

# 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 identify sex differences in a pediatric population with COVI-19.

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

**Results:** In 37 patients (19 males and 18 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 older than males ( $p < 0.01$ ); required more days of hospitalization ( $p < 0.04$ ); needed of treatment with multiple drugs; and had higher serum lactate dehydrogenase values ( $p < 0.04$ ) than males. Conversely, males had, although not significant, higher values of C reactive protein and erythrocyte sedimentation rate than females.

**Conclusions:** Based on the data listed above sex differences were detected in an Italian pediatric population. 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 diarrhea, or they may be asymptomatic.

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 multicenter 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 analyzed [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 comorbidity.

Studies have reported a higher incidence of COVID-19 in males than in females in the adult population [10]. In order to identify sex differences in pediatric population, in this study we analyzed 37 patients admitted with COVID 19 to Bambino Gesù Children's Hospital of Rome (Italy) in the period from March to May 2020.

## Methods

# Study design and participants

Thirty-seven patients (19 males and 18 females), admitted with COVID 19 to Bambino Gesù Children's Hospital of Rome (Italy) in the period from March to May 2020, were enrolled in this retrospective cohort study. Mean age of patients was 9 years (range 1–16 years). Seven patients were under one year: 4 patients averaged 9 months and 3 patients averaged 14 days. All patients analyzed had contracted the infection from their parents.

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 were 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.

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 average values of a continuous variable between two groups we used the Student' T test, and to analyze relationship between two categorical variables we used Chi Squared test. Statistical analysis was performed by correlations with Pearson correlation coefficient. The level of significance was determined at  $p < 0.05$  and  $p < 0.01$ .

## Results

### Features of patients at admission

At admission patients presented: fever (24 patients), cough (11 patients), seizures (5 patients), headache (5 patients), vomit (2 patients), diarrhea (5 patients) and pneumonia (2 patient). Moreover, 2 patients were asymptomatic and 4 patients had co-infections: 2 with Rhinovirus and 2 with Epstein-Barr virus (EBV) (Table 1). Some of analyzed patients had a history of pneumonia, bronchiolitis, asthmatic bronchitis, gastroenteritis and convulsions.

Table 1  
Features of patients at admission

Characteristics	Males (n = 19)	Females (n = 18)	p value
Age ( <i>average</i> ):			
<i>Years</i>	6.9 (range 1–13)**	11 (range 2–16)	**p < 0.01
<i>Months</i>	7 (rang 6–8)**	11.5 (range 10–13)	**p < 0.012
<i>Days</i>	13 (rang 8–18)	15	
Hospitalization (days)	9 (range 4–15)*	12 (range 6–22)	*p < 0.04
Signs and symptoms			
Asyntomatic	2 (10.5%)	0	
Fever	13 (68.4%)	11 (55.5%)	
Cough	6 (31.6%)	7 (38.8%)	
Vomit	0	2 (11%)	
Diarrhea	3 (15.8%)	2 (11%)	
Convulsions	1 (5.3%)	4 (22%)	
Headache	2 (10.5%)	3 (16.7%)	
Coinfection	2 Rhinovirus (10.5%)	2 EBV (11%)	
Pneumonie	2 (10.5%)	0	

From the data reported in the medical record at the time of admission some sex differences have been detected. As shown in Table 1, females were older than males ( $p < 0.01$ ) and required more days of hospitalization ( $p < 0.04$ ). Laboratory tests also showed that males had, although not significantly, higher values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and platelets (PLTs) than females. The females, on the other hand, had higher values of WBC (not significant data) and lactate dehydrogenase (LDH) ( $p < 0.04$ ) than males (Table 2).

Table 2  
Laboratory findings of patients with COVID-19

	Normal range	Males (n = 19)	Females (n = 18)	p value
CRP (mg/dL)	< 0.5	0.7 (range 0.03–4.16)	0.2 (range 0.03–1.57)	p = 0.147
Fibrinogen (mg/dL)	212–433	331.4 (range 43–566)	340.4 (range 212–540)	p = 0.872
ESR (mm/h)	0–15	16 (range 10–25)	14 (range 14–49)	p = 0.824
WBC (10 <sup>3</sup> /uL)	4–13.5	6.685 (range 3.98–13.60)	7.81 (range 2.23–15.26)	p = 0.246
RBC (10 <sup>6</sup> /uL)	4–5.2	4.70 (range 3.13–5.47)	4.72 (range 3.90–7.0)	p = 0.796
PLT (10 <sup>3</sup> /uL)	150–450	285.42 (range 135–426)	237.68 (range 170–329)	*p < 0.03
LDH (U/L)	120–300	263 (range 188–349)	<b>318</b> (range 194–453)	*p < 0.04
Procalcitonin (ng/ml)	< 0.5	0.218 (range 0.04–0.44)	0.045 (range 0.02–0.08)	p = 0.126

As shown in Table 2, CRP and ESR values were higher than the normal range in males only. White blood cells (WBCs), red blood cells (RBCs) and PLTs count was within the normal range in both sexes. While LDH values were higher the normal range only in females (p < 0.04). Procalcitonin values, although they were within normal range, were higher in males than females, (not significant data).

## Patient characteristics during hospitalization

During hospitalization 5 males developed mild thrombocytosis (**Table 3**). Three of these patients were less than 1 year; 1 patient was 2 years old and 1 patient was 12 years old.

Table 3.  
Clinical parameters of males COVID-19 positives, which develop thrombocytosis during hospitalization

	Normal range	During hospitalization
PLT (10 <sup>3</sup> /uL)	150 -450	586 (range 492 – to 663)
RBC (10 <sup>6</sup> /uL)	4 – 5.2	5.13 (range 434 to 557)
CRP(mg/dL)	< 0.5	2.78 (range 0.1 to 4.81)
LDH (U/L)	120 - 300	364 (range 277 to 557)
<b>Correlations</b>	<b>Rho</b>	<b>P value</b>
PLT/RBC	0.9547	p = 0.1924
PLT/CRP	0.3667	p = 0.6333
PLT/LDH	0.3666	p = 0.6334

Moreover, in these patients thrombocytosis correlated positively with a high number of RBC (Rho = 0.9547; p < 0.1924) and with high plasmatic values of CRP (Rho = 0.3667; p < 0.6333) and LDH (Rho = 0.3666; p < 0.6334).

## Patient treatments

Of the 37 patients analyzed, 13 (9 males and 4 females) were treated only with paracetamol as needed; 11 with paracetamol and antibiotics (4 males and 7 females); 3 males only with antibiotics e 3 males only needed oxygen. Interestingly, compared to males, in addition to paracetamol and antibiotics, females were treated with more drugs: corticosteroid (2 patients); antirheumatic drugs (6 patients), nonsteroidal anti-inflammatory drugs (3 patients) and heparin (3 patients).

## 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 March to May 2020, taking into account 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 16 years. In particular, we found that females with COVID-19 were older than males (p < 0.01), required more days of hospitalization (p < 0.04) and treatment with multiple drugs. In fact, in addition to paracetamol and antibiotics they needed of corticosteroid, antirheumatic drugs, nonsteroidal anti-inflammatory drugs and heparin. Interestingly, some significant gender differences emerged from the medical records such as the LDH

values, which we found higher in females ( $p < 0.04$ ), and others not significant, but higher than the normal range values, such as CRP and ESR, that we found more expressed in males. In addition, compared to females, males had higher values of procalcitonin, even if the values were within the normal range (not significant data). Moreover, during hospitalization we found that some male patients developed mild thrombocytosis that correlated positively with an increase in the RBC number and an increase in the CRP and LDH values.

CRP is an inflammatory marker that plays an important role in host defense against invading pathogens [11]. Sun et al., [12] shown that CRP was elevated in severe and critically adult patients with COVID-19.

Lactate dehydrogenase (LDH) is a cytoplasmatic 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 [13].

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 highlights for the first time the differences related to sex during infection. The mechanisms underlying these differences are not yet known. Many detailed 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

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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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