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The Role of the Hormone Estrogen on the Recovery of Women During COVID-19 Pandemic: A Systematic Review

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ABSTRACT Coronavirus Disease 2019 (COVID-19) is an infectious disease that attacks the respiratory tract and it is known that the female sex shows a higher cure rate than men due to hormonal influences, namely the hormone estrogen. This research aims to conduct a systematic review of the results of the latest research on the effect of the hormone estrogen on the recovery of female with COVID-19. The article search found 1373 articles from 4 electronic databases, namely PubMed, Research Gate, Science Direct, and Google Scholar which were published in 2020-2021 using keywords and the boolean operator AND. Then the articles were selected using the PRISMA Flow Diagram instrument so that 11 articles were obtained that met the inclusion criteria. The eleven articles were then analyzed to assess the quality of the articles using The Joanna Briggs Institute (JBI) instrument. An article that deserves a review if it gets a score of more than 50%. After analyzing the assessment with JBI, 11 articles were declared eligible for review because them get a score of more than 50%. Seven of the 11 articles stated that the hormone estrogen had a significant effect on healing COVID-19, especially in female. Four other articles stated that the hormone estrogen had no significant effect on the recovery of women with COVID-19 due to several influencing factors including age, Body Mass Index (BMI), comorbid diseases, and smoking habits. The hormone estrogen affects the recovery of female with COVID-19 especially in young female, normal BMI, no comorbid, and not smoking. It is necessary to carry out a further literature review on the effect of the hormone estrogen on healing COVID-19 in female by taking into account the number of samples, sample criteria, and measurement of estrogen hormone levels.

INDEX TERMS Estrogen, recovery of female with COVID-19.

I. INTRODUCTION

Coronavirus Disease-19 (COVID-19) is the name of a disease caused by a new type of Corona virus variant or commonly referred to as Novel Coronavirus. This disease attacks the respiratory tract (pneumonia), so by the World Health Organization (WHO) the virus that causes COVID-19 is called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1] People, both men and women of all ages, from babies, teenagers, adults and the elderly through droplets or airborne so that the spread of this virus cannot be controlled quickly and easily).[1] The male gender is known to be more at risk of experiencing the COVID-19 condition. More severe than women due to differences in immune responses).[2] The difference in immune responses between sexes is caused by different hormonal conditions, namely women have a better immune response so that women show a good COVID-19 condition and have a high cure rate).[1] The number of COVID-19 cases from 30 December 2019 to 06 September 2021 reached 114 million (51% women and 49% men) with deaths reaching 2 million (43% women and 57% men) in all countries (WHO, 2010). 2021). WHO (2021) also reported that in Indonesia, from 4 million cases, 52% were female and 48% were male, with deaths reaching 12,430 cases, dominated by 57% men and 43% women. In the UK, out of 17000 hospitalized patients 40% are women with a 20% lower mortality rate than men.[4]

Coronavirus interacts with ACE2 as a protein that enters cells, followed by TMPRSS-2 mediated proteolytic processing of viral proteins to promote viral penetration.[5]

Female sex hormones can affect ACE2.[6] Estrogen inhibits ACE while increasing ACE2 levels.[7] Because estrogen triggers the ACE2 production system, serum ACE2 activity is higher in women than in men[6] It also directly inhibits the replication of COVID-19.[8] Thus, higher levels of soluble ACE2 neutralize COVID-19 and prevent its attachment to ACE2.[9] Overall, these high levels of ACE2 can naturally suppress inflammation in women, and these hormonal effects may be the cause of the low COVID-19 mortality in women of all ages.[10]

This literature review aims to identify the presence or absence of the influence of the hormone estrogen on the recovery of women infected with COVID-19 by systematically reviewing the results of the latest research.

II. METHODS

This literature review uses the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram to select studies that are tailored to the objectives of the literature review. The process of searching for articles electronically from four databases, namely, PubMed, Research Gate, Science Direct, and Google Scholar. The keywords used are estrogen hormone, estradiol, sex hormone, female recovery, recovery of female, outcome disease for female, COVID-19, SARS-CoV-2, coronavirus disease-19. The articles you are looking for are articles with publications in 2020-2021. The Boolean operator used in the search is "AND". After the number of articles was obtained, the researcher then re-selected them according to the specified inclusion and exclusion criteria.

The article search process was carried out in September - October 2021. The article search used keywords that had been determined by the researchers and set limits on inclusion and exclusion criteria. The data obtained from PubMed, Research Gate, Science Direct and Google Scholar were then selected one by one by the researchers to determine the suitability of the articles desired by the researchers and delete the same articles. After getting the articles according to the researchers, the articles were analyzed one by one using the JBI (The Joanna Briggs Institute) instrument and grouped to get the results. The next step is to discuss based on the points obtained. Articles must get more than 50% points to be able to synthesize data. If the points obtained are less than 50%, they will be excluded to avoid bias on the validity of the results.

III. RESULTS

An initial literature search yielded 1373 articles (43 from PubMed, 346 from Science Direct, 106 from Research Gate, and 878 from Google Scholar). After reviewing the abstracts for relevance and fit with inclusion criteria, 11 articles were selected for full-text review and reviewed, as listed in FIGURE 1. Based on TABLE 1 above, it was found that most of the articles (64%) were published in 2021 and most of the articles (64%) used a case control study research design. The study database, almost half of the articles (45%) were obtained from the PubMed database with the language of all articles (100%) in English because the research was not carried out in Indonesia, and most articles (64%) showed the results that the hormone estrogen had an effect on women's recovery. with COVID-19.

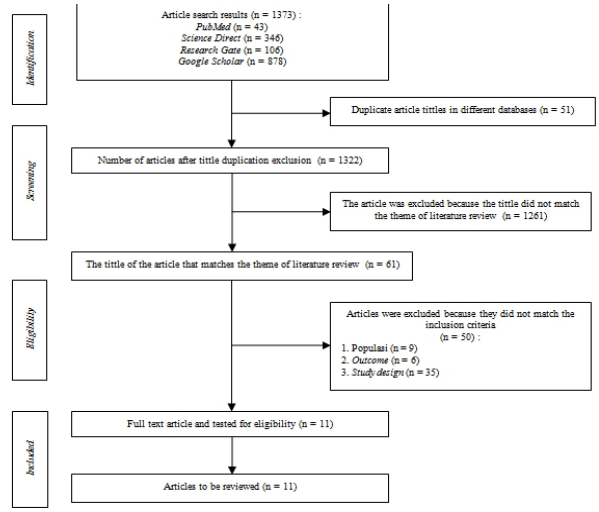

Figure 1 . PRISMA Diagram Flow Literature Review

Table 1
General Caracteristics Of Article Selection (N=11)

Categories	N	%
Publication of year		
2020	4	36
2021	7	64
Total	11	100
Study design		
Cross Sectional	1	9
Case Control	7	64
Cohort	3	27
Total	11	100
Database		
PubMed	5	45
ResearchGate	2	18
Science Direct	2	18
Google Scholar	2	18
Total	11	100
Language		
Indonesia	0	0
Inggris	11	100
Total	11	100
Result of research		
The estrogen hormone affects the recovery of female with COVID-19	7	64
The estrogen hormone hasn't affect the recovery of female with COVID-19	4	36
Total	11	100

IV. DISCUSSION

A. THE ESTROGEN HORMONE AFFECTS THE RECOVERY OF FEMALE WITH COVID-19

Women with COVID-19 tend to show a better prognosis than men[11]–[17] Not only that, the prognosis for nonmenopausal women shows a better condition than menopausal women[11], [16] But also in menopausal women,

postmenopausal women who previously received estrogen hormone therapy showed a decreased mortality rate.[16] Estrogen is a hormone produced by the ovaries, this hormone plays a role in inflammatory reactions, immune responses and the activity of Angiotensin Converting Enzym (ACE) receptors[18] Estrogen plays a major role in preventing heart problems, especially in non-menopausal women.[19] According to Heffner LJ & Schust DJ (2006), the effect of the hormone estrogen in preventing cardiovascular problems will decrease during menopause because the decrease in estrogen hormone levels is marked by the cessation of menstruation[20]

COVID-19 is a viral infectious disease that affects the cardiovascular system by using Angiotensin Converting Enzym 2 (ACE2) as a receptor[21] This COVID-19 then enters cells as a protein due to interaction with ACE2 and penetrates the virus with Transmembrane Protease / Serine Subfamily Member 2 (TMPRSS2) as a mediator in its proteolytic processing[5] Estrogen hormone has an effect on downregulating ACE and upregulating ACE2 and Angiotensin 2 receptors.[7] Because the hormone estrogen increases the production of ACE2/Angiotensin 1-7 so that serum ACE2 activity in women is higher than in men[6] This can directly inhibit the replication of COVID-19[8] The hormone estrogen also inhibits TMPRSS2 in promoting the entry of the virus into cells, which in turn causes high concentrations of soluble ACE2 so that it can neutralizes COVID-19 and prevents it from attaching to ACE2.[9]

Men and women both have the hormone estrogen but with different levels, namely men with lower levels of the hormone estrogen than women. Menopausal women experience decreased levels of the hormone estrogen so that it also affects their immune system which will result in a poor prognosis due to COVID-19 infection. In contrast, nonmenopausal women still have sufficient levels of estrogen to fight viruses that enter the body. Estrogen can not only be produced naturally by the body, but can also come from hormone replacement therapy. So that postmenopausal women can take hormone replacement therapy in the hope of reducing the risk of worsening conditions and even death from COVID-19.

B. THE ESTROGEN HORMONE HASN'T AFFECT THE RECOVERY OF FEMALE WITH COVID-19

Estrogen is known to have no significant effect on recovery due to several other influencing factors, including age)[22], [24],. Body Mass Index (BMI))[22], [24],, comorbid disease[22], [25]and habits smoking[25]

Age affects the severity of the condition of the disease because the older the immune function decreases so that old age shows more severe conditions than young age. [26] This is in line with research by Zhao, et al (2020) which states that elderly individuals will experience lymphopenia and a 3-fold risk of developing severe conditions due to COVID-19, because lymphocytes also affect the prognosis of a disease. Similar to body mass index, research conducted by Cai et al. (2020) stated that COVID-19 patients who are overweight are 1.84 times more likely to have a severe condition, while obese COVID-19 patients have a 3.40 times greater risk of developing severe conditions than COVID-19 patients who are overweight. normal body.

Apart from obesity, smoking can have an impact on health, especially on the lungs and heart (Nadia, 2016). Regarding ACE2 as a binding site for the COVID-19 virus, smoking can cause upregulation of ACE2 expression[27] This is in line with studies by Chertok (2020) and Adrish et al. (2020) which states that a more serious and fatal prognosis occurs in COVID-19 patients who smoke than non-smokers. Obesity and smoking can both cause side effects on health, namely the emergence of comorbidities such as diabetes, hypertension, heart disease, stroke, and chronic obstructive pulmonary disease[28]

The hormone estrogen affects the different prognosis due to COVID-19 infection, but there are other things that cause the estrogen hormone to have no effect. Other things include age, body mass index, comorbidities, and smoking habits. These four things can be interrelated with each other in influencing the prognosis of COVID-19 infection. Older people are more susceptible to being infected with COVID-19 and experiencing severe conditions due to decreased organ function. Comorbid conditions will further aggravate the condition, coupled with smoking habits where the possibility of breathing problems and having an excess body mass index will clearly experience complications of the disease and are more likely to die when infected with COVID-19.

Men and women when they enter old age will both experience a decrease in the function of their organs and have congenital diseases. While the excess body mass index and smoking habits tend to be male. So that more in-depth research is needed regarding the variables of the hormone estrogen, age, body mass index, comorbidities, and smoking habits on the effect of COVID-19 prognosis.

V. CONCLUSION

The hormone estrogen can affect the recovery of women with COVID-19, especially in women of childbearing age, have a normal body mass index, do not have comorbid diseases and do not smoke. Health workers can use the levels of the female hormone estrogen in early detection of the prognosis of COVID-19. However, further research is needed on the effect of the hormone estrogen by measuring the levels of the hormone estrogen and a larger and homogeneous sample so that it is clearer how big the effect is.

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