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Review

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Abstract: The COVID-19 pandemic caused by the RNA virus SARS-CoV-2, has had a significant impact not only on bodily metabolism but also at the genomic level. This study utilizes a bibliometric approach to map and identify the relationship between COVID-19 and DNA damage, genomic instability, and cell cycle deregulation. The research began with the development of in-depth research questions and conducted two rounds of literature search in the Scopus database with stringent filters to ensure relevance and accuracy. From an initial 1098 documents, 576 relevant documents were selected for further analysis. The collected data was then visualized using bibliometric methods, enabling the identification of important patterns, trends, and relationships among the research variables. Key findings indicate that DNA damage, which can induce apoptosis, is the worst impact of the infection on cells. Term frequency analysis and science mapping revealed a close relationship between "DNA damage" and "apoptosis". Furthermore, discussions on genomic instability highlight telomere regulation issues, while cell cycle deregulation during virus replication in mammalian cells indicates the importance of maintaining cell membrane integrity. This study confirms the importance of bibliometric analysis in detecting and understanding the impact of COVID-19 at the genomic level, proposing several potential research targets and enhancing our understanding of the biological response to viral infection.

Keywords: COVID-19; DNA damage; genomic instability; cell deregulation

Introduction

SARS-CoV-2, known as the RNA virus responsible for the COVID-19 pandemic, has been identified to affect a number of cellular processes (Gioia et al., 2023), not just at the metabolic level but also extending to the genomic level. However, the virus's impact on DNA integrity and related processes remains unclear and is a topic of debate in the scientific community.

A study elucidates that exposure to SARS-CoV-2 has long-term detrimental effects, marked by the progression towards organ damage and immunity impairment (Meagher, 2021). The most commonly reported impacted organs are the heart and blood vessels (Dennis et al., 2021), as well as the kidneys (Wang et al., 2022). This phenomenon is of serious concern, considering that organ damage invariably begins with cellular and tissue-level impairment. Furthermore, understanding the virus's characteristic of "hijacking" host cells in its life cycle, it is highly plausible that damage also occurs at the genomic level. Reports have also shown an increase in cell membrane damage, indicated by elevated levels of malondialdehyde (MDA), a marker of cellular damage, in COVID-19 patients (Gonçalves et al., 2022).

Analyses of the impact of COVID-19 on DNA damage, genomic instability, and cell deregulation were reviewed by Publo and team in 2021, including supporting evidence related to these destructive hypotheses (Pánico et al., 2022). Another study clarified the role of DNA damage response (DDR)-dependent telomere dysfunction through the expression of angiotensin-converting enzyme 2 (ACE2) (Sepe et al., 2022). Unfortunately, a comprehensive mapping in this domain of study was not conducted, potentially overlooking significant topics. Science mapping could allow us to analyze and evaluate the development and evidence of research quickly. Therefore, this study aims to provide

evidence-based proof through bibliometric mapping to analyze the relationship between the variables of DNA damage, genomic instability, and cell deregulation due to SARS-CoV-2 exposure in COVID-19.

Research Question

1. Is there a relationship between COVID-19 and induced DNA damage?
2. Is there a relationship between COVID-19 and Genomic Instability?
3. Is there a relationship between COVID-19 and Cell Cycle Deregulation during their replication in mammalian cells?

Method

This bibliometric study is designed to explore the impact of the virus causing COVID-19 at the genomic level. The initial phase involves the development of research questions aimed at understanding the correlation between the virus and DNA alterations. Based on the framework developed by Donthu (Donthu et al., 2021), we established a set of control vocabularies and relevant keywords, which were then utilized to filter and gather data from the available literature. This process was followed by stringent data selection and analysis, including the removal of outliers and distortions, as well as mathematical computations to gain deeper insights related to the research questions.

The literature search strategy involved two rounds using a combination of specific keywords in the Scopus database. The first round utilized the query "TITLE-ABS-KEY (('COVID-19' OR 'SARS-CoV-2' OR 'coronavirus') AND ('DNA damage' OR 'genomic instability' OR 'cell cycle'))", which yielded 1098 documents. The second round involved filtering to limit the results to research articles ('ar'), final publication stages ('final'), journal ('j') or proceedings ('p') source types, and documents in English, resulting in 576 relevant documents. This literature search was conducted on December 20, 2023, applying these filters to ensure the accuracy and relevance of the retrieved documents. This phase is summarized in a PRISMA flow diagram adapted from (Page et al., 2021).

Ronde 1: TITLE-ABS-KEY (("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("DNA damage" OR "genomic instability" OR "cell cycle"))

Ronde 2: TITLE-ABS-KEY (("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("DNA damage" OR "genomic instability" OR "cell cycle")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (SRCTYPE , "j") OR LIMIT-TO (SRCTYPE , "p")) AND (LIMIT-TO (LANGUAGE , "English"))

Following data collection, the next phase is data visualization using various bibliometric methods to map the relationship between COVID-19 and genomic changes. This visualization includes the creation of citation maps, co-citation analysis, and network analysis, all aiming to identify patterns, trends, and key relationships in the existing literature. The interpretation of these analytical results will provide critical insights into the impact of COVID-19 at the genomic level, as well as future directions for related research.
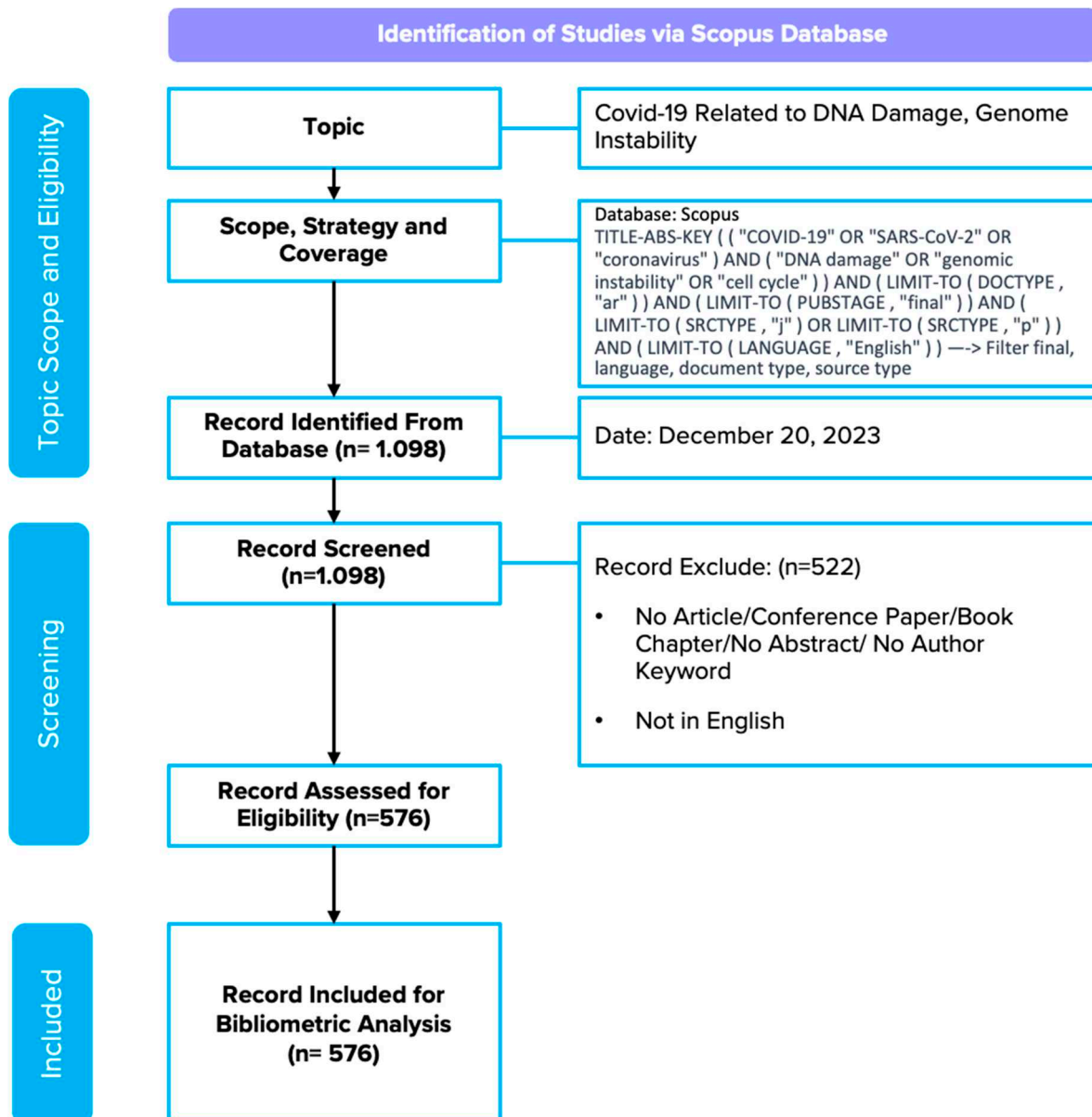
Figure 1. Document Selection Stages Adapted from the PRISMA Flow Diagram (Page et al., 2021).

Result and Discussion

The mapping of the 576 articles included in the bibliometric analysis reveals four main clusters: coronavirus (red), COVID-19 (green), DNA damage (blue), and oxidative stress (yellow), as shown in Figure 2 below. Each node represents a term, and nodes vary in size. The largest nodes, as seen in the figure below, indicate centrality, signifying a multitude of related topics. The distance between nodes also reflects the closeness of the studies. The closer the distance between nodes, the more they share in urgency. This can be observed in the proximity between apoptosis and DNA damage.
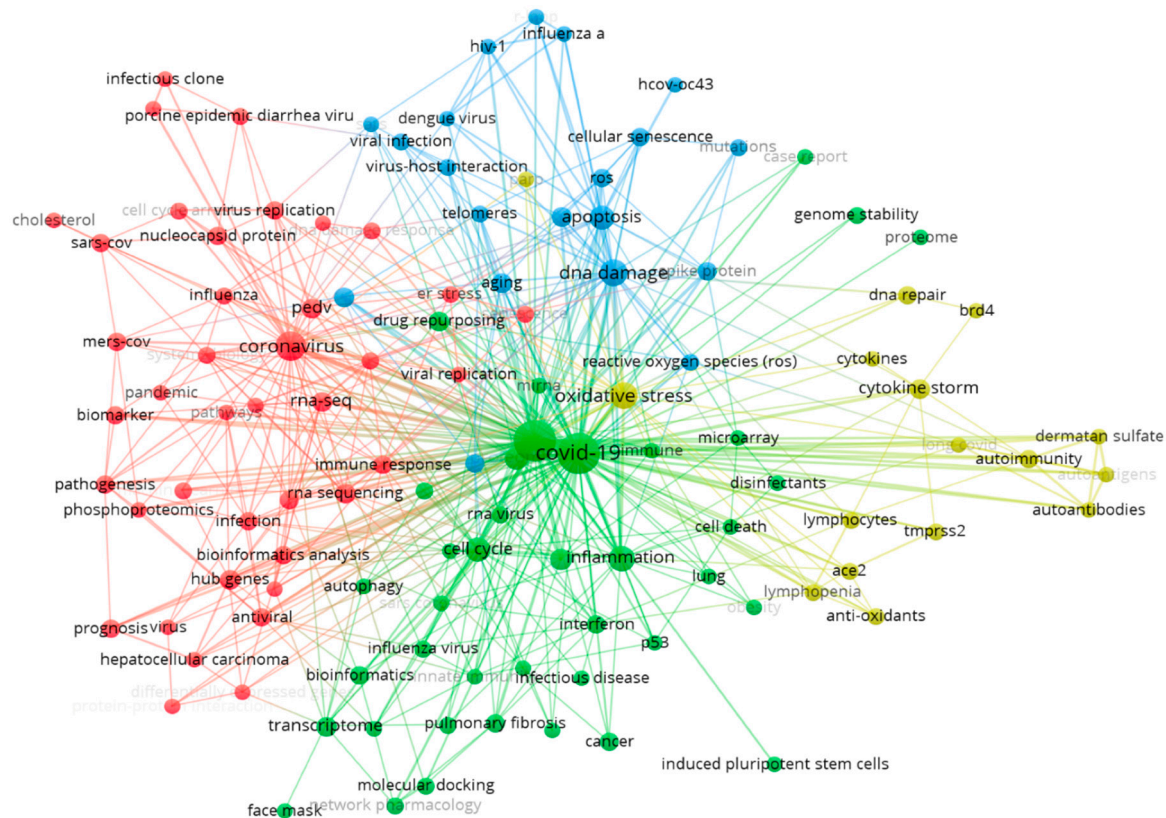
Type Analysis: Co-occurrence; Unit analysis: Author Keywords

Minimum number occurrence threshold: 3; Node amount: 115

Source: Scopus; Data preparation: Re-clustering term

Figure 2. Factors Involved in DNA Damage and Genomic Instability in COVID-19.

The illustration above displays the factors involved during the occurrence of an infection. The four clusters that have formed show interconnected factors. We can observe the proximity between the COVID-19 node and the nodes for DNA damage and oxidative stress, which are subsequently linked to apoptosis. This relationship provides an insight into the worst impact on the infected host cells, namely apoptosis.

3.1. Induce DNA damage

Errors in DNA synthesis, sequence reading, and DNA damage are common occurrences in biological systems. During the cell cycle, there are checkpoint control mechanisms in place to recognize and repair these errors (Rogan et al., 2021), akin to the balance between oxidants and antioxidants. This indicates that damage is tolerable within reasonable limits.

Unfortunately, the induction (intervention) of DNA damage beyond these thresholds leads to a state of imbalance. For instance, viral infection attacks by COVID-19 trigger the production of Reactive Oxygen Species (ROS) (Ming et al., 2022). This event can result in chromosomal damage (Rogan et al., 2021), cell apoptosis, and tissue damage. We analyzed this urgency through the study of scientific document evidence with term analysis. In the frequency analysis for the term "DNA damage," 33 out of 575 documents (6%) were found. To reinforce this analysis, node distribution mapping in the form of science mapping was conducted. The proximity of the "DNA damage" and "apoptosis" nodes indicates a high level of urgency and association (Figure 2). Furthermore, COVID-19 can lead to the depletion of host RNA binding proteins (RBPs) (Rogan et al., 2021).
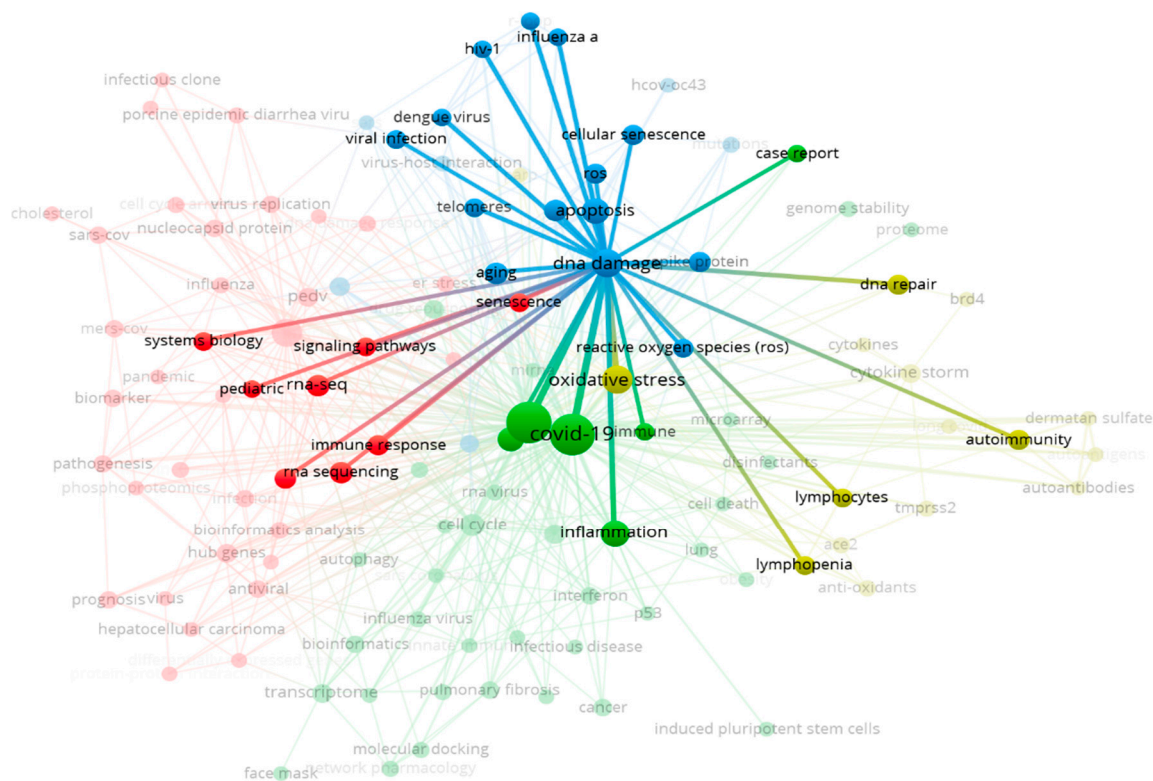
Figure 3. The Relationship with Factors Triggering DNA Damage by COVID-19.

3.2. Genomic instability

It is widely recognized that COVID-19 infection poses numerous problems for the human genome, particularly in terms of genomic stability (Iourov & Vorsanova, 2022). One aspect of genomic instability is the issue of telomere regulation (telomere dysregulation), which can lead to cell death (Sepe et al., 2022).
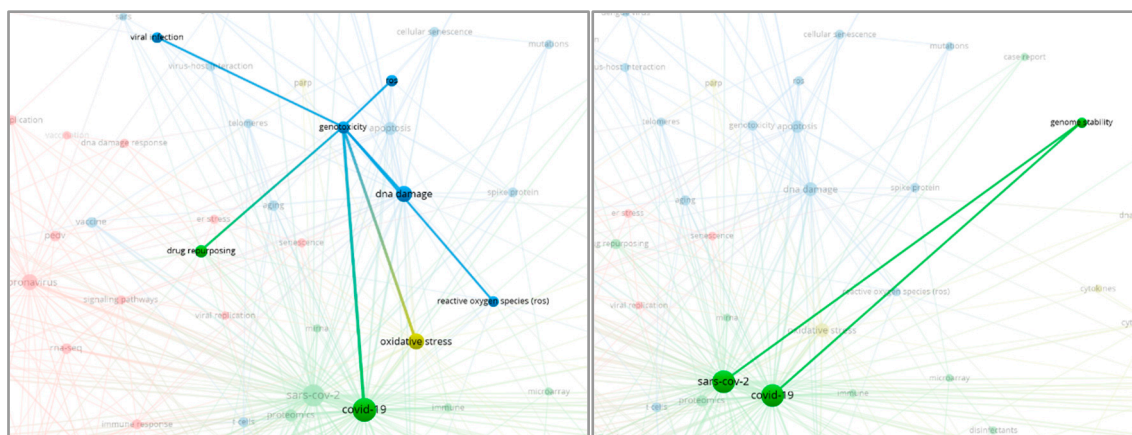

Figure 4. The Relationship with Factors Triggering Genomic Instability by COVID-19.

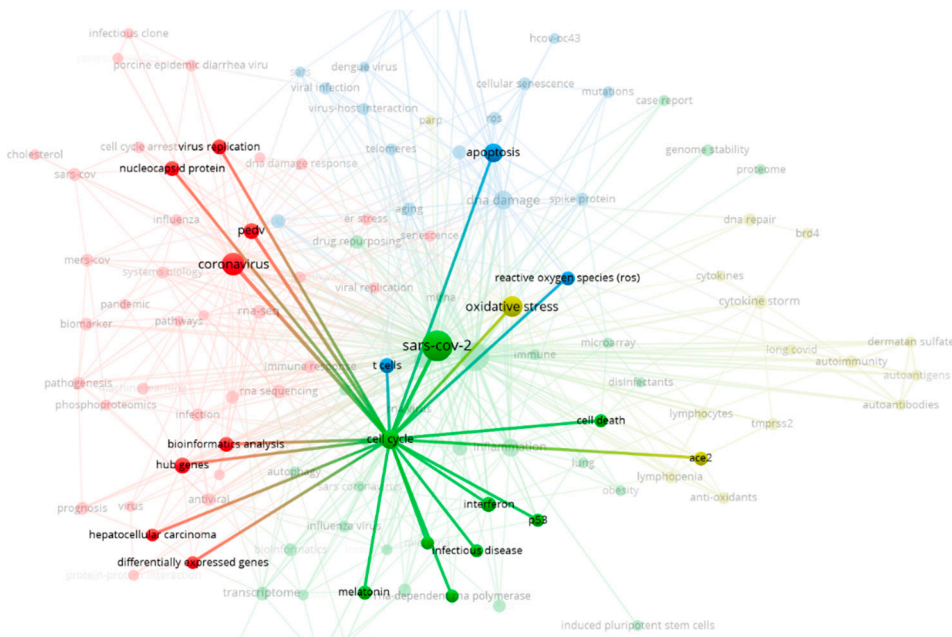*3.3. Cell cycle deregulation during their replication in mammalian cells*

Figure 5. The Relationship with Factors Triggering Genomic Instability by COVID-19.

The integrity of the cell membrane plays a crucial role. If the cell membrane is damaged, cells can undergo lysis and apoptosis. Research by Goncalves has demonstrated the dangers posed by COVID-19 protein fragments to the integrity of the cell membrane (Gonçalves et al., 2022). If this intervention is extensive, it can lead to DNA damage and cell death.

3.4. Technology Support for Identification

Identification at the genomic level is a complex task. There are a multitude of target genes that need to be identified, including the identification of genomic processes occurring with or without intervention. Marcus and his team (2007) discuss the DNA checkpoint. They emphasize the significance of understanding quantitative phospho-proteomics for identifying in vivo kinase substrates in DNA damage checkpoint kinases Mec1, Tel1, and Rad53 (orthologs of human ATR, ATM, and CHK2, respectively) (Smolka et al., 2007).

Similarly, with the impact of COVID-19 on DNA damage, there is a need for the design of biomarkers and the identification of appropriate target genes.

Conclusion

In the mapping of 576 scientific documents, four main clusters were identified: coronavirus, COVID-19, DNA damage, and oxidative stress. The analysis of the relationships and occurrences between these nodes reveals a close association between DNA damage and ROS, leading to oxidative stress, and potentially culminating in apoptosis. The bibliometric approach clearly demonstrates that COVID-19 is strongly linked to occurrences of DNA damage, genomic instability, and cell cycle deregulation.

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