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GASTROINTESTINAL SYMPTOMS AND THE BEST THERAPY WITH SEVERITY OFCORONAVIRUS DISEASE 2019: SYSTEMATIC REVIEW

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Abstract

Because the COVID-19 virus has spread around the world so quickly, there is a severe shortage of medical supplies in every region of the planet. This is especiallytrue of the supplies that are necessary for the treatment of patients who are in a critical condition, such as intensive care and ventilators. Emerging diseases such as COVID-19, which manifest in the respiratory system, are a significant reason for worry. In addition, people who have been identified with COVID-19 frequently have diarrhea in addition to other gastrointestinal symptoms; despite this, the relevance of these data has not been established. Remdesivir, lopinavir/ritonavir (LPV/r), steroids, tocilizumab, interferon alpha or beta, ribavirin, hydroxychloroquine/chloroquine alone or in combination with azithromycin, and baricitinib are some examples of drugs that have the potential to be useful in the treatment of HIV/AIDS. Other potential drugs include baricitinib. Because symptoms of the gastrointestinal tract (GI) and malfunction of the liver are frequently observed in COVID-19, it can be difficult to differentiate between the indicators of the illness and the potential negative consequences of treatment. When deciding on the most effective course of therapyfor COVID-19 patients, medical professionals need to take into account the possibility that gastrointestinal (GI) symptoms and liver dysfunction are caused either by disease presentations or by drug side effects.

Keyword: *Coronavirus Disease 2019 (COVID-19); Gastrointestinal Symptoms; Severity; Therapy*

INTRODUCTION

a. In the month of December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as 2019-nCoV, was first discovered in the province of Wuhan in China. Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, which produces a severe respiratory sickness.[1–3] The severe acute respiratory syndrome coronavirus 2 is the causative agent of the worldwide pandemic that is known as the outbreak of COVID-19. It is a highly infectious virus that has caused the deaths of a significant number of individuals and has infected millions of others all over the world.[2,4]

b. Many clinical studies are now looking at potential therapies or vaccines for this disease in an effort to lower the high morbidity and mortality ratesassociated with it. Emerging infections like COVID-19, which reveal themselves in the respiratory system, are a major cause for concern. In addition, patients diagnosed with COVID-19 typically have diarrhea in addition to other gastrointestinal symptoms; however, the significance of these observations has not been confirmed. An infection caused by a viruschanges the permeability of the intestinal wall, which ultimately leads to malfunction in the enterocytes.[5–7]

c. When we looked into what had happened with another coronavirus, we discovered that diarrhea was a common symptom in patients who had severe acute respiratory syndrome (SARS), happening in forty percent ofcases. There was a correlation between the severity of the infection and gastrointestinal issues as well. Patients who were suffering from diarrhea need an increased amount of breathing help and specialized care.[8] The SARS coronavirus was also found in biopsies taken from the terminal colon and the ileum. In relation to Middle East respiratory syndrome (MERS), a number of investigations demonstrated the occurrence of diarrhea in between 14 and 50 percent of cases that were documented.[9]

d. Remdesivir, lopinavir/ritonavir (LPV/r), steroids, tocilizumab, interferon alpha or beta, ribavirin, hydroxyv chloroquine/chloroquine alone or in combination with azithromycin, and baricitinib are examples of drugs thathave the potential to be useful in treating HIV/AIDS. Because gastrointestinal (GI) symptoms and liver dysfunction are commonly found in COVID-19, it can be challenging to discriminate between the signs of the illness and the potential adverse effects of therapy.[10,11]

e. Agents that are used for the treatment of COVID-19 can be categorized according to the type of agent, such as antiviral, antiparasitic, antibacterial, and immunomodulatory agents; according to the site of action on the SARS-CoV-2 virus, such as blocking the entry of virus, inhibiting viral replication, and having an anti-inflammatory effect; or according to the type of agent that is used. This article investigates COVID-19's effects onthe digestive system as well as the most effective treatment for severe cases.

METHODS

Protocol

f. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines served as the basis for this study'smethodology. The rules that were put in place were based on these factors.

Eligibility Criteria

g. This literature review on gastrointestinal symptoms and the best therapy with severity of COVID-19 was prepared to analyze the existing researchon these topics. These are the key concerns that were brought up in the research that is now being looked at. You are required to demonstrate thatyou can fulfill the following conditions in order for your work to be evaluated: 1) In order to be considered for publication, articles need to bewritten in English and highlight gastrointestinal symptoms and the best therapy with severity of COVID-19. 2) Articles that had been published after 2020 but before the period of this systematic review were taken intoconsideration for this evaluation. The following kind of writing will not be considered for inclusion in the anthology's publication: original research does not include editorials, submissions that do not have a DOI, reviews of articles that have already been published, or entries that are considerably similar to those that have already been published in the journal.

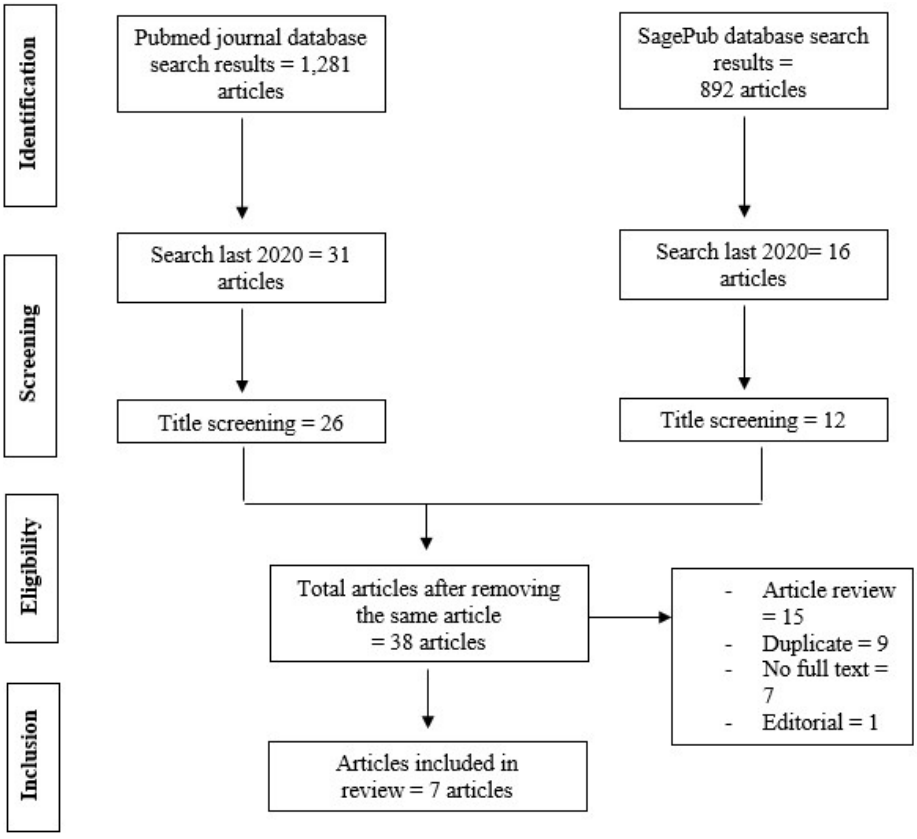
Search Strategy

h. The search for studies to be included in the systematic review was carried out from January, 12th 2023 using the PubMed and SagePub databases by inputting the words: "gastrointestinal symptoms" and "COVID-19 therapy". Where *("gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields] OR "gastrointestine"[All Fields]) AND ("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "symptom"[AllFields] OR "symptom s"[All Fields] OR "symptomes"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] 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 ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])* is used as search keywords.

Data retrieval

i. The author of the study altered the criteria for inclusion and exclusion afterconducting a literature assessment consisting of a review of the titles and abstracts of prior pieces of research. You can find the updated criteria in the supplemental materials that were provided with the research. This brought the extent of the problem into better focus and brought to light the aspects that require additional examination. This conclusion was reached by the author after conducting research on more studies that followed a comparable format. During the process of the systematic review, the only studies that were taken into consideration were those that satisfied all of the inclusion criteria.

j. This ensured that only relevant information was uncovered.We did not take into consideration any research suggestions that did not fulfill all of our requirements. This served as a guarantee that a thorough examination would be performed. The information relevant to the studies, such as theirtitles, authors, publication dates, locations, types of research investigations, and parameters, was obtained as a result of this endeavor. These are the kinds of items that can be picked up. These are things that can be learned. Information sources include: This information can be presented in several ways.



[2] Figure 1. Article search flowchart

Quality Assessment and Data Synthesis

a. Before settling on which articles to investigate, the authors each carried out their own individual investigation of a piece of the research that was mentioned within the titles and abstracts of the papers. After that, the complete texts of publications that meet the criteria for the systematic review will be reviewed in order to determine which papers will be included in the review. This will be done in order to decide which articleswill be included in the review. In order to make the process of selecting articles for the review less difficult. Which studies are of a high enough quality to be considered for inclusion in the review?

RESULT

b. First study showed lopinavir-ritonavir was not associated with a differencefrom standard care in the time to clinical improvement (hazard ratio [HR] for clinical improvement = 1.31; 95% confidence interval [CI] = 0.95- 1.80). Gastrointestinal adverse events were more common in the lopinavir-ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir-ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.[12] Beigel, et al[13] showed patient with remdesivir had a median recovery time of 10 days (95% CI =9-11), as compared with 15 days (95% CI = 13-18) among those who received placebo. Serious adverse events were reported in 131/532 patients who received remdesivir (24.6%).

c. Remdesivir use was not associated with a difference in time to clinical improvement (HR= 1,23 [95% CI = 0.87–1.75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio

1.52 [0.95–2.43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.[14]

d. Rocco, et al (2021)[15] showed at the 5-day study visit, symptom resolutiondid not differ between the nitazoxanide and placebo arms. Swabs collectedwere negative for SARS-CoV-2 in 29.9% of patients in the nitazoxanide arm versus 18.2% in the placebo arm (p=0.009). Viral load was reduced after nitazoxanide compared to placebo (p=0.006). The percentage viral load reduction from onset to end of therapy was higher with nitazoxanide(55%) than placebo (45%) (p=0.013). Other secondary outcomes were notsignificantly different. No serious adverse events were observed.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Cao, 2020[12]	China, UK,USA	Randomized,controlled, open-label trial	199 patients With laboratory-confirmed SARS-CoV-2 infection	Gastrointestinal adverse events were more common in the lopinavir-ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir- ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.
Beigel,2020[13]	China, UK,USA	Rouble-blind, randomized, placebo- controlled trial	1,062 patients	Patient with remdesivir had a median recovery time of 10 days (95% CI = 9-11), as compared with 15 days (95% CI = 13-18) among those who received placebo. Serious adverseevents were reported in 131/532 patients who received remdesivir (24.6%). Patients in this study had increased ASTand ALT
Wang,2020[14]	China	Randomised, double-blind, place bo controlled, multicentre trial	237 patients	The investigators ceased treating remdesivir recipients sooner than placebo receivers due to adverse events such as gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin elevations, and poorer cardiopulmonary status.
Rocco,2021[15]	Brazil	Multicentre, randomized, double-blind, placebo-controlled trial	1,575 patients	In the nitazoxanide group, ~3% stopped therapy due to gastrointestinal upset after COVID-19 symptoms had already improved.
Stone,2020[16]	United State of America	Randomized,double-blind, placebo- controlled trial	243 patients	Patients in this study had increased AST and ALT
Cavalca nti, 202017	Brazil	Multicenter, randomized, open-label, three-group, controlled trial	667 patients	Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxyl chloroquine, alone or with azithromycin, than in those who were not receiving either agent. Patients receiving azithromycin treatment experienced nausea and increased ALT.
Chang, 202018	China	Prospective, randomized, controlled, open-label multicenter trial	240 patients	During this trial, we detected 37 incidences of antiviral- associated adverse effects (AE) in the Favipiravir group and 28 incidences in the Arbidol group. All observed AE incidences were level 1. Favipiravir was associated with increased serum uric acid (3 (2.50%) in Arbidol group vs 16 (13.79%) in Favipiravir group, P=0.0014). No statistical difference was observed for the frequency of abnormal ALT/AST, psychiatric symptom reactions or digestive tract reactions. Most of these adverse reactions disappeared by the time patients being discharged.

e. Stone, et al (2020)[16] conducted a study with median age was 59.8 years (range, 21.7-85.4), and 45% of the patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% CI = 0.38-1.81; P = 0.64), and the hazard ratio for disease worsening was 1.11 (95% CI = 0.59-2.10; P = 0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease. At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.

f. Other study with 667 patients underwent randomization, when 504 patients had confirmed COVID-19 and were included in the modified intention-to-treat analysis. As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scaleat 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% CI = 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (OR = 0.99; 95% CI, 0.57 to 1.73; P=1.00). Prolongation ofthe corrected QT interval and elevation of liver-enzyme levels were morefrequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.[17]

g. Chang, et al (2020) conducted a study with 240 COVID-19 patients underwent randomization; 120 patients were assigned to receive Favipiravir, and 120 to receive Arbidol. Clinical recovery rate of Day 7 does not significantly differ between Favipiravir group (71/116) and Arbidol group (62/120) (P=0.1396, difference of recovery rate: 0.0954; 95% CI: -0.0305 to 0.2213). Favipiravir led to shorter latencies to relief for both pyrexia (difference: 1.70 days, P<0.0001) and cough (difference: 1.75 days, P<0.0001). No difference was observed of AOT or NMV rate (both P>0.05). The most frequently observed Favipiravir-associated adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014).

DISCUSSION

The global dissemination of COVID-19 has resulted in a lack of medical resourcesall over the world, particularly those that are required for the treatment of patientswho are in a critical condition, such as intensive care and ventilators.[19] There is an immediate need for clinical predictors in order to identify patients who may beat risk of developing critical illness. This will allow for close monitoring and earlyintervention before the disease worsens, thereby lowering the risk of morbidity and mortality associated with COVID-19 and easing the strain on limited medical resources. This meta-analysis provides crucial evidence regarding the link between gastrointestinal symptoms and the severity of COVID-19.[20]

Abdominal pain was associated with a 2.8-fold increased risk of severe COVID- 19 infection; the relationship between diarrhea and the severity of COVID-19 wasregionally different; the increased risk of nausea and vomiting needs to be verified. The severe rate was greater than 40% in COVID-19 patients who had gastrointestinal symptoms, and abdominal pain was associated with this increasedrisk. Because the data from the studies with small sample sizes did not adhere to a normal distribution when considering the incidence of gastrointestinal symptoms, we employ a random-effects model to pool the severity rate. In order to ensure the reliability of our conclusion, a sensitivity analysis was performed onthe pooled analysis of all of the results.[21,22]

Table 2. Gastrointestinal and hepatic side effects of possible COVID-19 therapies

Agent Therapy	Effect
Remdesivir	Elevation of liver enzymes
Lopinavir-ritonavir	Nausea, vomiting, abdominal pain, gastroenteritis
Hydroxychloroquine/chloroquine	Nausea, vomiting, abdominal pain, diarrhea
Steroids	Epigastric pain, peptic ulcer, risk of HBV reactivation
Interferon	Diarrhea, nausea, elevated alanine aminotransferase level
Ribavirin	Elevated liver enzyme levels
Umifenovir	Nausea, vomiting and deranged liver function
Bromhexine	Deranged liver function
Favipiravir	Diarrhoea, liver enzyme abnormalities
Nitazoxanide	Nausea, vomiting, diarrhoea and abdominal pain
Imervectin	Elevation of liver enzymes
Molnupiravir	Elevated alanine aminotransferase
Tocilizumab	Liver dysfunction
Baricitinib	Nausea, liver dysfunction
Azithromycin	Nausea, vomiting

The vast majority of studies that have investigated stomach pain have found that there is a direct connection between abdominal pain and severe COVID-19. It is not known what mechanism may make COVID-19 individuals who are experiencing gastrointestinal symptoms more prone to developing severe pneumonia.[22–24] The 'gut-lung axis,' which has been confirmed in influenza infection, may be one of the potential mechanisms, which would mean that the virus invades gastrointestinal cells, resulting in changes in the composition and function of gastrointestinal flora, and that these changes affect the respiratory tractthrough immune regulation.[25]

This would mean that one of the potential mechanisms is that the virus invades gastrointestinal cells, resulting in changes in the composition and function of gastrointestinal flora. The gut-lung axis is influenced by a number of factors, including viral load, the state of the gastrointestinal tract, and immunological function. We hypothesize, in light of the close connection that exists between viral load and the severity of COVID-19, that the viral load in the gastrointestinal tracts of COVID-19 patients who are experiencing abdominal pain is significantly higher than that of COVID-19 patients who are experiencing diarrhea, nausea, andvomiting.[24,25]

There are currently no medications that have been specially developed to treat COVID-19. However, the results of a number of trials suggest that particular medications may be useful in the treatment of COVID-19. Remdesivir, oseltamivir, azithromycin, vitamin C, vitamin D, antipyretics, anticoagulants, and a variety of other medications are among the medications that are often utilized inthe treatment of COVID-19.[26] COVID-19 is a pandemic illness with a significantmorbidity and fatality rate. Several medications are being studied for the treatment of the condition, although many are linked with GI and hepatic adverse effects. When providing these medicines to patients with GI symptoms such as diarrhea and vomiting, use caution and close monitoring.[27]

Liver impairment is a common finding in COVID-19 patients, study propose thatall patients with COVID-19 and liver impairment undergo tests for probable causes of liver illness, including viral hepatitis serology, especially in locations where HBV is widespread.[27] High-dose corticosteroids and tocilizumab have beenused to treat individuals with severe COVID-19. In patients with persistent HBVinfection who get this regimen, there is a risk of HBV reactivation, hepatitis flare,and possibly acute liver failure. Screening for HBsAg is advised, and individualswith COVID-19 who test positive for HBsAg during steroid treatment should getantiviral prophylaxis with nucleoside analogs.

CONCLUSION

When deciding on the most effective course of therapy for COVID-19 patients, medical professionals need to take into account the possibility that gastrointestinal(GI) symptoms and liver dysfunction are caused either by disease presentations orby drug side effects.

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