Particularities of the Evolution of SARS-CoV-2 Infection in Children

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Research

Keywords: human coronavirus, SARS-CoV-2, COVID-19 - PCR method, SARS-CoV-2 IgG / IgM serology

Posted Date: January 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-146701/v1

Abstract

Introduction

SARS-CoV-2 virus infection was first reported in China in late 2019 and has spread rapidly around the world. There is little information about the peculiarities of COVID-19 infection in children because the number of infected children was small, around 2% of all diseases.

Methods

In this retrospective study, we recruited 143 children infected with SARS-CoV-2 between March and October 2020, in Sibiu, Romania. RT-PCR tests, serum SARS-CoV-2 IgG/ IgM antibodies, lung radiography, biochemical and hematological tests were performed during the hospitalization.

Results

Of the 143 children selected in the study, 47.0% were male and 53% were female. At admission, all children tested positive for SARS-CoV-2, collecting nasopharyngeal exudate.

Clinical manifestations included: cough in 75.52% of cases, fever in 55.94% of cases, nasal obstruction in 50.34% of cases, rhinorrhea in 38.46% of cases, muscle pain in 26.57% of cases, fatigue in 17.48% of cases, diarrhea and headache in 14.68% of cases. In 21 children (14,68%), the number of leukocytes was increased. In 38 cases (26,57%), the lung radiograph showed changes similar to bronchopneumonia, and the other cases did not have pulmonary changes. The persistence of the virus in the body of infected children is above the average reported in studies performed in adults, the virus being identified in the respiratory tract between 16 and 34 days. IgG class antibodies in patients' serum appeared between the 4th day of hospitalization and up to a maximum of 25 days, with a mean of 16.5 days.

Conclusion

The persistence of the virus in the body of infected children is above the average reported in studies performed in adults, the virus being identified in the respiratory tract between 16 and 34 days. IgG class antibodies in patients' serum appeared within a mean of 16.5 days. All children were treated with symptomatic support without complications.

Introduction

SARS-CoV-2 virus is a new type of coronavirus and was identified as the cause of an outbreak of pneumonia in China in late 2019 [1, 2, 3, 4], SARS-CoV-2 causes a disease called COVID-19 (Coronavirus infectious disease 2019) [5]. The epidemic has spread worldwide [2, 6, 7, 8, 9, 10], despite efforts to limit the spread of the disease [11].

The virus can be transmitted by an infected person or an asymptomatic carrier and is an extremely contagious disease. The main route of transmission of the virus is the respiratory tract, through the Flügge droplets [12]. The incubation period is between 5 and 14 days [1]. The spread of the virus was rapid [13], so that the infection with the new coronavirus generated many cases of pneumonia worldwide.

Symptomatology of the disease is predominantly respiratory (fever, cough, difficulty breathing) [14, 15], the vast majority of cases with symptoms of minimal and moderate intensity and only in about 20% of cases may occur severe manifestations (bilateral interstitial pneumonia), with evolution to respiratory failure and acute respiratory distress (ARDS) [16]. There are also cases with gastrointestinal manifestations (especially diarrhea), and in some patients, hypo / anosmia (loss of smell) and hypo / dysgeusia (loss of taste) have been reported as early symptoms.

The reference test for the specific diagnosis of COVID-19 is a molecular biology test, performed by NAAT technology (nucleic acid amplification technology), respectively, reverse transcription real time PCR (RT-PCR) that detect the presence of viral RNA in the nasopharynx [13]. In order to show the body's response to infection, serological tests are performed that detect the presence of antivirus antibodies (SARS-CoV-2) [17,18], these antibodies being immunoglobulins belonging to classes A, M, G, less often D.

Tests that identify the virus should be performed taking into account the incubation period of the virus in the host organism, respectively after a period of 5-14 days. To identify the body's serological response, models from other viral infections should be considered, which generally have the following sequence of antibodies: IgA antibodies, closely followed by IgM, and finally IgG-type antibodies. which remain in high titers for a longer period of time [19].

Currently, the body's specific immune response to SARS-CoV-2 infection is the subject of numerous studies in all countries. To date, there is no complete validated information on the dynamics of antibody onset of infection and their persistence after SARS-CoV-2 virus clearance.

Our study wants to analyze the persistence period of the virus in the body of children identified positively with SARS-CoV-2 virus mas well as the peculiarities of their immune response.

Materials And Methods

The study included 143 patients, aged between 17 days and 18 years, hospitalized in the COVID Infectious Diseases Department of the Pediatric Clinical Hospital in Sibiu between March and October 2020. This series of cases was approved by the institutional ethics commission (no. 4065/12.06.2020). Demographic information was selected, including age and gender.

Patients underwent RT-PCR tests to identify the presence of the virus in the respiratory tract by collecting a nasal exudate and a pharyngeal exudate on the first day of hospitalization, and later on days 12-14 to see if there was persistence of the virus for discharge patient after the existence of 2 negative RT-PCR tests.

On day 12 after admission, patients' blood was collected to highlight the body's immune response by determining IgM/IgG antibodies by a rapid immunochromatographic test for the simultaneous detection of IgM/IgG antibodies in human blood (serum/plasma).

For RT-PCR testing, automatic extraction is used, on a 24-position extractor Lab-Aid 824 - Zeesan, and the amplification is done on a BIORAD CFX2s device. Other biochemical and hematological markers were investigated to assess the severity of the disease, as well as radiological images to highlight pneumonia.

For statistical analysis**, c**ategorical variables were expressed as number (%) while continuous variables were expressed as median (IQR – interquartile range). For laboratory measurements results are presented for both quantitative and qualitative (inside and outside normal ranges) versions. We used R version 4.0.1 (R Foundation for Statistical Computing; http://www.r-project.org/) for all analyses.

Results

The present study included 143 patients, with a median age of 10.95 years and a predominance of 76 female patients (53.0%). Data are presented by median (IQR) or n (%). The most common symptoms during the hospitalization were: cough in 108 cases (75.52%), fever that was defined as axillary temperature above 37,3^{0}C in 80 cases (55.94%), nasal obstruction in 72 cases (50.34%), rhinorrhea in 55 cases (38.46%), muscle pain in 38 cases (26.57%), fatigue in 25 cases (17.48%), diarrhea and headache in 21 cases (14.68%), chills, dysphagia and loss of smell in 8 cases (5.59%), hypovolemia, gastroenteritis, rhinopharyngitis, abdominal pain and vomiting, there were 4 cases (2.79%), (Fig 1).

During the hospitalization of the patients, an average of 7 tests were performed (with a variation of 6 - 10 tests / patient). The mean time from RT-PCR positive to RT-PCR negative was 26.5 days (IQR 6 - 34 days). IgG and IgM antibodies for serum SARS-CoV-2 were assayed, with antibodies averaging 11.5 days (IQR 1-17 days). All patients had unchanged oxygen saturation (Table 1).

After the appearance of IgG-type antibodies, all patients remained under observation due to the positive results of the median RT PCR COVID test - 19 was 16.5 days (IQR 4 - 25 days).

Most children did not have positive lung signs (73.42%), unilateral pneumonia being recorded at (11.88%), and bilateral pneumonia was recorded at (14.69%) from patients (Table 2).

Laboratory results are as follows: the number of leukocytes was normal in 114 cases (79.72%), decreased in 8 cases (5.59%), and increased in 21 cases (14.68%); the percentage of lymphocytes was decreased in 88 cases (61.53%), increased in 8 cases (5.59%); the percentage of neutrophils was low in 38 cases (26.57%), increased in 29 cases (20.27%);

C-reactive protein (CRP) was increased in 34 cases (23.77%). All patients had normal aspartate amino transferase (AST) values; 4 patients (2.79%) had elevated alanine amino transferase (ALT) values, all values were normal for urea; 4 patients (2.79%) had elevated creatinine (Table 3).

The values of the continuous variables were standardized (using z scores). We rescale the original variables to have equal range and/or variance for the variables in the graphic (the initial variables were measured at different scales). (Fig. 2)

Discussion

On 5 September 2020, there have been more than 29 million cases worldwide with more than 929,000 deaths [20] and the amount of children with COVID-19 is under 2% of all cases [21].

In China, the average age of infected children was 10.9 years, with the highest incidence in children between 5 and 14 years. The incidence between the sexes was slightly higher among females. The most common symptom, for which the child went to the doctor was cough, which was found in 73.52% of cases, other common symptoms were: fever, reported in 55.94% of cases, nasal obstruction in 50.34%, rhinorrhea in 38.46%, muscle pain in 26.57% of cases, diarrhea in 14.68% of cases, data that are consistent with the 2020 study by ZHENG F et al. [22].

Loss of smell and taste was a rare symptom in children, being recorded in 5.59% of cases, in accordance with the 2020 study performed by Luethgen M, et al., these symptoms meeting in the 5,18% of cases of SARS-CoV-2 [23].

In Romania, from the end of February 2020, when the first positive patient appeared, the number of cases was 164477. In the Sibiu area the total number of diseases was, until October 14, 4016 patients, of which 143 children under 18 years, representing a percentage of 3.56% of the total cases.

Considering the hemoleucogram, we noticed a decrease in lymphocytes in 61.53% of cases, compared to the study conducted by Xia et al. 2020 [1] where a percentage of 35% was reported, and C-reactive protein was increased in 23.77% of cases compared to the same study, in which C-reactive protein was modified in 45% of cases. Unilateral and bilateral pneumonia is much lower in children included in the present study 11.8%, respectively 14.69%, compared to studies conducted in 2020 by Zeng F, where unilateral pneumonia was found in 30%, respectively 20.8% of cases, and bilateral pneumonia in 50%, respectively 45.8% of cases [22].

Pediatric patients had a good prognosis with an average hospitalization of 26.5 days, the number of hospitalization days being high compared to other studies, in which the number of hospitalization days was lower, respectively 12.9 days [1].

During the hospitalization, a large number of tests were performed to identify the appearance of antibodies and the disappearance of viral RNA, the average of the tests performed being 7 (with a variation of 6 - 10 tests / patient). The mean time from RT-PCR positive to RT-PCR negative was 26.5 days, consistent with the study conducted by Bahar B. [24].

The mean time between the positive PCR-RT test and the appearance of serum IgG antibodies in the serum was 11.5 days, a lower average compared to the study conducted by Bahar B. in which this

average time was 18 days.

The current study showed that IgG antibodies are detected in children's serum samples before the virus is eliminated from the body, the antibodies being present at the same time as the presence of the virus in the body.

After the appearance of IgG antibodies in the serum, until the negation of the RT-PCR test, the virus was present in the body for another average period of 16,5 days. Oxygen saturation was unchanged for all pediatric patients.

The children were discharged after presenting two negative RT-PCR COVID - 19 tests at an interval of 2 days.

Conclusions

There are some particularities of SARS-CoV-2 infection in children. The average age of children infected with SARS-CoV-2 was 10.95 years, the highest number of cases being recorded in children aged 5-14 years. Female patients were more commonly affected.

The most obvious symptoms in children were cough and fever in concordance with the study of Martelletti L. et al. [25], unlike adults where fever, fatigue, loss of smell and taste were the most important symptoms. All children included in the study developed mild forms of the disease, in accordance with the literature [26, 27].

The persistence of the virus in the body of infected children is above the average reported in studies performed in adults, the virus being identified in the respiratory tract between 16 and 34 days.

IgG class antibodies in patients' serum appeared between the 4th day of hospitalization and up to a maximum of 25 days, with a mean of 16.5 days. IgG antibodies exist simultaneously with the presence of the virus, for a long time, different from the general model for other types of viral infections, which determines the need to identify not only antibodies at discharge but to highlight the absence of virus by RT-PCR test.

The long period of hospitalization required for children until the infection was negated generated high costs / patient and a sustained effort on the part of the medical team that had to manage the isolation problems caused by hospitalization in the limited space of the hospital ward.

To date, there is no specific treatment to reduce the rates of SARS-CoV-2 infection [28] but recent research has indicated that an optimal level of vitamin D in the blood may be an important factor in reducing SARS-CoV-2 infection. Vitamin D supplementation is beneficial for solving the public health problem of counteracting the general vitamin D deficiency among the pediatric population [29].

Declarations

Acknowledgement:

This study was supported by the ***Project financed by Lucian Blaga University of Sibiu & Hasso Plattner Foundation research grants LBUS-IRG-2019-05."***

Availability of data and materials

This study has several limitations of note, particularly its retrospective design. The authors also could not control harvest conditions.

Ethical approval

Approval was applied for and received from the Clinical Hospital of Pediatric, Sibiu. All procedures were conducted according to committee regulations.

Competing interests

The authors declare that they have no competing interests

Consent for publication

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

TM, AE and GC drafted the original manuscript and performed the data collection and analysis. MI, GGF, DL, SS, CS and GN participated in the data analysis and in its design. All coauthors revised the manuscript.

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References

1. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr Pulmonol* 2020;*55*(5):1169-1174.
2. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, Liu ZS. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr* 2020:1-9.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*2020;*395*(10223):497-506.
4. Nino G, Zember J, Sanchez-Jacob R, Gutierrez MJ, Sharma K, Linguraru MG. Pediatric Lung Imaging Features of Covid-19: A Systematic Review and Meta-*Pediatric pulmonology* 2020.
5. Di Wu JL, Ma X, Liu Q, Wang D, Gu Y, Li Y, He W. Coinfection of Influenza virus and severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). *Pediatr Infect Dis J* 2020;*39*(6):e79.
6. Tan YP, Tan BY, Pan J, Wu J, Zeng SZ, Wei HY. Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China. *Journal of Clinical Virology* 2020;127(104353):1-6.
7. Long QX, Deng HJ, Chen J, Hu J, Liu BZ, Liao P, Gong F, et al. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. medRxiv
8. Ma X, Liu S, Chen L, Zhuang L, Zhang J, Xin Y. The clinical characteristics of pediatric inpatients with SARS-CoV-2 infection: a meta-analysis and systematic review. *J Med Virol* 2020:1–7.
9. Kannan S, Ali PSS, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019)-recent trends. *Rev. Med. Pharmacol. Sci*2020;*24*(4):2006-2011.
10. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. *Int J Lab Hematol.* 2020;42(Suppl. 1):11–18.
11. Lin CY, Wang WH, Urbina AN, Tseng SP, Lu PL, Chen YH, et al. Importation of SARS-CoV-2 infection leads to major COVID-19 epidemic in Taiwan. *Pediatr Infect Dis J* 2020;97:240-244.
12. She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. *Journal of medical virology*, *J Med Virol* 2020;92:747–754.
13. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA* 2020;*323*(13):1313-1314.
14. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;*323*(11):1061-1069.
15. Du W, Yu J, Wang H, Zhang X, Zhang S, Li Q, Zhang Z. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China. *Infection*2020;*48*(3):445-452.
16. R. Otto, S. Geoghegan, L. C. Posch, L. M. Bell, S. E. Coffin, J. S. Sammons, R. M. Harris, A. R. Odom John, X.Luan, J. S. Gerber, The epidemiology of severe acute respiratory syndrome coronavirus 2 in a pediatric healthcare network in the united states. *J. Pediatric Infect. Dis. So*c., piaa074 (2020)
17. Long QX, Deng HJ, Chen J, Hu J, Liu BZ, Liao P, Gong F, et al. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. medRxiv

18. Li G, Chen X, Xu A. Profile of specific antibodies to the SARS-associated coronavirus. *N Engl J Mmed*2003;*349*(5):508-509.
19. Zhao J., Yuan Q., Wang H., Liu W., Liao X., Su Y. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Infect. Dis.* 2020pii: ciaa344
20. Johns Hopkins Coronavirus Resource Center, COVID-19 United States Cases by County (Johns Hopkins University, 2020).
21. Coronavirus Disease 2019 in Children – United States, Feb 12-April 2, 2020 (Morbidity and Mortality Weekly Reports, Centers for Disease Control and Prevention, Atlanta, GA, 2020).
22. Zheng F, Liao C, Fan QH, Chen HB, Zhao XG., Xie ZG, et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Current medical science* 2020;40(2):275-280.
23. Luethgen M, Eggeling J, Heyckendorf J, Lange C, Maier C, Reimann M, et al. Changes in taste and smell as an early marker for COVID-19. *Int J Infect Dis*2020;99:8-9.
24. Bahar B, Jacquot C, Mo YD, DeBiasi RL, Campos J, Delaney M. Kinetics of Viral Clearance and Antibody Production Across Age Groups in Children with Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J Pediatr* 2020;227(e1):31-37.
25. Martelletti L, Martelletti P. Air pollution and the novel Covid-19 disease: a putative disease risk factor. SN Compr Clin Med 2020;2:383–387.
26. Chinazzi M, Davis JT, Ajelli M, Gioannini C, Litvinova M, Merler S, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science* 2020;368(6489):395-400.
27. Lubrano R, Villani A, Berrettini S, et. al. Point of view of the Italians pediatric scientific societies about the pediatric care during the COVID-19 lockdown: what has changed and future prospects for restarting, *Italian Journal of Pediatrics* 2020;46(142):1-5.
28. Rabinowicz S, Leshem E, Pessach IM. COVID-19 in the Pediatric Population—Review and Current Evidence. *Current infectious disease reports* 2020;*22*(11):1-12.
29. Popescu, A. S. C., Grigore, C., Totan, M., & Grigore, N. (2019). Prevalence of suboptimal levels of vitamin D in Romania. *Clinica Chimica Acta*, *493*, S630.

Tables

Table 1. Paraclinical and other parameters in pediatric patients with COVID-19

Parameters	Measured values for all patients
Temperature	37,65^{0}C (36,80^{0}C -38,20^{0}C)
§ **<37.3** ^{0}C	46 patients (32,16 %)
§ **(37.3-38)** ^{0}C	55 patients (38,46 %)
§ **(38.1-39)** ^{0}C	38 patients (26,57 %)
§ **>39** ^{0}C	4 patients (2,79 %)
Oxygen saturation (%)	95 (94-97)
Number of COVID tests	7 (6-10)
Number of days of hospitalization	26,5 (16-34)
Ig G Antibodies	11,5 (1-17)
RT-PCR positive to RT-PCR negative	16,5 (4-25)

Table 2. Radiological findings in pediatric patients with SARS-CoV-2

Radiological findings	Patients (%)
Normal images	105 (73,42%)
Pneumonia	38 (26,57%)
· **unilateral**	17 (11,88%)
· **bilateral**	21 (14,69%)

Table 3. Biological parameters in pediatric patients with COVID-19

Parameter	Value	Patients (%)
Hemoleucogram	**Leucocytes**	
	o normal	114 (79.72%)
	o increased	21 (14,68%)
	o decreased	8 (5.59%)
	Neutrophils	
	o decreased	38 (26.57%)
	o increased	29 (20.27%)
	Lymfocytes	
	o decreased	88 (61.53%)
	o increased	8 (5.59%)
C reactive proteins	Increased	34 (23.77%)
ASAT	Normal	143 (100%)
ALT	Increased	4 (2.79%)
Urea	Normal	143 (100%)
Creatinine	Increased	4 (2.79%)

Figures

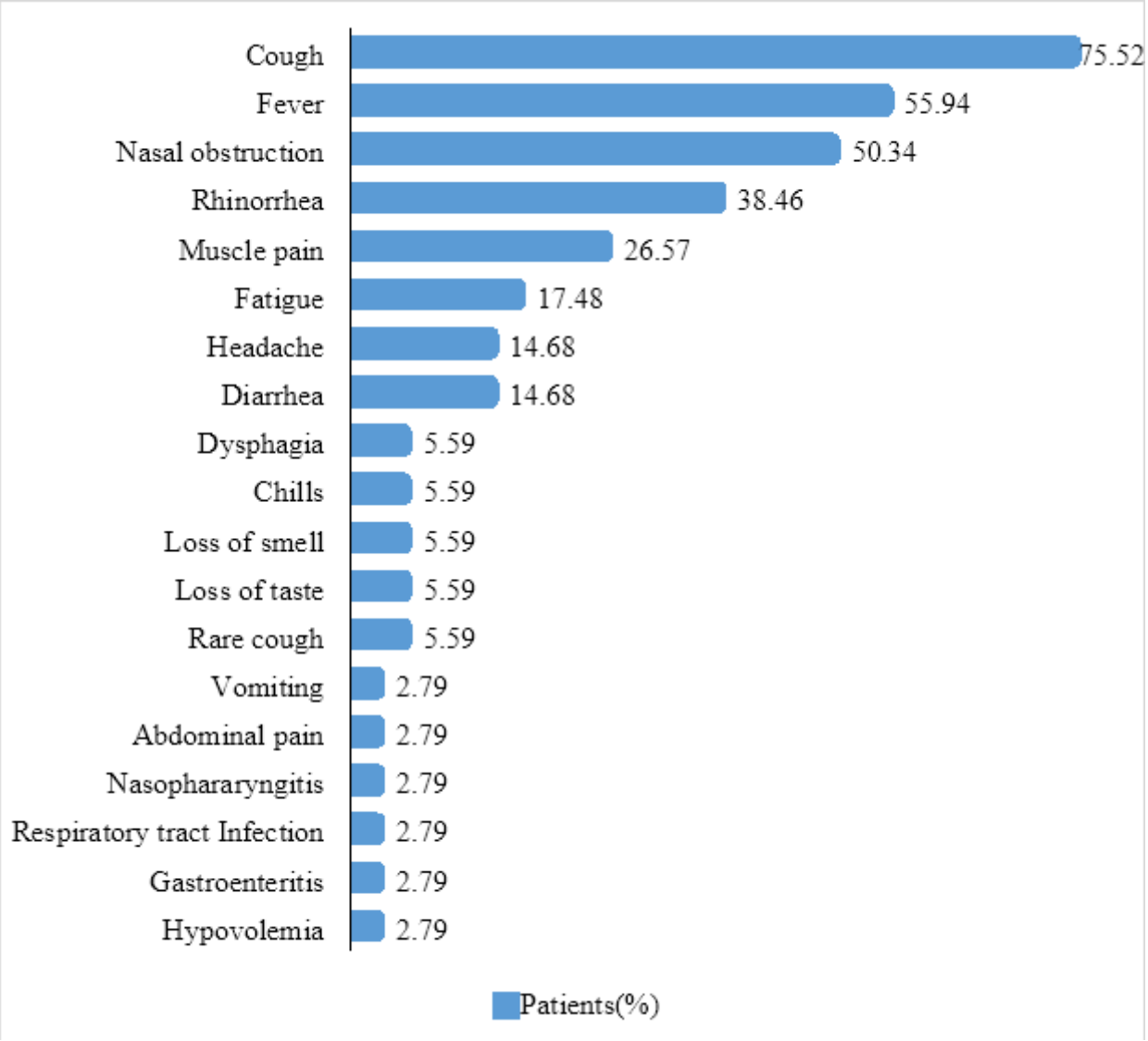

Figure 1

Clinical characteristics (symptoms and signs) in pediatric patients with COVID-19

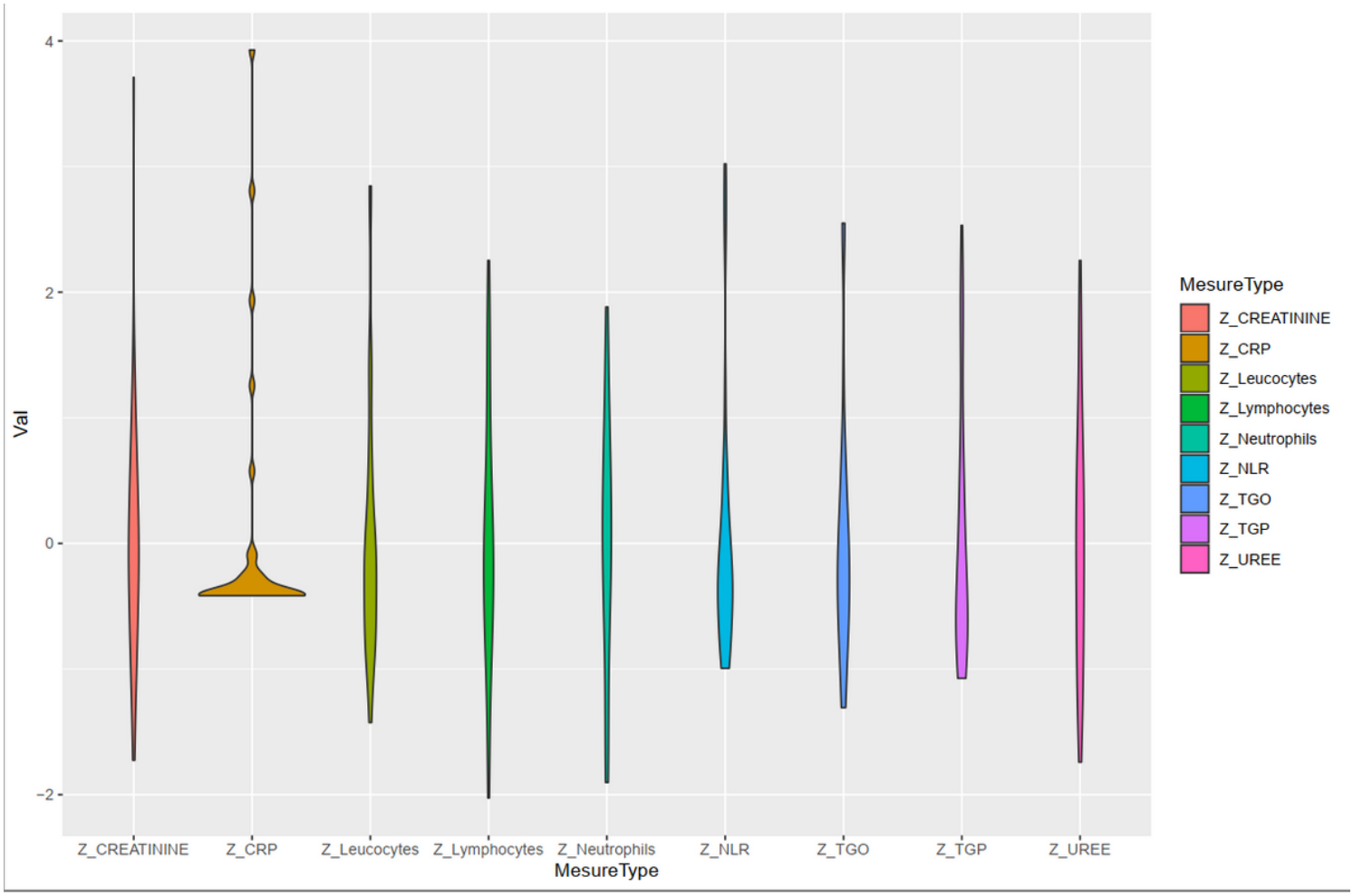

Figure 2

Z Scores for biological parameters