



Check for updates

SYSTEMATIC REVIEW

REVISED The relationship of age, sex and prothrombin time related to the severity of COVID-19 patients with diabetes mellitus: a systematic review and meta analysis

[version 6; peer review: 2 approved, 1 approved with reservations]
Previously titled: The relationship of age, sex and prothrombin time related to the severity and mortality of COVID-19 patients with diabetes mellitus: a systematic review and meta analysis

Audrey Fabianisa Mirza ¹, Ceria Halim ¹, Mutiara Indah Sari ²

¹Faculty of Medicine, Universitas Sumatera Utara, Medan, Sumatera Utara, 20155, Indonesia

²Department of Biochemistry, Universitas Sumatera Utara, Medan, Sumatera Utara, 20155, Indonesia

V6 First published: 01 Jul 2022, 11:729
<https://doi.org/10.12688/f1000research.107398.1>
Second version: 05 Jun 2024, 11:729
<https://doi.org/10.12688/f1000research.107398.2>
Third version: 21 Jun 2024, 11:729
<https://doi.org/10.12688/f1000research.107398.3>
Fourth version: 11 Jul 2024, 11:729
<https://doi.org/10.12688/f1000research.107398.4>
Fifth version: 25 Jul 2024, 11:729
<https://doi.org/10.12688/f1000research.107398.5>
Latest published: 08 Aug 2024, 11:729
<https://doi.org/10.12688/f1000research.107398.6>

Abstract

Background

SARS-CoV-2 first appeared in Wuhan, China, in December 2019. Looking at the prevalence data in the world and in Indonesia, the highest mortality rate due to COVID-19 involves age, gender and comorbidities such as diabetes mellitus. Severity of the condition also refers to coagulation abnormalities, such as abnormal prothrombin time values.


Methods

This systematic review study and meta-analysis used online literature sourced from PubMed, Science Direct, EBSCO, Cochrane and Google Scholar. The literature used here is literature that has data on age, sex and prothrombin time of COVID-19 patients with diabetes mellitus whose quality is assessed by the NOS (Newcastle-Ottawa Scale)

Open Peer Review

Approval Status   

	1	2	3
version 6			
(revision)	view	view	view
08 Aug 2024			
version 5			
(revision)	view		
25 Jul 2024			
version 4			
(revision)	view		
11 Jul 2024			
version 3			
(revision)	view		
21 Jun 2024			
version 2			
(revision)	view		
05 Jun 2024			
version 1			
01 Jul 2022	view		

1. Fajri Marindra Siregar , Universitas Riau,

criteria and processing data using Review Manager 5.4.

Results

Out of 8711 literatures that were traced from various search sources, there were 45 literatures that were included in this study. The results of the analysis on age showed the Standardized Mean Difference (SMD) value of 0.45 and $P < 0.0001$ (95% CI: 0.23–0.68), the gender analysis showed an Odds Ratio (OR) value of 3.28 and $P = 0.01$ (95% CI: 1.26–8.52) and the prothrombin time analysis showed SMD values of 0.41 and $P = 0.07$ (95% CI = -0.03–0.85).

Conclusion

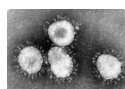
Patients with COVID-19 who have DM have a higher risk compared to those without DM. Among COVID-19 patients with DM admitted to hospitals, they were older compared to those without DM and prothrombin time values similar but slightly higher in COVID-19 patients with DM.

Keywords

age, sex, prothrombine time, COVID-19, diabetes mellitus





This article is included in the **Emerging Diseases and Outbreaks** gateway.



This article is included in the **Coronavirus** collection.

Pekanbaru, Indonesia

2. **Ipsa Arora** , Central Maine Medical Center, Lewiston, USA

3. **Chenxiao Wang** , Tulane University, New Orleans, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Mutiara Indah Sari (mutiara@usu.ac.id)

Author roles: **Mirza AF:** Conceptualization, Formal Analysis, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Halim C:** Formal Analysis, Writing – Original Draft Preparation, Writing – Review & Editing; **Sari MI:** Conceptualization, Formal Analysis, Funding Acquisition, Methodology, Project Administration, Supervision

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2024 Mirza AF *et al.* This is an open access article distributed under the terms of the **Creative Commons Attribution License**, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Mirza AF, Halim C and Sari MI. **The relationship of age, sex and prothrombin time related to the severity of COVID-19 patients with diabetes mellitus: a systematic review and meta analysis [version 6; peer review: 2 approved, 1 approved with reservations]** F1000Research 2024, 11:729 <https://doi.org/10.12688/f1000research.107398.6>

First published: 01 Jul 2022, 11:729 <https://doi.org/10.12688/f1000research.107398.1>

REVISED Amendments from Version 5

In this version, we have revised the abstract and typographical errors.

Any further responses from the reviewers can be found at the end of the article

Introduction

SARS-CoV-2 first appeared in Wuhan, China, on December 31, 2019 and quickly spread throughout the world. As of April 13, 2021, a total of 136,291,755 confirmed cases of COVID-19 infection with 2,941,128 confirmed cases of death have been reported in 223 countries and territories worldwide.¹ In Indonesia, according to the National Development Planning Agency/Bappenas, the first confirmed case of COVID-19 was on March 2, 2020. On April 14, 2021, there were 1,577,526 positive confirmed cases and 42,782 for the number of deaths (2.7% of the national confirmed number).²

Diabetes mellitus (DM) is an independent prognostic factor for COVID-19 patients. The survival rate of diabetic patients is lower, and the time from the on-set of the infection to death is shorter than that of non-diabetic patients.³ The mechanism of expression of angiotensin-converting enzyme 2 (ACE2) is increased in lung and other tissues of DM patients. This upregulation is associated with chronic inflammation, activation of endothelial cells and insulin resistance which exacerbates the inflammatory response, in short, the clinical course and prognosis of COVID-19 in DM patients is significantly worse.⁴

There is an increase in the number of cases and a greater risk of severe disease with age.⁵ The increase in male mortality is related to the regulation of ACE2 and the body's immune system.⁶ DM patients are in a prothrombotic state due to hyperglycemia and chronic hyperinsulinism.⁷

Studies on COVID-19 associated with diabetes comorbid conditions have been studied by several researchers. However, the results obtained regarding age, gender and prothrombin time showed a lot of variability, so further exploration is needed to determine their association with diabetes on COVID-19. This systematic review and meta-analysis aims to examine the relationship between age, gender and prothrombin time on the severity of COVID-19 patients with DM as a comorbidity.

Methods**Data sources and search strategy**

This research was conducted after obtaining approval from the Health Ethics Commission of Universitas Sumatera Utara (EC No.789/KEP/USU/2021). This study used online literature from PubMed, Science Direct, EBSCO, Cochrane and Google Scholar. The journals used were those which captured the data on COVID-19 patients having comorbid DM, accompanied by data on age, sex and prothrombin time values. The literature search was carried out according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analysis). The Checklist used in this meta-analysis was the PRISMA 2009 checklist.

This research was conducted in Medan, North Sumatra and was conducted between July–October 2021. Literature search was performed on the databases with the keywords “Age” AND (“Sex” OR “Gender”) AND (“Prothrombine Time” OR “PT”) AND (“COVID -19” OR “SARS CoV-2”) AND (“Diabetes Mellitus” OR “DM”) for articles published from 2019 to 2021. Filters on each database were utilized to aid the literature search: text availability (free full text), article attribute (associated data), article type (clinical trial and randomized control trial), and publication date (five years) for PubMed; years (2019, 2020, 2021), article type (research article, case reports, and data articles), publication title (International Journal of Infectious Diseases, the Lancet Infectious Diseases, the Brazilian Journal of Infectious Diseases), subject areas (medicine and dentistry, immunology and microbiology, nursing and health professions), language (English), and access type (open access and open archive) for Science Direct; date (custom range 2019-2021), topic (infectious diseases, endocrine & metabolic), Cochrane protocols, and Cochrane trials for Cochrane; custom range (2019-2021), sort by relevance, and any type for Google Scholar; and full text availability for Ebsco.

Inclusion criteria

All retrospective studies (cross-sectional, cohort and case-control) that had data on patients' age, sex and prothrombin time values who had been hospitalized either on the ward or in the ICU were considered eligible for this study. Eligible studies compared data on age in DM and non-DM patients, gender in DM patients and prothrombin time values in DM and non-DM patients.

Exclusion criteria

All duplications were removed at the initial screening, followed by a second screening in which articles that did not meet the inclusion criteria were removed, such as review articles, systematic reviews, meta-analytical studies, comments, letters, animal studies and studies that were not in Indonesian or English.

Journal quality review

The quality of the literature used in this study was determined based on criteria of NOS (The Newcastle Ottawa Scale) and for the selection a score of 7–9 (high quality study) was used.

Method of collecting data

All relevant data was collected using data collection standards that had been set by two reviewers (AFM and MIS). The data taken for the age variable was the Mean and Standard Deviation (SD) of COVID-19 patients with DM and non-DM, the gender variable noted the Odds Ratio (OR) and Standard Error (SE) data from COVID-19 patients with DM, the variables taken for prothrombin time were the median and Interquartile range (IQR) which are converted into the Mean and SD of COVID-19 patients with DM and non-DM. Data was obtained from patients who had COVID-19 confirmed through reverse-transcriptase polymerase chain reaction (RT-PCR). These patients were interviewed regarding congenital diseases and blood tests was used to determine whether they had DM before being admitted to the hospital.

Data analysis

This study used Review Manager 5.4 software (The Cochrane Collaboration, Oxford, UK) (RevMan, RRID: SCR_003581).⁵⁵ Standardized Mean Difference (SMD) and OR were used to analyze the variables in this study. The Confidence Interval (CI) was set at 95%. P value less than 0.05 indicated statistically significant data. Chi Square test was used to assess the heterogeneity of statistical data with the symbol I^2 . If the I^2 test was worth more than 50%, it indicated that there was heterogeneity between studies and the study was conducted using a random effects model. If the I^2 test was less than 50%, it indicated that there was homogeneity between studies, the research was carried out using a fixed effects model. To reduce heterogeneity, studies which method may lead to clinical diversity that conflict with the rest of the studies are excluded. Data input was rechecked by all reviewers to ensure that they are correct.

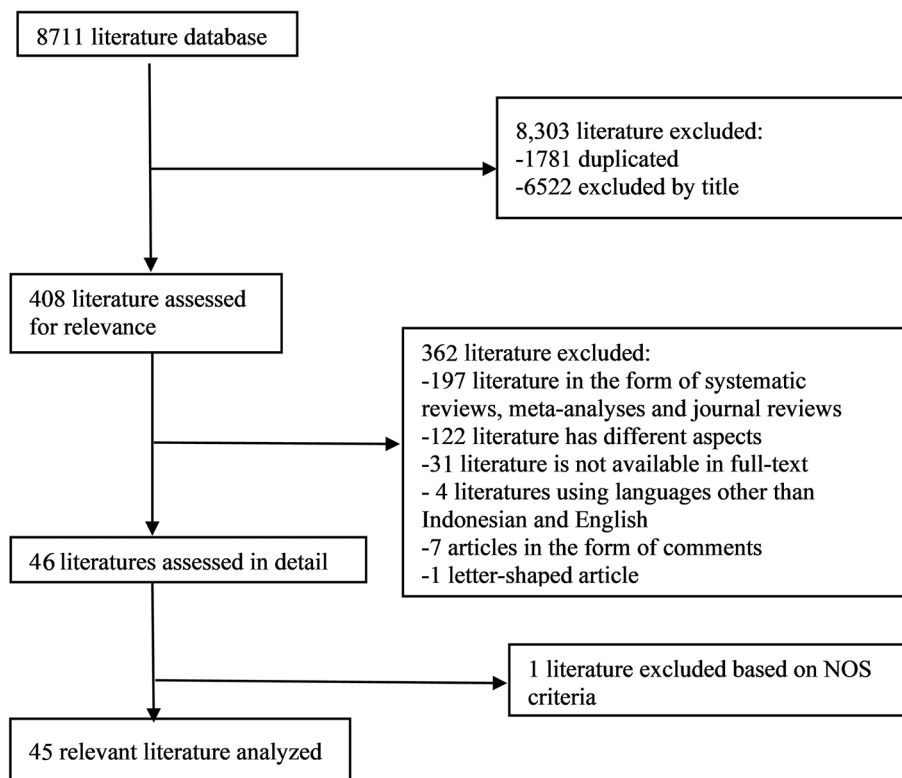


Figure 1. Literature Search.

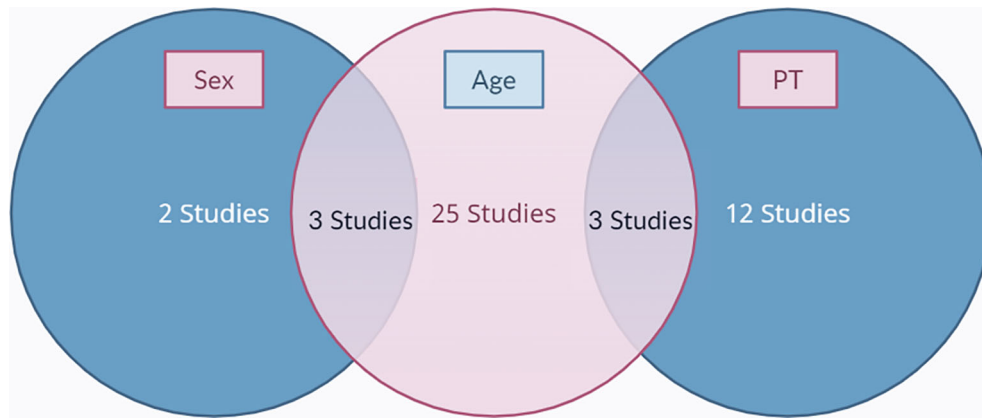


Figure 2. A Venn diagram of the included studies.

Results

Study characteristics

In the initial search, we found 8711 articles which can be seen in [Figure 1](#). The final results after selection got a total of 45 articles that were included in this meta-analysis study. Within these, 31 articles are used for age, 5 articles are used for gender, and 15 articles are used for prothrombin time. The number of studies included in each analysis is listed in [Figure 2](#).

This meta-analysis study included literature examining two groups, namely COVID-19 patients (controls) and COVID-19 patients with DM. Data from both groups were taken from medical records of patients who were treated either in the ward or in the Intensive Care Unit (ICU). Characteristics of patients based on the study literature are seen in [Table 1](#).

Table 1. Study characteristics.

Research by	Year	Location	Number of patients
Acharya <i>et al.</i> ¹⁶	2020	Korea	324
Alkundi <i>et al.</i> ¹⁹	2020	England	232
Ortega <i>et al.</i> ³⁹	2021	Spain	2,069
Alshukry <i>et al.</i> ²⁰	2021	Kuwait	417
Chen (a) <i>et al.</i> ⁷	2020	Wuhan, China	1,105
Chung <i>et al.</i> ²⁴	2020	South Korea	117
Dennis <i>et al.</i> ²⁵	2021	England	19,256
Pazoki <i>et al.</i> ⁴⁰	2021	Iran	574
Elemam <i>et al.</i> ⁸	2021	United Arab Emirates	350
Jing Liang <i>et al.</i> ²⁸	2020	Wuhan, China	211
Kim <i>et al.</i> ²⁹	2020	South Korea	1,082
Koh <i>et al.</i> ³⁰	2021	Singapore	1,042
Chen (c) <i>et al.</i> ²³	2020	Wuhan, China	904
Wang <i>et al.</i> ⁴⁶	2020	Wuhan, China	663
Liu (c) <i>et al.</i> ³⁴	2020	Wuhan, China	192
Chen (b) <i>et al.</i> ²²	2020	Hubei, China	208
Shang <i>et al.</i> ⁴⁴	2021	Wuhan, China	584
Zhang (a) <i>et al.</i> ⁵¹	2020	Wuhan, China	258
Zhang <i>et al.</i> ⁵⁰	2021	Wuhan, China	131
Leon-Abarca <i>et al.</i> ³¹	2021	Mexico	1,280,806

Table 1. *Continued*

Research by	Year	Location	Number of patients
Dozio <i>et al.</i> ²⁶	2020	Italy	33
Liu (a) <i>et al.</i> ³²	2020	Chengdu, China	95
Liu (b) <i>et al.</i> ³³	2020	Wuhan, China	268
Liu (d) <i>et al.</i> ³⁵	2020	Wuhan, China	934
Makker <i>et al.</i> ³⁶	2021	France	843
Mansour <i>et al.</i> ³⁷	2020	Iran	353
Orioli <i>et al.</i> ³⁸	2021	Belgium	192
Ozder <i>et al.</i> ¹³	2020	Turkey	640
Raghavan <i>et al.</i> ⁴¹	2021	India	845
Ricchio <i>et al.</i> ⁴²	2021	Italy	61
Seiglie <i>et al.</i> ⁴³	2020	America	450
Soliman <i>et al.</i> ¹¹	2020	Qatar	299
Sticchi <i>et al.</i> ¹⁴	2021	Italy	1,656
Wu (a) <i>et al.</i> ⁴⁷	2020	Wuxi, China	63
Wu (b) <i>et al.</i> ⁴⁸	2020	Jiangsu, China	2,455
Xu <i>et al.</i> ⁴⁹	2020	Wuhan, China	61
Zhang (b) <i>et al.</i> ⁵²	2020	Wuhan, China	166
Zheng <i>et al.</i> ⁵³	2021	Wuhan, China	71
Akbariqomi <i>et al.</i> ¹⁷	2020	Iran	595
Bhandari <i>et al.</i> ²¹	2021	Iran	53
Dyusupova <i>et al.</i> ²⁷	2021	Kazakhstan	1,961
Huang <i>et al.</i> ¹⁰	2020	Wuhan, China	1,443
Li <i>et al.</i> ¹²	2020	Wuhan, China	199
Shi <i>et al.</i> ⁴⁵	2020	Wuhan, China	306
Yan <i>et al.</i> ¹⁸	2020	Wuhan, China	193

Based on the entire literature that was included as many as 45 researched in 2020–2021, the most research was carried out in 2021 in as many as 28 studies. The country that researched the most literature in this meta-analysis was China, which was the initial location for the spread of COVID-19 as per as many as 21 literatures. Some studies have a small sample size, but the samples studied are COVID-19 patients who have been hospitalized and have moderate-severe symptoms so that they represent a patient population with a high risk of severity.

The relationship between age and diabetes mellitus in COVID-19 patients

The literature that was included in the age distribution associated with the incidence of COVID-19 in DM and non-DM was 31 literatures. Among them were 3 literature cross-sectional research designs, 9 literature cohorts and 19 case-control literatures. Characteristics of age in patients based on the study literature can be seen in [Table 2](#).

Table 2. Age studies in diabetes mellitus (DM) patients with COVID-19 and non-diabetic patients with COVID-19.

Journal	Research design	NOS Score	Age in DM (Mean ± SD)	Age in non-DM (Mean ± SD)
Acharya <i>et al.</i> ¹⁶	Cross-sectional	9	69.8 ± 13.5	51.9 ± 21.4
Alkundi <i>et al.</i> ¹⁹	Cross-sectional	8	71.4 ± 13.1	69.9 ± 17.1
Ortega <i>et al.</i> ³⁹	Cross-sectional	8	71.7 ± 11.9	66.6 ± 16.3
Alshukry <i>et al.</i> ²⁰	Cohort	9	56.4 ± 11.64	39.5 ± 16.59
Chen (a) <i>et al.</i> ⁷	Cohort	9	63.4 ± 12.8	55.3 ± 14.5
Chung <i>et al.</i> ²⁴	Cohort	8	66.3 ± 8.9	53.5 ± 17.9

Table 2. *Continued*

Journal	Research design	NOS Score	Age in DM (Mean \pm SD)	Age in non-DM (Mean \pm SD)
Dennis <i>et al.</i> ²⁵	Cohort	9	67.0 \pm 14.1	66.0 \pm 17.4
Pazoki <i>et al.</i> ⁴⁰	Cohort	9	65.0 \pm 12.1	53.2 \pm 16.7
Elemam <i>et al.</i> ⁸	Cohort	9	53.73 \pm 12.79	44.64 \pm 14.38
Jing Liang <i>et al.</i> ²⁸	Cohort	7	62.4 \pm 7.7	63.3 \pm 8.3
Kim <i>et al.</i> ²⁹	Cohort	9	68.3 \pm 11.9	56.5 \pm 18.0
Koh <i>et al.</i> ³⁰	Cohort	9	48.0 \pm 13.0	36.0 \pm 10.0
Leon-Abarca <i>et al.</i> ³¹	Case-control	7	57.4 \pm 13.4	41.8 \pm 14.7
Dozio <i>et al.</i> ²⁶	Case-control	8	72.6 \pm 15.8	55.6 \pm 22.5
Liu (a) <i>et al.</i> ³²	Case-control	8	59.36 \pm 12.31	58.0 \pm 19.24
Liu (b) <i>et al.</i> ³³	Case-control	8	65.54 \pm 11.28	64.82 \pm 10.98
Liu (d) <i>et al.</i> ³⁵	Case-control	8	64.5 \pm 10.0	61.6 \pm 14.5
Makker <i>et al.</i> ³⁶	Case-control	8	65.36 \pm 13.96	58.6 \pm 17.53
Mansour <i>et al.</i> ³⁷	Case-control	8	63.66 \pm 13.32	60.76 \pm 17.56
Orioli <i>et al.</i> ³⁸	Case-control	8	67.0 \pm 14.0	67.0 \pm 14.0
Ozder <i>et al.</i> ¹³	Case-control	7	57.0 \pm 11.03	58.02 \pm 12.16
Raghavan <i>et al.</i> ⁴¹	Case-control	8	60.0 \pm 13.0	51.0 \pm 17.0
Ricchio <i>et al.</i> ⁴²	Case-control	8	81.0 \pm 16.0	75.0 \pm 15.0
Seiglie <i>et al.</i> ⁴³	Case-control	8	66.7 \pm 14.2	61.1 \pm 18.8
Soliman <i>et al.</i> ¹¹	Case-control	8	52.1 \pm 12.67	36.22 \pm 11.43
Sticchi <i>et al.</i> ¹⁴	Case-control	8	70.9 \pm 11.0	66.3 \pm 14.0
Wu (a) <i>et al.</i> ⁴⁷	Case-control	7	47.98 \pm 15.11	51.0 \pm 12.6
Wu (b) <i>et al.</i> ⁴⁸	Case-control	8	52.55 \pm 13.7	47.98 \pm 15.11
Xu <i>et al.</i> ⁴⁹	Case-control	8	65.6 \pm 11.11	62.96 \pm 10.71
Zhang (b) <i>et al.</i> ⁵²	Case-control	7	65.6 \pm 11.4	59.4 \pm 16.0
Zheng <i>et al.</i> ⁵³	Case-control	8	63.0 \pm 10.03	54.31 \pm 14.35

NOS: Newcastle-Ottawa Scale.

Based on Table 2, the age distribution of the incidence of COVID-19 with DM compared to non-DM, almost all studies have data on patients with DM having an older age. Forest plot analysis of the relationship between age and the incidence of COVID with DM and non-DM can be seen in Figure 3.

The results of the literature analysis in the sub-group of cross-sectional study designs to see the comparison of age in COVID-19 patients with DM and non-DM resulted in $I^2 = 87\%$ indicating heterogeneity between studies. Subtotal SMD was 0.42 (95%CI = 0.07–0.78; $P = 0.02$) which indicates that the result was significant because $P < 0.05$ and the diamond did not touch the vertical line.

The results of the analysis in the cohort study design sub-group to see the comparison of age in COVID-19 patients with DM and non-DM resulted in $I^2 = 98\%$ which indicates heterogeneity between studies. Subtotal SMD was 0.63 (95%CI = 0.29–0.98; $P = 0.0003$) which is that the result was significant, because $P < 0.05$ and the diamond did not touch the vertical line.

The results of the analysis in the case-control study design sub-group to see the comparison of age in COVID-19 patients with DM and non-DM resulted in $I^2 = 98\%$ which indicates heterogeneity between studies. Subtotal SMD was 0.37 (95%CI = 0.11–0.63; $P = 0.006$) which indicates that the result was significant because $P < 0.05$ and the diamond did not touch the vertical line.

The results of the literature analysis to see the comparison of age in COVID-19 patients with DM and non-DM as a whole resulted in a value of $I^2 = 99\%$ which indicated heterogeneity between studies, so the random effects model was used. Total SMD 0.45 (95%CI = 0.23–0.68; $P < 0.0001$) with a population confidence interval of 0.23 to 0.68 ($P < 0.0001$) indicating there is a significant result because $P < 0.05$ and the diamond did not touch the vertical line. The SMD > 0 ,

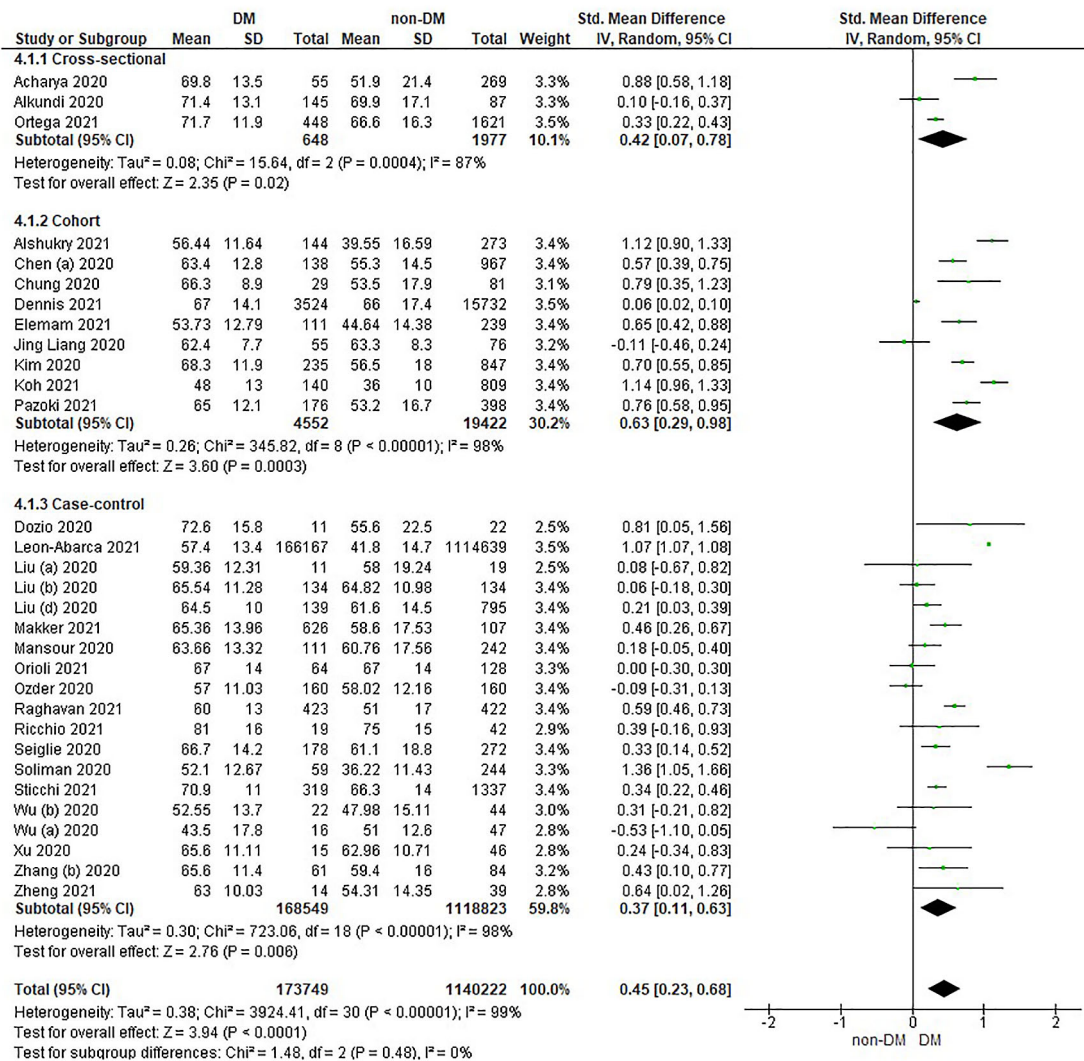


Figure 3. Forest plot of the relationship of age in diabetes mellitus to COVID-19 and non-diabetes mellitus to COVID-19.

indicated a difference between the two groups, where individuals in the diabetic group were slightly older than those in the non-diabetic group that might increase the risk of more severe illness.

The relationship between sex and diabetes mellitus in COVID-19 patients

The literature that was included in the sex distribution was associated with the incidence of COVID-19 in DM as many as 5 literatures. Among them were 2 literature cross-sectional research designs and 3 literature cohorts. Gender characteristics of patients based on the study literature can be seen in Table 3 below.

Table 3. Study of gender in diabetes mellitus patients with COVID-19.

Journal	Research design	NOS Score	Male vs. Female (OR, 95%CI)
Acharya <i>et al.</i> ¹⁶	Cross-sectional	9	0.948 (0.13–6.92)
Ortega <i>et al.</i> ³⁹	Cross-sectional	8	2.14 (1.014–4.5)
Chen (c) <i>et al.</i> ²³	Cohort	9	0.36 (0.17– 0.77)
Pazoki <i>et al.</i> ⁴⁰	Cohort	9	1.49 (0.77–2.87)
Wang <i>et al.</i> ⁴⁶	Cohort	9	2.81 (0.90– 9.21)

NOS: Newcastle-Ottawa Scale.

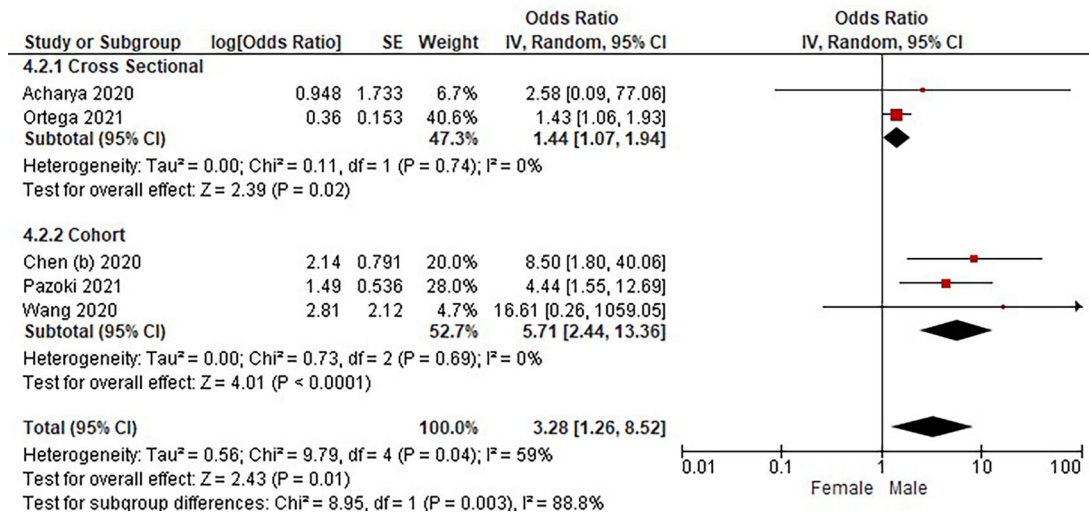


Figure 4. Forest plot of sex relationship in diabetes mellitus patients with COVID-19.

Based on [Table 3](#), the sex distribution of the incidence of COVID-19 with DM, overall data on the OR value shows that male patients are more at risk of exposure to the disease than women. The forest plot analysis of the sex relationship with the incidence of COVID with DM can be seen in [Figure 4](#).

Based on the results of the picture of the size of the square on the forest plot, the research by Ortega *et al.* (2021) has the largest square proportional to the greater weight value because it has a larger sample than other studies and has more influence on the results of this forest plot.

The results of the analysis on the sub-group cross-sectional study design to see the sex comparison in COVID-19 patients with DM resulted in $I^2 = 0\%$ which indicated the absence of heterogeneity between studies. Subtotal OR 1.44 (95%CI = 1.07–1.94; $P = 0.02$) which stated that the results were significant because $P < 0.05$ and the diamond did not touch the vertical line.

The results of the analysis on the cohort study design sub-group to see the sex comparison in COVID-19 patients with DM resulted in $I^2 = 0\%$ which indicated no heterogeneity between studies. Subtotal OR 5.71 (95%CI = 2.44–13.36; $P < 0.0001$) which indicates that the results were significant because $P < 0.05$ and the diamond did not touch the vertical line.

The results of the literature analysis to see the sex comparison between men and women in COVID-19 patients with DM overall yielded a value of $I^2 = 59\%$ which indicated heterogeneity between studies, so the random effects model was used. Total OR 3.28 (95% CI = 1.26–8.52; $P = 0.01$) with a confidence interval for the population between 1.26 to 8.52 ($P = 0.01$) indicated that the results were significant because $P < 0.05$ and the diamond did not touch the vertical line. The meta-analysis showed that the chance of developing a more severe illness is three times higher for male than female in diabetic group patients.

The Relationship between Prothrombin Time and Diabetes Mellitus in COVID-19 Patients

Fifteen literature included the distribution of prothrombin time values associated with the incidence of COVID-19 in DM and non-DM. Among them were 7 literature cohort research designs and 8 case-control literatures. Characteristics of prothrombin time in patients based on the study literature can be seen in [Table 4](#) below.

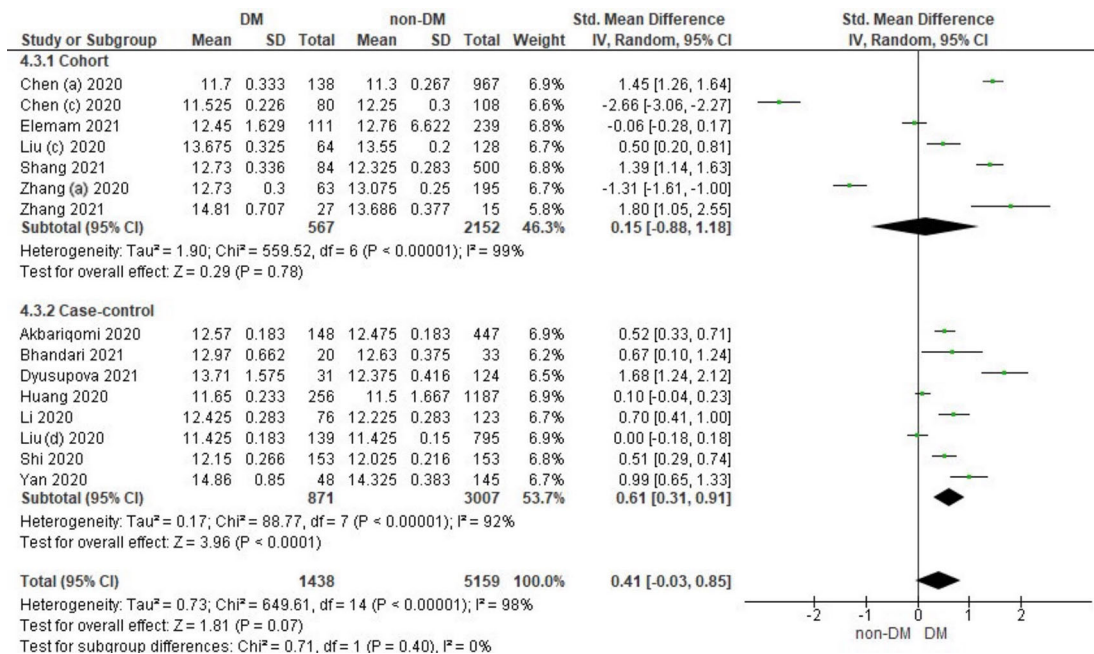
Based on [Table 4](#), the distribution of prothrombin time values in the incidence of COVID-19 with DM is compared with non-DM in the form of Median and IQR converted into the Mean and SD which has been converted in [Table 4](#).

Overall, it shows that the prothrombin time value in patients with DM has a slightly higher value compared to non-DM and as many as 3 studies have the opposite data. Forest plot analysis of the relationship between prothrombin time and the incidence of COVID with DM and non-DM can be seen in [Figure 5](#).

Table 4. Study of prothrombin time (PT) values in diabetes mellitus (DM) patients with COVID-19 and non-diabetic patients with COVID-19 in Mean and Standard Deviation (SD).

Journal	Research design	NOS Score	PT value on DM (Mean \pm SD)	PT value on non-DM (Mean \pm SD)
Liu (c) <i>et al.</i> ³⁴	Cohort	9	13.675 \pm 0.325	13.55 \pm 0.2
Elemam <i>et al.</i> ⁸	Cohort	9	12.45 \pm 1.629	12.76 \pm 6.622
Chen (a) <i>et al.</i> ⁷	Cohort	9	11.7 \pm 0.333	11.3 \pm 0.267
Chen (b) <i>et al.</i> ²²	Cohort	9	11.525 \pm 0.226	12.25 \pm 0.3
Shang <i>et al.</i> ⁴⁴	Cohort	9	12.73 \pm 0.336	12.325 \pm 0.283
Zhang (b) <i>et al.</i> ⁵¹	Cohort	9	12.73 \pm 0.3	13.075 \pm 0.25
Zhang <i>et al.</i> ⁵⁰	Cohort	9	14.81 \pm 0.707	13.686 \pm 0.377
Akbariqomi <i>et al.</i> ¹⁷	Case-control	8	12.57 \pm 0.183	12.475 \pm 0.183
Bhandari <i>et al.</i> ²¹	Case-control	7	12.97 \pm 0.662	12.63 \pm 0.375
Dyusupova <i>et al.</i> ²⁷	Case-control	8	13.71 \pm 1.575	12.375 \pm 0.416
Huang <i>et al.</i> ¹⁰	Case-control	8	11.65 \pm 0.233	11.5 \pm 1.667
Li <i>et al.</i> ¹²	Case-control	8	12.425 \pm 0.283	12.225 \pm 0.283
Liu (d) <i>et al.</i> ³⁵	Case-control	8	11.425 \pm 0.183	11.425 \pm 0.15
Shi <i>et al.</i> ⁴⁵	Case-control	8	12.15 \pm 0.266	12.025 \pm 0.216
Yan <i>et al.</i> ¹⁸	Case-control	8	14.86 \pm 0.85	14.325 \pm 0.383

NOS: Newcastle-Ottawa Scale.

**Figure 5.** Forest plot of the relationship between prothrombin time values in diabetes mellitus patients with COVID-19 and non-diabetes mellitus with COVID-19.

The results of the literature analysis in the cohort study design subgroup to compare the prothrombin time values in COVID-19 patients with DM and non-DM resulted in $I^2 = 99\%$ which indicated heterogeneity between studies. Subtotal Standardized Mean Difference (SMD) 0.15 (95%CI = -0.88–1.18; $P = 0.78$) which means that the result was not significant because $P > 0.05$ and the diamond touched the vertical line.

Results of literature analysis in the case-control study design sub-group to compare the prothrombin time values in COVID-19 patients with DM and non-DM produced $I^2 = 92\%$ which indicated heterogeneity between studies. Subtotal Standardized Mean Difference (SMD) 0.61 (95%CI = 0.31–0.91; $P < 0.0001$) which means that the result is significant because $P < 0.05$ and the diamond did not touch the vertical line.

The results of the literature analysis to see the comparison of the prothrombin time value in COVID-19 patients with DM and COVID-19 patients without a history of DM overall yielded a value of $I^2 = 98\%$ which indicated heterogeneity between studies, so the random effects model was used. Total Standardized Mean Difference (SMD) 0.41 (95%CI = -0.03–0.85; $P = 0.07$) with a confidence interval for the population between -0.03 to 0.85 ($P = 0.07$) showed that there were insignificant results because $P > 0.05$ and the diamond touched the vertical line. The SMD > 0 , indicated a difference between the two groups, where prothrombin time in the diabetic group were slightly prolonged than those in the non-diabetic group that might increased the risk more severe illness.

Discussion

This systematic review and meta-analysis included 45 articles with a total number of 1,325,334 patients who were positive for COVID-19 and divided into diabetic and non-diabetic groups which were analyzed for age, sex and prothrombin time values.

Diabetes is reported to be one of the comorbidities that increases the progression and mortality of COVID-19. Diabetes can be a risk factor because of the increase in serum ACE2 in diabetic patients. In addition, patients taking inhibitors of angiotensin-converting enzyme (ACEIs) and angiotensin II receptor blockers (ARBs) showed overexpression of ACE2, the COVID-19 entry receptor.⁸

The results of a systematic study and meta-analysis on the age variable, showed that patients with COVID-19 with DM were significantly older than non-diabetic patients. There is a correlation between age and the innate immune system as has been reviewed elsewhere and concluded that the elderly are particularly susceptible to developing more infections because the innate immune system declines gradually with older age.⁹

The relationship between age and the incidence of COVID-19 in the DM group compared to non-DM is in line with several research results which state that patients infected with COVID-19 with comorbid diabetes are older than non-diabetics. In both patients with or without diabetes the severity of the disease increases with age.¹⁰ Another study also found that diabetic patients were significantly older and had more severe symptoms than non-diabetic patients,¹¹ the COVID-19 patients with diabetes had a higher age than non-diabetics,¹² COVID-19 patients with pre-existing diabetes were older than those without.⁷ Another study stated that diabetic and non-diabetic population significantly different in age but a slightly older non-diabetic population.¹³

The results of the study on the gender variable, showed that men were more at risk of exposure to the disease and had more severe symptoms than women. Gender differences affect clinical outcome and prognosis, with males at higher risk than females. Male patients may express higher ACE2 which is regulated by male sex hormones.⁹

The relationship between sex and the incidence of COVID-19 in the DM group is in line with several research results, such as having a much larger male population than female,¹⁴ twice as many male patient subjects as confirmed positive for COVID-19, the presentation of diabetic men at high risk of mortality and the number of hospitalizations is higher in diabetic men than women and in other comorbid diseases.¹⁵ In contrast to a study, in the data there were more female patients than men, although there were more men in the diabetes group than non-diabetics but in both groups had more female patients.¹⁶

The prothrombin time variable showed the same prothrombin time value in both diabetic and non-diabetic patients. Theoretically, COVID-19 patients with DM have a prolonged prothrombin time value, as well as the results in the case-control study design sub-group as seen in [Figure 3](#) which shows a difference, namely a prolonged prothrombin time value in the DM group. Diabetic patients in a prothrombotic state due to hyperglycemia and chronic hyperinsulinism make all phases of coagulation abnormal.⁷ Non-survivors have a prolonged prothrombin time compared to survivors. The timing of increases in D-dimer, prothrombin time, and activated partial thromboplastin time, with decreased fibrinogen and platelet counts, also coincided with the duration of hospitalization, ranging from 7 to 10 days after admission. Patients who are still hospitalized or have good prognostic factors are likely to have non-prolonging prothrombin time.⁵⁴

The relationship between prothrombin time and the incidence of COVID-19 in the DM and non-DM groups is in line with several studies.¹⁷ The prothrombin time values in both groups were relatively the same and did not prolong.¹² The prothrombin time values were almost the same in both groups and within the normal range.¹⁰ In contrast to a study that

showed a slight difference in the prothrombin time value in the diabetic group, which was prolonged compared to the non-diabetic group, which was still within normal limits.¹⁸

This study has research limitations, there are only a few studies on COVID-19 with DM as the outbreak only occurred at the end of 2019. Research on COVID-19 with DM is relatively new, and it needs to be studied further. This meta-analysis also does not study the relationship between the onset and severity of COVID-19 with diabetes.

Conclusion

The results of our study indicate that patients with COVID-19 who have DM have a higher risk compared to those without DM. Among COVID-19 patients with DM admitted to hospitals, they were older compared to those without DM and prothrombin time values similar but slightly higher in COVID-19 patients with DM. Within COVID-19 patients with DM, there were more male patients compared to females.

Suggestion

Researchers are expected to conduct further studies on the relationship between age and gender in COVID-19 patients with DM, so that the data obtained from the results of this meta-analysis are more relevant when applied in Indonesia.

Clinicians are expected to provide health care, especially for patients with DM who are old and male in the era of the COVID-19 pandemic to reduce the risk factors for severity of diabetic patients being infected with COVID-19.

Researchers are expected to conduct further studies on prothrombin time in COVID-19 patients with DM for a more detailed understanding.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'The relationship of age, sex and prothrombin time related to the severity of COVID-19 patients with diabetes mellitus: a systematic review and meta analysis'. <https://doi.org/10.6084/m9.figshare.18865103>.⁵⁶

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Author contributions

Audrey Fabianisa Mirza: Conceptualization, formal analysis, methodology, investigation, visualization, writing – original draft preparation, writing – review & editing.

Ceria Halim: Formal analysis, writing – original draft preparation, writing – review & editing.

Mutiara Indah Sari: Conceptualization, formal analysis, methodology, project administration, supervision, funding acquisition.

Acknowledgements

I would like to thank and appreciate the researchers whose research contributed greatly to this meta-analysis.

References

- World Health Organization: **WHO Coronavirus (COVID-19) Dashboard**. 2021. accessed April 14th 2021. [Reference Source](#)
- Satuan Tugas Penanganan COVID-19: **Peta Sebaran COVID-19**. 2021. accessed April 14th 2021. [Reference Source](#)
- Hui Y, Li Y, Tong X, *et al.*: **The risk factors for mortality of diabetic patients with severe COVID-19: A retrospective study of 167 severe COVID-19 cases in Wuhan**. *PLoS One*. 2020; **15**(12): e0243602. [PubMed Abstract](#) | [Publisher Full Text](#)
- Gao YD, Ding M, Dong X, *et al.*: **Risk factors for severe and critically ill COVID-19 patients: A review**. *Allergy*. 2021; **76**(2): 428–455. [PubMed Abstract](#) | [Publisher Full Text](#)
- Davies NG, Klepac P, Liu Y, *et al.*: **Age-dependent effects in the transmission and control of COVID-19 epidemics**. *Nat. Med.* 2020; **26**(8): 1205–1211. [PubMed Abstract](#) | [Publisher Full Text](#)

6. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, *et al.*: **Impact of sex and gender on COVID-19 outcomes in Europe.** *Biol. Sex Differ.* 2020; **11**: 1–13.
[Publisher Full Text](#)
7. Chen X, Chen Y, Wu C, *et al.*: **Coagulopathy is a major extrapulmonary risk factor for mortality in hospitalized patients with COVID-19 with type 2 diabetes.** *BMJ Open Diabetes Res. Care.* 2021; **4**(2): e001851.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Elemam NM, Hannawi H, Salmi IA, *et al.*: **Diabetes mellitus as a comorbidity in COVID-19 infection in the United Arab Emirates.** *Saudi Med. J.* 2021; **42**(2): 170–180.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Biswas M, Rahman S, Biswas TK, *et al.*: **Association of sex, age, and comorbidities with mortality in COVID-19 patients: a systematic review and meta-analysis.** *Intervirology.* 2021; **64**(1): 36–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Huang J, Zhu L, Bai X, *et al.*: **Multidimensional Analysis of Risk Factors for the Severity and Mortality of Patients with COVID-19 and Diabetes.** *Infect. Dis. Ther.* 2020; **9**(4): 981–1002.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Soliman AT, Prabhakaran Nair A, Al Masalamani MS, *et al.*: **Prevalence, clinical manifestations, and biochemical data of type 2 diabetes mellitus versus nondiabetic symptomatic patients with COVID-19: A comparative study.** *Acta Bio-medica: Atenei Parmensis.* 2020; **91**(3): e2020010.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Li G, Deng Q, Feng J, *et al.*: **Clinical Characteristics of Diabetic Patients with COVID-19.** *J. Diabetes Res.* 2020; **2020**: 1–1652403, 5.
[Publisher Full Text](#)
13. Ozder A: **A novel indicator predicts 2019 novel coronavirus infection in subjects with diabetes.** *Diabetes Res. Clin. Pract.* 2020; **166**: 108294.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Sticchi A, Cereda A, Toselli M, *et al.*: **Diabetes and mortality in patients with COVID-19: Are we missing the link?** *Anatol. J. Cardiol.* 2021; **25**(6): 376–379.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Belice T, Demir I: **The gender differences as a risk factor in diabetic patients with COVID-19.** *Iranian journal of microbiology.* 2020; **12**(6): 625–628.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Acharya D, Lee K, Lee DS, *et al.*: **Mortality Rate and Predictors of Mortality in Hospitalized COVID-19 Patients with Diabetes.** *Healthcare (Basel, Switzerland).* 2020; **8**(3): 338.
[Publisher Full Text](#)
17. AkbariQomi M, Hosseini MS, Rashidiani J, *et al.*: **Clinical characteristics and outcome of hospitalized COVID-19 patients with diabetes: A single-center, retrospective study in Iran.** *Diabetes Res. Clin. Pract.* 2020; **169**: 108467.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Yan Y, Yang Y, Wang F, *et al.*: **Clinical characteristics and outcomes of patients with severe covid-19 with diabetes.** *BMJ Open Diabetes Res. Care.* 2020; **8**(1): e001343.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Alkundi A, Mahmoud I, Musa A, *et al.*: **Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: A retrospective single centre study.** *Diabetes Res. Clin. Pract.* 2020; **165**: 108263.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Alshukry A, Bu Abbas M, Ali Y, *et al.*: **Clinical characteristics and outcomes of COVID-19 patients with diabetes mellitus in Kuwait.** *Heliyon.* 2021; **7**(4): e06706.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Bhandari S, Shaktawat AS, Tak A, *et al.*: **Evaluating interactions between hyperglycemia and clotting factors in patients suffering with SARS-CoV-2 infection.** *Clinical Diabetology.* 2021; **10**(1): 114–122.
[Publisher Full Text](#)
22. Chen Y, Chen J, Gong X, *et al.*: **Clinical Characteristics and Outcomes of Type 2 Diabetes Patients Infected with COVID-19: A Retrospective Study.** *Engineering (Beijing, China).* 2020; **6**(10): 1170–1177.
[Publisher Full Text](#)
23. Chen Y, Yang D, Cheng B, *et al.*: **Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication.** *Diabetes Care.* 2020; **43**(7): 1399–1407.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Chung SM, Lee YY, Ha E, *et al.*: **The Risk of Diabetes on Clinical Outcomes in Patients with Coronavirus Disease 2019: A Retrospective Cohort Study.** *Diabetes Metab. J.* 2020; **44**(3): 405–413.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Dennis JM, Mateen BA, Sonabend R, *et al.*: **Type 2 Diabetes and COVID-19-Related Mortality in the Critical Care Setting: A National Cohort Study in England, March-July 2020.** *Diabetes Care.* 2021; **44**(1): 50–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Dozio E, Sitzia C, Pistelli L, *et al.*: **Soluble Receptor for Advanced Glycation End Products and Its Forms in COVID-19 Patients with and without Diabetes Mellitus: A Pilot Study on Their Role as Disease Biomarkers.** *J. Clin. Med.* 2020; **9**(11): 3785.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Dyusupova A, Faizova R, Yurkovskaya O, *et al.*: **Clinical characteristics and risk factors for disease severity and mortality of COVID-19 patients with diabetes mellitus in Kazakhstan: A nationwide study.** *Heliyon.* 2021; **7**(3): e06561.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Jing Liang J, Liu J, Chen Y, *et al.*: **Characteristics of laboratory findings of COVID-19 patients with comorbid diabetes mellitus.** *Diabetes Res. Clin. Pract.* 2020; **167**: 108351.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Kim MK, Jeon JH, Kim SW, *et al.*: **The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea.** *Diabetes Metab. J.* 2020; **44**(4): 602–613.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Koh H, Moh A, Yeoh E, *et al.*: **Diabetes predicts severity of COVID-19 infection in a retrospective cohort: A mediatory role of the inflammatory biomarker C-reactive protein.** *J. Med. Virol.* 2021; **93**(5): 3023–3032.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Leon-Abarca JA, Portmann-Baracco A, Bryce-Alberti M, *et al.*: **Diabetes increases the risk of COVID-19 in an altitude dependent manner: An analysis of 1,280,806 Mexican patients.** *PLoS One.* 2021; **16**(8): e0255144.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Liu D, Lan L, Luo D, *et al.*: **Lymphocyte subsets with the lowest decline at baseline and the slow lowest rise during recovery in COVID-19 critical illness patients with diabetes mellitus.** *Diabetes Res. Clin. Pract.* 2020; **167**: 108341.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Liu G, Zhang S, Hu H, *et al.*: **The role of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio in the prognosis of type 2 diabetics with COVID-19.** *Scott. Med. J.* 2020; **65**(4): 154–160.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Liu Z, Bai X, Han X, *et al.*: **The association of diabetes and the prognosis of COVID-19 patients: A retrospective study.** *Diabetes Res. Clin. Pract.* 2020; **169**: 108386.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Liu Z, Li J, Huang J, *et al.*: **Association Between Diabetes and COVID-19: A Retrospective Observational Study With a Large Sample of 1,880 Cases in Leishenshan Hospital, Wuhan.** *Front. Endocrinol.* 2020; **11**: 478.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Makker J, Sun H, Patel H, *et al.*: **Impact of Prediabetes and Type-2 Diabetes on Outcomes in Patients with COVID-19.** *Int. J. Endocrinol.* 2021; **2021**: 1–9.
[Publisher Full Text](#)
37. Mansour A, Sajjadi-Jazi SM, Kasaeian A, *et al.*: **Clinical characteristics and outcomes of diabetics hospitalized for COVID-19 infection: a single-centered, retrospective, observational study.** *EXCLI J.* 2020; **19**: 1533–1543.
38. Orioli L, Servais T, Belkhir L, *et al.*: **Clinical characteristics and short-term prognosis of in-patients with diabetes and COVID-19: A retrospective study from an academic center in Belgium.** *Diabetes Metab. Syndr.* 2021; **15**(1): 149–157.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Ortega E, Corcoy R, Gratacòs M, *et al.*: **Risk factors for severe outcomes in people with diabetes hospitalised for COVID-19: a cross-sectional database study.** *BMJ Open.* 2021; **11**(7): e051237.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Pazoki M, Keykhaei M, Kafan S, *et al.*: **Risk indicators associated with in-hospital mortality and severity in patients with diabetes mellitus and confirmed or clinically suspected COVID-19.** *J. Diabetes Metab. Disord.* 2021; **20**(1): 59–69.
[Publisher Full Text](#)
41. Raghavan A, Nanditha A, Satheesh K, *et al.*: **Profile and prognosis of patients hospitalized for COVID-19 virus infection with and**

- without diabetes - An observational study from South India.** *Diabetes Metab. Syndr.* 2021; **15**(4): 102143.
[Publisher Full Text](#)
42. Ricchio M, Tassone B, Pelle MC, *et al.*: **Characteristics, Management, and Outcomes of Elderly Patients with Diabetes in a Covid-19 Unit: Lessons Learned from a Pilot Study.** *Medicina (Kaunas).* 2021; **57**(4): 341.
[PubMed Abstract](#) | [Publisher Full Text](#)
 43. Seiglie J, Platt J, Cromer SJ, *et al.*: **Diabetes as a Risk Factor for Poor Early Outcomes in Patients Hospitalized With COVID-19.** *Diabetes Care.* 2020; **43**(12): 2938–2944.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Shang J, Wang Q, Zhang H, *et al.*: **The Relationship Between Diabetes Mellitus and COVID-19 Prognosis: A Retrospective Cohort Study in Wuhan, China.** *Am. J. Med.* 2021; **134**(1): e6–e14.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. Shi Q, Zhang X, Jiang F, *et al.*: **Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study.** *Diabetes Care.* 2020; **43**(7): 1382–1391.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Wang X, Liu Z, Li J, *et al.*: **Impacts of Type 2 Diabetes on Disease Severity, Therapeutic Effect, and Mortality of Patients With COVID-19.** *J. Clin. Endocrinol. Metab.* 2020; **105**(12): dgaa535.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. Wu D, Gao S: **Analysis of the lymphocyte count in type 2 diabetic patients with coronavirus disease (COVID-19): A retrospective study in a centralized treatment center.** *Diabetes Res. Clin. Pract.* 2020; **166**: 108340.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Wu J, Zhang J, Sun X, *et al.*: **Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection.** *Diabetes Obes. Metab.* 2020; **22**(10): 1907–1914.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Xu M, Yang W, Huang T, *et al.*: **Diabetic patients with COVID-19 need more attention and better glycemic control.** *World J. Diabetes.* 2020; **11**(12): 644–653.
[PubMed Abstract](#) | [Publisher Full Text](#)
 50. Zhang P, Wang M, Wang Y, *et al.*: **Risk factors associated with the progression of COVID-19 in elderly diabetes patients.** *Diabetes Res. Clin. Pract.* 2021; **171**: 108550.
[PubMed Abstract](#) | [Publisher Full Text](#)
 51. Zhang Y, Cui Y, Shen M, *et al.*: **Comorbid diabetes mellitus was associated with poorer prognosis in patients with COVID-19: a retrospective cohort study.** *MedRxiv* 2020.
 52. Zhang Y, Li H, Zhang J, *et al.*: **The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: A single-centre, retrospective, observational study in Wuhan.** *Diabetes Obes. Metab.* 2020; **22**(8): 1443–1454.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Zheng M, Wang X, Guo H, *et al.*: **The Cytokine Profiles and Immune Response Are Increased in COVID-19 Patients with Type 2 Diabetes Mellitus.** *J. Diabetes Res.* 2021; **2021**: 1–8.
[Publisher Full Text](#)
 54. Connors JM, Levy JH: **COVID-19 and its implications for thrombosis and anticoagulation.** *Blood.* 2020; **135**(23): 2033–2040.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. **Review Manager (RevMan) [Computer program]. Version 5.4.** *The Cochrane Collaboration.* 2020.
 56. Mirza AF, Halim C, Sari MI: **The relationship of age, sex and prothrombin time related to the severity of COVID-19 patients with diabetes mellitus: a systematic review and meta analysis', figshare. Dataset.** 2022.
[Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:   

Version 6

Reviewer Report 07 March 2025

<https://doi.org/10.5256/f1000research.169997.r368187>

© 2025 Wang C. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Chenxiao Wang 

Tulane University, New Orleans, USA

The manuscript systematically reviews and conducts a meta-analysis to investigate how age, sex, and prothrombin time (PT) values relate to COVID-19 severity among patients with diabetes mellitus (DM). The authors analyzed data from 45 studies sourced from prominent databases, applying robust inclusion and exclusion criteria. Overall, the study concludes that older age and male gender significantly increase COVID-19 severity risk among patients with DM, whereas prothrombin time values were slightly prolonged in DM patients compared to non-DM patients, though not significantly so overall.

The manuscript addresses a clinical issue, and the authors addressed all the questions reviewers raised.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COVID-19

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 27 August 2024

<https://doi.org/10.5256/f1000research.169997.r313402>

© 2024 Arora I. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Ipsa Arora 

Endocrinology, Central Maine Medical Center, Lewiston, Maine, USA

Mirza et al. conducted a systematic review and meta-analysis to examine the relationship between age, gender, and prothrombin time in COVID-19 patients requiring hospitalization, with or without diabetes as a comorbidity. They found that hospitalized COVID-19 patients with diabetes were generally older and predominantly male. Although a statistically significant association with prothrombin time was not identified, hospitalized patients with both COVID-19 and diabetes tended to have higher prothrombin time values.

I recommend the following clarifications to enhance the clarity and usefulness of this publication for the readers of this journal.

1. **Abstract:** The study's aim is not clearly articulated in the abstract.
2. **Conclusion:** The statement "patients with COVID-19 who have diabetes have a higher risk as compared to those without diabetes" is vague. Please specify the higher risk of what—e.g., higher risk of hospitalization, severe outcomes, or mortality.
3. **Introduction:** In the last sentence where the study's aim is mentioned, there seems to be a discrepancy. The study does not investigate the relationship between age, gender, and prothrombin time with the "severity of COVID-19." Instead, it examines these parameters in relation to COVID-19 cases requiring hospitalization. This should be clarified, especially since the limitations (under discussion) indicate that the meta-analysis does not explore the relationship with COVID-19 severity.
4. **Methods:** In the literature search section (2019-2021), it is recommended to specify the exact months for each year.
5. **Inclusion Criteria:** The first line states, "all retrospective studies... had data on patients' age, sex, and prothrombin time." It may be more accurate to say "age, sex, or prothrombin time," as not all 45 studies included data on all three variables.
6. **Page 7/25:** In the section discussing the relationship between age and diabetes in COVID-19 patients, "incidence" might not be the most appropriate term; "prevalence" could be more accurate. The same applies to page 9/25 regarding the relationship between sex and diabetes in COVID-19 patients.
7. **Page 10/25:** The phrase "Based on Table 3..." does not appropriately represent the study's

findings. It should be revised to indicate that "male patients with diabetes have a higher risk of hospitalization compared to female patients with diabetes."

8. **Page 10/25:** In the section discussing the relationship between prothrombin time and diabetes in COVID-19 patients, consider revising the conclusion to state that "no statistically significant difference was identified in prothrombin time between hospitalized COVID-19 patients with or without diabetes; however, values were generally higher in patients with diabetes."
9. **Page 12/25:** The last line of the results section ("The SMD >0... more severe illness") is unclear and may need to be rewritten, taking into account the points raised in comment 8.
10. **Discussion, Paragraph 3:** Please specify that the results discussed are applicable only to hospitalized patients.
11. **Discussion, Paragraph 4:** The term "incidence" is used incorrectly; please refer to comment 6 for guidance.
12. **Discussion, Paragraph 5:** The first statement may be inaccurate and should be revised based on the information discussed in comment 7.
13. **Discussion, Paragraph 7:** The conclusion should specify that it pertains to patients with COVID-19 requiring hospitalization.
14. **Discussion, Paragraph 8:** The mention of "incidence" should be corrected as indicated in comment 6.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Endocrinology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 August 2024

<https://doi.org/10.5256/f1000research.169997.r312342>

© 2024 Marindra Siregar F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Fajri Marindra Siregar 

Universitas Riau, Pekanbaru, Riau, Indonesia

The author has revised the manuscript according to the reviewer's input.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Not applicable

Are sufficient details of the methods and analysis provided to allow replication by others?

Not applicable

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Not applicable

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: biochemistry, health and medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 5

Reviewer Report 01 August 2024

<https://doi.org/10.5256/f1000research.169449.r306939>

© 2024 Marindra Siregar F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Fajri Marindra Siregar 

Universitas Riau, Pekanbaru, Riau, Indonesia

- 1) There is still a difference between the number of articles that entered the final stage in the abstract and results sections
- 2) The conclusion in the abstract still states "As diabetes is a comorbidity in COVID-19, it can be concluded that old age and male sex are associated with a more severe disease." this cannot be answered based on the results of the study presented.

Authors are advised to recheck the manuscript before submitting a revision, and ensure that what is written in the abstract is in line with the data presented in the contents of the manuscript.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Not applicable

Are sufficient details of the methods and analysis provided to allow replication by others?

Not applicable

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Not applicable

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: biochemistry, health and medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Aug 2024

Mutiara Indah Sari

Thank you for the review

- 1:** There is still a difference between the number of articles that entered the final stage in the abstract and results sections
- 2:** The conclusion in the abstract still states "As diabetes is a comorbidity in COVID-19, it can be concluded that old age and male sex are associated with a more severe disease." this

cannot be answered based on the results of the study presented.

Response: I apologize for any inconsistencies. I have reviewed the manuscript and ensured that it is revised before, I revised it again to match the abstract with the data content.

Sincerely,
Mutiara Indah Sari

Competing Interests: No competing interests were disclosed.

Version 4

Reviewer Report 19 July 2024

<https://doi.org/10.5256/f1000research.168875.r301754>

© 2024 Marindra Siregar F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Fajri Marindra Siregar

Universitas Riau, Pekanbaru, Riau, Indonesia

The revision submitted by the author has not addressed the reviewer's questions.

1) The author should clarify the criteria used to evaluate each variable in the article, considering the varying number of assessed articles. According to Figure 1, there are a total of 46 articles. However, out of these, only 31 articles are used for the age variable, 5 articles are used for gender, and 15 articles are used for Prothrombin Time. For every variable, why not use all of the articles in the final stage? Further clarification is required.

Apart from that, clarification is needed due to the inconsistency in the number of articles at the final stage, whether 46 or 45 because there is a difference between the abstract and the results section.

2) In the conclusion the author states "Since DM is a comorbidity in COVID-19, it can be concluded that older age and male sex are associated with more severe disease". While this proposition may be true in theory, the findings of this study do not address this particular aspect. It is advisable to omit that particular sentence from the conclusion.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Not applicable

Are sufficient details of the methods and analysis provided to allow replication by others?

Not applicable

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Not applicable

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: biochemistry, health and medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Jul 2024

Mutiara Indah Sari

Thank you for the review.

1: The author should clarify the criteria used to evaluate each variable in the article, considering the varying number of assessed articles. According to Figure 1, there are a total of 46 articles. However, out of these, only 31 articles are used for the age variable, 5 articles are used for gender, and 15 articles are used for Prothrombin Time. For every variable, why not use all of the articles in the final stage? Further clarification is required.

Apart from that, clarification is needed due to the inconsistency in the number of articles at the final stage, whether 46 or 45 because there is a difference between the abstract and the results section.

Response: The literature used is 45. We apologize for the discrepancy. We have thoroughly reviewed the literature used to process 45 data. There were duplicated references in Table 1 earlier, however, this does not affect the results of the forest plot data processing, only the numerical counts in the characteristics.

We cannot use all literature for each variable because not all data for each variable is available in every literature we used. Therefore, in total for the three variables, we used 45 literature sources, with 31 articles used for age, 5 articles for gender, and 15 articles for prothrombin time. Among these, there are overlapping articles that contain data for two variables.

2: In the conclusion the author states "Since DM is a comorbidity in COVID-19, it can be

concluded that older age and male sex are associated with more severe disease". While this proposition may be true in theory, the findings of this study do not address this particular aspect. It is advisable to omit that particular sentence from the conclusion.

Response: We have omit that particular sentence from the conclusion.

Sincerely,
Mutiara Indah Sari

Competing Interests: No competing interests were disclosed.

Version 3

Reviewer Report 05 July 2024

<https://doi.org/10.5256/f1000research.168129.r294009>

© 2024 Marindra Siregar F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Fajri Marindra Siregar

Universitas Riau, Pekanbaru, Riau, Indonesia

The author has made several improvements, but the following 2 things still concern reviewers:

1) The author should clarify the criteria used to evaluate each variable in the article, considering the varying number of assessed articles. According to Figure 1, there are a total of 46 articles. However, out of these, only 31 articles are used for the age variable, 5 articles are used for gender, and 15 articles are used for Prothrombin Time. Further clarification is required.

In the latest revision the author only mentions "The final results after selection got a total of 46 articles that were included in this meta-analysis study. Within these, 31 articles are utilized for age, 5 articles are utilized for gender, and 15 articles are utilized for prothrombin time." without any further explanation.

2) In the conclusion the author states "Since DM is a comorbidity in COVID-19, it can be concluded that older age and male sex are associated with more severe disease". While this proposition may be true in theory, the findings of this study do not address this particular aspect.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Not applicable

Are sufficient details of the methods and analysis provided to allow replication by others?

Not applicable

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Not applicable

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: biochemistry, health and medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Jul 2024

Mutiara Indah Sari

Thank you for the review. We will revise the manuscript based on your suggestions.

1: In the latest revision the author only mentions "The final results after selection got a total of 46 articles that were included in this meta-analysis study. Within these, 31 articles are utilized for age, 5 articles are utilized for gender, and 15 articles are utilized for prothrombin time." without any further explanation.

Response: For further explanation, we have added a venn diagram included studies for each variables.

2: In the conclusion the author states "Since DM is a comorbidity in COVID-19, it can be concluded that older age and male sex are associated with more severe disease". While this proposition may be true in theory, the findings of this study do not address this particular aspect.

Response: We have added some explanation related to our study in the results section. All samples in the articles we reviewed were hospitalized patients, where the severity was more severe than those who were only isolated at home. Among patients with severe disease, we compared diabetic and non-diabetic group.

Sincerely,
Mutiara Indah Sari

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 18 June 2024

<https://doi.org/10.5256/f1000research.167093.r286853>

© 2024 Marindra Siregar F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Fajri Marindra Siregar**

Universitas Riau, Pekanbaru, Riau, Indonesia

The author has made several improvements to complete the information, especially in the methods section, but several things still need to be clarified.

1. The author should clarify the criteria used to evaluate each variable in the article, considering the varying number of assessed articles. According to Figure 1, there are a total of 46 articles. However, out of these, only 31 articles are utilized for the age variable, 5 articles are utilized for gender, and 15 articles are used for Prothrombin Time. Further clarification is required.
2. In the results section, the author compares the average age and prothrombin time between COVID-19 patients with and without DM. However, regarding the gender variable, the author only examines the comparison of male and female genders in COVID-19 patients with DM. To ensure consistency with the age and PT variables, it would be appropriate to analyze the sex ratio in COVID-19 patients with and without DM for the gender variable.
3. In the results section, the sentence "Total Standardised Mean Difference (SMD) 0.41 (95%CI = -0.03-0.85; P = 0.07) with a confidence interval for the population between -0.03 to 0.85 (P = 0.07) showed that there were insignificant results because $P < 0.05$." should be corrected to "Total Standardised Mean Difference (SMD) 0.41 (95%CI = -0.03-0.85; P = 0.07) with a confidence interval for the population between -0.03 to 0.85 (P = 0.07) showed that there were insignificant results **because $P > 0.05$** ."
4. The conclusion section has not adequately addressed the concerns raised by the previous reviewer. I suggest revising the conclusion to align it with the results section. Specifically, the revised conclusion should state that the findings of this meta-analysis indicate that COVID-19 patients with comorbid DM tend to be older and male compared to COVID-19 patients without DM. However, there was no significant difference in the results of prothrombin time.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Not applicable

Are sufficient details of the methods and analysis provided to allow replication by others?

Not applicable

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Not applicable

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: biochemistry, health and medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Jun 2024

Mutiara Indah Sari

Dear Reviewer,

Thank you for the review. We will revise the manuscript based on your suggestions.

1: The author should clarify the criteria used to evaluate each variable in the article, considering the varying number of assessed articles. According to Figure 1, there are a total of 46 articles. However, out of these, only 31 articles are utilized for the age variable, 5 articles are utilized for gender, and 15 articles are used for Prothrombin Time. Further clarification is required.

Response: Further clarification is added as suggested.

2: In the results section, the author compares the average age and prothrombin time between COVID-19 patients with and without DM. However, regarding the gender variable, the author only examines the comparison of male and female genders in COVID-19 patients with DM. To ensure consistency with the age and PT variables, it would be appropriate to analyze the sex ratio in COVID-19 patients with and without DM for the gender variable.

Response: We analyzed gender differences between male and female to assess gender as a risk factor, particularly among COVID-19 patients with comorbid diabetes, to determine whether more male or female were hospitalized. We processed gender data using odds ratios, unlike age and prothrombin time variables, which utilized mean and standard deviation. Additionally, there was a lack of odds ratio data for non-diabetic patients in the literature we reviewed.

3: In the results section, the sentence "Total Standardised Mean Difference (SMD) 0.41

(95%CI = -0.03–0.85; P = 0.07) with a confidence interval for the population between -0.03 to 0.85 (P = 0.07) showed that there were insignificant results because P < 0.05." should be corrected to "Total Standardised Mean Difference (SMD) 0.41 (95%CI = -0.03–0.85; P = 0.07) with a confidence interval for the population between -0.03 to 0.85 (P = 0.07) showed that there were insignificant results **because P > 0.05.**"

Response: We will rectify the typographical error.

4: The conclusion section has not adequately addressed the concerns raised by the previous reviewer. I suggest revising the conclusion to align it with the results section. Specifically, the revised conclusion should state that the findings of this meta-analysis indicate that COVID-19 patients with comorbid DM tend to be older and male compared to COVID-19 patients without DM. However, there was no significant difference in the results of prothrombin time.

Response: We will revise the conclusion to align it with the results.

Sincerely,
Mutiara Indah Sari

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 16 May 2024

<https://doi.org/10.5256/f1000research.118616.r269067>

© 2024 Marindra Siregar F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Fajri Marindra Siregar

Universitas Riau, Pekanbaru, Riau, Indonesia

The author should properly clarify the search method utilised in each database, as each database has a unique search algorithm, so that other scholars can easily adapt it.

Next, the author must certify that the results of the literature search are articles published until when?

The analysis of statistical results states that there is very high (significant) variability in each variable; has the author made any efforts to lessen this heterogeneity? (Please refer to https://handbook-5-1.cochrane.org/chapter_9/9_5_3_strategies_for_addressing_heterogeneity.htm

)

Furthermore, the conclusions presented are not in accordance with the results obtained by the author. In the conclusion the author stated "Patients with older age with diabetes tend to have more severe disease than non-diabetics" even though the meta-analysis carried out only compared age between the Covid group with DM vs without DM, there was no study of morbidity variables.

Likewise, the statement "Patients with diabetes who are hospitalized are more likely to be male, indicating that males are more susceptible to severe disease" in our opinion is not appropriate considering that there are no variables for hospitalization status or degree of disease that were studied by the author in the meta-analysis section.

Furthermore, considering that there are still several limitations that may not be avoidable, these need to be explored further by the author in the discussion section, such as the influence of disease onset and disease degree.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

No

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: biochemistry, health and medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 May 2024

Mutiara Indah Sari

Dear Reviewer,

Thank you for the review. We will revise the manuscript based on your suggestions.

1: The author should properly clarify the search method utilised in each database, as each database has a unique search algorithm, so that other scholars can easily adapt it.

Response: We will add more details on the search strategy such as the filters for each database in the text.

2: Next, the author must certify that the results of the literature search are articles published until when?

Response: We will add the publication years for the included literatures in the text.

3: The analysis of statistical results states that there is very high (significant) variability in each variable; has the author made any efforts to lessen this heterogeneity?

Response: Referring to the handbook, we performed point 1 (rechecking the data) and 7 (studies exclusion) to reduce heterogeneity. We will add brief information on this in the text.

4: Furthermore, the conclusions presented are not in accordance with the results obtained by the author. In the conclusion the author stated "Patients with older age with diabetes tend to have more severe disease than non-diabetics" even though the meta-analysis carried out only compared age between the Covid group with DM vs without DM, there was no study of morbidity variables.

Likewise, the statement "Patients with diabetes who are hospitalized are more likely to be male, indicating that males are more susceptible to severe disease" in our opinion is not appropriate considering that there are no variables for hospitalization status or degree of disease that were studied by the author in the meta-analysis section.

Response: It is true that our result is comparing COVID patients with vs without DM, so we will make changes on the conclusion and a few other parts of the text (for consistency and clarification) based on your suggestion. However, we would like to note that as DM is a comorbidity in COVID, we use it as an indicator of a more severe disease.

5: Furthermore, considering that there are still several limitations that may not be avoidable, these need to be explored further by the author in the discussion section, such as the influence of disease onset and disease degree.

Response: We will add the limitations to the text as suggested.

Sincerely,
Mutiarah Indah Sari

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research