Neutrophil-to-lymphocyte ratio in the diagnosis of acute appendicitis. Assessment of its diagnostic accuracy

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ABSTRACT

Introduction. Acute appendicitis (AA) in pediatric patients requires an accurate diagnosis. The neutrophil-to-lymphocyte ratio (NLR) is an accessible parameter useful for its diagnosis.

Objective. To determine NLR accuracy to diagnose AA in patients with abdominal pain.

Population and methods. Diagnostic test study. A total of 520 patients seen at the Pediatric Emergency Department were included. Diagnostic accuracy was estimated based on sensitivity, specificity, predictive values, and likelihood ratios. A multiple logistic regression model was used to assess the effect of potentially confounding variables in the relationship between NLR and AA.

Results. The prevalence of AA was 49%. For a cut-off point of 5, sensitivity was 85.1%, specificity: 78.9%; positive predictive value: 79.5%; and negative predictive value: 84.6%. However, based on likelihood ratios, the NLR is not powerful enough to diagnose AA (positive likelihood ratio = 4.03 and negative likelihood ratio = 0.18) and did not exhibit diagnostic usefulness in complicated appendicitis (positive likelihood ratio = 1.57 and negative likelihood ratio = 0.55). Following adjustment for age, sex, obesity, time since symptom onset, and analgesic use, the NLR was an explanatory variable for the presence of AA (odds ratio = 23.53; 95% confidence interval: 13.14–42.15).

Conclusions. The NLR alone is not sufficiently accurate to confirm or rule out the presence of AA. However, the NLR can be used together with other tests to select patients in whom further study is necessary.

Key words: *sensitivity, specificity, appendicitis, abdominal pain, neutrophils.*

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INTRODUCTION

Acute appendicitis (AA) is the most common abdominal surgical emergency in pediatric emergency departments.[1,2] The diagnosis of AA should be made as early as possible, as any delay may increase the risk for complicated appendicitis or even death.[3,4] However, an early and accurate diagnosis can be a clinical challenge, given the difficulties in patient communication and the absence of typical symptoms.[5] The use of different laboratory parameters or assessment scales to screen patients with suspected AA results in non-invasive criteria in the diagnostic approach.[5] Recent research has shown that hematological ratios (e.g., neutrophil-to-lymphocyte ratio [NLR] or mean platelet volume-to-lymphocyte ratio) can be useful in the diagnosis of pediatric appendicitis.[2–4,6]

Neutrophilia and lymphopenia are common in pediatric patients with AA.[2,4,7–13] The onset of neutrophilia can occur within minutes to hours after the beginning of the inflammatory process and is caused by the mobilization of neutrophils.[14] Moreover, lymphopenia is associated with stress response and marginalization of lymphocytes within the reticuloendothelial system.[14,15] A recent meta-analysis reported that NLR is a useful parameter in the differential diagnosis of AA; a NLR of 4.7 had a sensitivity of 88%, a specificity of 91%, and an area under the curve (AUC) of 0.96.[16] In addition, the NLR may be significantly higher in patients with complicated appendicitis compared to patients with simple appendicitis.[8,10,14]

Unlike the adult population, only few studies have analyzed the diagnostic performance of NLR in AA in the pediatric population. The estimated sensitivity of the NLR in the diagnosis of AA in children ranges from 62% to 90% and the specificity, from 56% to 89%.[2,4,6] The cut-off points used to categorize patients range from 1.77 to 7.54.

The NLR is an accessible and easily interpreted parameter that may be valuable in the diagnosis of AA, especially in areas with limited diagnostic resources. However, not all studies demonstrate utility, and cut-off points for interpretation vary among studies.[17–19] Therefore, validation in each clinical setting is required. The primary objective of this study was to establish the cut-off point that better discriminates patients with AA from other causes of abdominal pain and assess the diagnostic accuracy of the NLR. The secondary objective was to assess whether the NLR is a useful parameter to discriminate patients with simple appendicitis from those with complicated appendicitis.

POPULATION AND METHODS

This was a cross-sectional, analytical study with a diagnostic test design. The study population was made up of all patients ≤ 16 years with suspected AA seen at the pediatric emergency department of a secondary care hospital in the city of Mérida, Yucatán, Mexico, between January 1st, 2019 and March 1st, 2020. Data were obtained retrospectively from the review of medical records. Patients in whom neutrophil and lymphocyte counts had been measured in their initial evaluation and who had a definitive diagnosis of the cause of abdominal pain were included in the study. Patients with a diagnosis of autoimmune disease, heart failure, peripheral vascular disease, known acute or chronic infection, liver disease, and use of anticoagulants and glucocorticoids were excluded from the study.

The sample size was estimated using the easyRoc® tool, version 1.3.1,[20] with a significance level of 0.01, a statistical power of 95%, an AUC of 0.764, and a ratio of patients without appendicitis to patients with appendicitis of 0.264, based on the results published by Prasetya et al.[6] The minimum sample size was 120 patients with suspected AA.

The diagnosis of AA was established according to the surgery findings and/or the result of the pathology report. Complicated AA was defined if necrosis, perforated appendix, abscess and/or generalized peritonitis were documented.[5,7,8,10] Neutrophils and lymphocytes were measured with a Sysmex XN-2000® hematology analyzer (Sysmex, Kobe, Japan). The NLR was obtained as the ratio between the absolute neutrophil count and the absolute lymphocyte count.

This study complied with the guidelines stipulated in international codes of ethics and was approved by the Local Ethics and Research Committee number 3201 of the Mexican Social Security Institute under registration number R-2021-3201-042.

Statistical analysis

Qualitative variables were described as number of cases and percentage. Quantitative variables were described as mean ± standard deviation and median (interquartile range), as applicable. The 95% confidence interval (CI) was calculated to estimate the accuracy of the parameters. The Mann-Whitney U test was used to compare the study groups, and the size of the differences was determined using the Z value (see *Supplementary material*).[21] The ability of the NLR to discriminate between the study groups (patients with AA versus without appendicitis; simple AA versus complicated AA) was determined using the AUC. The interpretation of the discrimination ability of the NLR was based on the cut-off points described in the supplementary material.[22,23] The Youden index was used to establish the optimal cut-off point of the NLR. The diagnostic accuracy was assessed based on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). The diagnostic power of the test based on the likelihood ratios was interpreted using the thresholds described in the supplementary material.[24]

The effect of age, sex, obesity, time since symptom onset, and use of analgesics on the relationship between the NLR and AA was assessed using a multiple logistic regression analysis based on the presence of AA as the dependent variable in the first model and the presence of complicated appendicitis in the second model. For the multivariate analysis, all variables with a p value ≤ 0.2 were included in the bivariate analysis. A value of $p < 0.05$ was considered statistically significant. The effect size of the association between AA and the NLR was established with the cut-off points for

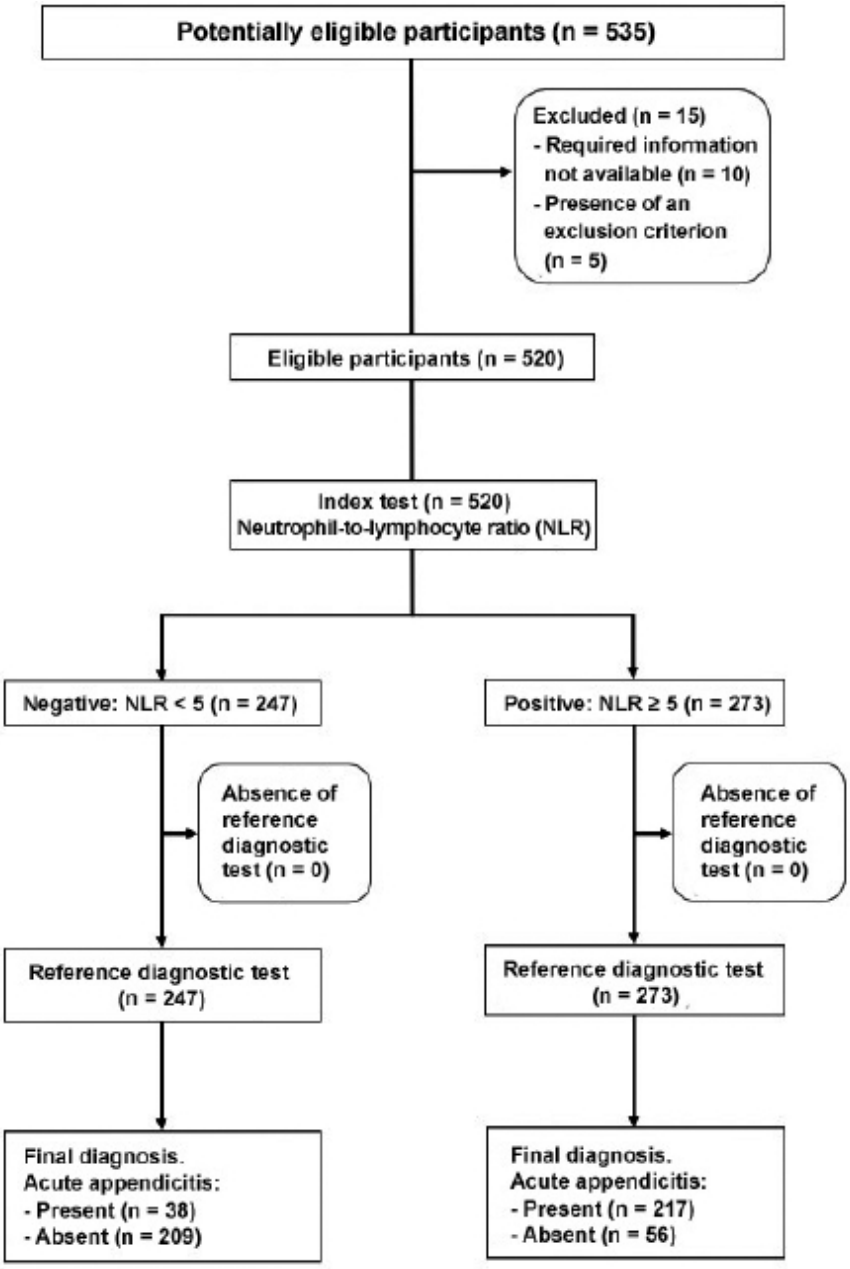
the interpretation of the odds ratio (OR) size[25] (*Supplementary material*). The statistical analysis was performed using the Stata statistical software, version 14 for MacOS® (StataCorp.2015. *Stata Statistical Software:* Release 14. College Station, TX: StataCorp LP) and the Graphad Prism software, version 8 for MacOs® (GraphPad Software, La Jolla California, USA).

RESULTS

Sample characteristics

The study flow chart is shown in *Figure 1*. A total of 520 patients with suspected AA were included; their mean age was 8.8 ± 3.1 years (minimum: 2, maximum: 15) and 18.8% (n = 98) were ≤ 5 years. The median time since symptom onset to the initial evaluation was 48 hours

FIGURE 1. *Study flow chart*



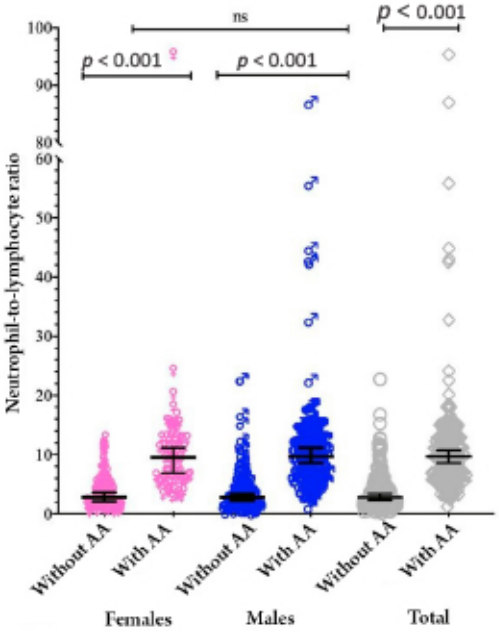
(minimum: 8 hours, maximum: 120 hours). The diagnosis of AA was confirmed in 49% (n = 255) of participants. AA was more frequent in boys compared to girls (57.72% versus 34.69%,

TABLE 1. *Clinical characteristics of the stratified sample in patients with and without acute appendicitis Quantitative data: median (interquartile range). Qualitative data: n (%)*

	Total (n = 520)	Without appendicitis (n = 265)	With appendicitis (n = 255)	*p* value[a]	Effect size[b]
Age (years)	9 (6)	8 (6)	9 (5)	< 0.001	0.19
Time since symptom onset (hours)	48 (48)	24 (24)	48 (24)	< 0.001	0.52
Temperature (ºC)	38 (0.5)	38 (0.5)	38 (0.5)	< 0.001	0.21
Leukocytes (cells/mm^3)	15 325 (8550)	10 500 (5500)	18 700 (4400)	< 0.001	0.74
Neutrophils (cells/mm^3)	11 930 (9558)	6960 (4396)	16 287 (4016)	< 0.001	0.77
Lymphocytes (cells/mm^3)	2015 (1473)	2312 (1644)	1701 (1120)	< 0.001	0.28
NLR	5.5 (7.74)	2.8 (3.08)	9.66 (6.70)	< 0.001	0.66
Clinical presentation					
Abdominal pain (%)	517 (99.42)	262 (98.87)	255 (100)	0.08	
Fever (%)	512 (98.46)	261 (98.49)	251 (98.43)	0.95	
Vomiting (%)	471 (90.58)	225 (84.91)	246 (96.42)	< 0.001	
Decreased appetite (%)	381 (73.27)	146 (55.09)	235 (92.16)	< 0.001	
Diarrhea (%)	280 (53.85)	124 (46.79)	156 (61.18)	0.001	
Tachycardia (%)	177 (34.04)	75 (28.30)	102 (40)	0.005	
Dysuria (%)	92 (17.69)	65 (24.53)	27 (10.59)	< 0.001	
Cough (%)	48 (9.23)	41 (15.47)	7 (2.5)	< 0.001	
Hypertension (%)	15 (2.88)	9 (3.40)	6 (2.35)	0.477	
Nutritional status					
Obesity (%)	78 (15)	8 (3.02)	70 (27.45)	< 0.001	
Malnutrition (%)	55 (10.58)	22 (8.30)	33 (12.94)	0.085	

[a] Mann-Whitney U test.
[b] Effect size = Z value in the Mann-Whitney U test/√n.
NLR: neutrophil-to-lymphocyte ratio.

FIGURE 2. *Comparison of the neutrophil-to-lymphocyte ratio in patients with and without acute appendicitis by sex*



Median. Error bars account for the 95% confidence interval.

$p < 0.001$), and patients with AA were significantly older than patients without appendicitis (10 versus 8 years, $p < 0.001$). Seventy-three percent (n = 384) of cases had received some analgesic prior to their evaluation. *Table 1* shows the clinical and demographic characteristics of the study participants.

Diagnostic accuracy of the NLR in acute appendicitis

The NLR was significantly higher in patients with AA compared to patients without appendicitis (9.6 versus 2.8, $p < 0.001$) (*Figure 2*). The AUC of the NLR for categorizing a patient with and without appendicitis was 0.883 (95%

TABLE 2. *Diagnostic accuracy of the neutrophil-to-lymphocyte ratio to discriminate acute appendicitis from other causes of acute abdominal pain in pediatric patients*

		Acute appendicitis (AA)		
		With AA	**Without AA**	**Total**
Neutrophil-to-lymphocyte ratio	≥ 5	217	56	273
	< 5	38	209	247
	Total	255	265	520

Prevalence = 49% (95% CI: 45.0–53.4%).
Sensitivity = 85.1% (95% CI: 80.1–89.2%).
Specificity = 78.9% (95% CI: 73,5–83.6%).
Positive predictive value = 79.5% (95% CI: 74.2–84.1%)
Negative predictive value = 84.6% (95% CI: 74.2–84.1%)
Positive likelihood ratio = 4.03 (95% CI: 3.17–5.11)
Negative likelihood ratio = 0.18 (95% CI: 0.14–0.25)

CI: confidence interval.

TABLE 3. *Estimated odds ratio based on the multiple logistic regression model to account for the presence of acute appendicitis in pediatric patients with suspected appendicitis*

Variable	**Odds ratio (standard error)**	**95% confidence interval**	***p* value**
Age			
≤ 5 years old	1		
> 5 years old	1.46 (0.53)	0.72–3.10	0.29
Sex			
Female	1		
Male	2.19 (0.62)	1.24–3.84	0.006
Obesity			
Absent	1		
Present	20.46 (11.51)	6.79–61.62	< 0.001
Analgesics			
Not used	1		
Used	1.83 (0.59)	0.97–3.44	0.059
Time since symptom onset			
< 24 hours	1		
24 to 48 hours	8.12 (5.24)	2.29–28.78	0.001
48 to 72 hours	48.79 (33.01)	12.95–183.77	< 0.001
> 72 hours	45.29 (5.66)	12.10–169.49	< 0.001
Neutrophil-to-lymphocyte ratio			
< 5	1		
≥ 5	23.53 (6.99)	13.14–42.15	< 0.001

Y variable: appendicitis (0 = absent, 1 = present). Pseudo R2 = 0.51.
Goodness of fit of the logistic regression model. Hosmer-Lemeshow test, $p = 0.26$.
Area under the ROC curve = 0.92.

CI: 0.854–0.911). There were no differences in the AUC between males and females (0.882 versus 0.878, $p = 0.091$) or between patients ≤ 5 years compared to those > 5 years (0.904 versus 0.873, $p = 0.372$). A NLR of 5.08 was the best cut-off point for discriminating patients with AA from patients without appendicitis. For a cut-off point of 5, the NLR identified 217 of the 255 cases of AA (sensitivity = 85.1%). A NLR < 5 was observed in 209 of the 265 patients without AA (specificity = 78.9%). *Table 2* shows the predictive values and likelihood ratios.

The logistic regression analysis showed that the NLR was one of the variables that significantly accounted for the presence of AA, after adjustment for age, sex, obesity, time since symptom onset, and analgesic use. The likelihood ratio of having AA compared to not having AA is 23 times higher in patients with a NLR ≥ 5 than in patients with a NLR < 5; the effect size is large. The variables included in the model accounted for 51% of the variance. The Hosmer-Lemeshow test showed that there were no significant differences between the observed results and those predicted by the model. The AUC of the model was 0.92, which suggests the model has a good discrimination (*Table 3*).

NLR accuracy to discriminate simple AA from complicated AA

Most of the cases included in the study (81%; n = 207) met the criteria for complicated appendicitis. The NLR was significantly higher in patients with complicated appendicitis compared to patients with simple appendicitis (10.5 versus 6.67, $p < 0.001$; moderate effect size). The AUC of the NLR for categorizing a patient with and without complicated appendicitis was 0.678. (95% CI: 0.59–0.76). The optimal cut-off point for NLR values discriminating cases of simple appendicitis from cases with complicated appendicitis was 7.41. For a cut-off point of 7.4, sensitivity was 68.6%, specificity: 56.3%, PPV: 87.1%, NPV: 29.8%, LR+: 1.57, and LR-: 0.55.

The logistic regression analysis showed that the NLR was one of the variables that significantly accounted for the presence of complicated AA, after adjustment for age, sex, obesity, time since symptom onset, and analgesic use. The likelihood ratio of having complicated AA compared to having simple AA is 3.8 times higher in patients

TABLE 4. *Estimated odds ratio based on the multiple logistic regression model to account for the presence of complicated appendicitis in pediatric patients with acute appendicitis*

Variable	Odds ratio (standard error)	95% confidence interval	*p* value
Age			
≤ 5 years old	1		
> 5 years old	0.40 (0.27)	0.11–1.49	0.17
Sex			
Female	1		
Male	0.54 (0.23)	0.23–1.25	0.15
Obesity			
Absent	1		
Present	5.3 (2.8)	1.87–14.97	0.002
Analgesics			
Not used	1		
Used	2.01 (0.80)	0.91–4.41	0.081
Time since symptom onset			
< 24 hours	1		
24 to 48 hours	31.48 (41.77)	2.33–424.08	0.009
48 to 72 hours	35.51 (46.57)	2.71–464.39	0.006
> 72 hours	32.40 (42.20)	2.52–416.00	0.008
Neutrophil-to-lymphocyte ratio			
< 7.4	1		
≥ 7.4	3.82 (1.38)	1.88–7.79	< 0.001

Y variable: complicated appendicitis (0 = absent, 1 = present). Pseudo R2 = 0.15.
Goodness of fit of the logistic regression model. Hosmer-Lemeshow test, $p = 0.85$.
Area under the ROC curve = 0.76.

with a NLR ≥ 7.4 than in patients with a NLR < 7.4; the effect size is moderate (*Table 4*).

DISCUSSION

The results of this study demonstrate that the NLR is significantly higher in patients with AA compared to the group of patients with abdominal pain without AA. The sensitivity and specificity of the NLR in the diagnosis of AA are consistent with those reported in previous studies. The estimated sensitivity of the NLR reported is 63–90% and specificity, 57–89%.[2,4,6,8,10,13,26,27] In our study, 81% of cases with AA developed complicated appendicitis; such prevalence is higher than that reported in previous studies. A recent systematic review reported complicated appendicitis in 35% of 2782 appendectomies performed in pediatric patients.[28] In studies that assessed the usefulness of the NLR in the diagnosis of AA in children, the reported prevalence of complicated appendicitis ranges from 11% to 68%.[10,29]

In this study, the pediatric surgeon was responsible for determining the need for surgery for suspected AA, after a clinical and analytical assessment. Since misdiagnosed appendicitis can have serious complications and even lead to death, the objective of diagnostic testing is to avoid false negatives. If the diagnosis of AA is to be based solely on the NLR result, clinicians should be aware of the high number of false positives (approximately 20%) and missed diagnoses (approximately 15% false negatives). Based on the result of the LR+ and LR-, the NLR is a poor test for the diagnosis of AA (LR+ = 4.03 and LR- = 0.18) and proved to be a test without diagnostic utility for discriminating simple appendicitis from complicated appendicitis (LR+ = 1.57 and LR- = 0.55).

It is widely recognized that the diagnostic performance of a test may vary according to the characteristics of the patients evaluated.[30–32] Therefore, the difference in the prevalence of complicated appendicitis should be taken into account when interpreting post-test likelihood values, especially in samples with a lower prevalence of complicated appendicitis. It is known that likelihood ratios do not change with disease prevalence.[24] However, the accuracy of likelihood ratios depends on sensitivity and specificity. The inclusion of a larger number of patients with complicated appendicitis may overestimate the sensitivity of the NLR (spectrum bias). Pediatric patients with complicated appendicitis are possibly easier to detect as they have a higher NLR than patients with simple appendicitis.

In the bibliography, the diagnostic accuracy of the NLR for discriminating patients with complicated appendicitis has inconsistent results. The NLR is significantly higher in pediatric patients with peritonitis compared to those with appendicitis but without peritonitis (13.5 versus 7.1, $p < 0.001$).[5] Another study reported that the NLR was a predictor of the presence of post-operative intra-abdominal abscesses.[33] Some authors reported that the NLR can help discriminate complicated from uncomplicated appendicitis.[5,34] However, other studies have not confirmed this finding.[4,8,13] The ability of the NLR to discriminate between simple and complicated appendicitis in children as measured by the AUC ranges from 0.66 to 0.84, with cut-off points between 4.8 and 10.4, and a sensitivity of 67% to 85%. In our study, the NLR was not a useful laboratory parameter for discriminating cases of simple AA from cases of complicated AA, given its poor discriminatory power (AUC < 0.7). The results obtained in this study are similar to those reported by Kelly et al.,[10] Paramita et al.,[29] and Kostakis et al.[8]

Our results suggest that the NLR cannot be used as a parameter to confirm or rule out the presence of AA. However, it can be used in conjunction with other tests, symptoms, and clinical signs to select patients in whom further tests are required. Some authors consider that the NLR may be an alternative to C-reactive protein.[5] In the multivariate analysis, the NLR significantly explained the presence of AA and the addition of clinical variables increased the model's diagnostic accuracy.

When interpreting our study results, the following limitations should be considered: 1) due to its retrospective design, it was not possible to assess other markers of inflammation (e.g., C-reactive protein) or use imaging studies (abdominal ultrasound or tomography); 2) the prevalence of complicated appendicitis is higher than that reported in previous studies (this may be partially explained by the fact that it is a referral hospital; it is expected for referral facilities to see cases with a higher morbidity); 3) by using a non-randomized sample, there is a potential selection bias, which we tried to limit by using consecutive case sampling and by including the largest number of patients who met the inclusion criteria; and 4) the combination of the NLR with clinical variables increased the AUC of the model. Further studies should assess whether the combination of clinical variables with the NLR can improve clinical decisions and reduce the number of complicated appendicitis.

CONCLUSIONS

AA is associated with an increased NLR. However, the NLR is not sufficiently accurate to diagnose AA or to discriminate between simple and complicated appendicitis. ■

Supplementary material available at:
https://www.sap.org.ar/docs/publicaciones/archivosarg/2022/2433_AO_Esquivel_Anexo.pdf

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