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RESEARCH ARTICLE

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Oxidative stress and decreased Nrf2 level in pediatric patients with COVID-19

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Abstract

The aim of this study was to investigate the change in nuclear factor erythroid 2-related factor (Nrf2), which plays a critical role in cytoprotection against oxidative stress, in pediatric patients with coronavirus disease 2019 (COVID-19) infection positivity, and to evaluate the relationship between Nrf2 and oxidative balance. The study included 40 children with confirmed COVID-19 infection and 35 healthy children. The groups were compared in respect of Nrf2, total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI), in addition to clinical findings of fever, cough, shortness of breath, contact history, and demographic data of age and gender. The mean Nrf2 values and TAS levels were determined to be statistically significantly low ($p < 0.001$) and the TOS level and OSI were statistically significantly high in the children with COVID-19 compared to the control group. A significant positive correlation was determined between Nrf2 and TAS ($p < 0.01$); as the Nrf2 value increased, so the TAS value increased. A significant negative correlation was determined between Nrf2 and TOS and OSI ($p < 0.01$); as the Nrf2 value increased, there was determined to be a significant decrease in the TOS and OSI values. COVID-19 infection in pediatric patients causes a decrease in the Nrf2 level. By causing a decrease in the TAS level and an increase in the TOS and OSI levels, the decrease in Nrf2 may explain the tissue damage which can be caused by COVID-19.

KEYWORDS
COVID 19, Nrf2, oxidative stress, pediatrics

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by SARS coronavirus-2 (SARS-CoV-2) was declared a global pandemic by the World Health Organization on March 11, 2020.[1] The disease spread to more than 220 countries worldwide. With global case numbers of 177 million and deaths having reached 3,829,037 (as of June 15, 2021), this global pandemic has become a public health crisis.[2] Just as COVID-19 may cause fever, cough, shortness of breath, sore throat, myalgia, headache, and diarrhea in children, in both children and young adults with an underlying disorder such as pulmonary function disorder or immunosuppression, the risk of COVID-19 has been reported to be higher.[3,4] Respiratory tract viral infections, primarily COVID-19, are generally associated with other pathological processes which may be related to cytokine production, inflammation, cell death, and redox imbalance or oxidative stress.[5–7]

Oxidative stress, which develops associated with reactive oxygen species (ROS), may be the point of connection explaining all the basic changes observed in inflammatory and infectious diseases.[8] Nuclear factor erythroid 2-related factor (Nrf2), which is a transcription factor, is responsible for the adaptation of cells under electrophilic or oxidative stress. Under normal conditions,

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Nrf2 is found in the cytoplasm bound to Keap1. In the presence of electrophiles or ROS, the Keap1–Nrf2 complex separates and Nrf2 migrates to the nucleus stimulated by transcription of target genes together with antioxidant response element sequences. Nrf2 controls the expression of genes participating in antioxidant response, redox homeostasis, and mitochondria biogenesis. The activation of these genes protects cells from inflammation.[9]

The aim of this study was to determine the relationship between Nrf2 and oxidative balance in pediatric patients with COVID-19, and to determine the roles of these in disease severity.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This prospective study included 40 pediatric patients who presented at the emergency polyclinic with clinical findings suggestive of COVID-19 or a history of contact with a COVID-19-infected case and were diagnosed with COVID-19 confirmed with reverse transcriptase polymerase chain reaction (RT-PCR) between July 2020 and July 2021, and a control group of 35 healthy children selected from those who presented at the general pediatric polyclinic for a routine health check-up.

Permission for the study was obtained from the Ministry of Health. Approval for the study was granted by the Ethics Committee of Harran University Medical Faculty (decision no: 25, session no: 11, dated 15.06.2020). All the study procedures were applied in compliance with the Declaration of Helsinki.

2.1.1 | Inclusion criteria

Cases aged <18 years with COVID-19 infection confirmed with RT-PCR.

2.1.2 | Exclusion criteria

Cases with a negative RT-PCR result despite a contact history or clinical suspicion of COVID-19, cases with a positive RT-PCR result who started treatment but were exposed to cigarette smoke or had a chronic systemic disease such as hypertension, chronic lung disease, diabetes mellitus, congenital heart disease, malignancy, or immune failure, or cases with a recent history of trauma.

2.1.3 | Collection of samples for COVID-19 and analysis

Nasopharyngeal smear samples were taken by an Ear, Nose, and Throat specialist from cases with suspected COVID-19 infection. The agent was investigated with RT-PCR of the samples collected.

Collection of blood samples and analysis

Blood sampling. A 2 ml venous blood sample was collected from all the cases in the study on first presentation at hospital before any treatment was started. The blood samples were withdrawn into red top plain blood collection tubes that did not contain any solution. The samples were centrifuged at 1000*g* for 10 min to separate the plasma. The plasma samples were stored at −80°C until analysis.

2.2 | Analyses

2.2.1 | Measurement of the Nrf2

Nrf2 levels were analyzed according to the commercially available ELISA kit method (BT-LAB). In this method, microplates coated with human Nrf2 antibodies are used. Serum samples are added to these plates and then incubated. After washing the plates, Streptavidin-horseradish peroxidase secondary antibody is added and again incubated. After the next washing, with the addition of substrate, a color is formed. The reaction is stopped by adding a stop solution and absorbance is measured at 450 nm on a microplate reader (Thermo-Go).

2.2.2 | Measurement of the TAS

The total antioxidant status measurements were made using brand commercial kits (Rel Assay Diagnostic Gaziantep) on a microplate reader system (Varioskan Lux; Thermo Scientific). Briefly, free radical reactions were initiated by the Fenton reaction and monitored by absorbance of the dianisidyl radicals. This reaction was measured spectrophotometrically at 660 nm. Using this method, the antioxidative effect was measured as the relative amount of free dianisidyl radicals.[10,11] The precision of this test has high accuracy (<3% error rate). The data were expressed in mmol Trolox equivalent/L.

2.2.3 | Measurement of the TOS

The total antioxidant status measurements were made using brand commercial kits (Rel Assay Diagnostic Gaziantep) on a microplate reader system (Varioskan Lux; Thermo Scientific). according to the method of Erel.[10,11] Briefly, oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically (at 530 nm), is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide, and the results are expressed as μmol H_2O_2 equivalent/L.

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2.2.4 | Calculation of the OSI

To calculate the OSI, the resulting TAS units were converted to mmol/L, and the OSI value was calculated according to the following formula: OSI (arbitrary unit) = TOS (mmol H_2O_2 equivalent/L)/TAS (mmol Trolox equivalent/L).

2.3 | Statistical analysis

Statistical analysis was performed using SPSS version 24.0 software (SPSS Inc.). Power analysis was performed using G*Power v3.1.9.4 to detect the sample size. Descriptive statistics were summarized as number, percentage, median (minimum–maximum), mean, and SD. The conformity of variables to normal distribution was investigated using visual methods (histogram and probability graphs) and the Kolmogorov–Smirnov test. Continuous variables were analyzed with either the Student's *t*-test or the Mann Whitney *U*-test depending on distribution and homogeneity of the data. Pearson correlation testing was used to investigate the relationships between parameters. The correlation coefficient (*r*) was found as a result of Spearman correlation analysis. A value of $p < 0.05$ was accepted as statistically significant.

3 | RESULTS

Evaluation was made of a total of 75 children comprising 36 (48%) females and 39 (52%) males with a mean age of 8.18 ± 3.72 years (range, 0–15 years), in two groups as 40 COVID-19-positive patients and a control group of 35 healthy children. Of the COVID-19-positive patients, 27 (67.5%) were symptomatic. Complaints were recorded of high temperature in 22 (55%) cases, listlessness in 12 (30%), cough in 6 (15%), respiratory problems in 5 (12.5%), diarrhea in 4 (10%), abdominal pain in 4 (10%), joint pain in 1 (2.5%), and vomiting in 2 (5%). There was no significant difference between the groups in respect of age or gender ($p > 0.05$). In the COVID-19-positive cases, the TAS and Nrf2 measurements were statistically significantly low ($p < 0.001$) and the TOS and OSI measurements were statistically significantly high ($p < 0.01$) (Table 1).

Comparisons were made within the group of COVID-19 positive cases according to symptomatic status. There was no significant difference between symptomatic and asymptomatic cases in respect of age and gender ($p > 0.05$). In the symptomatic cases, the Nrf2 measurements were statistically significantly low ($p = 0.03$) and the TOS and OSI measurements were statistically significantly high ($p < 0.01$). The TAS values were similar in both groups ($p > 0.05$) (Table 2).

A statistically significant positive correlation was determined between Nrf2 and TAS ($p < 0.01$). A statistically significant negative correlation was determined between Nrf2 and TOS and OSI ($p < 0.01$; Table 3 and Figure 1).

TABLE 1 Evaluations according to COVID-19 status

	COVID-19 (+) (*n* = 40) Mean ± SD	COVID-19 (−) (*n* = 35) Mean ± SD	*p*[a]
Age (years)	8.75 ± 4.09	7.54 ± 3.18	0.156
Gender; *n* (%)			
Male	21 (52.5)	18 (51.4)	0.926[b]
Female	19 (47.5)	17 (48.6)	
TAS (mmol Trolox equiv./L)	1.16 ± 0.15	1.50 ± 0.12	*0.001*[a]
TOS(μmol H_2O_2/L)	16.63 ± 4.46	12.05 ± 2.44	*0.001*[a]
OSI	1.45 ± 0.44	0.81 ± 0.19	*0.001*[a]
Nrf2 (μg/ml)	1.46 ± 0.38	3.08 ± 1.24	*0.001*[c]

Note: *p* values less than 0.05 are highlihted in italic.

Abbreviations: Nrf2, nuclear factor erythroid 2; OSI, oxidative stress index; TAS, total antioxidant status; TOS, total oxidant status.

[a]Student's *t*-test.

[b]Pearson χ^2 test.

[c]Mann Whitney *U*-test.

TABLE 2 Evaluations of the COVID-19 positive cases according to symptomatic status

COVID 19 (+)	Symptomatic (*n* = 27) Mean ± SD	Asymptomatic (*n* = 13) Mean ± SD	*p*[a]
Age (years)	8.11 ± 4.12	10.07 ± 3.86	0.15[a]
Gender, *n* (%)			
Male	15 (55.6)	6 (46.2)	0.57[b]
Female	12 (44.4)	7 (53.8)	
TAS (mmol Trolox equiv./L)	1.16 ± 0.16	1.14 ± 0.15	0.74[a]
TOS (μmol H_2O_2/L)	18.21 ± 3.68	13.36 ± 4.27	*0.001*[a]
OSI	1.59 ± 0.42	1.15 ± 0.31	*0.002*[a]
Nrf2 (μg/ml)	1.37 ± 0.32	1.65 ± 0.45	*0.032*[c]

Note: *p* values less than 0.05 are highlihted in italic.

Abbreviations: Nrf2, nuclear factor erythroid 2; OSI, oxidative stress index; TAS, total antioxidant status; TOS, total oxidant status.

[a]Student's *t*-test.

[b]Pearson χ^2 test.

[c]Mann–Whitney test.

TABLE 3 Correlations between the Nrf2 levels and TAS, TOS, and OSI

Nrf2 (μg/ml)	*r*	*p*
TAS (mmol H_2O_2 Eqv/l)	0.566	*0.000*
TOS (mmol Trolox Eqv/l)	−0.406	*0.000*
OSi (arbitrary unit)	−0.525	*0.000*

Note: *p* values less than 0.05 are highlihted in italic.

Abbreviations: Nrf2, nuclear factor erythroid 2; OSI, oxidative stress index; *r*, Spearman's correlation coefficient; TAS, total antioxidant status; TOS, total oxidant status.

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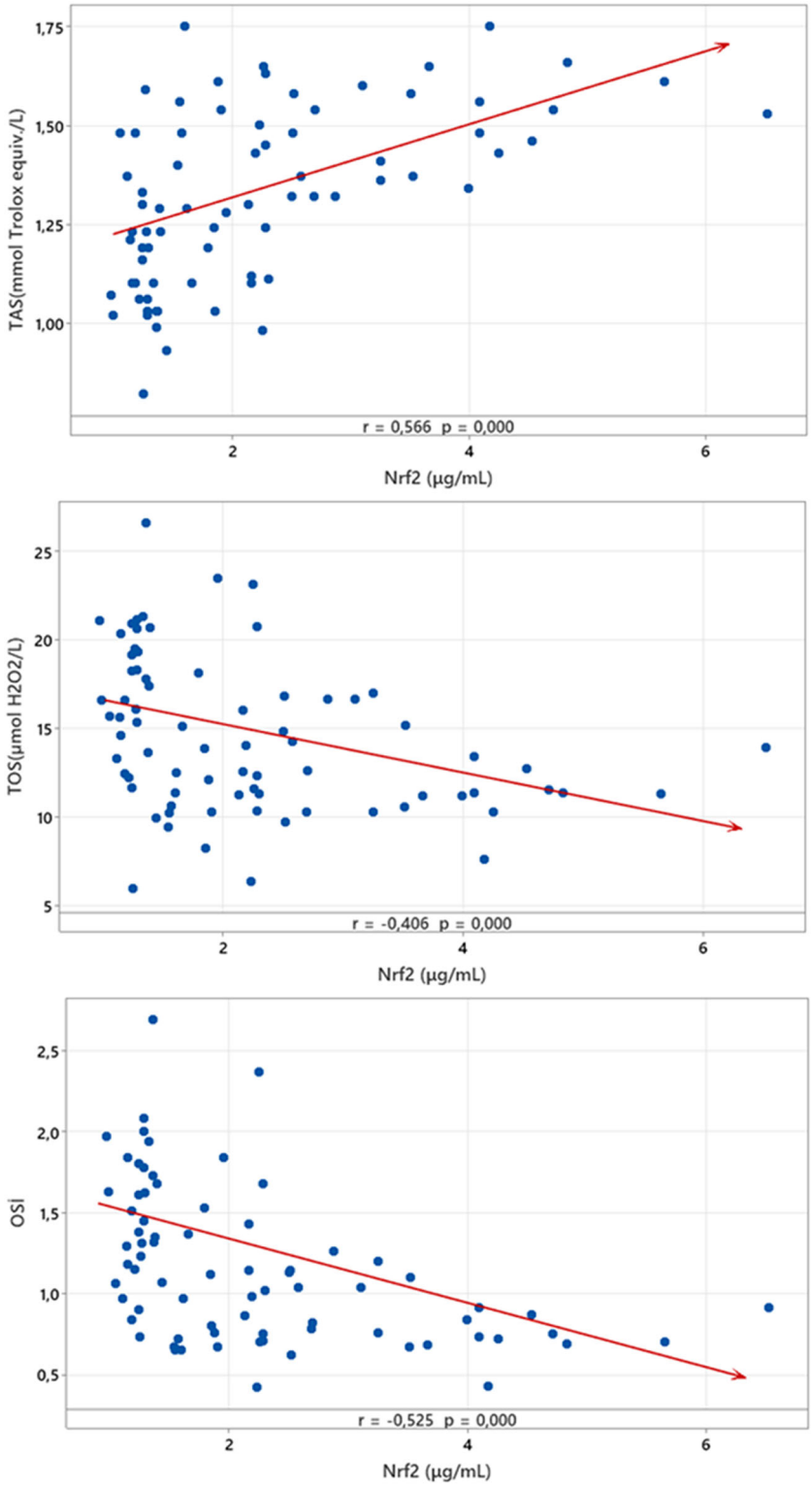

FIGURE 1 Correlation graphs between Nrf2 levels and TAS, TOS, and OSI. Nrf2, nuclear factor erythroid 2-related factor; OSI, oxidative stress index; TAS, total antioxidant status; TOS, total oxidant status

4 | DISCUSSION

The results of this study demonstrated that the Nrf2 level was significantly decreased in all COVID-19 patients, more significantly in symptomatic cases than in asymptomatic, and associated with this there was a significant increase in TOS and OSI values and a decrease in the TAS level. By leading to an increase in ROS, the decrease in Nrf2, which plays a key role in oxidative stress, may explain the tissue damage which can be caused by COVID-19.

As oxidative stress plays an important role in the response to infections, it may also be a significant player in the pathogenesis of COVID-19.[12,13] Studies have shown that oxidative stress regulates the host immune system in viral diseases

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such as hepatitis B, hepatitis C, herpes simplex virus, and influenza.[14–16] Oxidative stress has also been found to contribute to the pathogenesis of various pulmonary diseases in children such as pneumonia, asthma, acute bronchiolitis, cystic fibrosis, acute respiratory syndrome, and chronic neonatal pulmonary disease.[17,18] Studies have reported a potential link between oxidative stress and the pathogenesis, disease severity, and mortality risk of patients infected with SARS-CoV-2.[13,19] Karsen et al [20] determined a decrease in TAS and increase in TOS in Brucellosis patients. It was reported that increasing oxidative stress could cause lipid peroxidisation, protein denaturation, and DNA breakdown. In a study by Komaravelli et al.[21] respiratory tract disease caused by respiratory syncytial virus (RSV), pulmonary damage and the onset of inflammation, and the exacerbation of ROS production were reported to be associated with oxidative stress. Aykaç et al.[22] found a significantly high TOS level in children infected with COVID-19 compared to a healthy control group, and reported that there could be a correlation between serum oxidant and antioxidant stress parameters and disease severity in COVID-19 patients. In the current study, the TAS level was determined to be significantly low, and the TOS and OSI values were high in pediatric patients with COVID-19 positivity. When the cases diagnosed with COVID-19 were evaluated, the TOS and OSI values were determined to be high in symptomatic cases, and TAS levels were similar in symptomatic and asymptomatic patients.

In the last 10 years there have been many publications about Nrf2 and its effects on redox homeostasis, inflammation and immunity, neurodegeneration, ageing and age-related diseases, ischemia–reperfusion damage and several other areas, but there are relatively few studies about the role of Nrf2 in these. Although Nrf2 regulates a series of genes that form a defence against oxidative stress, including superoxide dismutases, catalases, innumerable peroxidases, and glutathione-synthesizing enzymes, it also regulates the redox balance.[23,24] Cho et al.[25] investigated RSV, which can be defined as the most important virus causing acute respiratory tract infections in children. Nrf2−/− rats infected with RSV were compared with similarly infected Nrf2+/+ rats and were found to show findings of bronchopulmonary inflammation, epithelial damage, mucous cell metaplasia, and nasal epithelial damage. The Nrf2−/− rats also showed significantly decreased viral clearance and IFN-y, and greater weight loss. McCord et al.[24] reported that if Nrf2-deficient cells could not provide sufficient Nrf2 activation to break the spontaneously continuing chain reaction, an uncontrolled cytokine storm could develop leading to host tissue destruction and death. In the current study, the Nrf2 level in COVID-19-positive pediatric patients was determined to be significantly decreased. Moreover, when the cases diagnosed with COVID-19 were evaluated, the Nrf2 level was determined to be even lower in symptomatic patients than in asymptomatic patients.

Nfr2 is a primary regulating transcription factor, and induces genes which play a critical role in cytoprotection against oxidative and xenobiotic stresses.[26] In a study by Komaravelli et al.[21] Nrf2 levels were determined to be reduced associated with RSV infection. It was reported that Nfr2 played a significant role in respiratory tract disease caused by RSV, pulmonary damage and the onset of inflammation, and the exacerbation of ROS production, and the reduction in Nfr2 was probably associated with secondary increasing ROS production and oxidative stress. Hybertson et al.[27] showed that Nfr2 activation reduced the rate of viral replication and weakened symptoms by limiting microvascular damage, and could provide the possibility of successful follow-up throughout the cytokine storm, which is a particular problem associated with COVID-19.

In the current study, the Nrf2 level was determined to be significantly decreased, together with a significant decrease in TAS, and significantly high TOS and OSI values in pediatric patients with COVID-19. A statistically significant positive correlation was determined between Nrf2 and TAS ($p < 0.01$), and as Nrf2 increased, so the TAS value also significantly increased. A statistically significant negative correlation was determined between Nrf2 and TOS and OSI ($p < 0.01$), and as Nrf2 increased, so the TOS and OSI values also significantly decreased.

5 | CONCLUSION

COVID-19 infection in pediatric patients causes a decrease in the level of Nrf2, which creates a defence against oxidative stress and regulates the redox balance. By causing a decrease in TAS level and an increase in TOS and OSI levels, the decrease in Nrf2 in pediatric COVID-19 patients may explain the tissue damage which can be caused by COVID-19.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study conformed to the principles of the 2008 Declaration of Helsinki and was approved by the local ethics committee of Harran University, Medical Faculty, Turkey (decision no: 25, session no: 11, dated 15.06.2020).

AUTHOR CONTRIBUTIONS

Concept: Huseyin Gumus and Tuğba Erat. *Design*: Huseyin Gumus. *Data collection and processing*: Huseyin Gumus, Tuğba Erat, and İsmail Koyuncu. *Analysis and interpretation*: İrfan Öztürk and Huseyin Gumus. *Literature review and writing*: Huseyin Gumus and Abit Demir. *Critical review*: Huseyin Gumus and Abit Demir.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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