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RESEARCH ARTICLE

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SARS-CoV-2 RNAaemia in children: An Iranian referral hospital-based study

Babak Pourakbari[1] | Shima Mahmoudi[1] | Yasmine Mahmoudieh[2] | Hamid Eshaghi[3] | Amene Navaeian[3] | Maryam Rostamyan[3] | Setareh Mamishi[1,3]

[1]Pediatric Infectious Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Molecular and Cell Biology, University of California, Berkeley, USA

[3]Department of Infectious Diseases, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Correspondence

Shima Mahmoudi and Setareh Mamishi, Pediatric Infectious Disease Research Center, Tehran University of Medical Sciences, Children's Medical Center Hospital, Dr. Gharib St, Keshavarz Blvd, Tehran, Iran.
Email: sh-mahmoudi@sina.tums.ac.ir and smamishi@sina.tums.ac.ir

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Abstract

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is generally detected in nasopharyngeal swabs, viral RNA can be found in other samples including blood. Recently, associations between SARS-CoV-2 RNAaemia and disease severity and mortality have been reported in adults, while no reports are available in pediatric patients with coronavirus disease 2019 (COVID-19). The aim of this study was to evaluate the mortality, severity, clinical, and laboratory findings of SARS-CoV-2 RNA detection in blood in 96 pediatric patients with confirmed COVID-19. Among all patients, 6 (6%) had SARS-CoV-2 RNAaemia. Out of the six patients with SARS-CoV-2 RNAaemia, four (67%) had a severe form of the disease, and two out of the 6 patients with SARS-CoV-2 RNAaemia passed away (33%). Our results show that the symptoms more commonly found in the cases of COVID-19 in the study (fever, cough, tachypnea, and vomiting), were found at a higher percentage in the patients with SARS-CoV-2 RNAaemia. Creatine phosphokinase and magnesium tests showed significant differences between the positive and negative SARS-CoV-2 RNAaemia groups. Among all laboratory tests, magnesium and creatine phosphokinase could better predict SARS-CoV-2 RNAemia with area under the curve levels of 0.808 and 0.748, respectively. In conclusion, 67% of individuals with SARS-CoV-2 RNAaemia showed a severe COVID-19 and one-third of the patients with SARS-CoV-2 RNAaemia passed away. Our findings suggest that magnesium and creatine phosphokinase might be considered as markers to estimate the SARS-CoV-2 RNAaemia.

KEYWORDS

COVID-19, pediatrics, RNAaemia, SARS-CoV-2, severity

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is thought to have originated from Wuhan, China, has become a worldwide epidemic. Diagnosing the disease has been integral in working to slow the spread of the disease globally.[1]

Coronavirus Disease 2019 (COVID-19) appears to have a milder disease course with a better prognosis and fewer deaths in children than in adults. Although fewer children seem to develop severe pneumonia, patients with severe COVID-19 may have signatures of dysregulated immune response with immunological alterations cytokines and chemokines cascades.[2,3] During the pandemic, children with SARS-CoV-2 infection manifested with Kawasaki-like disease and multiorgan involvement.[2,4] Despite the fact that the number of COVID-19 cases continues to increase worldwide, comprehensive detailed data on pediatric patients is limited or incomplete.

Although SARS-CoV-2 RNA is generally detected in nasopharyngeal swabs, viral RNA can be found in other samples including sputum, saliva, lung samples, peripheral blood, serum, stool, and even urine samples.[5–7] Recently, there have been associations between SARS-CoV-2 RNAaemia and disease severity and mortality reported in adults,[3,7–10] while there are no reports available in pediatric patients with COVID-19.

The aim of this study was to evaluate the mortality, severity, clinical and laboratory findings of SARS-CoV-2 RNA detection in blood in pediatric patients with confirmed COVID-19.

2 | MATERIALS AND METHODS

This study received ethical approval from the Tehran University of Medical Sciences in Tehran, Iran (IR. TUMS. CHMC. REC.1399.146). This study was performed at the Children's Medical Center, the primary center for pediatric medicine and research in Iran. More than 35,000 outpatients and 2,500 inpatients are admitted to our hospital monthly.

2.1 | Participants

Hospitalized patients with confirmed COVID-19 were included. All participants gave written informed consent, and the study was carried out following the guidelines of the Declaration of Helsinki. Signed informed consent was obtained from all patients who participated in the study. In cases where patients did not have the legal capacity to provide informed consent or had not reached the age of consent, their parents/legal guardians provided it for them.

A confirmed case of COVID-19 was defined as a positive result of SARS-CoV-2 real-time reverse-transcription polymerase chain reaction (rRT-PCR) using a nasopharyngeal swab.[2] The rRT-PCR assay was performed using the Premix Ex Taq™ (Probe qPCR; Takara) according to the manufacturer's instructions. The PCR cycle using N1 and N2 probes of the virus nucleocapsid gene and RNase P (RP) as an internal control was run as follows: 95°C for 3 min, followed by 45 cycles of 95°C for 3 s, and 58°C for 30 s. A cycle threshold value (C_t value) of less than 37 was considered as a positive result.

The severity of COVID-19 was categorized into two groups (severe/critical vs. mild/moderate) based on the clinical findings, severity of pneumonia, respiratory failure, shock, and other organ failures.[11] Severe pneumonia was defined based on the following criteria: hypoxia ($SpO_2 \leq 93\%$), increased respiration rate of RR ≥ 70/min (≤1 year), RR ≥ 50/min (>1 year), and blood gas analysis ($PaO_2 < 60$ mmHg, $PaCO_2 > 50$ mmHg).[4]

Demographic characteristics, baseline symptoms, and physical signs, laboratory findings, severity, and outcome of the disease were collected.

2.2 | Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc.). Categorical data were described as percentages and a comparison of the differences between the two groups was conducted using the χ^2 test. Comparison of the laboratory tests between the two groups, with and without SARS-CoV-2 RNAaemia, was performed using Mann–Whitney *U* tests. The results were presented in terms of the median (interquartile range [IQR]). The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to analyze the optimal cut-off for prediction of positive SARS-CoV-2 RNAaemia cases.

3 | RESULTS

3.1 | Demographic and clinical presentation

In this study, 96 COVID-19 positive patients were included into this study, 48% of the patients were male and 52% were female. Among all patients, 6 (6%) had SARS-CoV-2 RNAaemia, detected with rRT-PCR in the serum sample, and all of them were male.

Patients were divided into two groups based on the results of RT-PCR in serum samples for COVID-19. The age range of patients included in the study was from 18 days to 16 years with a median age of 7.5 years (IQR, 3.25–10.25) in cases with SARS-CoV-2 RNAaemia and 5 years (IQR, 1.5–11.25) in cases with the negative SARS-CoV-2 rRT-PCR blood results.

Out of 71 total blood type recorded patients with negative PCR blood tests, 18 were type A (25%), 23 were type B (32%), 4 were AB (6%) and 26 were O (37%). Out of the six recorded positive SARS-CoV-2 rRT-PCR blood tests, three patients had an A blood type (50%), one patient had AB (16.7%), one had B blood type (16.7%), and one had O (16.67%). A higher frequency of A blood type was seen in the cases with SARS-CoV-2 RNAaemia in comparison to the SARS-CoV-2 rRT-PCR blood negative results. The level of O_2 saturation did not differ between the two groups with and without SARS-CoV-2 RNAaemia (*p* value = .99).

Out of 87 recorded patients in the SARS-CoV-2 rRT-PCR blood test negative group, 50 patients had an underlying disease (57%); while, 5 of the 6 patients (83%) with SARS-CoV-2 RNAaemia had an underlying disease (*p* value = .39).

The median time between onset of symptoms to a positive test result for the six patients with SARS-CoV-2 RNAaemia was 2 days (IQR, 1.75–3.25), while the median for the 87 recorded negative blood test patients was 3 days (IQR, 1–7) (*p* value = .44). Presentation of symptoms such as fever, sore throat, cough, tachypnea, chest pain, rhinorrhea, diarrhea, abdominal pain, headache, and vomiting was recorded between the patients with and without SARS-CoV-2 RNAaemia (Table 1). Out of 88 recorded patients without SARS-CoV-2 RNAaemia, 67 patients

TABLE 1 The demographic and clinical characteristics of the patients with COVID-19

	Positive rRT-PCR blood test ($n = 6$)	Negative rRT-PCR blood test ($n = 90$)	p value
Parameter			
Age in years, median (IQR)	7.5 (3.25–10.25)	5 (1.5–11.25)	.63
Comorbid conditions, no. (%)	5 (83)	50 (57)	.39
Hospital stay, mean (*SD*)	17.0 (15.1)	12.66 (12.64)	.42
ICU admission, no. (%)	3 (50)	27 (30)	.38
Mechanical ventilation required, no. (%)	2 (33)	16 (18)	.32
Intubation required, no. (%)	2 (33)	9 (10)	.14
Severe disease, no. (%)	4 (67)	34 (37)	.21
Mortality, no. (%)	2 (33)	8 (9)	.12
Symptoms			
Duration of symptoms in days before positive test	2 (1.75–3.25)	3 (1–7)	.44
Fever, no. (%)	6 (100)	67 (76)	.33
Sore throat, no. (%)	0 (0)	3 (3.2)	>.999
Cough, no. (%)	3 (50)	30 (34.5)	.66
Tachypnea no. (%)	4 (47)	34 (39)	.22
Chest pain, no. (%)	0 (0)	5 (5.7)	>.999
Rhinorrhea, no. (%)	0 (0)	2 (2.3)	>.999
Diarrhea, no. (%)	0 (0)	17 (19)	.36
Abdominal pain, no. (%)	1 (17)	22 (25)	>.999
Headache, no. (%)	0 (0)	13 (15)	.59
Vomiting, no. (%)	3 (50)	26 (30)	.37

Abbreviations: IQR, interquartile range; *SD*, standard deviation.
Statistically significant ($p < .05$).

with a fever (76%). All six patients with SARS-CoV-2 RNAaemia had a fever. Out of 93 recorded patients, three patients experienced sore throat (3.2%). All of these three patients tested negative in their SARS-CoV-2 rRT-PCR blood test. Out of 87 recorded patients, 30 patients were recorded to have a cough (34.5%). Three out of the six in the SARS-CoV-2 rRT-PCR positive blood test group were also recorded to have a cough (50%). Within the SARS-CoV-2 rRT-PCR blood test negative group, 34 of the 87 total recorded patients suffered from tachypnea (39%). Although, four out of the six patients with positive blood test results had tachypnea (47%) (p value = .22). Out of 87 recorded SARS-CoV-2 rRT-PCR blood negative patients, 5 reported chest pain (5.7%). None of the patients in the positive group are reported chest pain (Table 1).

Out of the negative SARS-CoV-2 rRT-PCR blood test patients, 17 had diarrhea (19.3%). None of the positive SARS-CoV-2 rRT-PCR blood test patients presented with diarrhea (p value = .36). Out of 88 recorded blood-negative patients, 22 had abdominal pain (25%) while only one patient in the SARS-CoV-2 rRT-PCR blood-positive group is recorded to had abdominal pain (17%).

Out of negative SARS-CoV-2 rRT-PCR blood test patients, 26 had vomiting (30%) while three out of the 6 of the positive patients presented with vomiting (50%) (p value = .37).

3.2 | Mortality

Thirty-day all-cause mortality was calculated using all deaths within 30 days of confirmed patients with COVID-19. Out of all recorded patients in this study with COVID-19, 10 passed away. Two out of the 6 patients with SARS-CoV-2 RNAaemia passed away (33%). In comparison, 8 of the 90 total out of the SARS-CoV-2 rRT-PCR blood test negative patients passed away (9%) (p value = .12). Among six patients with positive SARS-CoV-2 RNAemia, 2 developed multi-organ failure and died.

3.3 | Severity

In 34 patients out of the 90 SARS-CoV-2 rRT-PCR blood test negative patients (38%), the disease manifested severely. Out of the six patients with SARS-CoV-2 RNAaemia, four (67%) had a severe form of the disease (p value = .213).

3.4 | ICU admission

The median duration of time spent in the hospital for the 90 recorded SARS-CoV-2 rRT-PCR blood negative patients was 8 days (IQR, 5–15). In comparison, the length of time was relatively longer for the 6 recorded patients with SARS-CoV-2 RNAaemia with a median of 11 days (IQR, 6.75–29.75).

Out of the 90 patients with negative SARS-CoV-2 rRT-PCR blood test, 27 (30%) were admitted to the ICU. On the other hand, 3 (50%) of the positive patients were admitted to the ICU (p value = .376).

Sixteen of 90 recorded patients (18%) in the negative test group needed ventilation while 2 (33%) of the positive patients needed ventilation. Among patients with the PCR blood test negative group, 9 patients were intubated (10%) (p value = .318). On the other hand, 2 of the patients with SARS-CoV-2 RNAaemia were intubated (33%) (p value = .144).

3.5 | Laboratory findings

The laboratory findings of the patients with negative SARS-CoV-2 rRT-PCR blood test are shown in Table 2. The median level of white blood count of negative SARS-CoV-2 rRT-PCR blood test was $9.4 \times 10^3/\mu l$ (IQR, 6.1–12.8). Comparatively, the median white blood count for patients with SARS-CoV-2 RNAaemia was $7.705 \times 10^3/\mu l$ (IQR, 0.7–9.27) (p value = .171). The lymphocyte counts of the patients with SARS-CoV-2 RNAaemia were at a median level of $1.1 \times 10^3/\mu l$ (IQR, 0.45–2.35). The median value for the patients with negative SARS-CoV-2 rRT-PCR blood tests was $2.1 \times 10^3/\mu l$ (IQR, 1.1–3.6) (p value = .141).

Platelet test counts were found to be at a median level of $238 \times 10^3/\mu l$ (IQR, 28.5–311.75) in the positive group and $255 \times 10^3/\mu l$ (IQR, 159–365.25) in the 90 recorded patients in the negative group (p value = .229).

Creatine phosphokinase tests showed notable differences between the positive and negative groups. The median value for the positive test group was 30.5 U/L (IQR, 22–54.75) and 60 U/L (35–102) for the patients' negative SARS-CoV-2 rRT-PCR blood test (p value = .045). There was a significant difference between the median level of magnesium between the groups (p value = .022). The positive group median was marked as 1.5 mg/dl (IQR, 1.4–1.85), while the negative group had a median level of 1.9 mg/dl (IQR, 1.7–2.2).

There was also a difference seen in the C-reactive protein (CRP) values between the groups. The median was recorded at 60.5 mg/L (IQR, 14.5–134.75) for the patient with SARS-CoV-2 RNAaemia. It was recorded at a lower level of 13.5 mg/L (IQR, 4–41.25) for the 86 recorded patients in the negative SARS-CoV-2 rRT-PCR blood test group (p value = .106). Erythrocyte sedimentation rate (ESR) level medians were also vastly different amongst the groups (p value = .068). The positive SARS-CoV-2 rRT-PCR blood test group had a median of 60.5 mm/h (IQR, 14.25–100.75), and the 82 recorded patients in the negative SARS-CoV-2 rRT-PCR blood test group had a median level of 24 mm/h (IQR, 11.75–45.25).

The AUC of all laboratory tests was used to predict SARS-CoV-2 RNAemia (Table 2). Among all tests, magnesium and creatine phosphokinase could better predict SARS-CoV-2 RNAemia with AUC levels of 0.808 and 0.748, respectively.

4 | DISCUSSION

As the COVID-19 outbreak progresses, it becomes increasingly important to quantify different aspects of pediatric cases of the disease. Increasing evidence suggesting that pediatric cases are less severe should be grounds to expand research, rather than focus efforts elsewhere, as the younger generation plays a large role in disease transmission.[12–14] Such research is key in developing therapies and precautionary policies in places where large bodies of children congregate, such as in schools, to slow the spread of COVID-19.[15] Our study on diagnostic testing for SARS-CoV-2 infection has potentially important implications on this aspect of public health. To our knowledge, this is the largest report that evaluated SARS-CoV-2 viral RNA in serum samples of pediatric cases with COVID-19.

As viral load in respiratory specimens of both asymptomatic and symptomatic patients might show, detection of SARS-CoV-2 may not accurately reveal the disease severity.[10,16]

In this study, 6% of patients had SARS-CoV-2 RNAaemia. Serum/plasma SARS-CoV-2 viral RNA was detected in 9.4% to 74.1%, with a pooled estimate of 34% (95% CI, 26%–43%) in patients with a positive nasopharyngeal swab RT-PCR test.[7–10,17,18]

Our results show that the symptoms that are more commonly found in cases with COVID-19 (fever, cough, tachypnea, and vomiting), were found at a higher percentage in the patients with SARS-CoV-2 RNAaemia. Less commonly observed symptoms (sore throat, chest pain, rhinorrhea, diarrhea, abdominal pain, and headache), were rare or not found in both the negative and positive PCR blood test groups.

As shown above, the patients with SARS-CoV-2 RNAaemia had a shorter average time between the onset of symptoms to a positive test result (p value = .49). This may indicate that the PCR blood test might be more accurate for patients that have a faster-progressing form of COVID-19. Moreover, out of the six patients with SARS-CoV-2 RNAaemia, four (67%) had a severe form of the disease. Tang et al.[18] reported that the COVID-19 manifested more severely in patients with SARS-CoV-2 RNAaemia. In our study, there is evidence that COVID-19 patients who test positive on a blood SARS-CoV-2 rRT-PCR test and a nasopharyngeal SARS-CoV-2

TABLE 2 Clinical laboratory data and receiver operator characteristic curves comparing the potential of different laboratory tests to predict the SARS-CoV-2 RNAaemia

	Patients with SARS-CoV-2 RNAaemia		Patients without SARS-CoV-2 RNAaemia				
Parameter	Median	IQR	Median	IQR	*p* value*	AUC	*p* value
White blood cell count (×10⁹ cells per L)	7.7	0.7–9.27	9.4	6.1–12.8	.171	0.668	.138
Red blood cell count (×10⁹ cells per L)	4.5	3.9–5.6	4.5	3.7–5.085	.576	0.568	.625
Haemoglobin (g/dl)	11.6	9.3–13.1	11.8	10.2–13.2	.694	0.548	.690
Platelet count (×10⁹ cells per L)	238	28.5–311.75	255.5	159.0–365.25	.229	0.647	.218
Neutrophil count (×10⁹ cells per L)	5.2	2.7–8.2	4.5	2.8–9.575	.973	0.505	.970
Lymphocyte count (×10⁹ cells per L)	1.1	0.45–2.35	2.1	1.1–3.6	.141	0.697	.095
Urea (mmol/L)	13	10.5–17.75	12.0	8.0–16	.462	0.590	.372
Creatinine (μmol/L)	0.6	0.4–0.7	0.6	0.4–0.7	.702	0.546	.651
Creatine phosphokinase (U/L)	30.5	22.0–54.75	60.0	35.0–102	**.045**	0.748	**.004**
Lactate dehydrogenase (U/L)	615.5	481.25–986.25	583.0	417.0–780.5	.61	0.563	.587
Calcium (mg/dl)	9.1	8.4–9.9	9.1	8.4–9.6	.81	0.532	.831
Phosphorus (mg/dl)	4.4	3.6–4.95	4.2	3.8–4.95	.97	0.500	.969
Magnesium (mg/dl)	1.5	1.4–1.85	1.9	1.7–2.2	**.022**	0.808	**<.001**
Sodium (meq/L)	135.5	130.5–138.25	136.0	132.0–138	.692	0.548	.707
Potassium (meq/L)	3.9	3.6–4.25	4.2	4.0–4.6	.105	0.698	.145
Alanine aminotransferase (U/L)	29.5	20.3–36	32.0	23.5–46	.39	0.606	.270
Aspartate aminotransferase (U/L)	19.5	13.0–27.5	21.0	14.0–44	.525	0.579	.419
Procalcitonin (ng/ml)	0.025	0.017–0.27	0.02	0.01–0.1	.482	0.583	.380
Prothrombin time (s)	13.3	13.1–14.65	13.3	12.5–14	.389	0.600	.368
Partial thromboplastin time (s)	31.5	30.0–35	33.0	30–37	.363	0.610	.361
International normalized ratio	1.1	1–1.1	1.1	1-1.2	.449	0.589	.275
C-reactive protein (mg/L)	60.5	14.5–134.75	13.5	4.0–41.25	.106	0.698	.164
Erythrocyte sedimentation rate (mm/h)	60.5	14.3–100.75	24.0	11.8–45.25	.068	0.724	.065

AUC, area under the curve.

*p values for differences between the two groups were obtained by a Mann–Whitney U test. Statistically significant ($p < .05$).

rRT-PCR test may have a more severe form of the disease than patients who test negative on the blood SARS-CoV-2 rRT-PCR test and positive on the nasopharyngeal PCR test. Moreover, a higher mortality rate was found for the patients with positive SARS-CoV-2 rRT-PCR blood tests compared to the patients who tested negative (p value = .12).

It is interesting to note that the blood markers are the most conclusive pieces of data in identifying differences with the patients with SARS-CoV-2 RNAaemia. Creatine phosphokinase and magnesium tests showed significant differences between the positive and negative SARS-CoV-2 RNAaemia groups. Among all laboratory tests, magnesium and creatine phosphokinase could better predict SARS-CoV-2 RNAemia with AUC levels of 0.808 and 0.748, respectively. It has been reported that magnesium deficiency might play a role in COVID-19 onset, progression, and severity.[19] In our study, the most notable differences between the SARS-CoV-2 rRT-PCR blood test positive and negative groups were found in the level of magnesium. Patients with SARS-CoV-2 RNAaemia had a significantly lower level of magnesium. This variation in levels of magnesium and creatine phosphokinase can be markers of a SARS-CoV-2 RNAaemia.

Similar to the previous report,[8] patients with SARS-CoV-2 RNAaemia had a longer median length of hospital stay. In this study, SARS-CoV-2 viremia is associated with inflammatory markers and disease severity too. In previous reports, higher CRP and IL-6 levels were found in cases with detectable RNAaemia.[9,10]

This study has several limitations. Firstly, the sample size, particularly the patients with SARS-CoV-2 RNAaemia, was relatively small, which

might have some impact on the statistical results. Second, as our hospital is a referral pediatrics center, children with a complicated disease are referred to our center; therefore, our research may reflect a more serious type of COVID-19, and results should be interpreted with caution. More research will need to be done to determine the importance and strength of our findings. Further targeted studies on comparison in the severity of COVID-19 cases in pediatric patients that have SARS-CoV-2 rRT-PCR blood positive and SARS-CoV-2 rRT-PCR blood negative are highly recommended. Further research in this vein, can have important implications on the usage of nasopharyngeal and blood SARS-CoV-2 rRT-PCR tests and what they can convey.

In conclusion, 67% of individuals with SARS-CoV-2 RNAaemia showed a severe COVID-19 and one-third of the patients with SARS-CoV-2 RNAaemia passed away. However, the sample size of the patients with SARS-CoV-2 RNAaemia was small and further studies with a larger sample size are highly recommended. Our findings suggest that magnesium and creatine phosphokinase might be considered as markers to estimate the SARS-CoV-2 RNAaemia.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Babak Pourakbari, Shima Mahmoudi, and Setareh Mamishi participated in the research design. Yasmine Mahmoudieh wrote a draft of the manuscript and Shima Mahmoudi revised it. All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

All analysis is available from the corresponding author on reasonable request. All the remaining data are included in this article.

ORCID

Babak Pourakbari https://orcid.org/0000-0001-7679-5899
Shima Mahmoudi https://orcid.org/0000-0003-3557-6432
Setareh Mamishi https://orcid.org/0000-0002-8851-3622

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