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Original Research Article

Dipeptidyl peptidase 4 levels as a novel potential early marker in the identification of complicated appendicitis

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ABSTRACT

Background: Appendicitis represents one of the most prevalent indications for emergency department care due to abdominal pain. Complications risk depends on how soon are diagnosed. Test like c-reactive protein (CRP) and neutrophil-lymphocyte index (NLI) can assist in diagnose complications, but they are not always precise. Dipeptidyl peptidase 4 (DPP4) has been employed as a new marker in other inflammatory pathologies; thus, exist the potential for its use in pathologies such as appendicitis. Evaluate the utility of serum levels of DPP4, CRP and INL in identify and differentiate complications in patients with histopathologically confirmed appendicitis.
Methods: A cohort study with diagnostic test analysis included patients aged 18-80 years with suspected appendicitis undergoing surgery. They had given informed consent to participate. A minimum of 30 subjects per group was considered. Complicated and uncomplicated appendicitis was diagnosed by histological examination of tissue samples. Sensitivity and specificity of DPP4, CRP levels and NL index in diagnosis of complicated appendicitis were determined.
Results: We observed higher levels of DPP4 (7820 vs 5250 pg/dl,) and CRP (4 vs 10 mg/dl) in complicated appendicitis group. These levels were statistically significant (p=0.03; p=0.02, respectively). Sensitivity for DPP4 was 50% versus 64% for CRP and 57% for INL. Specificity of DPP4 was 83% compared to 70% for CRP and 76% for INL.
Conclusions: Compared to CRP and INL, DPP4 levels showed lower sensitivity but higher diagnostic specificity in our population. In acute appendicitis, DPP4 levels could be an early indicator in addition to imaging and clinical assessment of patients.

Keywords: Dipeptidyl peptidase 4, Appendicitis, C-reactive protein, Neutrophil lymphocyte index

INTRODUCTION

Acute abdominal pain accounts for 7-10% of hospital emergency department visits, with acute appendicitis being a major cause of lower abdominal pain.[1-3] Its pathophysiology is related to obstruction of the appendiceal lumen, the incidence and presentation of which varies with age.[4] Rate of perforation ranges from 16% to 40%, being more common in people over 50 years of age (55-70%).[5] As inflammation and necrosis progress, appendix may perforate, leading to local abscesses or peritonitis. Perforation occurs at surgery time in between 10% and 20% of cases.[6,7]

Differential diagnosis of acute appendicitis and its complications combines clinical and paraclinical parameters.[8,9] Markers such as white blood cell count, CRP, NLI and erythrocyte distribution width have been

useful.[10,11] However, the sensitivity and specificity of the test vary significantly depending on the population under investigation. Anatomopathological examination results confirm the stage of development and degree of inflammation in accordance with the clinical suspicion of acute appendicitis in patients.[12,13]

DPP4, a serine protease is expressed in the luminal and apical cell membrane of a variety of organs and cells of immune system.[14,15] Recent studies have suggested that DPP4 plays a key role in regulating CD4+ lymphocyte-mediated immune responses.[16,17] Furthermore, it's up-regulation has been associated with inflammatory processes in various pathologies. This highlights its potential relevance as a marker in specific clinical contexts.[18-20]

The aim of the present study was to evaluate the utility of serum levels of DPP4 and CRP and INL in identifying and differentiating between the presence of complications such as perforation in patients with histopathologically confirmed appendicitis.

METHODS

A cohort study was conducted, followed by an analysis of diagnostic test. Protocol was approved by hospital regional de Alta Especialidad 'Dr Ignacio Morones Prieto' ethics and research committee (21-33). It was carried out from 31 May 2023 to 31 May 2024, in conformity with the declaration of Helsinki and international research guidelines.[21,22]

Inclusion criteria

Male or female patients, aged 18-80 years, with suspected appendicitis and scheduled for surgery were included. Who had signed informed consent form.

Exclusion criteria

Previous diagnosis of neoplastic, nephrological or rheumatological processes were excluded.

The sample size was calculated based on an internal pilot study that incorporated a minimum of 30 subjects per group, in accordance with good clinical practices.[23]

At enrolment, socio-demographic, anthropometric (body mass index, BMI) and clinical parameters were determined and peripheral blood was collected. Sample was processed according to protocol previously published by our group.[24] In short, serum DPP-4 levels were determined in duplicate at the translational research laboratory in pharmacology, using a commercial kit of ELISA human DPPIV/CD26 (#DY1180). Kit was supplied by R and D system. Levels of leukocytes, neutrophils, CRP and DPP4 were analysed.

As proposed by other authors, histological examination of tissue samples confirmed the presence of uncomplicated (grades I and II) and complicated (grades III and IV) appendicitis.[25] Grade I: acute mucosal inflammation, catarrhal. Grade II: acute appendicitis with vascular dilatation and congestion, fibrinopurulent exudate and transmural inflammation. Without necrosis in both cases. Grade III: gangrenous or necrotic pattern with friable appendiceal wall, transmural inflammation and areas of necrosis. Grade IV: appendicitis with perforation of wall, release of purulent material and extensive areas of necrosis.

Statistical analysis

Performed using up-to-date version of Rstudio Cloud. Depending on data normality, continuous variables were reported as mean and standard deviation or median and interquartile range. Discrete variables as proportions and percentages. Inferential analysis: Student's t-tests or Mann-Whitney U test, was used to analyse differences between groups. To determine diagnostic accuracy of the biomarkers with statistically significant difference between groups, predictive values were calculated and ROC curve analyses performed. Otherwise, published cut-off points were used to analyse diagnostic performance. $p<0.05$ was defined as being statistically significant.

RESULTS

Sixty-four patients who met selection criteria included during follow-up period. Based on histopathological characteristics, patients were classified into 2 categories: uncomplicated appendicitis (n=31) and complicated appendicitis (n=33). Mean age was 29 years with a range of 18 to 73. Of these, 54.7% were male, with no significant differences. Similarly, there were no differences in BMI between groups (Table 1). However, mean BMI for overweight or obese was 28.8 kg/m^2 (25.0- 40.9).

As far as leucocyte analysis is concerned, we observed differences between groups with a tendency towards significance (p=0.06), with a higher value for complications group (14.7 vs. 12.3 cells/ul). No differences were observed in neutrophils, lymphocytes NLR and haemoglobin (Table 1).

Both, CRP (Figure 1) and DPP4 levels (figure 2), were significantly higher in the group with complicated appendicitis (20.5 vs. 11.6 mg/dl, p=0.02), and (7820 vs. 5250 pg/dl, p=0.03) respectively.

A ROC curve analysis was performed on our data with the following findings (Figure 3): sensitivity and specificities of CRP for diagnosis of complicated appendicitis at a cutoff of 2.8 mg/dl, were 87% and 48%, respectively (AUC: 0.66, 95% CI: 0.523 to 0.799). For DPP4, sensitivity was similar (53%) to that of CRP at the cut-off point of 7133 pg/ml (AUC: 0.615, 95% CI 0.462-0.765), but the specificity was higher (83%). For NLR, the optimal published cutoff point (4.7) yields a sensitivity of 75% and a specificity of 53%, respectively (Table 2).[26]

Table 1: General characteristics and laboratory studies.

Variables	Total (n=64) (%)	Appendicitis, N (%)		P value
		Uncomplicated (n=31)	Complicated (n=33)	
Age (years)	33.0 (12.2)	32.5 (11.8)	33.4 (12.2)	0.9191
Sex				
Female	29 (45.3)	15 (48.4)	14 (42.4)	0.8192
Male	35 (54.7)	16 (51.6)	19 (57.6)	
BMI (kg/m^2)	25.8 (5.60)	25.9 (6.43)	25.6 (4.78)	0.316
Heart rate (bpm)	92.4 (20.2)	89.5 (16.4)	95.2 (23.1)	0.572
Mean blood pressure (mmHg)	87.1 (11.3)	89.5 (11.8)	84.9 (10.5)	0.10
Temperature (ºC)	36.6 (0.725)	36.5 (0.560)	36.8 (0.828)	0.094
Hemoglobin (g/dl)	14.6 (2.06)	15.0 (1.67)	14.3 (2.33)	0.138
Leukocytes cells/ul	13.5 (5.20)	12.3 (5.13)	14.7 (5.06)	0.06348
Neutrophils (/ml)	11.7 (10.8)	12.1 (14.5)	11.2 (5.30)	0.2019
(Missing)		0	2	
Lymphocytes (ul)	2.03 (1.68)	2.26 (2.14)	1.79 (1.02)	0.4274
(Missing)		0	2	
NLR	7.13 (5.35)	5.97 (4.30)	8.28 (6.08)	0.102
(Missing)		0	2	
CRP (mg/dl)	16.2 (21.2)	11.6 (17.1)	20.5 (23.9)	0.028
DPP4 (pg/dl)	6530 (4680)	5250 (3030)	7820 (5650)	0.03
(Missing)		1	3	

[1]Mean (SD) or Wilcoxon test; n / N (%), [2]Chi-squared test

Table 2: Biomarker diagnostic accuracy in complicated appendicitis compared.

Biomarkers	Cut-off point	Sensitivity	Specificity	PPV	NPV	AUC (95%IC)
DPP4 levels	7133	0.83	0.53	0.64	0.76	0.613 (0.462-0.765)
CRP levels	2.8	0.87	0.48	0.64	0.78	0.661 (0.523-0.799)
NLR	7	0.54	0.77	0.70	0.63	0.619 (0.476-0.762)

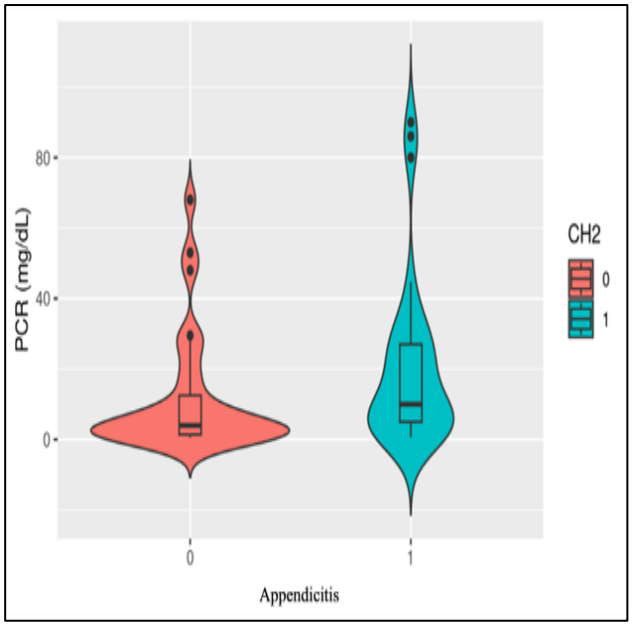

Figure 1: A comparison of CRP levels in the population under study, with patients classified as either uncomplicated (0) or complicated (1).
CH2=histopathological classification.

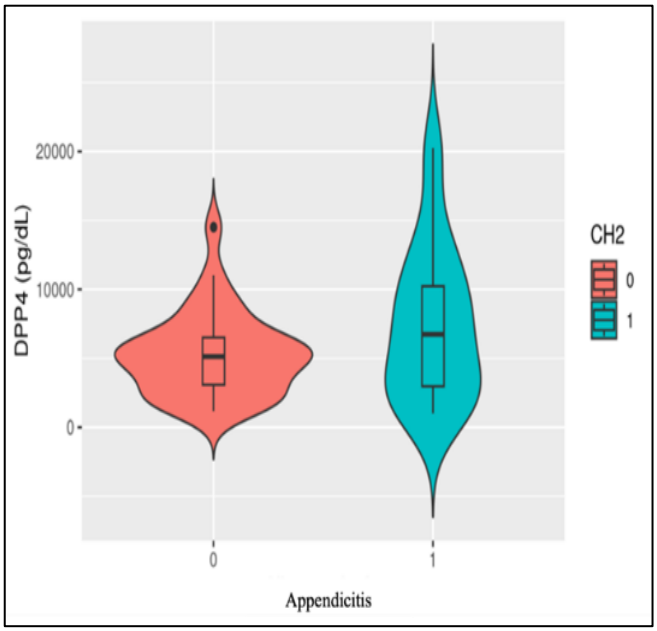

Figure 2: A A comparison of DPP4 levels in the population under study, with patients classified as either uncomplicated (0) or complicated (1).
CH2=histopathological classification.

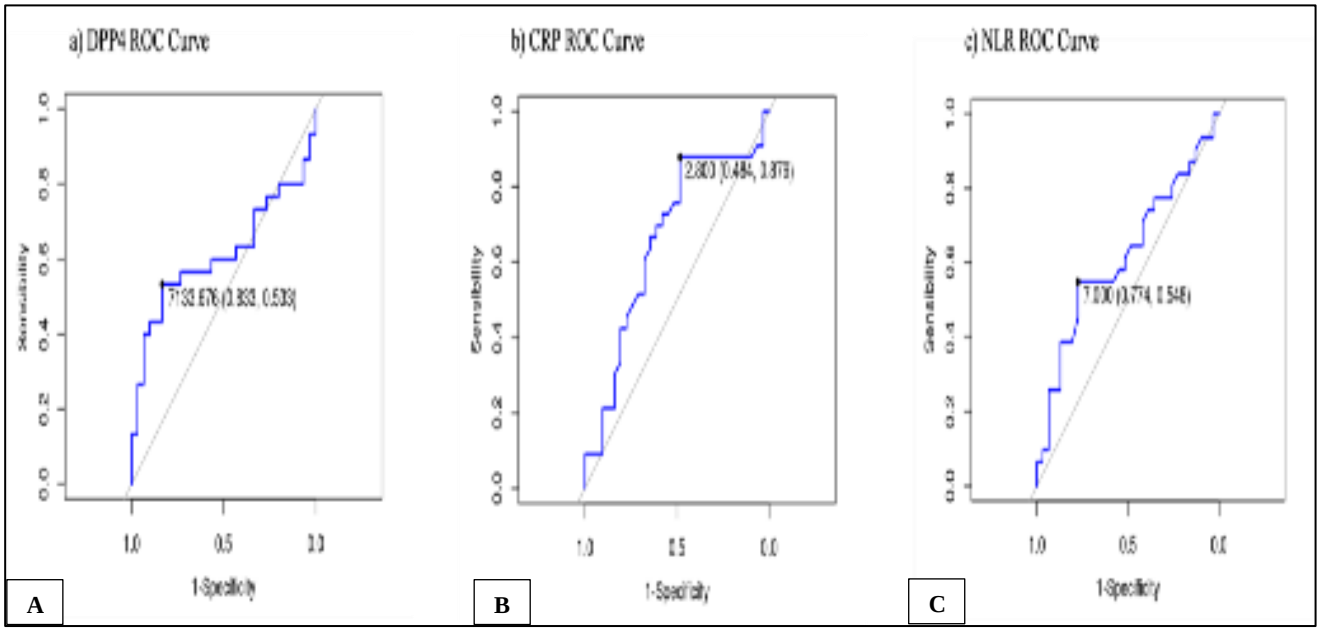

Figure 3 (A-C): ROC curve of diagnostic accuracy of biomarkers.

DISCUSSION

Having a biomarker to help us predict complications or adequately rule out cases of uncomplicated appendicitis remains a priority in the surgical emergency department, as evidenced in the literature.

The observed frequency of complications is highly variable and depends on the population studied. Other authors have reported frequencies as low as 11.3%, as high as 26.6% and as high as 29.5%.[27-29] This is different from that observed in the present study, which was 51.5%. However, it is in line with that previously reported in one of the longest retrospective series, which included more than 350 patients over 5 years.[30]

Concerning the general characteristics of the population, other authors, in studies aimed at predicting the severity of the disease, have found that age is a risk factor for complicated appendicitis, since the incidence of complicated appendicitis is higher in older patients.[27-29] Contrary to them, the subjects studied by our group did not show any differences. However, we observed that the group with complicated appendicitis had a higher age range, up to 73 years. These results are also similar to those of the 5-year retrospective series in which patients as young as 12 years of age were included.[30] The authors did not find any differences in the age range. However, as we found in our own results, cases with complicated appendicitis had an upper age limit. This is also consistent with what has been observed previously, in the analysis of complicated cases and ethereal groups such as older adults and patients with late diagnosis.[31]

Another factor that has been studied previously is the frequency of presentation of appendicitis by gender. In our study, the frequency of male versus female presentation (1.21:1) was similar to that previously reported (1.16:1).[29] In the previously described cohort where it was identified as a risk factor, this ratio was also higher (1.52:1).[30] In the regression model, however, it did not reach statistical significance. Nevertheless, in the review study, which included 44 countries, there was agreement that cases of complicated appendicitis were more likely to be seen in men.[32]

In terms of anthropometric variables, overweight/obesity has been associated with a high risk of complications in patients with acute appendicitis. However, obesity may delay diagnosis or increase postoperative complications and length of hospital stay, rather than directly increasing the risk of complicated appendicitis from the outset.[33,34] It is important to note that no differences were observed in our study. The mean body mass index in both groups was 25.5. It would therefore be necessary to study or categorise BMI, as suggested by other authors who have previously studied predictors of complications.[33-35]

Regarding the study of biomarkers such as INL in the diagnosis of complicated appendicitis, in the present study, the sensitivity, specificity and specifically the cut-off point of 7, differed from those previously reported in the meta-analysis that reviewed the cut-off points and particular characteristics of the populations included.[26] Nevertheless, regarding the study of biomarkers in the diagnosis of complicated appendicitis, it has been shown that the INL index of neutrophils and lymphocytes can be useful in predicting the severity of appendicitis independent of the population studied.[27,30,36,37] The observed variability could be explained by the time taken by some patients to come for examination or, in our case, by an obese BMI, which could mask appendiceal symptoms.

As far as the use of CRP as an early biomarker is concerned, it has so far been shown to be more specific than the white blood cell count.[38] However, sensitivity (57, 39-73%), specificity (87, 58-97%) and cut-off varied by population, time of development and diagnostic method. These results are similar to those observed in this study, where sensitivity was 85% but specificity was lower (48%). Cut-off point for PCR also varied from 30 to 110 mg/L. This variability may be due to the timing of serum CRP analysis and to the fact that its sustained increase is more likely to be seen in patients with an advanced inflammatory process, thus being associated as an indicator of severity.[39] In our study, the optimal cutoff point for CRP, as determined by receiver operating characteristic curve analysis, was lower than the values previously reported by several other authors.[30,37-39]

DPP4 is increasingly utilized as a biomarker in the context of inflammatory pathology. Prior research conducted by our team has indicated that this marker may exhibit heightened elevation in chronic phases of abdominal pathologies, such as cholecystectomy.[24] Similarly, DPP4 levels were higher in patients with Crohn's disease compared to active cases of ulcerative colitis.[40] Other authors have demonstrated the correlation between this new biomarker DPP4 and proinflammatory cytokines such as IL6 in other diseases such as rheumatoid arthritis or osteoarthritis of the knee.[41,42] However, this is the first study to propose its diagnostic utility in acute inflammatory diseases such as complicated appendicitis. Therefore, to confirm its diagnostic utility in daily practice and to help us differentiate between types of appendicitis with and without complications at an earlier stage, further extension studies in other populations are needed.

One of the primary limitations of the present study pertained to the delay in obtaining pathology results. In certain instances, it was not possible to obtain the relevant reports, which consequently rendered it challenging to include cases in the study. Additionally, there were instances of haemolysed blood samples, which could not be processed due to the potential inaccuracy of DPP4 quantification.

CONCLUSION

Compared to CRP and INL, DPP4 levels showed lower sensitivity but higher diagnostic specificity in our population. In acute appendicitis, DPP4 levels could be an early indicator in addition to imaging and clinical assessment of patients. This is the first study to demonstrate the usefulness of DPP4 in this patient population. However, it will be necessary to increase the size of the study population.

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