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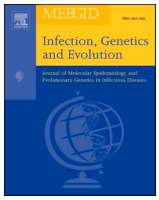

Genotoxic risks in patients with COVID-19

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ABSTRACT

The COVID-19 pandemic has caused numerous deaths worldwide. Despite the mitigation of infection manifestations in recent months, the possible consequences of the epidemic remain difficult to predict. Genotoxicity and subsequent development of neoplasms are possible outcomes. This review summarises the data on these questions. Studies from several countries have reported increased levels of DNA damage in nucleated blood cells of patients with severe forms of COVID-19 infection. The level of DNA damage can be used as a prognostic factor for the disease outcome. It is considered that SARS-CoV-2 spike proteins play a crucial role in DNA damage; however, the virus also inhibits the DNA repair system. Co-morbidities and use of antiviral drugs may also contribute to DNA damage in patients with COVID-19.

1. Introduction

The coronavirus disease (COVID-19) has caused numerous deaths worldwide. This process has continued until the fourth year when it was first detected. Although the mortality rate is decreasing, the virus is responsible for post-COVID-19 conditions. Survivors suffer from numerous sequelae, including respiratory pathologies, psychological problems, and cardiovascular, neurological, musculoskeletal, and gastrointestinal impairments (Løkke et al., 2023). Neoplasms have not yet developed; however, this possibility cannot be excluded. The effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on genome stability and DNA damage has received little attention because it is an RNA virus that replicates largely in the cytoplasm. Although there are limited studies on how SARS-CoV-2 infection affects certain molecular pathways, including oxidative stress and DNA damage, some have suggested that the virus causes damage to cellular DNA, as shown by the presence of micronuclei, DNA repair foci, and increased comet tails in infected cells. Genotoxic effects follow numerous other viral infections, including HIV, influenza viruses, Ebola virus, Zika virus, Enterovirus A71, Epstein-Barr virus, Parvovirus B19, and other viruses (Szewczyk-Roszczenko et al., 2025). Moreover, accumulation of the DNA breaks is characteristic of normal aging process (Delint-Ramirez and Madabhushi, 2025; Frey et al., 2025; Joudeh et al., 2024). DNA breaks are involved in the aetiology and pathogenesis of numerous diseases. Increased numbers of DNA breaks have been observed in patients with type 1 diabetes mellitus (Rostoka et al., 2021), type 2 diabetes mellitus (Blasiak et al., 2004), and gestational diabetes (Tola et al., 2022). It is also associated with rheumatoid arthritis (Galita et al., 2024), multiple sclerosis (Borisovs et al., 2019), Alzheimer's disease, and other neurodegenerative diseases (Roberts et al., 2024). The formation of additional DNA breaks can aggravate the course of a disease or trigger the development of pathologies.

Thus, the genotoxic effects of COVID-19 infection should be attentively monitored.

For the present review, PubMed database was used to search for keywords such as, “COVID-19 and DNA damage”, “SARS-CoV-2 and DNA damage”, and “COVID-19 and comet assay”.

Studies on humans. Early studies reported the importance of

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increased concentrations of oxidised guanine species in the serum of patients with COVID-19 as an indicator of poor prognosis associated with mortality (Lorente et al., 2021). Although the number of patients and controls was lower for statistically significant differences in micronucleated buccal mucosa cells of patients with COVID-19, a statistically significant increase in karyolysis and karyorexis was observed (Pinto et al., 2021). Several recent publications have reported increased levels of DNA breaks in nucleated blood cells of patients infected with COVID-19. In a study performed in Serbia (Mihaljevic et al., 2022), DNA damage in the lymphocytes of patients with severe forms of COVID-19 was compared with that in non-infected subjects. According to the alkaline comet assay data, the DNA in the lymphocytes of patients was heavily damaged. The level of DNA damage was slightly higher in female patients, and applied therapies (antibiotics, corticosteroids, anticoagulants, and antivirals) and chest X-rays have been shown to have genotoxic potential. Similar studies were performed in different parts of Türkiye during the pandemic. In a study by Doğan et al. (Doğan et al., 2023), DNA damage in patients with COVID-19 who were hospitalized due to severe infection was compared to that in healthy individuals. The case group exhibited increased levels of DNA damage. In another study conducted in Türkiye (Tepebaşı et al., 2023), participants with COVID-19 were grouped according to the severity of pneumonia. In the severe pneumonia group, the level of DNA damage in the lymphocytes was higher than that in patients with mild pneumonia. Decrease in the number of lymphocytes and increase in the number of neutrophils, as well as "cytokine storm", were reported in all above studies. Markers of oxidative stress increase in patients with COVID-19; thus, DNA damage by free radicals is considered the main mechanism of DNA break induction in COVID-19 (Tepebaşı et al., 2023). A recent report from Turkiye was performed on 50 patients with different disease severities, indicating increased levels of DNA breaks and oxidative stress parameters in COVID-19 infected individuals, and these parameters increased more dramatically in severe patients. SARS-CoV-2 infection may increase oxidative stress and DNA damage, and alter immune responses, which may be important in the pathophysiology of the disease (Basaran et al., 2023). Another study performed on a large group of patients (150 cases and 150 controls) confirmed increased levels of DNA damage, accompanied by an increase in oxidative stress and inflammation markers, and a decrease in the levels of antioxidant factors. These results indicate that induced DNA damage, inflammation, and oxidative stress can influence the prognosis and treatment strategies in patients with COVID-19 (Bektemur et al., 2023). However, in a study performed on 48 patients in Austria, increased DNA damage in white blood cells was observed only in patients younger than 69 years of age. Although they showed increased levels of oxidised glutathione, no other oxidative stress markers considerably changed (Draxler et al., 2023). In Armenia, DNA damage was elevated in the leukocytes of 65 patients with COVID-19 compared to controls. Increased DNA damage has been observed in severe cases, particularly in men. The authors proposed using the level of DNA damage as a prognostic indicator for disease outcomes (Harutyunyan et al., 2024). An Iranian team came to the same conclusion: they analysed 204 patients with COVID-19, all older than 60 years; the DNA break level and number of apoptotic cells were higher in the case group than in the control group. (Abiri et al., 2024a). Among individuals suffering from post-COVID syndrome, the study was performed on 231 individuals, and the level of DNA damage was not significantly higher compared to the healthy controls. However, when men and women were analysed as separate groups, some increase was detected among men (Martins et al., 2024). However, in another study conducted in Iran, a significant increase in DNA damage was observed in patients with a history of COVID-19 (Abiri et al., 2024b).

DNA was also damaged in the cardiac tissues of patients with COVID-19, although the virus had not been detected in the myocardium. Transcriptomic analysis of tissue samples taken during autopsy revealed an increase in genes involved in the DNA damage response (DDR) and expression of the DNA double-strand break marker, gamma-H2Ax histone (Kulasinghe et al., 2023). An in vitro study on cultured human cardiomyocyte AC16 also indicated the inability of SARS-CoV-2 to infect cardiomyocytes However, co-incubation of these cells with the serum of patients with COVID-19 increased the expression of gamma-H2Ax histone and markers of cell stress, indicating an indirect mechanism of DNA damage in the myocardium (Zhou et al., 2022). COVID-19 infection leads to DNA damage in spermatozoa, mainly via immune mechanisms (Depuydt et al., 2023) or oxidative stress, leading to decreased sperm quality (Osatd-Rahim et al., 2024), although SARS-CoV-2 has not been detected in semen.

Possible mechanisms of DNA damage. Increased DNA damage in patients with COVID-19 was predicted before the case/control studies were published (Pánico et al., 2022). In addition to oxidative stress, the authors suggested the possibility of dysregulating DNA repair mechanisms and controlling genomic stability via virion proteins. Lesiow et al. proposed a reasonable explanation for the DNA-damaging action of viral spikes (Lesiów et al., 2023). They demonstrated that two peptide fragments derived from the spike bind Cu[II] ions and form three-nitrogen complexes, which trigger the overproduction of reactive oxygen species (ROS), breaking DNA strands. ROS overproduction is observed mainly in the mitochondria. The observed increase in free mitochondrial DNA in the serum of patients with COVID-19 likely develops following the above mechanism (Valdés-Aguayo et al., 2021). When injected into mice, the spike protein triggers oxidative stress and double-stranded DNA breaks in the lung tissue of the animals. Similar effects were observed in human lung cell lines and explants, and the authors compared the spike-produced damage to the effects of ionising radiation (Greenberger et al., 2024). Spike protein S1, which binds to the angiotensin receptor, induces DNA breaks and premature senescence in cultured human endothelial cells (Villacampa et al., 2024). It exerts adverse effects on tumour cells by blocking p53 and other apoptosis-related factors, which decrease the sensitivity of cancer cells to chemotherapy (Zhang and El-Deiry, 2024).

SARS-CoV-2 infection interferes with DNA repair pathways via multiple mechanisms. In the peripheral blood mononuclear cells of patients with COVID-19, the base excision repair and DNA double-strand break repair pathways are up-regulated (Olsen et al., 2022). The oxidised base-specific glycosylase NEIL2 protects cells against SARS-CoV-2 infection; it binds to the 5′-UTR of the viral genomic DNA and synthesizes viral proteins (Tapryal et al., 2023). Infection by SARS-CoV-2 triggers a DDR in African monkey kidney cultured Vero cells by upregulating ataxia telangiectasia and Rad 3 related protein [ATR], enhancing phosphorylation of CKK1, a downstream effector of this pathway (Victor et al., 2021). A similar dysregulation of DNA repair pathways has also been observed in the leukocytes of hospitalized patients with COVID-19 (Polozov et al., 2023). In patients suffering from post-COVID-19 conditions, pulmonary pathology persists after the acute phase of the disease, and the efficiency of DNA repair is lower than that in healthy subjects, although the levels of DNA breaks and oxidative stress markers has not changed (Kankaya et al., 2023). Moreover, the SARS-CoV-2 proteins ORF6 and NSP13 degrade the DDR kinase CHK1 through proteasomes and autophagy. CHK1 loss leads to decreased deoxynucleoside triphosphate content in cells, causing S phase blockage, DNA damage, activation of pro-inflammatory pathways, and cellular senescence (Gioia et al., 2023). Polymorphisms in the DDR genes *XRCC1* and *XRCC4* are associated with susceptibility and resistance to SARS-CoV-2 infection (Senkal et al., 2023).

DNA damage facilitates the entry of SARS-CoV-2, DDR increases the expression of angiotensin-converting enzyme 2 (ACE2), the primary receptor of the virus (Jin et al., 2022). The expression of the ACE2 receptor increases upon telomere shortening, creating a risk factor for elderly individuals (Sepe et al., 2022). Furthermore, angiotensin II binds to its receptor and triggers ROS production in monocytes, resulting in DNA damage in neighbouring lymphocytes (Kundura et al., 2022). The possible mechanisms underlying the induction of DNA damage by SARS-CoV-2 are summarized in Fig. 1.

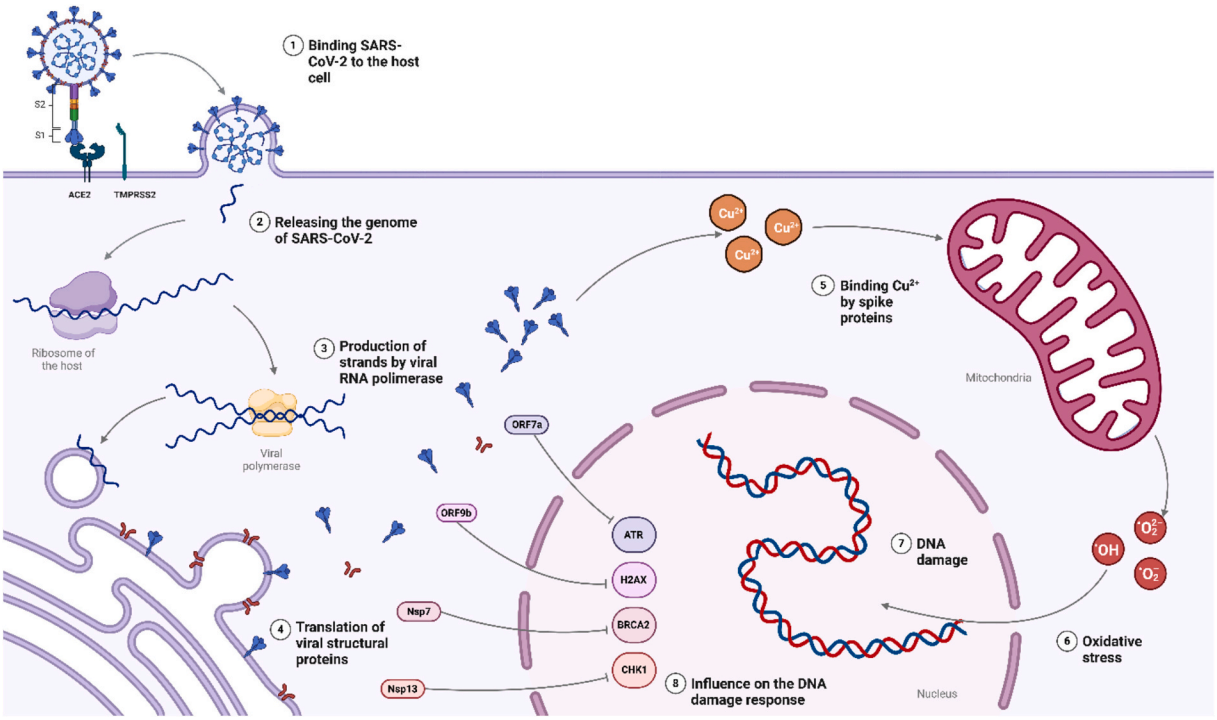

Fig. 1. Possible mechanisms of DNA damage by the SARS-CoV2 virus. The figure was originally created using BioRender software. PR holds a license for publishing of the figure.

Possible role of comorbidities. The contribution of the virus per se for the observed increase in DNA damage in patients with COVID-19 is difficult to evaluate. The observed differences in DNA damage between infected and non-infected individuals may be due to comorbidities. In the study by Tepebaşı et al. (Tepebaşı et al., 2023), most of the patients in the group with severe pneumonia suffered from different comorbidities: diabetes mellitus, cardiovascular diseases, and even malignancies. In the mild pneumonia group, fewer patients had comorbidities, and the difference in cases of diabetes mellitus was statistically significant. Numerous studies have reported increased DNA damage in patients with both type 1 (Rostoka et al., 2021) and type 2 (Møller et al., 2020) diabetes mellitus. Increased DNA damage has also been reported in other comorbidities found in the severe pneumonia group, such as chronic kidney and cardiovascular diseases (Møller et al., 2020). The level of DNA breaks determined by the comet assay predicts the risk of death from several diseases (Bonassi et al., 2021).

Vaccination and therapy. DNA damage can affect the efficiency of vaccination against SARS-CoV-2; increased oxidative stress and the level of DNA double-strand breaks were observed in the nucleated blood cells of elderly patients, and both processes were further increased by vaccination. The neutralising capacity of anti-SARS-CoV-2 antibodies inversely correlated with the pre-vaccination level of DNA double-strand breaks (Ntouros et al., 2022). Treatment with COVID-19 can also have genotoxic effects. For example, chest radiography appears dangerous from this perspective (Mihaljevic et al., 2022). Antiviral drugs can also exert genotoxic effects. Favipiravir, an antiviral drug approved for COVID-19 treatment in many countries, has adverse effects on the gastrointestinal system, heart, and skin. A genotoxicity study of the drug performed using the comet assay showed an increase in the DNA tail in H9c2 cardiomyoblasts and CCD-1079Sk skin fibroblasts treated with favipiravir. Furthermore, 8-OHdG levels were high in favipiravir-treated cells, indicating oxidative DNA damage (Gunaydin-Akyildiz et al., 2022). N4-hydroxycytidine, a metabolite of the anti-COVID-19 drug molnupiravir, when treated with cytidine deaminase, induces Cu[II]-mediated oxidative DNA damage in isolated DNA (Kobayashi et al., 2023). Some authors have warned about genetic risks associated with molnupiravir therapy (Waters et al., 2022). Hydroxychloroquine, a drug widely used against malaria and autoimmune diseases, is effective and recommended for the treatment of COVID-19. However, it induces oxidative DNA damage and mutations in vitro (Besaratinia et al., 2021).

Conclusions and perspectives. Thus, DNA damage plays multiple roles in COVID-19, and the pre-existing level of DNA breaks formed due to aging or environmental stress increases the susceptibility to viral infection. Moreover, some SARS-CoV-2 proteins directly induce DNA damage. Indirect action via triggering oxidative stress or inhibition of DNA repair pathways also occurs, further weakening the resistance to infection and forming a vicious circle. The level of DNA damage correlates with the severity of the disease and influences sequelae during the post-COVID-19 period. Antiviral therapies enhance the genotoxic effects of infections per se. These factors may increase the risk of carcinogenesis and mutation. Thus, patients with severe COVID-19 infection should be constantly monitored for health problems, and the level of DNA damage should also be evaluated.

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CRediT authorship contribution statement

Nurşen Başaran: Writing – original draft. **Olga Szewczyk-Roszczenko:** Writing – original draft, Visualization. **Piotr Roszczenko:** Writing – original draft. **Yegor Vassetzky:** Writing – original draft. **Nikolajs Sjakste:** Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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