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COVID-19 features in children and adolescents: a systematic review and pooled analysis

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Abstract

The purpose of the present study was to evaluate special features and probable correlations between symptoms, laboratory findings, treatment and outcomes of COVID-19 in children and adolescents, through a systematic review and pooled analysis. Following database (Pubmed, Google Scholar, Scopus and Embase) search, forty articles were considered eligible; a total of 2,971 confirmed pediatric COVID-19 patients were identified. Fever was reported in 55.1% of the cases while 28.4% were asymptomatic. Radiological signs of pneumonia were observed in more than half of the cases and in 40.7% of asymptomatic patients. Fever (sensitivity: 60.3%, specificity: 48.8%) showed the highest sensitivity, followed by cough (sensitivity 47.4%, specificity: 76.7%), rhinorrhea (sensitivity: 21.1%, specificity: 88.4%) and diarrhea (sensitivity: 10.3%, specificity: 88.4%) in differentiating cases with positive radiological signs for pneumonia. Compared to school age children, preschoolers (adjusted OR=6.01, 95%CI: 1.73-20.91) were more prone to pneumonia findings. Various combinations of treatments were used across studies, without following any strict guidelines. The majority of children (>90%) had full recovery. Fever seems to be the most frequent symptom in pediatric COVID-19. Asymptomatic cases were common but not the majority and a significant percentage had developed radiologic findings of pneumonia.

Keywords: COVID-19; SARS-CoV-2; pandemic; children; adolescent; fever; pneumonia

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Key Points Box

- Fever seems to be the most common symptom in pediatric patients with COVID-19.
- Pneumonia radiologic signs were observed even in asymptomatic pediatric patients.
- Preschoolers seem to be more prone to COVID-19 pneumonia findings.
- The majority of pediatric patients had full recovery.

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Introduction

Since December 2019, when there was the initial outbreak of the novel Coronavirus disease (COVID-19) (N. Zhu et al., 2020) and after its classification by the World Health Organization (WHO) as a pandemic, on 11 March, 2020, the world is struggling to solve the issues arising by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The accumulating knowledge and experience, resulting from the numerous cases around the globe, overwhelms the medical community with information that needs to be critically synthesized and presented in a reliable way, so it can be helpful for physicians. By May 1, 2020, there have been more than 3 million confirmed cases and around 233,000 deaths due to COVID-19 (WHO, 2020) . According to the literature, 0.9% of the recorded cases were aged less than 9 years, and 1.2% aged between 10 and 19 years (WHO, 2020).

Although there is a number of studies (Y. Hu et al., 2020) reviewing characteristics and symptoms of COVID-19, they are principally referring to adult population. Most review studies are management recommendations (Chen et al., 2020; Kanne, 2020; K. Shen et al., 2020), based on previously acquired knowledge on SARS caused by other known coronaviruses. There are only few studies or case reports referring exclusively to children and adolescents and describing with detail COVID-19 characteristics (Ludvigsson, 2020). This might be due to the fact that children and adolescents are more resilient to the disease (Ludvigsson, 2020), presenting with milder symptoms and have a very low mortality rate. Nevertheless, infants seem to be more prone to infections. The majority of deaths have been described in the age group between 10-19 years (Castagnoli et al., 2020). Thus, there is a need for a full description of the virus characteristics in children and adolescents, in order to guide early diagnosis and successful management.

Until now, there have been a few systematic reviews considering COVID-19 in children (Castagnoli et al., 2020; Chang et al., 2020; Ludvigsson, 2020). All of them have been based on a small number of reports, the majority of them deriving from China and often suffering from missing data. Castagnoli et al (2020) have highlighted the need for further studies and evaluation in a greater sample. The purpose of the present study is to perform a systematic review and pooled analysis in order to evaluate correlations between symptoms, laboratory findings, treatment and outcome of COVID-19 in children and adolescents. Specifically, this study aims to evaluate sensitivity, specificity, positive (PPV) and negative (NPV) predictive value of symptoms predicting pneumonia in radiological exams, as well as the association of pneumonia radiological findings with sex and age of children and adolescents.

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Materials, Methodologies and Techniques

Study Design

The present systematic review and pooled-analysis was performed according to the PRISMA guidelines. For this review, the Pubmed, Google Scholar, Scopus and Embase databases were searched for eligible studies for the period up to 15 April, 2020. The search was limited to this year's publications, as SARS-CoV-2 was first identified in December 2019. The following search algorithm was used: (Covid-19 OR SARS-CoV-19 OR SARS-CoV-2 OR "2019-nCoV" OR "novel coronavirus") AND (child OR children OR pediatric OR pediatrics OR kid OR kids OR youngster OR youngsters OR adolescent OR adolescents OR teen OR teens OR teenager OR teenagers). The references of all the articles that were considered eligible were also thoroughly checked.

Inclusion criteria

Only original research articles (cohort studies, cross-sectional studies, clinical studies, and case series) and case reports written in English were included. The eligible studies should refer to the symptoms, laboratory findings, treatment and infection outcome in children and adolescents exposed to SARS-CoV-2. In order to avoid misleading data, studies, where the infection was categorized into "types" without clearly mentioning the symptoms or several data were missing, were excluded. The reported patients should be under 18 years old with confirmed positive COVID-19 infection. No limitations concerning race, sex or journal were imposed. Overlapping populations and any type of unpublished material were excluded.

Eligibility assessment and risk of bias assessment

Two independent reviewers (E.P. and A.T.) performed the screening for eligibility of the retrieved studies. Concerning the risk of bias, the Newcastle-Ottawa Quality Scale (GA Wells, n.d.) was used to evaluate the quality of the included studies. Studies that did not meet the eligibility criteria, studies containing incomplete or irrelevant data, or studies with risk of bias were excluded.

Data extraction

The two reviewers (E.P. and A.T.) screened the studies that were considered eligible and extracted all relevant data. For each study the following parameters were collected: Author and year of publication, country where the study was conducted, study design, study period, number of specimens, mean age and age range, gender, health condition of patients before infection, symptoms caused by COVID-19, laboratory findings and final outcome of the disease. After the evaluation of data, results were tabulated. Case reports and case studies were categorized separately. All kinds of symptoms mentioned in every eligible study were

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recorded and infection severity was classified accordingly. Concerning laboratory findings, data were extracted about the total number of white blood cells (WBC), lymphocyte count, neutrophil count, C-reactive protein (CRP), procalcitonin (PCT), d-dimer and imaging findings; computed tomography (CT) scan and where not available, X-rays.

Statistical analysis

All data were recorded in the form of tables and were subjected to statistical analysis (pooled analysis). For categorical variables, frequency and percentage were calculated, while the mean, range and SD were calculated for continuous variables. To evaluate associations between nominal variables, Pearson's chi-squared test was implemented. Univariate and multivariate logistic regression analysis was performed to evaluate gender and age as potential risk factors of pneumonia radiological findings; odds ratios (ORs) and 95% confidence intervals (CIs) are reported. Kaplan-Meier curves were estimated, for time to negativity in nasal/throat swab and fecal tests, by age groups; log-rank tests were implemented to examine any differences. Statistical analysis was performed with STATA/SE version 13 statistical software (Stata Corp., College Station, TX, USA).

Results

The research in the databases retrieved 1,320 studies. After the removal of duplicates and the assessment of 401 items, a total of 40 articles (Zhang, 2020; Cai et al., 2020; Canarutto et al., 2020; Chan et al., 2020; CDC, 2020; Cui et al., 2020; Han et al., 2020; Z. Hu et al., 2020; Huang et al., 2020; Ji et al., 2020; Kam et al., 2020; Le et al., 2020; B. Li et al., 2020; W. Li et al., 2020; Li and Guo, 2020; Lin et al., 2020; H. Liu et al., 2020; M. Liu et al., 2020; Liu and Zhang, 2020; Y. Liu et al., 2020; Lou et al., 2020; Lu et al., 2020; Ma et al., 2020; Pan et al., 2020; Park and Han, 2020; Qian et al., 2020; Qiu et al., 2020; Robbins et al., 2020; Q. Shen et al., 2020; Sun et al., 2020; Tang et al., 2020; Wang et al., 2020; Wei et al., 2020; Xia and Shao, 2020; Xing et al., 2020; R. Xu et al., 2020; Y. Xu et al., 2020; Zhang et al., 2020; Zheng et al., 2020; L. Zhu et al., 2020) were considered eligible. The steps regarding the selection of eligible studies are presented in Figure 1.

Among them, 33 were case reports and case studies (118 patients), which presented detailed characteristics of the patients involved and seven were retrospective cohort studies (2,853 patients), a total of 2,971 patients. Low risk of bias was observed for cohort studies; however, the short follow-up periods could represent a factor compromising the quality of studies.

Case reports and case series

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Demographics

Data of case reports and case series (33 in total) are presented in Tables 1 and 2. Most studies derived from China, but there were also cases from Italy, Vietnam, USA and Singapore; a total of 118 children positive for SARS-CoV-2 were recorded [61 (51.7%) male and 57 (48.3%) female]. Their age ranged between 2 days and 18 years (mean age±SD 6.0±4.8 years). Only 13.5% of the sample were adolescents (>12 years). In the majority of patients (97.4%) the presence of SARS-CoV-2 RNA was detected by real-time fluorescence reverse-transcriptase polymerase-chain reaction (RT-PCR) either in nasopharyngeal and throat swabs or feces. Health status and co-morbidity were not clearly mentioned in most studies. Nevertheless, the majority seemed not to have other health problems. Only one case of a 2 month-old male with respiratory syncytial virus (RSV), one case of a 7 year old female with influenza, an 8 year old male with acute lymphoblastic leukemia, one case of a 10 month female with lacrimal sac dredge and one case of a 9 year old male with tonsillitis, were reported (Table 1).

Clinical Symptoms

The most frequently reported clinical finding of COVID-19 in children was fever (55.1% of the cases, 64/116), combined or not with other symptoms, while 28.4% (33/116) of the cases were asymptomatic. Fever was the only symptom in 19.8% of the cases (23/116). In a small percentage (16.4%, 19/116) fever was absent and the most commonly recorded symptoms and signs in these cases were cough, sore throat, diarrhea, vomiting, rhinorrhea, tachypnea and crackles, especially in infants. In two studies the clinical symptoms were not recorded (1.7%). It should be mentioned that all cases with tachypnea were admitted to intensive care unit (ICU) (Sun et al., 2020). Most asymptomatic cases were males (63.6%) and a marginal association emerged between asymptomatic status and male gender (Pearson's chi-squared=3.01, p=0.08). Clinical findings in children are represented in Figure 2A.

Laboratory and radiological findings

Detailed analysis of laboratory and radiological findings for each case is presented in Table 2. Some of the included studies did not provide laboratory or radiological findings (14.4%, 17/118). Less than 4% of cases presented deviations from the normal values of WBC, lymphocytes, neutrophils, CRP, PCT or d-dimer (Table 2). More than half of children (57.4 %, 58/101) had positive imaging findings (CT scans or X-rays) of unilateral or bilateral pneumonia. An interesting finding was that eleven of these children were asymptomatic. The

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rest of the cases had normal CT scans or X-rays (42.6%, 43/101), while 64.3% (27/42) presented variable symptoms. It is worth to mention that in 4 cases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated levels were recorded and in 22 cases prolonged viral shedding was observed in the feces of patients (Table 2).

Time to negativity in nasal/throat swab RT-PCR test (Table 1), by age groups, is shown in the Kaplan-Meier curve of Figure 3; no difference was shown regarding age groups (p=0.43, log-rank test) or gender (p=0.71, log-rank test). Similarly, no difference was noted in time to negativity of fecal tests by age (p=0.55) or gender (p=0.27).

Gender and age as risk factors of pneumonia

As noted above, 57.4% of the patients eventually developed radiological findings of pneumonia. Table 3 presents the results of univariate and multivariate logistic regression analysis examining risk factors for such radiological signs. Compared to children aged 5-11 years, those aged 1 to 4 years presented with 6-fold increased odds of pneumonia findings in CT or X-ray (adjusted OR=6.01, 95%CI: 1.73-20.91); adolescents also showed more frequently radiological images compatible with pneumonia (adjusted OR=2.52, 95%CI:0.79-8.03). Gender was not associated with pneumonia radiological findings (adjusted OR=0.75, 95%CI: 0.32-1.73).

Sensitivity and specificity of symptoms to predict pneumonia

The presence of symptoms predicted radiological pneumonia with a pooled sensitivity of 81.0% (47 out of 58 pneumonias, 95%CI: 68.6-90.1%) and a pooled specificity of 37.2% (16 out of 43 pneumonia-free cases, 95%CI: 23.0-53.3%). The pooled positive predictive value was 63.5% (95%CI: 51.5-74.4%), whereas the pooled negative predictive value was 59.3% (95%CI: 38.8-77.6%).

Among individual symptoms, fever (sensitivity: 60.3%, specificity: 48.8%) was most common, followed by cough (sensitivity 47.4%, specificity: 76.7%), rhinorrhea (sensitivity: 21.1%, specificity: 88.4%) and diarrhea (sensitivity: 10.3%, specificity: 88.4%). On the other hand, rhinorrhea and diarrhea showed the highest specificity in differentiating cases with positive radiological signs for pneumonia from negative ones.

Therapeutic management

Multiple combinations of treatments were used in every study (Figure 2B). In a small percentage (7.6%, 9/118) the treatment was not clearly recorded. A large number of cases,

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83.5% (91/109) received therapy, 24.2% (22/91) of them being asymptomatic. Only 16.35% (18/109) received no therapy at all. Most common treatments were symptomatic (antipyretics, oxygen therapy, vitamin C and Montelukast sodium chewable tablets). Alternative therapies were also applied, such as traditional Chinese medicine and oral probiotics. Antiviral therapy, such as lopinavir (9/109), ritonavir (9/109), ribavirin (14/109), oseltamivir (16/109), virazole (8/109), was mainly administered orally, while interferon was applied as spray inhalation or nebulization. Azithromycin was the most frequently used antibiotic (6/109), others being ceftriaxone (2/109), moxifloxacin (1/109), penicillin G (1/109). Patients in ICU received combined therapies together with hemopurification, enterostomy, transfusions of red blood cells, plasma and thrombocytes (1 case) and plasmapheresis (1 case). It should be pointed out that the majority of studies referred to therapies generally as "antiviral" or "antibiotics", without providing further details.

Outcome

Data was missing concerning the outcome of pediatric COVID-19 in 6 cases (5.1%). The majority of children had full recovery and presented no complications (105/112, 93.7%). Among them, 68.7% (77/112) were hospitalized, 24.6% (19/77) of them being asymptomatic. Only nine children (age range 2m to 1 year, mean±SD 7.3±5.8 years) were admitted to ICU (8.0%), among them the patient with acute leukemia, whose infection surprisingly was uncomplicated. No significant differences were observed between males and females concerning hospitalization (Pearson's chi-squared=1.06, p=0.30) and admission in ICU (Pearson's chi-squared=0.77, p=0.38). Radiological findings of pneumonia were associated strongly with admission to ICU (9/54 children with pneumonia were admitted to ICU vs. 0/41 without pneumonia, p=0.009, Fisher's exact test). Complications were recorded in 3.6% (4/112, 3 males and 1 female) of cases, leading to ICU admission. No deaths were reported.

Retrospective cohort studies

Demographic data about retrospective cohort studies (7 in total) are presented in Table 1. Studies, which did not provide clear data about COVID-19 characteristics in children and adolescents, were excluded. The study by Han et al. 2020 regardless of the small sample was included in this category as it did not provide personalized details about the patients and could not be considered as a case report. The majority derived from China, but there was also a study from the USA. Males represented the 56-63.9% while mean age ranged from 2 to 11 years. Comorbidities were observed more commonly in these studies, in low percentages

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though, except for the series of Xia et al. 2020 (35%). Symptoms, laboratory findings, treatments, and outcomes are summarized in Table 2. Fever was reported in the greater part of cases (ranging from 6.3% to 71.4%), while radiological findings of pneumonia were also observed in most of them (rate ranging from 52.8% to 72.7%). Other laboratory findings were relatively normal, expect for the series of Xia et al., 2020, where CRP was elevated in 35% of the cases and procalcitonin in 80%; in this study, other pathogens were also identified, such as *Mycoplasma pneumoniae* (12%), influenza virus type B (8%), and Enterobacter aerogenes (8%). Diarrhea was also a common symptom with rates up to 57.1% while Han et al. 2020 reported that digestive tract symptoms were more common in children than adults (p=0.012). Additionally elevated AST and ALT levels were also recorded as in case series (Table 2). There were a few data about treatment (3 out of 7 studies), with antiviral therapy and interferon being the commonest, with rates up to 100%. No complications were observed in the cohort studies but one case of death was reported, in a 10-month-old child with intussusception who presented multi-organ failure and died 4 weeks after admission (Lu et al., 2020); the gender or other details of the deceased child were not reported. Three more deaths are recorded in the case series from the USA but COVID-19 was not confirmed as the likely cause of death, without providing further information about the latter. Admission to ICU also showed a low rate (0.6-1.8%), while almost all patients presented full recovery.

Discussion

COVID-19 targets mostly adults, with the majority of the cases being in the age group between 30 and 79 years old (Chang et al., 2020). Children and adolescents under 18 years old represent less than 5% of cases, a lot of them being asymptomatic (Ludvigsson, 2020). The pandemic led to a great number of reports, mostly referring to adults and presenting insufficient data about children. The descriptive and detailed analysis of pediatric COVID-19 is essential in order to address special treatment needs and avoid complications in children and adolescents.

A total of 33 case reports and small case series were retrieved in this systematic review. These studies provided sufficient patient data and were subjected to pooled analysis. Additionally, a total of 7 cohort studies were identified, which did not present data at the individual level, but their findings confirmed the results of case reports. Considering the 33 studies, the pooled sample presented a wide age range (between 2 days and 18 years); on the

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other hand, in cohort studies male gender slightly predominated (56.0-63.9%), while mean age ranged from 2 to 11 years.

According to our systematic review and pooled analysis of 33 studies, fever was the most frequent symptom in pediatric patients with an incidence of 54.2% Asymptomatic patients were not rare but not the majority of reported cases (28.4%, 33/116), as described in previous studies (Castagnoli et al., 2020; Chang et al., 2020; Ludvigsson, 2020). Males slightly predominated in asymptomatic cases (p=0.08), which was an interesting finding, as in adults male sex is considered a risk factor. Diarrhea was the most frequent symptom (11%) after upper respiratory tract symptoms, a pattern that confirms previous reports (Castagnoli et al., 2020; Chang et al., 2020; Ludvigsson, 2020); accordingly, Han et al. 2020 reported a greater prevalence of digestive tract symptoms in children, compared to adults.

A high prevalence of radiological findings of pneumonia was noted in cohort studies, ranging between 52.8% and 72.7% (Table 2). Such findings were also observed in more than half of case reports, where the pooled analysis revealed that 40.7% of asymptomatic cases had pneumonia on radiologic exams (pooled NPV=59.3% (95%CI: 38.8-77.6%). This is an important observation which raises the question whether all positive pediatric patients need radiologic examination, a strategy that has been proposed by other authors as well (Ludvigsson, 2020; Shen and Yang, 2020), but not widely adopted, as COVID-19 pneumonia seems to be mild in children.

The presence of radiologic pneumonia was related to age, as preschoolers were found to develop pneumonia findings more frequently, at 6-fold increase in odds of positive radiological signs of pneumonia. Fever (sensitivity: 60.3%, specificity: 48.8%) showed the highest sensitivity, followed by (sensitivity 47.4%, specificity: 76.7%), rhinorrhea (sensitivity: 21.1%, specificity: 88.4%) and diarrhea (sensitivity: 10.3%, specificity: 88.4%) in the diagnosis of radiologic pneumonia. Additionally, radiological findings of pneumonia were strongly associated with admission to ICU.

Other laboratory findings did not seem to be affected, in the vast majority of case reports and case series. The findings in cohort studies were similar, except for the series of Xia et al. 2020, which presented high levels of co-infection with other pathogens. Elevated AST and ALT levels were also recorded in both sets of studies, a fact that should be taken into consideration.

An interesting remark pertains to the fact that administered treatments did not seem to follow any published recommendations (Shen and Yang, 2020); different drugs were administered, regardless of the presence of pneumonia radiological signs or not. Interferon in

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the form of nebulization was widely administered in both types of studies; nevertheless, none of the retrieved studies clarified whether the treatment had any effect upon the infection outcome. No complication or delay in the recovery was recorded in cases where no treatment was given. Additionally, no clear guidelines for hospitalization existed, as even asymptomatic children were hospitalized (24.6%, case series). About 90% of the cases recovered completely regardless of hospitalization or treatment administration. Thus, there is a need of further longitudinal studies, considering therapy management and guidelines.

Even if pediatric patients seem to have better outcomes, a small percentage was admitted in ICU (8% in case reports/case series and 0.6%-1.8% in cohort studies). Most recently, eight children's cases were described in the UK and were transferred in ICU presenting with toxic shock syndrome - Kawasaki-like inflammatory syndrome; four of them had confirmed family exposure to the novel coronavirus but only two had positive exams (one post-mortem) (Riphagen et al., 2020). Additionally, an increase was observed in inflammatory syndromes and Toxic Shock Syndrome (TSS) in many countries, not directly linked to COVID-19, but raising awareness (ECDPC, 2020). Two of the ICU patients in our systematic review (Sun et al., 2020) were reported with septic shock syndrome. No complications were observed in the cohort studies and full recovery was mentioned in both case series and cohort studies. It should be pointed out that all patients who required ICU admission in the case series presented with tachypnea, which should be taken into consideration as a manifestation of more severe disease. Therefore, pediatricians should keep in mind that severe complications of COVID-19 are rare but may occasionally occur.

None of the included case reports and case studies has recorded any deaths. Only one case of death was retrieved from the cohort studies, referring to a 10-month-old child with intussusception (Lu et al., 2020). Three deaths were reported in the series from USA (CDC, 2020) but COVID-19 was not confirmed as the likely cause of death. Infection fatality ratio of COVID-19 under 9 year old is estimated to be 0.00016% and 0.00695% in age groups between 10 and 19 year old (Verity et al., 2020).

Most studies from China followed a classification severity system with five types and a modified one with four types, according to officially published guidelines in China. Han et al, 2020 additionally classified pneumonia into mild (mild pneumonia, asymptomatic infection) and severe. No other specific severity stratification systems for children and adolescents with COVID-19 were recorded in the rest of the studies.

Commenting on the limitations of the study, due to the emergency of the subject, the research period was brief, which was also the problem in previous studies (Castagnoli et al., 2020).

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The majority of reports did not provide detailed data, leading to exclusion and reduction of the sample size. Numerous case series and studies were published at the outset of the pandemic and the case of overlapping populations is possible. Language restrictions may also have limited the pool of eligible reports. Another inherent limitation of the pooled analysis pertains to the fact that published case reports/case series are subject to considerable selection bias, as they may represent a subset of more severe cases, seeking treatment in health services.

On the other hand, strengths of this systematic review and pooled analysis include the large study sample, the separation of case reports and small case series from larger cohort studies, and the inclusion of a substantial proportion of cases from Europe and the USA, as previous reviews contained almost exclusively reports from China.

In conclusion, this systematic review and pooled analysis, highlighted fever as the most frequently reported clinical finding in pediatric COVID-19, followed by cough, rhinorrhea and diarrhea. Asymptomatic cases although not rare, were not the majority, whereas male gender was slightly associated with asymptomatic status. Positive radiological findings of pneumonia were recorded in more than half of the patients with higher prevalence in preschoolers. An important finding was that 40.7% of asymptomatic cases had pneumonia on radiologic examimation. Another interesting observation was that rhinorrhea and diarrhea present high specificity in cases with positive radiological findings, while tachypnea should be considered as a factor of severity. Concerning the outcome, our study confirms the knowledge that pediatric patients have full recovery and rarely present complications, while there is need for a thorough reassessment of treatment and management guidelines.

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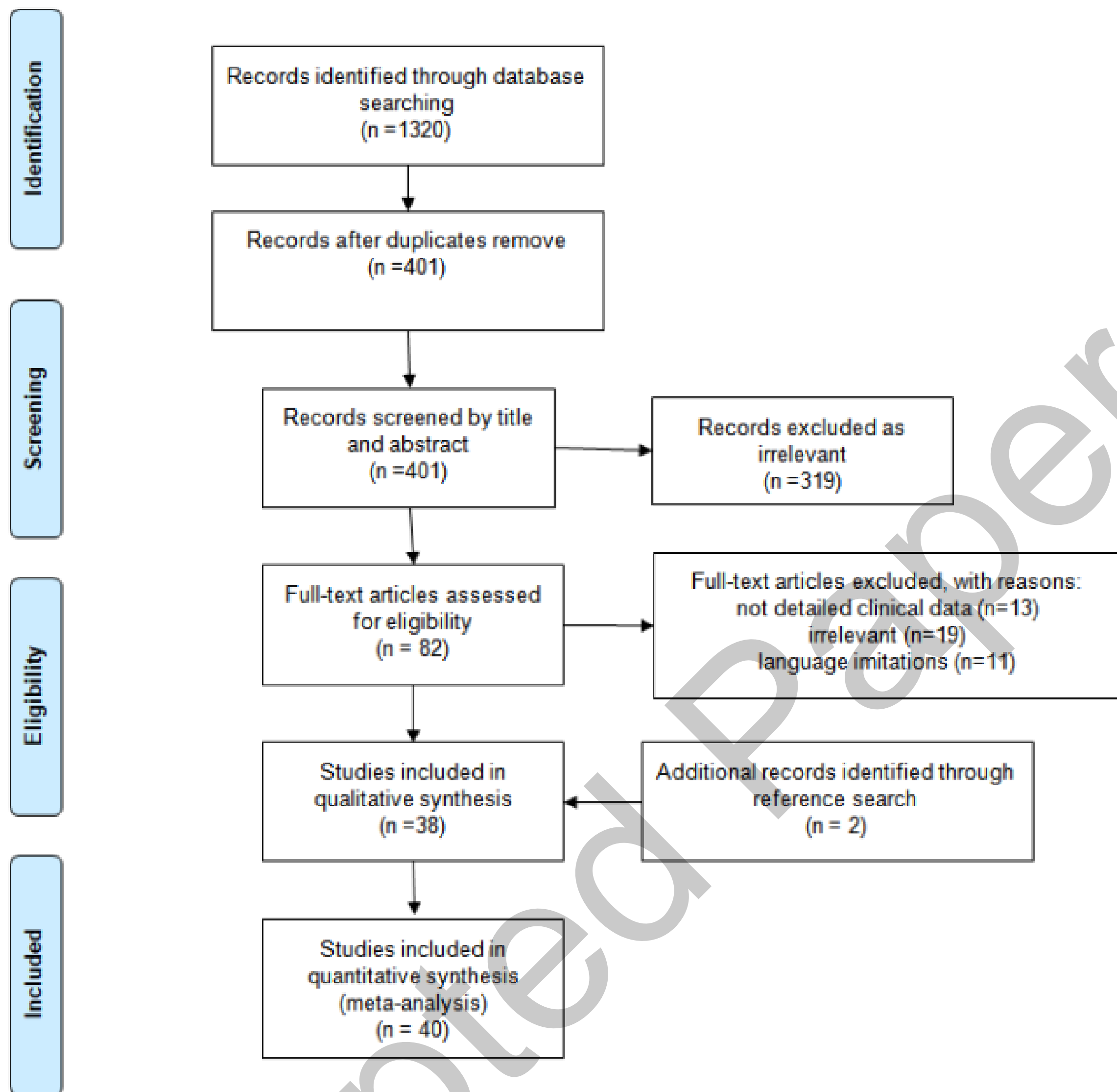

Figure 1: Prisma flow diagram.

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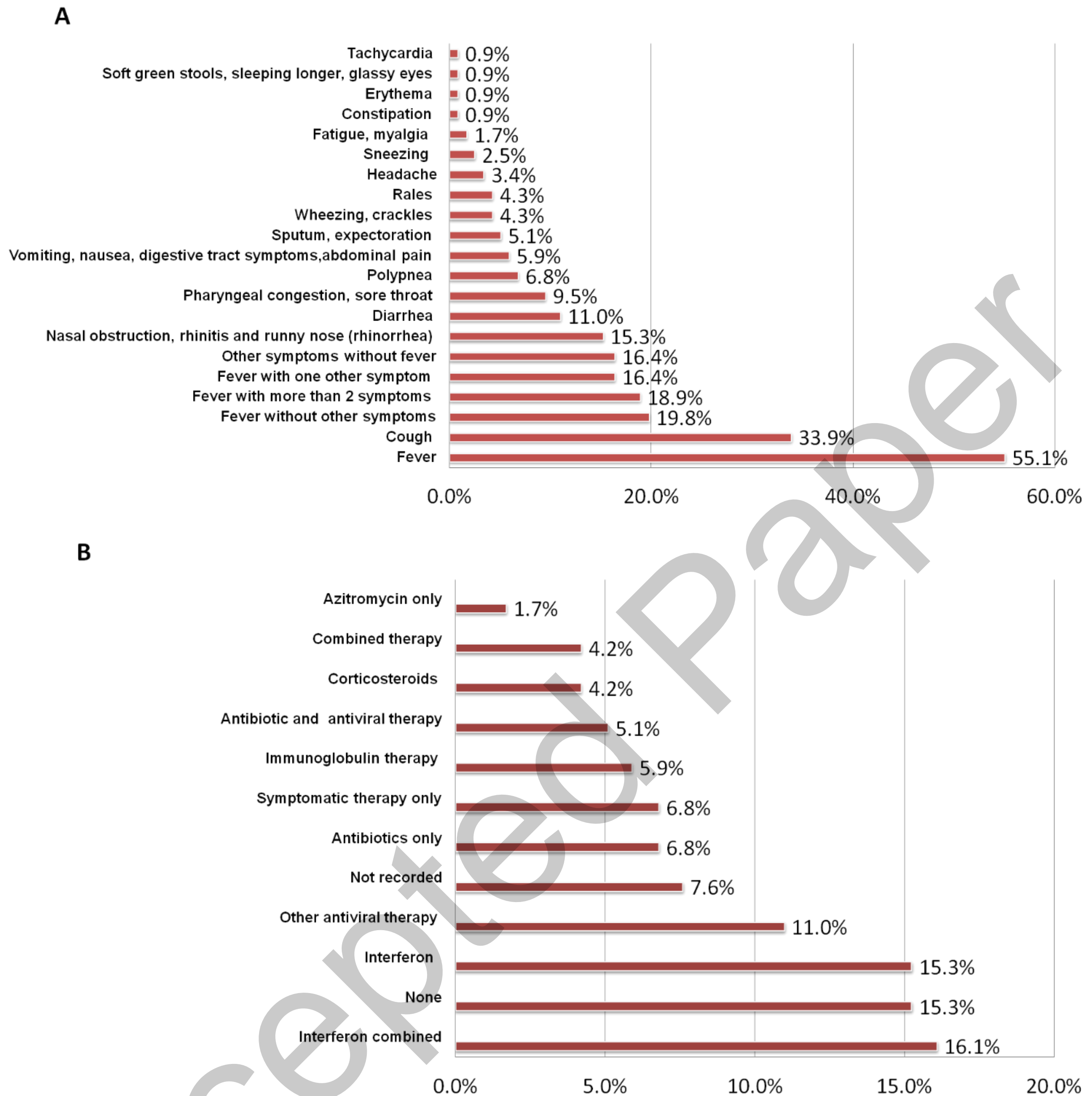

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Figure 2: Diagrams. A. Symptoms in children positive with Covid-19. B. Distribution of administered drugs and treatments.

**Combined therapy: Antibiotic treatment and antiviral treatment and interferon (spray inhalation or nebulization) and glucocorticoids and intravenous immunoglobulin and symptomatic treatment*

**Corticosteroids: alone or combined with other therapies*

**Immunoglobulin therapy: alone or with antivirals and antibiotics or interferon (spray inhalation or nebulization)*

**Other antiviral therapy such as lopinavir, ritonavir, ribavirin, oseltamivir, virazole*

**Interferon: spray inhalation or nebulization*

**Interferon combined: spray inhalation or nebulization, together with antibiotic, other antiviral or symptomatic therapy*

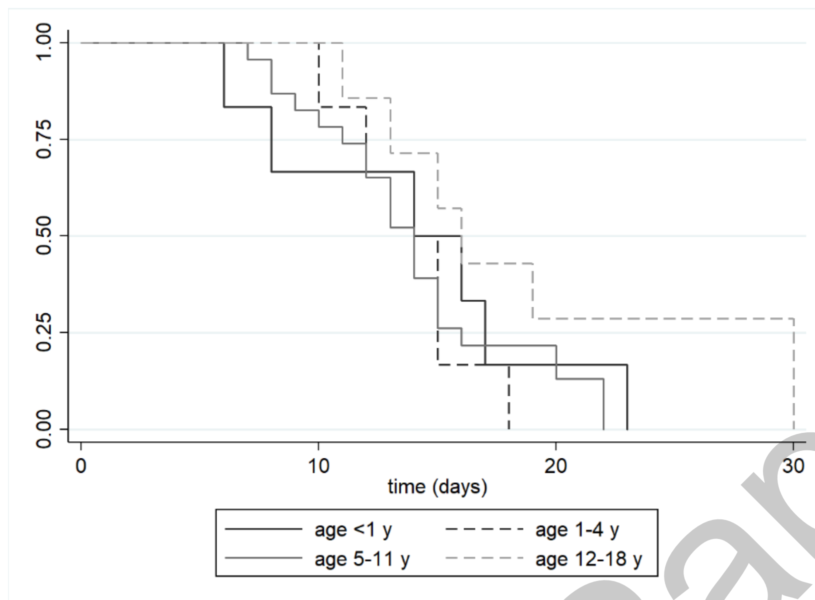

Figure 3: Kaplan Meier curve. Kaplan Meier estimates for negativity in nasal/throat swab RT-PCR test.

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Table 1: Eligible studies - demographic characteristics

CASE SERIES AND CASE REPORTS									
AUTHOR	COUNTRY	STUDY DESIGN	STUDY PERIOD	N		GENDER	AGE	TEST FOR COVID	COMORBIDITIES
Xu et al., 2020	China	case series	27/1/2020	2	patient 1	m	10y	RT-PCR and sputum samples	not recorded
					patient 2	f	18y	RT-PCR and sputum samples	not recorded
Xing et al.,2020	china	case series	17/1/20-23/2/20	3	patient 1	m	1.5y	RT-PCR, negative in 15 days	no
					patient 2	m	5y	RT-PCR, negative in 13 days	no
					patient 3	f	6y	RT-PCR, negative in 10 days	no
Canarutto et al., 2020	Italy	case report	Not recorded	1	patient 1	m	32 days	pharyngeal swab	no
Lin et al., 2020	China	case report	Not recorded	1	patient 1	f	7y	RT-PCR, negative in 20 days	influenza
Zhang et., 2020	China	case report	3-17/2/20	3	patient 1	m	9y	RT-PCR, negative in 14 days	tonsillitis
					patient 2	m	6y	RT-PCR, negative in 11 days	no
					patient 3	m	8y	RT-PCR, negative in 7 days	no
Liu et al., 2020	China	case report	Not recorded	5	Patient 1	m	5y	RT-PCR	not recorded
					Patient 2	m	2y	RT-PCR	not recorded
					Patient 3	f	7 m	RT-PCR	not recorded
					Patient 4	m	9y	RT-PCR	not recorded
					Patient 5	m	13y	RT-PCR	not recorded
Zhu et al. 2020	China	case series	24/1/20-22/2/20	10	patient 1	m	1,7y	RT-PCR	not recorded
					patient 2	f	9y	RT-PCR	not recorded
					patient 3	f	11y	RT-PCR	not recorded
					patient 4	m	6y	RT-PCR	not recorded
					patient 5	m	10y	RT-PCR	not recorded
					patient 6	m	4y	RT-PCR	not recorded
					patient 7	f	7y	RT-PCR	not recorded
					patient 8	m	14y	RT-PCR	not recorded
					patient 9	f	12y	RT-PCR	not recorded
					patient 10	f	17y	RT-PCR	not recorded
Shen et al., 2020	China	case series	8/1-19/2/20	9	patient 1	f	1y	RT-PCR negative in 14 days	not recorded
					patient 2	f	2y	RT-PCR negative in 10 days	not recorded
					patient 3	m	8y	RT-PCR negative in 20 days	not recorded
					patient 4	f	8y	RT-PCR remained positive	not recorded
					patient 5	m	8y	RT-PCR negative in 9 days	not recorded
					patient 6	f	9y	RT-PCR negative in 14 days	not recorded
					patient 7	f	9y	RT-PCR remained positive	not recorded
					patient 8	f	11y	RT-PCR negative in 13 days	not recorded
					patient 9	m	12y	RT-PCR remained positive	not recorded
Ma et al., 2020	China	case series		6	patient 1	f	8,1y	RT-PCR	not recorded
					patient 2	m	3,7y	RT-PCR	not recorded
					patient 3	f	2,9y	RT-PCR	not recorded
					patient 4	m	11 m	RT-PCR	not recorded

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					patient 5	f	9 y	RT-PCR	not recorded
					patient 6	f	3,7y	RT-PCR	not recorded
Le at al., 2020	Vietnam	case report	11/2/2020	1	patient 1	f	3 m	RT-PCR	no
An et al., 2020	China	case report	not recorded	1	patient 1	f	3y	RT-PCR	not recorded
Lou et al., 2020	China	case report	not recorded	3	patient 1	f	6y	RT-PCR	not recorded
					patient 2	f	8y	RT-PCR	not recorded
					patient 3	m	6m	RT-PCR	not recorded
Qian et al., 2020	China	case report	21/1-5/2/20	1	patient 1	f	13m	RT-PCR	no
Park et al., 2020	Korea	case report	18/2/2020	1	patient 1	f	10y	RT-PCR, negative in 13 days	no
Liu et al., 2020	China	case report	21/1/2020	1	patient 1	m	10y	RT-PCR	no
Huang et al., 2020	China	case report	25-27/1/20	1	patient 1	f	16y	RT-PCR	no
Sun et al. 2020	China	case series	Not recorded	8	patient 1	m	8y	RT-PCR	acute lymphoblastic leukemia
					patient 2	f	10 m	RT-PCR	Lacrimal sac dredge
					patient 3	m	1,1y	RT-PCR	not recorded
					patient 4	m	2 m	RT-PCR	not recorded
					patient 5	m	2,1y	RT-PCR	not recorded
					patient 6	f	15y	RT-PCR	not recorded
					patient 7	m	13.11y	RT-PCR	not recorded
					patient 8	m	13.5y	RT-PCR	not recorded
Li et al. 2020	China	case report	Not recorded	2	patient 1	m	4y	RT-PCR	not recorded
					patient 2	f	4y	RT-PCR	not recorded
Robbins et al. 2020	USA	case report	Not recorded	1	patient 1	m	58d	not recorded	No
Chan et al 2020	China	case report	Not recorded	1	patient 1	m	10y	RT-PCR	No
Ji et al. 2020	China	case report	Not recorded	2	patient 1	m	15y	Oropharyngeal swab tests	No
					patient 2	m	9y	Oropharyngeal swab tests	No
Cui et al. 2020	China	case report	Not recorded	1	patient 1	f	55d	RT-PCR	No
Wang et al. 2020	China	case report	Not recorded	1	patient 1	m	2d	RT-PCR, negative in 16 days	No
Hu et al. 2020	China	case report	Not recorded	6	patient 1	f	10y	RT-PCR, negative in 12 days	not recorded
					patient 2	m	5y	RT-PCR	not recorded
					patient 3	f	8y	RT-PCR	not recorded
					patient 4	f	14y	RT-PCR, negative in 13 days	not recorded
					patient 5	m	6y	RT-PCR	not recorded
					patient 6	m	15y	RT-PCR, negative in 11 days	not recorded
Liu et al. 2020	China	case report	Not recorded	4	patient 1	f	5y	RT-PCR	No
					patient 2	m	11m	RT-PCR	No
					patient 3	f	9y	RT-PCR	No

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					patient 4	m	2m	RT-PCR	RSV positive
Pan et al. 2020	China	case report	Not recorded	1	patient 1	m	3y	RT-PCR	not recorded
Kam et al. 2020	Singapore	case report	Not recorded	1	patient 1	m	6m	RT-PCR negative in 17 days	No
Liu et al. 2020	China	case series	Not recorded	6	patient 1	f	3y	RT-PCR	No
					patient 2	f	7y	RT-PCR	No
					patient 3	f	3y	RT-PCR	No
					patient 4	m	1y	RT-PCR	No
					patient 5	f	3y	RT-PCR	No
					patient 6	m	4y	RT-PCR	No
Li et al. 2020	China	case report	Not recorded	5	patient 1	m	1y5m	RT-PCR	not recorded
					patient 2	f	10m	RT-PCR	not recorded
					patient 3	m	3y	RT-PCR	not recorded
					patient 4	m	4y	RT-PCR	not recorded
					patient 5	m	6y	RT-PCR	not recorded
Wei at al., 2020	China	case series	8/12/2019-6/2/20	9	patient 1	f	9m	RT-PCR	not recorded
					patient 2	f	11 m	RT-PCR	not recorded
					patient 3	f	8 m	RT-PCR	not recorded
					patient 4	m	10m	RT-PCR	not recorded
					patient 5	f	7m	RT-PCR	not recorded
					patient 6	f	1 m	RT-PCR	not recorded
					patient 7	f	3 m	RT-PCR	not recorded
					patient 8	f	3m	RT-PCR	not recorded
					patient 9	m	6m	RT-PCR	not recorded
Tang et al. 2020	China	case report	30/1/2020		patient 1	m	10y	RT-PCR	No
Xu et al. 2020	China	single-center prospective observational study	22/1/20-20/2/20	10	patient 1	m	6y	RT-PCR, negative in 16 days	not recorded
					patient 2	f	12.6 y	RT-PCR, negative in 16 days	not recorded
					patient 3	f	7 y	RT-PCR, negative in 15 days	not recorded
					patient 4	m	13.8y	RT-PCR, negative in 15 days	not recorded
					patient 5	m	14m	RT-PCR, negative in 15 days	not recorded
					patient 6	m	3.4y	RT-PCR, negative in 18 days	not recorded
					patient 7	f	15.5y	RT-PCR, negative in 19 days	not recorded
					patient 8	m	13.5y	RT-PCR, negative in 30 days	not recorded
					patient 9	f	2m	RT-PCR, negative in 23 days	not recorded
					patient 10	m	2y	RT-PCR, negative in 14 days	not recorded
Cai et al. 2020	China	case series report	19/1/20-3/2/20	10	patient 1	m	7y	RT-PCR, negative in 12 days	not recorded
					patient 2	f	11 y	RT-PCR, negative in 22 days	not recorded
					patient 3	f	11 y	RT-PCR, negative in 8 days	not recorded
					patient 4	m	9y	RT-PCR, negative in 8 days	not recorded
					patient 5	f	7m	RT-PCR, negative in 6 days	not recorded
					patient 6	f	6y	RT-PCR, negative in 15 days	not recorded
					patient 7	f	3m	RT-PCR, negative in 8 days	not recorded
					patient 8	f	4y	RT-PCR, negative in 12 days	not recorded
					patient 9	m	8y	RT-PCR, negative in 14 days	not recorded

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					patient 10	m	5y	RT-PCR, negative in 15 days	not recorded
RETROSPECTIVE COHORT STUDIES									
AUTHOR	COUNTRY	STUDY DESIGN	STUDY PERIOD	N	N OF MALES	MEAN AGE-AGE RANGE		COMORBILITIES	TEST FOR COVID
CDC COVID-19 Response Team	USA	retrospective analysis	12/2/20-2/4/20	2572	1408/2490 (56.5%)	11	0-17	chronic lung disease (including asthma) (11.6%), cardiovascular disease (7.2%), and immunosuppression (2.9%).	not recorded
Li et al., 2020	China	Cohort (retrospective)	16/1-14/3/20	22	12/22 (54.5%)	8	-	not recorded	not recorded
Han et al., 2020	China	Cohort (retrospective)	31/1-16/2/20	7	4/7 (57.1%)	1.3	2 m to 13y	no	not recorded -93.8% laboratory confirmed
Qiu et al., 2020	China	cohort	17/1-1/3/20	36	23/36 (63.9%)	8.3	0 to 16y	not recorded	RT-PCR
Zheng et al., 2020	China	retrospective	1-10/2/20	25	14/25 (56%)	3	3m-14y	1 with congenital heart diseases, malnutrition, and suspected hereditary metabolic diseases and 1 with congenital heart disease	virus nucleic acid test.
Lu et al. 2020	China	retrospective	28/1/20-26/2/20(clinical outcomes upto 8/3)	171	104/171 (60.8%)	6.7	<1 – 15y	3 ICU patients; all had coexisting conditions (hydronephrosis, leukemia [for which the patient was receiving maintenance chemotherapy], and intussusception	Nasopharyngeal or throat swabs(World Health Organization. Country & technical guidance)
Xia et al. 2020	China	retrospective analysis	23/1/20-8/2/2020	20	13/20 (60.8%)	2y+1.5m	1d - 14y+7m	atrial septal defect surgery(2/20), epilepsy as a sequela of previous viral encephalitis(1/10) - sinus tachycardia 1/20, atrial arrhythmia 1/20, first-degree atrioventricular block, atrial and ventricular premature beat 1/20, incomplete right bundle-branch block 1/20	pharyngeal swab COVID-19 nucleic acid test

Table 2: Patients' characteristics – gender, age, symptoms, laboratory findings, treatment, outcome.

CASE SERIES AND CASE REPORTS								
AUTHOR	N		GENDER	AGE	SYMPTOMS	LABORATORY FINDINGS	TREATMENT	OUTCOME
Xu et al., 2020	2	patient 1	m	10y	asymptomatic	CRP increased, CT: normal	Interferon inhalation, Ribavirin, Traditional chinese medicine	no complications
		patient 2	f	18y	asymptomatic	CRP increased, CT: normal	Interferon inhalation, Ribavirin, Traditional chinese medicine	no complications
Xing et al., 2020	3	patient 1	m	1.5y	fever	WBC normal, neutrophil increased, lymphocytes increased, PLT increased, CRP normal, PCT normal,	Interferon inhalation, Ribavirin, Traditional chinese medicine	hospitalized, no complications

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						d-dimer elevated, Xray: bilateral lung markings, CT: ground glass opacity right, prolonged viral shedding in feces for 23 days		
		patient 2	m	5y	fever, cough, runny nose, abdominal pain, diarrhea	WBC normal, neutrophil normal, lymphocytes increased, PLT increased, CRP normal, PCT normal, d dimer normal, CT: consolidation changes left, prolonged viral shedding in feces for 33 days	Interferon inhalation, Ribavirin, Traditional chinese medicine	hospitalized, no complications
		patient 3	f	6y	fever	WBC normal, neutrophil normal, lymphocytes increased, mild neutropenia, PLT normal, CRP increased, PCT normal, d-dimer normal, X-ray: patchy shadows left	Interferon inhalation, Ribavirin, Traditional chinese medicine	hospitalized, no complications
Canarutto et al., 2020	1	patient 1	m	32 days	fever, rhinitis, cough	monocytosis, CRP negative, CT: normal	none	hospitalized, no complications
Lin et al., 2020	1	patient 1	f	7y	nasal obstruction	normal, Influenza A(+)	symptomatic, interferon nebulization, oseltamivir	hospitalized, no complications
Zhang et., 2020	3	patient 1	m	9y	fever, nasal obstruction, runny nose and digestive tract symptoms	CRP increased, WBC increased, lymphocytes normal, PLT normal, PCT normal, d-dimer normal, liver function normal, CT: thin strips of anterior medial basal segment, prolonged viral shedding in feces for 17 days	ceftriaxone,interferon atomization, vitamin C, oral Chinese medicine treatment.	hospitalized, no complications
		patient 2	m	6y	cough, expectoration and wheezing	WBC normal, lymphocytes normal, PLT normal, CRP normal, PCT normal, d dimer normal, liver function normal, FIB decreased, CT: ground-glass opacity right, prolonged viral shedding in feces for 16 days	ribavirin antiviral treatment, interferon atomization, vitamin C, oral Chinese medicine treatment.	hospitalized, no complications
		patient 3	m	8y	fever, nasal obstruction, runny nose and digestive tract symptoms.	WBC normal, lymphocytes normal, PLT normal, CRP normal, PCT normal, d- dimer normal, liver function normal, FIB decreased, CT: ground-glass opacity left	interferon atomization, vitamin C, oral Chinese medicine treatment.	hospitalized, no complications
Liu et al., 2020	5	Patient 1	m	5y	fever, dry cough and	blood test normal, CT: ground-glass	ribavirin and interferon	hospitalized, no

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					diarrhea	opacities left		complications
		Patient 2	m	2y	asymptomatic	blood test normal, CT: ground-glass opacities bilateral	ribavirin and interferon	hospitalized, no complications
		Patient 3	f	7 m	dry cough, fever < 38°c	CT: ground-glass opacities left	interferon	hospitalized, no complications
		Patient 4	m	9y	asymptomatic	CT: ground-glass opacity right	ribavirin and interferon	hospitalized, no complications
		Patient 5	m	13y	asymptomatic	normal	ribavirin and interferon	hospitalized, no complications
Zhu et al. 2020	10	patient 1	m	1.7y	asymptomatic	blood test normal, CT: positive, unilateral pneumonia	none	hospitalized, no complications
		patient 2	f	9y	cough	blood test normal, CT: normal	oxygen therapy, antiviral therapy	hospitalized, no complications
		patient 3	f	11y	cough	blood test normal, CT: unilateral pneumonia	antibiotic therapy	hospitalized, no complications
		patient 4	m	6y	asymptomatic	blood test normal, CT: normal	none	hospitalized, no complications
		patient 5	m	10y	fever, cough	blood test normal, CT: normal	none	hospitalized, no complications
		patient 6	m	4y	asymptomatic	blood test normal, CT: normal	none	hospitalized, no complications
		patient 7	f	7y	fever	blood test normal, CT: normal	antiviral	hospitalized, no complications
		patient 8	m	14y	fever, headache	blood test normal, CT: bilateral pneumonia	antiviral	hospitalized, no complications
		patient 9	f	12y	asymptomatic	blood test normal, CT: unilateral pneumonia	antiviral	hospitalized, no complications
		patient 10	f	17y	fever, headache	blood test normal, CT: bilateral pneumonia	antiviral	hospitalized, no complications

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Shen et al., 2020	9	patient 1	f	1y	asymptomatic	WBC increased, lymphocytes increased, ESR and CRP normal, CT: normal	antiviral therapy (lopinavir/ritonavir), azithromycin	hospitalized, no complications
		patient 2	f	2y	fever	WBC normal, lymphocytes normal, ESR increased, CRP increased, CT: Small ground-glass opacity	antiviral therapy (lopinavir/ritonavir), azithromycin, methylprednisolone	hospitalized, no complications
		patient 3	m	8y	fever	normal	antiviral therapy (lopinavir/ritonavir), azithromycin	hospitalized, no complications
		patient 4	f	8y	fever, diarrhea	normal	antiviral therapy (lopinavir/ritonavir)	hospitalized, no complications
		patient 5	m	8y	diarrhea	WBC normal, lymphocytes normal, ESR increased, CRP normal, CT: normal	antiviral therapy (lopinavir/ritonavir)	hospitalized, no complications
		patient 6	f	9y	sore throat	WBC normal, lymphocytes, normal, ESR increased, CRP normal, CT: small ground-glass opacity	antiviral therapy (lopinavir/ritonavir)	hospitalized, no complications
		patient 7	f	9y	asymptomatic	normal	antiviral therapy (lopinavir/ritonavir), azithromycin	hospitalized, no complications
		patient 8	f	11y	cough, temp < 37.2°c	WBC normal, lymphocytes, normal, ESR increased, CRP normal, CT: normal	antiviral therapy (lopinavir/ritonavir)	hospitalized, no complications
		patient 9	m	12y	fever < 38°c	normal	antiviral therapy (lopinavir/ritonavir), azithromycin	hospitalized, no complications
Ma et al., 2020	6	patient 1	f	8.1y	fever	not recorded	not recorded	no complications
		patient 2	m	3,7y	asymptomatic	not recorded -prolonged viral shedding in feces for 4 weeks	not recorded	no complications
		patient 3	f	2,9y	asymptomatic	not recorded -prolonged viral shedding in feces for 4 weeks	not recorded	no complications
		patient 4	m	11 m	asymptomatic	not recorded	not recorded	no complications
		patient 5	f	9 y	asymptomatic	not recorded	not recorded	no complications
		patient 6	f	3,7y	fever	not recorded-prolonged viral shedding	not recorded	no complications

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						in feces for 4 weeks		
Le at al., 2020	1	patient 1	f	3 m	rhinorrhea and nasal congestion, fever < 38°c	normal	azithromycin	hospitalized, no complications
An et al., 2020	1	patient 1	f	3y	fever < 38°c	CT: bilateral ground-glass opacity	azithromycin	not recorded
Lou et al., 2020	3	patient 1	f	6y	fever	CT: pneumonia findings	nebulised interferon	hospitalized, no complications
		patient 2	f	8y	fever and cough	CT: pneumonia findings	nebulised interferon	hospitalized, no complications
		patient 3	m	6m	fever	CT : pneumonia findings	none	hospitalized, no complications
Qian et al., 2020	1	patient 1	f	13m	asymptomatic	not recorded	none	hospitalized, no complications
Park et al., 2020	1	patient 1	f	10y	fever <38°c	blood test normal, CT: peripheral ground glass opacities, prolonged viral shedding in feces for 17 days	none	hospitalized, no complications
Liu et al., 2020	1	patient 1	m	10y	asymptomatic	normal, CT: pneumonia findings	ribavirin interferon	hospitalized, no complications
Huang et al., 2020	1	patient 1	f	16y	fever,sneezing, rhinorrhea, headache, diarrhea	WBC decreased, lymphocytes decreased, PLT decreased, other normal, CT: ground-glass opacities bilateral	ribavirin interferon, oseltamivir, moxifloxacin	hospitalized, no complications
Sun et al. 2020	8	patient 1	m	8y	fever, cough, expectoration, polypnea, rales	Leucocytes, neutrophils, lymphocytes and hemoglobin low, CRP high, PCT high, CT and Xray: Bilateral pneumonia [Multiple patch-like shadows, ground-glass opacity, "white lung" appearance]	oxygen therapy, mechanical ventilation (invasive), antibiotic treatment, antiviral treatment (virazole, oseltamivir and interferon), glucocorticoids, intravenous immunoglobulin, traditional Chinese medicine	ICU, no complications
		patient 2	f	10 m	cough, expectoration, nausea/vomiting, constipation, polypnea, crackles,	Leukocytes and neutrophils high, PLT low, Hemoglobin low, CRP/PCT high, d-dimer high, CT and Xray: Bilateral pneumonia [Multiple patch-like shadows, pleural effusion, ground-glass opacity]	oxygen therapy, antibiotic treatment, antiviral treatment (virazole, oseltamivir and interferon), glucocorticoids, intravenous immunoglobulin, enterostomy, hemopurification, transfusions of red blood cell,	ICU complications: intussusception, toxic encephalopathy, status epilepticus, DIC, septic shock, MODS

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							plasma and thrombocyte	
		patient 3	m	1,1y	fever, nausea/vomiting, diarrhea, polypnea, crackles	Hemoglobin low, CRP high, d-dimer high, CT and Xray: Bilateral pneumonia [Multiple patch-like shadows, ground-glass opacity]	oxygen therapy, mechanical ventilation (invasive), antibiotic treatment, antiviral treatment (virazole, oseltamivir and interferon), glucocorticoids, intravenous immunoglobulin, plasmapheresis	ICU complications: Septic shock, MODS, Kidney stone, hydronephrosis, cardiac insufficiency, coagulopathy
		patient 4	m	2 m	cough, expectoration, nausea/vomiting, polypnea, rales	Lymphocytes high, PLT high, CT and X-ray: Unilateral pneumonia [Multiple patch-like shadows]	oxygen therapy, antiviral treatment (virazole, oseltamivir and interferon),	ICU complications: hypoglobulinemia
		patient 5	m	2,1y	fever, cough, nausea/vomiting, diarrhea, polypnea, crackles	CRP/PCT high, CT and Xray: Bilateral pneumonia [Multiple patch-like]	antibiotic treatment, antiviral treatment (virazole, oseltamivir and interferon),	ICU complications: gastroenteritis
		patient 6	f	15y	fever, cough, fatigue/myalgia, headache, diarrhea, polypnea, rales	Leukocytes and neutrophils high, PLT high, CT and Xray: Bilateral pneumonia [Multiple patch-like shadows, ground-glass opacity]	antibiotic treatment, antiviral treatment(virazole, oseltamivir and interferon), glucocorticoids, intravenous immunoglobulin, traditional Chinese medicine	ICU, no complications
		patient 7	m	13.11y	fever, cough, polypnea, rales	Hemoglobin high, CRP/PCT high, CT and Xray: Bilateral pneumonia[Ground Glass Opacity]	oxygen therapy, antiviral treatment (virazole, oseltamivir and interferon), glucocorticoids, intravenous immunoglobulin, traditional Chinese medicine	ICU, no complications
		patient 8	m	13.5y	fever, expectoration, polypnea, rales	blood test normal, CT and Xray: Unilateral pneumonia[Multiple mottling, ground-glass opacity]	oxygen therapy, antiviral treatment(virazole, oseltamivir and interferon), traditional Chinese medicine	ICU, no complications
Li et al. 2020	2	patient 1	m	4y	cough, runny nose,	CRP high, CT: spots in the two upper lobes, right lower lobes, and left lower lobes	not recorded	remains in hospital

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		patient 2	f	4y	asymptomatic/ mild signs	blood test normal, CT: increased and slightly disordered bronchovascular bundles bilateral	supportive treatment, oxygen therapy	remains in hospital
Robbins et al. 2020	1	patient 1	m	58d	sleeping longer than normal, glassy eyes with mild surrounding erythema, mild nasal congestion, rectal temperature 38.4°c, stools softer and greener	lymphocytes low, mildly elevated ALP + Ca, CT: normal	one dose of intramuscular ceftriaxone and acetaminophen for fever.	no complications
Chan et al 2020	1	patient 1	m	10y	asymptomatic	ALP high, CT: ground-glass lung opacities	not recorded	no complications
Ji et al. 2020	2	patient 1	m	15y	fever, pharyngeal congestion,	WBC increased, CRP increased, CT normal	symptomatic	no complications
		patient 2	m	9y	diarrhea	normal	oral probiotic	no complications
Cui et al. 2020	1	patient 1	f	55d	rhinorrhoea, dry cough, pharyngeal hyperemia, productive cough accompanied by occasional tachycardia	Lymphocyte high, PLT high, CT: patchy shadows and ground-glass opacity in the right lung, 2nd: progressive pneumonia	inhaled interferon α-1b (15 µg, bid), amoxicillin potassium clavulanate (30 mg/kg, intravenous glucose tolerance test [IVGTT]), reduced glutathione, ursodeoxycholic acid, and traditional Chinese medicine lotus qingwen, sputum suctioning, oxygen through a nasal cannula, ambroxol, intravenous sodium creatine phosphate,	hospitalized, no complications
Wang et al. 2020	1	patient 1	m	2d	asymptomatic	lymphopenia, X-ray:showed thickened lung texture, CT: high-density nodular shadow under the pleura of the posterior segment of the upper lobe of the right lung and scattered with small pieces of patchy shadow	Intravenous penicillin G	hospitalized, no complications
Hu et al. 2020	6	patient 1	f	10y	fever	CT: ground-glass opacity or patchy shadows	interferon atomization	no complications
		patient 2	m	5y	asymptomatic	PCT high, d-dimer high, CT: normal	interferon atomization	hospitalized, no complications
		patient 3	f	8y	asymptomatic	PCT high, CT: normal	interferon atomization	hospitalized, no complications

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		patient 4	f	14y	asymptomatic	CRP high, CT: normal	interferon atomization	no complications
		patient 5	m	6y	asymptomatic	Lymphopenia, CT: normal	interferon atomization	hospitalized, no complications
		patient 6	m	15y	asymptomatic	CT: ground-glass opacity or patchy shadows	interferon atomization	no complications
Liu et al. 2020	4	patient 1	f	5y	fever, cough, fatigue	WBC decreased, neutrophil decreased, lymphocyte Increased, CRP normal, CT: normal	antiviral therapy	no complications
		patient 2	m	11m	fever, cough	WBC normal, neutrophil Decreased, lymphocyte increased, CRP normal, CT: single consolidation	antiviral therapy	no complications
		patient 3	f	9y	fever	WBC normal, neutrophil normal, lymphocyte normal, CRP normal, CT: single pure ground-glass opacity	antiviral therapy	no complications
		patient 4	m	2m	cough	WBC normal, neutrophil normal, lymphocyte normal, CRP increased, CT: Multiple consolidations, pleural effusion	antiviral therapy	no complications
Pan et al. 2020	1	patient 1	m	3y	asymptomatic	normal	not recorded	no complications
Kam et al. 2020	1	patient 1	m	6m	asymptomatic, 1 temperature record of 38.5°c	Neutropenia, CT: normal	none	no complications
Liu et al. 2020	6	patient 1	f	3y	fever, cough	CT: Patchy ground glass opacities in both lungs	ribavirin,oseltamivir,glucocorticoids,supplemental oxygen , intravenous immune globulin,empirically antibiotic agents	ICU admission
		patient 2	f	7y	fever, cough	CT: normal	oseltamivir, empirically antibiotic agents	not recorded
		patient 3	f	3y	fever, cough	CT: Patchy shadows in both lungs	oseltamivir,glucocorticoids, empirically antibiotic agents	not recorded
		patient 4	m	1y	fever, cough	CT: Patchy shadows in both lungs	oseltamivir,glucocorticoids, empirically antibiotic agents	not recorded
		patient 5	f	3y	fever, cough	CT: Patchy shadows in both lungs	oseltamivir,glucocorticoids, empirically	not recorded

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							antibiotic agents	
		patient 6	m	4y	fever, cough	CT: normal	ribavirin,oseltamivir,empirically antibiotic agents	not recorded
Li et al. 2020	5	patient 1	m	1y5m	asymptomatic	CRP high, CT: Patchy ground glass opacities	antiviral, anti-infective therapy, immunoglobulin therapy, interferon, lianhua qingwen granules	no complications
		patient 2	f	10m	asymptomatic	WBC high, CT: normal	montelukast sodium chewable tablets, immunoglobulin therapy	no complications
		patient 3	m	3y	runny nose, cough, sputum, sore throat, fever	WBC high, CT: Patchy ground glass opacities	antiviral, anti-infective therapy, immunoglobulin therapy	no complications
		patient 4	m	4y	asymptomatic	CT: Patchy ground glass opacities	montelukast sodium chewable tablets, immunoglobulin therapy	no complications
		patient 5	m	6y	asymptomatic	CT: normal	interferon, montelukast sodium chewable tablets, immunoglobulin therapy	no complications
Wei at al., 2020	9	patient 1	f	9m	fever	not recorded	none	hospitalized, no complications
		patient 2	f	11 m	fever	not recorded	none	hospitalized, no complications
		patient 3	f	8 m	asymptomatic	not recorded	none	hospitalized, no complications
		patient 4	m	10m	not reported	not recorded	none	hospitalized, no complications
		patient 5	f	7m	fever	not recorded	none	hospitalized, no complications
		patient 6	f	1 m	runny nose, cough	not recorded	none	hospitalized, no complications
		patient 7	f	3 m	cough, sputum production	not recorded	none	hospitalized, no complications
		patient 8	f	3m	fever	not recorded	none	hospitalized, no complications
		patient 9	m	6m	not reported	not recorded	none	hospitalized, no

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								complications
Tang et al. 2020	1	patient 1	m	10y	asymptomatic	normal, prolonged viral shedding in feces 17 days	abidol hydrochloride, interferon α-2b spray and traditional Chinese medical therapy	hospitalized, no complications
Xu et al. 2020	10	patient 1	f	6y	fever, cough, diarrhea	WBC slightly elevated, neutrophils elevated, lymphocytes decreased, d-dimer normal, ferritin normal, CRP normal, PCT elevated, ESR elevated, CT: normal, prolonged viral shedding in feces	α-interferon oral spray, azithromycin, IVIG	hospitalized, no complications
		patient 2	f	12.6 y	fever, sore throat, rhinorrhea	WBC normal, neutrophils normal, lymphocytes decreased, d-dimer normal, ferritin normal, CRP normal, PCT elevated, ESR normal, CT: ground-glass opacity, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
		patient 3	m	7 y	fever, sore throat, diarrhea	WBC normal, neutrophils normal, lymphocytes decreased, d-dimer normal, ferritin normal, CRP normal, PCT elevated, ESR elevated, CT: normal, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
		patient 4	m	13.8y	asymptomatic	WBC normal, neutrophils normal, lymphocytes normal, d-dimer normal, ferritin normal, CRP normal, PCT normal, ESR elevated, CT: normal, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
		patient 5	m	14m	fever < 38°c	WBC normal, neutrophils decreased, lymphocytes elevated, d-dimer normal, ferritine normal, CRP normal, PCT normal, ESR elevated, CT: normal, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
		patient 6	f	3.4y	rhinorrhea	blood test normal, CT: ground-glass opacity, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
		patient 7	m	15.5y	fever	WBC decreased, neutrophils decreased, lymphocytes normal, d-dimer normal, ferritin normal, CRP elevated, PCT normal, ESR elevated,	α-interferon oral spray	hospitalized, no complications

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						CT: ground-glass opacity		
		patient 8	f	13.5y	fever, cough, rhinorrhea	WBC normal, neutrophils normal, lymphocytes normal, d-dimer normal, ferritine normal, CRP elevated, PCT elevated, ESR normal, CT: ground-glass opacity, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
		patient 9	m	2m	cough and sore throat	WBC normal, neutrophils decreased, lymphocytes elevated, d-dimer increased, ferritin elevated, CRP normal, PCT elevated, ESR normal, CT: ground-glass opacity	α-interferon oral spray	hospitalized, no complications
		patient 10	m	2y	fever, cough, diarrhea	Not recorded, prolonged viral shedding in feces	α-interferon oral spray	hospitalized, no complications
Cai et al. 2020	10	patient 1	m	7y	fever, cough	WBC elevated, neutrophils elevated, lymphocytes normal, d-dimer elevated, CRP elevated, PCT normal, X RAY normal, prolonged viral shedding in feces > 30 days	Symptomatic treatment	hospitalized, no complications
		patient 2	f	11 y	fever, sore throat, stuffy nose	normal	symptomatic treatment	hospitalized, no complications
		patient 3	f	11 y	fever <38°c,cough sore throat, stuffy nose	WBC normal, neutrophils normal, lymphocytes normal, d-dimer normal, CRP elevated, PCT normal X-ray: opacity on left lung, prolonged viral shedding in feces > 20 days	symptomatic treatment	hospitalized, no complications
		patient 4	m	9y	fever, cough, sneezing, rhinorrhea, sore throat	WBC decreased, neutrophils decreased, lymphocytes normal, d-dimer elevated, CRP elevated, PCT normal X RAY: opacity on right lung, prolonged viral shedding in feces > 19 days	symptomatic treatment	hospitalized, no complications
		patient 5	f	7m	cough, sneezing, rhinorrhea, stuffy nose	WBC normal, neutrophils normal, lymphocytes normal, CRP normal, PCT normal, X RAY: opacity on right lung, prolonged viral shedding in feces > 18 days	symptomatic treatment	hospitalized, no complications

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		patient 6	f	6y	fever	normal	symptomatic treatment and antibiotics	hospitalized, no complications
		patient 7	f	3m	fever	WBC normal, neutrophils normal, lymphocytes elevated, d-dimer normal, CRP normal, PCT normal XRAY: normal, prolonged viral shedding in feces > 23 days	symptomatic treatment and antibiotics	hospitalized, no complications
		patient 8	f	4y	cough	WBC normal, neutrophils decreased, lymphocytes normal, CRP normal, PCT normal X RAY: opacity on right lung	symptomatic treatment and antibiotics	hospitalized, no complications
		patient 9	m	8y	fever and sore throat	WBC elevated, neutrophils normal, lymphocytes normal, PCT normal ,CRP normal, X RAY: normal	symptomatic treatment and antibiotics	hospitalized, no complications
		patient 10	m	5y	fever and cough	WBC elevated, neutrophils normal, lymphocytes normal, CRP normal, PCT normal, X RAY: normal	symptomatic treatment and antibiotics	hospitalized, no complications

RETROSPECTIVE COHORT STUDIES

AUTHOR	N	MEAN AGE-	AGE RANGE	SYMPTOMS	LABORATORY FINDINGS	TREATMENT	OUTCOME
CDC COVID-19 Response Team	2572	11	0-17	*fever 56% cough 54% shortness of breath 13% myalgia 23%, runny nose 7.2%, sore throat 24%, headache 28%, nausea 11%, abdom. pain 5.8%, diarrhea 13%	not recorded	not recorded	hospitalized 29% ICU 0.8% 3 deaths **
Li et al., 2020	22	8	-	fever 63.6%, cough 59%, asymptomatic 9%.	CRP and ESR elevated, CT positive 72.7%	not recorded	not recorded
Han et al., 2020	7	1.3	2 m to 13y	fever 71.4%, cough 71.4%, shortness of breath 42.8%, pharyngalgia 14.3%, diarrhea 57.1%	WBC elevated 28.6%, increased neutrophils 14.3%, X RAY and CT positive for pneumonia 71.4%, PLT elevated 14.3%, aPTT elevated 42.85%,d-dimer elevated 14.3%, CRP	oxygen therapy 28.6%, glucocorticoids 14.3%	no complication, full recovery 100%

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					elevated 28.6%, PCT elevated 42.85%		
Qiu et al., 2020	36	8.3	0 to 16y	fever 36.1%, dry cough 19.5%, dyspnoea or tachypnea 2.8%, pharyngeal congestion 2.8%, sore throat 5.6%, vomiting or diarrhea 5.6%, headache 8.4%	WBC decreased 19.5%, lymphocytes decreased 30.6%, PCT elevated 16.7%, CRP elevated 2.8%, d-dimer elevated 8.4%, CT positive 52.8%	oxygen inhalation 16.7%, interferon alfa 100%, lopinavir–ritonavir 27.8%	
Zheng et al., 2020	25	3	3m-14y	fever 52%, dry cough 44%, diarrhea 12%, nasal congestion 8%, dyspnea 8%, abdominal pain 8%, and vomiting 8%	Lymphopenia 40% CT: normal 33.3%, unilateral involvement 20.8% and bilateral involvement 45.8%	antiviral therapy (interferon, arbidol, oseltamivir, lopinavir/ritonavir 44% empirical antibiotics 52% invasive mechanical ventilation, systematic corticosteroids, and intravenous immunoglobulin 8% kidney replacement therapy 4%	hospitalized, full recovery 100%
Lu et al. 2020	171	6.7	<1 – 15y	asymptomatic 15.8%, asymptomatic but radiologic pneumonia 7%, upper respiratory tract infection 19.3%, pneumonia 64.5% cough 48.5%, pharyngeal erythema 46.2%, fever 41.5%, diarrhea 8.8%, fatigue 7.6%, rhinorrhea 7.6%, vomiting 6.4%, nasal congestion 5.3%, tachypnea on admission 28.6%, tachycardia on admission 42.1%, oxygen saturation <92% during period of hospitalization 2.3%	Lymphopenia 3.5% CT: Ground-glass opacity 32.7%, Local patchy shadowing 18.7%, Bilateral patchy shadowing 12.3%, Interstitial abnormalities 1.2%	not mentioned other than mechanical vent on 3 ICU patients – 1.75%	ICU+mechanical ventilation 1.75% death 0.6% discharged 87.1% remain 12.3%
Xia et al. 2020	20	2y+ 1.5 m	1d - 14y+7m	fever 60%, cough 65%, diarrhea 15%, nasal discharge 15%, sore throat 5%, fatigue 5%, vomiting 10%, tachypnea 10%	WBC low 20%- high 10%, lymphocytes low 35% - high 15%, CRP high 35%, PCT high 80%, CT: unilateral pulmonary lesions 30%, bilateral pulmonary lesions 50%, consolidation with surrounding halo sign 50%, ground-glass opacities 60% fine mesh shadow 20%, tiny nodules 15%	not recorded	no complications 100% full recovery

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** Symptoms available for 291 of 2,572 patients*

***COVID-19 is not confirmed as the likely cause of death*

WBC: white blood shells, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, FIB: Fibrinogen, PCT: procalcitonin, ALP: alkaline phospatase, PLT: platelel count, aPTT: activated Partial Thromboplastin Time, CT: Computed Tomography, ICU: Intensive Care Unit, DIC: Disseminated Intravascular Coagulation, MODS: Multiple Organ Dysfunction Syndrome.

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Table 3: Results of univariate and multivariate logistic regression analysis examining risk factors for pneumonia. Bold cells denoted statistically significant associations.

Factors associated with pneumonia	Category or increment	Frequency of pneumonia	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Male sex	Male vs. female	55.4% (31/56) vs. 60.0% (27/45)	0.83 (0.37-1.83)	0.75 (0.32-1.73)
Age (years)				
<1		61.1% (11/18)	2.15 (0.70-6.57)	2.17 (0.71-6.66)
1-4		81.0% (17/21)	**5.82 (1.68-20.09)**	**6.01 (1.73-20.91)**
5-11	Ref.	42.2% (19/45)	Ref.	Ref.
12-18		64.7% (11/17)	2.51 (0.79-7.98)	2.52 (0.79-8.03)

**CI: confidence interval; OR: odds ratio, Ref: Reference category*

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