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ORIGINAL ARTICLE

Time course response of inflammatory markers in pediatric appendicitis

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Abstract

Purpose We aim to evaluate the diagnostic value and time course response of the triple inflammatory markers: white blood cell count (WBC), neutrophil percentage (Neu), and C-reactive protein (CRP) in pediatric acute appendicitis.

Methods A retrospective review of clinical data pertaining to 1391 patients admitted with suspicion for pediatric appendicitis from 2012 to 2017 was conducted. Triple inflammatory markers were acquired upon admission. Appendicitis was confirmed histologically post-appendectomy. The diagnostic value and time course response of these markers was trended in relation to the duration of abdominal pain on admission.

Results 718 patients had histologically confirmed appendicitis. WBC and Neu demonstrate high sensitivity for early appendicitis at 94.6% and 80.0% at Day 1, while CRP demonstrates highest sensitivity of 97.9% at Day 4. The triple markers had poor overall diagnostic value when interpreted individually, however, had a high combined sensitivity of 99.7% and negative predictive value of 98.7% regardless of duration of disease. Overall negative appendectomy rate was 6.7% ($n=52$). Among 19 patients with triple markers negative who underwent appendectomy, 17 (89.5%) were histologically normal.

Conclusions The triple inflammatory markers have limited diagnostic value when interpreted individually, but are strong discriminators of pediatric appendicitis when combined. Their high sensitivity and negative predictive value could potentially help patients avoid unnecessary admissions or costly imaging studies, and reduce negative appendectomy rates. In addition, their objective nature confers an advantage over existing clinical scoring systems which comprise subjective elements.

Keywords White blood cells · Neutrophil · C-reactive protein · Appendicitis · Pediatrics · Diagnosis

Introduction

Acute appendicitis is a common surgical problem in children seen at the Emergency Department or outpatient clinics [1]. Misdiagnosis and delayed diagnosis are associated with appendiceal perforation, phlegmon or peritonitis, and their associated morbidity [2]. On the other hand, a false-positive diagnosis of appendicitis leads to negative appendicectomy, which significantly increases clinical and healthcare financial burden [3].

The diagnosis of appendicitis relies on a triad of concise clinical history and examination, laboratory tests and imaging studies. However, accurate clinical evaluation of abdominal pain in the pediatric population can often be challenging due to inherent difficulties in communicating symptoms [4], as well as atypical disease presentations, which can occur in up to 45% of patients [5]. Objective laboratory tests and imaging studies are, therefore, crucial for making accurate

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diagnosis. Ultrasound (US) followed by computed tomography (CT) scans are common imaging studies for diagnosing appendicitis [6, 7]. However, their disadvantages include their cost, operator dependency and radiation exposure, and hence should not be routine first-line diagnostic options in children [6, 8].

Serum inflammatory markers such as white blood cells (WBC), neutrophils (Neu) and C-reactive protein (CRP) are widely accepted laboratory tests in the workup of abdominal pain with suspected appendicitis [9]. Each inflammatory marker is thought to respond to specific disease stages: an elevated WBC is a marker of uncomplicated appendicitis, while CRP tends to be markedly elevated following appendiceal perforation or abscess formation [10]. However, individually they are neither sensitive nor specific enough for diagnosing or ruling out appendicitis [11]. A few papers, including a recent study conducted by our institution, have demonstrated that combination of the triple inflammatory markers has a dramatically improved diagnostic value for appendicitis [10, 12, 13]. The combined sensitivity of WBC, Neu and CRP is close to 100% although it is unclear why this combination of inflammation markers significantly increases diagnostic value.

We hypothesize that each individual inflammatory marker has a specific time-dependent response in the course of acute appendicitis. Combining all three markers will increase the diagnostic accuracy regardless of the stage of appendicitis. To test these hypotheses, we evaluated the time course response of each inflammatory marker in pediatric appendicitis, and determined the predictive values of WBC, Neu and CRP, both individually and collectively as triple markers.

Materials and methods

Study design

This is a large-scale retrospective cohort study for children admitted to the surgical unit of an urban tertiary pediatric hospital in Singapore between July 2012 and August 2017, for right lower quadrant abdominal pain with suspicion of acute appendicitis. This study was conducted in accordance with the guidelines of the ethics committee of our institution (IRB number: 2016/2646).

Children admitted to the surgical ward from Children's Emergency with suspicion of acute appendicitis, based on clinical history and physical examination findings of right iliac fossa tenderness were included. In our institution, patients are triaged in the Children's Emergency and admissions are at the discretion of emergency physicians. All patients with prior surgery or appendicectomy, gastrointestinal conditions particularly inflammatory bowel disease, pregnancy, malignancy, or who were non-communicative at baseline, were excluded.

All eligible patients were reviewed upon admission by an experienced pediatric surgeon. For each patient, a standardized set of blood tests including WBC, Neu and CRP was obtained within 4 h after admission as per usual clinical practice. WBC and Neu measurements were performed using a Sysmex XE-5000 analyzer. CRP levels were measured with the Abbott Architect c8000 analyzer. Cut-off points for the three inflammatory markers were set as the following: 10,000/μL (WBC), 75% (Neu) and 5 mg/L (CRP), based on our previous study [13]. The diagnostic value of WBC, Neu and CRP was assessed individually and collectively as a set of triple markers. 'Triple markers positive' indicated that one or more of the markers were above the cut-off values, and 'triple markers negative' indicated that all were below the cut-off values.

Each serum inflammatory marker also trended in relation to the duration of abdominal pain at the point of admission, which was used as a surrogate parameter for duration of disease. For example, blood samples taken at admission for a patient with a 3-day history of symptoms were considered 'Day 3' samples. All patients with confirmed diagnosis of acute appendicitis, based on presentation, laboratory testing and/or radiologic imaging, were offered appendicectomy. None were treated conservatively in this study.

Additional data collection included patient demographic characteristics, intra-operative findings at appendicectomy, and histopathological diagnosis of the appendix specimen.

Outcome measures

Appendicitis: Patients were confirmed to have appendicitis based on histopathological diagnosis, as defined by the presence of mucosal or transmural inflammatory infiltrates. Serosal inflammation or presence of faecolith without any inflammation was not considered appendicitis in our study. Complicated appendicitis was defined as appendicitis associated with perforation or abscess formation [14].

Non-appendicitis: The diagnosis of non-appendicitis was based on clinical evaluation with or without radiologic imaging, or a finding of histologically normal appendix after surgery. This group of patients was observed in the ward until their symptoms improved for at least 24 h based on current institution practice. In addition, they were contacted within 3 days after discharge to confirm resolution of symptoms.

Statistical analysis

The data were tested for normality of distribution with Kolmogorov–Smirnov test, using parametric or non-parametric tests as appropriate. Statistical analysis was performed using the two-tailed Student's *t* test, one-way ANOVA with

Table 1 Demographics and clinical characteristics (APP vs non-APP)

	Appendicitis (mean ± SD)	Non-appendicitis (mean ± SD)	*P* value
Number of patients	718	673	
Gender (M:F)	460:258	354:319	< 0.0001
Age (years)	12.1 ± 3.3	10.2 ± 3.4	0.024
WBC (10^9/L)	15.4 ± 5.0	10.1 ± 4.1	< 0.0001
Neutrophil (%)	78.2 ± 11.8	62.8 ± 15.6	< 0.0001
CRP (mg/L)	59.9 ± 78.4	31.2 ± 63.0	< 0.0001
Duration of pain (days)	1.6 ± 1.1	2.1 ± 1.7	< 0.0001

Table 2 Demographics and clinical characteristics (simple vs complicated APP)

	Simple APP	Complicated APP	*P* value
Number of patients	525	193	
Gender (M:F)	345:185	120:73	0.525
Age (mean + SD)	12.4 ± 3.2	11.3 ± 3.7	< 0.0001
WBC (10^9/L)	15.0 ± 4.7	16.6 ± 5.7	< 0.001
Neutrophil (%)	76.8 ± 12.5	82.4 ± 8.5	< 0.0001
CRP (mg/L)	33.6 ± 40.5	131.6 ± 106.8	< 0.0001
Duration of pain (days)	1.3 ± 1.0	2.3 ± 1.1	< 0.0001

Bonferroni post-test, Mann–Whitney *U* test and chi-square test. Data were presented as mean ± standard deviation (SD). A *P* value of < 0.05 was considered significant.

Results

Demographics and clinical characteristics

A total of 1391 patients between the ages of 2 and 16 years were included in this study. As shown in Table 1, histologically confirmed appendicitis (APP) was seen in 718 (51.6%) of patients, while the remaining patients without appendicitis (non-APP) had predominantly non-surgical conditions including, but not restricted to, mesenteric adenitis, gastroenteritis and constipation colic.

There was a greater predominance of males in the APP group (64.1%) vs non-APP group (52.7%; $P < 0.0001$; Table 1). Presentation after onset of abdominal pain was also earlier in the APP group (1.6 ± 1.1 days) as compared to the non-APP group (2.1 ± 1.7 days; $P < 0.0001$; Table 1). The overall serum levels of all three inflammatory markers (WBC, Neu and CRP) were significantly elevated in the APP group compared to non-APP group ($P < 0.0001$; Table 1).

Within the APP group, a subset analysis was performed to compare patients with simple ($n = 525$) and complicated ($n = 193$) appendicitis. Patients with complicated appendicitis were found to present later (2.3 ± 1.1 days) than those with simple appendicitis (1.3 ± 1.0 days; $P < 0.0001$; Table 2). The levels of triple inflammatory markers were significantly more elevated in the complicated appendicitis group compared to the simple appendicitis group, in particular CRP ($P < 0.0001$), correlating with the later stage of presentation of complicated appendicitis.

Time course response of inflammatory markers in APP and non-APP

To assess the time course response of inflammatory markers in APP and non-APP cases, the trend of serum levels of each inflammatory marker in relation to the duration of abdominal pain was analyzed. The number of patients presenting at Days 1–5 of abdominal pain is presented in Supplementary Table 1. Average WBC and Neu levels remained relatively constant from Days 1 to 5 of appendicitis (Fig. 1). On the contrary, CRP levels demonstrated a more acute elevation alongside disease progression, rising from 20 mg/L on Day 1, to 117 mg/L by Day 4 in the APP group. In non-APP cases, serum levels of the triple inflammatory markers showed a similar trend overall, although the increase in CRP was not as dramatic as compared to the APP cases over the same duration of disease progression.

The sensitivity of each inflammatory marker was obtained by calculating probability (percentage) of the result being above cut-off value, among patients with appendicitis. Although changes in the average level of WBC and Neu was minimal within the first 5 days of appendicitis, the sensitivity of WBC and Neu decreased as disease progressed. WBC and Neu had the highest sensitivities of 94.6% and 80.5% from Day 1, and decreased to 64.9% and 51.1%, respectively, by Day 5. Conversely, CRP sensitivity was 60.9% at Day 1 and increased to 97.9% by Day 4. When interpreted collectively, the combined sensitivity of these triple inflammatory markers was high at 99.7% from Day 1, and remained consistently high for at least the first 5 days from disease onset (Fig. 2; Supplementary Table 2). Compared to the consistent near-100% sensitivity in APP group, triple markers were positive in approximately 80% of the non-APP group across Days 1–5 (Supplementary Fig. 1).

Diagnostic value of inflammatory markers in pediatric appendicitis

Each individual inflammatory marker demonstrated poor overall diagnostic value, with sensitivities of WBC, Neu and CRP at 87%, 73% and 82%, and specificities of 53%, 67% and 41%, respectively (Table 3). None had a negative or positive predictive value exceeding 80%, thereby limiting their individual clinical application in diagnosing appendicitis. On the contrary, the combined triple markers exhibited a

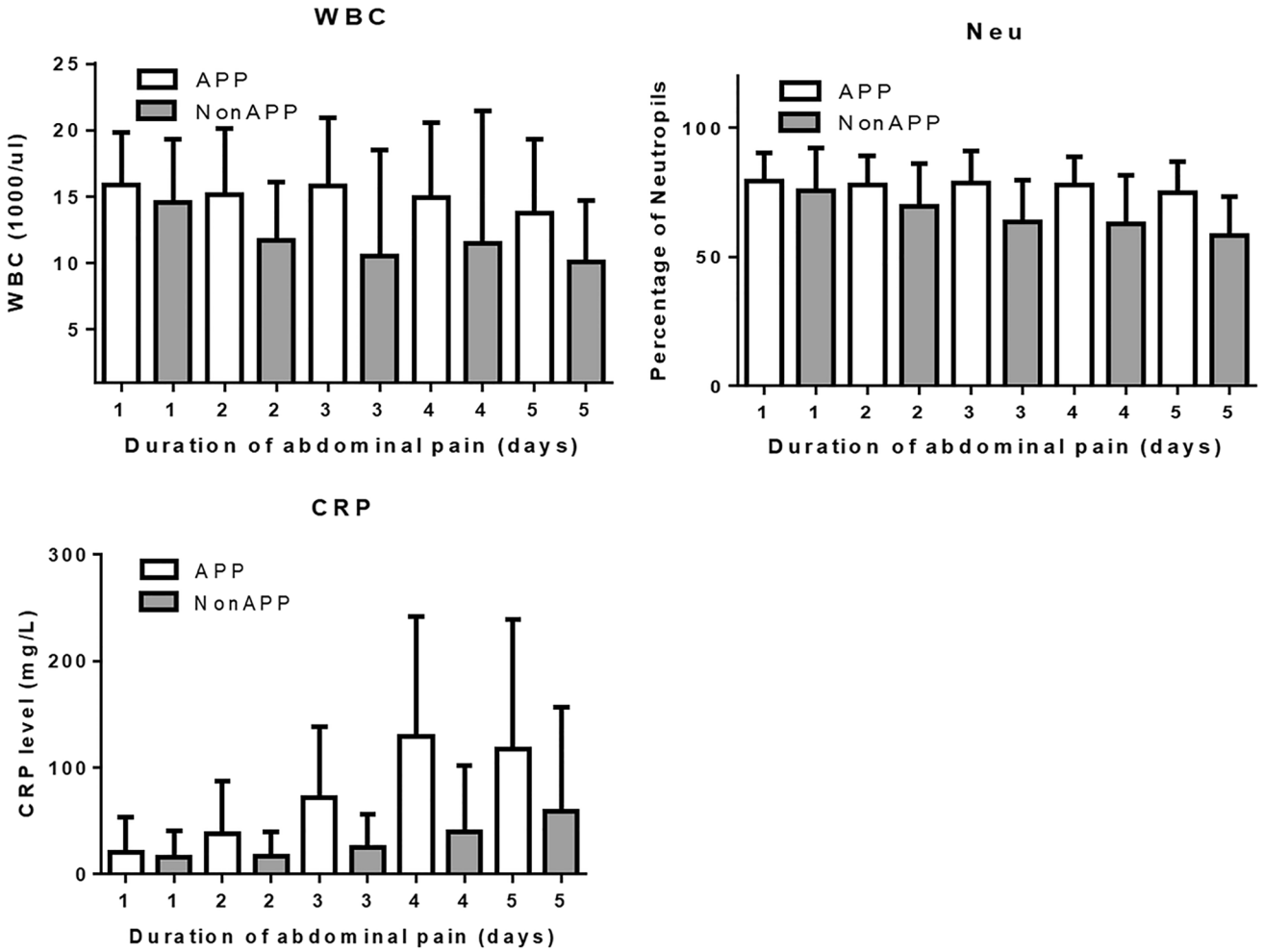

Fig. 1 Time course response of WBC, Neu and CRP in patients with appendicitis (APP) vs non-appendicitis (non-APP)

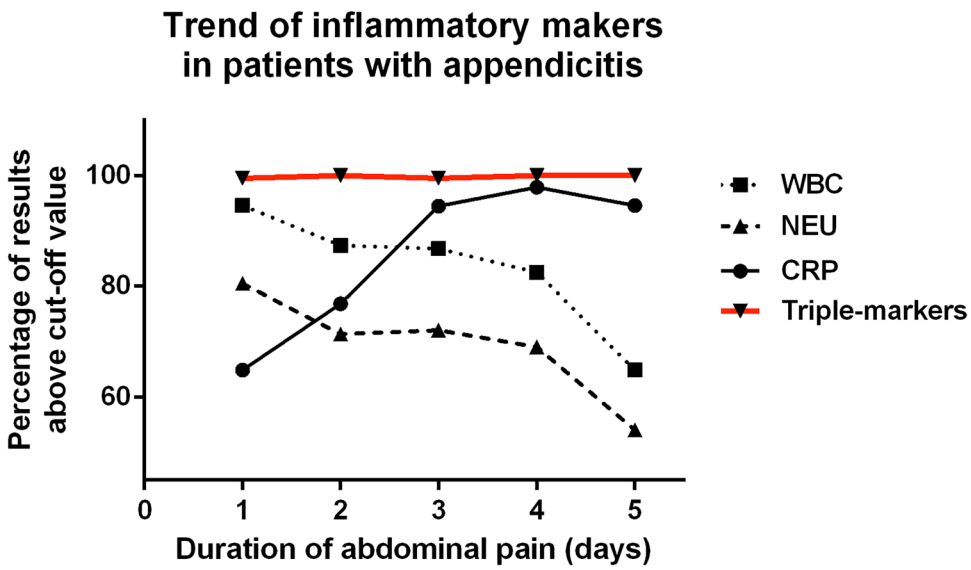

Fig. 2 Time course of percentages of inflammatory markers above cut-off value in patients with appendicitis (APP)

high overall sensitivity of 99.7% and a high negative predictive value of 98.7% (Table 3).

Specificity of each inflammatory marker was obtained by calculating probability (percentage) of results below cut-off value, among patients with non-appendicitis conditions. In contrast to their high sensitivity, specificity of the inflammatory markers was low—not exceeding 85.2% in the analysis for individual markers, with a value of 23.6% for the combined triple markers. The combined triple markers demonstrated low AUC (area under receiver operating curve) values from Days 1 to 5, ranging between 0.55 and 0.63, likely contributed to by the low specificity (Supplementary Table 2).

Further sub-set analysis comparing the diagnostic performance of the combined triple markers in patients below 7 years of age, vs 7 years and above (Supplementary Table 3), was conducted. This was arbitrarily chosen as the age above which children may be better able to report their own symptoms. A similar pattern was demonstrated across both groups: sensitivity and NPV were high at 99.7 to 100%, and 98.7 to 100%, respectively. Specificity and PPV were conversely low at 9.9 to 26.6%, and 11.4 to 63.4%, respectively.

In our cohort, 161 patients (11.6%) had triple markers negative, of which 159 had non-APP conditions. The remaining 2 (0.01%) were found to have early uncomplicated appendicitis. Conversely, 76.4% of the non-APP group had triple markers positive, with a low overall specificity of 23.6% and low PPV of 70.2%. The data, therefore, demonstrate the utility of these triple markers in ruling out appendicitis, but reflects their poor performance as a stand-alone predictive tool in diagnosing appendicitis.

Negative appendicectomy

770 patients underwent surgery, with a negative appendicectomy rate of 6.7% ($n=52$). As shown in Fig. 3, among 751 patients with triple markers positive, the negative appendicectomy rate was only 4.7% ($n=35$). However, of the 19 patients with triple markers negative who underwent appendicectomy, the negative appendicectomy rate significantly increased to 89.5% ($n=17$; $P<0.0001$).

Discussion

There are many studies in the existing literature investigating the role of serum inflammatory markers in the diagnosis of pediatric appendicitis. To the best of our knowledge, this is the first study evaluating the time course response of the triple inflammatory markers WBC, Neu and CRP, across days of appendicitis progression. We found that WBC and Neu demonstrated high sensitivity for early appendicitis, whereas CRP performs better later on in the disease course. In addition, our data demonstrated that the combination of triple markers has a high sensitivity for acute appendicitis exceeding 99%.

These results may be explained by the pathophysiological responses to the underlying inflammatory processes: appendicitis is typically secondary to bacterial infection. The invading pathogen activates the innate immune system, which stimulates the bone marrow to produce and release

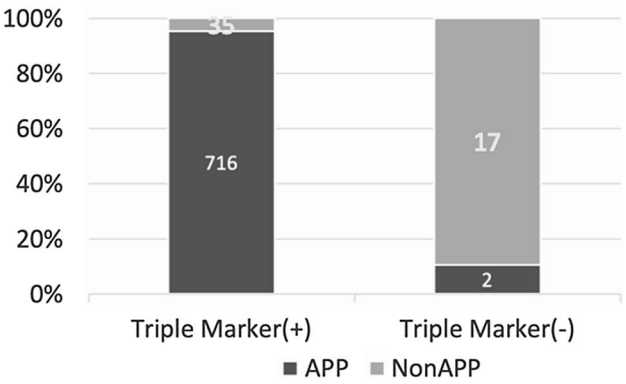

Fig. 3 APP vs non-APP patients with triple markers positive and negative

Table 3 Overall diagnostic value of the inflammatory markers

Cut-off value		APP	Non-APP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC ≥ 10,000/μL	Y	625	319	87.0	52.6	66.2	79.2
	N	93	354				
Neu ≥ 75%	Y	524	224	73.0	66.7	70.1	69.8
	N	194	449				
CRP ≥ 5 mg/L	Y	589	394	82.0	41.4	59.9	68.4
	N	129	279				
Combined triple markers	Y	716	514	99.7	23.6	70.2	98.7
	N	2	159				

Y above cut-off value, *N* below cut-off value, *PPV* positive predictive values, *NPV* negative predictive values

leukocytes via various cytokine and inflammatory mediators [15]. Serum levels of leucocytes and neutrophils increase significantly immediately after infection, after which neutrophils exit from the peripheral vasculature and migrate to the site of infection. In severe or later phases of appendicitis, neutrophil consumption often exceeds its production, resulting in the decreased peripheral leucocyte count and neutrophil percentage [16]. Hence, serum WBC and Neu demonstrate a high sensitivity in early but not later stages of appendicitis.

CRP is a widely used acute phase protein that is synthesized in the liver. The average doubling time for CRP during infection is approximately 8 h and, therefore, requires almost 24 h to exceed its cut-off value (5 mg/L) from an average baseline level of 0.8 mg/L [17]. CRP will continue to rise in the presence of inflammation, and can reach above 500 mg/L in severe infection, making it an excellent marker for delayed and severe inflammation [18].

In children, history taking is often difficult and inaccurate, especially in the pre-verbal age group. Significant morbidity can arise from delays in diagnosing and treating appendicitis, including perforation, pelvic abscess, prolonged hospital stay, late adhesive bowel obstruction [19]; on the other hand, over-diagnosis exposes children to unnecessary radiation exposure and potential risk of surgical complications. Inappropriate or unnecessary admissions, furthermore, increase the financial burden on healthcare systems. Having the right tools to make a timely and accurate diagnosis is, therefore, essential. Serum markers comprise part of the basic diagnostic workup, and understanding the time course response of the triple inflammatory markers aids the clinician in making a more accurate diagnosis [20]. WBC and Neu levels may be considered more relevant in patients presenting with a shorter history of pain, while CRP is more reliable in patients with a later presentation. The triple combination of WBC, Neu and CRP in our study was consistent in achieving almost 100% overall sensitivity and negative predictive value for pediatric appendicitis, regardless of the duration of disease onset. A pediatric patient with triple markers positive should, therefore, be carefully considered for further imaging workup if clinical symptoms and signs for appendicitis are equivocal.

On the contrary, if there is clinical suspicion of acute appendicitis, having all triple markers negative can help to exclude it in 98.7% of cases. Of the patients with triple markers negative in our cohort, the negative appendicectomy rate was 89.5%—in retrospect, it was found that most had false-positive radiological findings. This implies that having triple markers negative can help the patient avoid unnecessary and often costly imaging scans, and consequently reduce the incidence of negative appendicectomy.

Existing scoring systems have been widely reported in the literature, mostly validated for the adult population, such as the Alvarado score. Samuel et al. [19] published a simple Pediatric Appendicitis Score (PAS) in 2002, and Kharbanda et al., developed and validated the Pediatric Appendicitis Risk Calculator (pARC) in 2018, both of which incorporate the use of WBC. pARC additionally uses neutrophil count, and includes subjective assessors such as tenderness associated with walking, migratory pain and abdominal guarding. These scores have not been widely validated for very young children of pre-verbal age, and the PAS, which has been primarily validated in studies conducted by Children's Emergency physicians, has variable accuracy and limited clinical use on external validation [21]. Patients with intermediate risk scores of 4 and above would still require further diagnostic studies. The use of the triple inflammatory markers is advantageous as an objective tool incorporating simple and readily obtained serum blood tests in the assessment of children with suspected appendicitis, and overcomes the issues of subjective or inaccurate histories encountered with younger children (Supplementary Table 3). Furthermore, the triple inflammatory markers have an excellent NPV of 98.7%, which is superior to other clinical scoring systems in excluding appendicitis.

A natural extension to this study would be to examine the diagnostic utility of the triple markers as point of care investigations in Children's Emergency. Our patients were pre-selected as all inpatients had already undergone triage and assessment in Children's Emergency prior to admission. Many of them were non-APP conditions and might have avoided admission to the surgical department if they had their triple markers evaluated in ED. This utility might extend even to a general practice setting, thus reducing unnecessary hospital burden, given that most non-surgical causes of abdominal pain may be treated in the community.

Strengths

Our study has a large cohort of 1391 patients, all of whom were treated at a dedicated pediatric institution serving the majority of the pediatric population in Singapore. All patients were managed as per standard department protocol with regard to choice of blood investigations, and decisions on radiologic imaging. They were closely monitored in hospital and routinely followed up with a telephone call 3 days after discharge, to minimize the risk of missed appendicitis.

Limitations

Our study is limited by its retrospective nature, with blood tests mostly done at a single time point for each patient. An ideal evaluation of the time course response of the inflammatory markers would have involved a prospective longitudinal study where these markers are repeated at pre-determined time intervals. However, such a prospective longitudinal study is

ethically impossible as timely diagnosis is crucial and to avoid complications of appendicitis.

Another limitation is that the poor specificity (23.6%) of triple markers limits its value in diagnosis of appendicitis. Only 23.6% non-APP patients in our cohort have triple markers negative. Although appendicitis can be confidently ruled out in this scenario, the rest of non-APP patients (76.4%) have 1 or more positive inflammatory markers, and may require further investigations such as radiologic imaging in the diagnostic workup for appendicitis.

Conclusion

The triple inflammatory markers WBC, Neu and CRP have limited diagnostic utility on their own, but are strong discriminators of pediatric appendicitis when interpreted in combination given their high sensitivity and NPV. These simple serum tests should always be included as part of the diagnostic workup of pediatric patients with suspected appendicitis. Appendicitis can be more confidently ruled out in patients with triple markers negative, therefore, potentially avoiding unnecessary admissions, radiologic imaging, surgery, and their associated costs. However, the poor specificity of the triple marker implies that further investigations, such as radiologic imaging, may still be required. Triple markers are, therefore, best applied as a test to exclude appendicitis, and they do that quite well.

Author contributions Study conception and design: Dr Angus, Dr Yap, Dr Nah, Dr Low, Dr Jacobsen, Ms Choo and Dr Chen. Data acquisition: Dr Angus, Dr Chiang, Dr Yap and Dr Chen. Analysis and data interpretation: Dr Angus, Dr Chiang, Dr Yap and Dr Chen. Drafting of the manuscript: Dr Chiang and Dr Chen. Critical revision: Dr Angus, Dr Chiang, Dr Yap, Dr Nah, Dr Low, Dr Jacobsen, Ms Choo and Dr Chen.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

Ethical approval This study was approved by centralized institutional review board in Singapore, SingHealth (CIRB number: 2016/2646). All procedures performed in studies were in accordance with the ethical standards of the institution.

Informed consent A waiver of informed consent was approved in accordance with the local ethical standards for non-interventional, retrospective study.

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