Comparison of mortality and severity in Coronavirus disease 2019 (COVID-19) patient with and without diabetes mellitus: a systematic review

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ABSTRACT
Background: Coronavirus disease-19 (COVID-19) has been a global pandemic since it was first discovered in Wuhan, China, on December 2019. Several studies found that comorbidity in COVID-19 patients, such as diabetes mellitus is a risk factor for mortality and more severe infection in COVID-19 patients. This systematic review aims to review the comparison of mortality and severity in COVID-19 patients with and without DM.

Method: This systematic review was performed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) diagram Google Scholar, PubMed, and Europe PMC as electronic database sources. We used a checklist from Joanna Briggs Institute for cross sectional, cohort, and case-control studies for quality assessment.

Result: We included 24 studies in this systematic review, consisting of 19 cohort studies, three cross sectional studies, and two case-control studies. All studies included were classified as good studies by study quality assessment. Most study samples are male patients with an average age of more than 50. All studies found a higher mortality rate and severe infection in COVID-19 patients in the DM group compared with the non-DM group. COVID-19 patients in the DM group have a 7.67 higher mortality risk compared with the non-DM group. While for the severity, COVID-19 patients in the DM group have a 6.07 greater risk for severe infection than the non-DM group.

Conclusion: There is a higher mortality rate and more severe infection in COVID-19 patients in the DM group compared with the non-DM group.

Keywords: COVID-19, diabetes mellitus, SARS-CoV-2, mortality, severity.


INTRODUCTION
Coronavirus disease-19 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that has been a global pandemic since it was first discovered in Wuhan, China, on December 2019.1 Since the COVID-19 pandemic began, it has been infected more than 604 million people, which 6.5 million people have died all over the world.2 In Indonesia, the total cases of COVID-19 infection until August 2022 reached 6.36 million cases with a 2.48% mortality rate.3 Clinical manifestation of COVID-19 infection varies from asymptomatic mild, moderate and severe cases. Mild cases are often marked by fever, cough and fatigue. Patients with moderate cases could have shortness of breath or pneumonia, while severe cases marked with severe pneumonia, acute respiratory distress syndrome (ARDS), the need for an intensive care unit (ICU), multiple organ failure or death.4-6

Several risk factors are known to be associated with more severe COVID-19 infection and higher mortality rates; one of them is comorbidity. The most common comorbidity found in the patient with severe COVID-19 infection or death COVID-19 patient is diabetes mellitus. Diabetes mellitus is the common type of diabetes mellitus marked by insulin resistance, causing high blood sugar. Several studies have shown a significant relationship between DM with higher mortality and severity in COVID-19 patients.5-8 Data from WHO-China joint mission report stated a high case fatality rate (CFR) of COVID-19 patients with DM-type comorbidities.9 The CFR of COVID-19 patients with DM was 9.2%, second only to cardiovascular disease comorbidities (13.2%) and higher than COVID-19 patients with hypertension (8.4%). The mortality rate of COVID-19 patients with DM is increasing with age, with the most increased mortality among elderly patients over 80 years old, with an estimated CFR of 14.8%.10

Several possible pathophysiological explanations exist for the relationship between DM and COVID-19 infection. Patients with uncontrolled DM have a weakened immune system which makes them susceptible to infection, particularly COVID-19. Moreover, DM patients with COVID-19 infection are also more susceptible to experiencing cytokine storm, an inflammatory condition in COVID-19 infection that can cause severe conditions such as ARDS, MOF, and high mortality rates.5,8 Several studies were done to explore the intermediate risk factors explaining the higher mortality burden and...
more severe COVID-19 infection among DM patients with COVID-19. Thus, this systematic review gathered and analyzed a study that compares the mortality and severity rates between COVID-19 patients with and without DM.

METHODS

Study eligibility
The study eligibility criteria for this systematic review use some inclusion and exclusion criteria. Inclusion criteria were research articles about diabetes mellitus as a predictor or risk factor for COVID-19 severity or mortality, using adult patients as the sample (age ≥18 years old), clinically assessed or compared the mortality and severity between COVID-19 patients with and without DM. The exclusion criteria were studies that included children, not compared between the DM and non-DM group, studies that were a systematic review, meta-analysis, case report or letter to the editor and studies that were not available in English or Bahasa.

Search strategy and study selection
A systematic literature search was performed in three online databases: Google Scholar, PubMed, and Europe PMC. We used Boolean Operator with keywords [("diabetes mellitus") AND ("non-diabetes mellitus" OR "without diabetes mellitus") AND ("COVID-19" OR "SARS-COV-2") AND ("severity") AND ("mortality") AND ("comparison")] . Duplicate results were removed, and two authors independently screened the selected study’s abstract for its relevance to the topic. We read the full text of the relevant studies comprehensively according to the eligibility criteria. Studies that meet the eligibility criteria are then included in the final analysis to extract the principal point of the studies (Figure 1).

Quality assessment of the study
We performed a critical appraisal to determine the study quality. We used a checklist from Joanna Briggs Institute for cross-sectional, cohort, and case-control studies. Each item on the checklist contributes one point and is classified as a good study if it scores at least half the maximum total point.

Data synthesis
All relevant studies that meet eligibility criteria were included in a narrative synthesis. As a qualitative report, our systematic review tried to gather information regarding diabetes mellitus as a predictor for COVID-19 severity and mortality. From the included studies, we extracted data such as author, year, country, study design, age, gender, and comparison between the DM and non-DM patients based on mortality or severity.

RESULTS

Study Characteristics
We retrieved 352 studies from three electronic databases. After excluding 49 duplicate studies, we got 303 studies to screen through the abstract. About 249 studies were excluded through the abstract assessment, and 54 were analyzed for their eligibility criteria. Thirty studies did not meet our inclusion and exclusion criteria. Thus, only 24 studies were included in the systematic review analysis. All of the studies were observational studies consisting of 19 cohort studies, three cross-sectional studies, and two case-control studies. Studies included in the analysis came from several countries such as Belgium, China, India, Indonesia, Iran, Italy, Kazakhstan, Kuwait, Qatar, Saudi Arabia, Turkey and the USA. All of the studies used adult COVID-19 patients and compared the outcome between COVID-19 patients with and without DM. Most study samples are male patients with an average age of more than 50. Detailed characteristics of the study are shown in Table 1.
Comparison of mortality rates between COVID-19 patients with DM and non-DM

All of the included studies in this systematic review showed higher mortality rates in COVID-19 patients in the DM group compared with the non-DM group.\textsuperscript{4,5-14,16-37} The highest mortality rate in COVID-19 patients with DM was found in a study by Hui et al. conducted in China with an 80% mortality rate and another by Nadzifah et al. conducted on 412 COVID-19 patients in Indonesia with a 58.3% mortality rate as stated in Table 1.\textsuperscript{15-22}\textsuperscript{30} Despite all of the 24 studies showed higher mortality rate in DM group, only 13 studies the association between DM in COVID-19 patients with death outcome.\textsuperscript{15,16,18,19,21,24,25,29,30,33,35,37} Out of 13 studies, 10 studies found a significant relationship between DM with mortality in COVID-19 patients.\textsuperscript{13,15,16,21,25,39,39-36,37} While, three other studies by Fu et al., Fox et al., and Liu et al. did not find any significant relationship between those two variables.\textsuperscript{18,19,24} From the 10 studies, we found the biggest hazard ratio in a study by Harbuwono et al. They found that COVID-19 patients in the DM group have 7.67 greater risks for mortality compared with COVID-19 patients in the non-DM group.\textsuperscript{21} Meanwhile, the other study found varied hazard ratios for mortality ranging from 1.52 - 7.67 for COVID-19 patients in the DM group, as stated in Table 2.\textsuperscript{15,16,21,25,29,30,33,35-37}

Comparison of severity rates between COVID-19 patients with DM and non-DM

Among 24 studies included in the analysis, 18 compared the severity rate between COVID-19 patients in DM and non-DM groups. The severity assessed in those studies was sepsis condition, acute respiratory distress syndrome (ARDS), shortness of breath observed in the patient, intensive care unit (ICU admission), inflammatory cytokine condition and the need for mechanical intubation. We found COVID-19 patients in the DM group have a more severe condition than the COVID-19 patient in the non-DM group. The detailed comparison of the severity rate between the two groups is stated in Table 1.\textsuperscript{15-18,20,21,23-25,27,29,31,32,34,36,37} Four studies showed that COVID-19 patients with DM have a significantly greater risk of experiencing severe COVID-19 infection. Badedi et al. stated that COVID-19 patients with DM have a 2.5 greater risk of severe infection than non-DM COVID-19 patients.\textsuperscript{16} The other study by Mokoagow et al. involved 506 COVID-19 patients and showed that COVID-19 patients in the DM group have a 6.07 greater risk of experiencing severe infection than the non-DM group.\textsuperscript{29} The other two studies by Harbuwono et al. and Zakerkish et al. found a greater risk for severe infection in the DM group compared with a non-DM group of 1.98 and 1.43, respectively.\textsuperscript{21,36}

DISCUSSION

COVID-19 infection has a broad spectrum of clinical manifestations and varies from asymptomatic to severe infection. Severe infection is marked by severe pneumonia, sepsis, the requirement of mechanical ventilation, and multiple organ failure until death.\textsuperscript{14} Study found several factors influencing COVID-19 outcomes, such as age, gender, comorbidity, or pre-existing illness. One of the common comorbidities found in COVID-19 patients is diabetes mellitus.\textsuperscript{5,8} In this systematic review, we found higher mortality rates in COVID-19 patients with diabetes mellitus than those without diabetes mellitus. We also found COVID-19 patients with diabetes mellitus have higher severity rates compared with COVID-19 patients without diabetes mellitus. The outcome severity researched in those studies is ICU admission, the need for mechanical intubation, ARDS, and other clinical condition such as sepsis, kidney injury, shortness of breath, pneumonia, and inflammatory or cytokine storm.\textsuperscript{15-18,20,21,23-25,27,29,31,32,34,36,37}

Patients with diabetes mellitus are highly susceptible to infection, including COVID-19 infection. Based on COVID-19 pathogenesis, the SARS-CoV-2 virus enters the cell through human angiotensin-converting enzyme 2 (ACE-2). The angiotensin-converting enzyme 2 (ACE-2) is a type 1 membrane protein that is abundantly expressed in the lung, heart, kidney and intestine. The SARS-CoV-2 infection is divided into three stages: the viremia phase, the acute phase, and the severe or recovery phase.\textsuperscript{38,39} Patients with competent immune functions can produce effective and adequate immune responses to the infection. Meanwhile, non-immunocompetent patients, such as diabetes mellitus patients, can have a higher risk of failing immune responses to combat the infection, leading to more severe conditions or mortality.\textsuperscript{8}

The other mechanism is patients with diabetes mellitus have increased expression of the receptor ACE-2, which increases the binding of SARS-CoV-2 and facilitates viral replication. Moreover, diabetes mellitus is a pro-inflammatory syndrome marked by improper and excessive cytokine response. The DM patients had Interleukin-6 (IL-6) and C-reactive protein (CRP) levels in the bloodstream that were significantly higher than non-DM patients. In patients with diabetes mellitus, exaggerated production of advanced glycation end (AGE) products and the oxidative stress process also drive tissue inflammation. The outburst production of pro-inflammatory cytokine can lead to cytokine storm, leading to severe COVID-19 infection and even mortality.\textsuperscript{5-8}

The clinical implications we found from our systematic review is that it is important to closely monitor blood glucose, particularly with patients with known DM. As we know, poor glycemic control could worsen viral infections.\textsuperscript{34,35} Respiratory distress caused by the viral infection could lead to pancreatic beta cell apoptosis that consequently causes insulin insufficiency, leading to a more complicated diabetic condition in the patients. It is also important for clinicians to consider the anti-diabetic with non-pro-inflammatory effects. The pro-inflammatory effect of the anti-diabetic drug such as Thiazolidinediones (TZD) could contribute to the progression of severe COVID-19 by elevating the expression of ACE-2.\textsuperscript{21,23}

Some studies included in this systematic review stated no significant relationship exists between DM condition and mortality in COVID-19 patients.\textsuperscript{18,19,24} This finding can be caused due to the influence of other comorbidities also analyzed in those studies. The other affecting factor is also the relatively small sample size. Meanwhile, the limitation
Table 1. Detail characteristics of the study.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Age (Mean or Median) (years)</th>
<th>Male (%)</th>
<th>Mortality DM (%)</th>
<th>Non-DM (%)</th>
<th>Mortality DM (%)</th>
<th>Non-DM (%)</th>
<th>Severity</th>
<th>Outcome measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkunda et al., 2020, United Kingdom</td>
<td>Retrospective sectional study</td>
<td>70.5 ±15.7</td>
<td>62.5</td>
<td>55.1</td>
<td>44.9</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Alishukry et al., 2021, Kuwait</td>
<td>Retrospective study</td>
<td>56.44 ±11.64</td>
<td>62.82</td>
<td>34.7</td>
<td>3.7</td>
<td>42.4</td>
<td>7.7</td>
<td></td>
<td>Mortality, sepsis, ARDS, kidney injury.</td>
</tr>
<tr>
<td>Badedi et al., 2022, Saudi Arabia</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>62.4</td>
<td>9.3</td>
<td>1.2</td>
<td>10.5</td>
<td>4.9</td>
<td>Mortality, ICU admission.</td>
<td></td>
</tr>
<tr>
<td>Yusupova et al., 2021, Kazakhstan</td>
<td>Case-control study</td>
<td>N/A</td>
<td>6.5</td>
<td>0</td>
<td>41.9</td>
<td>4.0</td>
<td></td>
<td></td>
<td>Mortality, severity degree.</td>
</tr>
<tr>
<td>Fox et al., 2021, USA</td>
<td>Retrospective study</td>
<td>66.42±12.67</td>
<td>71.54</td>
<td>27</td>
<td>19</td>
<td>29</td>
<td>22</td>
<td></td>
<td>Mortality, need for intubation.</td>
</tr>
<tr>
<td>Fu et al., 2020, China</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>49.3</td>
<td>19</td>
<td>12.7</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Guo et al., 2020, China</td>
<td>Retrospective study</td>
<td>59 (49–67)</td>
<td>43.7</td>
<td>16.5</td>
<td>0</td>
<td>20.8</td>
<td>15.4</td>
<td></td>
<td>Mortality, shortness of breath, inflammatory storm.</td>
</tr>
<tr>
<td>Harbuwono et al., 2022, Indonesia</td>
<td>Retrospective study</td>
<td>41.8 (16.8)</td>
<td>52.06</td>
<td>21.28</td>
<td>2.77</td>
<td>54.45</td>
<td>6.55</td>
<td></td>
<td>Mortality, pneumonia.</td>
</tr>
<tr>
<td>Hui et al., 2020, China</td>
<td>Case-control study</td>
<td>65.0 (56.0–72.0)</td>
<td>65.3</td>
<td>80</td>
<td>58</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Khalili et al., 2021, Iran</td>
<td>Retrospective study</td>
<td>65.70±12.51</td>
<td>55.9</td>
<td>22.8</td>
<td>15</td>
<td>15</td>
<td>6.3</td>
<td></td>
<td>Mortality, ARDS, invasive ventilation.</td>
</tr>
<tr>
<td>Liu et al., 2020, China</td>
<td>Retrospective study</td>
<td>64.5 ± 10.0</td>
<td>47.5</td>
<td>2.9</td>
<td>2.2</td>
<td>10.8</td>
<td>4.3</td>
<td></td>
<td>Mortality, highest level of illness severity.</td>
</tr>
<tr>
<td>Liu et al., 2021, China</td>
<td>Retrospective study</td>
<td>64.0 (52.0–71.0)</td>
<td>49.4</td>
<td>22.5</td>
<td>5.9</td>
<td>48.8</td>
<td>12.2</td>
<td></td>
<td>Mortality and disease severity.</td>
</tr>
<tr>
<td>Mirsoleymani et al., 2021, Iran</td>
<td>Prospective cohort study</td>
<td>60.96 ±17.01</td>
<td>71.2</td>
<td>13.72</td>
<td>9</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Mithal et al., 2020, India</td>
<td>Prospective cohort study</td>
<td>59.8±12.1</td>
<td>68.82</td>
<td>6.3</td>
<td>1.4</td>
<td>20.1</td>
<td>9</td>
<td></td>
<td>Mortality and ICU admission.</td>
</tr>
<tr>
<td>Moftakhar et al., 2021, India</td>
<td>Retrospective cohort study</td>
<td>59 (49–67)</td>
<td>54.55</td>
<td>14.40</td>
<td>3.30</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Mokoagow et al., 2022, Indonesia</td>
<td>Retrospective study</td>
<td>51 (22)</td>
<td>43.68</td>
<td>45.14</td>
<td>20.72</td>
<td>86.11</td>
<td>47.79</td>
<td></td>
<td>Mortality, intensive care admission.</td>
</tr>
<tr>
<td>Nadzifah et al., 2022, Indonesia</td>
<td>Cross sectional study</td>
<td>N/A</td>
<td>51.61</td>
<td>58.3</td>
<td>30.43</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Orioli et al., 2021, Belgium</td>
<td>Retrospective study</td>
<td>69±14</td>
<td>48</td>
<td>25</td>
<td>15.6</td>
<td>18.8</td>
<td>18.8</td>
<td></td>
<td>Mortality, ICU admission.</td>
</tr>
<tr>
<td>Satman et al., 2021, Turkey</td>
<td>Retrospective study</td>
<td>53</td>
<td>44</td>
<td>6.9</td>
<td>1.6</td>
<td>22.5</td>
<td>14.5</td>
<td></td>
<td>Mortality, ICU admission.</td>
</tr>
<tr>
<td>Silverii et al., 2021, Italy</td>
<td>Retrospective study</td>
<td>73.31</td>
<td>54.1</td>
<td>37.1</td>
<td>8.2</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Soliman et al., 2020, Qatar</td>
<td>Retrospective study</td>
<td>52.1±12.67</td>
<td>N/A</td>
<td>3.57</td>
<td>0</td>
<td>30.36</td>
<td>7</td>
<td></td>
<td>Mortality, ICU admission.</td>
</tr>
<tr>
<td>Wulandari et al., 2022, Indonesia</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>52.36</td>
<td>20</td>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Mortality.</td>
</tr>
<tr>
<td>Zakerkish et al., 2021, Iran</td>
<td>Cross sectional study</td>
<td>61.3 (12.53)</td>
<td>54</td>
<td>17.5</td>
<td>12</td>
<td>35.4</td>
<td>27.7</td>
<td></td>
<td>Mortality, ICU admission.</td>
</tr>
<tr>
<td>Zhang et al., 2020, China</td>
<td>Retrospective study</td>
<td>64 (56.70)</td>
<td>53.5</td>
<td>11.1</td>
<td>4.1</td>
<td>38.1</td>
<td>19.5</td>
<td></td>
<td>Mortality, ARDS.</td>
</tr>
</tbody>
</table>

*Abbreviation: A RDS=Acute Respiratory Distress Syndrome; DM=Diabetes Mellitus; ICU=Intensive Care Unit; N/A=Not available; USA=United States of America
of our systematic review was some of the included studies were pre-prints, but the author has ensured that only good studies were included. Most of the included studies are retrospective and come from China and Indonesia. Thus, these systematic review findings are most applicable in those two countries.

**CONCLUSION**

We conclude that mortality and severity rates were higher in COVID-19 patients with diabetes mellitus comorbidity compared with non-DM patients. Diabetes mellitus was also significantly related to mortality and more severe clinical manifestation in COVID-19 infection.

**CONFLICT OF INTEREST**

There was no conflict of interest in the writing of this research.

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**AUTHOR’S CONTRIBUTION**

The author contributed to the writing of this research report, from the stage of proposal preparation, data collection and analysis to the preparation of reports in the form of publications.

**REFERENCES**


