Coronavirus Disease 2019 and Gastrointestinal Involvement: a Systematic Review

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Abstract

Introduction: The World Health Organization (WHO) announced the Coronavirus 2019 (COVID-19) as a Public Health Emergency of International Concern (PHEIC) toward the end of January 2020. There is still limited evidence to explain the gastrointestinal involvement in COVID-19. In this study, we aimed to further investigate current evidence describing the gastrointestinal involvement in COVID-19 patients.

Methods: This systematic review has been registered in PROSPERO (CRD42020181584). A systematic search of literature for observational and randomized controlled trial was conducted in PubMed, PubMed central, and Google Scholar through April 16, 2020. Two reviewers independently searched and selected. The risk of bias was evaluated using the Newcastle-Ottawa Quality assessment tool.

Results: A total of 1,480 articles were screened from which 12 articles with 5584 subjects were selected. SARS-CoV-2 can invade human body by binding to angiotensin converting enzyme 2 (ACE-2) receptor which also located to small intestinal epithelial cells, crypt cells and colon. The virus itself may cause disorders of the intestinal flora. The diagnosis should be based on a set of symptoms diarrhoea, nausea, vomiting, abdominal discomfort or pain, combined with positivity of faecal PCR test. Treatment of COVID-19 mainly is supportive care. The probiotic may modulate the gut microbiota to alter the gastrointestinal symptoms and reduced enteritis, ventilator associated pneumonia, and reverse certain side effect of antibiotics**.**

Conclusion: Our synthesis of literature showed that there was no good evidence yet in overall area of gastrointestinal manifestations in COVID-19. Future research is needed to explore all areas, especially in mechanism and treatments

Introduction

On December 31 2019, Word Health Organization (WHO) mentioned a case of cluster pneumonia with unidentified etiology in Wuhan City, Hubei Province, China. This case continues to distribute and grow until there are reports of deaths and cases found outside of China. In early 2020, China has identified pneumonia of unknown etiology as a new type of coronavirus. The WHO suggested the disease name as COVID-19 and has announced this as a Public Health Emergency of International Concern (PHEIC) toward the end of January 2020. Then as of February 24, 2020, more than 80,000 confirmed cases including more than 2,700 deaths have been accounted for around the world, influencing at any rate 37 nations. On March 2020 Indonesia reported two cases of COVID-19 confirmation and WHO established COVID-19 as a pandemic.[1,2] As February 15th, 2020, WHO reported total 108,579,352 confirmed cases worldwide COVID-19 outbreak and in Indonesia reached 1,223,930 cases.[2]

COVID-19 is the seventh human coronavirus detected and appears to have major similarities with two other highly pathogenic human respiratory coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2004 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012–2016. COVID-19, SARS-CoV and MERS-CoV belong to the betacoronovirus family, which potentially share a similar source in bats. Such betacoronaviruses cause respiratory symptoms and gastroenteritis in hosts of humans and animals. [3,4]

Patients typically present with fever and respiratory symptoms, nevertheless, some patients also have gastrointestinal manifestations with diarrhoea, vomiting and abdominal pain.[5] Based on several scientific studies, it was confirmed that COVID-19 could be transmitted human-to-human primarily via respiratory droplets when an infected person cough or sneeze, not through the air.[3] Studies have identified the SARS-CoV-2 RNA in anal / rectal swabs and stool specimens.[5,6,7] Therefore considerations must be given to the possibility of faecal-transmission in COVID-19 infection. There were many articles published recently, but the results were conflicting. The aim of this study is to know the current evidence of COVID-19 and gastrointestinal involvement. In this systematic review, we will evaluate current articles related to digestive symptoms and COVID-19.

Material and Methods

This systematic review is registered at PROSPERO (International database of prospectively registered systematic reviews) (CRD42020181584).)

A literature search was performed on electronic databases, including PubMed (https://www.ncbi.nlm.nih.gov/pubmed/?term=COVID-19+AND+gastrointestinal+involvement+AND+%22risk+factors+OR+clinical+manifestations+OR+diagnosis+OR++treatment%22) PubMed central

(https://www.ncbi.nlm.nih.gov/pmc/?term=COVID19+AND+gastrointestinal+involvement+AND+%22risk+factors+OR+clinical+manifestations+OR+diagnosis+OR+treatment%22) and Google Scholar

(https://scholar.google.co.id/scholar?as_ylo=2019&q=COVID19+AND+gastrointestinal+involvement+&hl=id&as_sdt=0,5).

A literature was conducted on April 16, 2020, using keywords listed in Table 1. The results obtained from database corresponded to clinical questions using the Boolean system presented in Table 1.

The literature search process was continued using the limits of the literature research and then the titles and abstracts were selected from each database. Studies were included in this review if met the following inclusion criteria: representation for clinical question (P: adult COVID-19; I: Gastrointestinal involvement; O: risk factors, mechanisms, symptoms and signs, diagnosis and treatment), type of study was review article, observational study and clinical trial, and if the full-text was available. Timing of outcome is any time. The studies were excluded the population is pregnant women or the articles were not in English language.

Two independent reviewers (MM and AK) selected the articles, extracted the data, and analysed the data. Any discrepancies were resolved by consensus between the reviewer. The reviewers evaluated the tittle and abstract for all studies that were identified through PRISMA search strategy. Full texts were evaluated when there was insufficient information in the title and abstract to make decisions about inclusion and exclusion. References in reviewed and excluded articles were examined to identify studies that may not has been identified through the primary search strategy. The search was limited to English language. A list of potential studies for inclusion in the systematic review was generated through the process.

Data extraction

Extracted data included details regarding authors, since 2019, country of study population, inclusion/exclusion criteria (patient characteristics), and description of outcomes. Data were also extracted regarding the COVID-19 (confirmation cases by PCR swabs), study outcomes (e.g. risk factors, mechanism, symptoms and signs, diagnosis, and treatment).

Multiple article checks were performed in the three databases. The appropriate study was the read in full paper and appraised. A critical appraisal was made based on a critical appraisal was mad based on the oxford's Centre for Evidence-based medicine which assesses the validity,

importance and applicability of each article. A flow diagram describing the study selection process is shown in Figure 1.

Outcomes definitions

Outcomes included (1) risk factors: what is the risk factor for gastrointestinal involvement in COVID-19; (2) mechanism: How is the gastrointestinal be involved in COVID-19 pathogenesis; (3) diagnosis: How is COVID-19 diagnosed if there are no respiratory symptoms and (4) treatment: Is there any specific symptoms for gastrointestinal involvement in COVID-19 infection.

Quality assessment

The Newcastle-Ottawa Quality (NOQ) assessment of observational trials was used to measure the risk of bias in this systematic review. Two independent researchers (MM and AK) to assess methodological quality and standard of outcome reporting in the included studies. The quality of evidence was assessed using the GRADE (Cochrance Group) analysis of findings will not be done.

Results

Literature search

A total of 1,480 articles were identified through the search strategy. Figure 1 presents the PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). After duplicates were removed, the two primary reviewers (MM and AK) screened titles and abstracts for 1,480 articles. For the articles that remained after the initial screened, 54 full text were reviewed for eligibility. Most articles are excluded because they did not include information on outcomes selected for our reviews or did not include comparison groups. Ultimately, 12 articles were selected (all articles index) with a total of 5574 patients. Overview of included studies were presented in table 2.

Overview of included studies

Table 2 provides the characteristic of included studies. There are 6 observational studies, 1 case report and 5 review articles.

Diagnosis of COVID-19 was using RT-PCR nasal or nasopharyngeal swab. Only two observational studies[27,28] and one case report[15] evaluate the gastrointestinal involvement using RT-PCR faeces. Only one study included children population.[28]

Primary outcomes

Risk factors

None of articles or studies reported the risk factors of gastrointestinal involvement in COVID-19. One observational study reported comorbidity related to gastrointestinal disease.[7] One review article evaluates the risk factor of COVID-19 infection in patients with existing gastrointestinal disease. Patients with comorbidities of inflammatory bowel disease especially in immunosuppressive agents, malnutrition, hypertension, diabetes, and on pregnant were at risk.[10]

Mechanisms

There were four observational studies[7,27,28,33] mentioned about the potential mechanism of gastrointestinal involvement in COVID-19. There were 4 review[2,5,10,23] and commentary[11] articles discussed the mechanism of COVID-19 infection.

Infectious virions are secreted to the virus-infected gastrointestinal cells. The genome sequences showed that SARS-CoC-2 shared 79.6% sequence identity to SARS-CoV, both encoding and expressing the spike (S) glycoprotein that could bind to the entry receptor ACE-2.[5] The receptor found abundantly expressed in glandular cells of gastric, duodenal, and rectal epithelial.[27] After the virus entry the mucosa, the gastrointestinal wall will increase its permeability. Enteropathic viruses may directly damage the intestinal mucosa and cause digestive symptoms.[11] The symptoms of diarrhoea will occur by invaded enterocytes malabsorption.[7]

The virus itself may cause disorders of the intestinal flora, which could result in digestive symptoms. Decreased expression of antimicrobial peptides and showed altered gut microbial composition.[2] The viral nucleic acids found in the faecal samples and anal swabs.[33] It can be last longer than it found in nasal and pharyngeal swab has become negative.[28]

Diagnosis

Gastrointestinal involvement in COVID-19 infection should be based on a set of symptoms diarrhoea, nausea, vomiting, abdominal discomfort or pain, combined with positivity of faecal PCR test. Duration time of positivity of the test 1-12 days. In one study faecal PCR test found positive in 39 (53.4%) patients. Furthermore, 17(23.29%) found still positive of faecal test after the respiratory sample has become negative.[27] The diagnosis in children is the same as do in adult.[28]

Treatment

Treatment of COVID-19 mainly is supportive care, some case was given broad spectrum antibiotics.[15] Management gastrointestinal involvement in COVID-19 infection mentioned in one study was probiotic treatment. The probiotic may modulate the gut microbiota to alter the gastrointestinal symptoms[23] and reduced enteritis, ventilator associated pneumonia, and reverse certain side effect of antibiotics.[2] Antiviral therapy with alpha interferon oral spray (8,000 Unit, two spray, there times a day) may be used in children, however further clinical trial was needed.[28]

Quality assessment

From six observational studies evaluated using Newcastle-Ottawa quality assessment, three was only one study "good"[7], the others two studies "fair"[27, 33] and the others three studies "bad" [28, 24, 17]

Discussion

To be best of our knowledge, this systematic review is the first evaluate the gastro-intestinal involvement in COVID-19. This review evaluated the whole aspects from the risk factors to treatment specific if COVID-19 had gastro-intestinal

involvement. The COVID-19 is the systemic disease and one of the involvements is in gastrointestinal tract.

From the published articles related gastrointestinal in COVID-19, none of the articles shared information about the risk factors of gastrointestinal involvement. Most of studies shared about severity cases of COVID-19 to become ARDS or death. COVID-19 patients who only complaint the gastrointestinal symptoms, should further be evaluated the risk factors of severity cases.

There are many reasons why COVID-19 appears to cause digestive symptoms. SARS-CoV-2 is similar to SARS-CoV and can invade the human body by binding to the human angiotensin converting enzyme 2 (ACE-2) receptor, which causes liver tissue injury by up- regulation of ACE-2 expression in liver tissue caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells. [7] COVID-19 patients could manifest with gastrointestinal involvement for instance nausea/vomit, diarrhea and abdominal discomfort/pain. Not rare, gastrointestinal symptom was the initial and the only symptom complaint by the patients. From the included studies, there were still limited data regarding the correlation between lung and gastrointestinal symptoms in COVID-19 patients. The explanation why several patients showed gastrointestinal symptoms only, should be answered in further observational studies focus on risk factors evaluation.

Coronavirus human transmissibility and pathogenesis mainly depend on the interactions, including virus attachment, receptor recognition, protease cleaving and membrane fusion, of its transmembrane spike glycoprotein (S-protein) receptor-binding domain, specific cell receptors (ACE2), and host cellular transmembrane serine protease (TMPRSS), with binding affinity of 2019-nCoV about 73% of SARS-CoV.[3,4,7,11] The S protein is responsible for facilitating entry of the CoV into the target cell. It is composed of a short intracellular tail, a transmembrane anchor, and a large ectodomain that consists of a receptor binding S1 subunit and a membrane-fusing S2 subunit. Receptor binding motif (RBM) in the S protein showed that most of the amino acid residues essential for receptor binding have sequence similarities between SARS-CoV and SARS-CoV-2, suggesting that the two CoV strains use the same host receptor for cell entry. Lu et al proved structural similarity between the receptor-binding domains of SARS-CoV and COVID-19 by molecular modelling which means COVID-19 could use ACE2 as the receptor. For SARS-CoV entry into a host cell, its S protein needs to be cleaved by cellular proteases at two sites, termed S protein priming, so the viral and cellular membranes can fuse. Specifically, S protein priming by the serine protease *TMPRSS2* is crucial for SARS-CoV infection of target cells and spread throughout the host. Hoffmann et al. investigated if SARS-CoV-2 entry is also dependent on S protein priming by TMPRSS2. [2,12,13,5]

The virus itself may cause disorders of the intestinal flora, which could result in digestive symptoms. Mechanistically, ACE2 has a RAS-independent function, regulating intestinal amino acid homeostasis, expression of antimicrobial peptides, and the ecology of the gut microbiome. ACE2 mutants could decrease expression of antimicrobial peptides and showed altered gut microbial composition. Therefore, we speculate that COVID-19 may have some relationship with the gut microbiota.[2]

Finally, the intestine is the largest immune organ in the body. Changes in the composition and function of the digestive tract flora affect the respiratory tract through the common mucosal immune system, and respiratory tract flora disorders also affect the digestive tract through immune regulation. The effect is called the "gut-lung axis" which may further explain why patients

with COVID-19 pneumonia often have digestive symptoms.[7]

Current recommendation by US CDC requires the use of BOTH nasal and throat swabs to obtain specimen from upper respiratory tract of potential case with COVID-19 for diagnostic testing using RT-PCR to confirm the cases. However, initial rapid guidelines from China only indicated the use of throat swabs. Yang et al (2020) specific for COVID-19 have found that testing of specimens obtained from nasal swabs, as well as from sputum, are more effective than throat swabs, for the detection of SARS-CoV-2 concluded that "sputum is most accurate for laboratory diagnosis of (COVID-19), followed by nasal swabs, while throat swabs was not recommended for the diagnosis." However, the authors recognized the limitation that preliminary investigations only found about a quarter of COVID-19 patients showed sputum production.[9]

A study by To et al (2020) have found that SARS-CoV-2 was detected in saliva samples from 11 out of 12 COVID-19 patients. This suggests that saliva samples could be a potential alternative or additional specimen for diagnostic testing, especially in scenarios with limited trained healthcare providers outside of the hospital setting, and with aim to reduce exposure risk during specimen collection.[14,9]

Gastrointestinal involvement of SARS-CoV-2 infection and isolation of SARS-CoV-2 from faecal samples of patients are in support of the importance of faecal–oral route in SARS- CoV-2 transmission.[5] The positivity of COVID-19 virus still remain although the improvement of lung lesion and the nasopharyngeal swab had become negative.

Currently, there is no validated treatment for COVID-19. The main strategies are symptomatic and supportive care, such as keeping vital signs, maintaining oxygen saturation and blood pressure, and treating complications, such as secondary infections or organs failure.[20] The antivirus such as lopinavir/ritonavir did work in early evidence[34], but not after large RCT came out. Remdesivir showed benefit in moderate and severe cases.[35] Controlling several comorbidities such as hypertension[36] and diabetes[37] showed benefit, but not in dyslipidemia using statin.[38] Others risk factors such as anemia[39] and thyroid disease[40] should also be managed.

Currently no direct clinical evidence proved that modulation of gut microbiota has the therapeutic role in treatment of COVID-19[41], but we suppose that targeting gut microbiota might be a new therapeutic option or at least adjuvant therapeutic choice. In early February, Guidance from China's National Health Commission (Version 5) recommend that in the treatment of severe patients with COVID-19 infection, probiotics can be used to maintain the balance of intestinal microecology and prevent secondary bacterial infection which showed that growing awareness of the importance of gut microbiota in COVID-19 infection has been accepted by Chinese government and first-line medical staff.[2]

There are several potential therapeutic approaches. Development of a spike1 subunit protein-based vaccine may rely on the fact that ACE2 is the SARS-CoV-2 receptor. Cell lines that facilitate viral replication in the presence of ACE2 may be most efficient in large-scale vaccine production.[22]

Conclusion

There is still limited evidence to evaluate gastrointestinal involvement in COVID-19. Further studies should evaluate the risk factors of with gastrointestinal involvement only in COVID-19 patients. The interaction between microbiota and local and systemic immune system, and the consequences of pro or prebiotic treatment that modulate systemic immune system should also be sought.

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