. Retrospective, nonrandomized studies report that delayed appendectomy results in fewer overall complications, wound infections, abscesses and reoperations. Better quality, randomized studies refute this and recommend early appendectomy. The failure rate for nonoperative management ranges between 25% and 35%. Variability exists as to which specific factors promote failure.

The aims of this study were to identify factors associated with nonoperative treatment failure in pediatric perforated appendicitis and to compare the results of children with nonoperative treatment to immediate laparoscopic appendectomy based on early or late presentation.

1. Methods

1.1. Cohort

After Institutional Review Board (IRB) approval, between September 2016 and August 2017, complete data were prospectively collected for children, between 1 and 18 years of age, diagnosed with suspected perforated appendicitis at one University Children's Hospital. All presented with their first episode of appendicitis and no previously reported attacks of abdominal pain. Because this study involved deidentified data with minimal risk to subjects, the IRB granted a waiver of consent. We

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defined appendiceal perforation as a hole in the appendix identified after pathologic examination [3]. Only children that met this criterion were included.

Children were designated to undergo an immediate appendectomy or nonoperative management based on clinician-specific practice. Review of case logs revealed one surgeon favored appendectomy, even if a well-formed abscess was present on imaging. Two surgeons had an equal division of cases between surgery and nonoperative management. However, in children with a well-formed abscess on imaging, nonoperative management was favored by these two.

Immediate appendectomy was defined as the surgeon's initial decision to perform appendectomy without trial of nonoperative management and without radiologic drain placement for preoperative imaged abscess. For patients undergoing immediate appendectomy the median time from consult to appendectomy was 11.9 h (range 0.5–106.5 h). The variance in range was because of one child aspirating on induction requiring respiratory stabilization prior to appendectomy. All children in the immediate appendectomy group followed the same antibiotic protocol as the nonoperative management group. Nonoperative management consisted of the administration of intravenous piperacillin/tazobactam and metronidazole, followed by oral augmentin and metronidazole for a total of ten days. Oral antibiotics were administered when the child tolerated a regular diet meal without emesis. If an abscess was identified on imaging, an interventional radiologist evaluated for drain placement and drainage was performed if the abscess was amenable [4].

Nonoperative management was considered failed if the child never tolerated one full regular diet meal within 5 days of admission. If the child developed unrelenting abdominal pain, intestinal obstruction, or returned to the hospital after discharge for continued symptoms prior to the designated interval appendectomy, they were considered failed [5,6]. Laparoscopic interval appendectomy was planned between 6 and 8 weeks after hospital discharge [7].

All laparoscopic appendectomies were performed by the standard three-port technique and open was through a McBurney's incision. All operations were evenly distributed between three surgeons with over 20 years of experience.

1.2. Variables

Variables recorded were age, gender, days of abdominal pain prior to presentation, and the first white blood cell (WBC) count obtained on admission. The results of radiographs, computed tomography (CT) scans and ultrasounds (US), obtained either before or after appendectomy, were documented. The presence of an abscess, abscess size in centimeters and whether the abscess was drained were recorded. The use of a nasogastric tube (NGT) at any point during hospitalization was documented.

Intraoperative variables included operative time and any conversion to an open procedure. The presence of a fecalith was identified from the pathology report. Any operation for mechanical obstruction was also documented.

The specific time to appendectomy was recorded, including whether it was performed on the first admission as planned immediate appendectomy or as an immediate failure, a discharge and return for failure, or as a planned interval appendectomy. Postoperative variables identified were time to tolerate one regular diet meal without emesis, time from discharge to readmission, hospital length of stay (LOS) during the first admission, LOS following appendectomy, and total hospital days for all appendicitis related admissions.

1.3. Variable comparison, statistical analysis, logistic regression

For the cohort, the median time between the first report of abdominal pain and initiation of either nonoperative management or appendectomy was three days (range: 1–9 days). Children with appendectomy or initiation of nonoperative therapy on day one or two from pain onset (early) were compared to those with treatment initiation on day three or later (late). Subgroup analysis was performed to examine those with abscess on initial imaging at time of presentation and compare nonoperative treatment to immediate laparoscopic appendectomy based on early or late presentation.

Categorical and continuous variables were analyzed by chi-square and t-tests, respectively. A P-value less than 0.05 was considered statistically significant. Data were reported as mean and standard deviation, median and range. Logistic regression analysis evaluated for variable independence.

2. Results

2.1. Cohort

The study cohort is illustrated in Fig. 1. Two-hundred and one children with suspected perforated appendicitis were designated by their clinician to undergo immediate appendectomy or nonoperative management. Twenty-five (12.4%) had no evidence of perforation on pathologic examination and were excluded. Of the remaining 176 (87.6%), 101 (57.4%) had an immediate appendectomy and 75 (42.6%) underwent nonoperative management. Within the nonoperative group, 24 (32.0%) were considered to have failed.

Male gender was distributed as 59.1% of the cohort, 67.3% in the immediate appendectomy group and 48.0% in the nonoperative group. It was never statistically significant.

For the cohort, 163/176 (92.6%) underwent a successful laparoscopic appendectomy. Of the 13 (7.4%) with an open appendectomy, eight (61.5%) were planned open owing to appendiceal location or other comorbidities and five (38.5%) were conversions to open. Within the five converted, three were for obstruction, one for repair of multiple enterotomies, and one for technical difficulty.

2.2. Nonoperative management

Seventy-five children (42.6%) initially underwent nonoperative management for suspected perforated appendicitis. Fifty-one (68.0%) returned for interval appendectomy at the specified time-point. Children that succeeded are compared to those that failed in Table 1.

Of the 24 children that failed, six (25.0%) had an unresolving mechanical obstruction during their initial hospitalization necessitating operation. Eighteen (75.0%) were initially discharged, but returned to hospital, prior to the specified interval appendectomy, owing to recurrent symptoms or the development of an obstruction. The children that failed were evenly distributed between early and late groups (Fig. 1).

Children that failed were significantly younger ($p = <0.01$), had lower WBC counts ($p = 0.01$), had fewer abscesses ($p = 0.02$), and the abscess diameter was significantly smaller ($p = <0.01$).

Operative times were significantly shorter ($p = 0.02$) for the successful interval appendectomy group. Four children that failed required conversion to open procedure for three obstructions and one for technical difficulties, whereas no patient in the successful interval group required conversion. For the failures, LOS after operation, as well as total days in hospital, was significantly longer ($p = <0.01$).

Logistic regression revealed that failure of nonoperative management was independently associated with treatment initiation within 2.75 days from pain onset (OR: 0.07, 95% CI: 0.57–0.98) ($p = 0.01$) and a lower WBC at presentation (OR: 0.03, 95% CI: 0.81–0.98) ($p = 0.01$).

2.3. Comparison of immediate appendectomy to nonoperative management

For the study period, children with an immediate appendectomy are compared to those with nonoperative management, and stratified by early or late treatment initiation, in Table 2. Children with early presentation and treatment that underwent immediate appendectomy had significantly shorter initial hospital stays ($p = <0.01$), fewer readmissions for any reason ($p = 0.01$), shorter operative times ($p = <0.01$), fewer days

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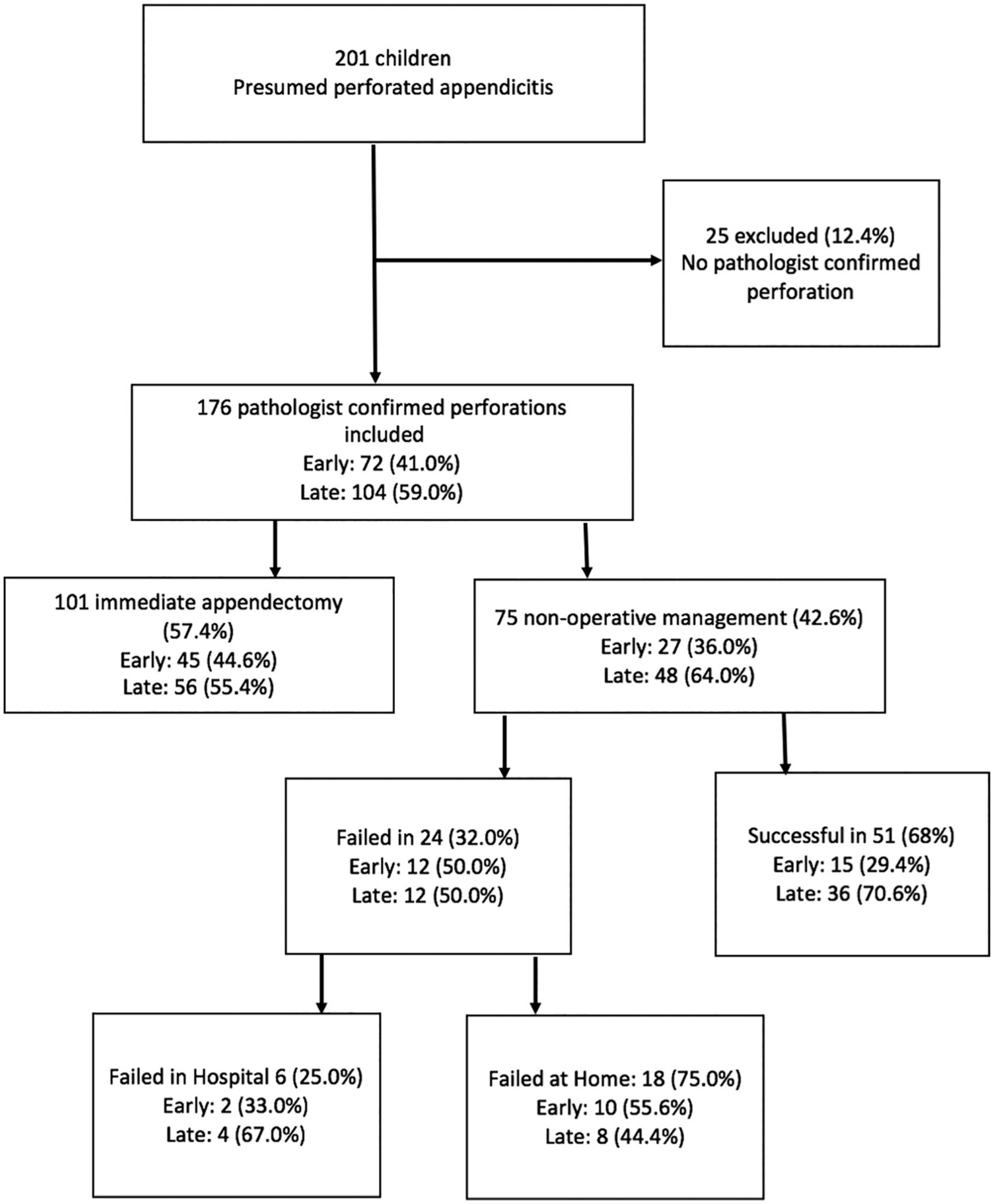

Fig. 1. Treatment strategy and outcome for the cohort stratified by treatment initiation time from pain onset.

to tolerate regular diet ($p = 0.03$), and fewer overall total hospital days ($p = <0.01$).

Within the late group, children with immediate appendectomy had significantly fewer CT scans ($p = <0.01$). Although the hospital stays immediately following appendectomy, for interval appendectomies, in the nonoperative management group were significantly shorter than those with immediate appendectomy ($p < 0.01$), overall, children with nonoperative management and late presentation spent significantly more time in hospital ($p = 0.02$).

2.4. Comparison of immediate appendectomy to nonoperative management in 53 children with a preoperative imaged abscess

A subgroup analysis was performed for 53 children who, at time of presentation, had an imaged abscess (Table 3). This group was analyzed based on early or late presentation and initial treatment modality (immediate appendectomy vs nonoperative management).

Results of this subgroup analysis demonstrate that for the cohort, the only statistically significant difference was that children with imaged abscesses at time of presentation in the nonoperative group had larger abscesses.

When groups were stratified based on symptom duration at time of presentation (early vs late), abscess size at presentation was significantly smaller in the early immediate appendectomy group ($p = 0.02$). Additionally, time to regular diet was significantly shorter in the early presentation immediate appendectomy group when compared to their early nonoperative management counterparts ($p = 0.04$). No other factor was significantly different.

For children with imaged abscess at presentation, 22/37(59.5%) underwent drainage procedure and those that were not drained were considered to have abscesses too small or not amenable to drainage procedure owing to anatomic location.

Two children in the late nonoperative management group underwent conversion to open appendectomy and none in the early presentation

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Table 1
Factors associated with failure of nonoperative treatment for perforated appendicitis.

Demographics/presentation (n = 75)	Failure n = 24 (%)	Success n = 51 (%)	P
Age (years)[a]	7.3 (3.8) (7.5, 2.0–14.0)	10.0 (3.7) (11.0, 2.0–16.0)	<**0.01**
Pain onset to presentation (days)	2.8 (1.4) (2.5, 1.0–5.0)	4.1 (2.7) (3.0, 1.0–14.0)	**0.02**
WBC count	14.9 (6.3) (16.9, 1.7–24.6)	18.9 (5.9) (18.2, 3.7–33.2)	**0.01**
Imaged abscess	8 (33.3)	29 (56.9)	0.08
Abscess drained	6 (25.0)	28(54.9)	**0.02**
Abscess diameter (cm)	1.7 (2.6) (0.0, 2.0–10.0)	4.9(2.2) (5.0, 0.0–9.0)	<**0.01**
>1 CT scan	4 (16.7)	14 (27.5)	0.39
NG placed	8 (33.3)	9 (17.6)	0.15
1st admission LOS (days)	9.4 (11.6)[b] (5.5, 1.0–58.0)	6.4 (5.5) (5.0, 1.0–35.0)	0.11
Time to appendectomy (days)	79.9 (71.9)[c] (57.0, 3.0–275.0)	121.6 (74.8) (103.0, 44.0–395.0)	**0.05**
Obstruction operations (no abscess in 5/6)	6 (25)	0	NA
Appendectomies (n = 75)			
Operative time (min)	127.8 (61.1) (107.5, 57.0–339.0)	101.2 (22.6) (99.0, 56.0–147.0)	**0.02**
Fecalith	12 (50.0)	28 (54.9)	0.80
Conversion to open	4 (16.7)	0	NA
Time to regular diet (days)[d]	6.5 (9.0) (3.0, 1.0–43.0)	3.8 (3.2) (2.0, 1.0–14.0)	0.06
LOS after appendectomy (days)[c]	4.7 (2.9) (4.0, 0.0–11.0)	0.4 (1.0) (0.0, 0.0–5.0)	<**0.01**
Total hospital LOS (days)[e]	12.9 (11.3) (9.5, 5.0–58.0)	6.7 (5.9) (5.0, 1.0–38.0)	<**0.01**

Values in bold represent significant findings as demonstrated by p-value ≤ 0.05.
[a] Continuous data are presented as mean +/— standard deviation, median and range.
[b] Includes 6 appendectomies that failed during 1st admission with obstruction.
[c] Includes 18 children, as 6 underwent appendectomy on first admission when they failed.
[d] Initial hospitalization.
[e] All hospital days related to appendicitis treatment.

Table 2
Comparison of nonoperative treatment to appendectomy stratified by early or late presentation.

Demographics/presentation	Early (day 1 or 2)			Late (day 3 or >)		
	Appendectomy n = 45(%)	Nonop n = 27(%)	P	Appendectomy n = 56(%)	Nonop n = 48(%)	P
Age (years)[a]	7.8 (3.5) (8.0, 2.0–17.0)	8.6 (4.4) (9,.0, 2.0–16.0)	0.27	9.5 (3.9) (9.5, 1.8–17.0)	9.4 (3.7) (10.0, 2.0–16.0)	0.91
WBC	16.4 (5.1) (17.0, 5.6–26.0)	16.7 (5.3) (17.5, 1.7–27.7)	0.77	16.9 (6.1) (16.3, 6.3–37.5)	18.0 (6.8) (19.0, 2.8–33.2)	0.33
Imaged abscess	7 (15.5)	5 (18.5)	0.75	9 (16.1)	32 (66.7)	<**0.01**
>1 CT scan	2 (4.4)	4 (14.3)	0.19	3 (5.4)	18 (38.3)	<**0.01**
NG placed	6 (13.3)	4 (14.3)	1.0	18 (32.1)	13 (27.0)	0.67
1st admission LOS (days)[a]	3.6 (2.3) (3.0, 1.0–11.0)	7.0 (6.9) (4.0, 1.0–35.0)	< **0.01**	5.6 (4.3) (4.0, 1.0–24.0)	7.6(8.7) (5.0, 1.0–58.0)	0.12
Any readmission[b]	2 (4.4)	10 (35.7)	<**0.01**	0	14 (29.2)	NA
Time to readmission (days)	11.5 (6.4) (11.5, 7.0–16.0)	78.3 (69.4) (59.0, 11.0–245.0)	0.22	0	108.1 (109.9) (79.5, 8.0–395.0)	NA
Obstruction operations	0	4 (14.3)[c]	NA	1 (1.8)[d]	5 (10.4)[e]	0.09
Appendectomies (n = 176)						
Operative time (min)	88.6 (27.2) (87.0, 33.0–144.0)	110.6 (33.5) (104.5, 56.0–228.0)	< **0.01**	99.8 (30.8) (98.0, 43.0–209.0)	112.1(49.1) (99.5, 57.0–339.0)	0.14
Conversion to open	0	1 (3.6)	NA	1 (1.8)	3 (6.4)	0.33
Time to regular diet (days)	2.5 (2.1) (2.0, 1.0–9.0)	4.2 (4.1) (2.0, 1.0–17.0)	**0.03**	4.4 (4.1) (3.0, 1.0–23.0)	4.9 (6.6) (3.0, 0.0–43.0)	0.64
LOS after appendectomy (days)	3.6 (2.3) (3.0, 1.0–11.0)	2.4 (3.0) (1.5, 0.0–11.0)	0.06	5.6 (4.3) (4.0, 1.0–24.0)	1.3 (2.5) (0.0, 0.0–11.0)	<**0.01**
Total hospital LOS (days)	3.6 (2.3) (3.0, 1.0–11.0)	8.8 (8.0) (7.0, 2.0–29.0)	<**0.01**	5.6 (4.3) (4.0, 1.0–24.0)	8.6 (8.8) (6.0, 1.0–58.0)	**0.02**

Values in bold represent significant findings as demonstrated by p-value ≤ 0.05.
[a] Continuous data are presented as mean +/— standard deviation.
[b] No readmission was for intraabdominal abscess formation.
[c] Four adhesive obstructions, no abscess.
[d] One obstruction from abscess
[e] Four obstructions owing to abscess, 1 adhesive obstruction without abscess.

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Table 3
Preoperative imaged abscess for 53 children: Comparison of nonoperative treatment to appendectomy stratified by early or late presentation.

	Cohort			Early (days 1–2)			Late (Day 3 or greater)		
	Appendectomy n = 16%)	Nonop n = 37(%)	P	Appendectomy n = 7(%)	Nonop n = 5(%)	P	Appendectomy n = 9 (%)	Nonop n = 32(%)	P
Age (years)[a]	8.4 (3.7) (8.5, 2.0–15.0)	10.1 (4.1) (11.0, 2.0–16.0)	0.16	6.8 (4.1) (8.0, 2.0–12.0)	11.0 (5.4) (11.0, 3.0–16.0)	0.16	9.7 (2.9) (9.0, 6.0–15.0)	10.0 (3.9) (10.5, 2.0–16.0)	0.81
Size of Abscess (cm)[a]	3.0 (1.3) (2.7, 1.3–5.3)	4.7 (2.4) (4.2, 0.0–10.0)	**0.01**	2.3 (0.9) (2.0, 1.3–4.0)	4.5 (2.0) (4.0, 2.0–7.0)	**0.02**	3.5 (1.3) (3.0, 2.0–5.3)	4.7 (2.5) (4.5, 0.0–10.0)	0.18
Preop Drain	0	22	NA	0	3	NA	0	19	NA
Operative Time (min)[a]	100.9 (30.9) (94.5, 56.0–144.0)	112.8 (55.3) (94.0, 56.-339.0)	0.44	98.0 (35.2) (92.0, 56.0–144.0)	84.3 (28.0) (85.0, 56.0–112.0)	0.57	103.2 (29.0) (97.0, 58.0–143.0)	116. 2 (57.1) (95.0, 66.0–339.0)	0.52
Time to Regular Diet (days)[a]	3.7 (3.5) (2.0, 1.0–15.0)	4.8 (7.2) (3.0, 0.0–43.0)	0.56	2.0 (0.6) (2.0, 1.0–3.0)	4.4 (2.7) (4.0, 2.0–9.0)	**0.04**	5.0 (4.2) (5.0, 1.0–15.0)	4.9 (7.7) (2.5, 0.0–43.0)	0.96
1st admission LOS (days)[a]	4.6 (3.2) (4.0, 1.0–15.0)	7.6 (9.6) (5.0, 1.0–58.0)	0.22	3.3 (0.8) (3.0, 2.0–4.0)	5.4 (3.1) (4.0, 2.0–10.0)	0.11	5.6 (4.1) (6.0, 1.0–15.0)	8.0 (10.3) (5.0, 1.0–58.0)	0.50
Total Hospital LOS (day)[a,b]	4.6 (3.2) (4.0, 1.0–15.0)	8.3 (9.7) (5.0, 1.0–58.0)	0.14	3.3 (0.8) (3.0, 2.0–4.0)	5.4 (3.1) (4.0, 2.0–10.0)	0.11	5.6 (4.1) (6.0, 1.0–15.0)	8.7 (10.3) (5.5, 1.0–58.0)	0.38

Values in bold represent significant findings as demonstrated by p-value ≤ 0.05.
[a] Continuous data are presented as mean +/− standard deviation, median and range.
[b] Total hospital days for all appendicitis related admissions: initial and interval appendectomy stays.

group were converted. All children in the early nonoperative management group underwent outpatient interval appendectomies. Those in the late group had a median stay of one day and ranged from zero to six days.

3. Discussion

This study prospectively compares children with successful nonoperative treatment for perforated appendicitis to those that failed. Rapid perforation, within 2.75 days of pain onset, and a lower WBC count at presentation, are independently associated with nonoperative management failure. It demonstrates significantly younger children fail and an overall failure rate of 32%, comparable to previous studies. These findings are consistent with others that report a high incidence of perforated appendicitis in younger children, a rapid onset of perforation symptoms and a complex clinical course. A recent retrospective study reported a failure rate of 63% in children less than five years of age [8].

This study identifies that a lower WBC count at presentation is independently associated with nonoperative management failure. Conflicting reports exist regarding the impact of the WBC count on the diagnosis and the clinical course of perforated appendicitis in children [1]. The finding that a lower WBC count independently predicts failure, contrasts with several previous studies [6]. Many of these reports, however, contain older children and document a much longer initial clinical history before evaluation and therefore, may not be comparable to the children in this study.

In addition to a lower WBC count, both our study and previous studies, demonstrate younger children that fail have fewer and smaller abscesses on initial imaging [6]. Younger children mount a less aggressive immune response to the inflammatory process of appendicitis.

When children designated to undergo immediate appendectomy are compared to nonoperative management, overall, they spend significantly less time in hospital and tolerate diet faster. Morbidity is most significantly reduced in the younger, early presentation group. The later presentation group also spends significantly less time in hospital when treated with immediate appendectomy. A recent randomized trial found a significantly longer hospital stay and overall higher adverse event rate in children treated with nonoperative management [7]. It recommends immediate appendectomy for the majority of cases of perforated appendicitis, with or without an abscess. Similarly, we found that early appendectomy, despite presence of preoperative imaged abscess, is beneficial.

Similarly, a large, administrative database analysis reports that 30% of children discharged without an appendectomy return to hospital [9]. Consistent with our findings, both studies conclude that children with perforated appendicitis benefit from immediate appendectomy. Additionally, one randomized control trial that evaluated quality of life from parent's perspective demonstrated worse quality of life in children undergoing interval appendectomy [10].

A significantly greater number of children with a late presentation and nonoperative management, undergo more than one abdominal CT scan. Others report a three-fold increase in the number of CT scans in children with late presentation, or failure of nonoperative management. We promote the institution of an imaging protocol to reduce radiation exposure [5].

There are several limitations to our study. It is a single institution study, but this limitation is offset by a large sample size. All data were complete, prospective and contemporaneously collected. A strict pathologic definition of appendiceal perforation was applied to all included cases. Children were not randomized; however, when the cohort was divided by the median time from pain onset to treatment initiation, it was divided into comparable groups.

In conclusion immediate appendectomy, despite length of symptoms prior to presentation, is beneficial. Nonoperative management failure is associated with rapid perforation, younger age and lower WBC at presentation.

CRediT authorship contribution statement

Amanda Munoz: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Rajaie Hazboun:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Ian Vannix:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Victoria Pepper:** Data curation, Writing - original draft, Writing - review & editing. **Tabitha Crane:** Data curation, Writing - review & editing. **Edward Tagge:** Data curation, Writing - review & editing. **Donald Moores:** Data curation, Writing - review & editing. **Joanne Baerg:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

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