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Frequency of Positive Results for SARS-CoV-2 Infection in Symptomatic Pediatric Patients Treated in the Emergency Department of a Regional Hospital

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Abstract: Objectives: Since 11 March 2020, when the World Health Organization declared the COVID-19 pandemic, trials have found that the pediatric population is the least affected, and most positive cases are asymptomatic or have mild symptoms such as fever and cough. Aims: The main objective of this study was to describe the percentage of positive tests among children who presented to the emergency department for symptoms compatible with SARS-CoV-2. Additional objectives were to identify clinical screening criteria to identify candidates to perform a polymerase chain reaction or antigen screening test. Patients/Methods: The study had a mixed cross-sectional and case-control design. Data were obtained from the electronic medical records of the emergency service of Hospital Sant Camil, Sant Pere de Ribes (Spain), from May 2020 to September 2021. Patients included had symptoms compatible with COVID-19 and a positive polymerase chain reaction or antigen SARS-CoV-2 screening test. Results: The study included 1508 patients with a mean age of 4.5 years (SD 4.2): 670 of whom were female (44.4%). The percentage of children with a positive polymerase chain reaction or antigen test was 3.51%. For the secondary objectives, some rules were created to create groups in which all patients tested negative: (1) Patients with abdominal pain, who did not present with diarrhea or fatigue, (2) Patients with asthma or allergies, (3) patients older than 3.5 years, with asthenia but without abdominal pain, and (4) patients younger than 3.5 years with abdominal pain and rash. Conclusions: The frequency of children who tested positive for COVID-19 was low among those with a clinical suspicion tested in the emergency room. Some combinations of symptoms and personal history were without exception associated with a negative polymerase chain reaction result for SARS-CoV-2 and could therefore help rule out the disease.

Keywords: SARS-CoV-2; pediatric population; COVID-19 symptoms; polymerase chain reaction; nasal smear; emergency department

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1. Introduction

As of 11 March 2020, the World Health Organization (WHO) officially declared coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic [1]. The impact of this disease was different depending on the age group, with the pediatric population being the least affected, according to most studies [2–5]. Following a study of a pediatric cohort carried out in China in 2020, with 2135 patients, it was discovered that more than 90% of those affected by the disease were asymptomatic or had mild symptoms, with no significant differences based on gender [6].

The most frequent symptoms in children infected with SARS-CoV-2, as described in published studies, have been fever and cough [7]. However, other symptoms, such as nasal

congestion or odynophagia have been observed, and although less frequently, headache, nausea, vomiting, diarrhea, abdominal pain, anosmia, ageusia, and rashes (i.e., urticarial, vesicular, macular, and papular). A few cases that progressed to bilateral pneumonia, acute respiratory distress syndrome (ARDS), or multiple organ failure have also been reported [8].

To unify COVID-19 early detection criteria among the pediatric population, Spanish pediatric societies such as the Spanish Association of Pediatrics (AEPED), the Spanish Association of Primary Care Pediatrics (AEPAP), the Spanish Society of Pediatric Infectious Diseases (SEIP), and the Spanish Society of Out-of-hospital Pediatrics and Primary Care (SEPEAP), established that a case was to be deemed suspicious in the presence of fever or a low-grade fever (>37.5 °C), cough, respiratory distress, odynophagia, headache, nasal congestion, abdominal pain, vomiting or diarrhea. In adolescents, taste and smell alteration, muscle pain, and general malaise were added as suspicious symptoms. Both nasal congestion and odynophagia were considered potential symptoms if accompanied by those mentioned above [9].

However, the widespread presence of respiratory viruses that cause similar symptoms during the winter months raises doubts regarding diagnosis, forcing physicians to perform COVID screening tests in most pediatric patients, even repeatedly. The timing of sample collection is essential to obtain reliable results from these molecular tests. Screening tests should ideally be performed on nasopharyngeal secretions collected at the beginning of the disease [10], when there are signs of rhinopharyngitis, as the viral load decreases in the upper airway and increases in the lower airways favoring the onset of lung disease [11]. Antigen tests are cheaper and faster than PCR, but they have a higher rate of false negatives, so if clinical suspicion is high, it is advisable to confirm the results of negative antigen tests with a PCR test [12].

Previous retrospective studies have identified the most common disease symptoms in pediatric patients. However, a clear criterion to define the cases that require PCR testing has not yet been established, beyond preventive action to avoid transmission.

The high number of pediatric patients who present to the emergency room with symptoms compatible with COVID-19, also common to other conditions, combined with the lack of effective triage tools, make it necessary to carry out tests to identify SARS-CoV-2 in a generalized manner. This testing requires extensive time and resources and leads to the saturation of emergency services.

The main objective of this study was to describe the percentage of positive patients among children who consulted the emergency department for symptoms compatible with SARS-CoV-2. Additional objectives were to identify clinical criteria to select candidates for a PCR or antigen screening test.

2. Materials and Methods

2.1. Study Design

The study had a mixed cross-sectional and case-control design. We used data from the electronic medical records of the population under 15 years old who consulted the emergency service of Hospital Sant Camil, Sant Pere de Ribes (Spain), from May 2020 to September 2021, with symptoms compatible with COVID-19 for whom a SARS-CoV-2 PCR or antigen screening test was requested.

The study was divided into two parts. The first part was a cross-sectional study analyzing the percentage of positive nasal swab PCR or antigen tests for SARS-CoV-2 performed in the pediatric emergency department from May to September 2021. In the second part, we analyzed the collected positive cases and evaluated the factors potentially associated with the positivity of the test. Since studying the symptoms of all the children who received care for suspected COVID-19 would not have been feasible for the researchers, for this second stage, a case-control design was applied, and four controls were randomly chosen (i.e., a negative result in a nasal swab PCR), matched by age and gender with each positive case.

Primary Objective: To study the frequency of positive nasal swab PCR or antigen tests for SARS-CoV-2 infection among children with symptoms compatible with COVID-19 tested in the hospital's emergency services according to routine clinical practice.

Secondary Objectives: To optimize the use of nasal swab PCR tests by establishing the clinical screening criteria to request the SARS-CoV-2 screening test in children with suspected COVID-19 in the emergency room (studying the validity of clinical symptoms for the detection of the infection).

2.2. Ethical Statement and Data Management

The study was approved by the Medical Research and Ethics Committee (CEIC) of Bellvitge Hospital and was conducted following the principles outlined in the current revised version of the Declaration of Helsinki and Good Clinical Practices (GCPs). Only the data necessary for this study were collected to keep the data minimization principle. As it was not feasible to obtain informed consent, the data were pseudonymized for analysis, thus guaranteeing compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on Data Protection (RGPD), and Organic Law 03/2018, of December 5.

2.3. Subjects

All children under 15 years old classified as suspected cases of COVID-19 were included in the study. The definition of a suspected case was the established definition at the time the study was conducted, by consensus of the main scientific pediatrics societies in the country (AEPED, AEPAP, SEIP, and SEPEAP) [9]. According to these criteria, a case was suspicious if it presented with a fever, cough, respiratory distress, headache, abdominal pain, vomiting, or diarrhea. Nasal congestion or odynophagia was added if accompanied by any of the above symptoms. In the case of adolescents, taste and smell alteration, muscle pain, and general malaise were added as suspicious symptoms.

All patients were tested for SARS-CoV-2 at the pediatric emergency service of Hospital Sant Camils from May 2020 to September 2021. Patients had to meet the following requirements to participate in the study:

Inclusion Criteria: Patients under 15 years old with symptoms compatible with SARS-CoV-2 infection who underwent a PCR or antigen test in the emergency department.

Exclusion Criteria: (1) Asymptomatic patients tested for SARS-CoV-2 through a nasal swab PCR or an antigen test for being in close contact with a positive COVID-19 case; (2) patients who required admission to the pediatric ward due to another diagnosis (i.e., urinary infection, appendicitis, fracture, head trauma) and who underwent a nasal swab PCR or antigen test as part of the hospital protocol in a pandemic situation.

2.4. Variables Analyzed

The researchers collected the data from the hospital's electronic medical records. The variables analyzed were (1) gender; (2) age; (3) result of nasal swab PCR or antigenic testing for 0SARS-CoV-2, 4) symptoms of study subjects including rash, cough, runny nose, respiratory distress, dyspnea, fever >38 °C, low-grade fever >37.2 °C, conjunctivitis, odynophagia, arthralgia, diarrhea, abdominal pain, vomiting, headache, fatigue, asthenia, hyporexia, myalgia, dysgeusia, or anomia; (5) personal history including recurrent bronchitis, asthma, food allergies, environmental allergies, celiac disease, heart disease, type 1 diabetes mellitus, obesity, chronic inflammatory disease, immunodeficiency, and others; (6) chronic treatment including inhaled or oral corticosteroids, inhaled long-acting B2 agonists, prophylactic antibiotics, and others; (7) chest radiology practice (answer yes or no); and (8) known contact with a COVID-19-positive case (answer yes or no).

Laboratory Test Analyzed

The doctors requested the test following the recommendations of different scientific societies, including AEPED, AEPAP, SEIP, and SEPEAP. The protocols included confir-

mation through the PCR testing of all suspicious cases with a negative antigenic test for SARS-CoV-2.

The PCR tests used to detect SARS-CoV-2 were the Cepheid Xpert® Xpress SARS-CoV-2 assay (Cepheid, Sunnyvale, CA) (target genes: N2 and E; limit of detection (LoD) of 250 copies/mL and specificity $\geq$ 98%); and the Abbott RealTime SARS-CoV (target genes: RdRP and N; limit of detection (LoD) of 100 copies/mL)

The rapid test for antigenic determination was the Panbio™ COVID-19 Ag Rapid Test Device (Abbott Diagnostics, Jena, Germany), [sensitivity 93.3% (83.3–98.2%), >95% in symptomatic patients; and specificity 99.4% (97–100%)], which detects nucleocapsid proteins.

2.5. Development of the Decision Trees

A case-control approach was carried out to study the symptoms associated with positivity. Four negative controls were randomly selected for each positive case of SARS-CoV-2. Cases and controls were matched by age, tolerating a maximum difference of two years between cases and controls. The frequency of the symptoms was studied in both groups and supervised machine learning (ML) techniques, specifically decision trees (DTs), were applied to search for detection patterns. DTs were optimized to maximize the diagnostic cost-effectiveness of SARS-CoV-2 screening tests. The DTs techniques were used to generate directly interpretable models based on decision rules to apply them in clinical practice.

DTs were built to find the most relevant rules fulfilled in the database. DTs are a common technique in ML and are generally used to create simple classifier models. A peculiarity of this model is that it is made up of quickly interpretable rules. In this case, they were not used as classifier model generators but rather to select those relationships between the different symptoms that grouped the most significant number of cases and indicated the same PCR result with a level of certainty. Data collected were used to generate the models and carry out a hyper-parametrization with the screening criteria with the classes' weight. Finally, the trees that applied to the entire database obtained, which had a sensitivity of 100% and a specificity of $\geq$30%, were selected. Eight models were obtained that met the proposed criteria. From the structure of the tree rules, the most representative paths (in the number of PCRs with the same result and shorter path length) were extracted and restructured in the form of unique rules. Finally, it was verified in the database that these rules only pointed to PCRs with the same result, and the number of patients who met them was reported.

2.6. Sample Size

The sample size was not determined a priori. However, it was anticipated that a random sample of 1118 individuals would be sufficient to estimate, with 95% confidence and a precision of $+/-1$ percentage units, a predicted percentage of positive screening tests of around 3%.

2.7. Statistical Analysis

The frequency of patients infected with SARS-CoV-2 was calculated from the total number of positive nasal swab PCR tests carried out during the study period.

Categorical variables were described by counts and percentages, whereas continuous variables were described by the mean and the standard deviation (SD) or the median with the first and last quantile. The number of non-missing observations for each of the variables is also shown. Adjustment of the data to the normal distribution was studied using the Shapiro–Wilk test. Univariate logistic models were used for assessing the raw association of each variable with the test result, corrected by the cluster effect of the matching done by age and gender. The odds ratios of the associations are presented in tables.

The conditions of application of the model were validated, and whenever possible, 95% confidence intervals were calculated for the estimators. All analyses were carried out with R (v.4.0.3, 10 October 2020): "dplyr" and "tidyr" packages were used for data

processing, the "stats" package was used for performing the base logistic regression model, and "sandwich" and "lmtest" were used for correcting the model by the cluster effect.

3. Results

3.1. Patient Characteristics

The study included 1508 patients with a mean age of 4.5 years (SD 4.2), 670 of whom were female (44.4%).

3.2. First Part of the Study (Primary Objective)

Of the 1508 patients included in the study, 53 tested positive for COVID-19 [43 (81.1%) through a PCR test and 10 (18.8%) in an antigen test], resulting in a percentage of children with a positive test (nasal swab PCR test or antigen test) of 3.51% (n = 53/1508; 95% CI: 2.58–4.45%).

3.3. Second Part of the Study (Secondary Objectives)

Of the 1508 patients included in the first part of the study, 52 patients with a positive test and 203 with a negative test were selected. Five controls were discarded due to data transcription errors. The demographic characteristics, clinical history, and symptoms of the patients, based on the result of the nasal swab PCR and its respective odds ratio, are collected in Table 1. Odds ratios adjusted by age, sex, and previous respiratory disease (bronchitis or asthma) are shown in Table 2.

Table 1. Demographic characteristics, clinical history, and clinical symptoms of the patients in the second part of the study based on the result of the SARS-CoV-2 nasal swab PCR or antigen test result, and their respective odds ratio.

	All N = 255	**Negative n = 203**	**Positive n = 52**	**Odds Ratio [CI95%]**	***p***
Demographic Characteristics, mean (SD or %)					
Age	6.49 (4.84)	6.48 (4.82)	6.54 (4.98)	1 [0.99;1.01]	0.652
Female sex	116 (45.49%)	88 (43.35%)	28 (53.85%)	1.52 [0.81;2.86]	0.188
Clinical History, n (%)					
Bronchitis	38 (14.90)	32 (15.76)	6 (11.54%)	0.7 [0.25;1.93]	0.486
Asthma	10 (3.92)	10 (4.93)	0 (0.00)	-	-
Allergies	7 (2.75)	7 (3.45)	0 (0.00)	-	-
Environmental allergies	11(4.31)	11 (5.42)	0 (0.00)	-	-
Celiac	1 (0.39)	1 (0.49)	0 (0.00)	-	-
Heart disease	2 (0.78)	2 (0.99)	0 (0.00)	-	-
Diabetes mellitus 1	0 (0.00)	0 (0.00)	0 (0.00)	-	-
Obesity	3 (1.18)	3 (1.48)	0 (0.00)	-	-
EI	0 (0.00)	0 (0.00)	0 (0.00)	-	-
Immunodeficiency	0 (0.00)	0 (0.00)	0 (0.00)	-	-
Symptoms, n (%)					
Exanthema	10 (3.92)	38 (18.72)	2 (3.85)	0.97 [0.21;4.57]	0.974
Cough	86 (33.73)	67 (33.00)	19 (36.54)	1.17 [0.59;2.33]	0.658
Rhinorrhea	75 (29.41)	64 (31.53)	11 (21.15)	0.58 [0.29;1.18]	0.132
Respiratory Difficulty	27 (10.59)	24 (11.82)	3 (5.77)	0.46 [0.12;1.72]	0.246
Dyspnea	16 (6.27)	13 (6.40)	3 (5.77)	0.89 [0.23;3.49]	0.873
Fever	154 (60.39)	117 (57.64)	37 (71.15)	1.81 [0.97;3.38]	0.061
Low-grade fever	32 (12.55)	26 (12.81)	6 (11.54)	0.89 [0.34;2.3]	0.806
Conjunctivitis	4 (1.57)	1 (0.49)	3 (5.77)	-	
Odynophagia	29 (11.37)	24 (11.82)	5 (9.62)	0.79 [0.31;2.03]	0.629
Arthralgia	3 (1.18)	3 (1.48)	0 (0.00)	-	
Diarrhea	44 (17.25)	35 (17.24)	9 (17.31)	1 [0.46;2.19]	0.991

Table 1. *Cont.*

	All N = 255	Negative n = 203	Positive n = 52	Odds Ratio [CI95%]	*p*
Abdominal pain	43 (16.86)	39 (19.21)	4 (7.69)	0.35 [0.12;1.03]	0.056
Vomiting	48 (18.82)	40 (19.7)	8 (15.38)	0.74 [0.34;1.61]	0.451
Headache	33 (12.94)	23 (11.33)	10 (19.23)	1.86 [0.79;4.37]	0.152
Weakness	24 (9.41)	21 (10.34)	3 (5.77)	0.53 [0.15;1.84]	0.532
Anorexia	18 (7.06)	15 (7.39)	3 (5.77)	0.77 [0.2;3]	0.317
Myalgia	6 (2.35)	3 (1.48)	3 (5.77)	4.08 [0.77;21.77]	0.100
Dysgeusia	0 (0.00)	0 (0.00)	0 (0.00)	-	
Anosmia	1 (0.39%)	1 (0.49)	0 (0.00)	-	

Abbreviations: SD, standard deviation; PCR, polymerase chain reaction; ID, inflammatory disease; CI confidence interval.

Table 2. Association between the presence of each symptom compatible with COVID-19 and the positivity of the confirmation test. Adjusted odds ratios.

	Negative n = 203	Positive n = 52	Adjusted Odds Ratio * [CI95%]
Symptoms			
Exanthema	38 (18.72)	2 (3.85)	1.03 [0.22;4.81]
Cough	67 (33.00)	19 (36.54)	1.31 [0.66;2.62]
Rhinorrhea	64 (31.53)	11 (21.15)	0.59 [0.29;1.2]
Respiratory Difficulty	24 (11.82)	3 (5.77)	0.57 [0.15;2.16]
Dyspnea	13 (6.40)	3 (5.77)	1.11 [0.28;4.32]
Fever	117 (57.64)	37 (71.15)	1.75 [0.94;3.25]
Low-grade fever	26 (12.81)	6 (11.54)	0.88 [0.34;2.26]
Conjunctivitis	1 (0.49)	3 (5.77)	-
Odynophagia	24 (11.82)	5 (9.62)	0.69 [0.27;1.76]
Arthralgia	3 (1.48)	0 (0.00)	-
Diarrhea	35 (17.24)	9 (17.31)	0.94 [0.43;2.06]
Abdominal pain	39 (19.21)	4 (7.69)	0.33 [0.11;0.96]
Vomiting	40 (19.7)	8 (15.38)	0.71 [0.33;1.55]
Headache	23 (11.33)	10 (19.23)	1.9 [0.81;4.45]
Weakness	21 (10.34)	3 (5.77)	0.41 [0.1;1.68]
Anorexia	15 (7.39)	3 (5.77)	0.71 [0.18;2.78]
Myalgia	3 (1.48)	3 (5.77)	4.42 [0.83;23.56]
Dysgeusia	0 (0.00)	0 (0.00)	-
Anosmia	1 (0.49)	0 (0.00)	-

* Odds ratio Adjusted by age, sex, and previous respiratory disease (bronchitis or asthma).

The rules were extracted from all the models and, after discarding duplicate rules, the following rules were obtained in which all the patients who meet them present a negative PCR:

- Patients with abdominal pain, without diarrhea and fatigue, n = 31 (11.8%);
- Patients with any allergy or asthma, n = 25 (9.5%);
- Patients $\geq$ 3.5 years, with asthenia and without abdominal pain, n = 12 (4.6%);
- Patients aged $\leq$ 3.5 years with abdominal pain and rash n = 7 (2.7%).

4. Discussion

The study showed that the percentage of children who presented to the emergency room with symptoms suspicious of COVID-19 and a positive SARS-CoV-2 PCR or antigen test was low (3.51%).

During the study, we did not find specific symptoms of COVID-19 with a substantial positive predictive value. On the other hand, there were symptoms and clinical conditions with a high negative predictive value, making it possible to rule out COVID-19. We used these symptoms to build decision trees to identify cases in which the combination of age

and symptoms (or lack of specific symptoms) always had a negative PCR result. Until May 2021, the predominant SARS-CoV-2 variant in Spain was the Alfa (B.1.1.7 predominant). From that moment on, the Delta variant (B.1.617.2 predominant) began to grow in frequency, until it was practically hegemonic at the end of the study in December 2021 [13].

In our search, we have only found one study that analyzes the proportion of positive patients treated in the emergency department among pediatric patients with suspicious symptoms. In that study, carried out from March to May 2020 by Stacevičienė et al. [14] in the emergency department of Vilnius University Hospital Santaros Klinikos, 1348 symptomatic and asymptomatic pediatric patients were included, who underwent PCR to rule out COVID-19. Of the total number of patients with suspicious symptoms of COVID-19 (811/1348, 60.2%), such as fever (785/811, 96.8%), cough (178/811, 21.9%), or shortness of breath (16/811, 2.0 %), only 0.9% (7/811) were positive for SARS-CoV-2 through PCR testing, a lower figure than that found in our study (3.51%). This difference is not surprising, considering that the incidence rate, as well as the clinical presentation of COVID-19, have differed between countries [14–16]. The research conducted by Stacevičienė et al. took place in Lithuania during the first three months of the pandemic, when the Baltic countries had a much lower incidence than the rest of Europe, possibly due to the adoption of early measures implemented by their governments in the face of the new pandemic [17].

So far, some published studies have investigated the most frequent symptoms in patients who tested positive for SARS-CoV-2 [18,19]. Şık et al. [18] report the results of 45 pediatric patients who were tested for COVID-19 in the emergency department (with or without symptoms) between March and June 2020. Among the 24 children with symptoms, a fever (34.1%) and a cough (27.3%) were the most frequently reported. Similar to ours, King et al. found that a cough was a frequent symptom among patients with confirmed COVID-19, but also among those without COVID-19. In their study, anosmia/ageusia and nausea were the most predictive symptoms of COVID-19 (likelihood ratio for the combination: 65.92). We did not have enough reported cases of anosmia/ageusia recorded to evaluate this point and, in our case, nausea was also frequent in patients without COVID-19, so it was not found to be a reliable predictor of a positive test. We did not find symptoms with a good validity for the detection of COVID-19, but we did find combinations of symptoms in which the test was never positive, and which were therefore considered of good validity to rule out the disease: patients with abdominal pain and rash, or patients with abdominal pain, but without diarrhea or fatigue.

We have used decision trees to identify rules to better select children to be tested for COVID-19. Machine learning techniques have been used previously during the pandemic, for example, to estimate the trend of incidence, but we are not aware of other works that have used them to identify guiding symptoms that improve diagnostic performance in children [20]. The decision tree was prepared based on the observation of all the variables collected from patients with negative PCR tests using the procedure described in the *Data Management* section. These findings could be helpful if they are confirmed in subsequent studies.

In addition to the general limitations associated with its retrospective design, our study may have problems of generability, as it was conducted in a single site and included a relatively small number of cases. Furthermore, the low number of positive PCR tests prevented us from building decision trees with the most significant variables related to the SARS-CoV-2 PCR positive result.

In the context of previously published studies reporting their experience in children presenting to the emergency services with symptoms suspicious of COVID-19, our study provides valuable complementary evidence. The results from this study using an unusual approach may be helpful for clinicians and researchers to reformulate the criteria for requesting SARS-CoV-2 PCR testing.

5. Conclusions

In this study, it has been determined that the proportion of positive COVID-19 tests among symptomatic children seen in the emergency room is very low. Therefore, it is important to identify symptom profiles that help better screen children who should be tested for COVID-19. Using decision trees, we analyzed four patients who tested negative for COVID-19 per each positive case. We have found some combinations of symptoms and personal history which were without exception associated with a negative PCR result for SARS-CoV-2 and could therefore help rule out the disease: (1) Patients with abdominal pain, who did not present with diarrhea or fatigue, (2) Patients with asthma or allergies, (3) patients older than 3.5 years, with asthenia but without abdominal pain, and (4) patients younger than 3.5 years with abdominal pain and rash.

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Informed Consent Statement: Patient consent was waived as it was an observational and retrospective review of clinical data, and the patient's personal data were anonymized for its publication.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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