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Biomarkers of Acute Appendicitis Severity: Diagnostic Test Study

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Abstract: Appendicitis (AA) is one of the most frequent abdominal surgical pathologies in the world, with appendectomy being the most frequently performed emergency surgery worldwide. This study was conducted to determine the possible biomarkers to detect the severity in AA for diagnostic purposes, and for the timely management of appendicitis and, thereby avoiding possible complications. This research was conducted based on a randomized sampling, where a total of 239 patients diagnosed with AA at the Hospital Regional de Orinoquia, Colombia was recruited for this study. Blood count, C–reactive protein (CRP), and neutrophil/lymphocyte ratio (NLR) records were analyzed, further their relationship with the surgical findings of AA described by Guzman–Valdivia was established. The study showed that, in the emergency department, these reactants are capable of making an approximate diagnosis and as biomarkers of the severity of AA, with CRP>15mg/dL (diagnostic accuracy 76.15%), and the percentage of neutrophils>85% (diagnostic accuracy 61.09%) being the best initial operative performance. For complications, such as intestinal perforation, CRP>15mg/dL and neutrophil percentage>85% were found statistically to be the biomarkers with the highest predictive performance, with OR 14.46, and OR 2.17, respectively, which is consistent with the findings described by Guzman–Valdivia. In conclusion, elevated level of CRP and neutrophil percentage>85 is the acute phase reactants with the best diagnostic characteristics and predictors of possible complications of AA.

Keywords: Appendicitis; Perforation; Biomarkers; Severity; Acute appendicitis

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1. Introduction

Appendicitis is defined as an inflammation of the vermiform appendix, which is the most common (approximately 60% of total appendicitis) symptoms of acute abdominal. Therefore, appendectomy is the most commonly performed emergency surgery globally [1-4]. It has been estimated that the lifetime risk of developing this disease is approximately 12% [2,3,5], with young people under 29 years of age accounted of 45% from the total appendicitis patients [4,6–9].

This pathology occurs due to inflammation of the cecal appendix, secondary to obstruction of its lumen by faecaliths, lymphoid hyperplasia, tumors, parasites, and others. This condition will disrupt the local blood flow, irritating the adjacent peritoneum, subsequently causing pain. This eventually leads to perforation of the anatomical structure with the release of intestinal contents into the abdominal cavity,

resulting in complications such as peritonitis, sepsis, shock, and in some severe cases can cause death [10–12].

To avoid the completion, therefore it is important for the earlier clinical picture and the pathology identification. However, the diagnosis process becomes late due to the great variety in the presentation of the disease between different individuals, age groups, and genders. In addition, the symptoms of appendicitis are not very specific, thereby often lead to misdiagnosis or late diagnosis in up to 1 in 5 patients [13–17].

In order to achieve a timely diagnosis and decrease the complication rate in patients with the abdominal pain, the clinical component and diagnostic tests (paraclinical) should be combined during the diagnosis procedure, thereby reducing the misdiagnosis or late diagnosis by an estimated 5% to 22%, representing a cost reduction of up to 200,000 Euros per year [18]. This is why a number of scales have been developed in an attempt to help the clinician to recognize which patients with abdominal pain is most likely to suffer from this disease. Among the available scales are the Alvarado scale, the pediatric appendicitis score (PAS), and the RIPASA score, where all the scores are correlated to the clinical manifestations, followed by incorporation of laboratory test results during the diagnosis process [18–21]. However, there is no biomarker with optimal performance, which can independently and effectively diagnose acute appendicitis (AA) or can predict severity or complications of the disease [19–21].

The aim of this article is to analyze the biomarkers which can be used to estimate the severity of the AA during the diagnostic purposes, and for timely management in the emergency department surgical disease diary.

2. Materials and methods

2.1. Population

The universe of the study was the entire population with a diagnosis of AA, which were identified by using the international disease code (ICD–10) as follows: K37: Appendicitis; K35.9: Acute catarrhal, fulminant, gangrenous, obstructive, retrocecal, and suppurative appendicitis; K35.1: AA with peritoneal abscess; K35.0: AA, perforation, peritonitis or rupture; A06.8: Amoebic appendicitis; and K36: Obstructive appendicitis, who attended the Hospital Regional de la Orinoquia (HORO) in Yopal between January 1, 2013 to December 31, 2018.

The following variables were taken into account to calculate the study sample size: The population attended according to the clinical records of the institution was 760 people who were diagnosed with appendicitis, the prevalence of appendicitis is 24.6% [22], margin of error of 5% and 95% confidence interval (95% CI), therefore 239 people were included in this study, which were selected by simple random probability sampling.

2.2. Inclusion criteria

The population seen at the HORO from 2013 to 2018 with a score on the Alvarado scale [22] was included. A score of 5 to 6 is compatible with a diagnosis of AA, 7 to 8 indicates probable appendicitis, and 9 to 10 indicates very probable appendicitis, together with an imaging study of ultrasound or tomography and histopathological study to further confirm the diagnosis. In addition, the patient has to present the Guzman–Valdivia scale according to the intraoperative findings.

2.3. Exclusion criteria

Medical records with incomplete or non–existent blood count (or CBC), C–reactive protein (CRP), neutrophil/leukocyte ratio (NLR), and patients under 18 years of age were excluded from this study.

2.4. Variables

Based on the study conducted by Calvo et al., [23] a list of variables was established for this study, including:

(1) Socio–demographic: Sex, age, rural, or urban origin
(2) Clinical parameters: Acute epigastric pain radiating to the right iliac fossa and fever
(3) Paraclinical data: White blood cell count greater than 11,000, neutrophil percentage>85%, lymphocyte percentage>10%, INL greater than 5.5, and CRP greater than 15mg/dL.

2.5. Statistical analysis

The collected information was recorded in Excel, version 2013, and analyzed in the SPSS statistical software, version 22. The univariate analysis was performed by means of descriptive statistics for the selected population, and the absolute and relative frequencies were determined for categorical variables. In the case of quantitative variables, measures of central tendency (mean, median) and of dispersion (standard deviation and interquartile range) were calculated, according to the distribution of the variable.

The cutoff values for leukocyte count (>11,000/mm^3), neutrophil percentage (>85%), lymphocyte percentage (>10%), CRP (>15mg/dL), and INL (>5.5) were used to differentiate between severe and uncomplicated cases, and the cutoff values were determined using receiver operating characteristics (ROC) curve by means of SPSS software. Finally, to determine the possible associations between the categorical variables, tetrachoric tables were made with measurement of the diagnostic Odds Ratio with their respective 95% CI [<1: As a predictor of mild severity or without perforation; >1: As a predictor of severe severity (perforation); and =1: With no association]. Additionally, the operative characteristics of the analyzed paraclinical tests were estimated to determine the operative characteristics of the different diagnostic tests (sensitivity, specificity, positive predictive value, and negative predictive value), which are most frequently performed during hospitalization of the patients with AA.

2.6. Bias

This study considered to have a low risk of bias, since the scale used as a reference method (Guzman and Valdivia) is based on the findings during the surgical procedure, which are classified into 4 grades; 0: No appendicitis (prophylactic appendicitis, no post–surgical antimicrobial scheme); Ia: Oedematous and ingurgitated; Ib: Abscessed or phlegmonous (with seropurulent fluid around the appendix); Ic: Necrotic without perforation; II: Perforated with localized abscess; III: Complicated appendicitis with generalized peritonitis). The usage of this scale maintains a low risk of error in addition to the dichotomization of the same, in order to assess severity. The qualitative variables were taken as dichotomous in order to facilitate the analysis, and to perform an adequate calculation of the operational characteristics, which will further facilitate the assessment and grouping of the participants.

2.7. Ethical considerations

Based on the resolution 8430 of 1993, it was considered a free-risk study, as the study was conducted based on the review of medical records. In addition, the appropriate permissions were requested from the institution in charge of the custody of the medical records.

3. Results

A total of 239 patient records with diagnosed with AA were evaluated, and the process for choosing the appropriate study sampling were shown as in **Figure 1**.

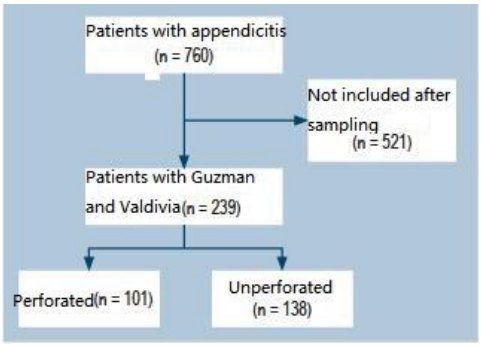

Figure 1. Process for patient recruitment and selection according to sample size

3.1. Socio-demographic characterization

The mean age of the population was 26.35 years, SD ± 6.4 years (coefficient of variation 24%), with a minimum of 18 years and a maximum of 46 years. **Table 1** shows the characteristics of the population.

Table 1. Population characteristics

Variable	N	%	IC95%	
Sex				
–Female	127	53	46.81	59.46
–Male	112	47	40.54	53.19
Residence				
–Urban	155	64.8536	65.21	79.31
–Rural	84	35.1464	29.09	41.2
Grade according to the Guzman-Valdivia scale				
–1a	65	27.1967	21.56	32.84
–1b	51	21,3389	16.15	26.53
–1c	22	9.20502	5.54	12.87
–2	32	13.3891	9072	17.71
–3	69	28.8703	23.13	34.62

Regarding the characteristics of the inflammatory reactants, the mean value of the leucocyte count was 15,512.2/mm^3 with an SD ± 5,386.84/mm^3 (minimum 1,904.1/mm^3; maximum 32,000/mm^3). The neutrophil percentage averaged was 12.625 with SD ± 5,338.36/mm^3 (minimum 1,294.72/mm^3; maximum 27,840/mm^3). Lymphocytes had a mean value of 2,271.28/mm^3 with SD ± 2,125.6/mm^3 (minimum 443/mm^3 and maximum 17,908/mm^3). Meanwhile, the INL averaged was 8.5 with an SD ± 6.8 (minimum of 1 and maximum of 31). The CRP averaged was 47.46 mg/dL with an SD ± 60.7 mg/dL (minimum of 0.50 mg/dL and maximum of 316 mg/dL).

A ROC curve was performed to determine the most accurate cutoff point for each of the variables, and the following values were found from the ROC curve: Leukocyte count>11,000/m^3; percentage of neutrophils>85%; CRP>15mg/dL; percentage of lymphocytes>10%; and INL>5.5 as shown in **Figure 2**.

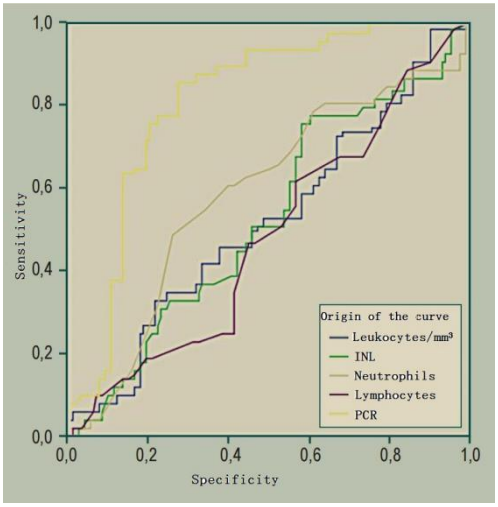

Figure 2. ROC curve

3.2. Diagnostic tests

In total, 101 persons had severe degrees of appendicitis, meaning that around 42.2% of total appendicitis persons had an appendiceal perforation. The results indicate that patients with a neutrophil percentage>85% are 2 times more likely to have intestinal perforation, while patients with CRP>15mg/dL are 14 times more likely to have this complication (**Table 2**).

Table 2. Tetrachoric table between paraclinicals with histopathology

Paraclinical	**Acute appendicitis**		**OR**	**IC 95%**
	Perforated (n=101)	**Unperforated (n=138)**		
Leukocyte count than 11,000	79	107	1.04	0.56; 1.93
	22	31		
Percentage of neutrophils>85%	55	47	2.17	1.28; 3.66
	46	91		
Percentage of lymphocytes>10%	68	93	0.99	0.57; 1.72
	33	45		
INL>5.5	62	78	1.22	0.82–1.52
	39	60		
PCR>15mg/dL	88	44	14.46	7.3; 28.6
	13	94		

3.3. Characteristics of diagnostic tests

Interestingly, it was found that the tests with the highest ability to detect people with appendiceal perforation (sensitivity) were CRP and leukocyte count greater than 11,000/mm^3, with data of 87.13% and 78.22%, respectively (**Table 3**).

The tests with the best ability to detect persons with a non–perforated appendix (specificity) were CRP and the percentage of neutrophils>85%, with 68.12% and 65.94%, respectively (**Table 3**). Finally, the test with the highest diagnostic accuracy was CRP with 76.15% (**Table 3**).

Table 3. Characteristics of diagnostic tests

Operational characteristics	Leukocytes	Neutrophils	Lymphocytes	INL	PCR
Sensitivity	78.22%	54.46%	67.33%	61.39%	87.13%
Specificity	22.46%	65.94%	32.61%	43.48%	68.12%
Positive predictive value	42.47%	53.92%	42.24%	44.29%	66.67%
Negative predictive value	58.49%	66.42%	57.69%	60.61%	87.85%
Diagnostic accuracy	46.03%	61.09%	47.28%	51.05%	76.15%
Likelihood ratio of the positive test	1009	1599	0.999	1086	2733
Likelihood ratio of the negative test	0.9697	0.6907	1002	0.8881	0.189

4. Discussion

In the present study, the population studied represents a relatively young population, with an average age of 26.35 years, which allows a comparison with epidemiological data from other studies, such as the research conducted by of Canovas et al., and Escalona et al., where the average age at presentation of appendicitis was 21 and 29 years, respectively [24,25]. This allows us to find no significant difference in the results obtained. However, this study in contrast with the study conducted by Jonge et al., which had an average age of 55 years [26].

On the other hand, the majority of people diagnosed with AA were women, 53% of the total population, consistent with the results shown in other publications, such as that of Jonge et al., [26], in which the base population was female with 51.2%. However, in another study the majority of patients are male, for example study conducted by Padierna and colleagues, in which it was 50.81% [27]. However, there are no significant differences in terms of gender with regard to the occurrence of AA. Although, it is important to mention that the female gender is more difficult to diagnose, especially during childbearing age or pregnancy, as this characteristic could lead to a confusion at the time of diagnosis [28,29]. Another important feature is that more patients come from the urban areas, than rural areas.

It should be taken into account that the numerous studies documents that the pathophysiological stages of appendicitis can be divided into three groups, with respect to the time of clinical evolution: Incipient: 0–12 hours; Acute: 12–24 hours; and Perforated: 24–48 hours [1,4,10].

In this study, we did not look for the relationship between clinical evolution and the presence of perforation, however, we investigated the comparison of the results of the different stages according to the Guzman–Valdivia classification [30], which indicates that the higher the grade, the greater the severity of the disease, and by using the research of Martinez and collaborators [31], in which the following results were obtained in the present study: Grade 0: 4 patients; Grade 1A: 26 patients; Grade 1B: 32 patients; Grade 1C: 27 patients; Grade 2: 22 patients; and Grade 3: 11 patients, for a total of 122 patients.

From these results we found that the percentages were higher in our investigation, with a percentage difference in grades 1A (5.88%) and 3 (19.96%), which indicates that the most serious complication is perforation with generalized peritonitis occurred more frequently in this study. Where, in other studies conducted by Rigual et al., [19] and Beltran et al., [4], the perforation was found to have a prevalence of 10% and 24%, respectively which is still low compared to our study where we obtained a prevalence of 42.25% in perforations.

With regard to inflammatory reactants, leukocytosis and neutrophilia were found to be associated with the diagnosis of AA. According to the results obtained in this study, having a neutrophil percentage>85% increases the likelihood of an outcome of appendiceal perforation (OR 2.17; 95% CI 1.28–3.66) as shown in **Table 2**. Similarly, an NLI greater than 5.5 which is above baseline was found in patients diagnosed with AA (OR 1.22; 95% CI 0.82–1.52).

It is noteworthy that patients with AA were found to have a significant CRP positivity (47.46mg/dL). Statistical analysis showed in this study, the population with a CRP>15 mg/dL showed a statistically significant OR (OR 14.46, 95% CI 7.3–28.5; 1.5); 95% CI 7.3–28.6), which is parallel with other publications regarding the usefulness of this biomarker as a diagnostic aid. For example, a study conducted by Ishizuka et al., who analyzed the relationship of INL with gangrenous and perforated appendicitis in 314 patients, establishing a figure of 8 as the cutoff point, with a sensitivity and specificity of 73% and 39%, respectively [32], with results lower than those of our study.

Therefore, based on the results obtained from the present study, the diagnostic tests with the best operational performance in the emergency department in a patient suspected with AA are CRP (sensitivity: 87.13%; specificity: 68.12%; diagnostic accuracy: 76.15%), and the percentage of neutrophils>85% (sensitivity: 54.46%, specificity: 65.94%, diagnostic accuracy: 61.09%). These results are similar to previous studies conducted by Aguirre and colleagues, where they showed a similarity in the relationship between CRP, eosinophilia, and pathology [28]. Overall, the results provide us with valuable tools for daily clinical practice, however, we believe that there is a greater need for further research in this field to achieve uniformity of information on a national basis, and to obtain tools that will allow us to address issues such as AA at an earlier stage.

The study by Padierna et al., compared only CRP and white blood cell count as predictors of severity, obtaining a sensitivity of 98.3% and specificity of 88.9% for CRP, and a sensitivity of 80% and specificity of 61% for white blood cell count [27]. This makes it possible to determine that the results obtained are consistent with this research in terms of PCR value, but there is a significant difference with respect to the results of the leucocyte count, since a sensitivity of 78.22% and specificity of 22.46% was obtained, with a diagnostic accuracy of 46.03%. This determines that the results are totally unequal in this study, and that this leucocyte count should not be used as one of the pillars for determining prognosis in the emergency department, due to its low specificity.

This is also seen in the study by Acharya et al., where CRP was evaluated with a sensitivity of 75% and specificity of 50% and the leucocyte count with a sensitivity of 79% and specificity of 55%, as well as other paraclinicals such as bilirubin, procalcitonin, IL-6, and urinary serotonin, as other diagnostic and prognostic factors for AA [29]. In this case, the leucocyte count had a higher value than CRP, which is a notable difference based on the results obtained, as well as in relation to the rest of the literature reviewed. These results could perhaps be explained by the multiple limitations in the study, as well as potential sources of bias due to blinding of the researchers in the literature reviewed.

It is important to note that according to the study conducted by Prasetya et al., the NLI had a high diagnostic accuracy for AA in children, with sensitivity percentages of 84.6% and specificity of 56.5%, which are higher than those obtained in our study of 61.39% and 43.48%, respectively. This is probably due to the difference in the age of the study population, since the maximum age in the study was 18 years, and also to the fact that this is a retrospective study, which is a limitation that should be considered when taking into account when interpreting the results [33].

5. Conclusions

Currently, AA remains a challenge for both diagnosis and prognosis in the emergency department, both for the general practitioner and the specialist, because there is still no biomarker to define how advanced the disease is and what its possible complications are. However, this study was able to determine the operational characteristics of inflammatory reactants as a predictor of severity in AA, and thus prevent possible complications. CRP was found to have the highest specificity and sensitivity, and was also the most positive OR predictor compared to the other reactants.

Similarly, it was found that a white blood cell counts greater than 11,000/mm^3 and a neutrophil

count >85% were associated with the diagnosis of AA. In addition, according to the results obtained in this study, a neutrophil percentage>85% increases the likelihood of a complication of the condition (OR 2.17), while a CRP greater than 15mg/dL increases the likelihood of a complication of the condition (OR 14.46). This could be a definitive characteristic for finding the likelihood of complications in AA in any age group.

In conclusion, this study allowed us to determine the cutoff points for paraclinical variables widely used to predict and prevent complications of AA, such as perforation, which would allow us to optimize in-hospital management, which would ultimately have an impact on final care costs, further shorter the patient recovery time.

Disclosure statement

The authors declare no conflict of interest.

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