ORIGINAL ARTICLE

# Development and validation of a risk score predicting acute uncomplicated appendicitis

## Développement et validation d'un score prédictif d'appendicite aigue non compliquée

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**Abstract**

**Introduction-Aim**: Acute appendicitis (AA) is the most frequent emergency among non-traumatic abdominal emergencies. The aim of this study was to identify independent predictive factors for acute uncomplicated appendicitis (UCAA) and to define a predictive score.

**Methods**: A retrospective study was conducted in the surgical department B of Charles Nicolle's Hospital of Tunis from January 1, 2013 to December 31, 2014. All consecutive patients operated on for AA were included. The diagnosis was confirmed by operative findings, macroscopic and histological examination of the removed appendix. Complicated acute appendicitis (CAA) was defined by the intraoperative findings of an appendicular abscess or generalized peritonitis. The Score was developed based on a logistic regression to identify the independent and predictive factors among the pre, intra and postoperative variables.

**Results**: This study (335 patients) allowed us to identify the independent factors predictive of CAA, i.e. the duration of pain evolution in the right lower quadrant (OR = 1,444; 95% IC = [1,204 - 1.725]; p < 10-3), guarding of the right lower quadrant (OR = 2.234; 95% CI = [1.051 - 4.749]; p = 0.037) and CRP > 86,8 mg/l (OR = 1.012; 95% CI = [1.008 - 1.016]; p < 10-3). The area under the curve of the score was 0.884 with a 95% CI [0.837 - 0.980]; p < 0.001. This score was validated on a sample of 236 patients culled between January 1, 2015 to May 16, 2016.

**Conclusion**: Patients, admitted for AA with a duration of symptom progression less than 2 days, without right lower quadrant guarding on clinical examination and with a CRP level < 86.8 mg/l have a risk of 96% (95%CI = [93% - 99%]) of having a UCAA.

**Key words**: Acute Appendicitis, complicated acute appendicitis, Uncomplicated acute appendicitis, prognosis, predictive variables, predictive score

**Résumé**

**Introduction-Objectif**: L'appendicite aiguë (AA) est l'urgence la plus fréquente parmi les urgences abdominales non traumatiques. Cette étude visait à identifier les facteurs prédictifs indépendants d'une appendicite aiguë non compliquée et à définir un score prédictif.

**Méthodes**: Une étude rétrospective a été menée dans le service de chirurgie B de l'hôpital Charles Nicolle de Tunis du 1er janvier 2013 au 31 décembre 2014. Tous les patients consécutifs opérés pour AA ont été inclus. Le diagnostic a été confirmé par les découvertes opératoires, l'examen macroscopique et histologique de l'appendice enlevé. L'appendicite aiguë compliquée a été définie par la constatation peropératoire d'un abcès appendiculaire ou d'une péritonite généralisée. Le score a été développé à l'aide d'un modèle de régression logistique pour identifier les facteurs indépendants et prédictifs parmi les variables pré, intra et postopératoires.

**Résultats**: Cette étude (335 patients) a permis d'identifier les facteurs indépendants prédictifs de AAC, à savoir la durée d'évolution de la douleur dans le quadrant inférieur droit (OR = 1,444 ; IC 95% = [1,204 - 1. 725] ; p < 10-3), la défense du quadrant inférieur droit (OR = 2.234 ; IC 95% = [1.051 - 4.749] ; p = 0.037) et la CRP > 86,8 mg/l (OR = 1.012 ; IC 95% = [1.008 - 1.016] ; p < 10-3). L'aire sous la courbe du score était de 0,884 avec un IC à 95% [0,837 - 0,980] ; p < 0,001. Ce score a été validé sur un échantillon de 236 patients abattus entre le 1er janvier 2015 et le 16 mai 2016.

**Conclusion**: Les patients admis pour AA avec une durée d'évolution des symptômes inférieure à 2 jours, sans défense du quadrant inférieur droit à l'examen clinique et avec un taux de CRP < 86,8 mg/l ont un risque de 96% (IC95% = [93% - 99%]) d'avoir un AA non compliquée.

**Key words**: Acute Appendicitis, complicated acute appendicitis, Uncomplicated acute appendicitis, prognosis, predictive variables, predictive score

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# Introduction

Acute appendicitis (AA) is the most frequent emergency among non-traumatic abdominal emergencies [1]. The main corner stone of treatment is appendectomy until the appearance of randomized trials [2 - 8] questioning the surgical attitude in case of an uncomplicated acute appendicitis (UCAA) by proposing a first line medical treatment. This new attitude is based on a viral theory [9 - 10]. The resulting question is how to identify uncomplicated acute appendicitis (UCAA).
This study aimed to identify the independent predictive factors for acute uncomplicated appendicitis (UCAA) and to define a predictive score.

# Methods

This is a retrospective study conducted in the surgical department B of Charles Nicolle's Hospital of Tunis over a two-year period from January 1, 2013 to December 31, 2014.

## Inclusion criteria

All consecutive patients operated on for acute appendicitis were included, regardless of age, sex and health status. The diagnosis of complicated acute appendicitis (CAA) was based on clinico-biological arguments with or without morphological examinations. The diagnosis was confirmed by operative findings, macroscopic data and histological examination of the removed appendix for all patients.

## Non-inclusion Criteria

We did not include appendicular plastron which correspond to a progressive form of acute appendicitis characterized by a focus of localized exudative peritonitis leading to numerous adhesions and clinically manifested by a sensation of parietal shielding. Were not included patients who were operated on with the diagnosis of acute appendicitis, but the operative findings and histological examination of the appendix rejected the diagnosis of acute appendicitis.

## Main Outcome measure

Complicated acute appendicitis was defined by the intraoperative findings of an appendicular abscess or generalized peritonitis.

## Data Collection

A grid was established including:
1) Preoperative variables which were age, sex, co-morbidity, surgical history, ASA score, NYHA score, Symptoms, duration of pain progression, signs of physical examination, biological data (white blood cell count), percentage of neutrophil polynuclear cells (NPC), C-reactive protein (CRP), blood creatinine, natremia and Kaliemia and medical imaging.
2) Intraoperative variables which were the duration of the operation, the approach, intraoperative findings, location of the appendix, the procedures performed and intraoperative accidents.
3) Postoperative variables including postoperative follow-up, medical complications, surgical complications with or without reoperation, death, admission to intensive care, and pathological examination of appendix.

## Statistical analysis

**Score development**:
We conducted a descriptive analysis followed by a comparative analysis.
o *Descriptive analysis*:
All data were entered into SPSS software (statistical package for the social science version 20.0). Qualitative variables were expressed as absolute values and percentages, quantitative variables were expressed with the mean and standard deviation when the distribution was Gaussian, otherwise with the median and interquartile ranges (IQR).

o *Comparative analysis*:
A prognostic study was conducted to identify independent factors predictive of the main outcome measure. We performed a bivariate analysis comparing the "CAA" group to the "UCAA" group using the appropriate statistical tests. For the qualitative variables we used the chi2 test and the Fisher exact test when appropriate, for the quantitative variables we used the Student test and the Mann-Whitney U test when the distribution was not Gaussian.

o *Logistic regression (multivariate analysis):*
Variables that were associated with a p≤5% in the bivariate analysis were entered into a logistic regression model to identify the independent variables predictive of CAA. These independent variables were expressed with their Odds ratio accompanied by the 95% confidence interval.
From then on, we established a CAA predictive score corresponding to the following model:

$$\mathbf{Ln^*(OR^*) = \beta1(X1) + \beta2(X2) + \beta3(X3) + constant.}$$

*Ln = Natural logarithm *OR = Odds ratio (OR = p / (1-p)
X1, X2, X3= independent variables predictive of CAA.
β1, β2, β3= weights provided by the logistic regression model for each selected variable (called also coefficients of regression).
p = the probability of having CAA; 1-p = the probability of not having CAA (on other words having UCAA).

o *Model performance:*
The performance of the model was evaluated by two methods: the "c-statistic" and the "Hosmer-Lemeshow" test.
The discrimination power measured by the "c-statistic" which is obtained by calculating the area under the ROC curve, the "c-statistic" indicates how well the model predicts CAA. It takes values ranging from 0.5 to 1; 0.5

indicates that the model is no better than chance and 1 indicates that the model has a perfect prediction. The model is considered to have strong discriminative power when "c-statistic" is greater than 0.8.

For the quantitative predictive variables of the CAA, we established the ROC curve (receiver operating characteristic) with the area under the curve and its 95% confidence interval in order to identify the cutoff point corresponding to the best sensitivity/specificity couple (using the free Medcalc software as Demo). We proceeded in the same way for the variable probability of having a CAA provided by the model. The significance threshold for all comparisons was set at 0.05.

The probability of having a CAA was calculated according to the formula:

$p = e^A / 1 + e^A$ (**$A=\beta1(X1) + \beta2(X2) + \beta3(X3) + constant$**).

This probability was calculated using the SPSS software which allowed us to establish the ROC curve and then we subsequently established the informational indices of the model when the risk factor(s) is (are) absent.

The "Hosmer-Lemeshow" test was used to measure the calibration. It allows for the detection of biases when predicting the risk of CAA. The data were ranked by the predictive probability of CAA and then divided into 10 risk groups (of equal size). If there is a tendency for the model to over- or underestimate the risk of CAA, the Hosmer-Lemeshow test shows a statistically significant difference. On the other hand, when the Hosmer-Lemeshow test does not show a statistically significant difference ($p > 0.05$) the model is considered to have a better prediction. A graphical representation was added in which the mean of the "expected" predictive probabilities versus the mean of the observed probabilities was reported.

**Validation of the predictive score of CAA:**

All consecutive patients operated on for acute appendicitis from January 1, 2015 to May 16, 2016 were included using the same methodology. We applied the new score with the same variables to this population. We redid the logistic regression, established the ROC curve and the calibration.

## Results

During the study period, we culled 335 patients having been operated on for acute appendicitis in the surgical department B of Charles Nicolle's hospital in Tunis.

### Descriptive analysis sample 335 patients (table 1)

The mean age of the patients was 33.7 years ± 16.1. The median was 31 years with extremes ranging from 14 to 86 years. There were 206 men (61.5%) and 129 women (38.5%). The sex ratio was 1.59.

Sixty-eight patients (20%) had co-morbidity. They were dominated by cardiac disease and diabetes. Forty-two patients (12%) had a history of abdominal surgery.

The duration of pain progression was defined by the number of days between the onset of symptomatology and the visit to the emergency department. The median of this duration was two days with extremes ranging from 1 to 21 days.

Abdominal pain was the main reason for consultation in 100% of cases. The site of pain was the right lower quadrant in 289 patients (86.3%). Pain was diffuse throughout the abdomen in 34 patients (10%). It was localized in the right upper quadrant in 12 patients. Pain was isolated in 34 patients (10%). It was associated with fever in 153 patients (45.7%), vomiting or nausea in 269 patients (80%), diarrhea in 18 patients and intestinal obstruction in 14 patients.

The mean temperature (± standard deviation) was 37.9°C ± 0.6. One hundred and eighty patients (53.7%) had a temperature greater than or equal to 38°C.

Physical examination found tenderness of the right lower quadrant in 247 patients (73.7%).

Sixty-seven patients (20%) had guarding of the right lower quadrant. Eight patients had a sub umbilical guarding and six patients had a generalized abdominal guarding. Seven patients had a right lower quadrant mass. One patient had an abdominal contracture. Rectal examination was performed in all patients; it was painful in 166 (49.6%).

**Table 1.** Demographic data: sample of 335 patients

| Variables | Mean (SD) or median | (IQ range) or number (%) |
|---|---|---|
| Age (mean +/-SD) | 33.7 | ± 16.1 |
| Male | 206 | 61.5% |
| Patient with systemic diseases | 68 | 20% |
| Arterial hypertension | 26 | 7.7% |
| Diabetes mellitus | 21 | 6.2% |
| Past history of abdominal surgery | 42 | 12% |
| Duration of pain evolution (Median [IQR]) | 2 | [1 – 21] |
| Nausea and vomiting | 269 | 80% |
| Diarrhea | 18 | 5.3% |
| Interruption in the forward flow of intestinal contents | 14 | 4.1% |
| Temperature (mean +/-SD) | 37.9° c | ± 0.6 |
| Abdominal tenderness | 247 | 73.7% |
| Abdominal guarding in the right iliac fossa | 67 | 20% |
| White blood cell count per $mm^3$ (Median [IQR]) | 14 800 | [560 – 33 770] |
| C-reactive protein (mg/l) (Median [IQR]) | 47.8 | [0.2 – 466.5] |
| Renal failure | 4 | 1.1% |
| Complicated appendicitis | 76 | 23% |
| Appendicular abscess | 34 / 76 | 45% |
| peritonitis | 42 / 76 | 55% |

The mean white blood cell count was 14,845 ± 4,637 elements/ml. The median was 14,800 elements/ml with range values between 560 to 33,770 elements/ml. Two hundred and eighty-two patients (84.1%) had a white blood cell count greater than 10,000 elements/ml. The percentage of neutrophil polynuclear cells (NPC) was on average 78%±9. The CRP assay was performed in 327 patients (97.6%). The median was 47.8 mg/l with extremes ranging from 0.2 to 466.5 mg/l.

Renal function was assessed by creatinine levels. It was evaluated in 310 patients (92.5%). Thirteen patients had a creatinine level more than 120 µmol/l, nine out of 13 were owing to chronic renal failure and four related to acute renal failure.

Abdominal ultrasound was performed in 122 patients (36.4%). The appendix was not detected in 30 (25%). Ultrasonography showed an intraperitoneal effusion or collection with an abnormal appendix in 68 patients (56%). Abdominal CT scan was performed in 109 patients (32.4%). An intraperitoneal effusion or collection with an abnormal appendix was observed in 72 patients (66%).

## Establishment of the predictive CAA score (sample of 335 patients)

- **Bivariate analysis (table 2):**

Demographic variables and symptoms associated with CAA were age, medical conditions, duration of pain progression, intestinal obstruction, and diarrhea.

**Table 2**. Bivariate analysis comparing UCAA versus CAA (sample of 335 patients)

| Variables | Uncomplicated acute appendicitis n=259 | Complicated acute appendicitis n=76 | P |
|---|---|---|---|
| Age (mean ±SD) | 31,3 ±13,9 | 43,1 ±18,4 | **<0.001** |
| Gender | | | 0.464 |
| Male | 162 (62,5%) | 44 (57,9%) | |
| Female | 97 (37,5%) | 32 (42,1%) | |
| Patient with systemic diseases | | | **0.002** |
| without | 216 (83,4%) | 51 (67,1%) | |
| with | 43 (16,6%) | 25 (32,9%) | |
| Past history of abdominal surgery | | | 0.078 |
| No | 231 (89,2%) | 62 (81,6%) | |
| Yes | 28 (10,8%) | 14 (18,4%) | |
| Duration of pain evolution (Median + IQR) | 1 [1 – 14] | 3 [1 – 21] | **< $10^{-3}$** |
| Interruption in the forward flow of intestinal contents | 253 (97,7%) 6 (2,3%) | 68 (89,5%) 8 (10,5%) | **0.002** |
| Diarrhea | | | **0.004** |
| No | 250 (96.5%) | 67 (88.2%) | |
| Yes | 9 (3.5%) | 9 (11.8%) | |
| Temperature (Mean ±SD) | 37.8 ± 0.6 | 38.2 ± 0.6 | **< $10^{-3}$** |
| Abdominal tenderness | | | **< $10^{-3}$** |
| No | 43 (16.6%) | 45 (59.2%) | |
| Yes | 216 (83.4%) | 31 (40.8%) | |
| Abdominal guarding in the right iliac fossa | | | **< $10^{-3}$** |
| No | 218 (84.2%) | 50 (65.8%) | |
| Yes | 41 (61.2%) | 26 (34.2%) | |
| Abdominal guarding under umbilical area | | | **< $10^{-3}$** |
| No | 259 (100%) | 68 (89.5%) | |
| Yes | 0 | 8 (10.5%) | |
| Generalized abdominal guarding | | | **< $10^{-3}$** |
| No | 259 (100%) | 70 (92.1%) | |
| Yes | 0 | 6 (7.9%) | |
| Abdominal rigidity | | | **< $10^{-3}$** |
| No | 259 (100%) | 75 (98.7%) | |
| Yes | 0 | 1 (1.3%) | |
| Abdominal mass | | | **< $10^{-3}$** |
| No | 259 (100%) | 69 (90.8%) | |
| Yes | 0 | 7 (9.2%) | |
| White blood cells count/ml (mean SD) | 14 555 ± 4 433 | 16 037 ± 5 202 | **0.079** |
| Percentage of neutrophils (mean SD) | 77.2 ± 10.1 | 81.0 ± 8.3 | **0.02** |
| CRP* (mg/l) (Median [IQR]) | 31.1 [0.2 – 371.6] | 207 [1.5 – 466.5] | **< $10^{-3}$** |
| Creatinine level (mg/dl) (Median [IQR]) | 0.773 [0.5 – 12.148] | 0.898 [0.545 – 8.795] | **< $10^{-3}$** |

***CRP**: C-reactive protein, **SD**: standard deviation, **IQR**: interquartile range

The physical signs and biological data associated with CAA were temperature, abdominal tenderness, right iliac fossa guarding, sub umbilical guarding, generalized abdominal guarding, abdominal contracture, existence of an abdominal mass, CRP level and creatinemia level.

- **Multivariate analysis:**

The independent predictor variables of CAA were the duration of pain (OR = 1.444; 95% CI [1.204 - 1. 725]; p < 10-3), guarding of the right lower quadrant at examination (OR = 2,234; 95% CI [1,051 - 4,749]; p = 0,037) and CRP rate (OR = 1,012; 95% CI [1,008 - 1,016]; p < 10-3) (table 3).

**Table 3.** Multivariate Analysis: identification of independent and predictive variables of Complicated Acute Appendicitis (sample of 335 patients)

| | OR* | 95% CI* | p |
|---|---|---|---|
| Duration of pain evolution | 1.444 | [1.204 – 1.725] | **< $10^{-3}$** |
| Abdominal guarding (right lower quadrant) | 2.234 | [1.051 – 4.749] | **0.037** |
| C-reactive protein (mg/l) | 1.012 | [1.008 – 1.016] | **< $10^{-3}$** |

***OR** : Odds ratio ; **CI** : Confidence interval – Percentage of well classified : 86,6% (Hosmer et Lemeshow test : p=0,789)

o Duration of pain evolution:

For the variable "duration of pain progression", the area under the curve was 0.807 with a 95% CI [0.760 - 0.848] statistically different from 0.5 (p < 0.0011) (figure 1)

A duration of pain progression of more than two days had a sensitivity of 70% with 95%CI [58.1 - 79.8] and a specificity of 80% with 95%CI [74.1 - 84.3] with a positive likelihood ratio (LR+) = 3.41 with 95%CI [2.57 - 4.52]. (Table 4)

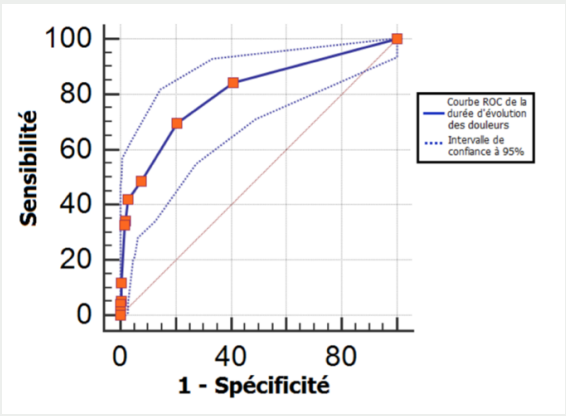


**Figure 1**. Courbe ROC de la durée d'évolution des douleurs

o The CRP:

For CRP, the area under the curve was 0.856 with 95%CI [0.813 - 0.892] statistically different from 0.5 (p < 0.0011). A CRP value ≥ 86.8 mg/l has a sensitivity of 80% with 95%CI [69.2 - 88.4] and a specificity of 77% with 95%CI [71.8 - 82.5] with a positive likelihood ratio (LR+) = 3.55 95%CI [2.75 - 4.59]. A CRP value ≥ 200 mg/l has a sensitivity of 49% 95%CI [38 - 61] and a specificity of 95% with 95%CI [92 - 98] and a positive likelihood ratio (LR+) = 9.6 with 95%CI [5.39 - 17.1] (figure 2 and Table 5)

**Table 4.** Informational indices of duration of pain progression in the diagnosis of Complicated Acute Appendicitis

| | Se [95%CI] | Sp [95%CI] | PPV [95%CI] | NPV [95%CI] | LR+ [95%CI] | LR- [95%CI] |
|---|---|---|---|---|---|---|
| duration of pain > 2 days: percentage with 95% CI | 70% [58.1 – 79.8] | 80% [74.1 – 84.3] | 50% [40 – 60] | 90% [86 – 94] | 3.41 [2,57 – 4,52] | 0.38 [0.27 – 0.54] |

**CI**: confidence interval, **Se**: sensitivity, **Sp** : Specificity, **PPV**: positive predictive value, **NPV**: negative predictive value, **LR**: Likelihood ratio

**Table 5**. Informational Indices of C Reactive Protein in the Diagnosis of Complicated Acute Appendicitis

| | Se [95%CI] | Sp [95%CI] | PPV [95%CI] | NPV [95%CI] | LR+ [95%CI] | LR- [95%CI] |
|---|---|---|---|---|---|---|
| CRP ≥ 86,8 mg/l | 80%[69.2 – 88.4] | 77% [71.8 – 82.5] | 51% [42 – 60] | 93% [89 – 96] | 3.55 [2,75 – 4,59] | 0.26 [0.16 – 0.42] |
| CRP ≥ 200 mg/l | 49% [38 – 61] | 95% [92 – 98] | 74% [62 – 86] | 86% [82 – 90] | 9.6 [5.39 – 17.1] | 0.53 [0.43 – 0.67] |

**CRP**: C Reactive Protein, **CI**: confidence interval, **Se**: sensitivity, **Sp** : Specificity, **PPV**: positive predictive value, **NPV**: negative predictive value, **LR**: Likelihood ratio

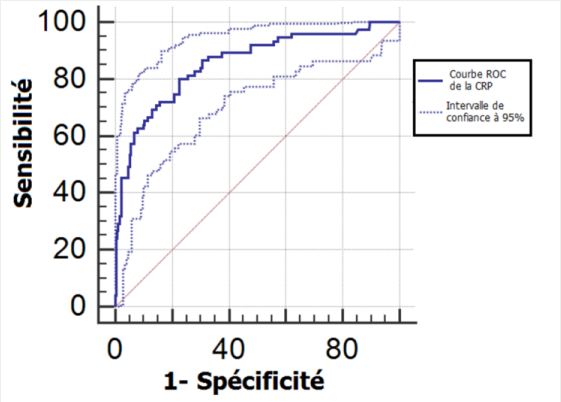


**Figure 2.** Courbe ROC de la CRP

- **CAA predictive score:**

We established a score based on the three independent variables, allowing us to calculate the probability for each patient to have a CAA.

The score was established according to the following formula:

**Ln*(OR)* = 0.336 x [Duration of pain evolution] + 0.012 x [CRP] - 0.804 x [guarding in the right lower quadrant (Yes = 0; No = 1)] - 3.009.**

The probability of having a CAA was established according to the following formula:

Ln* (OR*) = A; $e^A$ = p / 1-p then p = $e^A$ /1 + $e^A$

This probability was provided by the calculation using the SPSS software version 20 which allowed us to establish the ROC curve of the predictive probabilities of CAA. The area under the curve was 0.884 with 95%CI [0.837 - 0.980], statistically different from 0.5 with p < 0.001.

According to this score we retained only the stratum corresponding to patients **who had concurrent pain of the lower right quadrant lasting less than 2 days, lack of right lower quadrant guarding and a CRP < 86.8 mg/l.** The combination of these criteria when negative (all three signs are negative: no **right lower quadrant guarding**, duration of symptom progression < 2 days and CRP < 86 mg/l) provided a negative predictive value of 96% with a 95%CI (93 - 99) (table 6).

**Table 6.** informational indices of the predictive score of Complicated Acute Appendicitis when all 3 signs are negative (no right lower quadrant guarding, duration of symptom progression < 2 days and a CRP < 86 mg/l):

| Se [IC 95%] | Sp [IC 95%] | Prevalence | PPV [IC 95%] | NPV [IC 95%] | LR+ [IC 95%] | LR- [IC 95%] |
|---|---|---|---|---|---|---|
| 92%[86 – 98] | 61% [55 – 67] | 23% [18 – 27] | 41% [34 – 49] | **96% [93 – 99]** | 2.38 [2,01 – 2,81] | 0.13 [0.06 – 0.28] |

**Se**: sensitivity – **Sp**: Specificity – **PPV**: Positive Predictive Value – **NPV**: Negative Predictive Value – **LR**: Likelihood ratio – **CRP**: C Reactive Protein

The Figure 3 showed the ROC curve of the predictive probabilities of CAA provided by the score (sample of 335 patients).

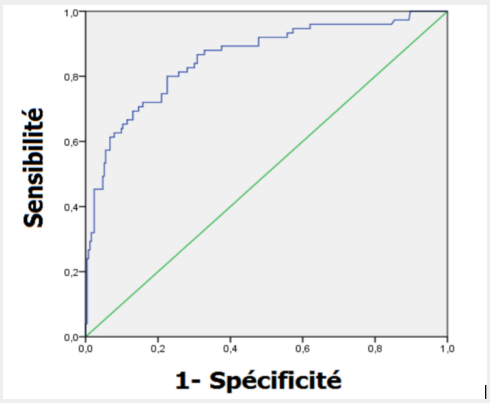


**Figure 3**. ROC curve of the predictive probabilities of CAA provided by the score (sample of 335 patients). The area under the curve was 0.884 95%CI [0.837 - 0.980], with p < 0.001.

The area under the curve was 0.884 95%CI [0.837 - 0.980], with p < 0.001.

- **Clinical Involvement**

In other words, a patient consulting for right lower quadrant pain less than 2 days old without guarding associated to CRP < 86.8 mg/l has a 96% chance of having an UCAA with a 4% risk of being wrong (type I error).

## Validation of the predictive CAA score on a sample of 236 patients

This predictive score of CAA, established from a sample of 335 patients collected during the period from January 1, 2013 to December 31, 2014, was validated on a sample of 236 patients culled from January 1, 2015 to May 16, 2016. We used the same grid with the same variables. Logistic regression on the sample of 236 patients to

predict CAA, using the same variables identified to establish the score on the 335 patients, provided similar results (Table 7, figure 4). The area under the ROC curve predicting Complicated acute appendicitis was 0.934 with $^{95\%}$CI [0.893 - 0.975], statistically different from 0.5 ($p < 0.001$). The figure 5 showed a good calibration of the predictive model.

**Table 7**. Logistic regression of predictive score validation (sample of 236 patients)

| | OR* | 95% CI* | p |
|---|---|---|---|
| Duration of pain evolution | 1.855 | [1.420 – 2.423] | **< $10^{-3}$** |
| Abdominal guarding (right lower quadrant) | 2.865 | [1.017 – 8.064] | **0.046** |
| C-reactive protein (mg/l) | 1.014 | [1.009 – 1.019] | **< $10^{-3}$** |

***OR** : Odds ratio ; **CI** : confidence interval; Percentage of well classified=89,7% (Hosmer et Lemeshow test : p= 0,298

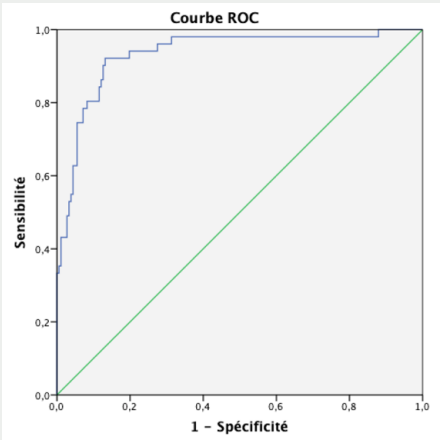


**Figure 4.** ROC curve of the predictive predicting Complicated acute appendicitis (sample of 236 patients)

The area under the ROC curve predicting Complicated acute appendicitis was 0.934 with 95%CI [0.893 - 0.975], statistically different from 0.5 ($p < 0.001$).

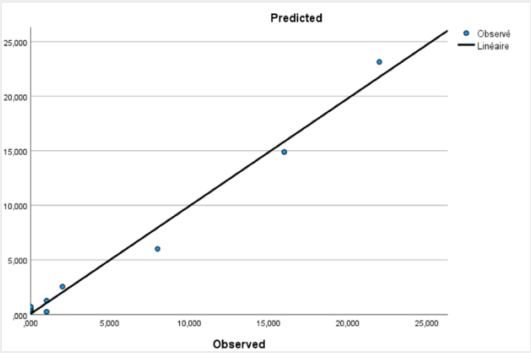


**Figure 5.** Calibration of the predictive model

## Discussion

Our study (335 patients) allowed us to identify the independent factors predictive of CAA, i.e. the duration of pain evolution in the right lower quadrant (OR = 1,444; IC95% = [1,204 - 1.725]; p = < 10-3), guarding of the right lower quadrant (OR = 2.234; 95% CI = [1.051 - 4.749]; p = 0.037) and CRP > 86,8 mg/l (OR = 1.012; 95% CI = [1.008 - 1.016]; p = < 10-3; AUC = 0,856 with 95% CI [0.813 - 0.892] and p value < 0,0011).

Patients admitted for AA with a duration of symptom progression of less than 2 days, without right lower quadrant guarding on clinical examination and with a CRP level < 86.8 mg/l have a risk of 96% (95%CI = [93% - 99%]) of having a UCAA.

The area under the curve was 0.884 with a 95% CI [0.837 - 0.980], statistically different from 0.5 with $p < 0.001$.

Different scoring systems exist to identify acute appendicitis **by available tools** such as duration of symptoms, clinical examination, and biology findings. We can enumerate the Alvarado score introduced on 1986[11], the RIPASA score on 2010[12] and others such as Fenyo[13], Tzanakis[14] and Ohmann scores[15]. Theses scores are in fact used to identify with a strong specificity and sensitivity patients with acute appendicitis. However, they did not distinguish between an acute non complicated appendicitis or a complicated form.

**As concerns duration of symptomatology**, Ripasa score [12], the Fenyo[13] used the duration of the symptomatology as one criterion. Duration more than 48h is considered as a cutoff point to identify acute appendicitis. Moreover, it is a predictive factor of complicated presentation when exceeding two days. This finding has been established on 2022 by Rebeiro et al. [16] including 841 patients, it is also used in the Atema scoring [17] which is a score used to distinguish between complicated and non-complicated presentations.

In 2023, Strohäker et al. [18], using a logistic regression model, found that age, gender, ASA score, symptom duration, free fluid on US, White Blood Count, and CRP are statistically significant. In 2018 Hansson [19] et al. found also that “there was a longer duration of pre-hospital pain in patients”. Furthermore, a multivariate analysis showed that age and preoperative duration of pain were two independent factors predictive of perforation (19).

Maxim Avanesov [20] and Michal Pedziwiatr [21] have found that a duration of symptomatology evolution superior to 48 hours is an independent and predictive factor of CAA.

### Lower right quadrant guarding

Clinical findings are used to stratify the risk of acute appendicitis in different score systems. In fact, in the alvarado score [11], we found rebound tenderness and right iliac fossa tenderness as items of the score. In contrast to our study, the presence of right iliac fossa guarding alone does not consistently emerge as a significant predictive factor for complicated appendicitis in various studies.

The AIR score [22] incorporates the assessment of abdominal guarding, and the AAS (Acute Appendicitis Score) evaluates pain in the right lower quadrant (RLQ) along with abdominal guarding. However, it's important to note that these scoring systems are primarily designed to determine the presence of appendicitis rather than distinguishing between complicated and uncomplicated forms of the condition. Their primary purpose is to provide a more accurate diagnosis of appendicitis

However, it's worth noting that some scoring systems

designed to predict complicated appendicitis include it as one of the contributing factors, such as the "SMART-LAB" score developed by Shabir et al. [23]. This scoring system, which aims to predict the diagnosis of complicated appendicitis, incorporates several indicators, including sonography (S), migratory right iliac fossa pain (M), anorexia (A), rebound tenderness (R), tenderness (T), leukocytosis (L), acute-phase protein-CRP (A), and serum bilirubin (B).

### C Reactive Protein

Much like our ongoing series, numerous studies have underlined the pivotal role of C-reactive protein (CRP) as a predictive marker for complicated cases of acute appendicitis. Nevertheless, a definitive threshold for CRP values, beyond which we can confidently classify cases as 'complicated,' remains elusive.

For instance, consider the study conducted by Rebeiro[16], where the designated cut-off value for distinguishing complicated from non-complicated cases of acute appendicitis was notably high, set at 115 mg/L. Ribeiro (16) concluded that " C-reactive protein proved to be a good independent predictor of complicated acute appendicitis and, therefore, when an assay of this protein exceeds 63.3 mg/L, faster surgical approach should be considered due to the high probability of the presence of a complicated picture of this clinical entity'.

Similarly, in a publication by Imaoka et al. in 2016[24], CRP levels exceeding 4.7 mg/dL were deemed predictive of complicated appendicitis. Imaoka (24) concluded that the three factors, body temperature ≥37.4 °C, C-reactive protein ≥4.7 mg/dl, and fluid collection surrounding the appendix on CT, are useful in predicting cases of complicated appendicitis preoperatively and can thus facilitate decisions regarding emergency surgery. The scoring system can avoid emergency surgery at night or on a holiday and lead to non-operative management. The Atema score [17], on the other hand, assumes that a CRP level above 100 mg/L is an indicator of complicated cases. A case-control study, using logistic regression model, published in 2020 by Sasaki et al. [25], showed various potential predictive factors for non-complicated acute appendicitis. These factors included symptoms and their duration, gender, the medical history of patients, physical examination findings, and laboratory results. Among them, it was observed that in the complicated appendicitis group, heart rate, body temperature, and serum CRP levels were notably higher compared to the non-complicated group. Conversely, glomerular filtration rate (GFR) and serum sodium levels (natremia) were significantly lower in the complicated appendicitis group. However, using logistic regression, only CRP values emerged as statistically significant.

These studies serve as examples and do not comprise an exhaustive survey of the existing literature. Nevertheless, what these studies have in common is the considerable importance attached to CRP values as predictive markers. However, it is worth noting that a consensus regarding the precise cut-off point above which we can confidently identify complicated cases of acute appendicitis remains elusive.

### Several authors using the same methodology found different risk scores

Kang et al [26] established the probability of having complicated appendicitis (CA) based on clinical and biological variables that were selected as predictors of CA using logistic regression, namely (temperature, abdominal guarding, white blood cell count, neutrophil/lymphocyte ratio and CRP level). They calculated a ROC curve of the predictive probabilities of CA. The area under the curve was 0.857; 95% CI [0.806 - 0.908]; $p < 0.001$.

Atema et al [13] developed a predictive CBA score that included clinical, biological and CT data. This score included three clinical data (age, temperature and duration of symptomatology), two biological data (white blood cell count and CRP) and CT-based data (extra digestive air bubbles, effusion of the right iliac fossa and the presence of stercholite). The area under the curve was 0.880; 95% CI [0. 850 - 0.920]; the predictive value of this score was 94.7% [89.8 - 97.7].

Von-Mühlen (22) developed the AIR score. Shabir (23) developed another score called "SMART-LAB" score including clinical and biological variables

### Limitations of our proposed score

Actually, several score are available, however there is NO consensus. We developed and validated an easy risk score predicting an Uncomplicated Acute Appendicitis: Patients admitted for AA with a duration of symptom progression of less than 2 days, without right lower quadrant guarding on clinical examination and with a CRP level < 86.8 mg/l have a risk of 96% (95%CI = [93% - 99%]) of having a UCAA. The area under the curve was 0.884 with a 95% CI [0.837 - 0.980], statistically different from 0.5 with $p < 0.001$. However, it was not possible to include imaging variables because all patients did not have US or Computed tomography in emergency. This score was adapted to our environmental conditions.

Future clinical implications: Our study has defined a population of low-risk CAA patients to whom, in the future, medical treatment could be applied either deliberately or as part of a randomized trial comparing medical treatment versus appendectomy. This question is still being debated. In June 2024, Rosen (27) reported an original article that aimed to describe a new strategy concerning the use of the Decision Support Tool (DST) for the treatment of appendicitis. "The use of this DST is now part of a national implementation program aimed at improving the way surgeons share information about appendicitis treatment options" (27).

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