Original Article

Refining Paediatric Appendicitis Severity Assessment through a Novel Logistic Regression Model Utilising Routine Biomarkers

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Abstract

Introduction: Acute appendicitis is a common paediatric emergency, with higher risks of complications than in adults. Accurately distinguishing uncomplicated appendicitis (UA) from complicated appendicitis (CA) is essential for guiding appropriate management, particularly as non-operative treatment for UA gains acceptance. However, existing scoring systems and single biomarkers lack sufficient specificity, especially in paediatric populations. This study assesses whether common inflammatory markers can predict UA and CA in children, providing a supplementary diagnostic tool for resource-limited settings where imaging may be limited. **Methods:** We conducted a retrospective analysis of paediatric patients aged 16 years or younger who underwent appendectomy at two tertiary hospitals. Data included demographic information, symptoms and pre-operative blood markers such as C-reactive protein (CRP), total leucocyte count (TLC), neutrophil count and platelet count. Inflammatory marker values were incorporated into a multivariate logistic regression model to predict the likelihood of CA. Diagnostic accuracy was evaluated using the receiver operating characteristic curve analysis, reporting sensitivity, specificity and optimal cutoffs for the identified markers. **Results:** Of 247 paediatric appendectomy cases, 60.7% were UA and 39.2% were CA. Elevated CRP (≥76.8 mg/L) had a specificity of 78.7% and a sensitivity of 60.3% for CA. Combined markers (TLC, neutrophils, lymphocytes and platelets) improved sensitivity to 70.1%. The logistic regression model incorporating neutrophil count, lymphocyte count and platelet count achieved a sensitivity of 78.4% and specificity of 52.7% at a threshold score of 1.20. This model effectively stratified risk, providing diagnostic support when advanced imaging is limited. **Conclusion:** Our study introduces a logistic regression model using routine blood markers to differentiate between UA and CA in paediatric patients. While not a replacement for imaging or clinical evaluation, the model offers a valuable adjunct in settings with limited resources, improving sensitivity for detecting complicated cases. Prospective studies are warranted to validate these findings in the real-time clinical applications.

Keywords: Complicated appendicitis, inflammatory markers, paediatric appendicitis, predictive model

Introduction

Acute appendicitis is a common surgical emergency in children, presenting a diagnostic challenge due to the, at times, nonspecific nature of clinical findings and the risk of progression to perforation being higher in children compared to adults.[1]

While studies have focused on distinguishing appendicitis from non-appendicitis conditions, the challenge remains in differentiating between uncomplicated appendicitis (UA) and complicated appendicitis (CA) – which can range from an inflamed but intact appendix to perforation, peritonitis or a gangrenous appendix. The ability to accurately differentiate between UA and CA is critical as it determines the appropriate management strategy. This differentiation has gained significance as the operative treatment of UA is being increasingly challenged. Growing evidence supports the safety of non-operative management for UA, underscoring the need for diagnostic tools to guide treatment.[2-7]

The WSES Jerusalem guidelines recognise the limitations of scoring systems in accurately differentiating between

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UA and CA appendicitis, especially in the paediatric population.[7-12]

Several serum biomarkers, including total leucocyte count (TLC), differential count and C-reactive protein (CRP), have shown promise in reducing unnecessary explorations and improving diagnostic specificity for acute appendicitis and its behaviour in disease staging.[7,13-20] However, the diagnosis based on single laboratory tests lacks the specificity needed to reliably distinguish between CA and UA, carrying a considerable risk of false positives.[1,21]

Although these biomarkers offer valuable diagnostic information, they cannot replace clinical examinations or imaging studies as essential parts of the diagnostic process.[7,12,19,22,23]

Most studies examining biomarkers to differentiate between CA and UA have focused on adults or included both adult and paediatric cases without specifically analysing paediatric populations save a few.[1,24] Our study focuses only on the paediatric population, addressing this gap to provide insights relevant to paediatric appendicitis. While clinical examination, ultrasound and computed tomography (CT) are the standard diagnostic methods, our study aims to see if commonly ordered and easily accessible inflammatory markers can provide additional predictive value individually or in combination to differentiate between UA and CA effectively in paediatric patients. In resource-limited settings, reliance on routine biomarkers becomes particularly important, as advanced imaging techniques, such as ultrasound or CT scans, may not be readily accessible.[25-27]

Our study aims to provide a supplementary tool to support clinical decision-making by focusing on routine biomarkers.

What is new in the study

Our study introduces a novel logistic regression equation that integrates common inflammatory markers into a cohesive diagnostic tool for calculating the probability of UA and CA in the paediatric population. Rather than replacing clinical and imaging data, this model is intended to supplement these methods, offering a tool where comprehensive diagnostic options are limited.

Methods

Rationale and objectives

Our study aimed to evaluate the effectiveness of readily available inflammatory markers, individually or in combination, in distinguishing between CA and UA. The objectives were to identify independent inflammatory markers that predict the severity of appendicitis and determine whether combining multiple markers enhances diagnostic accuracy compared to individual markers. In addition, we sought to create a model that incorporates significant inflammatory markers to achieve a more accurate differentiation between CA and UA. By developing a logistic regression model incorporating significant inflammatory markers, we aimed to provide a practical diagnostic tool that could complement existing clinical approaches. While we did not directly compare these biomarkers with diagnostic modalities such as CT scans or ultrasound in this study, we hope this model can serve as an adjunct in settings where access to such imaging techniques is limited.

Study design and setting

This retrospective observational study was conducted and reported in accordance with the STROBE guidelines. The diagnostic accuracy was reported in accordance with STARD 2015. guidelines. Medical records from two tertiary teaching hospitals in India and Oman were reviewed, both had robust data collection protocols and comparable healthcare delivery standards.

Participants

The cohort comprised children aged 16 years and below who underwent appendectomy between July 1, 2014 and July 30, 2019. Inclusion criteria mandated a confirmed diagnosis of acute appendicitis based on the operative findings supported by histopathological analysis. Cases with incomplete medical records were excluded to maintain data integrity.

Data collection

Data on patient demographics, including age and gender, the interval between symptom onset and care-seeking, presenting symptoms, pre-operative blood work including routine inflammatory markers (CRP levels), intra-operative findings, histopathological reports and postoperative outcomes were systematically collected. In addition to the laboratory data, clinical and radiological findings were reviewed where available. Although these were not consistently available for all patients, they were compared with histopathological findings to ensure the alignment of findings and to validate the severity of appendicitis (UA vs. CA) where possible. Radiological data were not available for all patients across the cohort and were, therefore, not included in the final logistic regression model. This decision was made to maintain uniformity in data and prevent bias introduced by incomplete radiological information. As a result, only routinely available blood markers, universally available in all settings, were included in the predictive model.

Laboratory procedures

The pre-operative laboratory evaluations included CRP levels and a complete blood count (CBC). The CRP levels were analysed using an immunoturbidimetric assay on a fully automated chemistry analyser, with the values expressed in mg/L. The CBC was analysed using a blood count analyser and the results were expressed as $\times 10^9$/L.

Outcomes

The primary outcome of this study was the accurate diagnosis of appendicitis severity, classified as uncomplicated or complicated based on the operative findings corroborated by histopathological analysis, which served as the gold standard.[22]

Exposures

The exposures in this study were inflammatory markers, including CRP levels and other blood count parameters, which were assessed preoperatively.

Predictors

Predictors of appendicitis severity were identified using the logistic regression analysis. These included inflammatory markers such as CRP levels, TLC, DLC and platelet count.

The factors influencing the relationship between exposures (inflammatory markers) and the outcome (appendicitis severity) were assessed. Age and gender were considered as potential confounders in this study.

Diagnostic criteria

The diagnosis of acute appendicitis was confirmed based on the operative findings supported by the histopathological analysis, which served as the gold standard diagnostic criteria for this study.

Ethical considerations

Ethical clearance was granted by the respective institutional review boards (MREC No. 2065; IECCMCL.128892019), ensuring compliance with ethical standards for retrospective studies.

Statistical analysis

The categorical data were summarised as frequencies and percentages, whereas continuous variables were described using the medians and interquartile ranges. The normality of distributions was verified using the Kolmogorov–Smirnov test. Quantitative variables between the two groups were compared using the Mann–Whitney test. Qualitative variables between the two groups were compared using the Chi-square test/ Fisher's exact test.

The receiver operating characteristic (ROC) curve was used to find out the optimal cutoff point, sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy for predicting CA. The Youden Index method was used to choose the cutoff in ROC. Multivariate logistic regression was used to find out the predictors of CA. The ROC analysis with multiple biomarkers yields a cutoff value, which is based on a linear combination of the estimated parameters of the logistic regression model. The logistic regression equation with multiple independent variables is: Log $(p/[1-p]) = \beta_0 + X_1\,\beta_1 + X_2\,\beta_2 + \ldots\ldots\ldots\ldots\ldots\ldots + X_n\,\beta_n$, where $X_1, X_2, \ldots\ldots X_n$ are the independent predictors whose effect on the odds ratio of complicated: uncomplicated ($=p/[1-p]$) was specified by the parameters $\beta_1, \beta_2, \ldots\ldots, \beta_n$, respectively.

A ROC analysis of this model yields the threshold probability q that maximises the Youden index, which is mathematically equivalent to the value of q that maximises the sum of sensitivity and specificity. Therefore, this value q was substituted for P in the above equation and rearranged to obtain the proper cutoff value for the linear combination of multiple biomarkers:

$$X_1\,\beta_1 + X_2\,\beta_2 + \ldots\ldots\ldots\ldots\ldots\ldots + X_n\,\beta_n \geq \log\,(q/[1-q]) - \beta_0 \quad (1)$$

The cutoff value equals the right-hand side of the above inequality. If the left-hand side of the inequality exceeds the cutoff value, it favours the prediction of CA over UA, whereas the opposite is true for lower values of the left-hand side.

$P < 0.05$ was considered statistically significant. The data were entered in MS EXCEL™ spreadsheet, and analysis was done using the Statistical Package for the Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Our analysis included 247 paediatric patients who had undergone appendectomy. Based on intra-operative findings and histopathological reports, the study participants were divided into UA and CA. One hundred and fifty (60.7%) patients had UA and 97 (39.2%) had CA.

Age and gender analysis revealed no gender or age bias between the two groups, although the majority of children were in the 6–10 years age group in both categories. The demographic and clinical symptomatology were comparable in both groups except for pain, which was a significantly more common presentation in the CA group ($P = 0.003$).

C-reactive protein and sensitivity/specificity

CRP levels ≥76.8 mg/L demonstrated a high specificity of 78.7% for detecting CA, meaning that it correctly identified CA in nearly 79% of cases. However, the sensitivity of CRP was moderate, capturing 60.3% of true CA cases, which means that it missed some cases of CA. This resulted in a diagnostic accuracy of 69.6% [Table 1a].

Neutrophil count

A neutrophil count $\geq 10 \times 10^9$/L showed a higher sensitivity of 70.1%, but slightly lower specificity, leading to a diagnostic accuracy of 60.3%. This illustrates that while neutrophil count is a more sensitive marker for detecting CA, it may overestimate complicated cases.

The combined analysis of inflammatory markers, including TLC, neutrophils, lymphocytes and platelets, achieved an area under the curve (AUC) of 0.708 (95% confidence interval [CI] 0.642–0.775). This was higher than the AUCs for individual markers, showing that the combined approach increased the diagnostic sensitivity for CA to 70.1% [Table 1b].

Univariate logistic regression highlighted all the inflammatory parameters as significant predictors for CA at the established cutoffs from the ROC analysis, except for platelets [Table 2a]. The odds of having CA were 4.6 times higher for patients with a CRP level ≥76.8 mg/L and similarly increased for other markers at their respective cutoffs [Table 2a]. The multivariate analysis yielded a logistic regression equation to predict CA based on the strongest predictors [Table 2b].

Table 1a: Receiver operating characteristic analysis for the predictors of complicated appendicitis

	AUC	95% CI (lower–upper)	*P*	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy
TLC ($\times 10^9$/L)	0.653	0.584–0.723	<0.001	≥14	56.7	68	53.3	70.8	63.6
Neutrophil ($\times 10^9$/L)	0.664	0.595–0.732	<0.001	≥10	70.1	54	49.6	73.6	60.3
Lymphocyte ($\times 10^9$/L)	0.611	0.541–682	0.003	≤1.8	58.8	61.3	48.3	69.6	59.1
CRP (mg/L)	0.715	0.649–0.780	<0.001	≥76.8	55.7	78.7	62.8	73.3	69.6
NLR	0.685	0.619–0.752	<0.001	≥6.3	61.9	71.3	57.1	71.4	65.6
Platelets	0.557	0.481–0.632	0.133	≥325.6	51.5	54.7	42.3	63.6	53.4
PLR	0.625	0.554–0.697	0.001	≥201.1	52.8	66	50	68.3	60.7

NPV: Negative predictive value, PPV: Positive predictive value, AUC: Area under curve, NLR: Neutrophil to lymphocyte ratio, PLR: Platelets lymphocyte ratio, TLC: Total leucocyte count, CRP: C-reactive protein, CI: Confidence interval

Table 1b: Receiver operating characteristic analysis for combined predictors of complicated appendicitis

	AUC	95% CI (lower–upper)	*P*	Sensitivity (%)	Specificity (%)
TLC + neutrophil + lymphocyte + platelets	0.708	0.642–0.775	<0.001	70.1	63.3
TLC + neutrophil + lymphocyte	0.711	0.645–0.776	<0.001	69.1	69.3
TLC + lymphocyte + platelets	0.696	0.629–0.762	<0.001	52.6	78.7
TLC + neutrophil + platelets	0.666	0.598-0.735	<0.001	52.6	78.7
Neutrophil + lymphocyte + platelets	0.693	0.627–0.759	<0.001	78.4	52.7
Neutrophil + platelets	0.666	0.598–0.735	<0.001	52.6	78.7
Lymphocyte + platelets	0.635	0.563–0.706	<0.001	66	57.3
TLC + PLR + NLR	0.680	0.612–0.749	<0.001	73.2	56
TLC + PLR	0.676	0.608–0.744	<0.001	71.1	60
TLC + NLR	0.685	0.618–0.753	<0.001	69.1	60
PLR + NLR	0.671	0.603–0.739	<0.001	75.3	56

AUC: Area under the curve, PLR: Platelets lymphocyte ratio, TLC: Total leucocyte count, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio

Table 2a: Univariate logistic regression for predictors of complicated appendicitis

	Coefficient *B*	*P*	OR	95% CI	
				Lower	Upper
TLC ≥14	1.023	<0.001	2.783	1.641	4.719
Neutrophil ≥10	1.013	<0.001	2.753	1.603	4.726
Lymphocyte ≤1.8	0.763	0.004	2.144	1.274	3.610
CRP ≥76.8	1.533	<0.001	4.631	2.646	8.103
NLR ≥LR	1.204	<0.001	3.333	1.937	5.736
Platelets ≥325.6	0.249	0.340	1.283	0.769	2.140
PLR ≥201.1	0.766	0.004	2.152	1.276	3.629

TLC: Total leucocyte count, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelets lymphocyte ratio, CI: Confidence interval, CRP: C-reactive protein, OR: Odds ratio

- Neutrophil counts ≥10 × 10^9/L
- Platelet counts ≥325.6 × 10^9/L
- Lymphocyte counts ≤1.8 × 10^9/L, [Table 2b].

When these inflammatory markers were combined, they achieved an AUC of 0.693 (95% CI 0.627–0.753, $P < 0.001$), which was comparable to that of CRP alone ($P = 0.634$), highlighting the robust nature of the model.

To predict CA, we developed a logistic regression model integrating commonly available blood markers. The final equation is shown below:

$$1.20 \leq 0.089 \times \text{Neutrophil} - 0.335 \times \text{Lymphocyte} + 0.003 \times \text{Platelet}$$

This equation calculates a score based on the patient's neutrophil, lymphocyte and plat elet counts. This threshold of 1.20 was identified as the optimal cut-off point for the model, offering a sensitivity of 78.4% and a specificity of 52.7% for predicting CA. If the score is equal to or >1.20, the model predicts that the patient is more likely to have CA.

The model achieved a sensitivity of 78.4%, meaning it correctly identified most cases of CA. However, the specificity was 52.7%, indicating that some patients with UA were misclassified as complicated. Although the specificity is lower than CRP alone, the higher sensitivity ensures that most complicated cases are identified, which is critical in preventing severe outcomes in pediatric patients.

Overall, these figures underscore the predictive accuracy of our model, which integrates the selected inflammatory markers into a single, laboratory diagnostic tool.

To demonstrate the practical application of our model, consider the following example from one of our patient cohorts:

- Neutrophil count = 12 × 10^9/L
- Lymphocyte count = 1.5 × 10^9/L
- Platelet count = 340 × 10^9/L.

Table 2b: Multivariable logistic regression for the predictors of complicated

	Coefficient B	P	OR	95% CI	
				Lower	Upper
Lymphocyte	−0.335	0.018	0.715	0.542	0.944
Neutrophil	0.089	0.002	1.093	1.034	1.156
Platelets	0.003	0.032	1.003	1.000	1.006

OR: Odds ratio, CI: Confidence interval

Using the regression equation:

Score = (0.089 × 12) − (0.335 × 1.5) + (0.003 × 340) = 1.068 − 0.502 + 1.02 = 1.586

Since the calculated score of 1.586 is greater than the cutoff value of 1.20, the model predicts CA for this patient which the patient had. This demonstrates how the model can assist clinicians in differentiating between UA and CA cases based on routine blood markers.

Due to the incomplete availability of radiological data (ultrasound and CT scans), this model focuses solely on laboratory biomarkers. Although clinical and ultrasound findings were reviewed where available, they were not included in the final model due to inconsistent data. Future prospective studies incorporating clinical examination and radiological imaging alongside these biomarkers would be expected to further improve the model's predictive accuracy.

Discussion

The timely differentiation between UA and CA has profound implications, CA is associated with increased postoperative morbidity and longer hospital stays.[28] Our cohort, comprising 247 paediatric patients, revealed a significant proportion of complicated cases (39.2%), underscoring the need for precise pre-operative diagnostic methods to guide clinical decisions.

Our study explored the utility of accessible biomarkers for distinguishing between simple (UA) and CA in paediatric patients, addressing a gap in current research, which often lacks age-specific analysis despite physiological differences influencing the inflammatory response in children.[29] By focusing exclusively on paediatric cases, our logistic regression model is tailored to the specific characteristics of appendicitis in younger patients, providing a more precise tool for risk stratification in this group. Studies have highlighted the need for age-specific models due to physiological differences that affect inflammatory responses in children.[1,24]

Our study emphasised the use of accessible blood markers in developing this model to differentiate UA from CA, unlike models developed for adult populations that incorporate a broader range of variables – including markers such as bilirubin, D-dimer, albumin levels and imaging features. Our model relies solely on routine laboratory tests, such as neutrophils, lymphocytes, platelets and compared with CRP, all of which are readily accessible across the healthcare settings. This focus on commonly ordered markers maintains the model's simplicity and enhances its feasibility in resource-limited environments, increasing its utility across the diverse healthcare settings.

The logistic regression model is designed to be practical and easily incorporated into routine clinical workflows. It uses routine blood tests, such as neutrophils, lymphocytes and platelets, which are already commonly ordered for all patients presenting with suspected appendicitis. By inputting these values into the model, clinicians can quickly obtain a score that helps determine the likelihood of CA. This model complements and in no way attempts to replace clinical examination and imaging studies, such as ultrasonography (USG) and CT scans, by providing an additional layer of diagnostic support, particularly in resource-limited settings. Future studies combining this model with imaging modalities could enhance sensitivity and specificity.

Radiological constraints and biomarker utility

While radiological investigations such as ultrasound and CT scans are valuable, they often face limitations due to availability, cost, radiation exposure and operator variability. Ultrasound sensitivity varies from 73% to 100%, with specificity between 80% and 97%, but heavily depends on the operator's experience. In many settings, access to these imaging modalities is further constrained by regulations which limit ultrasound use.[22,27,30-33]

This makes biomarkers such as TLC, neutrophils and CRP important alternatives, given their accessibility and cost-effectiveness.

Model performance and biomarker utility

Our findings align with previous studies, confirming that biomarkers such as TLC, neutrophils and CRP are elevated in CA compared to uncomplicated cases.[19,23,24] While CRP alone offers some predictive power, our analysis shows that a multi-marker strategy improves diagnostic precision.

Our model achieved a sensitivity of 78.4% and a specificity of 52.7% at the established cut-off of 1.20 for predicting CA, aligning with similar adult-focused studies where sensitivity was prioritised to avoid missed cases of CA. This approach aligns with findings from similar studies that have created models using a combination of markers.[17,23,34-36] The model prioritises sensitivity over specificity because it is crucial to avoid missing cases of CA, which can lead to serious complications if untreated. With a sensitivity of 78.4%, the model successfully identifies most patients with CA, minimising the risk of missed diagnoses. However, the model's specificity of 52.7% means that some patients with UA may be incorrectly classified as having CA. This trade-off is particularly relevant in paediatric populations, where timely and accurate identification of CA is crucial to prevent adverse outcomes.

Our retrospective analysis indicates that the logistic regression model correlates with intraoperative findings of CA noted

during surgery in the CA group. However, prospective studies would be beneficial to verify the predictive accuracy of the model in clinical practice.

Conclusion

Our study introduces a practical, paediatric age group-specific logistic regression equation that uses widely accessible biomarkers to distinguish between CA and UA. This equation has strong potential for application in a range of healthcare environments. While it should complement – not replace – clinical and imaging assessments, this model offers a valuable addition to current diagnostic practices, enhancing sensitivity for identifying complicated cases.

Prospective implications

While this study is retrospective, our methodology lays the groundwork for a prospective validation study. Such a study could evaluate the clinical utility of biomarker thresholds in real-time decision-making for children presenting with appendicitis symptoms. Inputting biomarker values into the multivariate logistic regression equation could provide real-time assessments, with a larger sample size collected prospectively to validate the model further.

Limitations

Our retrospective study design inherently carries the typical limitations and potential biases of such an approach. Although our retrospective analysis shows that the model correlates well with intra-operative findings of CA, the moderate specificity suggests that it should not be used in isolation. The study's focus was on patients with histologically confirmed appendicitis, thereby excluding those who received conservative management for abdominal pain. This may limit the generalisability of our findings to the broader population of children presenting with appendicitis-like symptoms. In addition, radiological data were not consistently available for all patients. While biomarkers such as TLC, neutrophils and CRP provide valuable diagnostic insights, they cannot replace clinical examination or imaging studies. Future studies should incorporate both clinical and radiological data to refine the model further.

Including a high-income country hospital was intended to evaluate the diagnostic biomarkers across diverse healthcare infrastructures (varied clinical settings), although the constraints in healthcare access and delivery may not be the same as those of low- and middle-income countries. In addition, our study presumed greater accessibility to basic haematological testing over other imaging modalities such as ultrasound CT scan on the premise that such tests are more practical and cost-effective in the resource-limited settings.

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Conflicts of interest

There are no conflicts of interest.

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