Original Article

Risk Factors for COVID-19 Severity: Meta-Analysis Approach

Susilorini[1], F.C. Cahyaningrum[2] , Iwang Y[3], S.W. Purnami [4].

ABSTRACT

Objective

Coronavirus is a new type of virus that causes COVID-19 where the disease causes a fatal impact on sufferers. This study aimed to explore risk factors against the severity of COVID-19, i.e. *dyspnea*, cough, fever, diarrhea, history of diabetes, hypertension, Chronic Obstructive Pulmonary Disease (COPD), impaired liver function, and Cardiovascular Disease (CVD).

Materials and Methods:

The author conducted a study search on Friday, March 27th, 2020 at 07.00 – 08.30 PM through the PubMed website. The study search strategy uses the keywords of "COVID-19" or "corona virus", "symptoms", "clinical", "severe", and other words related to COVID-19. Studies used for meta-analysis must meet inclusion and exclusion criteria.

Results and Discussion:

Meta-analysis results for significant risk factors include: dyspnea (OR=3.53, 95% CI: 2.62-4.75), diarrhea (OR=1.73, 95% CI: 1.03-2.89), history of diabetes (OR=2.65, 95% CI: 1.77-3.98), hypertension (OR=2.25, 95% CI: 1.64-3.08), COPD (OR=6.26, 95% CI: 2.47-15.87), and CVD (OR=2.84, 95% CI: 1.64-4.90).

Conclusion

Patients who have dypsnee and diarrhea symptoms have higher riks of falling into severy COVID. Risk factors for cough symptoms, fever symptoms, and history of impaired liver function are not related to the severity of COVID-19. Patients with comorbidity such as diabetes, hypertension, COPD dan CVD have higher risk to get severe COVID-19.

Keywords

comorbidities; COVID-19; fixed effect; odds ratio; dyspnea; cough; diarrhea; diabetes; hypertension; COPD; impaired liver function; CVD

INTRODUCTION

COVID-19 is a new disease caused by the novel coronavirus in which the virus belongs to a new virus that comes from the same family as severe acute respiratory syndrome (SARS) and some kind of common cold[1]. The disease was first identified in Wuhan, China in 2019 and until now it has spread to various countries in the world very quickly. WHO has declared that COVID-19 is a public health emergency of international concern. On February 25th, 2020, as many as 81,109 laboratory-confirmed cases had been documented globally[2,3].

According to Rahman et al the COVID-19 incidence rates increased with an increase in urban population percentage, monthly consumption, and the number of health workers within a district[4]. Novel coronavirus can be transmitted through direct contact with sputum splashes from an infected person (through

1. Susilorini, Department of Pathology Anatomy of Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia
2. F.C. Cahyaningrum, Department of Statistics, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia
3. Iwang Y, Department of Biology of Faculty of Medicine, University Islam Sultan Agung, Semarang, Indonesia.
4. Santi Wulan Purnami, Department of Statistics, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia. E-mail: santi_wp@statistika.its.ac.id

Correspondence

Santi Wulan Purnami, Department of Statistics, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia.
E-mail: santi_wp@statistika.its.ac.id

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coughing and sneezing contact), and it touches surfaces contaminated by the virus. The virus is able to survive for several hours on the surface, but a simple disinfectant can kill it[5].

Symptoms that appear due to novel coronavirus infection include fever, cough, breathless, and Anosmia[6]. Two reliable biomarkers (D-dimer and S. ferritin) are correlated with disease severity and useful for better management of COVID positive patients. In more severe cases, the infection can cause pneumonia or difficulty breathing. Although rare, this disease can be fatal. In addition, some symptoms of infection can be characterized by digestive problems such as diarrhea and also fatigue in sufferers. Novel coronavirus can affect people of any age, but so far there have been very few reported cases of COVID-19 in children. So far, COVID-19 has mostly occurred in older people with pre-existing medical conditions.

Various studies about COVID-19 have been carried out to provide an overview and inference about COVID-19. Several studies with the same framework can give varying results. In this study, a meta-analysis will be conducted to get conclusions from various studies on the symptoms and influence of the history of disease on COVID-19 severity which found several studies showing dissimilar conclusions. With the meta-analysis, it is expected that the conclusions obtained can provide insight into the medical world regarding risk factors that can affect the severity of COVID-19.

METHODS

Odds Ratio

The odds ratio is the comparison between the chance of occurrence after exposed to risk factors and the chance of events in a controlled state[3]. Given a contingency table 2 × 2 as in Table 1. The odds ratio formula can be written as equation (1)[7].

$$OddsRatio = \frac{AD}{BC} \quad (1)$$

In the process of meta-analysis, the odds ratio calculation is diverted to the log scale, both for fixed effect and random effect. Next, the summary of effect size in the log scale is converted back to get a summary of odds ratio. The following are the formula of log odds ratio, variance of log odds ratio, and standard error of log odds ratio.

$$LogOddsRatio = \ln\left(OddsRatio\right) \quad (2)$$

$$V_{LogOddsRatio} = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D} \quad (3)$$

$$SE_{LogOddsRatio} = \sqrt{V_{LogOddsRatio}} \quad (4)$$

Equation (5) is a formula for converting log odds ratio into odds ratio, while equations (6) and (7) are odd ratio confidence interval (CI) formulas after converting from log odds ratio.

$$OddsRatio = \exp\left(LogOddsRatio\right) \quad (5)$$

$$LL_{OddsRatio} = \exp\left(LL_{LogOddsRatio}\right) \quad (6)$$

$$UL_{OddsRatio} = \exp\left(UL_{LogOddsRatio}\right) \quad (7)$$

Heterogeneity Test

Variability in effect size interventions evaluated in various studies is known as heterogeneity statistics. If the heterogeneity test shows significant result, then random effects for meta-analysis are better to use. However, if the heterogeneity test shows a failed reject H0, then the fixed effect is more appropriate to use. The hypotheses used for heterogeneity test are as follows[8].

H_0: Effect size between homogeneous studies

H_1: Effect size between heterogeneous studies

Test statistics:

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i} \quad (8)$$

where the elements for calculating Q are obtained in the process of calculating fixed effects described in the next sub-chapter. The area of rejection is to reject H_0 if $Q > \chi^2$ with a degree of freedom (k-1), *k* is the number of studies that is used for meta-analysis or *P* value < α (α = 0.05).

Fixed Effect

Meta-analysis using fixed effect assumes that the actual effect size is the same/identic for all research. If there is a variation in the effect size between studies, then this is caused by sampling error or error in estimating the effect size. The relative weight of fixed effects tends to vary. Equations (9) to (12) are the formulas for calculating weight, variance of summary log odds ratio, standard error of summary log odds ratio, and summary log odds ratio.

$$W_i = \frac{1}{V_{Y_i}} \quad (9)$$

$$V_M = \frac{1}{\sum_{i=1}^{k} W_i} \quad (10)$$

$$SE_M = \sqrt{V_M} \quad (11)$$

$$M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \quad (12)$$

The equations (13) and (14) are the lower limit and upper limit formulas of the log odds ratio.

$$LL_M = M - 1,96 \times SE_M \quad (13)$$

$$UL_M = M + 1,96 \times SE_M \quad (14)$$

Furthermore, equation (15) is a statistical test for summary effect size, as well as equations (16) and (17) respectively are the formula to calculate *P* value for one-way and two-way testing where $\phi(Z)$ is the standard normal cumulative distribution.

$$Z = \frac{M}{SE_M} \quad (15)$$

$$p = 1 - \phi(\pm|Z|) \quad (16)$$

$$p = 2[1 - (\phi(\pm|Z|))] \quad (17)$$

Forest Plot

Forest plot is an important tool used to summarize the information of individual studies, provide conclusions from a number of heterogeneous studies in visual form, and show the results of common effect estimation in one image[9].

Symptoms of COVID-19

Common symptoms of COVID-19 according to UNICEF Indonesia, such as[5]:

1. Fever is a condition when the body temperature exceeds 37°C caused by the presence of disease or inflammation.
2. Cough is a natural response from the body as a defense system to remove substances and particles from the respiratory tract, as well as preventing foreign bodies from entering the lower respiratory track.
3. Breathless (dyspnea), is a condition in which a person has difficulties breathing freely into his lungs.

Comorbidities of COVID-19 Patients

Several studies that have conducted research on COVID-19, include comorbidities as clinical characteristics that are suspected to have an influence to the severity of COVID-19, the diseases such as[5]:

1. Diabetes is a chronic disease characterized by high levels of blood sugar (glucose).
2. Hypertension is a condition when blood pressure is at a value of 130/80 mmHg or more.
3. Chronic Obstructive Pulmonary Disease or COPD is a lung disease that causes the sufferers having difficulty to breathe. This disease occurs due to the complication of two disease caused by smoking, namely chronic bronchitis and emphysema.
4. Impaired liver function is a disease that occurs when the liver is damaged, lost function, or injured due to something. As the result, liver performance decreases and causes various kind of complaints.

Cardiovascular Disease or CVD, is a series of disorders that attack the heart and vessels, including coronary heart disease.

Study Search Strategy:

The author conducted a study search on Friday, March 27th, 2020 at 07.00 - 08.30 PM through the PubMed website. The study search strategy uses the keywords “COVID-19” or “corona virus”, “symptoms”, “clinical”, “severe”, and other words related to COVID-19.

Flow Diagram of Study Selection:

Figure 1 is a flowchart that describes the study selection process that will be conducted meta-analysis.

Study Characteristics for Meta-Analysis:

Table 2 shows the identity of the studies used for meta-analysis.

Characteristic of the participant:

Inclusion Criteria

Studies used for meta-analysis meet inclusion criteria including: (1) samples taken are COVID-19 sufferers who are divided into severe groups or Intensive Care Units/ICU and non-severe or Non-ICU groups, (2) COVID-19 sufferers are 40 years old and above, (3) accurate study descriptions of patients in severe and non-severe groups with symptoms include dyspnea, cough, diarrhea, fever and contain comorbidities data namely diabetes, hypertension, COPD, impaired liver function, and CVD, (4) data can be extracted into meta-analysis.

Exclusion Criteria

Criteria used to exclude studies in meta-analysis, such as: (1) the age of COVID-19 sufferers is less than 40 years old, (2) studies are not divided into severe/ICU and non-severe/Non-ICU groups, (3) data are not available for meta-analysis (do not contain data on symptoms.

RESULTS

Symptoms of Dyspnea or Shortness of Breath

The relationship between dyspnea symptoms and the severity of COVID-19 patients based on four studies are shown in Table 3. Total COVID-19 patients in four studies used for meta-analysis with risk factors for dyspnea symptoms as many as 1082 patients in which 29.02% of the total patients have dyspnea symptoms and 70.98% of the total patients do not have dyspnea symptoms. When reviewed based on its severity, as many as 45.09% (207/275) of the total patients who entered the severe group have dyspnea symptoms. Meanwhile, the percentage of COVID-19 patients who have dyspnea symptoms in the non-severe group is 16.95% (190/1121).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the association between dyspnea symptoms and the severity of COVID-19 disease are significant as indicated by a value of $Z = 8.2995$ with P value < 0.0001. This means that patients with COVID-19 who have dyspnea symptoms have a higher risk of entering the severe group. Pooled odds ratio (OR=3.53, 95% CI: 2.62-4.75) also shows a significant association between dyspnea symptoms and the severity of COVID-19 disease indicated by interval odds ratios. It doesn't contain a value of 1. It can also be interpreted that patients with COVID-19 who have dyspnea symptoms have a risk of $3.53 \approx 4$ times greater to fall into the category of severe compared to COVID-19 patients who do not show dyspnea symptoms. The forest plot of relationship between dyspnea and COVID-19 severity is shown in Figure 2.

Cough Symptoms

The relationship between cough symptoms and the severity of COVID-19 patients based on four studies are shown in Table 4. Total COVID-19 patients in four studies used for meta-analysis with risk factors for cough symptoms as many as 1398 patients in which 67.81% of the total patients have cough symptoms and 32.19% of patients do not have cough symptoms. When reviewed based on its severity, as many as 72.36% (199/275) of the total patients who entered the severe group have cough symptoms. Meanwhile, the percentage of patients who have cough symptoms in the non-severe group is 66.7% (749/1123).

Heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the relationship between cough symptoms and the severity of COVID-19 disease are not significant, which is indicated by a value of $Z = 3.9842$ with P value $= 0.1282$. This means that patients with COVID-19 who have or do not have cough symptoms have the same risk to enter the severe and non-severe groups. Pooled odds ratio (OR=1.26,95% CI: 0.94-1.70) also indicates a significant association between cough symptoms and the severity of the disease indicated by interval odds. The ratio contains a value of 1. The forest plot of relationship between cough symptoms and the COVID-19 severity is shown in Figure 3.

Symptoms of Diarrhea

The relationship between diarrhea symptoms and the severity of COVID-19 patients based on four studies are shown in Table 5. Total COVID-19 patients in four studies used for meta-analysis with risk factors for diarrhea symptoms as many as 1414 patients where 0.05% of the total patients have diarrhea symptoms and 99.95% of patients do not have diarrhea symptoms. If reviewed based on its severity, as many as 0.09% (31/279) of the total patients who entered the severe group have diarrhea symptoms. Meanwhile, the percentage of patients who have diarrhea symptoms in the non-severe group is 0.04% (31/1135).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the association between diarrhea symptoms and the severity of COVID-19 disease are significant which is indicated by Z = 2.0748 with P value = 0.038. This means that patients with COVID-19 who have diarrhea symptoms have a higher risk of entering the severe group. Pooled odds ratio (OR=1.73,95% CI: 1.03-2.89) can be interpreted that patients with COVID-19 who have diarrhea symptoms have a risk of 1.77 ≈ 2 times greater to enter the in the category of severe compared to COVID-19 patients who do not show diarrhea symptoms. The forest plots of relationship between diarrhea symptoms and COVID-19 severity is shown in Figure 4.

Symptoms of Fever

The relationship between fever symptoms and the severity of COVID-19 patients based on four studies are shown in Table 6. Total COVID-19 patients in four studies used for meta-analysis with risk factors for fever symptoms as many as 1655 patients where 45.98% of the total patients have fever symptoms and 54.02% of patients do not have fever symptoms. When reviewed based on its severity, as many as 66.7% (182/273) of the total patients who entered the severe group have fever symptoms. Meanwhile, the percentage of patients who have fever symptoms in the non-severe group is 52.21% (579/1109).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the relationship between fever symptoms and the severity of COVID-19 disease are not significant shown with a value of Z = 1.6243 with P value = 0.125. This means that patients with COVID-19 who have or do not have fever symptoms have the same risk of entering the severe or non-severe group. Pooled odds ratio (OR=1.28,95% CI: 0.93-1.76) indicates the absence of a significant association between fever symptoms and the severity of the disease indicated by the interval odds ratio contains a value of 1. Fever symptoms are a common symptom in which COVID-19 patients who fall into severe and non-severe groups also experience symptoms of fever, so these symptoms are not significant to affect the severity of the patient. The forest plots of relationship between fever symptoms and COVID-19 severity is shown in Figure 5.

Diabetes

The relationship between diabetes and the severity of COVID-19 patients based on four studies are shown in Table 7. Total COVID-19 patients in four studies used for meta-analysis with diabetes risk factors as many as 1698 patients where 0.07% of the total patients have diabetes and 99.93% of the total patients do not have diabetes. When reviewed based on its severity, as many as 16.07% (45/280) of the total patients who entered the severe group have diabetes. Meanwhile, the percentage of patients who have diabetes in the non-severe group is 0.07% (579/1138).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The results of the relationship test between diabetes and the severity of COVID-19 disease are significant which is indicated with Z = 4.7225 and P value < 0.001. This means that COVID-19 patients who have diabetes before getting COVID-19 have a higher risk of entering the severe group. Pooled odds ratio (OR=2.65,95% CI: 1.77-3.98) can be interpreted that patients with COVID-19 who have diabetes before getting COVID-19 have a risk of 2.65 ≈ 3 times greater to enter the in the category of severe than COVID-19 patients who do not have diabetes. The forest plots of relationship between diabetes and COVID-19 severity is shown in Figure 6.

Hypertension

The relationship between hypertension and the severity of COVID-19 patients based on four studies are shown in Table 8. Total COVID-19 patients in four studies used for meta-analysis with hypertension risk factors as many as 1418 patients where 22.3% of the total patients have a history of hypertension and 77.7 % of the total patients do not have history of hypertension. When reviewed based on its severity, as many as 30.71% (86/280) of the total patients who entered the severe group have a history of hypertension. Meanwhile, the percentage of patients who have a history of hypertension in the non-severe group is 22.5% (579/1138).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the association between hypertension and the severity of COVID-19 disease are significant as indicated by a value of Z = 5.0117 with P value < 0.0001. This means that patients with COVID-19 who have hypertension before getting COVID-19 disease have a higher risk of entering the severe group. Pooled odds ratio (OR=2.25,95% CI: 1.64-3.08) indicates a significant relationship between a history of hypertension and the severity of the disease indicated by the interval odds ratio contains a value of 1. The forest plot of relationship between hypertension and COVID-19 severity is shown in Figure 7.

Chronic Obstructive Pulmonary Disease

The relationship between COPD and the severity of COVID-19 patients based on four studies are shown in Table 9. Total COVID-19 patients in four studies used for meta-analysis with risk factor COPD as many as 1420 patients where 1.33% of the total patients have a history of COPD and 98.67% of patients do not have history of COPD. When reviewed based on its severity, as many as 4.63% (13/281) of the total patients who entered the severe group had a history of COPD. Meanwhile, the percentage of patients who have a history of COPD in the non-severe group of 5.26×10-3% (6/1139).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the relationship between COPD and the severity of COVID-19 disease are significant as indicated by a value of Z = 3.8628 with P value = 0.0001. This means that patients with COVID-19 who have COPD before getting COVID-19 disease have a higher risk of entering the severe group. Pooled odds ratio (OR=6.26,95% CI: 2.47-15.87) can be interpreted that patients with COVID-19 who have COPD disease before getting COVID-19 disease have a risk of 6.26 ≈ 6 times greater to enter the in the category of severe than COVID-19 patients who do not have a history of COPD. The forest plot of relationship between COPD and COVID-19 severity is shown in Figure 8.

Impaired Liver Function

The relationship between impaired liver function and the severity of COVID-19 patients based on four studies are shown in Table 10. Total COVID-19 patients in four studies used for meta-analysis with risk factors for impaired liver function as many as 1418 patients where 2.54% of the total patients have impaired liver function and 97.46% of the total patients do not have history of impaired liver function. When reviewed based on severity, as many as 1.78% (5/281) of the total patients who entered the severe group have a history of impaired function liver. Meanwhile, the percentage of patients who have a history of impaired liver function in the non-severe group is 1.92% (31/1616).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the association between impaired liver function and the severity of COVID-19 disease are insignificant as indicated by a value of Z = -0.7033 with P value = 0.4819. This means that patients with COVID-19 who have or do not have impaired liver function before being stricken with COVID-19 disease have the same risk of getting into the severe and non-severe groups. Pooled odds ratio (OR = 0.69.95% CI: 0.25-1.93) can be interpreted that patients with COVID-19 who have impaired liver function before getting COVID-19 disease or do not have the impaired liver function have an equally great risk of getting into the category of severe or non-severe pain. The forest plot of relationship between impaired liver function and COVID-19 severity is shown in Figure 9.

Cardiovascular Disease

The relationship between CVD and the severity of COVID-19 patients based on four studies are shown in Table 10. Total COVID-19 patients with in four studies used for meta-analysis with CVD risk factors as many as 1418 patients where 4.23% of the total patients have a history of CVD and 95.77% of the total patient do not have history of CVD. When reviewed based on its severity, as many as 6.18% (26/421) of the total patients who entered the severe group have a history of CVD. Meanwhile, the percentage of patients who have a history of CVD in the non-severe group is 35.05% (34/97).

The heterogeneity test shows that the results of meta-analysis are significantly homogeneous, so the effect used is fixed effect. The test results of the relationship between CVD and the severity of COVID-19 disease are significant as indicated by a value of Z = 3.7420 with P value = 0.0002. This means that patients with COVID-19 who have CVD disease before getting COVID-19 have a higher risk of entering the severe group. Pooled odds ratio (OR =2.84,95% CI: 1.64-4.90) can be interpreted that patients with COVID-19 who have CVD before getting COVID-19 disease have a risk of 2.84 ≈ 3 times greater to enter the in the category of severe than COVID-19 patients who do not have a history of CVD. The forest plot of relationship between CVD and COVID-19 severity is shown in Figure 10.

DISCUSSION

COVID-19 patients who have dyspnea and diarrhea symptoms have a higher risk of falling into the category of severe. Meanwhile, if reviewed based on comorbidities owned by COVID-19 patients, patients who have diabetes, hypertension, COPD, and CVD have a higher risk to be categorized into severe. Therefore, those who have symptoms or comorbidities need to get intensive care. This result is in line to the possibility of the role of gut dysbiosis in the pathomechanisms of severe COVID-19[10]. Previously it was known that early report in Wuhan 1-10% COVID 19 patient had diarrhea sypmtoms, but recently it was reported more than 39%[11–14]. Gut dysbiosis lead to leaky gut and cytokine storm. These trigger hyperiflammation, tissue and vascular damage which can increased severity of COVID-19[14].

According to Clerbaux et al (2022), the mechanism by which gut dysbiosis increases the severity of COVID 19 is not fully understood. However, this is possible through mechanisms either directly or indirectly. The first mechanism is through the ability of the SARCOV virus protein S to bind to the angiotensin converting enzyme 2 (ACE2) receptor which causes disruption of amino acid metabolism and triggers homeostasis disorders in the intestine. The second mechanism is a mechanism that occurs indirectly, including mechanisms that occur through inflammation triggered by SARCOV-2 and through the mechanism of bacterial translocation due to the occurrence of leaky gut[15,16].

Gut dysbiosis can also occur before SARCOV 2 infection because in elderly people it is known that there is a decrease in gut microbiome diversity that occurs physiologically and this will be severe if they have comorbidities such as Diabetes Mellitus and obesity[17,18]. A decrease in microbiome diversity in older people can lead to aging of the immune system, which makes them more susceptible to viral and secondary bacterial infections[19].

The use of antibiotics can also aggravate gut dysbiosis that may have occurred before. The use of antibiotics is known to alter the balance of the gut microbiome leading to an increase in the growth of bacteria such as Enterococcus and a decrease in Roseburia[20]. Therefore, the use of antibiotics in patients with COVID-19 is recommended to be given only in conditions where it is proven that there is a secondary infection[21]. The use of probiotics is one of the options that can be used to overcome gut dysbiosis that occurs in COVID-19 patients. In severe gout dysbiosis, fecal transplant therapy is another strategy of choice[22]. Gut dysbiosis is a big problem that must be considered, because this gut dysbiosis not only affects physical but also mental health. It is currently known that gut dysbiosis can cause neuropsychiatric syndromes such as anxiety, depression and post-traumatic stress disorder[23].

In this study, the cough symptoms, fever symptoms, and impaired liver function do not significantly affect the severity of COVID-19 patients.

The results of this study are expected to improve the preventive and therapeutics strategies especially on pharmaceutical service of community pharmacists in low and middle-income countries. In addition, the results of this study are also expected to be used to design post-COVID-19 syndrome prevention strategies related to not only physical health but also mental health[24–26]. However, due to the variety of study designs included and the lack of consistent measures used in the included studies, a meta-analysis of the findings was not possible. Another strength of this review is that no dates were placed on dates in the search process. The limitations are related to the studies identified, which generally reporting on English. The other is that the majority of outcome measures assessed were evaluated immediately after the intervention. Only one study evaluated the effect eight months after the intervention with mystery shoppers. Therefore, future studies are needed to examine the duration of the effects of contact-based educational interventions for community pharmacists, as well as the effectiveness of indirect measures of repeated interventions of actual practice and whether booster training is necessary.

CONCLUSION

The outcome of this study may be valuable to recognize high risk patient and to specify futher medical consideration to prevent severe COVID-19. This review also showed gut dybiosis can have a significant impact on key constructs of severe COVID-19. Gut microbiome interventions may be a powerful method of improving treatment and prevent of severe COVID-19.

Ethical of Study

Not applicable (review article)

Conflict of interest

None

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Authors' contributions

Data gathering and idea owner of this study: *S.W. Purnami, F.C. Cahyaningrum*

Study Design: *F.C. Cahyaningrum*

Data Gathering: *F.C. Cahyaningrum*

Writing and Submission of Manuscript: *Susilorini, Iwang*

Editing and Approval of Final Draft:

Susilorini, Iwang

Table 1. Contingency Table 2 × 2 After Treatment

	Events	Non-Events	N
Treatment	A	B	n_1
Control	C	D	n_2

Table 2. Characteristics of Studies

Reference	Country	Year	Design	Risk Factors
Zhang et al	China	Feb, 2020	Retrospective	dyspnea, cough, diarrhea, fever, diabetes, hypertension, COPD, impaired liver function, and CVD
Huang et al	China	Feb, 2020	Retrospective	
Guan et al	China	Feb, 2020	Retrospective	
Wang et al	China	Feb, 2020	Retrospective	

Table 3. Meta-Analysis of Dyspnea and COVID-19 Severity

Study	Dyspnea (+)		Dyspnea (-)	
	Severe	Total	Severe	Total
Zhang, et al	24	44	29	76
Huang, et al	12	22	1	17
Guan, et al	65	205	108	894
Wang, et al	23	43	13	95
Total	**124**	**314**	**151**	**1082**
Heterogeneity: Q=7.7866, df=3 (*P* value=0.0506)				
Test for overall effect: Z=8.2995 (*P* value<0.0001)				

Table 4. Meta-Analysis of Cough and COVID-19 Severity

Study	Cough (+)		Cough (-)	
	Severe	Total	Severe	Total
Zhang, et al	45	90	8	30
Huang, et al	11	31	2	10
Guan, et al	122	745	51	354
Wang, et al	21	82	15	56
Total	**199**	**948**	**76**	**450**
Heterogeneity: Q=3.9842, df=3 (*P* value=0.2632)				
Test for overall effect: Z=1.5212 (*P* value=0.1282)				

Table 5. Meta-Analysis of Diarrhea and COVID-19 Severity

Study	Diarrhea (+)		Diarrhea (-)	
	Severe	Total	Severe	Total
Zhang, et al	9	18	48	121
Huang, et al	0	1	13	37
Guan, et al	10	42	163	1057
Wang, et al	6	14	30	124
Total	**25**	**75**	**254**	**1339**
Heterogeneity: Q=0.7417, df=3 (*P* value=0.8634)				
Test for overall effect: Z=2.0748 (*P* value=0.0380)				

Table 6. Meta-Analysis of Fever and COVID-19 Severity

Study	Fever (+)		Fever (-)	
	Severe	Total	Severe	Total
Zhang, et al	51	110	2	10
Huang, et al	13	41	0	1
Guan, et al	82	473	89	608
Wang, et al	36	137	0	2
Total	**182**	**761**	**91**	**621**
Heterogeneity: Q=1.6243, df=3 (*P* value=0.6539)				
Test for overall effect: Z=1.5341 (*P* value=0.125)				

Table 7. Meta-Analysis of Diabetes and COVID-19 Severity

Study	Diabetes (+)		Diabetes (-)	
	Severe	Total	Severe	Total
Zhang, et al	8	17	50	123
Huang, et al	1	8	12	33
Guan, et al	28	81	145	1018
Wang, et al	8	14	28	124
Total	**45**	**120**	**235**	**1298**
Heterogeneity: Q=7.6768, df=3 (*P* value=0.0532)				
Test for overall effect: Z=4.7225 (*P* value<0.0001)				

Table 8. Meta-Analysis of Hypertension and COVID-19 Severity

Study	Hypertension (+)		Hypertension (-)	
	Severe	Total	Severe	Total
Zhang, et al	22	42	36	98
Huang, et al	2	6	11	35
Guan, et al	41	165	132	934
Wang, et al	21	43	15	95
Total	**86**	**256**	**194**	**1162**
Heterogeneity: Q=4.9880, df=3 (*P* value=0.1727)				
Test for overall effect: Z=5.0117 (*P* value<0.0001)				

Table 9. Meta-Analysis of COPD and COVID-19 Severity

Study	COPD (+)		COPD (-)	
	Severe	Total	Severe	Total
Zhang, et al	2	2	56	139
Huang, et al	1	1	12	41
Guan, et al	6	12	167	1087
Wang, et al	3	4	33	134
Total	**13**	**19**	**268**	**1401**
Heterogeneity: Q=0.1674, df=3 (*P* value=0. 9827)				
Test for overall effect: Z=3.8628 (*P* value=0.0001)				

Table 10. Meta-Analysis of Impaired Liver Function and COVID-19 Severity

Studies	Impaired Liver Function (+)		Impaired Liver Function (-)	
	Severe	Total	Severe	Total
Zhang, et al	4	8	54	132
Huang, et al	0	1	13	40
Guan, et al	1	23	172	1076
Wang, et al	0	4	36	134
Total	**5**	**36**	**275**	**1382**
Heterogeneity: Q=2.4037, df=3 (*P* value=0.4930)				
Test for overall effect: Z=-0.7033 (*P* value=0.4819)				

Table 11. Meta-Analysis of CVD and COVID-19 Severity

Study	CVD (+)		CVD (-)	
	Severe	Total	Severe	Total
Zhang, et al	4	7	54	133
Huang, et al	3	6	10	35
Guan, et al	10	27	163	1072
Wang, et al	9	20	27	118
Total	**26**	**60**	**395**	**1358**
Heterogeneity: Q=0.3784, df=3 (*P* value=0.9447)				
Test for overall effect: Z=3.7420 (*P* value=0.0002)				

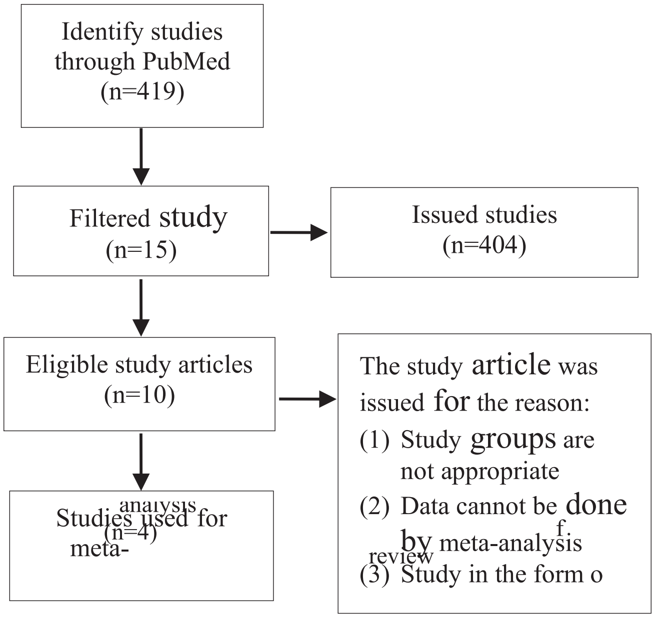

Figure 1. Flow Diagram of Study Selection

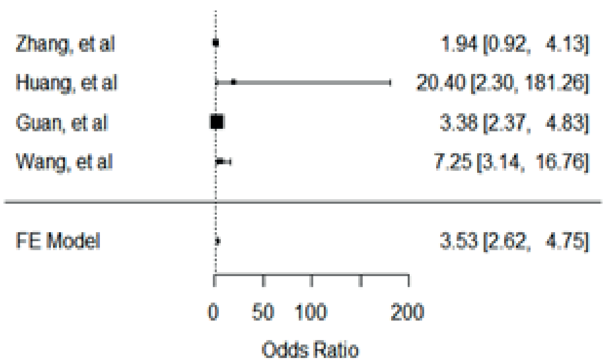

Figure 2. The Forest Plot of Relationship Between Dyspnea and COVID-19 Severity

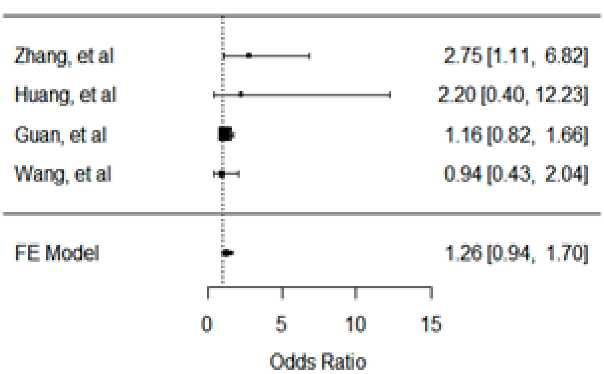

Figure 3. The Forest Plot of Relationship Between Cough and COVID-19 Severity

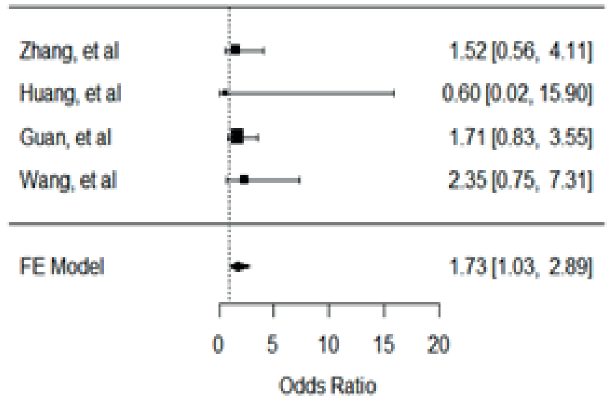

Figure 4. The Forest Plot of Relationship Between Diarrhea and COVID-19 Severity

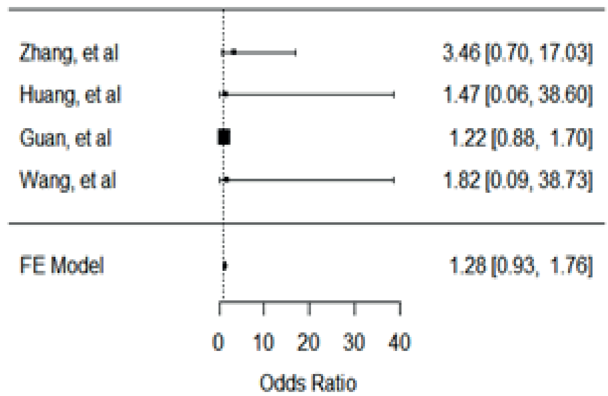

Figure 5. The Forest Plot of Relationship Between Fever and COVID-19 Severity

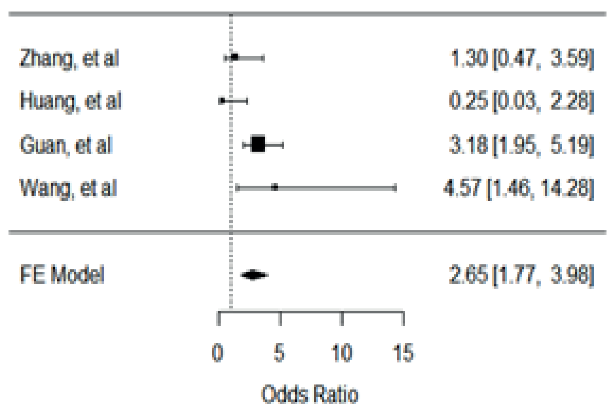

Figure 6. The Forest Plot of Relationship Between Diabetes and COVID-19 Severity

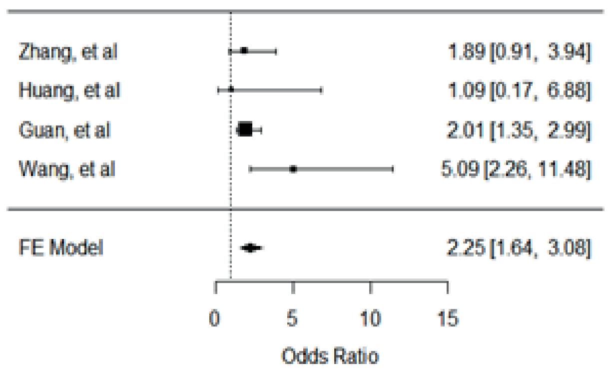

Figure 7. The Forest Plot of Relationship Between Hypertension and COVID-19 Severity

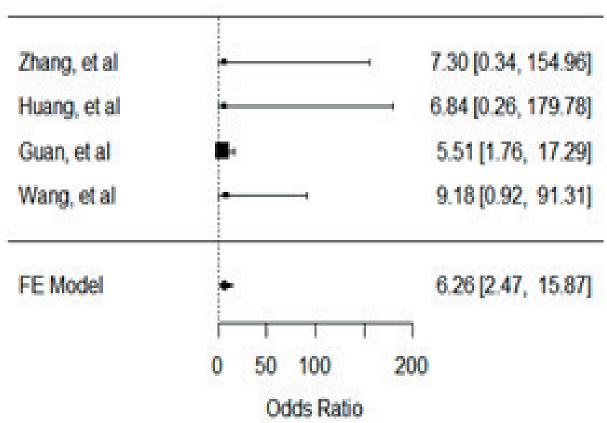

Figure 8. The Forest Plot of Relationship Between COPD and COVID-19 Severity

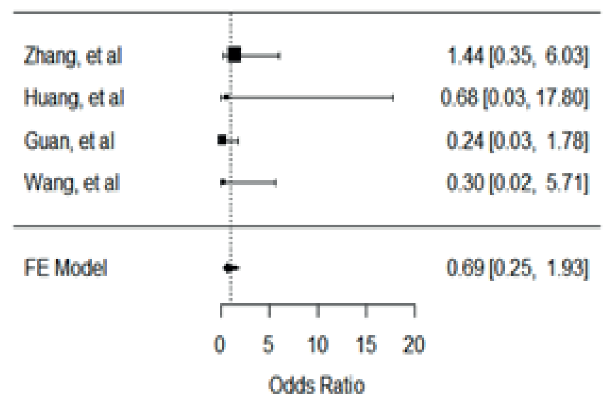

Figure 9. The Forest Plot of Relationship Between Impaired Liver Function and COVID-19 Severity

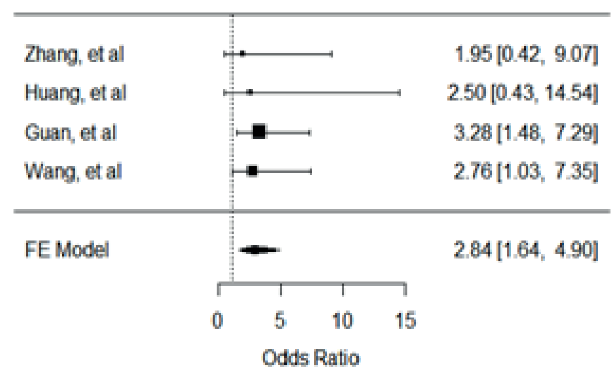

Figure 10. The Forest Plot of Relationship Between CVD and COVID-19 Severity

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