

Diarrhea as a Prognostic Factor for Severe COVID-19

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ABSTRACT

In March of 2020, the WHO has declared the state pandemic of Coronavirus disease (COVID-19) that started in the city of Wuhan, China. The widespread of cases resulted in 2,877,476 cases and 73,582 death reported in Indonesia. It is commonly known that the respiratory system was the main problem in COVID-19, but it is recently reported that gastrointestinal involvement has a higher likelihood to develop into severe cases. Moreover, it is found that diarrhea is the most highly prevalent of the gastrointestinal signs and symptoms in COVID-19 patients.

The aim of this evidence-based case report is to understand the association between diarrhea and severe cases of COVID-19. A search on Pubmed, Scopus and Cochrane result in five articles to be appraised using Centre for Evidence-Based Medicine (CEBM) critical appraisal tool. The most recent systematic review by Ghimere S et al (2020), found COVID-19 patients with diarrhea has higher likelihood of developing into a severe case (OR = 1.63, 95% CI: 1.11 – 2.38). While the cohort studies showed several prognostic factors that may potentially effect the outcome of severe COVID-19 cases.

It is concluded that severe COVID-19 cases were more likely to be found in patients presenting with diarrhea. Thus, Confirmed COVID-19 patients with diarrhea should be carefully evaluated to anticipate worsening of symptoms.

Keywords: *Coronavirus Disease (COVID-19), diarrhea, digestive signs and symptoms, prognosis*

ABSTRAK

Pada bulan Maret tahun 2020 lalu, seluruh dunia diguncangkan oleh pandemi infeksi Sars-CoV-2 yang berawal di Wuhan, China. Tingginya tingkat penyebaran tercatat dengan 2.877.476 kasus terkonfirmasi dan 73.582 kematian yang dilaporkan di Indonesia. Walaupun gejala pernafasan merupakan gejala utama kasus COVID-19, kini beberapa kasus menggambarkan bahwa kasus Coronavirus disease (COVID-19) dengan manifestasi gejala pencernaan meningkatkan kemungkinan kasus dengan derajat berat. Selebihnya, disebut bahwa diare merupakan gejala pencernaan dengan prevalensi tertinggi di kasus COVID-19.

Laporan kasus berbasis bukti ini bertujuan untuk mengetahui hubungan antara kejadian diare pada kasus COVID-19 derajat berat. Pencarian strategis yang dilakukan pada Pubmed, Scopus dan Cochrane menghasilkan lima artikel yang ditelaah menggunakan CEBM critical appraisal tools. Tinjauan sistematis terbaru yang dilakukan oleh Ghimere S et al (2020) menemukan bahwa gejala diare pada kasus COVID-19 dapat memprediksi

prognosis derajat klinis berat (OR = 1.63, 95% CI: 1.11 – 2.38). Sedangkan, studi kohort yang diinklusi menjelaskan mengenai faktor prognostik yang dapat mempengaruhi kasus COVID-19 dengan derajat berat.

Maka dapat disimpulkan bahwa gejala diare lebih sering ditemukan pada kasus COVID-19 derajat berat dan pasien terkonfirmasi COVID-19 yang mengeluhkan diare perlu dipantau dengan seksama untuk mengantisipasi perburukan.

Kata kunci: Coronavirus disease (COVID-19), diare, digestive signs and symptoms, prognosis

INTRODUCTION

In late 2019, there were series of atypical pneumonia cases reported in Wuhan, China.¹ The cases grew exponentially and in March 2020, the WHO declared a pandemic of novel coronavirus.² This new coronavirus commonly known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the one responsible for Coronavirus Diseases 2019.^{3,4} As of March 2021, there have been 2,877,476 confirmed cases and 73,582 death in Indonesia, widespread cases have disrupted economic, social and health status of the country.⁵

Most patients are present with respiratory symptoms such as cough and dyspnea accompanied with systemic symptoms like chills or fever.^{6,7} Nevertheless, there is a trend shifting towards gastrointestinal involvement in COVID-19 clinical manifestations.^{6,7} While it is known that the general mechanism of gastrointestinal involvement in SARS-CoV-2 infection is mediated by angiotensin converting enzyme-2 (ACE2), the exact mechanism is not yet known. ACE2 play a role as the port of entry of the virus, which are not only localized in the respiratory system but are also found in gastrointestinal linings.⁸

There are growing evidence showing how gastrointestinal involvement is associated with severe cases.^{6,7,9,10} Moreover, it is also stated early in the early phase of the pandemic that diarrhea is the most prevalent gastrointestinal involvement in COVID-19.¹ Therefore, this paper is interested in looking into diarrhea as an independent prognostic factor by investigating available studies on the association between the presence of diarrhea and severe cases of COVID-19.

CASE ILLUSTRATION

A 28-year –old woman presented with a 2-day history of watery diarrhea five to six times per day. Diarrhea was accompanied by fever and cough. There was a history of contact with a confirmed case within her workplace. On initial presentation, body temperature was 38°celcius there were course bibasal

crackles on chest examination and mild abdominal tenderness without rigidity and rebound. Initial workup revealed normocytic normochromic anemia and thrombocytopenia. The patient’s polymerase chain reaction (PCR) result was positive for SARS-CoV-2 infection.

METHOD

The search was conducted on three major databases (Pubmed, Scopus and Cochrane) with “COVID-19” “SARS-CoV-2” “diarrhea” “Signs and Symptoms, Gastrointestinal” “prognosis” “severity” as keywords (Table 1). Studies that were included are full-text articles in English following the eligibility criteria which are studies with confirmed COVID-19 cases as the targeted population comparing ratio of gastrointestinal involvement and case severity as the outcome.

Studies included in this article were limited to systematic reviews/meta-analyses of cohort studies and cohort studies. Chosen articles were assessed using systematic review and cohort study assessment tool from the University of Oxford 2010 Center for Evidence-based Medicine (CEBM).

Table 1. Keyword and search strategy

Database	Search strategy	Hits	Included
PubMed	((COVID-19) OR (SARS-CoV-2)) AND ((Signs and Symptoms, Gastrointestinal) OR (Signs and Symptoms, Digestive) OR (Gastrointestinal symptoms)) OR (Diarrhea)	155	13
Scopus	OR (Gastrointestinal involvements)) AND ((Severity) OR (Prognosis))	73	9
Cochrane		0	0

RESULTS

The research yielded twenty-two studies from the three major databases. After the removal of duplicates, eighteen studies were screened based on their title and abstract. Thirteen studies were excluded for not meeting the eligibility criteria (Figure 1).

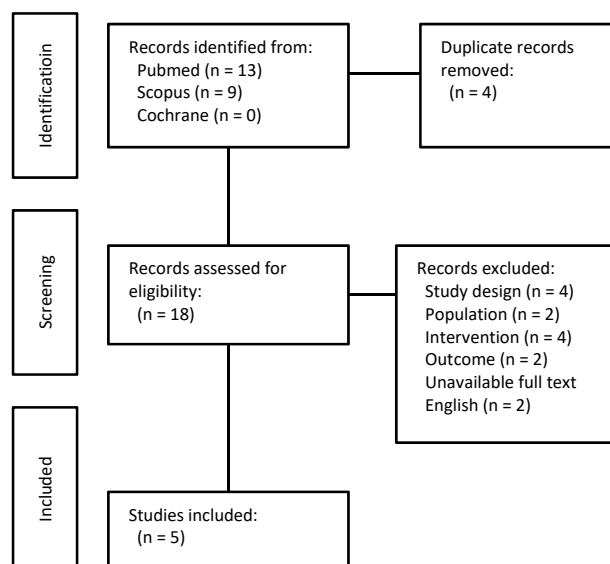


Figure 1. Search strategy flowchart and study selection

Three out of five selected articles were systematic reviews involving an adequate amount of studies. The two retrospective cohort studies by Deane K et al (2021) and Hegazy MA et al (2021) recruited 520 and 190 participants, respectively. All of the studies included confirmed COVID-19 cases having positive polymerase chain reactive (PCR) results for SARS-CoV-2 infection. The outcomes however slightly differ between studies whereas the study by Mao R et al (2020) and Ghimere S et al (2020) defined severe cases as those required for ICU admission, SpO₂ < 90% or other signs of ARDS. While a study by Hegazy MA et al (2021) defined severe cases as having respiratory rate >30 times/minute or SpO₂ < 90%. Lastly, Wang H et al (2020) and Deane K et al (2021) defined it as ICU admission.

Overall qualities of selected studies were adequate though some are better than the others (Table 2 and Table 3). Between the three systematic reviews Wang H et al (2020) has the least quality due to the absence of quality assessment within included studies. A systematic review by Ghimere S et al (2020) was the most recent one and it involves studies located in multiple centers around the world. Additionally Wang H et al (2020) fail to involve more than one database. Deane K et al (2021) as one of the cohort studies selected, fail to describe the initial point of disease within the cohort and did not adjust for potentially important prognostic factors.

Out of all five studies, two studies by Ghimere S et al and Hegazy MA et al showed a significant association between diarrhea and severe cases of COVID-19 with a ratio of OR = 1.63 (95% CI: 1.11-2.38) and OR = 2.7 (95% CI: 1.4-5.2), respectively. While three studies by

Mao R et al, Wang H et al, and Deane K et al found no significance in the presence of diarrhea and prevalence of severe COVID-19 disease (OR = 1.22, 95% CI: 0.81-1.84; OR = 1.24, 95% CI: 0.90-1.72; OR = 0.82, 95% CI: 0.47-1.44).^{1, 9-12}

DISCUSSION

This evidence-based case report aims to identify the prognosis of confirmed COVID-19 presenting with diarrhea. The main question here is best answered from the highest available article, which is the systemic reviews. A systematic review done by Ghimere S et al (2020) found all except only one of the evidence in their meta-analysis showed significance between diarrhea and disease severity of COVID-19.⁹ Although Mao R et al (2020) and Wang H et al (2020) did not find significant results regarding diarrhea as a prognostic factor.^{1,12} Mao R et al found that gastrointestinal involvement (including nausea, vomiting and abdominal pain) and abdominal pain alone were a significant predictor of severe COVID-19 cases.¹ Different results between the three studies can be explained by evidence showing an increase of Protein S mutation in a late phase of the pandemic, resulting in a higher case of gastrointestinal involvement in SARS-CoV-2 infection.¹³ Where in the latest systematic review, the meta-analysis show significance of diarrhea as a prognostic factor for severe COVID-19 cases.

A retrospective study by Hegazy MA et al (2021) found significant factors between the mild and severe cohorts.¹⁰ Where age, sex, presence of chronic lung diseases and metabolic comorbidities were factors that have a significant impact on COVID-19 severity.¹⁰ These factors were then used to adjust the analysis of diarrhea as an independent prognostic factor.¹⁰ Between the two cohort studies, one has clinical significance while the other does not.

Cohorts in the Hegazy MA et al (2021) showed participants with diarrhea has a 2.7 times higher likelihood of requiring ICU admission.¹⁰ The study also identifies age, sex and metabolic comorbidities as predictors of severe cases.¹⁰ This finding is in accordance with the previous studies as older age, male and metabolic comorbidities were associated with a higher prevalence of severe manifestations.¹⁴⁻¹⁷ Additionally Deane K et al report an increase in the duration of hospitalization in participants with diarrhea, nausea and vomiting collectively, this finding is in line with previous studies.^{1,11}

Table 2. Description of selected studies

Author	Study design	Patient group	Intervention and comparison	Outcome and method of assessment	Key results	Comments
Mao R (2020) ¹	Systematic review	35 studies with 6686 patients with COVID-19	This study compares patients with and without diarrhea and severe COVID-19 prevalence	Odds ratio subgroup analysis	No significance between patients with severe disease and the presence of diarrhea	Outcomes of severity were defined from ICU admission, SpO ₂ < 90% or ARDS. Mainly done in China
Wang H (2020) ¹²	Systematic review	21 studies with 3024 Covid-19 infected adult	This study compares the prevalence of diarrhea between severe and non-severe COVID-19 patients	Odds ratio by logistic regression	No significance in the prevalence of diarrhea between severe and severe cases	Severity was defined from ICU admissions. Mainly done in China
Ghimire S (2021) ⁹	Systematic review	38 studies with 8407 patients	Comparing severe COVID-19 patients with and without diarrhea	Odds ratio through meta-analysis	Significantly show diarrhea were more likely to have severe disease	with ICU or SpO ₂ < 90%. Mostly China
Deane K (2021) ¹¹	Retrospective cohort	520 patients with Sars-Cov-2 infection	Compared patients with gastrointestinal symptoms and without	Odds ratio and p-value	Diarrhea with vomiting and prevalence is higher in severe diseases though diarrhea alone show no significance	Outcomes are defined as ICU admissions. Done in NYC, United States population.
Hegazy MA (2021) ¹⁰	Retrospective cohort	190 patients with PCR confirmed Covid-19 cases	Association between gastrointestinal symptoms and disease severity	Odds ratio through multivariate logistic regression	Patients with diarrhea had the odds of severity in longer duration of symptoms	Severity is outcome defined as longer hospitalization

Table 3. Critical appraisal of selected studies

Author, year	Study design	Validity	Importance	Applicability	Level of evidence	Critical relevance	Comments	
Mao, R. (2020) ¹	Systematic Review	<p>F – Is it unlikely that relevant studies were missed? +</p> <p>A – Were the criteria used to select articles for inclusion appropriate? +</p> <p>I – Were included studies sufficiently valid? +</p> <p>T – Were the results similar from study to study? +</p>	<p>H - Heterogeneity</p> <p>1.22 (0.81-1.84)</p>	<p>Clinically important impact</p> <p>-</p>	1a	+	<p>Population</p> <p>+</p> <p>Determinant</p> <p>+</p> <p>Outcomes</p> <p>+</p>	<p>This study mainly included studies in one geographic area</p> <p>Systematic review quality is not adequate</p> <p>While this study has less geographic bias</p>
Wang, H. (2020) ¹²	Systematic Review	<p>F – Is it unlikely that relevant studies were missed? -</p> <p>A – Were the criteria used to select articles for inclusion appropriate? +</p> <p>I – Were included studies sufficiently valid? -</p> <p>T – Were the results similar from study to study? +</p>	<p>H - Heterogeneity</p> <p>1.24 (0.90 – 1.72)</p>	<p>Clinically important impact</p> <p>-</p>	2a	+		
Ghimire, S. (2021) ⁹	Systematic Review	<p>F – Is it unlikely that relevant studies were missed? +</p> <p>A – Were the criteria used to select articles for inclusion appropriate? +</p> <p>I – Were included studies sufficiently valid? +</p> <p>T – Were the results similar from study to study? +</p>	<p>H - Heterogeneity</p> <p>1.63 (1.11 – 2.38)</p>	<p>Clinically important impact</p> <p>+</p>	1a	+		
Deane, K. (2021) ¹¹	Retrospective Cohort	<p>F – Is it unlikely that relevant studies were missed? -</p> <p>A – Were the criteria used to select articles for inclusion appropriate? +</p> <p>I – Were included studies sufficiently valid? +</p> <p>T – Were the results similar from study to study? +</p>	<p>H - Heterogeneity</p> <p>0.827 (0.475 – 1.442)</p>	<p>Clinically important impact</p> <p>+</p>	2c	+	<p>Population</p> <p>+</p> <p>Determinant</p> <p>+</p> <p>Outcomes</p> <p>+</p>	<p>This cohort study quality is less adequate</p>
Hegazy, MA. (2021) ¹⁰	Retrospective Cohort	<p>F – Is it unlikely that relevant studies were missed? +</p> <p>A – Were the criteria used to select articles for inclusion appropriate? +</p> <p>I – Were included studies sufficiently valid? +</p> <p>T – Were the results similar from study to study? +</p>	<p>H - Heterogeneity</p> <p>2.7 (1.4 – 5.3)</p>	<p>Clinically important impact</p> <p>+</p>	2b	+		

The results of this evidence-based case reported varied results on the prevalence of diarrhea in COVID-19 cases. This finding is in accordance with the previous observation by D'amico et al which also reported a wide range of 2% to 50%. It is ought to believe that the difference was due to the lack of ability to identify diarrhea clinically and theoretically as there are various incorrect definitions of diarrhea.^{12,13,18,19}

Furthermore, the mechanism of diarrhea in COVID-19 infection is explained by previous evidence that suggested SARS-CoV-2 alters the permeability of the gastrointestinal tract causing malabsorption within the enterocytes.²⁰ There is also evidence demonstrating ACE2 involvement in the gastrointestinal linings directly disrupts the homeostasis of gut microbes.²¹ Nevertheless, the pathophysiology of diarrhea in severe cases of COVID-19 has not been fully understood.

Though an article proposed that cytokine storm play a role in causing hypoxia and later ischemia of the intestine which will promote diarrhea.²² Additionally, Wang H et al implied that investigation towards the side effects of diarrhea from antiviral consumption should be done because it is known that some antibiotics and antiviral caused drug-induced diarrhea.¹²

CONCLUSION

Severe COVID-19 infection is more likely to be found in confirmed cases presenting with diarrhea. Although this study assessed a wide range of corresponding literature, the result of the studies involved was mainly limited to those being admitted to a hospital. Therefore, confirmed COVID-19 patients presenting to the hospital with diarrhea should be carefully evaluated to anticipate a worsening condition.

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