

The Coagulation Profile as a Marker for Acute Appendicitis in the Paediatric Population: Retrospective Study

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Abstract

Introduction: Appendicitis is the commonest and most frequently misdiagnosed acute abdominal surgical illness in the paediatric population worldwide. The aim of this study is to evaluate the role of coagulation profile in acute appendicitis (AA) in children. **Materials and Methods:** we retrospectively collected data of patients submitted to appendectomy from 2011 to 2017. According to histopathology, patients were divided into three groups: not histologically confirmed AA (NAA), simple AA (SAA) and complicated AA (CAA). White blood cell (WBC) count, relative neutrophilia (Neutr%), C-reactive protein (CRP), prothrombin time ratio (PTratio), activated partial thromboplastin time ratio (APTratio) and fibrinogen (Fib) were compared among groups. **Results:** Three hundred and seven patients were included: 57 NAA, 184 SAA and 66 CAA. WBC was significantly different among groups: CAA (mean $16.67 \times 10^3/\text{ml}$), SAA ($14.73 \times 10^3/\text{ml}$, $P = 0.01$) and NAA ($10.85 \times 10^3/\text{ml}$, $P < 0.0001$). Significant differences were found for Neutr% (mean CAA 81.14 vs. SAA 77.03 $P = 0.006$, vs. NAA 63.86 $P < 0.0001$) and CRP (mean NAA 2.56, SAA 3.26, CAA 11.58, $P < 0.0001$). PTratio and Fib increased with the severity of AA receiver operator characteristic curves were similar for CRP (0.739), Fib (0.726), WBC (0.746) and Neutr% (0.754), while for PTratio and APTratio were 0.634 and 0.441, respectively. **Conclusions:** extrinsic coagulation pathway is altered in AA, especially in CAA. Coagulation can be useful in the diagnostic and perioperative anaesthetic management of AA in children. Fib seems to have the highest accuracy.

Keywords: Appendicitis, children, coagulation

INTRODUCTION

Appendicitis is the most common and most frequently misdiagnosed acute abdominal surgical illness in the paediatric population worldwide.^[1] Since the initial presentation of the disease is often obscure and closely mimicked by other common paediatric diseases, the precise diagnosis of acute appendicitis (AA) still remains a challenge for general and paediatric surgeons.^[2,3] In the majority of children with suspected AA, the combination of clinical history and physical examination should be sufficient to formulate the diagnosis.^[4] To improve diagnostic accuracy, much has been argued about the sensitivity and specificity of elevated white blood cell (WBC) count and C-reactive protein (CRP).^[5] Furthermore, AA is often associated with a systemic inflammatory response^[6] and this leads to the activation of the coagulation cascade. Indeed,

abdominal infection and inflammation almost invariably lead to haemostatic abnormalities, ranging from insignificant laboratory changes to disseminated intravascular coagulation,^[7] which may impact on anaesthesia and surgical technique. However, limited data relative to coagulation changes in AA are available.

The aim of this study was to correlate blood tests that are routinely performed pre-operatively to histological findings, focussing in particular on the alterations of coagulation markers and their relationship with degrees of the severity of appendicitis.

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MATERIALS AND METHODS

Study population

This single-centre retrospective study enrolled consecutive patients who underwent appendectomy at our Institution between June 2011 and December 2017. Only patients who had an International Classification of Diseases, Ninth Revision–Clinical Modification procedure code of appendectomy for AA (47.01, 47.09, ×47.2, 47.99) were recruited. Incidental appendectomies were excluded from the study. Patients with a history of Vitamin K deficiency, haemorrhagic, thrombotic, hepatic or renal diseases, and those who received Vitamin K antagonists or heparin in the 2-weeks before surgery were also excluded. Patients' files and reports were reviewed. Patients with incomplete records were also excluded. According to histological findings, the population was divided into three groups: not histologically confirmed AA (NAA), simple AA (SAA) and complicated AA (CAA, including patients with appendicular abscesses and patients with perforated appendixes). NAA included those cases whose histology did not show signs of inflammation and were, therefore, designated as control group. Data were collected and stored according to Data Protection Act. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and according to the ethical standards of our Institution.

Protocol

Pre-operative blood tests were performed in all patients admitted for suspected AA, according to the Institutional protocol (Protocol P. 003.500). These included, among others, WBC count, relative neutrophilia (Neutr%), CRP, fibrinogen (Fib), prothrombin time ratio (PTratio) and activated partial thromboplastin time ratio (aPTTratio). Children with the unequivocal clinical picture of appendicitis underwent appendectomy without further delay. Children with equivocal clinical presentation underwent consecutive physical examinations, observation and occasional Ultrasound imaging, according to surgeons' preference.

Laboratory analysis

Blood samples were collected by venipuncture on admission, and all analyses were completed within 2 h from the collection. PTratio was calculated by RecombiPlasTin 2G (DiaPharma Group, West Chester, Ohio); the aPTTratio was measured by SyntASil (Instrumentation Laboratory, Brussels, Belgium); Fib was measured by Fib-C XL (DiaPharma Group, West Chester, Ohio); WBC and the Neutrophil fraction counts were performed with XE-2100 Sysmex (Sysmex America Inc-Lincolnshire, Illinois). CRP was measured with the particle enhanced immunoturbidimetric test (Roche/HirtachicobasC system).

Statistical analysis

Data are presented with descriptive statistic as mean (range, standard deviation [SD]). Pre-operative blood examinations were analysed and compared among groups. The Kruskal–Wallis and Wilcoxon Mann–Whitney rank-sum tests were used for comparison among groups. To evaluate the diagnostic accuracy of the different parameters, multiple logistic regression models were fitted, and the receiver operator characteristic (ROC) curves were derived. Statistical analysis was performed using the software Stata (version 13, TStat S.r.l, Sulmona, Italy).

RESULTS

During the study period, 579 children, 336 males (58%) and 243 females (42%), underwent appendectomy. Due to the inclusion and exclusion criteria, 307 patients (53%) were included in the study: the mean age was 10.64 years (SD ± 5.8, range 0.6–17.9 years). Fifty-seven patients (19%) had a NAA, 184 (60%) a SAA, and 66 (21%) a CAA [Figure 1].

Blood test results of the three groups are reported in Table 1.

These results show that WBC, Neutr%, CRP, Fib, were significantly different among all groups, increasing according to the severity of the disease. PTratio was not significantly different between NAA and SAA but was significantly higher

Table 1: Blood test results

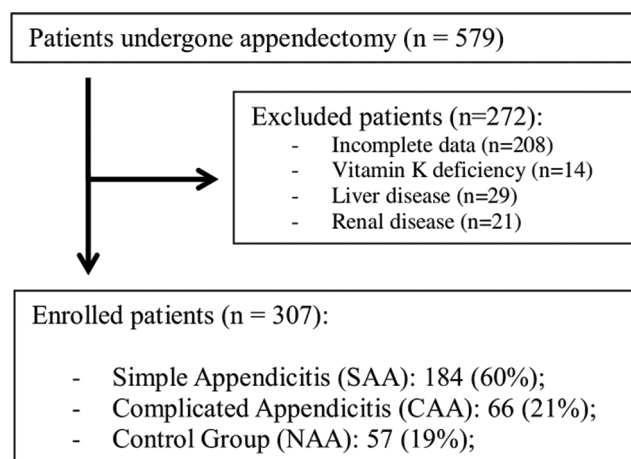
	Mean ± SD			P
	NAA	SAA	CAA	
WBC	10856±4973.5	14733±4675.5	16660±5862.2	NAA versus SAA $P<0.0001^*$, NAA versus CAA $P<0.0001^*$, SAA versus CAA $P=0.01^*$
Neutrophils %	63.86±16.85	77.03±10.80	81.14±8.01	NAA versus SAA $P<0.0001^*$, NAA versus CAA $P<0.0001^*$, SAA versus CAA $P=0.007^*$
CRP (mg/dl)	2.56±5.41	3.26±3.93	11.58±9.92	NAA versus SAA $P<0.0001^*$, NAA versus CAA $P<0.0001^*$, SAA versus CAA $P<0.0001^*$
PT ratio	1.16±0.14	1.19±0.15	1.32±0.16	NAA versus SAA $P=0.078$, NAA versus CAA $P<0.001^*$, SAA versus CAA $P<0.001^*$
aPTT ratio	1.02±0.10	1.01±0.16	0.97±0.10	NAA versus SAA $P=0.461$, NAA versus CAA $P=0.012^*$, SAA versus CAA $P=0.021^*$
Fib (mg/dL)	317.2±130.7	369.7±111.4	555±192.2	NAA versus SAA $P=0.0001^*$, NAA versus CAA $P<0.0001^*$, SAA versus CAA $P<0.0001^*$

NAA: Not-histologically confirmed acute appendicitis, SAA: Simple acute appendicitis, CAA: Complicated acute appendicitis, WBC: White blood cells, Neutrophils %: Relative neutrophilia, CRP: C-reactive protein, PT ratio: Prothrombin time, aPTT ratio: Activated partial thromboplastin time ratio, Fib: Fibrinogen (Wilcoxon rank-sum Mann-Whitney test), SD: Standard deviation

Table 2: Results of receiver operator characteristic curve analysis in patients with acute appendicitis

	Observed	ROC area	Standard error	95% CI
White blood cells	307	0.7465	0.0409	0.6662-0.8267
Neutrophil %	307	0.7546	0.0387	0.6787-0.8304
CRP	307	0.7398	0.0412	0.6589-0.8206
Fibrinogen	307	0.7260	0.0378	0.6518-0.8001
PT ratio	307	0.6343	0.0403	0.5552-0.7133
aPTT ratio	307	0.4416	0.0420	0.3592-0.5240

CI: Confidence interval, ROC: Receiver operator characteristic, CRP: C-reactive protein, PT ratio: Prothrombin time, aPTT ratio: Activated partial thromboplastin time ratio

**Figure 1:** Patients at study

in CAA compared both to NAA and SAA. APTT ratio was, on the contrary, significantly lower in CAA when compared to both SAA and NAA. As for PTratio no differences were found between NAA and SAA.

ROC curve analysis was applied to evaluate the accuracy of the blood tests in the diagnosis of AA [Table 2].

Neutr% showed the largest ROC curve area (ROC area = 0.7546). ROC curves were similar for CRP (0.739), Fib (0.726), WBC (0.746) and Neutr% (0.754), while for PTratio and aPTT ratio were 0.634 and 0.441, respectively.

DISCUSSION

Appendicitis is the most common surgical disease in children (0–18 years), its incidence ranging from 1 to 2 cases/1000 children in the age group of 0–4 years to 25 cases/1000 children in the group of 10–17 years.^[8]

It is considered a surgical urgency, since a missed diagnosis can lead to severe consequences, such as appendicular rupture, peritonitis and lethal spreading infection.

The diagnosis of appendicitis is essentially clinical, based on the classical triad of manifestations: typical abdominal pain worsening over time, anorexia or vomit, and fever, the

latter being due to systemic immune response associated to abnormal blood tests (left-shifted leucocytosis, raised CRP level and altered coagulation tests).^[4] However, this pattern of symptoms is present only in 50%–60% of the patients and many studies have been done to find complementary diagnostic tools, such as ultrasound scan (US), computed tomography (CT), abdominal X-ray and upper gastrointestinal contrast imaging.

Indeed, Kaiser *et al.*,^[9] in a study performed on 600 children between 1991 and 2000, showed that after the introduction of US and CT the negative appendectomy rate was substantially reduced, while the rate of perforation after admission was not increased.

In a retrospective study on 923 children admitted to an Emergency Department for suspected appendicitis Di Cesare *et al.*^[4] found that clinical assessment remains the milestone to diagnose appendicitis. They also concluded that the use of imaging (expressly US) should be limited to cases with misleading history, equivocal findings and in girls over 10 years.

Our study shows that WBC, Neutr%, Fib level and CRP significantly correlate with the histological severity of the disease, as well as PTratio and APTT ratio, although the derangement of the latter does not clearly differentiate between NAA and SAA. We, therefore, suggest that all these information can usefully improve the diagnostic accuracy.

Many studies have shown the importance of WBC and Neutr%, which are routinely obtained in children with suspected appendicitis, in supporting the diagnosis. In a comprehensive review of 42 studies on the topic, Bundy *et al.*^[2] stated that a WBC count of <10,000/ μ L decreases the likelihood of appendicitis (likelihood ratio [LR] 0.22; 95% confidence interval [CI], 0.17–0.30), as well as an absolute neutrophil count of 6750/ μ L or lower (LR, 0.06; 95% CI, 0.03–0.16). Even though the clinical relevance of these tests is still debatable,^[2,4,5] at least the first observation is in keeping with our results.

Increased levels of CRP are useful, complementing the diagnosis of AA.^[2,4] It has been reported that children showing CRP levels of 1.7 mg/dL or higher are more likely to have appendicitis than children with lower levels (LR 2.9; 95% CI, 1.2–7.0).^[10] Increased CRP, in combination with the neutrophil count, markedly improves specificity and positive predictive value.^[11] Nevertheless, CRP neither alone nor in combination with WBC seems to be significantly better than the WBC alone.^[4,12]

The use of other blood tests to confirm diagnosis of AA is still strongly debated. Some centres have proposed to look for endotoxin from Gram-negative bacteria, although regional and systemic bacteraemia was detected only in a small proportion of patients with AA.^[5,13] Bacterial endotoxin or exotoxin may be responsible of a generalised inflammatory response, as they activate the pro-inflammatory cytokine network.^[6,14]

Other studies compared the diagnostic accuracy of serum inflammatory markers in differentiating between simple and complicated appendicitis in children. These included interleukin (IL) level (IL-1, IL-4, IL-6, IL-8, IL-10), neutrophil cluster of differentiation 64 expression,^[6,15] tumour necrosis factor-alpha (TNF-alpha), acid alpha-glycoprotein, endotoxin^[16] and procalcitonine.^[11] As cytokine measurements have known limitations, including a flawed correlation between biological activity and immunoassay, they may not accurately reflect temporal trends.^[6] In general, all these markers are characterised by a questionable diagnostic accuracy, are expensive, and thus they are not routinely used.

Mean platelet volume (MPV), which is part of a standard full blood count, is a marker of platelet production and function, and it has been shown to mirror the severity of inflammation. Significant changes in MPV were found in cardiovascular, cerebrovascular and rheumatoid joint diseases and in some other inflammatory disorders.^[17] In a retrospective analysis of 100 patients with AA, a significant reduction in the MPV was noticed in patients with AA when compared to healthy subjects. Therefore, MPV turned out to be useful in diagnosing AA. However, its sensitivity and specificity were statistically lower than WBC count and Neutr%.^[17]

PTratio and APTTratio are part of pre-operative work out in most Western countries, and are routinely performed in patients with suspected appendicitis. In a steady-state, there is a homeostatic balance between coagulation and fibrinolysis, while the coagulation pathway is disordered during inflammation when cytokines (TNF alpha, IL1 and IL6), leukocytes (neutrophils and monocytes) and CRP activate a shift toward antifibrinolysis and coagulation. In our study, we showed a significant prolongation of the PTratio with the severity of appendicitis. However, PTratio was not useful to differentiate between NAA and SAA, showing that its prolongation is particularly helpful in identifying complicated cases of AA. When considering APTTratio our study showed that its values were on the contrary significantly lower in patients with CAA, while no differences were found between SAA and NAA.

This observation confirms that of Li *et al.*,^[14] who evaluated the extrinsic and intrinsic coagulation pathways in patients with AA. They found that factor VII (FVII): C was significantly lower in patients with AA than in controls, while there were no significant differences in FIX: C, suggesting that coagulation changes involved predominantly the extrinsic pathway. The decrease of FVII levels should be ascribed to a tissue factor coagulation pathway, rather than to decreased liver synthesis.^[18] In this study, FVII blood increased turnover and redistribution of activated FVII secondary, on turn, to the activation of the concentration significantly decreased with the increasing severity of appendicitis, suggesting that it may be a sensitive marker, as well as PTratio in our study, of severe complicated cases of AA, nearly evolving into severe sepsis.

Our study also confirms the previous observation by Feng *et al.*, who reported increased plasma Fib level in patients with AA, significantly correlating with disease severity. These Authors suggested its use as a predictive marker of appendicular perforation.^[19]

From a practical point of view, the results of these blood tests, routinely performed preoperatively in most Western countries, may help in identifying complicated cases of AA which will require prompt treatment. At the same time, they may identify those patients, with initial degree of inflammation, who may benefit from a 'wait and see' approach, aiding to reduce the proportion of negative appendectomies. Alternatively, they may support investigations aimed to identify other surgical diseases encompassed in the differential diagnosis of appendicitis.

The routine use of broad-spectrum antibiotic therapy is contraindicated in children with fever and abdominal pain. Rather, the antimicrobial treatment for paediatric patients with complicated intra-abdominal infection should take into account the putative focus of infection and the severity of illness.^[20] As alterations of extrinsic coagulation tests suggest an increased likelihood of severe or complicated appendicitis, the usually empiric antibiotic therapy should be adapted accordingly.

The results of this study also point out possible implications in perioperative and anaesthetic management. Spinal anaesthesia in children is not commonly performed for lower abdominal surgery in western countries. However, in countries with limited resources, or drug and equipment constraints,^[21,22] its use can be considered a safe, simple, and relatively inexpensive alternative to general anaesthesia. A positive medical history of major dysfunction of the coagulation system^[22,23] represents a contraindication to spinal anaesthesia, as cases of neuroaxial haematomas, although few, in children undergoing lumbar puncture have been reported.^[24] As our results show that the extrinsic coagulation pathway is significantly altered in patients with CAA, and that the degree of derangement correlates with the severity of the disease, a clinically severe form of appendicitis may prompt patient referral or the use of general anaesthesia, where available, rather than spinal anaesthesia.

Transversus abdominis plane (TAP) blocks are widely used to provide postoperative analgesia after abdominal wall surgery in the general and paediatric population.^[25] Contraindications to TAP blocks include patient refusal, infection of the soft tissue and skin of the abdominal wall, or abnormality of needle's insertion site. Abnormal coagulation is currently a controversial contraindication, and it will require further investigation.^[26] Therefore, any form of local or regional anaesthesia technique for abdominal surgery should take into consideration the risk/benefit ratio, in particular in cases of severe and complicated appendicitis.

The current study presents some limitations, mainly its retrospective nature, with its inherent biases. Furthermore, there was no standardisation of the time interval between onset

of symptoms, collection of blood samples, and appendectomy, which may have affected the disease progression. Finally, the control group encompasses patients that received the same diagnosis of appendicitis and underwent surgery, not taking into consideration patients suffering for abdominal pain for different aetiology (e.g., gastroenteritis, adnexal disease, inflammatory bowel diseases, etc.). The retrospective type of the study also hindered the possible correlation between clinical and histological findings, which should be better investigated in further prospective studies.

However, this study clearly shows that besides the clinical picture, WBC, Neutr%, increased Fib levels, PTratio, and raised CRP, taken alone or in combination, are useful to differentiate severe forms of AA from NAA.

Ethics approval and consent to participate

Written informed consent was collected from parents before surgery. We conducted the study in accordance with the Declaration of Helsinki. To protect personal information, patient name, hospital number, date of birth, and social security number were deleted after assigning a serial number.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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