Sex Differences in COVID-19 Mortality: A Meta-Analysis with E-COVID Study

Karlinda¹, Santy Irene Putri² *
¹ Universitas Muhammadiyah Muara Bungo, Jambi, Indonesia
² Poltekkes Wira Husuda Nusantara Malang, East Java, Indonesia

ABSTRACT

Background: COVID-19 disease spreads rapidly and becomes more widespread with the emergence of new variants. The ratio of death cases due to the Coronavirus (COVID-19) in men is greater than in women. Recent research has found that men are more likely to have COVID-19 with severe symptoms and more at risk of death. This study aimed to examine the effect of sex on mortality in COVID-19 patients without comorbidities. Methods: This research was a systematic review and meta-analysis. The articles were obtained from several electronic databases including Google Scholar, PubMed, Scilit, Emerald Insight, Plos One, Sage Journal, JSTOR, World Cat, and ProQuest. The articles used in this study were articles that had been published from 2010-2019. The keywords to search for articles were as follows: gender and COVID-19 and HR, "gender and COVID-19 mortality and HR", "sex and COVID-19 mortality and HR", and "gender and COVID-19 mortality and HR". The articles included were full-text with an observational study design/cohort study. The articles were collected using PRISMA diagrams and analyzed using the Review Manager 5.3 application. Results: Males have 1.42 times the risk of dying from COVID-19 compared to females (in non-comorbid conditions) (aHR=1.42; CI 95%=1.27 to 1.59; p<0.001). Conclusion: Male sex is associated with an increased risk of mortality.

Keywords: Sex, COVID-19, Mortality.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) results in high infection and death rates worldwide, and despite efforts globally, no specific therapies are available for COVID-19 (Gabutti et al., 2020). While COVID-19 severity and mortality rates are higher in men than women, the underlying molecular mechanisms are unclear. Men are considered the weaker sex in aspects related to control of immunity and infection (Gadi et al., 2020).

Sex also has a significant influence related to health services, where males and females have different behaviors in accessing health services. Although females systemically experience structural problems in health services, the percentage of females accessing health facilities is higher than males. This is because the male population tends to ignore health problems and avoid health services. Coupled with the male social structure associated with masculinity that makes men feel strong and can self-medicate (Princess &; Karlinda, 2021). In terms of sex, males’ tendency to ignore health problems has the potential to result in delays in checking into health facilities when they have a disease, which ultimately contributes to a greater risk of death due to late diagnosis. In the case of the COVID-19 pandemic, the mortality rate in the male population (62.30%) is higher than that of women (37.70%). This is due to the low use...
of health facilities by the male population compared to females due to reluctance to check themselves when experiencing health complaints. Males tend to have more risky behaviors such as smoking and drinking alcoholic beverages than females which can cause chronic diseases that are proven to affect the severity of illness due to COVID-19. This may be the cause of the high number of deaths in the male population. Especially when considering that in this pandemic condition, males continue to travel and do their jobs so they are vulnerable to exposure to the SARS-CoV-2 virus. This study aimed to measure the effect of sex on mortality rates from COVID-19 without comorbid diseases.

RESEARCH METHODS

This research is a systematic review and meta-analysis. The articles used in this study are articles that have been published from 2010-2019 and obtained from several electronic databases including Google Scholar, PubMed, Scilit, Emerald Insight, PLoL One, Sage Journal, JSTOR, World Cat, and ProQuest. The keywords used in searching for articles are gender and COVID-19 and HR, "gender and COVID-19 mortality and HR", "sex and COVID-19 mortality and HR", and "gender and COVID-19 mortality and HR".

The articles included in this study are text articles with observational studies that have been published from 2010-2019. The selected articles discuss the sex differences in COVID-19 patient mortality. The included articles were published in English and Indonesian. The samples of the studies in the included articles were hospital patients. The studies used multivariate analysis and reported the results using the hazard ratio (HR). The exclusion criteria were articles with RCT study design, review, case-control, quasi-experiment, and protocol study; articles not published in English or Indonesian; the results were not in HR; the patients did not have comorbid diseases or other medical conditions.

Data processing was done by using the Review Manager (RevMan 5.3) by calculating effect size and heterogeneity to determine the combined study model and display the results in a forest plot.

RESULT

The process of searching for articles using journal databases is shown in Figure 1. Figure 2 indicates the area where the articles were collected based on the inclusion criteria. The articles were obtained from 4 continents, i.e. Asia, Europe, North America, and South America.

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Figure 1. PRISMA Flow Diagram

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Sex Differences in COVID-19 Patient Mortality

Table 1 shows that there are 22 articles of observational studies (cohort studies) with sex as a predictor of mortality in COVID-19 patients.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>aHR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apea et al. (2020)</td>
<td>London</td>
<td>1.47</td>
<td>1.15 - 1.88</td>
<td>0.002</td>
</tr>
<tr>
<td>Hothorn et al. (2021)</td>
<td>Switzerland</td>
<td>1.49</td>
<td>1.43 - 1.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Huang et al. (2021)</td>
<td>China</td>
<td>2.22</td>
<td>1.31 - 1.74</td>
<td>0.003</td>
</tr>
<tr>
<td>Cifuentes et al. (2021)</td>
<td>Colombia</td>
<td>1.74</td>
<td>1.44 - 2.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Takeuchi et al. (2021)</td>
<td>Japanese</td>
<td>1.59</td>
<td>1.53 - 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pantoja et al. (2021)</td>
<td>Mexico</td>
<td>1.69</td>
<td>0.95 - 3.02</td>
<td>0.050</td>
</tr>
<tr>
<td>Sha et al. (2021)</td>
<td>Brazil</td>
<td>1.13</td>
<td>1.09 - 1.18</td>
<td>0.050</td>
</tr>
<tr>
<td>Carter et al. (2020)</td>
<td>United Kingdom</td>
<td>1.11</td>
<td>1.00 - 1.23</td>
<td>0.018</td>
</tr>
<tr>
<td>Radujkovic et al. (2020)</td>
<td>German</td>
<td>2.50</td>
<td>0.80 - 7.81</td>
<td>0.001</td>
</tr>
<tr>
<td>Grasseli et al. (2020)</td>
<td>Italian</td>
<td>1.57</td>
<td>1.31 - 1.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Williamson et al. (2020)</td>
<td>English</td>
<td>1.59</td>
<td>1.53 - 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivera et al. (2020)</td>
<td>United States</td>
<td>1.03</td>
<td>1.01 - 1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wang et al. (2020)</td>
<td>China</td>
<td>1.75</td>
<td>1.17 - 2.60</td>
<td>0.006</td>
</tr>
<tr>
<td>Rossi et al. (2020)</td>
<td>Switzerland</td>
<td>3.84</td>
<td>1.96 - 7.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sapey et al. (2020)</td>
<td>United Kingdom</td>
<td>1.60</td>
<td>1.20 - 2.10</td>
<td>0.050</td>
</tr>
<tr>
<td>Musthaq et al. (2020)</td>
<td>Italian</td>
<td>1.03</td>
<td>0.70 - 1.52</td>
<td>0.880</td>
</tr>
<tr>
<td>Costa et al. (2020)</td>
<td>Spanish</td>
<td>1.24</td>
<td>1.05 - 1.46</td>
<td>0.010</td>
</tr>
<tr>
<td>Nachtigall et al. (2020)</td>
<td>German</td>
<td>1.45</td>
<td>1.15 - 1.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rutten et al. (2020)</td>
<td>Dutch</td>
<td>1.84</td>
<td>1.54 - 2.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hagg et al. (2020)</td>
<td>Swedish</td>
<td>1.11</td>
<td>0.60 - 0.26</td>
<td>0.050</td>
</tr>
<tr>
<td>Renelus et al. (2020)</td>
<td>York</td>
<td>1.50</td>
<td>1.15 - 1.96</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Figure 3. Forest plot of the effect of sex on COVID-19 patient mortality.

Figure 3 shows the forest plot of the effect of sex on COVID-19 patient mortality. It shows that males have a 1.42 times risk of dying in COVID-19 patients compared to females. The results are statistically significant (p < 0.001). Heterogeneity (I²) = 97% indicates the random effect model.

Figure 4. Funnel plot of the effect of sex on COVID-19 patient mortality.

Figure 4 shows that there is a publication bias characterized by asymmetry in the graph. There are 14 plots on the right and 8 plots on the left. The left plot has a standard error of 0.4 to 0 while the plots on the right have a standard error between 0.6 and 0. Bias also occurs from unbalanced distances between studies of both the right plot and the left plot where the studies on the right side have a longer distance from the study than the left plot.

DISCUSSION

This systematic review and meta-analysis focus on the sex differences in COVID-19 patient mortality. The independent variable is sex while the dependent variable is COVID-19 patient mortality. Studies that can provide data on COVID-19 patient mortality are considered important because of their rarity. There are only a few published and accessible relevant studies that are not free from data excess problems (data duplication) (Murti, 2018). The majority of the statistical results were reported in percentage or crude odd ratio (cOR) where confounders were not controlled.
Estimation of the combined effect of sex on COVID-19 patient mortality was processed using the RevMan 5.3 application with a generic inverse-variance method (Anulus et al., 2019). This method was used to analyze rate, time-to-event, hazard ratio, ordinal scale, adjusted estimate, and difference of mean or ratio of mean.

Results of systematic and meta-analysis were presented with forest plot and funnel plot. The forest plot shows the magnitude of variation (heterogeneity) (Azwar et al., 2020). The funnel plot shows the relationship between the effect size and sample size of the studies which can be measured in different ways.

Funnel plots show the asymmetry of the studies, which is the number of points on the right and left sides compared to the standard error and the balance of the number of studies on the right and left sides.

A study found that the majority of patients confirmed positive for COVID-19 were aged 60 to 69 years (68%) and male (66%). About 50 percent of patients experienced typical symptoms of COVID-19, such as fever, cough, and shortness of breath. The rest came with atypical symptoms. The mortality rate of elderly patients with COVID-19 in the study (23%) was higher than the national rate (14.9%). As many as 90% of patients who died were male (Kushwaha et al., 2020). There are several mechanisms that can explain why men are more susceptible to adverse outcomes in COVID-19 cases. One of them is because the decrease in the number of B cells and T cells in elderly men is greater than in women (Hoffmann et al., 2020). As a result, the resulting immune response is not adequate. In addition, the testosterone hormone, commonly known by the public as the male sex hormone, apparently affects the expression of TMPRSS2 which plays an important role in the process of entry of the SARS-CoV-2 virus into the body's cells (Mollica et al., 2020). As a person ages, their immune system increasingly malfunctions. As a result, elderly COVID-19 patients are increasingly vulnerable to experiencing "cytokine storms" that can cause problems in various organs of the body and trigger respiratory failure events (Yanez et al., 2020). The presence of comorbidities is one of the factors that can increase the risk of death in COVID-19 patients. The results of this study showed that hypertension and diabetes mellitus are comorbidities commonly found in patients. Some patients even had more than one comorbidity (Chen et al., 2020).

Researchers found that men are more likely to die from coronavirus infections that cause COVID-19 disease than women. Based on research, this is due to ACE2 enzyme levels in the lungs of men higher than in women. This enzyme helps the SARS-CoV-2 virus that causes COVID-19 to survive longer in men's lungs (Viana et al., 2020). The study reinforced previous studies conducted in several countries. In the study, it was explained that men are more susceptible to infection and death from the COVID-19 virus. It states that men have a 50 percent higher chance of dying from COVID-19 than women. Data showing men's higher risk of death from COVID-19 than women's was first recorded in China. The mortality rate showed that 2.8 percent of men who contracted the virus have died, compared to women at 1.7 percent (Azzolina et al., 2020). Italy and Korea also showed the same data. In the literature, it is widely assessed that sex is one of the COVID-19 mortality risk factors; a literature review showed a COVID-19 mortality rate significantly higher in men than in women (RR = 1.60, 95%CI 1.53-1.68) among the European countries (Newall et al., 2020). In South Korea, the overall estimate of the CFR was 2.39% (3.05% for men and 1.92% for women). In every age stratum where deaths were reported, men were found to have significantly higher CFR than women (Kaseb et al., 2021). The study found higher concentrations of angiotensin-converting enzyme 2 (ACE2) in male subjects compared to females. ACE2, which is found in several organs, including the lungs, binds to SARS-CoV-2. This binding allows SARS-CoV-2 to more easily infect healthy cells. High ACE2 content in the lungs plays an important role in COVID-19 infection. Research also revealed a higher ACE-2 content than women. This fact could potentially explain why men are more at risk of dying from COVID-19 than women (Shibata et al., 2020). The researchers also raised several other theories, besides the ACE2 receptor, about why men seem to be more susceptible to the virus. Men tend to be more susceptible to pre-existing conditions that worsen virus infection, such as high blood pressure or diabetes (Conti & Younes, 2020). In many countries, men smoke more than women, and some studies show men have a lower tendency to wash their hands. Another reason that a woman's immune system may function differently is because of the extra X chromosome that women have. Women have two X chromosomes (XX) while men have only one (XY). This type of chromosome is considered relevant to the immune response because a large number of genes that regulate the human immune response are encoded on the X chromosome (Gemmati et al., 2020).

Studies showed that viral RNA clearance is delayed in men with COVID-19. A recent study has shown that the testicles can harbor the coronavirus, and as a result, men show delayed clearance of the virus. However, the
involvement of testicular roles in COVID-19 severity and mortality requires further research. Men and women show different immune system responses with women eliciting stronger immune responses against pathogens. This difference in immune system response may be a major factor contributing to viral load, disease severity, and mortality. In addition, differences in sex hormone effect can also be a determinant of viral infections such as estrogen is immunoenhancing while testosterone is immunosuppressive. The sex-specific severity of COVID-19 infection suggests that more research to understand sex differences is needed. Including both men and women in basic research and clinical trials is needed to provide important information about sex differences that can help to better understand diseases and therapies (Amirfakhryan & Safari, 2020).

During the coronavirus 2019 (COVID-19) pandemic, studies have largely focused on the elderly or those with congenital/comorbid diseases such as obesity, hypertension, and diabetes as those who have a high risk of contracting and/or dying from COVID-19. However, it is now known that men are also at higher risk of infection with the COVID-19 virus. Epidemiological findings reported in different parts of the world indicated that there is higher morbidity and mortality in males than in females (Yi et al., 2020). While it is still too early to determine why the sex gap is emerging, a study pointed to several possible factors such as higher expression of angiotensin-2-converting enzyme (ACE 2; receptor for coronavirus) in men than women, immunological differences driven by sex hormones and X chromosomes. Furthermore, most of these differences in the number of deaths are due to the behavior or lifestyle of each sex, i.e. smoking and drinking alcohol behavior in men is higher compared to women. One study reported that women have better preventive attitudes towards the COVID-19 pandemic than men. The attitude in question is an effort to take preventive measures such as frequent hand washing, wearing masks, and staying at home. Men are about 60% more likely than women to become seriously ill or die from COVID-19 complications (Jin et al., 2020).

It was found that male patients tend to have more severe cases of the disease. More than 70 percent of patients in the large COVID-19 dataset who died were male. This means men have almost 2.4 times higher mortality rates than women (Verma et al., 2020). Thus, sex is also a significant risk factor for disease severity, regardless of age. When the researchers analyzed data taken from SARS patients, they also found a significantly higher mortality rate among men. In addition, levels of a protein called ACE2, which is found in cells attacked by the viruses that cause COVID-19 and SARS, tend to be higher among men, those with cardiovascular disease, and patients with diabetes, all of whom have been found to have worse outcomes if they develop COVID-19 (Mueller et al., 2020).

The researchers found that women, including the elderly, have stronger immune responses involving T lymphocytes, which are a type of white blood cell that can recognize viruses and eliminate them. In contrast, older men had weaker T cell activity – the older they are, the weaker their response. Men overall also produce more cytokines, which are inflammatory proteins that form another part of the body's natural immune defense. However, severe cases of COVID-19 have been linked to what is known as a "cytokine storm", when the immune system becomes overexcited, which is dangerous and potentially deadly. Men who showed high concentrations early on were more likely to have severe cases of the disease, while women who also showed significant levels of cytokines also appeared worse (Capuano et al., 2020).

The limitation of this study is that the research articles collected were only published from 2010-2019. In addition, only 9 databases were used in searching for articles. Future analysis should expand the article search by adding new indexing databases and searching for articles that have been published in different time ranges.

CONCLUSION

Males have 1.42 times the risk of dying from COVID-19 than females without comorbid.

ACKNOWLEDGMENTS

We thank electronic database providers Google Scholar, PubMed, Scilit, Emerald Insight, Plos One, Sage Journal, JSTOR, World Cat, and ProQuest.
CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in this research.

REFERENCES


