

# Sex differences in an Italian pediatric population covid-19 positive

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## Research

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# Abstract

**Background:** Since December 2019 coronavirus disease (COVID-19) emerged in Wuhan and spread rapidly worldwide. Despite the high number of people affected, data on clinical features and prognostic factors in children and adolescents are limited. We propose a retrospective study aimed to evaluate clinical characteristics of children infected with SARS-CoV-2 in Italy.

**Methods:** A pediatric population admitted with COVID-19 to Bambino Gesù Children's Hospital of Rome (Italy) in the period from the end of February to May 2020 has been studied taking into account gender. Medical history, comorbidities, symptoms and laboratory findings were obtained from patients' electronic medical records.

**Results:** In 41 patients (21 males and 20 females) we found that: i) fever and cough were the dominant symptoms, while gastrointestinal symptoms were rare; and ii) all ages of childhood were susceptible to COVID-19. Moreover, we found that females with COVID-19, were significantly

( $p = 0.04$ ) older than males and required more days of hospitalization ( $p = 0.01$ ).

Moreover, compared to females, a greater number of males had high values of C reactive protein (3 males vs 1 female) and erythrocyte sedimentation rate (2 males vs 1 female).

**Conclusions:** Compared to the adults we found that COVID-19 infection in children is a non-severe inflammatory disease in both males and females. In any case, many detailed studies should be conducted.

## Background

Since mid-December 2019, an infection caused by a new type of coronavirus (SARS-COV-2) emerged in Wuhan (Hubei Province, China) and spread rapidly worldwide. The emerging SARS-COV-2 is a beta coronavirus that can cause COVID-19, officially named by the World Health Organization (WHO) on February 11, 2020. This virus is highly contagious and can be transmitted by an infected person or an asymptomatic carrier through respiratory droplets, tear fluid and close contacts. The incubation period is variable. It has been estimated that the median incubation period is 5.1 days and that 97.5% of infected patients will develop symptoms within 11.5 days of infection.

Despite the high number of people affected, data on clinical features and prognostic factors in children and adolescents are limited. Children are part of a very special group. Similarly to the SARS-COV 2002-2003 epidemic [1,2], pediatric COVID-19 appears to be mild or asymptomatic [3,4]. Children become less ill than adults and most of them contract the infection mainly through close contact with their parents or other family members with COVID-19. Many children infected with SARS-COV-2 manifest a mild disease that often does not require hospitalization. Compared to adults, children have a lower chance of developing interstitial pneumonia, one of the most serious complications of the infection, which in the

advanced form requires hospitalization in intensive care. As for the adults, the presence of congenital heart disease, lung and airway disease, malnutrition and cancer makes children more susceptible to COVID-19.

There are several hypotheses on the mechanisms underlying the lower susceptibility of children to COVID-19 infection than adults: i) a more efficient immune response due to the stimulation given by typical age vaccinations; ii) a lower expression of the angiotensin-converting enzyme 2 (ACE2) receptor to which the virus would bind to enter cells [5]; iii) an "immaturity" of the ACE2 receptors, which makes it difficult for the virus to enter the body [6]; and iv) external factors (before the lockdown, children were less likely than adults to visit places that could have facilitated the spread of the virus, such as railway stations and airports) [7].

In children with COVID-19, fever and cough are the most common clinical manifestations, sometimes accompanied by fatigue, myalgia, nasal congestion, sneezing, sore throat, headache, dizziness, vomit and abdominal pain. Moreover, some children do not manifest fever, but only cough or diarrhoea, or they may be asymptomatic. The latter, even if they do not manifest symptoms, may play significant roles in the transmission of Covid-19 in the community.

Italy was one of the European countries most affected by the COVID-19 pandemic. By 16 April 2020, 1,123 children, up to nine years of age, and 1,804 adolescents, aged between 10 and 19 years old were tested positives for COVID-19 [8].

In Italy most of the data on COVID-19 pediatric patients derive from a multicentre study promoted by the Italian Society of Paediatric Infectious Diseases (SITIP), within the Italian Society of Paediatrics (SIP). In this study 168 children aged 1 day to 17 years, 94 (55.9%) males and 74 (40.1%) females, with confirmed COVID-19 were analysed [9]. 65.1% of these children were hospitalized: of these, only 17 (15.5%) were sent to the hospital after seeing a paediatrician or family doctor. Moreover, 5.9% of children documented co-infections with other viruses such as respiratory syncytial virus, rhinovirus, Epstein-Barr virus, influenza A virus and a non-SARS coronavirus. Bacterial co-infection with *Streptococcus pneumoniae* has also been documented. Pre-existing chronic pathologies, such as chronic lung diseases (n = 7), congenital malformations or complex genetic syndromes (n = 14), cancer (n = 4), epilepsy were found in 33 children. Moreover, gastrointestinal (n = 2) or metabolic (n = 1) disorders were found. Among these patients 4 were immunosuppressed and 3 immunocompromised. The hospitalization rate was similar between children with and those without co-morbidity.

Studies have reported a higher incidence of COVID-19 in males than in females in the adult population [10]. This study is aimed to evaluate clinical characteristics of children infected with SARS-CoV-2 in Italy, taking into account gender.

For this purpose, 41 patients admitted to Bambino Gesù Children's Hospital of Rome (Italy) in the period from the end of February to May 2020 were analysed.

# Methods

## *Study design and participants*

Forty one patients (21 males and 20 females), admitted with COVID-19 to Bambino Gesù Children's Hospital of Rome (Italy) in the period from the end of February to May 2020, were enrolled in this retrospective cohort study. Mean age of patients was 9 years (range  $\leq$  1-18 years).

All patients analyzed had contracted the infection from their parents and they were hospitalized because showed signs and symptoms such as fever, cough, vomit, diarrhea, convulsions, headache or pneumoniae. Only 3 patients were asymptomatic (2 males and 1 female), but they were hospitalized and monitored until they tested negative at the swab (**Table 1**).

The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki principles for ethical research. Ethics approval and written informed consent were waived due to the rapid emergence of this infectious disease. Three researchers and a physician collected and reviewed the data. Medical history, underlying comorbidities, symptoms and laboratory findings both at admission and during hospitalization, were obtained from patients' electronic medical records.

The date of disease onset was defined as the day when the symptoms were noticed.

## *Laboratory measurements*

All patients underwent nasopharyngeal, eye, urine and stool swab. The presence of SARS-CoV-2 in respiratory specimens was detected by real-time reverse transcription (RT-PCR) methods. Analyses by gene amplification reaction and Real Time RT-PCR were also carried out to exclude evidence of other viral infections, including influenza, respiratory syncytial virus, avian influenza, para-influenza, adenovirus and rhinovirus. Routine bacterial and fungal examinations were also performed. Moreover, EBV infection was routinely screened and detected by using a test that identifies antibodies to EBV in the blood.

Data include all paediatric patients in whom COVID-19 was documented by at least one nasal/pharyngeal swab specimen positive for SARS-CoV-2 nucleic acid using RT-PCR assay.

## *Statistical analysis*

To compare medians and range of values between two groups we used the Mann-Whitney's U test and the Median test. The level of significance was determined at  $p < 0.05$ .

# Results

### *Features of patients at admission*

At admission patients presented: fever (25 patients), cough (13 patients), headache (7 patients), vomit (3 patients), diarrhoea (5 patients) and pneumonia (2 patients). Moreover, 3 patients were asymptomatic and 4 patients had co-infections: 2 with Rhinovirus and 2 with Epstein-Barr virus (EBV) (**Table 1**). Some analyzed patients had a history of pneumonia, bronchiolitis, asthmatic bronchitis, gastroenteritis and convulsions. Furthermore, at admission only 23 patients (15 males and 8 females) presented bronchospasm and underwent chest x-ray. In 3 males and 5 females, a modest thickening of the peri-broncho-vascular interstitium was found.

Interestingly, from the analysis of medical records we found that females: i) were significantly ( $p = 0.04$ ) older than males and ii) required more days of hospitalization than males ( $p = 0.01$ ).

Moreover, laboratory tests showed that in almost all pediatric population CRP, ESR, fibrinogen and procalcitonin values were within the normal range in both males and females. Except for 3 males (median of values: 3.3 mg/dL; range of values: 1.8 – 4.16 mg/dL) and 1 female (1.57 mg/dL) that had increased CRP levels and 2 males (25 and 17 mm/h respectively) and 1 female (49 mm/h) that had increased ESR levels. Furthermore, only 2 males (349 and 557 U/L) and 2 females (376 and 453 U/L) had LDH values above the normal range.

Compared to females, 6 males aged between 7 and 16 years had RBC number above the normal range (median number:  $5 \times 10^6/\mu\text{L}$ ; range of values: 457 –  $527 \times 10^6/\mu\text{L}$ ). Conversely, five females, aged between 8 and 18 years had mild lymphopenia (median number:  $3 \times 10^3/\mu\text{L}$ ; range of values: 2.33 –  $3.8 \times 10^3/\mu\text{L}$ ).

### *Patient characteristics during hospitalization*

During hospitalization 5 males developed mild thrombocytosis (median number of PLTs:  $607 \times 10^3/\mu\text{L}$ ; range of values: 496 –  $663 \times 10^3/\mu\text{L}$ ) and an increase in inflammation measured in terms of high CRP levels (median of values: 2.546 mg/dL; range of values: 1.07 -4.61 mg/dL). Three of these patients were less than 1 year; 1 patient was 2 years old and 1 patient was 12 years old. During hospitalization, patients less than 1-year-old manifested gastrointestinal symptoms and diarrhea; the 2-year-old patient had inflammation of the airways and pharyngitis and previously hospitalized for bronchiolitis; the 12-year-old patient developed salmonella gastroenteritis. On the basis of these data we can speculate that reactive thrombocytosis occurring in these patients may be due to an inflammatory process related to gastrointestinal disorders or inflammation of the airways.

### *Patient treatments*

There are no specific protocols to guide treatment of children with COVID-19. Analyzing the medical records we found that 3 patients (2 males and 1 female) did not receive any therapy (they were asymptomatic and afebrile); 13 patients (9 males and 4 females) were treated only with paracetamol as needed; 11 patients were treated with paracetamol and antibiotics (4 males and 7 females); 3 males were treated only with antibiotics and 3 males only needed oxygen. Moreover, in addition to paracetamol and antibiotics, 2 females were treated with corticosteroid (they manifested bronchiolitis or cough); 1 female with anti-rheumatic drugs; 3 females with anti-inflammatory drugs and 2 females with heparin (they showed high values of inflammatory parameters and one of them was suffering from rheumatoid arthritis).

## Discussion

This study describes the characteristics of a sample of children admitted with COVID-19 to Bambino Gesù Children's Hospital of Rome (Italy) in the period from the end of February to May 2020, taking into account possible gender differences. In this retrospective study based on medical records data, we found that, compared to adults, the pediatric population gets less COVID-19 and had less severe clinical manifestations. Fever and cough were the dominant symptoms, while gastrointestinal symptoms were rare. Moreover, we found that all ages of childhood were susceptible to COVID-19: from a few days of life to 18 years. In particular, we found that females with COVID-19 were significantly ( $p = 0.04$ ) older than males and required more days of hospitalization ( $p = 0.01$ ). Interestingly, from medical records we found high LDH values in 2 males and 2 females and lymphopenia only in 5 females. Lactate dehydrogenase (LDH) is a cytoplasmic enzyme present in all major organ systems and is released into the peripheral blood after cell death. Increased serum LDH levels are associated with pulmonary disease such as obstructive diseases, microbial pulmonary diseases and interstitial lung diseases such as acute respiratory distress syndrome [11].

Furthermore, we found that inflammatory parameters such as CRP, ESR and fibrinogen were within normal ranges except for 3 males and 1 female that had increased CRP levels and 2 males and 1 female that had increased ESR levels.

During hospitalization some male patients developed mild thrombocytosis and exhibited increased inflammation evaluated in terms of high CRP values. CRP is an inflammatory marker that plays an important role in host defense against invading pathogens [12]. Sun et al., [13] shown that CRP was elevated in severe and critically adult patients with COVID-19.

It has been found that in virus mRNA positive patients a decline of LDH in the serum correlated with viral mRNA elimination, suggesting that constitutive decrease of LDH levels probably predict a favourable response. LDH can thus be used as indicators of disease progression [2].

Platelets have been increasingly recognized as an important component of the immune response to infections, an increase in their number above the normal range (thrombocytosis) has often been

considered a sign of normal inflammatory reaction. Compared to primary thrombocytosis, the reactive thrombocytosis is not associated with higher risk of cardiovascular or thrombotic events [14].

## Conclusions

Compared to other pediatric studies on COVID-19, this retrospective study, in addition to evaluate clinical characteristics of children infected with SARS-CoV-2 in Italy, takes into account the sex of patients. However, in order to have significant differences, the number of patients must be increased and further prospective studies should be conducted.

## Abbreviations

ACE2: Angiotensin-converting enzyme 2; CRP: C-reactive protein; EBV: Epstein-Barr virus; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; PLTs: Platelets; RBCs: Red blood cells; RT-PCR: Real-time reverse transcription; SIP: Italian Society of Paediatrics; SITIP: Italian Society of paediatric Infectious Diseases; WBCs: white blood cells.

## Declarations

### Acknowledgments

We thank all patients involved in the study. Authors reviewed and approved the final manuscript for publication.

### Author contributions

All authors have made substantial contributions to this work. I.T., R.V., A.V. and E.S. contributed equally to this work. Acquisition, analysis, or interpretation of data C.C., L.C. and E.S. Statistical analysis: C.C. and L.G. Concept and design: E.S., A.V., I.T., A. M. and R.V.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Ethics approval and consent to participate**

Ethics approval and written informed consent were waived due to the rapid emergence of this infectious disease.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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## Table

### Table 1 Features of patients at admission

| <b>Characteristics</b>                      | <b>Males<br/>(n = 21)</b> | <b>Females<br/>(n = 20)</b> | <b>p value</b> |
|---|---------------------------|-----------------------------|----------------|
| <b>Age, median (range)-years</b>            | 7 (range ≤ 1 - 18)        | 11 (range ≤ 1- 16)          | *p =0.04       |
| <b>Hospitalization, median (range)-days</b> | 7 (range 4 – 15)*         | 10 (range 5 – 22) *         | *p = 0.01      |
| <b>Signs and symptoms</b>                   |                           |                             |                |
| <b>Asyntomatic</b>                          | 2 (9.5%)                  | 1 (5%)                      |                |
| <b>Fever</b>                                | 13 (61.9%)                | 12 (60%)                    |                |
| <b>Cough</b>                                | 6 (28.6%)                 | 7 (35%)                     |                |
| <b>Vomit</b>                                | 1 (4.8%)                  | 2 (10%)                     |                |
| <b>Diarrhea</b>                             | 3 (14.3%)                 | 2 (10%)                     |                |
| <b>Convulsions</b>                          | 1 (4.8%)                  | 4 (20%)                     |                |
| <b>Headache</b>                             | 4 (19%)                   | 3 (15%)                     |                |
| <b>Coinfection</b>                          | 2 Rhinovirus (9.5%)       | 2 EBV (10%)                 |                |
| <b>Pneumonie</b>                            | 2 (9.5%)                  | 0                           |                |

For age and hospitalization days both median and range of values (from the lowest value to the highest value) detected in male and female patients are shown.

For signs and symptoms both patients number and percentage of patients are shown.