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Original Research Article

Predictive value of hemostatic markers for complicated acute appendicitis in children: a key role for international normalized ratio

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ABSTRACT

Background: Acute appendicitis (AA) is a common surgical emergency worldwide. The primary adverse event in patients with AA is the progression to complicated appendicitis. Although various scoring systems exist to improve diagnostic accuracy, there remains a need for simple, inexpensive, and readily available biomarkers. This study aims to identify the value of coagulation tests as a predictor of complicated acute appendicitis in pediatric patients.
Methods: We conducted a retrospective, cross-sectional study to evaluate the diagnostic performance of hemostatic markers. The study included medical records from pediatric patients who underwent an emergency appendectomy at our general surgery department between January 2022 and July 2022.
Results: A total of 84 patients were included, with an incidence of complicated acute appendicitis (CAA) of 35.71%. Receiver operating characteristic (ROC) curve analysis revealed good diagnostic performance for INR (AUC=0.803; 95% CI 0.697-0.908; p<0.001) and acceptable performance for PT (AUC=0.774; 95% CI 0.667-0.881; p<0.001) and fibrinogen (AUC=0.769; 95% CI 0.666-0.872; p<0.001). Partial thromboplastin time (PTT) did not show significant predictive value.
Conclusions: International normalized ratio (INR) is a valuable and readily available biomarker for predicting complicated AA in the pediatric population. Fibrinogen and PT also demonstrate significant, albeit lower, predictive utility. These hemostatic markers can serve as objective tools to aid in early risk stratification and optimize clinical management.

Keywords: Acute appendicitis, Complicated appendicitis, Pediatrics, Hemostatic markers, International normalized ratio

INTRODUCTION

Acute appendicitis (AA) is globally recognized as a primary indication for emergency surgery.[1] Although abdominal pain is a common presenting symptom in pediatric surgical clinics, constituting 5% of encounters, only a fraction of these cases are ultimately attributed to AA.[2] The lifetime risk for an individual is estimated at 7-9%, with incidence rates culminating between the ages of 10 and 19.[3]

A major clinical concern is the substantial rate of progression to complicated appendicitis.[4,5] The pediatric population is particularly vulnerable, with reports indicating that 30% to 74% of children present with complicated disease. These rates escalate dramatically in

younger age groups, from 69-93% among toddlers and preschoolers to as high as 100% in infants, with an overall perforation rate approaching 20%.[6,7]

However, the diagnostic pathway for AA is often fraught with uncertainty, despite the classic signs and symptoms.[8] This is largely due to atypical presentations, as only one-third of patients exhibit canonical gastrointestinal manifestations. The clinical picture is frequently confounded by diagnostic mimics including gastroenteritis, ileitis, and pancreatitis, which can delay or prevent an accurate diagnosis.[9]

The pathophysiology of AA evolves along a continuum, from uncomplicated inflammation to severe sequelae such as phlegmon, generalized peritonitis, or intraperitoneal abscess formation. These advanced stages represent approximately 30% of all diagnoses and are associated with a significant economic burden and heightened patient morbidity.[10] Such outcomes include iatrogenic injury, systemic dissemination of infection, and complex postoperative events like bowel obstruction, fistula, and surgical site infections.[11]

This diagnostic challenge is further amplified in the preschool population, where atypical clinical features frequently lead to misdiagnosis and subsequent perforation.[9,12] Moreover, significant disparities exist in diagnostic strategies among institutions. A landmark retrospective study of 13,328 pediatric patients by Rice-Townsend et al revealed stark variations in the approach to suspected appendicitis, noting a 3.5-fold difference in preoperative imaging and a 5-fold difference in laboratory utilization.[13] Collectively, these diagnostic inconsistencies create a compelling rationale for the identification and validation of objective biomarkers to standardize and enhance clinical management.

Since Fitz's report in 1886, appendicitis has been considered an irreversibly progressive disease that must be treated with an appendectomy. Currently, appendicitis is classified into two distinct types: simple (non-perforated) and complex (gangrene, perforation, and formation of abscesses or phlegmons).[14]

Prospective studies using antibiotic therapy for simple or uncomplicated pediatric appendicitis have resulted in success rates of 92% to 94% in hospitalized patients, with 30-day success rates of 89%. In CAA (perforation or abscess), primary antibiotic therapy can achieve a hospital success rate of 66%.[15] However, the presence of CAA features or an appendicolith on imaging has been shown to be a risk factor for the failure of conservative treatment.[16] The precise selection of patients whose appendiceal inflammation could be controlled with antibiotics can improve the success rate of non-surgical treatment.[17] Meanwhile, as pediatric surgical care becomes increasingly centralized away from low volume centers.[18] The accurate identification of CAA or the presence of an appendicolith on preoperative imaging can aid in treatment decision-making for patients with uncomplicated appendicitis.[16,19] However, the traditional paradigm that all children with appendicitis require an appendectomy is now being challenged by the concept that a subgroup of children with a low risk of disease progression can be successfully treated non-surgically with only antibiotics and supportive care.[20]

CAA is treated in one of three ways: early appendectomy at the time of presentation, initial antibiotic treatment followed by interval appendectomy, or antibiotic treatment alone without interval appendectomy. Early appendectomy has become the treatment of choice in many centers, as some evidence suggests it reduces adverse events and unplanned readmissions.[10] Although infectious postoperative complications are common, occurring in about 20% of patients.[21] Both non-surgical treatment (i.e., with antibiotics and/or percutaneous drainage).[22] Surgical treatment have been widely accepted for children with an appendiceal mass or abscess, although in these children, appendectomy is associated with greater morbidity.[20] On the other hand, children with perforated appendicitis with localized or generalized purulent/fecal peritonitis are treated with an appendectomy.[14] Conversely, overdiagnosis and the unnecessary excision of a healthy appendix are an opposing reality, despite the aid of detection capabilities with ultrasonography and computed tomography with rates varying in the literature from 1% to around 20%, with large variations among age and gender groups.[23] Given the prevalence of abdominal pain and the difficulty in diagnosing appendicitis, several criteria and scores have been devised.[2] This highlights the importance of being able to diagnose simple versus complicated appendicitis, as it allows the surgeon to choose the best surgical approach, ranging from antibiotics and delayed appendectomy to laparotomy.

Determining the optimal algorithm for the diagnostic procedure in CAA can not only reduce the number of unnecessary operations but also the frequency of complications and can contribute significantly to reducing the cost of treating patients with acute abdominal conditions.[9] Therefore, classification systems for the diagnosis of pediatric appendicitis have been developed, and laboratory and radiological findings play an important role in this diagnosis.[24] Currently, different scoring systems are used to diagnose appendicitis. The modified Alvarado score for pediatrics and the pediatric appendicitis score are specially designed for the pediatric age group. These scoring systems consider symptoms and signs along with leukocytosis and have been shown to be useful in diagnosing appendicitis.[25] Despite the availability of advanced diagnostic tools such as inflammatory markers, imaging studies, and clinical prediction rules and protocols, the diagnosis of appendicitis in young children remains a challenge. According to Hao et al, the misdiagnosis rate can reach up to 57% in children aged 3 to 5 years and 70% to 100% in children younger than 3 years.[26,27] To increase the accuracy of AA detection, some researchers have focused on studying many laboratory

parameters, including the neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and red blood cell distribution width (RDW).[28] The present study will focus on the utility of coagulation tests, and it has recently been reported that fibrinogen (FB) is a useful biomarker in the diagnosis of appendicitis.[26] For this, interpretation values of the receiver operating characteristic (ROC) curve test will be used (regular 0.41 to 0.60, acceptable from 0.61 to 0.80, good >0.80).

Prada et al enrolled a total of 82 patients in their study (27 NSAP, 17 uncomplicated appendicitis, and 38 complicated). WBC and ANC had moderate diagnostic accuracy for appendicitis versus NSAP (WBC: AUC 0.66, ANC: AUC 0.67). CRP and FB had good diagnostic accuracy for appendicitis versus NSAP (CRP: AUC 0.78, FB: AUC 0.77). WBC and ANC are not useful for discriminating complicated versus uncomplicated appendicitis (WBC: AUC 0.43, ANC: AUC 0.45). CRP and FB had good diagnostic accuracy for complicated versus uncomplicated appendicitis (CRP: AUC 0.80, FB: AUC 0.73).[26] For their part, Morandi et al included 307 patients for the study of the coagulation profile: 57 NAA, 184 SAA, and 66 CAA. WBC was significantly different between the groups: CAA (mean 16.67×10^3/ml), SAA (14.73×10^3/ml, $p=0.01$) and NAA (10.85×10^3/ml, $p<0.0001$) and PCR (mean of NAA 2.56, SAA 3.26, CAA 11.58, $p<0.0001$). PT ratio and Fib increased with the severity of AA. The receiver operating characteristic curves were similar for CRP (0.739), Fib (0.726), WBC (0.746), and Neutr % (0.754), while PT ratio and aPTT ratio were 0.634 and 0.441, respectively.[29] These findings could be because AA is often associated with a systemic inflammatory response, and this leads to the activation of the coagulation cascade. In fact, infection and abdominal inflammation almost invariably lead to hemostatic abnormalities, ranging from insignificant laboratory changes to disseminated intravascular coagulation, which can affect the anesthetic and surgical technique. However, limited data are available regarding coagulation changes in AA.[29]

This study aims to identify the value of coagulation tests as a predictor of complicated acute appendicitis in pediatric patients at the General Regional Hospital Number 1, Obregón, Sonora, Mexico.

METHODS

Study design and setting

We conducted an observational, analytical, retrospective, cross-sectional study at the General Regional Hospital Number 1 of the Mexican Institute of Social Security, Obregón, Sonora, Mexico. This institution is a tertiary care center and serves as a high-specialty surgical referral unit for the northwestern region of the country. This report adheres to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.

Population and sample

The study population consisted of the medical records of pediatric patients aged 6 to 17 years who were treated for acute appendicitis between 01 January 2022, and 31 July 2022. Case selection was performed using a non-probabilistic, consecutive sampling method.

Sample size calculation

The sample size was calculated using the formula for estimating the sensitivity of a diagnostic test. A reference sensitivity of 73% for fibrinogen in diagnosing complicated appendicitis, as previously reported by Prada et al, was used, with a 95% confidence level ($Z\alpha=1.96$) and a 10% margin of error.[26] The initial calculation yielded a sample size of 76 patients. After applying a 10% adjustment for potential incomplete data, the final sample size was established at 83 patients.

Selection criteria

Inclusion criteria

Medical records were included if they met the following: patient age between 6 and 17 years; diagnosis of acute appendicitis with definitive treatment via appendectomy; and a complete clinical record, including an admission hemogram, coagulation profile, and a postoperative histopathology report.

Exclusion criteria

Records were excluded for patients with a history of hepatic, renal, hemorrhagic, or thrombotic disease; a concomitant diagnosis of typhoid fever; vitamin K deficiency; or use of hepatotoxic or anticoagulant drugs (vitamin K antagonists or heparin) within the two weeks prior to surgery. Records with incomplete data were also excluded from the analysis.

Data collection and study variables

Data were collected retrospectively by reviewing clinical records using a standardized data collection form designed for this study. The primary outcome was the type of acute appendicitis, confirmed by the histopathological report and classified dichotomously as the following.

Uncomplicated

Histopathological findings of suppurative, intraluminal, mucosal, or submucosal inflammation without evidence of transmural necrosis or perforation.

Complicated

Histopathological findings of gangrenous or perforated appendicitis, or the presence of an abscess.

The predictor variables of interest were the markers from the coagulation profile: fibrinogen (mg/dl), prothrombin time (PT) (seconds), partial thromboplastin time (PTT) (seconds), and INR. Additionally, demographic data, clinical variables (signs of peritoneal irritation), and other laboratory parameters such as the complete blood count and C-reactive protein (CRP) were collected.

Statistical analysis

The collected data were entered into a Microsoft Excel 2019 database and analyzed using IBM statistical package for the social sciences (SPSS) statistics v24. For descriptive statistics, measures of central tendency and dispersion (mean, standard deviation, median, and ranges) were used. For inferential statistics, receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off points for the coagulation markers. Their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. A p value of <0.05 was considered statistically significant. The results were presented in tables and figures.

Ethical considerations

The study was conducted in accordance with institutional ethical guidelines, the Mexican General Health Law on Health Research, and the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, which involved no patient intervention or risk, the committee waived the requirement for informed consent. Patient confidentiality and anonymity were maintained throughout the study.

RESULTS

Baseline characteristics of the study population

A total of 84 pediatric patients met the inclusion criteria and were included in the analysis. The mean age of the cohort was 9.06±3.69 years, with a predominance of male patients (64.29%; n=54). At admission, laboratory parameters revealed leukocytosis, with a mean white blood cell count of 14.38±5.06×10³ cells/µl and a mean neutrophil percentage of 80.47±7.99%. The mean values for the coagulation profile were fibrinogen 614.10±151.59 mg/dl, PT 13.81±2.01 seconds, and INR 1.18±0.16. The complete demographic and clinical characteristics are detailed in Table 1.

Clinical and histopathological findings

The clinical presentation was consistent with acute appendicitis, highlighted by 100% sensitivity for pain in the right lower quadrant and a 92.86% rate of a positive rebound tenderness sign. Based on intraoperative and histopathological findings, the rate of complicated acute appendicitis (CAA) in the study cohort was determined to be 35.71% (n=30). The distribution of appendicitis grades is presented in Table 2.

Table 1: Baseline demographic, clinical, and laboratory characteristics of the study cohort (n=84).

Characteristic	Value (n or mean±SD)	Percentage
Demographics		
Age (years)	9.06±3.69	–
Sex		
Male	54	64.29
Female	30	35.71
Laboratory findings at admission		
White blood cell count (×10³/µl)	14.38±5.06	–
Neutrophil percentage (%)	80.47±7.99	–
Fibrinogen (mg/dl)	614.10±151.59	–
Partial thromboplastin time (PTT, seconds)	32.30±3.27	–
Prothrombin time (PT, seconds)	13.81±2.01	–
International normalized ratio (INR)	1.18±0.16	–
Clinical findings		
Right lower quadrant tenderness	84	100.00
Rebound tenderness	78	92.86
Abdominal guarding	31	36.90
Diagnostic imaging used		
Ultrasound (US)	12	14.29
Computed tomography (CT) scan	1	1.19

Data are presented as mean±standard deviation (SD) for continuous variables and n (%) for categorical variables, n=number of cases, source: study protocol developed at General Regional Hospital Num. 1. Obregón, Sonora, Mexico

Diagnostic performance of coagulation markers

The ROC curve analysis for predicting CAA demonstrated good diagnostic performance for INR (AUC=0.803; 95% CI: 0.697-0.908; $p<0.001$) and acceptable predictive utility for PT (AUC=0.774; 95% CI: 0.667-0.881; $p<0.001$) and fibrinogen (FB) (AUC=0.769; 95% CI: 0.666-0.872; $p<0.001$). In contrast, the PTT did not show statistically significant discriminatory capacity (AUC=0.484; p=0.805) (Figure 1).

The plot compares the diagnostic performance of fibrinogen (AUC=0.769), PTT (AUC=0.484), PT (AUC=0.774), and INR (AUC=0.803). The diagonal line represents a reference test with no discriminatory ability (AUC=0.5).

The optimal cut-off analysis revealed that while the sensitivity of the markers was moderate (50.00% for all three), INR, PT, and fibrinogen exhibited high specificity

(85.19%, 81.48%, and 85.19%, respectively). This indicates their ability to correctly identify uncomplicated cases. Detailed diagnostic performance metrics are presented in Table 3 and Figures 2-5.

Table 2: Classification and frequency of appendicitis findings (n=84).

Variables	Frequency (n=84)	Percentage
Intraoperative findings		
Grade 1	10	11.9
Grade 2	44	52.38
Grade 3	17	20.24
Grade 4	13	15.48
Histopathological findings		
Catarrhal	3	3.57
Phlegmonous	4	4.76
Necrotic	4	4.76
Perforated	7	8.33
Appendicitis type		
Uncomplicated	54	64.29
Complicated	30	35.71

n=number of cases, source: study protocol developed at General Regional Hospital Num. 1. Obregón, Sonora, Mexico

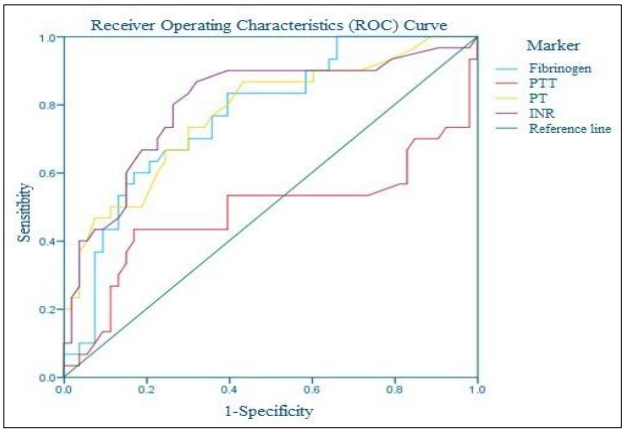

Figure 1: ROC curves for coagulation markers in predicting complicated acute appendicitis.

Table 3: Diagnostic performance of coagulation markers in predicting complicated acute appendicitis.

Test variable	AUC	95% CI	P value
Fibrinogen	0.769	0.666-0.872	<0.001
PTT	0.484	0.334-0.633	0.805
PT	0.774	0.667-0.881	<0.001
INR	0.803	0.697-0.908	<0.001

AUC: area under the curve; CI: confidence interval; PTT: partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio

The bar chart in Figure 2 stratifies patients based on a fibrinogen level of 717 mg/dl, showing the number and percentage of uncomplicated versus complicated cases in each group.

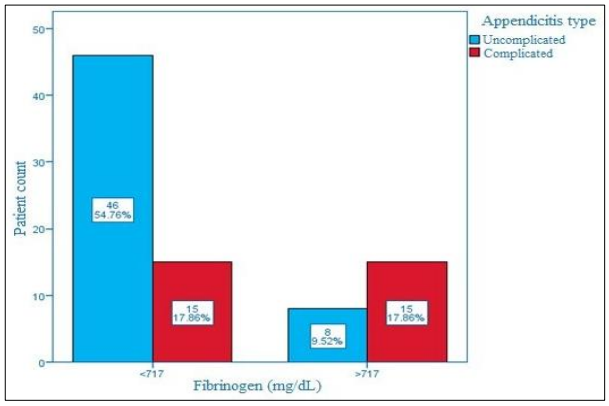

Figure 2: Distribution of uncomplicated and complicated appendicitis cases based on the optimal fibrinogen cut-off value.

The bar chart in Figure 3 stratifies patients based on a PTT of 32.7 seconds, showing the number and percentage of cases in each group.

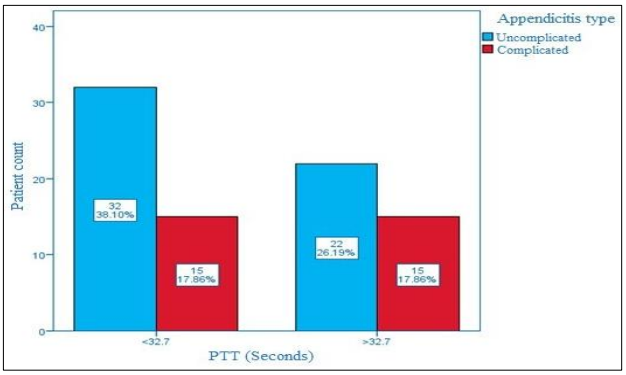

Figure 3: Distribution of uncomplicated and complicated appendicitis cases based on the optimal PTT cut-off value.

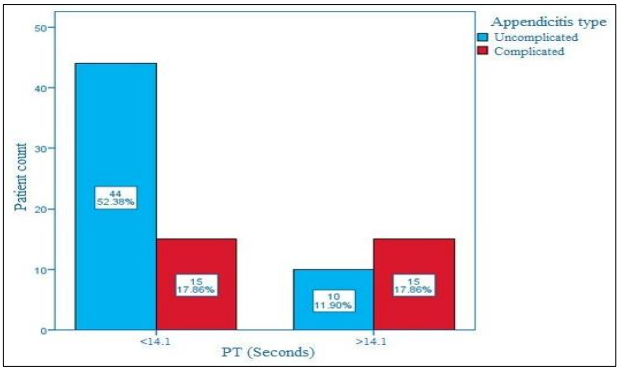

Figure 4: Distribution of uncomplicated and complicated appendicitis cases by prothrombin time cut-off.

The chart in Figure 4 shows the number and percentage of patients in each category, stratified by the optimal PT cut-off value of 14.1 seconds.

The chart in Figure 5 shows the number and percentage of patients in each category, stratified by the optimal INR cut-off value of 1.22.

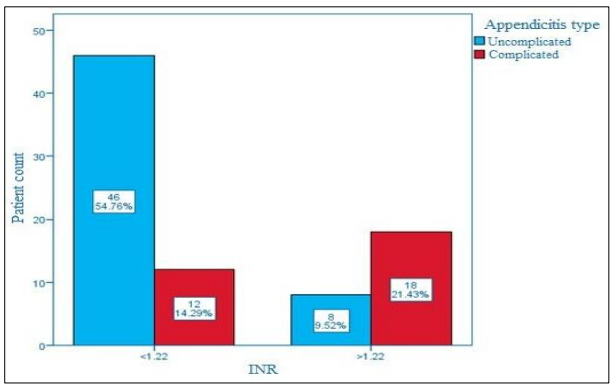

Figure 5: Distribution of uncomplicated and complicated appendicitis cases by international normalized ratio cut-off.

DISCUSSION

AA stands as the most frequent surgical emergency in the pediatric population, where timely diagnosis is crucial to prevent severe complications.[1] While diagnosis is primarily based on clinical presentation, its often-ambiguous nature has driven the search for complementary diagnostic tools.[2] The principal finding of our study is the utility of INR, PT, and fibrinogen as predictors of complicated acute appendicitis (CAA). These markers, which are routinely ordered preoperatively at our institution, demonstrated good diagnostic performance, with INR exhibiting the strongest predictive power. Our results suggest that an alteration in these coagulation parameters may reflect the intensity of the systemic inflammatory response associated with more severe forms of the disease.

The clinical implications of these findings are direct and practical. By utilizing readily available data, clinicians can better stratify patient risk. Elevated levels of INR, PT, or fibrinogen could alert the surgical team to a higher probability of encountering CAA, thereby allowing for optimized therapeutic planning and more vigilant postoperative monitoring.

Our findings align with and expand upon the work of Morandi et al, who also investigated the coagulation profile in a pediatric appendicitis cohort.[29] They found that markers of the extrinsic coagulation pathway, such as prothrombin time, were altered in CAA and that fibrinogen levels correlated with disease severity. However, our study identifies the INR as the most robust predictor (AUC=0.803), a more specific finding than their general evaluation of the prothrombin time ratio. Notably, our result that PTT was not a significant predictor also aligns with their finding of a low AUC for aPTT ratio (0.441), suggesting the extrinsic pathway is more significantly involved in the pathophysiology of appendicitis.

Regarding fibrinogen, our results (AUC=0.769) are highly consistent with those of Prada-Arias et al, who reported good diagnostic accuracy for fibrinogen in discriminating appendicitis in preschoolers (AUC=0.77).[26] This reinforces the role of fibrinogen as a reliable, though perhaps secondary, marker for complicated appendicitis across different pediatric age groups.

While our study focuses on hemostatic markers, it is important to situate these findings in the broader context of established inflammatory biomarkers. Numerous studies have validated the use of CRP and WBC count as predictors of CAA. For example, Zouari et al identified a CRP level ≥20 mg/l as a strong predictor of AAC in children, while Hajibandeh et al found that a neutrophil-to-lymphocyte ratio (NLR) >8.8 was a strong predictor of complicated disease.[7,12] Our study does not aim to replace these established markers but suggests that coagulation parameters, particularly INR, offer a complementary and valuable dimension for risk stratification. These hemostatic changes likely reflect a different aspect of the systemic inflammatory response, such as the endothelial dysfunction and prothrombotic state that can accompany severe intra-abdominal infections.

Limitations

We acknowledge several limitations in our study. First, its retrospective and single-center design may limit the generalizability of our findings to other patient populations or hospital settings. The reliance on existing medical records also carries a potential risk of information bias. Second, the sample size of 84 patients, while statistically adequate for our primary analysis, is modest. Larger, prospective, multicenter studies are necessary to validate these observations and to more precisely define optimal cut-off values for INR, PT, and fibrinogen. Finally, while we have compared our results to the existing literature, this study did not directly compare the performance of hemostatic markers against established clinical scoring systems, such as the Alvarado or Pediatric Appendicitis Score, within the same patient cohort. Such a direct comparison would be a valuable direction for future research to establish the relative clinical utility of INR.

CONCLUSION

Our study demonstrates that INR is a valuable and readily available biomarker for predicting complicated acute appendicitis in pediatric patients. While PT and fibrinogen also show acceptable predictive utility, INR exhibits the strongest performance. Incorporating these hemostatic markers into the initial assessment can aid in risk stratification and optimize clinical management.

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