Original Article

Identifying Preoperative Laboratory Parameters to Predict Complicated Acute Appendicitis in Children: A Retrospective Audit

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Abstract

Background: Acute appendicitis (AA) is a common surgical condition among children. Assessing the prognosis stage of the disease evolution is particularly crucial, and is still challenging. **Aim**: To analyse the preoperative parameters of children with confirmed AA, and to determine the predictive factors of complicated appendicitis (CA). **Methods**: The data of 402 children younger than 16 years with a confirmed diagnosis of AA were retrospectively evaluated. Enrolled children were divided into two groups: group A (children with non-complicated AA (NCA), n=221) and group B (children with CA, n=181). Preoperative biological parameters were comparatively analysed between the two groups to determine predictive factors for CA. **Results**: White blood cell count (WBC), absolute neutrophil count (ANC), neutrophil percentage (NE%), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width (RDW), systemic immune inflammatory index (SII), and C-reactive protein (CRP) were higher within group B than group A children (p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.002, p=0.01, p=0.04, respectively). The best area under the curve (AUC) to predict CA was for CRP (0.83, p<0.0001), followed by SII (0.64, p<0.0001), PLR (0.63, p<0.0001), NLR (0.62, p<0.0001), WBC (0.61, p=0.0002), and ANC (0.60, p=0.0002). The best cut-off for CRP in predicting CA was 73 mg/L (sensitivity: 73.89%; specificity: 82.11%), 3610.3 for SII (sensitivity: 41.67%; specificity: 82.11%), 174.53 for PLR (sensitivity: 67.22%; specificity: 57.14%), 9.54 for NLR (sensitivity: 54.44%, specificity: 66.97%), 18.33×103 cells/µL for WBC (sensitivity: 46.11%, specificity: 76.36%), and 15.65×103 cells/µL for ANC (sensitivity: 42.22%, specificity: 78.54%). **Conclusion**: CRP level followed by SII, PLR, NLR, WBC and then ANC can be used in differentiating simple from CA in children.

Keywords: Acute Appendicitis, Complicated Appendicitis, Risk Prediction, Biomarkers, Children.

Introduction

Acute appendicitis (AA) is the most atraumatic abdominal condition that a surgeon could confront in children aged 2 years and older,[1] up to 8% of children with acute abdominal pain present AA as an aetiology. Acute appendicitis can occur at any age but the incidence in childhood was estimated to pass from 2 to 25 cases per 10,000 children per year in age groups of 0 to 4 years and 10 to 17 years, respectively.[1] Nevertheless, the incidence of complicated appendicitis (CA) among children decreased considerably and continuously with age, reaching 54% in the first year of life and 10% in patients above 16 years old.[2] The overall incidence of CA in childhood was estimated to reach 16.8%.[2] Importantly, assessing the prognosis stage of the disease evolution is particularly crucial. Firstly, mortality and morbidity of patients who underwent appendectomy because of AA is conditioned by the severity course of the disease and associated comorbidities.[3] Secondly, determining whether the AA is simple or complicated should be considered before deciding the timing of surgery and which appropriate

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postoperative care is the most suitable.[3] The aim of this study was to analyse the preoperative biological parameters of children who presented with confirmed AA and to determine the predictive factors of complicated forms of the disease.

Participants and Method

A total of 402 children during a study period of 7 years from May 2015 to April 2022 were enrolled. In this retrospective single-centered study, all children aged less than 16 years old, of both genders, who underwent appendectomy in our Department of Pediatric Surgery because of AA, and in whom the diagnosis was confirmed on the basis of histological analysis of the resected appendix, were included. Patients with pathological history of a chronic inflammatory disease, haemopathy, active autoimmune disease, recent infectious disease, ischaemic or cardiovascular pathology, recent trauma, or with lack of data in their medical documentations were excluded. Included children were divided into two groups considering the intraoperative appearance and histological analysis of the appendix: in group A were children who presented NCA, and in group B were those with CA. Inflammatory or suppurative appendicitis with a clean abdominal cavity were considered as NCA. However, if perforation of the appendix, intraperitoneal abscess formation or purulent ascites were present, the appendicitis was defined as complicated. These intraoperative findings were considered only if they had been confirmed pathologically by histological analysis of surgical specimens. Preoperative biological parameters (white blood cell count (WBC), absolute neutrophil count (ANC), neutrophil percentage (NE%), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width (RDW), systemic immune inflammatory index (SII), and C-reactive protein (CRP)), intraoperative appearance of the appendix and peritoneal cavity, and pathological analysis of the resected appendix were collected from medical records of all included patients. The SII was calculated with the formula: neutrophil × PLT/lymphocyte counts.

Statistical Analysis

A descriptive analysis was performed. Continuous variables were presented as averages, standard deviations, and qualitative variables were described using frequencies and percentages. Also, a univariate analysis was performed using Chi-square or Fischer's test to compare categorical variables. For quantitative variables, the normality of data was verified with the Kolmogorov-Smirnov test. Student's t-test was used for comparison of means between CA and NCA groups if data were normally distributed, or Mann-Whitney U test if not. Next, receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated for each laboratory parameter. Also, the optimal cutoff point, sensitivity, and specificity for each parameter that were suggestive of predicting the diagnosis of CA were specified. A p-value of less than 0.05 and AUC of more than 0.60 were considered to be statistically significant. The statistical analysis was done using IBM SPSS statistics for Windows, version 21.0 (IBM corp., New York, USA).

Ethics Statement

Before performing this study, an institutional approval from the Ethics Committee for Biomedical Research of our Faculty of Medicine (order number: 05/2021) was obtained.

Results

A total of 402 patients were enrolled: 221 children (55%) presented with NCA and 181 (45%) presented with CA. The mean age was 9.6 ± 3.1 years. Notably, CA was diagnosed more often in younger children with a mean age was 8.9 years compared to 10.2 years in the NCA group (p=0.0001).

Table 1: Comparison of laboratory parameters between children with non-complicated and complicated acute appendicitis

Parameter	Total (N=402)	Group A (n=221)	Group B (n=181)	*p*-value
WBC (10^3/µL)	16.3 ± 5.8	15.3 ± 5.1	17.6 ± 6.5	0.0001
ANC (10^3/µL)	13.3 ± 5.5	12.3 ± 5.1	14.5 ± 5.9	0.0001
NE% (%)	79.3 ± 10.9	77.8 ± 12.2	81.2 ± 8.8	0.002
NLR	9.9 ± 6.9	8.7 ± 6.5	11.4 ± 7.2	0.0001
PLT (10^9/L)	298.1 ± 85.6	288.2 ± 82.2	310 ± 88.3	0.01
MPV (fL)	10.2 ± 1	10.2 ± 1	10.1 ± 0.9	0.5
PLR	214.5 ± 122	188.2 ± 100.1	246.2 ± 137	0.0001
RDW (%)	12.9 ± 1.7	12.7 ± 1	13.1 ± 2.3	0.04
SII (10^9/L)	2931.7 ± 2227.5	2477.8 ± 1943	3481.4 ± 2423.5	0.0001
CRP (mg/L)	96.1 ± 97.2	50.5 ± 68.5	151.4 ± 98.4	0.0001

Values are presented as means ± standard deviations. WBC: white blood cell count, ANC: absolute neutrophil count, NE%: neutrophil percentage, NLR: neutrophil-to-lymphocyte ratio, PLT: platelet count, MPV: mean platelet volume, PLR: platelet-to-lymphocyte ratio, RDW: red blood cell distribution width, SII: systemic immune inflammatory index, CRP: C-reactive protein.

Table 2: The performance of evaluated laboratory parameters in predicting complicated appendicitis

Parameter	AUC	95% CI	Cutoff point	Sensitivity	Specificity	*p*-value
WBC (10^3/µL)	0.61	0.55-0.66	18.33	46.11	76.36	0.0002
ANC (10^9/L)	0.60	0.55-0.66	15.65	42.22	78.54	0.0002
NE% (%)	0.58	0.52-0.63	82.01	58.33	56.16	0.006
NLR	0.62	0.57-0.68	9.54	54.44	66.97	<0.0001
PLT (10^3/µL)	0.57	0.51-0.62	310	46.67	66.06	0.01
PLR	0.63	0.58-0.69	174.53	67.22	57.14	<0.0001
RDW (%)	0.55	0.49-0.61	12.60	54.80	55.56	0.09
SII (10^9/L)	0.64	0.58-0.69	3610.30	41.67	82.11	<0.0001
CRP (mg/L)	0.83	0.78-0.87	73.08	73.89	82.11	<0.0001

Cutoff values were obtained based on the best sensitivity-specificity association. AUC: area under the (ROC) curve, ROC: receiver operating characteristics, CI: confidence interval, WBC: white blood cell count, ANC: absolute neutrophil count, NE%: neutrophil percentage, NLR: neutrophil-to-lymphocyte ratio, PLT: platelet count, PLR: platelet-to-lymphocyte ratio, RDW: red blood cell distribution width, SII: systemic immune inflammatory index, CRP: C-reactive protein.

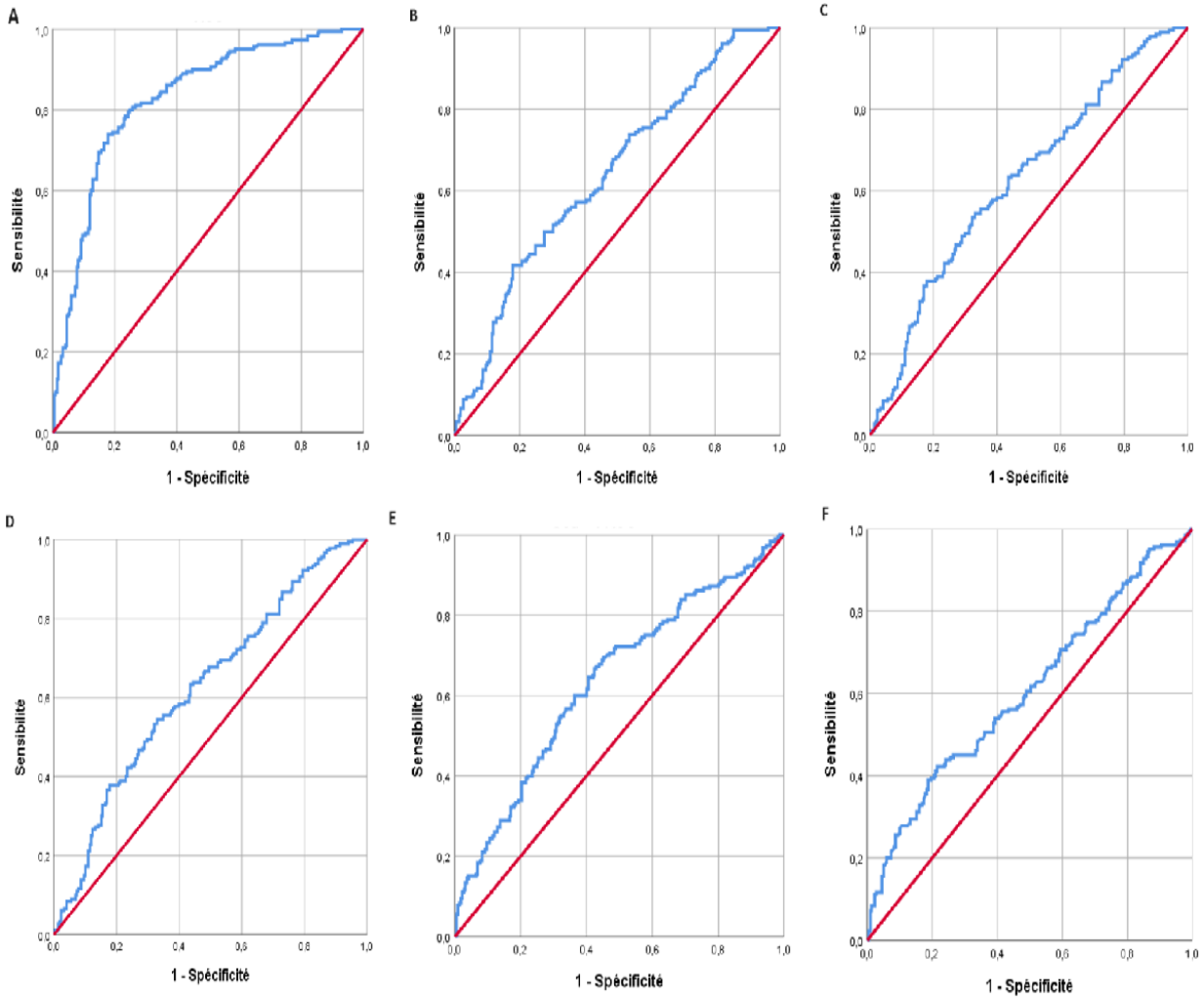


Figure 1: Receiver operating characteristic (ROC) curves with corresponding area under the curve (AUC) for C-reactive protein (CRP) (A), systemic immune inflammatory index (SII) (B), platelet-to-lymphocyte ratio (PLR) (C), neutrophil-to-lymphocyte ratio (NLR) (D), white blood cell count (WBC) (E), and absolute neutrophil count (ANC) (F) in predicting complicated appendicitis in children

Table 3: Predictive value of preoperative biomarkers in diagnosing complicated appendicitis in children; comparison of our results with previous studies

Parameters	Diagnosis performance	Doğan *et al.*[25]	Zachos *et al.*[4]	Güngör *et al.*[5]	Bălănescu *et al.*[22]	Tekeli *et al.*[19]	Our findings
Sample size		88	72	251	599	1072	402
NCA							
CA		77	42	148	435	796	221
		11	30	103	164	276	181
CRP (mg/L)	AUC	0.62	0.67	0.82	0.72	0.85	0.83
	Cut-off	>18.30	>71	>33.85	>34.30	>39	>73.08
	Sensitivity %	71.10	50	75.70	68.90	79.65	73.89
	Specificity %	64.80	83.70	73	65.29	79.53	82.11
	p-value	0.12	0.015	<0.001	<0.0001	<0.001	<0.0001
WBC (10^3/µL)	AUC	0.61	0.666	0.63	-	0.60	0.61
	Cut-off	>15.46	>14.70	>15.80	-	>14.40	>18.33
	Sensitivity %	100	63.30	64.10	-	65.70	46.11
	Specificity %	36.20	69	59.50	-	51.29	76.36
	p-value	0.08	0.017	<0.001	-	0.002	0.0002
ANC (10^3/µL)	AUC	-	0.71	0.61	-	0.59	0.60
	Cut-off	-	>10.10	>12.85	-	>12.60	>15.65
	Sensitivity %	-	90	62.10	-	48.84	42.22
	Specificity %	-	53.40	57.40	-	66.16	78.54
	p-value	-	0.007	0.004	-	0.004	0.0002
NLR	AUC	0.51	-	-	0.77	0.62	0.62
	Cut-off	>8.60	-	-	>8.39	>5.36	>9.54
	Sensitivity %	54.50	-	-	73.17	73.84	54.44
	Specificity %	67	-	-	70.11	45.69	66.97
	p-value	0.91	-	0.18	<0.0001	<0.001	<0.0001
PLR	AUC	-	-	-	0.68	0.62	0.63
	Cut-off	-	-	-	>201.40	>223	>174.53
	Sensitivity %	-	-	-	63.41	66.19	67.22
	Specificity %	-	-	-	64.14	44.77	57.14
	p-value	-	-	-	<0.0001	<0.001	<0.0001
SII (10^9/L)	AUC	-	-	-	-	0.64	0.64
	Cut-off	-	-	-	-	>2358.03	>3610.30
	Sensitivity %	-	-	-	-	56.40	41.67
	Specificity %	-	-	-	-	67.67	82.11
	p-value	-	-	-	-	<0.001	<0.0001

NCA: non-complicated acute appendicitis, CA: complicated acute appendicitis, CRP: C-reactive protein, WBC: white blood cell count, ANC: absolute neutrophil count, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, SII: systemic immune inflammatory index.

A male predominance in our population was observed with 63.2% of the boys represented. There was no difference between the two groups. WBC, ANC, NLR, PLR, SII, CRP, NE%, PLT and RDW levels in serum were higher within group B than group A children at preoperative biological evaluation (p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.002, p=0.01, p=0.04, respectively). However, no difference was seen when comparing MPV level between the two groups. Biological data are presented comparatively in Table 1. Moreover, the diagnostic accuracy of relevant laboratory parameters in predicting complicated forms of AA was further studied. As result, the best AUC found was 0.83 for CRP (95% confidence interval [CI] 0.78-0.87, p<0.0001), followed by 0.64 for SII (95% CI 0.58-0.69, p<0.0001), 0.63 for PLR (95% CI 0.58-0.69, p<0.0001), 0.62 for NLR (95% CI 0.57-0.68, p<0.0001), 0.61 for WBC (95% CI 0.55-0.66, p=0.0002), and 0.60 for ANC (95% CI 0.55-0.66, p=0.0002). In addition, the optimal cutoff values of parameters with the best AUC as well as the associated sensitivity and specificity were determined. When the cutoff point of CRP was specified as 73 mg/L, the sensitivity and specificity of this parameter to predict CA were 73.89% and 82.11%, respectively. In the same way, the cut-off point for SII was 3610.3 (sensitivity: 41.67%, specificity: 82.11%), 174.53 for PLR (sensitivity: 67.22%, specificity: 57.14%), 9.54 for NLR (sensitivity: 54.44%, specificity: 66.97%), 18.33 × 103 cells/µL for WBC (sensitivity: 46.11%, specificity: 76.36%), and 15.65 × 103 cells/µL for ANC (sensitivity: 42.22%, specificity: 78.54%). The accuracy of different parameters and

their ROC curves are shown in Table 2 and Figure 1.

Discussion

Since the prediction of the prognosis of appendicitis preoperatively aids in management planning and disease outcome,[4] we sought in this study to investigate preoperative biological parameters that can predict complications in children with a confirmed diagnosis of AA. Indeed, biological markers contribute mainly to the diagnosis of AA. However, there are variations in the diagnostic accuracy of testing biomarkers individually or in association, especially in differentiating complicated from non-complicated forms of AA.[4]

CRP level, WBC and ANC are among the routinely tested biomarkers that have shown interest in predicting CA based on previous studies conducted in children, which have demonstrated remarkable comparative differences in their findings.[4-7] Importantly, Chung *et al.,* demonstrated prospectively in 1996 that CRP level presents a diagnostic value in differentiating NCA from CA but did not study its precise accuracy.[8] Thereafter, subsequent works have elucidated the high prognostic value of CRP to predict complicated forms of AA.[6,7,9,10] Fujii *et al*., reported a CRP level of more than 40 mg/L to be correlated with CA based on a multivariate analysis.[11] The same value (40 mg/L) was also found to be an optimum cutoff to predict CA.[12] Interestingly, a CRP level at admission of more than 120 mg/L was described to be predictive of increased morbidity among children with confirmed CA.[13] In other settings, a CRP level greater than 30 mg/L was strongly associated with complicated forms of the disease, while greater morbidity was observed on admission to the paediatric intensive care unit, intestinal obstruction, a longer LOS, and postoperative intra-abdominal abscess occurrence.[14] In our children, CRP level was the best biological predictive parameter (AUC = 0.82), and a value of 73 mg/L is considered the best cutoff point for predicting complication among children with AA. Moreover, children with CA showed higher WBC and ANC than those with simple appendicitis.[11,15,6,16]

However, WBC count presented no significance in differentiating children with NCA from those with complicated forms according to other case series.[12] Likewise, Monsalve *et al*., concluded that WBC has more important value in diagnosing AA than in staging of the disease.[17] Indeed, a higher accuracy and sensitivity were attributed to WBC count in diagnosing simple AA than CRP level.[18] Nevertheless, WBC showed similar sensitivity in comparison to CRP in diagnosing perforated appendicitis which can reach 100% if they are combinedly considered.[18] Thus, WBC was proven to have major interest in diagnosing AA and secondarily in predicting complications despite its low accuracy.[19] However, according to the study by Okamoto *et al*., WBC had diagnostic value in distinguishing children with NCA from those with CA only if the pain duration before surgery is longer than 48 hours.[10] In contrast, WBC was considered as a good predictor for perforated AA in other settings.[16] According to the findings of Zani *et al*., WBC can predict CA only in children that are 5 years of age or above, whereas no difference was found for ANC between children with NCA and CA regardless of their age.[20] Also, preoperative WBC was considered as a predictor of postoperative complications in children with appendectomy because of AA regardless of the surgical approach (laparoscopic or open surgery).[21] Our results show that WBC and ANC have a prediction value for CA but remain weaker in terms of accuracy than the other biomarkers (CRP, SII, NLR, PLR).

Furthermore, novel biomarkers were assessed in children to demonstrate their performance in distinguishing CA from NCA. Interestingly, NLR was described as a reliable predictable parameter for appendicular peritonitis even with superior accuracy compared to CRP level.[22] An NLR value superior to 8.39 was considered in favor of appendicular peritonitis in children with AA[22] Similarly, an NLR greater than 7.53 was considered predictable for severe appendicitis in childhood where 30-day postoperative complication rate and LOS were significantly higher.[23] These findings were validated prospectively afterwards which highlight the value of NLR as a simple adjunct in predicting the severity of the disease.[24] In addition, SII followed by PLR were described as the best predictors for CA after CRP level compared to other routinely tested biomarkers.[19] In summary, Table 3 shows the diagnostic accuracy of different preoperative biomarkers in distinguishing CA from simple AA in previous studies in children, by comparing them with our results. [4,5,19,22,25]

This is a retrospective single-center study conducted in an academic institution. Therefore, prospective multicentric studies including more patients in similar settings are recommended to validate and discuss critically our findings

Conclusion

The early prediction of complication occurrence in children with AA is clearly important for surgical strategy, further management, and prognosis of disease course postoperatively. Preoperative biological findings may predict the stage of disease evolution. CRP level followed by SII, PLR, NLR, WBC and then ANC can be used in differentiating simple from complicated AA in children.

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Conflicts of interest

There are no conflicts of interest.

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