The Impact of SARS-CoV-2 Infection on Patients with Aortic Stenosis

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ABSTRACT
Objective: To investigate the potential treatments for aortic stenosis and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using bioinformatics and systems biology.

Study Design: Observational study.

Place and Duration of the Study: Jiading District Central Hospital affiliated Shanghai University of Medicine & Health Sciences, Shanghai, China, from August to December 2022.

Methodology: GSE147507 was chosen as the SARS-CoV-2 infection dataset from the Biotechnology Information (NCBI) GEO database, while GSE153555 was chosen as the dataset of patients with aortic stenosis (AS). This analysis predicted protein-drug interactions (PDIs) and found therapeutic compounds for AS and COVID-19.

Results: One hundred and four DEGs were shared between the two datasets. Researchers built a PPI network to identify 10 hub genes from the network. Researchers discovered that COVID-19 and AS shared certain pathogenic pathways and found a relationship between hub genes and transcription factors and miRNAs, as well as a connection between hub genes and proposed treatments.

Conclusion: Hub genes were identified as potential pathogenic pathways in SARS-CoV-2 infection and AS. In addition, new prescription medication options for treating both illnesses were provided.

Key Words: SARS-CoV-2 infection, COVID-19, Aortic stenosis, Differentially expressed genes, Hub genes, Gene-disease, Drug molecule.


INTRODUCTION

Coronavirus disease (COVID-19), is due to SARS-CoV-2 infection, which began a global outbreak in 2019. According to information provided to the World Health Organization (WHO) as of 20 April 2022, there were more than 504.4 million confirmed cases of COVID-19 and more than 6.2 million deaths associated with the disease worldwide. In January 2022, COVID-19 was the leading cause of death for people between the age of 45 and 84. Some young and healthy patients had almost no symptoms, while elderly patients with multiple chronic diseases developed respiratory failure, cytokine storms, and circulatory failure that ultimately led to death. COVID-19 has been linked to cardiovascular events, despite the fact that the exact pathophysiological processes are unknown.

Aortic stenosis (AS) is a progressive aortic valve disease that can lead to syncope, sudden death, and heart failure if not treated promptly and effectively. Patients with AS are especially susceptible to negative effects from SARS-CoV-2 infection. Related studies have shown that the overall prevalence of AS in people ≥70 years is about 1-3%. Severe AS most commonly affects older patients, and is often strongly associated with comorbidities, such as coronary atherosclerotic heart disease, which is most likely to cause adverse outcomes after COVID-19. However, only a limited number of studies have demonstrated that SARS-CoV-2 infection negatively affects individuals with severe AS. The aim of the study was to use bioinformatics analysis to look at the effect of SARS-CoV-2 infection on patients with AS and suggest if some medicines can be useful for both the conditions.

METHODOLOGY

Using datasets and microarrays from the National Centre for Biotechnology Information (NCBI) GEO database, researchers identified the genetic correlation between AS and SARS-CoV-2. GSE147507 was selected as the dataset for SARS-CoV-2 infection. The AS dataset was GSE153555 comprising of human aortic valve tissue, of which 10 were AS samples and 10 were healthy controls. The top 10 statistically significant pathways were found by ranking the p-values in ascending order.
To view the PPI network and conduct more PPI network tests, researchers utilised Cytoscape (v.3.7.1). The top 10 hub genes in the PPI network were identified using Cytohubba and Maximal Clique Centrality (MCC). miRTarBase and TarBase are valid databases to identify miRNA-target gene interactions. Researchers retrieved miRNAs that interact with hub genes from these databases. Next, researchers utilised NetworkAnalyst to investigate the relationship between miRNA and hub genes, concentrating on the topological analysis. Then, using Cytoscape, researchers visualised the network of interactions between the TFs and the miRNA genes. One of the core parts of this study was to predict protein–drug interactions (PDIs) and to identify drug molecules for AS and COVID-19. Using NetworkAnalyst, researchers analysed the gene-disease relationships to identify the hub DEGs that are associated with chronic conditions.

RESULTS

In the SARS-CoV-2 infection dataset, the study discovered 1781 DEGs, of which 391 had down-regulated genes and 1390 had up-regulated genes. In the AS dataset, the study discovered 1525 DEGs, of which 618 showed down-regulation and 907 showed up-regulation. The cross-comparative study using Jvenn revealed 104 common DEGs between AS and SARS-CoV-2 infection. Figure 1a shows the retrieval of individual DEGs and the comparison of the two datasets. Researchers rank the top 10 terms according to the categories including biological processes, molecular activities, and cellular components. According to KEGG, BioCarta, Reactome and WikiPathways identified the pathways of common DEGs.

As shown in Figure 1b, the typical DEG PPI network had 100 nodes and 225 edges. On analysing the PPI network, researchers identified hub genes (TNF, MMP9, IL6, VCAM1, CD80, FCGR3B, FCGR3A, ITGB3, THY1 and SDC1). Researchers used the Cytohubba plug-in and then created a network of submodules as displayed in Figure 2a.

Figure 2b displays the interaction between the TF and the common DEGs. Figure 3a shows the location of the miRNA monitor to the hub genes. Researchers found 68 transcription factors (TF) and 213 post-transcriptional (miRNA) factors from the study of the TF-gene and miRNA-gene interaction networks.

The study identified 10 drug molecules that have common DEGs as candidate therapeutic targets for AS and COVID-19. According to the p-value, the top 10 chemical compounds corresponded to the hub DEGs. These ten potential drugs can be used as common therapeutic compounds for both diseases. Effective medicine for hub DEGs are shown in Table I.

According to NetworkAnalyst’s study of the gene-disease association, researchers noticed that liver cirrhosis, autistic disorder, systemic lupus erythematosus (SLE), malignant mesothelioma, and albuminuria were highly associated with hub genes. Figure 3b displays the relationship between genes and diseases.

DISCUSSION

Cardiovascular disease patients are particularly vulnerable to SARS-CoV-2 infection. A major risk factor for SARS-CoV-2 infection had been identified as AS. Nonetheless, the damaging aspects of SARS-CoV-2 exposure in individuals with severe AS are not yet conclusively understood. In this investigation, researchers evaluated the effects of SARS-CoV-2 exposure on individuals with AS using bioinformatics analysis.
Among the biological processes, 13 genes involved in inflammatory response and 18 genes in cytokine-mediated signalling pathway were the most prominent. Inflammation is a usual pathogenesis of many long-lasting diseases, including cardiovascular diseases, diabetes, cancer, intestinal diseases, and arthritis. Elderly patients with AS were essentially in a chronic inflammatory state, and such patients were often accompanied by severe cardiovascular complications, which were the key causes of death in individuals with SARS-CoV-2 exposure. One of the main features of COVID-19 was the overwhelming inflammation observed in some patients, especially those who developed severe illness. Keeping secondary infections away from critically sick patients may also improve their prognosis, so this is something to keep in mind. AS pathology is defined by an abnormal state of valve mineralisation, which is associated with neovascularisation and inflammation. Inflammation inside the valve is brought on by endothelial damage and lipid accumulation. When lymphocytes and macrophages infiltrate the endothelium, they release pro-inflammatory cytokines that boost calcific processes and establish fibrotic, contributing to increased valve stiffness. This leads to accelerated valve calcification. Cytokines are induced by viruses and are characterised by over-production of pro-inflammatory cytokines. This is the primary cause of mortality in COVID-19 because it leaves patients with severe tissue destruction and acute respiratory distress. The severity of COVID-19 symptoms is significantly influenced by cytokine signalling activities.

In molecular function experiments, the body frequently experiences acute heart damage, acute respiratory syndrome, dysfunctional gas exchange, oedema, and secondary infections as a result of cytokine overexpression. The key stages in SARS-CoV-2 infection may include the depletion of the antiviral defense system linked to the innate immune response and an increase in inflammatory cytokine production. A cytokine storm is a common name for the increased cytokine levels in the blood that are linked to a number of infectious and immune-mediated illnesses. A cytokine storm has a significant role in COVID-19 mortality and is correlated with the extent of illness. As a result, researchers believed that controlling cytokine storms early in the disease with therapies such as immunomodulators and cytokine antagonists is critical for improving COVID-19 patients' survival. Scientists had identified approximately 50 chemokines and 20 chemokine receptors (CCRs) that play a significant part in infectious diseases. Increased CCR1, CCR2, and CCR5 expression in humans pulmonary dorsal motor nucleus after SARS-CoV-2 infection demonstrates that inflammatory mediators influence the activation of nerve cells in the lung. Chemokine receptors, CCR1, CCR5, XCR1, and XCR9 could now be genetic susceptibility loci, as suggested by a genome-wide analysis of COVID-19 patients who already had respiratory failure. Therefore, more investigation is required to pinpoint the specific host genes that influence COVID-19 severity in people.

Tertiary granules serve primarily as a storage area for the membrane receptors and extracellular matrix-degrading enzymes necessary for neutrophil extravasation and dialysis. Researchers can conclude that tertiary granules are further involved in COVID-19 genesis via the actions of cytokines and chemokines. However, there are not many studies on this topic, and it would be interesting to conduct additional relevant studies in the future.

Immune cells release the cytokine tumour necrosis factor-alpha (TNF-α), which can cause tumour regression and stop tumour cell growth. Initial studies identified TNF-α as an antitumour agent, but now TNF-α and its family partners have been shown to be involved in a range of pathophysiology, including autoimmune diseases, tumours, respiratory diseases, nervous system, metabolic diseases, and cardiovascular diseases. Until now, there is no effective drug to prevent or reduce AS other than valve replacement surgery. Therefore, knowledge of the disease's underlying infectious mechanisms is essential for identifying potential therapy targets. TNF-α could be helpful in the treatment and prevention of AS.

Bioinformatics analysis identified the hub-genes as a prospective therapeutic target for SARS-CoV-2 infection in patients with AS patients. ACE2 and TMPRSS2 are widely used as markers for identifying cells having SARS-CoV-2 infection. Cellular tropism mediated by TMPRSS2 and ACE2 in COVID-19 may depend on the coordinated regulation of multiple TFs. STAT1 is the most important condition in patients with SARS-CoV-2.
Earlier analyses showed that miRNAs play an important role in developmental processes, such as fibrogenesis, angiogenesis and apoptosis. In patients with cirrhosis who tested positive for SARS-CoV-2, the 30-day mortality was significantly high. In addition, many cirrhotic patients infected with COVID-19 developed liver decompensation, even without any respiratory symptoms. The above studies were of great significance to clinicians in terms of risk stratification, clinical diagnosis, treatment, and prediction of prognosis in patients with SARS-CoV-2 and liver cirrhosis. Therefore, researchers concluded that low-threshold detection of SARS-CoV-2 in patients with decompensated new-onset cirrhosis is necessary.

The COVID-19 pandemic had triggered social isolation and disruption of services, causing psychological distress for people around the world. People with autistic disorders were more prone to COVID-19. Patients with SLE were at an increased risk of contracting SARS-CoV-2 infection because of increased baseline inflammation and innate immune disturbances, and once infection occurred, the clinical course was more severe than in uninfected individuals. Adaptive and congenital immunological disturbances prevalent in SLE increased susceptibility to COVID-19, leading to prolonged virus shedding or predisposition to more serious illness. Although the aetiologies of COVID-19 and malignant mesothelioma are different, their psychological effects are similar. In both diseases, there is a sense of exposure to invisible killers through airborne transmission, and affected individuals may experience personality disorders, anxiety, depression, and post-traumatic symptoms such as helplessness, despair, and destructive thoughts. As a result, researchers proposed that public health services, such as hospitals, communities, and neighbourhood councils need to implement comprehensive interventions to address the psychological distress and spiritual needs of COVID-19 patients and caregivers. A large range of 28–84% had been described for the occurrence of proteinuria in COVID-19, whether or not, accompanied by concomitant acute kidney injury (AKI). The illness known as COVID-19-associated nephropathy (COVAN) affected susceptible people of African descent who are high-virus carriers and characterised by nephrotic range proteinuria and AKI brought on by collapsed glomerulopathy pathology. The breakdown of the glomerular capillary wall in COVAN and poor tubular reabsorption during ATI may each play a role in the proteinuria caused by COVID-19. More research is required to better understand the causes, prevalence, and patient outcomes of newly developed proteinuria in COVID-19 cases. There are several chemical agents and drugs that are potential therapeutic agents against COVID-19 and AS. Paxlovid proved to be effective against SARS-CoV-2. However, currently only few approaches are available for treating or preventing Coronavirus infections. Hence, identifying new therapeutic agents is one of the most important agenda in the current medical community. Researchers recognised beclomethasone for the prevention and control of asthma-induced symptoms (shortness of breath and wheezing). It can reduce swelling of the airways of lungs, hence make breathing easier. Another extracted drug was hesperidin. Studies had shown that they have significant binding affinities to ACE2, S, M and RBD proteins, while they do not bind to the N protein. This suggested that they play a significant role in influencing the early duplication stage and invasion of SARS-CoV-2. Therefore, researchers believed that hesperidin can serve as a prospective medicine for the cure of SARS-CoV-2 infection. Cytochalasin D inhibits CT26 tumour growth by inhibiting cell proliferation, inhibiting tumour angiogenesis and inducing apoptosis. Hydroxytyrosol (HOTYR) can positively regulate the antioxidant defense system in vascular endothelial cells and inhibit platelet aggregation, providing the molecular basis for the use of HOTYR to prevent cardiovascular diseases. SARS-CoV-2 infection involves multi-system diseases, including cardiovascular diseases, cancer and immunodeficiency diseases. Therefore, these drugs provided new research ideas for the therapy of COVID-19.

Nonetheless, the present research was primarily based on bioinformatics and systems biology methods. Researchers had not conducted basic animal experiments to verify the results of this research. In the next step, researchers will aim to carry out basic experiments to make the results of this research more rigorous and credible. The combination of clinical diagnosis and treatment will provide new ideas for solving practical clinical problems.

CONCLUSION

The bioinformatics analysis revealed that AS patients were at a greater risk of developing SARS-CoV-2 infection. In all, based on the transcriptomic analysis, researchers identified 104 common DEGs between AS and SARS-CoV-2 infection. Of these, the PPI network identified 10 hub genes. These hub genes functioned as cutting-edge biomarkers and therapeutic targets for these illnesses. However, additional animal experiments will be required to verify these results.

AVAILABILITY OF DATA AND MATERIAL:
The datasets generated and/or analysed during the current study are available in the GSE153555 repository (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE153555) and in the GSE147507 repository (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147507).

ETHICAL APPROVAL:
The Clinical Research Ethics Committee of the Jiading District Central Hospital approved the procedure (2022k14 dated 14 July 2022).

PATIENTS’ CONSENT:
The participants gave their permission for publishing the data.

COMPETING INTEREST:
All authors affirmed that there were no financial or commercial ties that may be viewed as a possible conflict of interest.

AUTHORS’ CONTRIBUTION:
MY, YS, XX: Data analysis and creation of an original manuscript.
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CZ, HL: Implementing the validation experiment and creating the illustrations.
XH: Focus on figure layout and design.
The manuscript was co-written by all authors, who also read and approved the final version to be published.

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