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Diagnostic Indexes Findings in Early Stages of Appendicitis (DIFESA Study): a reanalysis from the POSAW study database

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ABSTRACT

Purpose: The resection of a normal-looking appendix during laparoscopic appendicectomy (LA) remains a dilemma. The optimal approach requires reliable macroscopic judgment by the surgeons. The aim of this study is to assess the surgeon's ability to laparoscopically diagnose acute appendicitis (AA) in its initial uncomplicated grades. **Method:** Subgroup analysis from the POSAW study, 2016. Patients diagnosed with initial grades of AA (0 - 1) who underwent LA were included (n=718). The median age was 29.4 years, and 52% were female. The accuracy of the macroscopic intraoperative diagnosis was assessed with the histopathological examination of the resected specimens, and the agreement between the surgeon's and the pathologist's judgment was established. **Results:** Of the 79 appendices classified intraoperatively as normal-looking, 18 (22.8%) had some inflammation degree. Of the 639 appendices classified intraoperatively as inflamed, 101 (15.8%) were normal. The intraoperative surgeon's judgment had an accuracy of 83.4% and a moderate to low agreement (Kappa 0.42). The sensitivity and specificity values were 96.8% and 37.7%, and the positive and negative predictive values were 84.2% and 77.2%, respectively. **Conclusion:** The surgeon's intraoperative diagnosis of uncomplicated AA's initial grades is not sufficiently accurate to establish good reliability for appendicectomy. The surgeon overestimates the presence of appendicular inflammation.

Keywords: Appendicitis; Appendectomy; Laparoscopy, Diagnosis.

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INTRODUCTION

Acute appendicitis (AA) is among the most common causes of acute abdominal pain. It is one of the main indications for emergency surgery globally, with a global incidence ranging from 100 to 151 cases per 100,000 inhabitants per year [1]. The lifetime risk of developing AA is estimated to be 8.6% to 12% in men and 6.7% to 23.1% in women, with a peak incidence from 10 to 19 years of age [2]. AA can be stratified into complicated or uncomplicated, with complications being defined by the presence of necrosis, perforation, or abscess, which significantly increase mortality rates [3, 4].

The diagnosis and preoperative stratification of AA can be challenging, as they involve a critical analysis of a set of clinical, laboratory, and imaging findings. Even with the advances observed in imaging techniques, neither Magnetic Resonance (MRI) nor Computed Tomography (CT) can differentiate complicated and uncomplicated AA [5, 6], which results in a late diagnosis, usually inside the operating room.

Appendectomy has historically been the treatment of choice for AA, with the laparoscopic approach currently being advocated for having the highest success rates and the lowest rates of complications, the shortest hospital stay, and overall best quality of life [6 - 10]. The intraoperative visualization of the appendix's signs of inflammation is seen as the main factor in deciding between performing the appendicectomy or leaving the appendix *in situ* [11]. Studies point to a moderate diagnostic accuracy of the surgeon when graduating AA, being lower for uncomplicated cases [12 - 14]. This can mean low reliability in the intraoperative differentiation between a normal appendix and an inflamed appendix. Thus, whether the macroscopically normal appendix should be removed remains a dilemma in the literature.

This study aims to evaluate, from a multicenter perspective, the surgeon's ability to laparoscopically diagnose AA in its initial uncomplicated forms, in order to quantify the basis of the decision-making regarding the intraoperative diagnosis and the subsequent therapeutic strategy.

MATERIAL AND METHODS

Study Design

This study is a post-hoc analysis of the Prospective Observational Study on acute Appendicitis Worldwide (POSAW) at 116 medical centers in 44 countries over six months [15]. During this period, all patients admitted with a diagnosis of AA were sequentially studied and followed up until hospital discharge or transfer to another hospital, with a total of 4,284 patients recruited. The service protocols and the conducts adopted by each institution were preserved. The data were compiled by the coordinators of each institution and monitored by a coordination center. The study was approved and supervised by the World Society of Emergency Surgery (WSES) and strictly followed all ethical guidelines.

Ethics Declaration

As this is an observational study, the ethics committee's approval was not required to analyze the data to develop the POSAW study. The WSES was responsible for the study protocol's direction and approval, which guarantees good ethical conduct. The data used for analysis were used anonymously, and the risks of the research were minimal.

Patient Eligibility

Inclusion criteria were patients of any gender or age diagnosed with AA who underwent laparoscopic appendicectomy. In order to analyze the disease in its initial forms, the exclusion criteria were patients who were in more advanced

stages of the disease, thus excluding those who presented complicated forms of AA (such as suppuration, phlegmon, abscess, necrosis, or perforation) observed by the surgeon or at the final histopathology. Only those with all the variables delimited to the study were considered. Patients treated with open surgery or appendectomies performed during other surgical procedures were omitted.

Studied Variables

The demographic variables studied were patients' sex and age. The variable chosen for diagnostic accuracy analysis was the laparoscopic classification proposed by Gomes *et al.* and recommended by the WSES [16]. This classification is based on clinical, imaging, and laparoscopic findings to delimit the evolution of AA into five degrees: 0 = normal-looking appendix (endoappendicitis or periapendicitis), 1 = inflamed appendix (hyperemia, edema, fibrin, with or little pericolic fluid), 2 = necrosis (A: segmental necrosis / B: necrosis of the base), 3 = inflammatory tumor (A: phlegm, B: abscess less than 5 cm without peritoneal air, C: abscess greater than 5 cm without peritoneal free air), 4 = perforated (diffuse peritonitis, with or without peritoneal free air) (TABLE 1).

Table 1: Clinical, imaging, and laparoscopic classification of acute appendicitis

Non Complicated Acute Appendicitis	
Grade 0 – Normal-looking Appendix (Endoappendicitis or sublocalized Periapendicitis)	
Grade 1 - Inflamed Appendix: Hyperemia, edema ± Fibrin with or without a small amount of pericolic fluid	
Complicated Acute Appendicitis	
Grade 2 - Necrosis	A - Segmental Necrosis (with or without a small amount of pericolic fluid)
	B - Base necrosis (with or without a small amount of pericolic fluid)
Grade 3 – Inflammatory Tumor	A- Phlegm
	B - Abscess <5cm (without pneumoperitoneum)
	C - Abscess> 5 cm (without pneumoperitoneum)
Grade 4 - Perforated: diffuse peritonitis with or without pneumoperitoneum	

Gomes et al. (2015)

The histopathological result was used as the gold standard for diagnosing AA, defined by transmural inflammation of the appendix and neutrophilic invasion of the muscle layer [17]. Histopathological evaluation makes it possible to differentiate between periapendicitis (invasion restricted to serous and subserous, without affecting the mucosa) and endoappendicitis (invasion of the mucosa and ulceration) [18, 19]. This examination is recommended in all appendectomies [4, 20]

Therefore, only uncomplicated initial forms of AA were included for this study, with only patients with grade 0 or 1 by Gomes *et al.* and those with histological results showing a normal appendix, periapendicitis endoappendicitis, or

inflammation. Complicated cases, such as intraoperative grades 2A, 2B, 3A, 3B, 3C, or 4 and histopathological results that denote suppuration, gangrene, or perforation, were excluded from the analysis.

Statistical Analysis

The data were organized and analyzed using the OpenEpi version 3.0 program. A 95% Confidence Interval (CI) was established, with p-values below 0.05 being considered significant. A 2X2 contingency table was used as a diagnostic test to calculate sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. The unweighted Kappa coefficient and the percentage of the agreement were used to define the degree of interobserver agreement between the laparoscopic classification and the histopathological results according to the criteria of Landis and Koch [21]: low or at random (<0.00), light (0.0 - 0.2), reasonable (0.21-0.4), moderate (0.41 - 0.6), significant (0.61 - 0.8) and excellent or almost perfect (0.81 - 1.0). McHugh's interpretation [22] for Kappa values was also considered and is based on the percentage of reliable data in the sample: none (0.0 - 0.2), minimum (0.21-0.4), low (0.41 - 0.6), moderate (0.61 - 0.8), strong (0.81 - 0.9) and almost perfect (> 0.9).

RESULTS

Demographic Analysis (n = 718)

A total of 718 patients were included in the study. Regarding the demographic distribution, 372 (51.8%) patients were female and 346 (48.2%) male. The mean age was 29.4 years, and the median age was 26 years.

Anatomopathological study of the resected specimens

The anatomopathological result showed that 556 (77.4%) appendices were inflamed, 89 (12.4%) were normal, and 73 (10.2%) had periapendicitis. No cases of endoappendicitis were reported.

Surgeon's macroscopic evaluation during the appendectomy

In the laparoscopic macroscopic evaluation, 79 (11%) patients were classified with AA grade 0, and 639 (89%) were classified as grade 1. Of the appendices classified as grade 0, the histopathological study revealed inflammation in 18 (22.8%). Of the appendices classified as grade 1, the histopathological study revealed normality in 35 (5.5%) and periapendicitis in 66 (10.3%). Results are summarized in Table 2.

Table 2: Result of the comparison between the laparoscopic classification *[1] and the histopathological study in patients undergoing laparoscopic appendectomy.

Surgeons Macroscopic Classification (n=718)	Histopathological Study (n= 718)		
	Inflamed (%)	Normal *[2] (%)	Total (%)
Grade 1	538 (74.9)	101 (14.1)	639 (89)
Grade 0	18 (2.5)	61 (8.5)	79 (11)
Total	556 (77.4)	162 (22.6)	718 (100)

*[1]Gomes CA, Sartelli M, Di Saverio S, et al. Acute appendicitis: proposal of a new comprehensive grading system based on clinical, imaging, and laparoscopic findings. World J Emerg Surg. 2015; 10:60. *[2] Normal: includes normal appendices and periapendicitis. No cases of endoappendicitis have been reported.

Results of the interobserver agreement analysis: percentage of agreement and Kappa coefficient

In the histologically inflamed appendices group, there was an agreement with the surgeon in 538 out of 556 cases (Percentage of agreement 96.8%). There was agreement in the group of pathology-free appendices in the histopathological study in 54 of 89 cases (Percentage of agreement 60.7%). In the group of appendices with periapendicitis in the histopathological study, there was agreement in 7 of 73 cases (Percentage of agreement 9.6%). The overall disagreement rate was 16.6%, and the Kappa confficient of the agreement was 0.42 (95% CI: 0.35 - 0.49).

Result of calculations of laparoscopic diagnostic indexes in initial forms of AA: sensitivity, specificity, and predictive values

Five hundred ninety-nine patients were correctly diagnosed by the surgeon, which resulted in an accuracy of 83.4%. The sensitivity and specificity values were 96.8% and 37.7%, while the positive and negative predictive values were 84.2% and 77.2%, respectively. The results and their corresponding confidence intervals are reported in Table 3.

Table 3: Sensitivity, specificity, accuracy and predictive values of laparoscopy in early forms of Acute Appendicitis

Índex	Calculation (%)	CI 95%
Sensitivity	96.76	94.9 – 97.9
Specificity	37.7	30.6 – 45.3
Accuracy	83.4	80.5 – 86
Positive Predictive Value	84.2	81.2 – 86.8
Negative Predictive Value	77.2	66.8 - 85
Cohen’s Kappa	0.42	0.35 – 0.49

DISCUSSION

The management of the visually normal appendix during laparoscopy is considered a dilemma in the literature due to conflicting arguments both for and against its removal and the lack of recommendations with a high level of evidence. The decision between removing the normal appendix or leaving it *in situ* must analyze the risks and benefits of appendectomy, the individual clinic of each patient, and the surgeon's diagnostic accuracy [4, 23]. The intraoperative visualization of signs of inflammation of the appendix is seen as the main factor in the decision to perform the appendectomy [11], and the graduation of complications is critical to define the procedures regarding complicated and uncomplicated cases, the prolongation of antibiotic therapy and the surgical technique employed.

In this study, it was observed that the surgeon does not have good accuracy in the diagnosis of uncomplicated forms of AA, with an accuracy value of only 83.4% and sensitivity and

specificity values of 96.8% and 37.7%, respectively. The predictive values were found to show a rate of 84.2% for appendices classified as inflamed and 77.2% for appendices classified as normal. This demonstrates a low diagnostic threshold in macroscopic criteria used during surgery, which often overestimate the presence of appendicular inflammation. These data corroborate with other studies that point out that the surgeon's intraoperative diagnosis is not reliable to predict abnormalities of the appendix [24, 25].

Furthermore, analyzing the agreement rates between the macroscopic and histological classification, we observed a higher rate of agreement in the group of histologically inflamed appendices (96.8%), lower rates in the histologically normal group (60.7%), and the lowest in the group with periapendicitis, with only 9.6% agreement. This resulted in an interobserver agreement rate considered moderate to low by the adopted criteria (Kappa 0.42 - 95% CI: 0.35 - 0.49). Studies show that this agreement rate between the surgeon and the pathologist has considerable variability [26, 27]. The study conducted by Strong *et al.* obtained a more significant agreement (Kappa 0.57) when including complicated forms of AA in his analysis, which may demonstrate a greater difficulty in classifying the initial forms of the disease [13]. Another study by Van Den Boom *et al.* assessed the intraoperative classification agreement among surgeons with varying degrees of experience and observed a high rate of disagreement among these evaluators [14].

The rate of negative appendectomy, defined as removing a histologically normal appendix without intramural neutrophilic invasion, was 22.6% in this study. These rates can vary from 6 - 8% to 17 - 36% in some centers [28, 29]. There has been a decrease in negative appendectomy rates over the years. The prospective analysis of the database with 7964 patients from the Swiss Association of Laparoscopic and Thoracoscopic Surgery demonstrated a reduction in the number of negative appendectomies: from 12.7% in 1995 to 2.8% in 2006 [30]. The observed rates' significant variability was related to preoperative factors, such as the routine use of clinical scores and imaging methods. The Alvarado score was able to reduce these rates to <8% and, associated with CT, managed to reduce it to 3.3% [28]. Besides, female gender, younger age group, absence of peritonitis, pain lasting less than 24 hours, pain with migratory nature, altered white blood cell count, and fever were identified as positive predictors of negative appendectomy [31, 32]. Another study showed that these rates were considerably higher in females than males (31.0% vs. 16.8%) [33]. Some suggest that CT scan should not be performed routinely due to the risk of false negatives [28]. However, it can be considered in cases of diagnostic doubt, female patients of childbearing age and patients with a high risk of atypical presentations [34].

Removing a normal appendix is not risk-free, and some recent studies show that it has similar rates of complications compared to appendectomy of inflamed appendices [35 - 38]. In a recent cohort study with 1413 patients, no significant differences were found in the rates of morbidity between negative appendectomy and uncomplicated appendectomy (6.3% vs. 6.9%; P = 0.48), which evidences the need to improve the selection criteria of patients who must undergo the procedure [31]. Another relevant point is the loss of the organ's immune function and the storage of bacteria, capable of restoring the intestinal microbiota in dysbiosis situations [39]. Thus, some studies advocate preserving the normal appendix during diagnostic laparoscopy if there are no

signs of other pathologies that justify the patient's clinical condition [31, 35, 36].

On the other hand, the risk of leaving an abnormal appendix must be balanced against the risks related to surgery. Also, it is worth mentioning that the surgeon's intraoperative judgment does not improve over time, and the degree of experience does not increase intraoperative accuracy [12,13, 40]. The World Society of Emergency Surgery (WSES) and the European Association of Endoscopic Surgery (EAES) recommend removing a macroscopically normal appendix in the absence of other intra-abdominal procedures due to the high chance of recurrence, persistence of symptoms, or possibility of sub localized malignancy.

As limitations of this study, we can mention the absence of analysis of ultrasound and computed tomography patterns, which may correlate with negative appendectomy rates and the absence of reported cases of endoappendicitis.

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