

Predictive biomarkers for complicated acute appendicitis: A prospective Ecuadorian study

Biomarcadores predictores de apendicitis aguda complicada: estudio prospectivo en Ecuador

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Abstract

Aim: The aim of the study was to determine the usefulness of known biomarkers as pre-operative predictors of complicated acute appendicitis (CAA) and perforated appendicitis (PA). **Materials and methods:** This was an observational, analytic, cross-sectional, and prospective study at Hospital Teodoro Maldonado Carbo (August 2016-December 2017). Evaluated biomarkers: white blood cells count, neutrophil percentage (N%), neutrophil-to-lymphocyte ratio, glucose, total bilirubin, C-reactive protein, and procalcitonin (PCT). The statistical analysis was performed by means of the area under the receiver operating characteristics (AUROC) curve estimation. Biomarkers' cutoff point was identified using Youden's index. Sensitivity, specificity, positive, and negative predictive value (NPV) (positive predictive value [PPV] and NPV) were estimated. **Results:** One hundred and twenty-eight cases were included (median age 30 years, 44% female), 70 cases (54%) corresponded to CAA (PA 38/70). N% and PCT obtained an AUROC of 78% and 80% for CAA (PA 76% and 81%), respectively. A N% > 78.1% predicted CAA with a sensitivity, specificity, PPV, and NPV of 82%, 62%, 72%, and 72% (> 74.9%, PA: 94%, 53%, 46%, and 96%), respectively. PCT > 0.14 ng/dL predicted CAA with sensitivity, specificity, PPV, and NPV of 69%, 79%, 80%, and 68% (PA: 84%, 69%, 53%, and 91%). **Conclusion:** The N% and PCT represent useful pre-operative biomarkers for discarding PA when an acute appendicitis is suspected.

Key words: Appendicitis. Biomarkers. Neutrophils. Procalcitonin.

Resumen

Objetivo: Determinar la utilidad de conocidos biomarcadores como predictores de apendicitis aguda complicada (AAC) y perforada (AP). **Método:** Estudio observacional, analítico, transversal, de recuperación prospectiva, realizado en el Hospital Teodoro Maldonado Carbo (agosto de 2016 a diciembre de 2017). Biomarcadores evaluados: glóbulos blancos, porcentaje de neutrófilos (%N), índice neutrófilo/linfocito, glucosa, bilirrubina total, proteína C reactiva y procalcitonina (PCT). El análisis estadístico se realizó mediante estimación del área bajo la curva ROC (Receiver Operating Characteristics). Se individualizó el valor de corte mediante el índice de Youden. Se estimaron la sensibilidad, la especificidad, el valor predictivo positivo (VPP) y el valor predictivo negativo (VPN). **Resultados:** Se incluyeron 128 casos (mediana de edad 30 años, 44% mujeres), de los

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Date of reception: 02-04-2020

Date of acceptance: 24-04-2020

DOI: 10.24875/CIRU.20000256

Cir Cir. 2020;88(5):599-607

Contents available at PubMed

www.cirugiaycirujanos.com

que 70 (54%) correspondieron a AAC (AP 38/70). El %N y la PCT obtuvieron un área ROC del 78% y el 80% para AAC (AP 76% y 81%), respectivamente. Un %N > 78.1% predijo AAC con una sensibilidad, una especificidad, un VPP y un VPN del 82%, 62%, 72% y 72% (> 74.9%, AP: 94%, 53%, 46% y 96%). Una PCT > 0.14 ng/dl predijo AAC con una sensibilidad, una especificidad, un VPP y un VPN del 69%, 79%, 80% y 68% (AP: 84%, 69%, 53% y 91%). **Conclusión:** El %N y la PCT constituyen biomarcadores útiles en el descarte de AP cuando se sospecha una apendicitis aguda.

Palabras clave: Apendicitis. Biomarcadores. Neutrófilos. Procalcitonina.

Introduction

Acute appendicitis (AA) is the most frequent surgical emergency around the world^{1,2}. AA could be classified in four stages: catarrhal (stage I), phlegmonous (Stage II), gangrenous (Stage III), and perforated (Stage IV); the two last ones have been considered as complicated AA (CAA)³. In reference hospitals, an important number of CAA is attended⁴. An association between laparoscopic appendectomy and the development of comorbidities related to the surgical act has been documented in cases of both stages of CAA, but more in the context of a Stage IV or perforated appendicitis (PA)¹. In these situations, the learning curve is the main limitation of the laparoscopic approach, when the McBurney's incision is preferred⁵. However, the diagnosis of AA usually poses a challenge to the surgeon; it is even more difficult to estimate its stage.

A predictive biomarker is defined as that condition that increases the risk of suffering from a disease, or that allows it to be diagnosed⁶. By apposition, a prognostic biomarker is a condition that allows estimating or establishing the prognosis of a pathology, *per se* or after a treatment. In this context, certain classic laboratory tests have been established as pre-operative biomarkers for CAA prediction^{1,6,7}, namely: white blood cell (WBC) count, neutrophil percentage (N%), neutrophil-to-lymphocyte ratio (NLR), glucose, total bilirubin (TBil), C-reactive protein (CRP), and Procalcitonin (PCT). Its predictive usefulness differs according to the literature. Even though laparoscopic surgery is a safe way to approach CAA⁸, considering both surgeon experience and the context of each patient, estimating AA-stage will allow for a more individualized surgical behavior, as the possibility of a McBurney incision approach when suspicion of CAA. Thus, an important proportion of CAA can be predicted, the greater the number of patients benefited with a personalized indication. This will positively impact the prognosis, in terms of a lower frequency of comorbidities associated with the surgical act.

The aim of the study was to determine the usefulness of WBC, N%, NLR, glucose, TBil, CRP, and PCT as pre-operative biomarkers of CAA prediction at a

Hispanic population from a public South American hospital. As a secondary objective, we also purposed to verify the usefulness of these biomarkers as predictors of PA, through a data sub-analysis.

Materials and methods

Study design

The following was an independent, observational, analytical, cross-sectional, and consecutive collected case-control study. It was carried out in patients attended due to any stage of AA at Emergency Department of Hospital Teodoro Maldonado Carbo (HTMC), a tertiary referral hospital at Guayaquil – Ecuador, from August 2016 to December 2017. The present study was presented in accordance with the strengthening the reporting of observational studies in epidemiology statement⁹.

Population

There were included patients ≥ 13 years old, in whom an open or laparoscopic appendectomy was performed due to clinical suspicion of AA. There were excluded patients with the history of abdominal pathology during 30 days before the diagnosis of AA; patients with history of comorbidities that may affect acute phase reactants (e.g., respiratory or renal infections, inflammatory bowel disease, and cancer ongoing specific treatment), or liver metabolism (e.g., acute or chronic hepatitis, and liver cirrhosis, choledocholithiasis); pregnancy or puerperium; cases in which AA has been ruled out due after histopathological analysis; as well as those patients whom clinical reports described partial information for the purpose of the present study.

Monitoring and retrieval of information

PRE-OPERATIVE STAGE

Once a case was enrolled in the present study, J.E-O. and I.R-R. recovered the demographic data as well

as the results of the following biomarkers requested as part of the diagnosis of AA before surgery: WBC count, N%, NLR, glucose, TBil, CRP, and PCT.

OPERATIVE STAGE

During surgery, H.S-A. confirmed the presence and stage of AA, corroborating it with the description of the first operator in the final surgical report.

POST-OPERATIVE STAGE

J.F-O. and M.P-A recovered the histopathological result of the surgical pieces, as well as the stage of AA, if applicable.

DATA RECOVERY, INTEGRATION, AND ENCRYPTION

The information was retrieved by the previous mentioned researchers, through a data collection form particularly designed for each stage of the study. Finally, the data were integrated into a single database by R.O. and C.T-H, and encrypted by J.B-B.

Statistical analysis

TECHNICAL CONSIDERATIONS

The data analysis was performed by M.P-T using the program R v3.6.3 (R Foundation for Statistical Computing; Vienna, Austria). $p < 0.05$ was considered to be statistically significant.

SAMPLE SIZE CALCULATION

The sample size was calculated using *power.diagnostic.test* function from the *MKmisc* (v1.6; Kohl M, 2019) package¹⁰. The sample size was estimated considering a 98% specificity of PCT for gangrenous and PA, as well as corresponding disease prevalence of 23% described by Molina-Saenz et al.¹¹; a $\delta = 10\%$, an α and β -error of 5% and 20%, respectively. Through the previous described parameters, a sample size of 43 cases and 13 controls was estimated, with an 80% statistical power. To respect the Central Limit Theorem (30 observations are necessary to reach a Gaussian distribution), we preferred to analyze no less than 30 patients in control group along study period¹².

DESCRIPTIVE STATISTICS

Continuous variables were described as mean (standard deviation) or median (minimum-maximum range), depending on their distribution (normal or skewed), determined by the Kolmogorov-Smirnov test. The categorical variables were described in frequencies (%).

INFERRENTIAL STATISTICS

Study variables difference among each AA-stage confirmed by histopathology was verified by the Kruskal-Wallis test for continuous variables, and Pearson's Chi-squared or Fisher's exact test for categorical variables. The area under the receiver operating characteristics (AUROC) curve was determined for each biomarker with statistical significance among AA-stages. Each biomarker was contrasted with two outcomes (gold standards) formed from the four AA-stages grouped: CAA (AA-stage III and IV) and PA (AA-stage IV). AUROC from each biomarker was contrasted among both outcomes using *roc.test* function from the *pROC* (v1.16.2; Robin X, 2020) package¹³. In those cases in which AUROC $\geq 75\%$ ¹⁴, the appropriate cutoff value for the biomarker test was determined by Youden's index. Subsequently, the diagnostic accuracy of such tests was determined through the following estimators: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) positive and negative likelihood ratio (+LR and -LR, respectively), observed coincidence, and diagnostic odds ratio (OR). Figure 1 details the inferential statistical process in accordance with the study results.

Ethic aspects

The presented study respected the stipulations of the Declaration of Helsinki (2008). Approval of the Medical Faculty Graduate School Institutional Review Board of Universidad Espíritu Santo and Clinical Research and Teaching Department of HTMC was obtained. All patients included in the study signed informed consent.

Results

The population selection is detailed in figure 2. Along study period, a total of 128 patients were

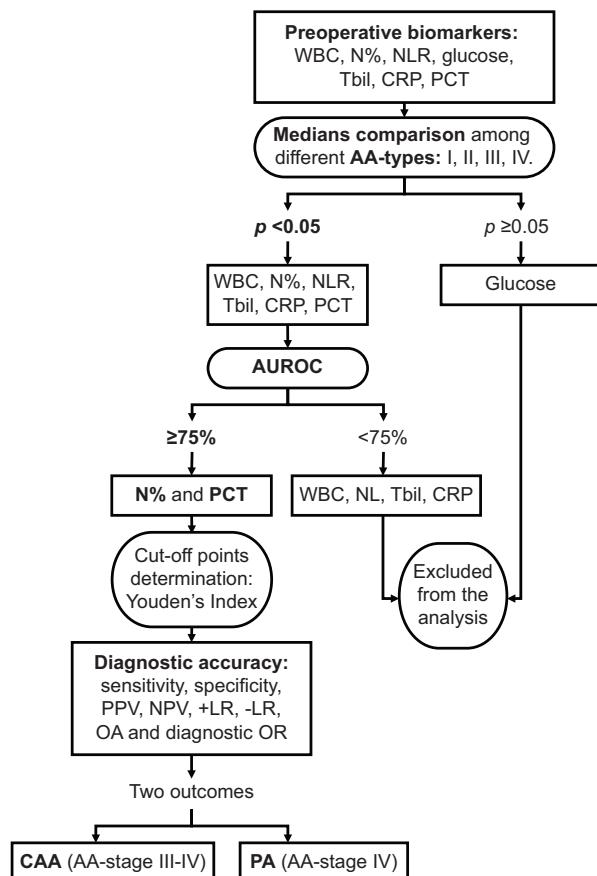


Figure 1. Approach of the inferential statistical process applied in the usefulness estimation of the different preoperative biomarkers for CAA and PA prediction. AA: acute appendicitis; CAA: complicated acute appendicitis; CRP: C-reactive protein; PA: perforated appendicitis; NLR: neutrophil-to-lymphocyte ratio; N%: neutrophil percentage; NPV: negative predictive value; OA: observed agreement; OR: odds ratio; PCT: procalcitonin; PPV: positive predictive value; TBil: total bilirubin; WBC: white blood cell count; +LR: positive likelihood ratio; -LR: negative likelihood ratio.

enrolled. Forty-four cases (34.4%) were female. According to post-surgical diagnostic and further histopathological confirmation, there were 6/128 (4.7%) AA-stage I (or catarrhal), 52/128 (40.6%), AA-stage II (or phlegmonous), 32/128 (25%), AA-stage III (or gangrenous), and 38/128 (29.7%) AA-stage IV (or perforated) cases. Both AA-stage III and IV represented the total of CAA cases (70/128; 54.7%). There was no significant statistical difference among age, gender, or median glucose concentration versus each AA-stage. Nonetheless, median concentrations of TBil, N%, WBC count, NLR, CRP, and PCT show statistically significant difference among different AA-stages. This difference consisted in a gradual rise of median concentration of such values directly correlated to AA-stages. WBC count measurement for AA-stage I, II, III, and IV was: 11.16, 12.30, 15.40, and

16.05 $10^3/\mu\text{L}$ ($p < 0.001$); N%: 74.0%, 70.6%, 82.0%, and 85.1% ($p < 0.001$); NLR: 5.52, 4.81, 5.69, and 5.59 ($p < 0.001$); TBil: 0.88, 0.69, 0.98, and 1.01 mg/dL ($p < 0.001$); CRP: 4.82, 0.33, 24.70, and 3525.0 mg/dL ($p < 0.001$); and PCT: 0.08, 0.05, 0.14, and 0.64 ng/dL ($p < 0.001$); respectively (Table 1).

The N% and PCT values presented an AUROC $\geq 75\%$ for predicting CAA (AA-stage III and IV) and PA (AA-stage IV) (Fig. 3), while WBC count, NLR, and TBil reached AUROC values between 60% and 73% for both outcomes. CRP reached an AUROC of 75.3% for predicting CAA, but 69.7% for predicting PA, thus CRP was also excluded for further statistical analysis along with WBC, NLR, and TBil, in accomplishment with the proposed methodology. There is important to remark that there was no statistical difference between CAA versus PA AUROC in any of the analyzed pre-operative biomarker (Table 2).

According to Youden's index estimation, the cutoff point of N% among CAA or PA was 78.1%-74.9%, respectively. Regarding PCT, the cutoff point for an optimal diagnostic accuracy was 0.14 ng/dL for both CAA and PA. Considering both cutoff values, there were a statistically significant association between N% and PCT versus CAA ($p < 0.001$) and PA ($p < 0.001$) prediction.

Considering the previous described cutoff values, N% and PCT diagnostic accuracy for predicting CAA and PA were estimated and summarized in table 3. For CAA, N% reached a sensitivity, specificity, PPV, NPV, observed agreement, and diagnostic OR of 80%, 62%, 72%, 72%, and 6.55, respectively; for PA sub-analysis, 95%, 52%, 46%, 96%, 65%, and 8.36, respectively. PCT reached also a sensitivity, specificity, PPV, NPV, observed agreement, and diagnostic OR of 69%, 79%, 80%, 68%, 73%, and 20.57 for predicting CAA; and 84%, 69%, 53%, 91%, 73%, and 11.81 for predicting PA, respectively. Both N%/PCT sensitivity and NPV were particularly higher for PA sub-analysis.

Discussion

The aim of the present study was to determine the usefulness of the different pre-operative biomarkers in patients with clinical suspicion of CAA. The role of certain biomarkers in the prediction of perforation of the appendix has been described in the literature: WBC count, N%, NLR, glucose, TBil, CRP, and PCT^{1,6,7}. From these examinations, in the present study, there were confirmed a high diagnostic

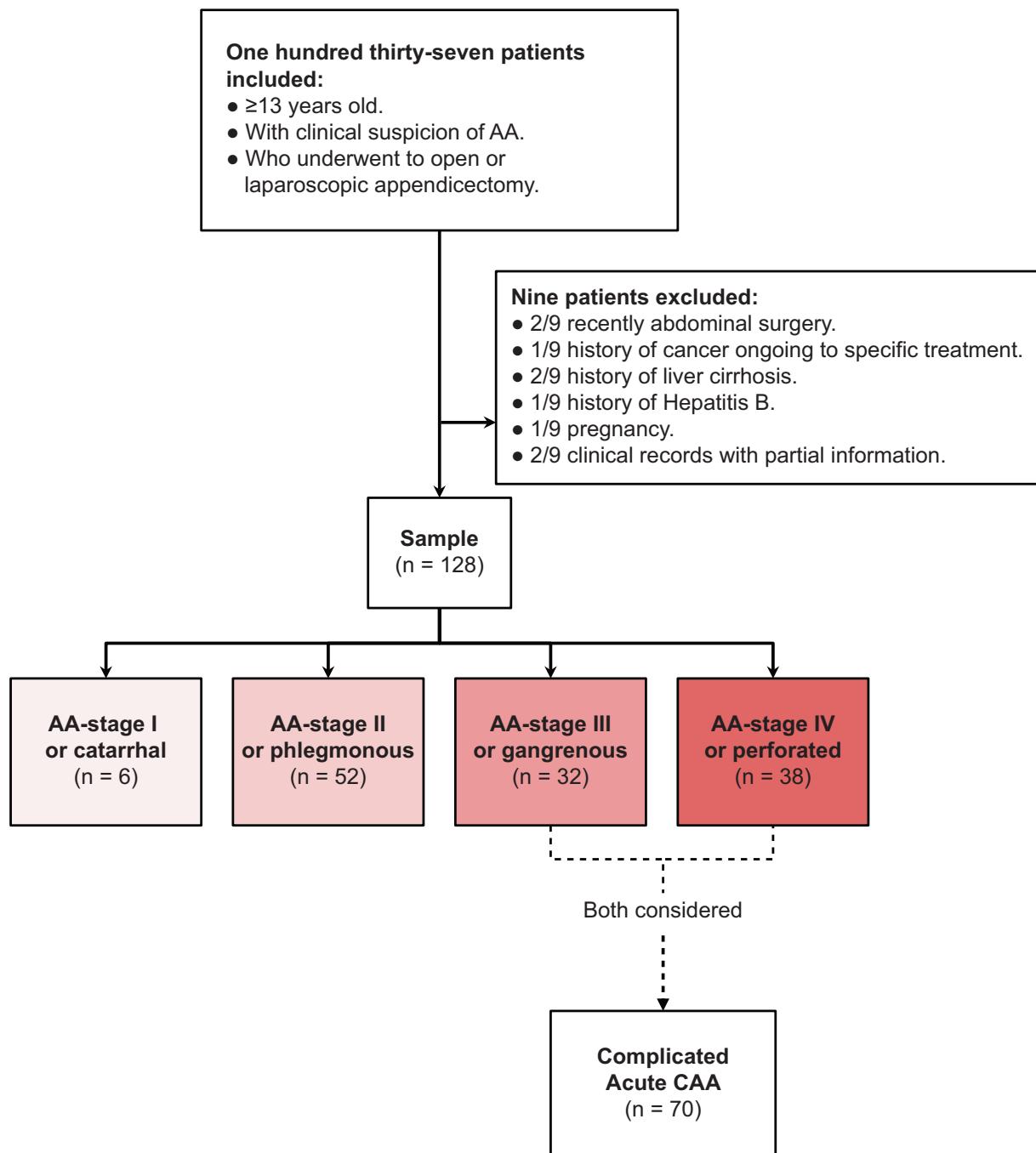


Figure 2. Strengthening the reporting of observational studies in epidemiology patient's selection flowchart. AA: acute appendicitis; CAA: complicated acute appendicitis.

accuracy for N% (AUROC of 78% and 76%; $p = 0.809$) and PCT (AUROC of 80% and 81%; $p = 0.939$) for predicting both CAA and PA, respectively. A non-significant difference between CAA and PA-AUROC in both biomarkers let us understand that they must be interpreted conjunctively. N% and PCT reached a very good sensitivity and PPV for predicting CAA (80%) and PA (80%). N% and PCT NPV were

particularly higher for PA sub-analysis: N% 96%, PCT 91%; in contrast with CAA analysis: N% 72%, PCT 68%. A negative N% ($\leq 74.9\%$) or PCT (≤ 0.14 ng/dL) represented potential biomarkers for discarding a PA from a highly suspected case with AA. NLR did not show statistical significance for predicting CAA. In our series, it was due to a limited AUROC, in correspondence with diagnostic accuracy for

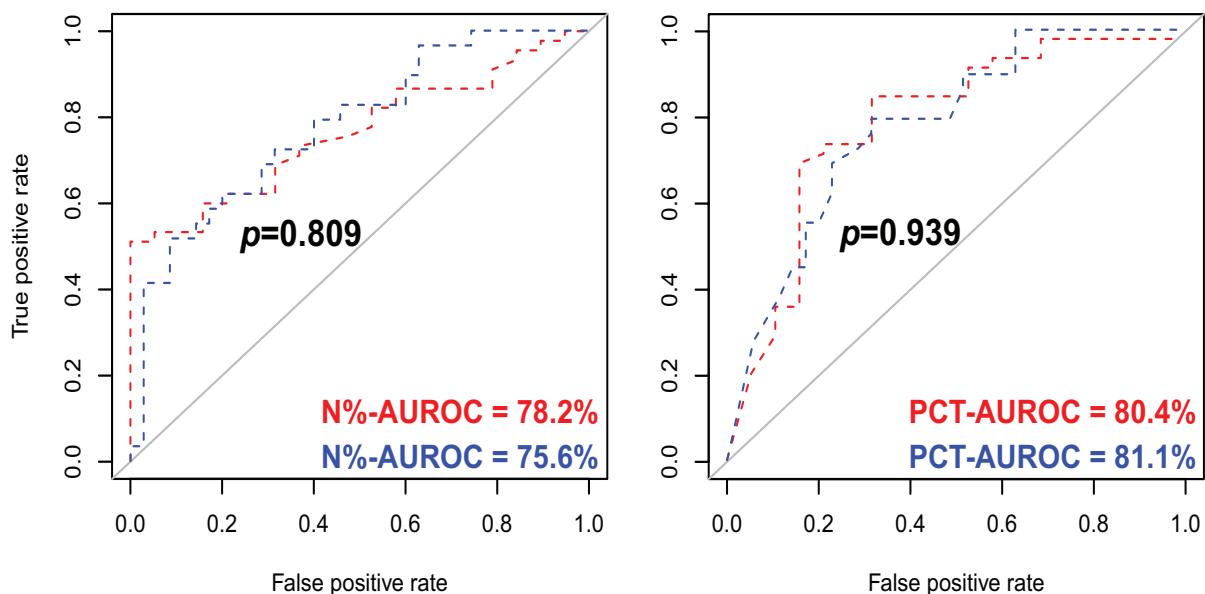


Figure 3. Pre-operative biomarkers which reached an area under the receiver operating characteristics curve $\geq 75\%$ considering as outcomes CAA and PA. **A:** neutrophil percentage (N%; %) versus CAA (blue curve) and PA (red curve); **B:** procalcitonin (PCT; ng/dL) versus CAA (blue curve) and PA (red curve). CAA: complicated acute appendicitis; PA: perforated appendicitis.

distinguishing among CAA versus non-CAA described by Beecher et al.¹⁵, but in opposition with reported results by another authors¹⁶⁻¹⁸.

N% as a preoperative biomarker of CAA has been recently less studied in comparison with other biomarkers as LNR, CRP, or PCT. Park et al. designed an observational retrospective study where they analyzed WBC count, N%, CRP, and immature granulocyte percentage (IG%) between AA patients and a non-AA control group. N% reached higher diagnostic accuracy compared with CRP and IG%, with a sensitivity, specificity, PPV, NPV, +LR, and -LR of 67%, 64%, 66%, 66%, 1.88, and 0.51 for predicting AA.

Beltrán et al. determined in a similar study that CRP and TBil showed greater sensitivity and specificity (75% and 51%, respectively). As strength of this study, the validation of the cutoff points of the different biomarkers can be highlighted. As a limitation, the difference between the study groups, from which the results were inferred: the simple appendicitis group was almost double than the PA group¹⁹. PCT has been considered as a pre-operative biomarker for AA prediction in more recently studies²⁰. Molina-Sáenz et al. performed an analysis of PCT for the prediction of CAA. Here, the sensitivity and specificity of this marker were 56% and 98%, respectively. These results are more consistent with the present study¹¹.

In the present study, PCT reached a very high maximum range for AA-type III and IV (12990.0 and 9990.0 ng/dL, respectively), while the maximum ranges for AA-type I and II were lower than the standard cutoff (0.13 and 0.97, respectively). As described by Godínez-Vidal et al., in a Mexican series of 182 patients with abdominal sepsis diagnosis, PCT reached a median of 9.76 ± 24.63 ng/dL²¹. Precursive inflammatory cascade from a potential abdominal sepsis in the context of a CAA is an explicable way to understand the statistically significant difference between median PCT levels among CAA versus non-CAA cases, and even the slightly higher PCT-AUROC in PA sub-analysis when comparing with AA-type I-III.

Acharya et al. performed a 62 full-text articles systematic review, which analyzed different biomarkers as predictive factors of AA. There were including seven researches which considered to study PCT. For the diagnosis of PA, the pooled sensitivity of PCT was 0.69 (95% CI 0.62-0.76; I² = 93 %) and pooled specificity was 0.67 (95% CI 0.62-0.71; I² = 97 %), giving an AUROC of 0.83 ± 0.07 ²².

The present study has the following strengths: it was developed at a referral center of the Ecuadorian Social Security System (HTMC), which provides clinical attention to an important percentage of the population from Guayaquil, the largest city at Ecuador²³; all

Table 1. Baseline, clinical, and pathological characteristics according to the histopathological diagnosis of acute appendicitis

	Overall (n = 128)	AA-stage I or catarrhal (n = 6)	AA-stage II or phlegmonous (n = 52)	AA-stage III or gangrenous (n = 32)	AA-stage IV or perforated (n = 38)	p-value
Age (years), median (range)	30 (13-90)	32 (26-43)	25 (13-65)	27.5 (16-90)	42 (13-76)	0.043 ^a
Sex (female), n (%)	44 (34.4)	2 (33.3)	18 (34.6)	6 (18.8)	18 (47.4)	0.097 ^b
AA evolution until surgery, n (%)						< 0.001 ^b
< 24 h	62 (48.4)	6 (100.0)	28 (53.8)	22 (68.8)	6 (15.8)	
24-48 h	24 (18.8)	0	12 (23.1)	4 (12.5)	8 (21.1)	
> 48 h	42 (32.8)	0	12 (23.1)	6 (18.8)	24 (63.2)	
WBC count (10 ³ /µL), median (range)	15.32 (4.93-31.29)	11.16 (9.82-16.85)	12.30 (4.93-22.23)	15.40 (6.29-23.13)	16.05 (11.43-31.29)	< 0.001 ^a
≤ 13 × 10 ³ /µL	42 (32.8)	4 (66.7)	28 (53.8)	6 (18.8)	4 (10.5)	
> 13 × 10 ³ /µL	86 (67.2)	2 (33.3)	24 (46.2)	26 (81.3)	34 (89.5)	
n %, median (range)	80.80 (45.50-94.60)	74.0 (45.5-74.6)	70.6 (48.4-90.8)	82.0 (47.2-93.6)	85.1 (75.2-94.6)	< 0.001 ^a
≤ 74%	42 (32.8)	4 (66.7)	28 (53.8)	10 (31.3)	0	
> 74%	86 (67.2)	2 (33.3)	24 (46.2)	22 (68.8)	38 (100.0)	
NLR, median (range)	5.28 (1.25-37.28)	5.52 (4.07-7.59)	4.81 (1.60-21.11)	5.69 (1.25-37.28)	5.59 (3.04-35.00)	0.037 ^a
≤ 5	54 (42.2)	2 (33.3)	32 (61.5)	12 (37.5)	8 (21.1)	
> 5	74 (57.8)	4 (66.7)	20 (38.5)	20 (62.5)	30 (78.9)	
Glucose (mg/dL), median (range)	102.00 (67.00-361.00)	110.0 (103.0-122.0)	97.0 (71.0-361.0)	113.0 (80.0-169.0)	108.0 (67.0-150.0)	0.171 ^a
≤ 110 mg/dL	74 (57.8)	4 (66.7)	38 (73.1)	12 (37.5)	20 (52.6)	
> 110 mg/dL	54 (42.2)	2 (33.3)	14 (26.9)	20 (62.5)	18 (47.4)	
TBil (mg/dL), median (range)	0.90 (0.11-2.43)	0.88 (0.79-0.92)	0.69 (0.11-2.08)	0.98 (0.40-2.02)	1.01 (0.36-2.43)	< 0.001 ^a
≤ 1.0 mg/dL	80 (62.5)	6 (100.0)	40 (76.9)	16 (50.0)	18 (47.4)	
> 1.0 mg/dL	48 (37.5)	0	12 (23.1)	16 (50.0)	20 (52.6)	
CRP (mg/dL), median (range)	4.59 (0.04-37760.00)	4.82 (0.27-3990.0)	0.33 (0.04-22990.0)	24.70 (0.16-37760.0)	3525.0 (0.10-32280.0)	< 0.001 ^a
≤ 1 mg/dL	48 (37.5)	2 (33.3)	32 (61.5)	8 (25.0)	6 (15.8)	
> 1 mg/dL	80 (62.5)	4 (66.7)	20 (38.5)	24 (75.0)	32 (84.2)	
PCT (ng/dL), median (range)	0.12 (0.02-12990.00)	0.08 (0.06-0.13)	0.05 (0.02-0.97)	0.14 (0.02-12990.0)	0.63 (0.02-9990.0)	< 0.001 ^a
≤ 2 ng/dL	102 (79.7)	6 (100.0)	52 (100.0)	24 (75.0)	20 (52.6)	
> 2 ng/dL	26 (20.3)	0	0	8 (25.0)	18 (47.4)	

AA: acute appendicitis; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; N%: neutrophil percentage; PCT: procalcitonin; TBil: total bilirubin; WBC: white blood cells. a: Kruskal-Wallis test; b: Pearson's Chi-squared test; c: Bonferroni's correction.

patients were prospectively enrolled and fully treated at HTMC; it counted with a very strong methodology, sampling size, and statistical analysis. Among the

main limitation of this study is its observational design, where it depends on the request and availability of laboratory reagents to carry out the studies that have

Table 2. Area under the receiver operating characteristics curve for each preoperative biomarker where the null hypothesis was rejected ($p < 0.05$) during the median comparison among each stage of AA, considering as outcomes CAA and PA

Biomarkers	CAA (AA-stage III and IV)	PA (AA-stage IV)	p-value
White blood cells count	71.8%	72.8%	0.972
Neutrophils percentage	78.2%	75.6%	0.809
Neutrophil-to-lymphocyte ratio	64.6%	60.2%	0.826
Total bilirubin	71.7%	70.8%	0.591
C-reactive protein	75.3%	69.7%	0.423
Procalcitonin	80.4%	81.1%	0.939

AA: acute appendicitis; CAA: complicated acute appendicitis; PA: perforated appendicitis.

Table 3. Diagnostic accuracy of the value of neutrophils percentage (N%) and PCT, for predicting CAA and PA

	CAA (AA-stage III and IV)	PA (AA-stage IV)
Neutrophil percentage (n %)		
Sensitivity, % (95% CI)	56/70 (80.00 [68.73-88.61])	36/38 (94.74 [82.25-99.36])
Specificity, % (95% CI)	36/58 (62.07 [48.37-74.49])	48/90 (53.33 [42.51-63.93])
PPV, % (95% CI)	56/78 (71.79 [64.22-78.31])	36/78 (46.15 [40.43-51.98])
NPV, % (95% CI)	36/50 (72.00 [60.70-81.07])	48/50 (96.00 [86.00-98.94])
+LR (95% CI)	2.11 (1.49-2.99)	2.03 (1.61-2.56)
-LR (95% CI)	0.32 (0.19-0.54)	0.10 (0.03-0.39)
OA, % (95% CI)	71.88 (63.25-79.46)	65.62 (56.72-73.79)
Diagnostic OR (95% CI)	6.55 (2.97-14.42)	8.36 (3.72-18.83)
Procalcitonin (PCT)		
Sensitivity, % (95% CI)	48/70 (68.57 [50.71-83.15])	32/38 (84.21 [60.42-96.62])
Specificity, % (95% CI)	46/58 (79.31 [60.28-92.01])	62/90 (68.89 [53.35-81.83])
PPV, % (95% CI)	48/60 (80.00 [65.46-89.41])	32/60 (53.33 [41.51-64.79])
NPV, % (95% CI)	46/68 (67.65 [55.33-77.92])	62/68 (91.18 [78.22-96.75])
+LR (95% CI)	3.31 (1.57-7.00)	2.71 (1.68-4.36)
-LR (95% CI)	0.40 (0.23-0.67)	0.23 (0.08-0.66)
OA, % (95% CI)	73.44 (64.91-80.85)	73.44 (64.91-80.85)
Diagnostic OR (95% CI)	20.57 (4.67-90.63)	11.81 (4.43-31.45)

AA: acute appendicitis; CAA: complicated acute appendicitis; CI: confidence interval; NPV: negative predictive value; OA: observed agreement; OR: odds ratio; PA: perforated appendicitis; PPV: positive predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio.

been analyzed in this project. Biomarkers as Interleukin-6 or 5-Hydroxyindoleacetic acid urinary serotonin²² would be interesting to include in this analysis. Another limitation was the low number of non-CAA cases, especially AA-type I, despite local regulations that they should be attended at a secondary hospital. A non-healthy control group is another aspect to be considered in the study design.

Conclusion

Pre-operative biomarkers such as WBC count, NLR, glucose, TBil, or CRP appears to have a low predictive power for differentiating CAA from non-CAA, compared with N% and PCT. The NPV of a N% $> 74.9\%$ or PCT > 14 ng/dL could be useful to discard

a PA in the clinical context of a highly suspected patient with AA. Considering our results, the design of diagnostic trials with a larger population could be necessary to define the role of N%, PCT, or another novel pre-operative biomarker for differentiating CAA from non-CAA.

Acknowledgments

The authors thank the authorities of the HTMC for allowing the development of the present research.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

The authors received no specific funding for this work.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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