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ASSOCIATION COVID-19 VIRAL LOAD AND DISEASE SEVERITY: A SYSTEMATIC REVIEW

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Abstract

The global pandemic SARS-CoV-2 or COVID-19 has caused a significant healthcare crisis. This disease profile is recognized as the leading cause of severe disease in the adult population and the focus of the evidence and treatment guidelines reflect that adults predominately experience COVID-19. A high temperature, a dry cough, dyspnea, headache, tiredness, loss of taste and/or smell, and gastrointestinal difficulties are among the symptoms of COVID-19. The results of the laboratory tests indicate that the levels of liver enzymes are elevated, that there is a shortage of lymphocytes (also known as lymphocytopenia), and that there is an increased level of C-reactive protein. The infection will, in the long run, cause acute respiratory distress syndrome, which could lead to death in the end. The reverse transcription-polymerase chain reaction (RT-PCR) was the single most essential tool for detecting the amounts of viral load. The identification of viral nucleic acid by RT-PCR assays is the gold standard for the diagnosis of COVID-19. This is because these tests can detect minute traces of the virus. We are able to obtain an indirect number for the viral load (C t) following the diagnosis using this procedure, which enables us to do so in a way that is both speedy and painless. The primary theory may be explained by the connection between the amount of viral load and inflammatory factors, both of which are obviously associated with the degree to which the disease has progressed. This connection may be explained by the correlation between the degree to which the disease has progressed and the amount of viral load. Because elderly patients typically have a higher viral load, it is possible that any potential links between COVID19 viral load and the severity of the disease could be explained by the fact that elderly patients often have a higher viral load.

Keyword: *COVID-19; CT value; Disease Severity; Viral Load*

INTRODUCTION

The acute respiratory syndrome known as coronavirus disease 2019 (COVID-19) is caused by the coronavirus 2 (SARS-CoV-2), and it is characterized by inflammation as well as the involvement of multiple organs in the body. On January 30, 2020, the World Health Organization (WHO) designated this disease as a "public health emergency of worldwide significance".[1,2] When SARS-CoV reaches lung cells, it immediately begins attacking the lower respiratory tract and attaching itself firmly to its receptors in the lungs, which are angiotensin-converting enzyme receptors in particular.[3,4]

This abnormal response eventually leads to elevated levels of cytokines, which is known as cytokine storms or hypercytokinemia. It occurs when an infection in the lower respiratory tract activates immune cells such as neutrophils and macrophages, which then releases several chemokines and cytokines that activate the immune system like B and T cells. As a consequence of this, acute pneumonia affecting several organs may develop, which may result in a wide variety of symptoms and indicators, in addition to psychological damage as a direct consequence.[3–5]

The symptoms of COVID-19 include a high temperature, a dry cough, dyspnea, headache, exhaustion, loss of taste and/or smell, and gastrointestinal issues. According to the findings of the laboratory tests, the levels of liver enzymes are elevated, there is a deficiency in lymphocytes (referred to as lymphocytopenia), and there is an elevated level of C-reactive protein. In the long run, the virus will induce acute respiratory distress syndrome, which could ultimately result in death.[2,6]

SARS-CoV-2 is an enveloped virus that has a positive-sense, single-stranded RNA genome that is around 30 kilobytes in size. It is a member of the Nidovirales order, which is classified under the Coronaviridae family and the Coronavirinae subfamily. Since it first appeared in the wild, the SARS-CoV2 virus has undergone a number of modifications, which have led to the development of varieties of the virus that are either less deadly or even more dangerous. The SARS-CoV strain is constantly changing, and with each new mutation, the virus could become more contagious or lethal. The World Health Organization (WHO) has so far identified four different strains of SARS-CoV-2 as "variants of concern", each of which is responsible for COVID-19.[7,8]
This article investigate the association between COVID-19 viral load and disease severity.

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist served as the basis for the rules controlling the conduct of this systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on "COVID-19 viral load" and "disease severity". These are the topics that were discussed in the research that was taken into consideration. In order for your work to be taken into consideration, the following criteria need to be satisfied: 1) Articles have to be accessible online in their entirety; 2) Articles have to be written in English; and 3) Articles have to have been published after 2020, but before the time this systematic review is prepared. Textual contributions of the following nature shall under no circumstances be accepted: 1) Editorial letters, 2) contributions that do not have a Digital Object Identifier (DOI), and 3) article reviews and submissions that are similar to those.

Search Strategy

The search for studies to be included in the systematic review was carried out from November 12-17th, 2022 using the PubMed and SagePub databases by inputting the words: "COVID-19 viral load" and "disease severity". Where *("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("viral load"[MeSH Terms] OR ("viral"[All Fields] AND "load"[All Fields]) OR "viral load"[All Fields]) AND ("severity of illness index"[MeSH Terms] OR ("severity"[All Fields] AND "illness"[All Fields] AND "index"[All Fields]) OR "severity of illness index"[All Fields] OR ("disease"[All Fields] AND "severity"[All Fields]) OR "disease severity"[All Fields])* is used as search keywords.

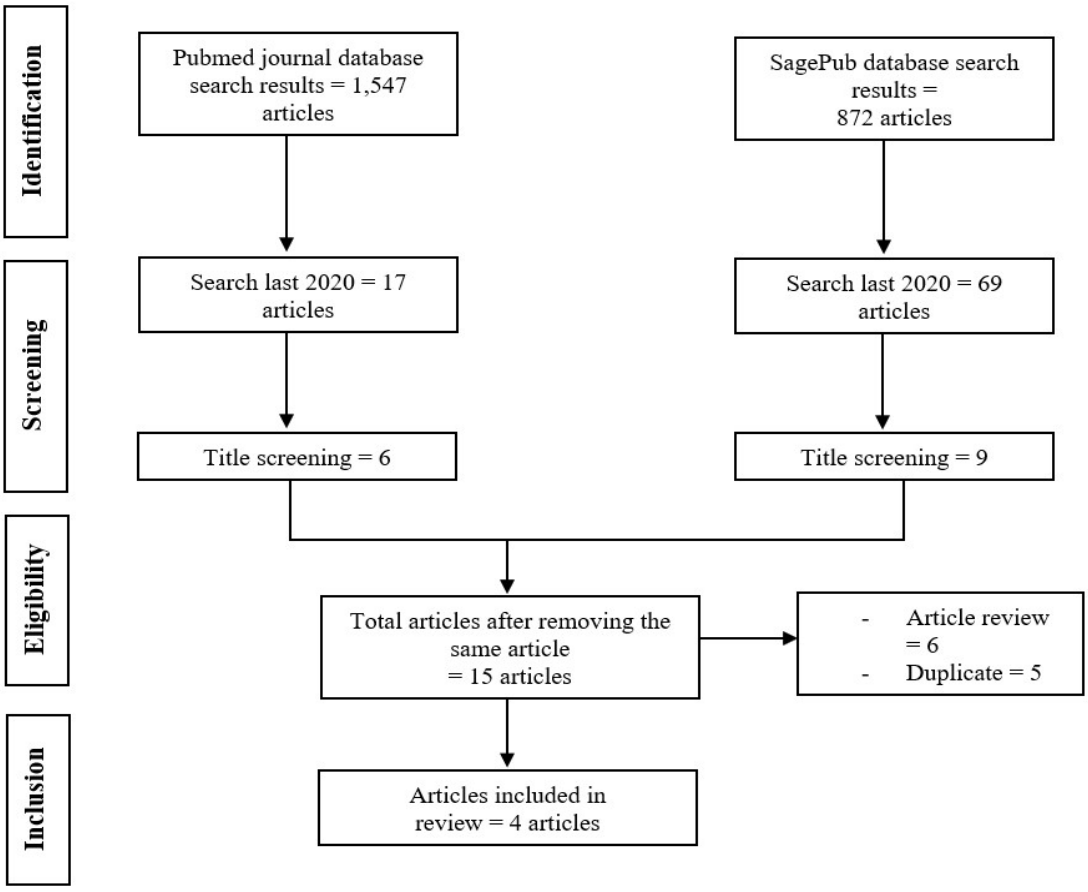

Figure 1. Article search flowchart

Data retrieval

The author of the study altered the criteria for what should be included in the study and what should not be included in the study after completing a literature search and reading the titles and abstracts of previously published studies. In the process of compiling the systematic review, consideration was given only to those research projects that were successful in fulfilling each and every one of the conditions. It is possible to gather information about each individual study in the form of a title, author, publication date, origin of study location, research study design, and research variables.

Quality Assessment and Data Synthesis

To determine which studies might be eligible for consideration, the authors conducted their own independent reviews of a selection of the studies found in the articles' titles and abstracts. Following this, the full texts of the studies that qualify for inclusion in the systematic review will be read in order to determine which studies can be used as final inclusions for the purpose of the review.

RESULT

Aoki (2021)[9] showed area under the curve in a receiver operating characteristic analysis of 524 individuals who tested negative for SARS-CoV-2 was found to be 0.957 with a standard deviation of 0.063. When a cut-off value of 1.34 pg/ml was utilized, the percentage of sensitivity that was achieved was 91.7%, the percentage of specificity that was achieved was 98.5%, and the percentage of overall agreement that was achieved was 98.2%. The value of 1.03 pg/ml represented the 99.5 percentile position within the distribution of negative cases. There was a strong relationship between the amount of viral load that was determined by the RT-PCR cycle threshold value and the amount of antigen that was present in the sample. It was shown that a correlation existed between the tendency for the antigen concentration to decrease with time following the onset of sickness and that of the viral load.

Aydin (2021) showed clinical course of the patients was monitored for one month, and the findings revealed that 56% of patients had a mild condition, 26.4% of patients had a moderate disease, 9.6% of patients had a severe disease, and 8 percent of patients had a critical or fatal disease. The average cycle threshold values of SARS-CoV-2 in saliva samples were measured to be 22.28, whereas those in ONP samples were measured to be 24.19. It was discovered that the cycle threshold value of saliva is significant in determining the severity of the condition (Eta coefficient 0.979). The severity of the disease was shown to have a correlation with the mean Ct-values of the ONP samples, and this correlation was determined to be statistically significant ($p < 0.05$). When gender, age, body mass index, and the presence of other diseases were compared to the severity of the disease, there was found to be no statistically significant difference.[10]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size / Characteristic	Result
Aydin, 2021[10]	Turkey	Case series	125	Their forecast did not take into account the influence that the SARS-CoV-2 virus load had on saliva or any other chemicals.
Calle, 2021[11]	Spain	Cross sectional	455	At the time of admission, patients who presented with respiratory failure had a greater viral load than those who did not.
Aoki, 2021[9]	Japan	Cross sectional	24	There was a strong relationship between the amount of viral load that was determined by the RT-PCR cycle threshold value and the amount of antigen that was present. After the onset of disease, there is a trend toward decreasing antigen concentration over the course of time, which is associated with viral load.
Cho, 2020[12]	China	Prospective study	75	There was no correlation between the recovery time of olfactory or gustatory disorders and the Ct value of PCR that was sampled indirectly from nasopharyngeal swabs and deep throat samples. These samples reflected the viral load of SARS-CoV-2.

Cho, et al (2020) study showed thirty-nine (47.0%) and 36 (43.4%) COVID-19 patients reported olfactory and gustatory dysfunction, respectively. The results of one-way analysis of variance did not show statistically significant relationships between the Ct values and severity of olfactory and gustatory dysfunction (P = .780 and P = .121, respectively). Among the COVID-19 patients who reported smell and taste loss, 28/39 (71.8%) and 30/36 (83.3%) experienced complete recovery, respectively. The mean recovery time was 10.3 ± 8.1 days for olfactory dysfunction and 9.5 ± 6.8 days for gustatory dysfunction. The recovery time was not correlated with the Ct values (Pearson correlation coefficient, smell: −0.008, P = .968; taste: −0.015, P = .940).[12]

Calle *et al* showed value of the Ct in the middle was 28 (IQR: 24–32). 130 patients (28.6%) had a high viral load, 175 patients (38.5%) had an intermediate viral load, and 150 patients (33.5%) had a low viral load. Predictive factors for respiratory failure included advanced age, male sex, presence of cardiovascular disease, laboratory markers such as lactate dehydrogenase, lymphocyte count, and C-reactive protein, as well as a high viral load on admission. In addition, respiratory failure was associated with a higher mortality rate. A Ct value of less than 25 was related to an increased likelihood of respiratory failure occurring during admission (odds ratio: 2.99, 95% confidence interval: 1.57–5.69). It is possible to accurately forecast the onset of respiratory failure in COVID-19 inpatients by measuring the SARS-CoV-2 viral load using the admission Ct value.[11]

DISCUSSION

The global pandemic SARS-CoV-2 or COVID-19 has caused a significant healthcare crisis. This disease profile is recognized as the leading cause of severe disease in the adult population and the focus of the evidence and treatment guidelines reflect that adults predominately experience COVID-19. The World Health Organization (WHO) has declared the 2019–20 coronavirus outbreak a Public Health Emergency of International Concern (PHEIC).[13] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19.[14]

The gold standard for diagnosing COVID-19 is the identification of viral nucleic acid by RT-PCR tests. Using this method, we can quickly and simply acquire an indirect viral load value following diagnosis. Previous investigations have shown a correlation between this parameter and the capacity of the virus to disseminate and to persist longer in respiratory samples.[15,16] In addition, it has been demonstrated that patients with severe disease have significantly higher viral loads than patients with mild disease, and Zou and colleagues reported that patients admitted to the intensive care unit had detectable viral RNA in nasopharyngeal exudates 10 days after the onset of symptoms. However, few research have sought to determine whether a correlation exists between viral load at diagnosis and illness progression.[17–19]

In late 2019, SARS-CoV-2 was discovered for the first time in China. This novel coronavirus was later shown to be responsible for COVID-19 and has since spread over the world. On January 30, 2020, the World Health Organization (WHO) designated this disease as a public health emergency of international significance. Although SARS-CoV2 has the ability to cause severe pneumonia, it is also capable of involving other organs and causing a wide range of symptoms, including physical signs like fever, cough, and dyspnea, as well as psychological and gastrointestinal problems.[2,20,21]

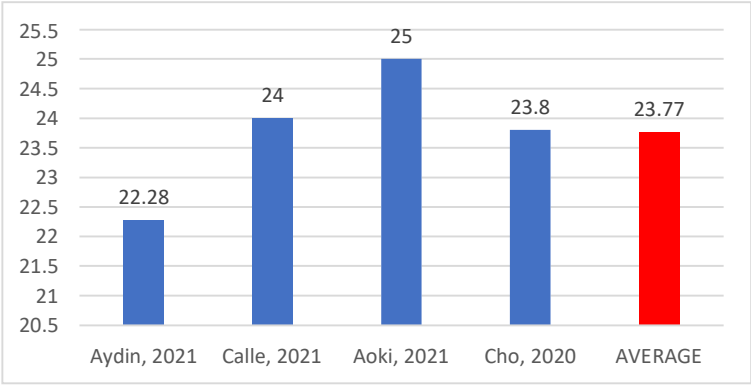

Figure 2. Comparison of CT values in patients with severe COVID-19

Community education, border controls, lockdown, social distancing, wearing masks in public, hand hygiene, and schools shutting down are just some of the interventions and measures that have been taken to control the situation and prevent the virus from further spreading. Other measures include social distancing and social distance. These measures to improve public health not only slowed down the transmission of SARS-CoV2, but they also resulted in a decrease in the fatality rate.[2,20,21]

The RT-PCR was the most important method for determining the levels of viral load. When it comes to the diagnosis of COVID-19, the identification of viral nucleic acid by RT-PCR assays is the gold standard. With the use of this method, we are able to quickly and painlessly obtain an indirect value for the viral load (C t) after the diagnosis. The primary theory may be explained by the connection between the amount of viral load and inflammatory factors, both of which are obviously associated with the degree to which the disease has progressed.[11]

It is well knowledge that a high level of proinflammatory cytokines and chemokines being released into the bloodstream correlates to the severity of clinical outcomes in a variety of infections. Therefore, our findings that the plasma concentrations of IFN, IFN, IP10, MIG, and IL6 were elevated in the severe and critical cases at 5–10 days from the onset of symptoms suggest that the higher plasma concentrations of proinflammatory cytokines after approximately a week from the beginning of symptoms may have a role in the enhancement of the severity of the condition. An intriguing finding from a recent longitudinal research was that patients with severe COVID-19 had plasma IFN levels that remained elevated throughout the clinical course of their illness, but individuals with moderate COVID-19 had plasma IFN levels that decreased.[22,23]

According to the findings of He *et al*.,[24] a larger viral load was shown to be positively linked with COVID19 severity. This discovery shows how important it is to monitor the viral kinetics in order to identify patients who are at a greater risk of developing severe pneumonia in the future. Similar findings were reported by Guo *et al*.,[25] who discovered that the viral RNA load of SARS-CoV-2 in the upper respiratory tract at the time of hospital admission is an independent prognostic predictor of COVID-19. Nevertheless, there were a few research that produced contradictory findings. One study that illustrates this debate is the one that was conducted by Hasanoglu and colleagues.[26]

They showed that asymptomatic patients have higher SARS-CoV-2 viral loads than symptomatic patients, and contrary to the findings of the few studies that have been published on the topic, they found that the viral load of nasopharyngeal and oropharyngeal samples significantly decreased as the severity of the disease increased. In a study conducted in the same vein, Cho et al.[12] discovered that there is no correlation between the intensity of these symptoms and the amount of SARS-CoV 2 in the patient's body. Le Borgne et al.,[27] discovered that measuring the respiratory viral load on the first nasopharyngeal swab (by RT-PCR) during early therapy of SARS-CoV-2 infection in the emergency department is neither a predictor of severity nor a predictor of mortality in SARS-CoV-2 infection.

CONCLUSION

There is a possibility that any potential connections between COVID19 viral load and disease severity could be explained by the fact that elderly patients often have a greater viral load.

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