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ORIGINAL ARTICLE

Acute appendicitis guided by plasma and urine biomarkers. Case-control study

Apendicitis aguda guiada por biomarcadores plasmáticos y de orina. Estudio de casos y controles

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What do we know about the subject matter of this study?

The diagnosis of appendicitis in pediatrics can be challenging due to its unspecific clinical presentation and the broad differential diagnosis.

What does this study contribute to what is already known?

A prospective observational case-control analytical study showed that leukocyte and neutrophil count, neutrophil-to-lymphocyte ratio, and TNF- α were useful blood biomarkers in discriminating the diagnosis of acute appendicitis in childhood from other causes of abdominal pain.

Abstract

Acute appendicitis is a surgical emergency in pediatrics. An accurate diagnosis, based on new biomarkers, could reduce associated complications. **Objective:** to assess the usefulness of blood and urine biomarkers in the diagnosis of acute appendicitis in pediatrics. **Patients and Method:** Prospective, analytical, observational case-control study, conducted in a single center between 2019-2022. The study population consisted of 160 children aged between 0 and 15 years, divided into two groups (80 children with acute appendicitis and 80 without it), who consulted due to abdominal pain suggestive of acute abdomen, evaluated with biochemical markers and ultrasound for diagnosis. For evaluation, blood markers included C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), proadrenomedullin (proADM), pentraxin 3 (PTX3), tumor necrosis factor alpha (TNF-alpha), and interleukin

Keywords:
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6 (IL6) and the urine marker leucine-rich alpha-2-glycoprotein (LRG). Simple binary logistic regression models were estimated to study their association with the variables analyzed, estimation of a multiple model with a stepwise entry method, and subsequent obtaining of adjusted ORs and construction of ROC curves. We considered a $p < 0.05$ as significant. **Results:** Compared with controls, leukocyte count (AUC 0.829), neutrophils (AUC 0.836), and NLR (AUC 0.797) were significantly higher in the appendicitis group ($p < 0.001$), while the TNF-alpha elevation (AUC 0.959) reduced the prediction of appendicitis, without differences in the other biomarkers analyzed. **Conclusions:** The values of leukocytes, neutrophils, NLR, and TNF-alpha are those that best discriminate acute appendicitis from other etiologies of abdominal pain.

Introduction

Acute appendicitis is an entity widely known by pediatricians since it is the main cause of acute surgical abdomen in children, representing up to 10% of the cases of abdominal pain evaluated in emergency departments[1].

Due to the lack of specificity of its clinical presentation in childhood, especially in children under 4 years of age[2], and its wide differential diagnosis with other pathologies of similar clinical presentation[3], diagnostic failure rates can reach up to 30% in some studies[4].

Diagnosis is based mainly on anamnesis and physical examination, along with complementary tests such as laboratory tests and ultrasound. In addition, clinical prediction scales are used, such as the Pediatric Appendicitis Score (PAS). However, these tools are often not very specific in young children, and, in the case of the PAS, it is not validated for children under 4 years of age[5].

For this reason, numerous studies have proposed the search for new biomarkers that can help differentiate which children may have acute appendicitis. However, the published results have been varied and sometimes inconclusive.

The objective of the study was to assess the usefulness of biomarkers in blood and urine in the diagnosis of acute appendicitis in pediatrics.

Patients and Method

Study conducted jointly between the *Hospital Universitario Doctor Peset* and the Department of Pediatrics, Obstetrics and Gynecology of the *Universidad de Valencia*, approved by the Clinical Research Ethics Committee of the hospital (12/19).

Prospective, single-center analytical observational case-control study designed based on available resources according to the approved budget for biomarker analysis by the Faculty of Medicine of Valencia in partnership with the Foundation for the Promotion of Health and Biomedical Research of the Valencian Community, conducted on a sample composed of 80 children with abdominal pain due to appendicitis and 80 children with abdominal pain from other causes.

Inclusion criteria considered children aged under 15 years with clinical suspicion of appendicitis, who agreed to the collection of blood and urine samples, with informed consent obtained from their parents and from the patient when older than 12 years. No child was recruited who met any of the following exclusion criteria: history of gastrointestinal diseases requiring follow-up in pediatric outpatient care, medical history of hematological, oncological, hepatic, infectious, or inflammatory disease, either present or diagnosed in the month before the onset of symptoms; appendectomy or any major surgical intervention within the previous 3 months; chronic treatment with anti-inflammatory drugs, immunosuppressants, or corticosteroids in the last month; or that their parents/guardians or the child her/himself declined to participate in the study.

We used and analyzed the determination of various markers in blood samples [C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), proadrenomedullin (ProADM), pentraxin 3 (PTX3), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6)] and urine [leucine-rich alpha-2-glycoprotein (A2GRL)], the latter being of special interest in pediatrics, as it is the least invasive to obtain.

For sample collection, a peripheral blood draw (10 ml) was performed, requested with the "acute abdomen" profile specifically created for the study by the laboratory, which included a complete blood count, biochemistry with CRP, coagulation study, and an additional biochemistry tube from which aliquots of plasma, serum, and cellular series were separated into cryotubes. A urine sample was collected using the midstream technique in a sterile container, then transferred to a dry vacuum tube (10 ml, without prior asepsis), and all samples were stored at -80ºC until analysis. These last two samples were processed independently by the laboratory service and sent to the *Universidad*

de Valencia for the study of the markers, except for the CRP values analyzed by nephelometry (Image from Beckman Coulter Brea Cal. USA) and NLR, which were analyzed directly from the values obtained in the pediatric emergency department (analyzed directly in the hospital laboratory).

The aliquots sent from the hospital laboratory were processed in the Pediatrics laboratory of the Faculty of Medicine of the *Universidad de Valencia*. Blood samples were processed by centrifugation at 3500 rpm for 10 minutes in a refrigerated centrifuge at 4ºC (Hettich, Universal 320 R, D-78532 Tübingen, Germany) to separate serum and plasma. TNF-alpha and IL-6 levels were measured using the Milliplex MAP Multiplex assay (Millipore Merck) with the Luminex technique on a LABScan 100 system (Merck Millipore, Merck KGaA, Darmstadt, Germany), using Luminex 3.1 software (Austin, TX, USA).

For the analysis of ProADM, PTX3, and A2GRL in urine, ELISA kits were used, applying the sandwich ELISA technique. ProADM was measured using the human mid-regional ProADM MR kit from Mybiosource (San Diego, CA, USA), and PTX3 and A2GRL were measured using enzyme-linked immunosorbent assay kits ABK1-E2822 and ABK1-E1787, respectively, from Abyntek (Zamudio, Basque Country, Spain).

Study variables

The following qualitative and quantitative variables were collected (Table 1):

- Demographic: Age and sex.
- Clinical: Pain location (right iliac fossa), duration of symptoms and right iliac fossa tenderness, presence of fever, nausea, vomiting, and hyporexia.
- Laboratory tests: CRP level, leukocyte count, absolute and percentage neutrophil count, and levels of biomarkers included in the study in both blood and urine.
- Ultrasound: Diagnosis made; in case of acute appendicitis, appendix diameter and presence of indirect signs.
- PAS: Assessed to determine its discriminatory power between groups.

Statistical analysis

Simple binary logistic regression models were estimated to study the association between the classification group (appendicitis case/non-appendicitis control) and patient profile variables. The odds ratio (OR) and 95% confidence intervals of the unadjusted association were calculated. A selection of the most relevant variables ($p < 0.1$) was used to estimate a multiple model using the stepwise entry method, with the subsequent calculation of adjusted ORs. The resulting models were compared in terms of ROC curves and predictive validity. The significance level used in the analyses was 5% ($\alpha = 0.05$). For a logistic model estimated in the current sample ($n = 160$), the achieved power was 90.4% to detect statistically significant appendicitis rates of 25% and 50% between two patient groups, assuming a 95% confidence level.

Results

The research sample consisted of 160 pediatric patients suffering from abdominal pain who were finally diagnosed with appendicitis (80 cases) or non-appendicitis (80 controls). They consisted of 89 males (55.6%) and 71 females (44.4%) with an overall mean age of 10.9 ± 2.9 years, ranging from 3 to 15 years.

Several variables and certain biomarkers were strongly associated with the diagnosis.

Table 1 presents the results of logistic regression models to assess the degree of association of all biomarkers with patient classification (appendicitis vs. control).

- ***As for the biomarkers detected in the analysis:***

We can say that each additional CRP unit increased the odds of appendicitis by +1% (OR = 1.01; $p = 0.014$). Each additional unit of NLR multiplied the odds of appendicitis by 1.20, that is, increased the risk by 20% ($p < 0.001$), so both markers could help us predict appendicitis.

In contrast, the increase of TNF-α reduced the odds of being part of the appendicitis group (OR = 0.81; $p < 0.001$). Each additional unit of TNF-α resulted in a 19% decrease in the odds.

For leukocytes, an increase of 1000 units raised the risk of presenting appendicitis by 29.6% (OR = 1.00026; $p < 0.001$). For lymphocytes, an increase of 100 units reduced the risk of presenting appendicitis by 4.5% (OR = 0.99965; p=0.035). For neutrophils, an increase of 1000 units elevated the risk of presenting appendicitis by 32.3% (OR = 1.00028; $p < 0.001$). Each additional percentage point in the percentage of neutrophils multiplied the odds of appendicitis by 1.09, that is, increased the risk by 9% ($p < 0.001$).

The main objective was to evaluate the predictive potential of the different biomarkers, for which the ROC curve was estimated for each analytical marker (Figure 1).

Table 3 summarizes the diagnostic validity indicators for each of the parameters that were found to be significant at the optimal cut-off points.

- ***Regarding the PAS clinical prediction scale***

Each additional unit of the PAS multiplied the odds of the appendicitis group by 1.76, that is, in-

Table 1. Simple binary logistic regression model for probability of acute appendicitis compared to other causes of abdominal pain

	Category	OR	95% CI	p-value
CRP		1.01	1.00 – 1.02	0.014*
Leukocytes		1.00026	1.00017 – 1.00036	< 0.001***
Lymphocytes		0.99965	0.99933 – 0.99998	0.035*
Neutrophils		1.00028	1.00018 – 1.00037	< 0.001***
Neutrophils (%)		1.09	1.06 – 1.12	< 0.001***
NLR		1.20	1.11 – 1.29	< 0.001***
IL6		1.00	0.99 – 1.01	0.415
TNF-alpha		0.81	0.75 – 0.86	< 0.001***
ProADM		0.99	0.98 – 1.00	0.674
A2GRL		0.95	0.86 – 1.05	0.297
PTX3		0.99	0.98 – 1.01	0.739
PAS		1.76	1.43 – 2.16	< 0.001***
Risk level	Low	1		< 0.001***
	Intermediate	3.65	0.77 – 17.3	0.104
	High	20.6	4.27 – 99.6	< 0.001***
Ultrasound findings	Normal	1		< 0.001***
	AA	682.5	73.6 - 6330	< 0.001***
	Other	1.17	0.07 – 19.5	0.915
	Inconclusive	1.00	1.00 – 1.00	1.000
Diameter		6.84	2.83 – 16.6	< 0.001***
Indirect signs	No			
	Yes	975.3	158.5 – 6002	< 0.001***

Unadjusted OR estimates. *CI: confidence interval; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; IL6: interleukin 6; TNF-alpha: tumor necrosis factor alpha; ProADM: proadrenomedullin; A2GRL: alpha-2-glycoprotein rich in leucine; PTX3: pentraxin-3; PAS: Pediatric Appendicitis Score.

creased the risk by 76% ($p < 0.001$). Mean PAS values of 5.1 were obtained in controls and 7.1 in the appendicitis group.

The level of risk derived from the PAS was also significantly associated with the patient's group. There were no differences between intermediate and low levels (OR = 3.65; $p = 0.104$); but there were differences between high and low levels (OR = 20.6; $p < 0.001$). Table 2 shows that the rate of appendicitis cases increases as the low-, intermediate-, and high-risk levels increase: 12.5%, 34.2%, and 74.6%, respectively.

- ***Regarding ultrasound***

The ultrasound result was a remarkable predictor of diagnosis. When the ultrasound was normal, there were no cases of appendicitis. When it concluded acute appendicitis, in 95.2% the diagnosis was confirmed. When it found other non-appendicitis findings, only 3.23% of patients there were finally appendicitis cases. Finally, if the ultrasound result was inconclusive, no case of appendicitis was confirmed either. An ultrasound finding of appendicitis raised the odds of appendicitis almost 700-fold ($p < 0.001$).

The measured diameter was also significantly associated with diagnosis. The impact of an additional 1 mm implied an almost 7-fold elevation of the odds (OR = 6.84; $p < 0.001$).

The presence of indirect signs also determined a high probability of a diagnosis of appendicitis (OR = 975.3; $p < 0.001$).

Discussion

Acute appendicitis is the most frequent cause of acute surgical abdomen[5]. Its diagnosis is based fundamentally on anamnesis and physical examination and may be supported by inflammatory markers, imaging tests, or clinical prediction scales.

Many studies have proposed various biomarkers that could help in its diagnosis[6-39]. According to the results of this study, the values of leukocytes, neutro-

Table 2. Appendicitis risk by study group, stratified by PAS risk levels

	Group					
	Total		Controls		Cases	
	N	%	N	%	N	%
Total	160	100.0%	80	50.0%	80	50.0%
Low PAS	16	100.0%	14	87.5%	2	12.5%
Intermediate PAS	73	100.0%	48	65.8%	25	34.2%
High PAS	71	100.0%	18	25.4%	53	74.6%

PAS: Pediatric Appendicitis Score

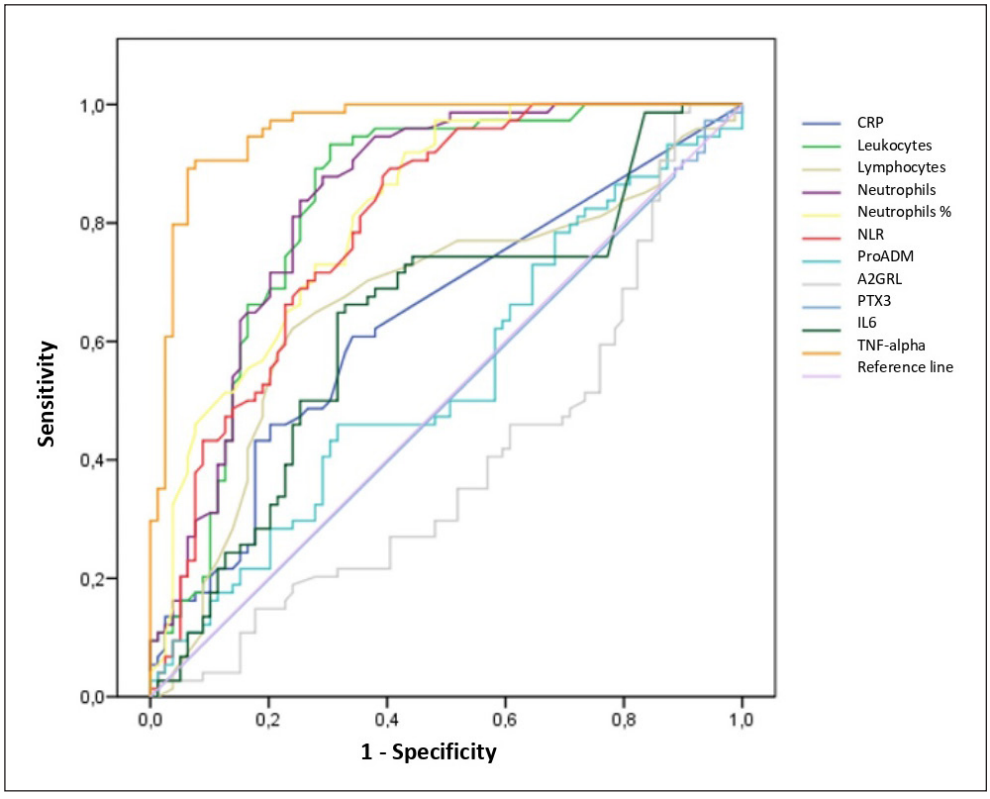

Figure 1. ROC curves of individual biomarkers to differentiate acute appendicitis from other causes of abdominal pain. TNF-alpha, neutrophils (and %), leukocytes and NLR show the highest AUCs, thus indicating the highest predictive relevance due to larger enclosed areas. *CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; IL6: interleukin 6; TNF-alpha: tumor necrosis factor alpha.

Table 3. Predictive validity of acute appendicitis for key blood biomarkers

	CRP	Leukocites	Lymphocytes	Neutrophils	Neutrophils %	NLR	TNF-alpha
AUC (95% CI)	0.637 (0.549-0.725); p = 0.003**	0.829 (0.761-0.897); p = 0.001**	0.665 (0.576-0.754); p < 0.001***	0.836 (0.771-0.901); p < 0.001***	0.818 (0.752-0.883); p < 0.001***	0.797 (0.726-0.867); p < 0.001***	0.959 (0.929-0.989); p < 0.001***
Cutoff point	15.5	10450	1750	7300	60.5	3.0	18.3
Sensitivity (%)	46.3%	92.5%	61.3%	86.3%	96.3%	86.3%	88.8%
Specificity (%)	80.0%	70.0%	76.3%	71.3%	51.3%	60.0%	92.5%
PPV (%)	69.8%	75.5%	72.1%	75.0%	66.4%	68.3%	92.2%
NPV (%)	59.8%	90.3%	66.3%	83.8%	93.2%	81.4%	89.2%
Accuracy (%)	63.1%	81.3%	68.7%	78.7%	73.7%	73.1%	90.6%

Results from ROC curve analysis (AUC) and optimal cutoff points per Youden Index. *CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; TNF-alpha: tumor necrosis factor alpha; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

phils, NLR, and TNF-α were those that best distinguish acute appendicitis. The PAS scale, which considers some of the aforementioned analytical parameters (absolute value of leukocytes and neutrophils), found significant differences in diagnosis between low- and high-risk values. In addition, ultrasound proved to be a useful diagnostic tool, with high ORs for the parameters analyzed (transverse diameter and presence of indirect signs).

Regarding the biomarkers analyzed, the values of leukocytes, neutrophils (absolute value and percentage), and NLR extracted from the usual analysis performed in the emergency department, were significantly higher ($p < 0.001$) in the group with appendicitis, which coincides with other studies published in the literature[6-16]. Additionally, both TNF-α and NLR were statistically significant ($p < 0.001$), which could favor their inclusion in the diagnostic algorithms for abdominal pain in pediatric emergencies, while the analysis of the rest of the biomarkers was not useful.

It is interesting to highlight the role of NLR since, in some studies such as the one by Delgado Miguel C. et al, in 2023[13], it was observed that an elevated value could be associated with the presence of appendicitis[13-16]. This could be because, in appendicitis, there is an inflammatory response that can result in neutrophilia and/or lymphopenia, which would increase this ratio. However, we must keep in mind that NLR is not specific to appendicitis and could be elevated in other inflammatory and/or infectious conditions. Therefore, and according to our results, we propose that NLR could be useful as an additional marker for the diagnosis of appendicitis, always accompanied by other parameters, being easy and cost-effective to perform in the emergency department. The measurement of this parameter could be especially useful in hospital centers where access to new biomarkers can be very difficult and costly.

The elevation of TNF-α in the control group could be useful as a diagnostic marker of appendicitis. This could be because TNF-α is a mediator of intestinal inflammatory processes, being one of the main cytokines involved in the pathogenesis of inflammatory bowel disease[35]. Most of the patients included in the control group were diagnosed with conditions secondary to intestinal infectious-inflammatory processes, such as acute gastroenteritis, mesenteric adenitis, and/or non-specific abdominal pain, mostly secondary to intercurrent infectious processes in childhood. These conditions may have led to a greater increase in TNF-α levels due to the production of a more generalized intestinal inflammation, among other possible factors[36-37]. Therefore, we could hypothesize that elevated TNF-α levels, mostly secondary to generalized infectious and/or inflammatory gastrointestinal conditions[35], would make the likelihood of appendicitis lower. Most of our appendicitis diagnoses corresponded to uncomplicated cases, with inflammation located in the right iliac fossa, which could correspond to lower levels of this biomarker.

Finally, we must highlight the usefulness of traditional markers (leukocytes, neutrophils, and CRP), which can be analyzed from a blood sample collected in the emergency department, as already proposed by some authors such as Prada-Arias M. et al, 2018[5] and their usefulness within the clinical scale of appendicitis prediction, PAS. In recent decades, several clinical-analytical prediction scales have been developed for the diagnosis of appendicitis, with their clinical use being associated with increased diagnostic accuracy. PAS is the best evaluated in pediatric patients, although it should be interpreted with caution since it has not been validated in children under 4 years of age[5]. This scale, which uses clinical and analytical parameters to which it assigns a score, categorizes patients according to the risk of suffering appendicitis in different subgroups: low (1-3 points), intermediate[4-6], or high[7-10] risk. It is recognized as useful for stratifying patients into low and high-risk groups, coinciding with the results of our study, in which it may be unnecessary to perform other diagnostic tests[40-41]. Some studies recommend performing an ultrasound study only at intermediate risk levels (4-6 points), since at low-risk levels, it could increase false positives and therefore, the number of unnecessary surgeries, contributing little to high-risk scores or acting even as a confounding factor due to the significant number of false negatives associated with perforated appendicitis[44].

The clinical diagnosis of appendicitis is difficult in children, due, among other causes, to the wide differential diagnosis, its atypical clinical presentation, and the greater diagnostic difficulty and lower index of suspicion in very young children. Ultrasound has been proposed as a useful tool, available in most hospitals and increasingly in Spanish healthcare centers, proving to be useful to establish the definitive diagnosis of this pathology, as we concluded in this work[42]. Some studies even propose that its diagnostic performance can be superior to clinical and laboratory findings, increasing its diagnostic certainty by associating it with these parameters[43]. The results obtained are consistent with those of the literature and confirm that ultrasound is a useful tool for the diagnosis of acute appendicitis in children[42-44]. Regarding the parameters measured within the ultrasound, we highlight those analyzed in this work (transverse diameter and presence of indirect signs), which presented high ORs.

In conclusion, we state that the analytical values of leukocytes, neutrophils, NLR, and TNF-α are values to be considered in suspected appendicitis, which can increase their diagnostic yield in combination with ultrasound, proposing the use of ultrasound in the presence of intermediate-risk scores in the PAS. We must not forget that the results of published studies on the use of specific biomarkers for the diagnosis of appendicitis are still very varied and should be analyzed in detail as to their diagnostic use alone, highlighting in most of them the usefulness of their analysis together with other parameters[17-34; 38-39].

The limitations of this study derive from its single-center design, a small sample size, the atypical presentation of appendicitis in young children, and the early presentation to the emergency department (mean abdominal pain duration of 24.9 hours), which may have led to misclassification and exclusion of some patients due to alternative suspected diagnoses at the time of consultation. Additional limitations include reduced availability and involvement of the medical personnel responsible for patient inclusion, especially during the COVID-19 pandemic, and greater difficulty in sample collection during that period.

Medical research should continue to explore new biomarkers to improve the diagnosis of appendicitis. More studies are needed in this area, which will help to improve the diagnostic specificity and timeliness of appendicitis in childhood.

Conclusions

The traditional diagnosis of appendicitis is still based on a combination of clinical history, physical examination, and complementary tests such as blood tests (leukocytes, neutrophils, CRP) and abdominal ultrasound. NLR and TNF-α are proposed as markers to be considered for the diagnosis of acute appendicitis, in combination with the rest of the parameters.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

To carry out the study, specifically the determination of biomarkers, the laboratory of the Faculty of Medicine at the *Universidad de Valencia* was contacted, and funding was provided in collaboration with the Foundation for the Promotion of Health and Biomedical Research of the Valencian Community.

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