Meta-Analysis Correlation between Dementia and the Risk of Mortality in COVID-19 Patients

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ABSTRACT

Background: Dementia is a common cause of morbidity and mortality in the elderly population. The elderly have a higher risk when exposed to COVID-19, especially if they have serious medical conditions such as dementia (senility). The purpose of this study was to determine the effect of dementia on the risk of mortality in COVID-19 patients based on previous primary studies.

Subject and Method This research is a systematic review and meta-analysis study using PRISMA diagrams. The article search was conducted based on the eligibility criteria using the PICO Model. P: COVID-19 patients, I: dementia, C: no dementia, O: mortality. The articles used were from 3 databases, namely Pubmed, Google Scholar and Science Direct. The search keywords for articles were as follows: dementia AND (death OR Mortality) AND COVID-19 OR Sars-Cov-2. The inclusion criteria in this study include full text articles with cohort study designs, full text available articles, the size of the relationship used is the adjusted Odds Ratio or Risk Ratio, the year the article used is in the 2019-2022 range and the research outcome is mortality. Articles were analyzed using the Review Manager 5.3 application.

Results: There are 9 articles in this study from New York, United States, Spain, Korea with 2 articles, and England with 4 articles. The article was analyzed using the PRISMA flow diagram. The results of the study show that COVID-19 patients with dementia have a mortality risk of 2.02 times greater than COVID-19 patients without dementia. These results were statistically significant (aOR= 2.19; 95% CI = 1.48 to 2.75; p<0.001).

Conclusion: Dementia increases the risk of mortality from COVID-19

Keywords: Dementia, mortality, COVID-19, SARS-COV-2

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BACKGROUND

Coronavirus Disease 2019 (COVID-19) is a disease caused by a new type of coronavirus, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which was first reported in December 2019 in the city of Wuhan, China. The transmission and spread of COVID-19 to various cities and countries occurred in a fairly short time, so

WHO designated this case as an Emergency of International Concern (PHEIC)/Public Health Emergency that is troubling the world (KMMD) which is troubling the world then COID-19 was declared as pandemic in March 2020 (WHO, 2021).

The manifestations of Corona Virus Disease (COVID-19) infection are non-specific and varied, ranging from mild and

uncomplicated manifestations, mild-to-severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), to Sepsis Shock. Symptoms and signs of an upper respiratory tract infection such as sore throat or rhinorrhea. The most common symptoms found in hospitalized patients are fever, dry cough, fatigue dyspnea, and myalgia (Huang et al., 2020)

Dementia is a common cause of morbidity and mortality in the elderly population. The elderly have a higher risk when exposed to COVID-19, especially if they have serious medical conditions such as dementia (senility). The elderly are more at risk of experiencing more serious COVID-19 symptoms and requiring hospitalization, requiring intensive care, or dying. Currently, several studies have shown dementia to be a comorbid factor for COVID-19 (Nelis et al., 2019).

According to The Alzheimer's Association, an estimated 5.8 million Americans are 65 years or older and 50 million people worldwide live with dementia. In Indonesia, it is estimated that there are around 1.2 million people with dementia in 2015, which will increase to 2 million in 2030 and 4 million people in 2050. Research data in Yogyakarta shows that around 20 percent of the elderly experience memory disorders that interfere with daily life (Alzheimer's Indonesia, 2021).

Strong risk factors for cognitive decline and dementia include cardiovascular disease, diabetes, obesity, and hypertension (Baumgart et al., 2015).

Dementia is caused by damage to certain parts of the brain's nerve cells, reducing the ability to communicate with the rest of the body's nerves, and causing symptoms to appear according to the area of the brain that is damaged, which allows bacteria and viruses to more easily access the brain and makes the patient more susceptible to bacterial infections viruses and fungi. In addition, memory impairment associated with dementia may impair a patient's ability to comply with COVID-19 precautions such as social distancing, wearing masks, and frequent hand washing (Iadecola et al., 2016).

SARS-CoV2 has also been shown to affect the brain directly with reports of encephalitis, thrombotic events, and brain invasion. An early sign of the disease is the loss of the senses of taste and smell. In addition, the brain is affected by organ failure elsewhere (eg, heart or lung), and hypoxemia is a hallmark of severe infection, and in itself can lead to cerebral edema and brain damage. Therefore, dementia is a factor of dementia morbidity and mortality (Mayeda et al., 2016).

Based on the description above, researchers are interested in conducting research through a systematic review and Meta-Analysis approach to investigate relevant epidemiological studies in order to assess the influence of dementia on the risk of mortality in COVID-19 patients. Studies with large populations and locations are urgently needed to determine whether there is an influence of dementia on the risk of mortality in COVID-19 patients, especially using a Meta Analysis approach that has never been done before.

SUBJECTS AND METHOD

1. Study Design

This study was conducted using a systematic review and meta-analysis using secondary data, where the data were obtained from the results of previous studies. Article searches were carried out using 3 databases, namely: Pubmed, Google Scholar, and Science Direct, with the year the article was published in 2019-2022. Article searches were conducted using the following keywords:

"dementia AND (death OR Mortality) AND COVID-19 OR Sars-Cov-2".

2. Steps in Conducting Meta-Analysis

Meta-analysis was conducted through five steps, as follow:

a. Formulate research questions in PICO (Population, Intervention, Comparison and Outcome)
b. Search for primary study articles from various databases (Google Scholar, Pubmed and Springerlink)
c. Perform screening and conduct critical quality primary studies
d. Perform data extraction and enter the estimated effect of each primary study into the RevMan 5.3 application
e. Interpret the result and draw conclusion

Assessment of research quality was carried out using the Checklist for critical appraisal for cohort study (Survey) sourced from the Center for evidence based management (CEBMa) (2014) which consisted of 11 questions, these questions were answered by giving a score of 0: no and 1: yes. Primary studies are carried out if the total score is at least 10, then input into RevMan.

3. Inclusion Criteria and Exclusion Criteria

The inclusion criteria in this study include full text articles with cohort study designs, full text available articles, the size of the relationship used is the adjusted Odds Ratio or Risk Ratio, the year the article used is in the 2019-2022 range and the research outcome is mortality.

Exclusion criteria in this study include published articles in languages other than English, experimental studies, and articles used before 2019.

4. Study Variables

The independen variables is Dementia and the dependen variable is Covid-19 Patient Mortality

5. Operational Definition of Variables

Dementia is a condition with a decrease in a person's cognitive and functional abilities, which can occur later in life due to neuro-degenerative and cerebrovascular processes. Categorized with dementia and not dementia.

COVID-19 Patient Mortality is the death of a person caused by COVID-19. Categorized by dead and alive groups.

6. Study Instrument

The instrument used in the study was Critical Appraisal Checklist from a cohort study (survey) from the Center for evidence-based management (CEBMa) (2014).

The following are indicators in critical appraisal:

1. Can the cohort research method answer the research question?
2. Did the subject matter enough to determine that the findings did not occur by chance?
3. Was the cohort selection based on objective and validated criteria?
4. Is the cohort representative of the defined population?
5. Were the observations made in sufficient time?
6. Are objective and unbiased outcome criteria used?
7. Are effect sizes practically relevant?
8. Is there a belief intervention provided?
9. Have confounding factors been taken into account?
10. Does this research address a clearly focused problem?
11. Can the results be applied to your research?

7. Data Analysis

Articles that were selected based on pre-determined criteria were then analyzed based on variations between studies with the fixed effect model analysis model and the random effects model using Revman 5.3 software. by the Cochrane collaboration. The function of the Revman software is to calculate the overall Or value by describing

the 95% Confidence Interval (CI) using an effects model and data heterogeneity.

RESULTS

Research on the effect of dementia on the risk of mortality in COVID-19 patients contains 9 articles. The articles come from New York, United States, Spain, Korea with 2 articles, and England with 4 articles. The article review process is carried out using a PRISMA flow diagram, with the search flow as follows.

Article searchs were conducted using 3 data base. The data base are; google scholar, pubmed, and science direct. The keywords used in the search process were related to dementia and COVID-19 or SARS-COV-2. Based on the occurrence of the COVID pandemic, the researcher limits the articles, namely articles published in 2019 to 2022. Researchs limit English articles to locations around the world, not only in Indonesia.

After conducting an initial search on the database, 1,215 articles were found, then 422 published duplicate articles were deleted to obtain 793 articles. Followed by the article selection process by issuing as many as 525 so that there are still 47 full text articles that are considered feasible. Then as many as 31 full text articles were issued, leaving 9 final articles that will be included in a qualitative synthesis. This is shown in Figure 1 PRISMA flow.
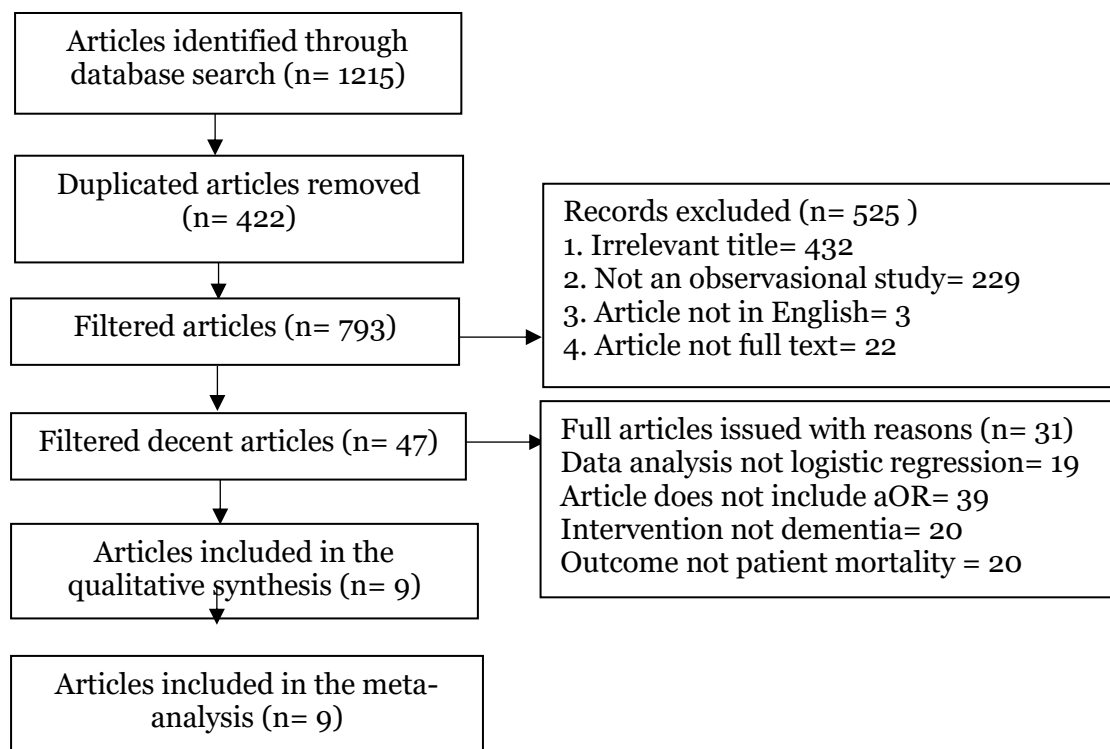
Figure 1. PRISMA Flowchart

Figure 2. Study Map Area Correlation between Dementia and the Risk of Mortality in COVID-19 Patients

Figure 2 is a map of the distribution of research article locations. The articles contained in the review process are articles from 3 continents. The search results obtained 9 articles with search locations around the world. The article is then assessed to determine its quality using an examination draft from a cohort study (survey). The assessment criteria consisted of 11 questions with each question given a score of 0 = if you answered no, and 1 = if you answered yes.

a. Forest Plot

Forest plot in Figure 3 indicates that there was an effect effect of dementia on mortality of COVID-19 patients. COVID-19 patients with dementia had a mortality risk of 2.02 times compared with COVID-19 patients without dementia, and the effect was statistically significant (aOR= 2.02; 95% CI= 1.48 to 2.75; p<0.001). The distribution of effect estimates between studies in this meta-analysis was high (I^2 = 83%). Thus, the overall effect estimation is calculated using the Random Effect Model approach.

b. Funnel plot

Funnel plot in figure 4 shows that the distribution of effect estimates tends to be more to the right of the mean vertical line of effect estimates than to the left. Thus the funnel plot indicates that there is publication bias. Because the distribution of effects in the funnel plot lies to the right of the vertical line in the same direction as the average effect estimate on the forest plot image, the publication bias indicates an overestimation (true effect).

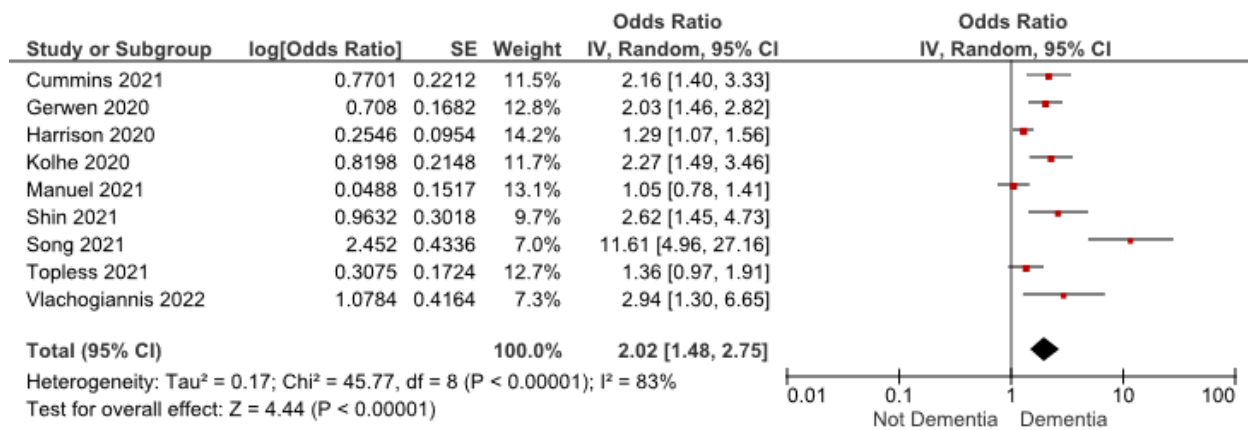**Table 1. Description of Primary Studies included in Meta-analysis**

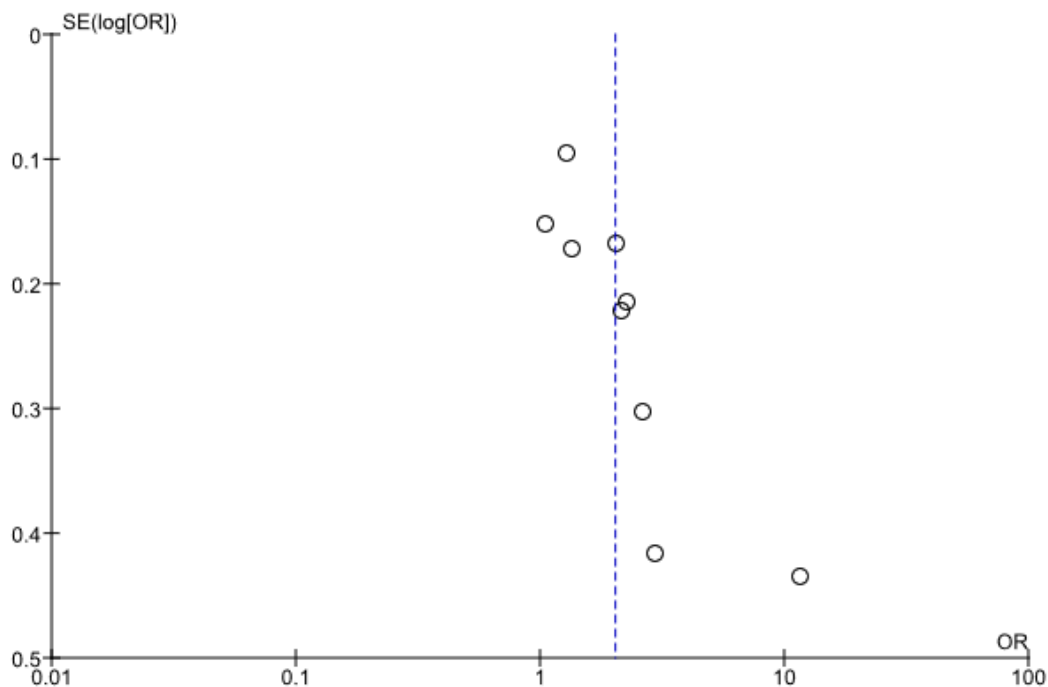| No	Author (Year)	Country	Study Design	Sample	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	aOR (95 % CI)
1	Cummins et al. (2021))	English	Retrospective cohort	1781	Adult inpatient nurse confirmed COVID-19	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	2.03 (1.46-2.83)
2	Gerwen et al. (2020)	New York	Retrospective cohort	3703	Laboratory adult patient confirmed COVID-19	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	2.03 (1.46-2.83)
3	Harrison et al. (2020	United States of America	Retrospective cohort	31,461	Adult patient confirmed COVID-19	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	1.29 (1.07-1.56)
4	Kolhe et al. (2020)	English	Retrospective cohort	4759	Inpatient confirmed COVID-19	COVID-19 patients with dementia	COVID-19 patients not with dementia than average	Mortality	2.27 (1.49-3.44)
5	Manuel et al. (2021)	Spanish	Retrospective cohort	2771	Elderly inpatient confirmed COVID-19	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	1.05 (0.78-1.41)
6	Shin et al (2021)	Korea	Retrospective cohort	5771	Inpatient confirmed COVID-19	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	2.62 (1.45-4.72)
7	Song et a.l (2021)	Korea	Retrospective cohort	5621	Laboratory adult patient confirmed COVID-19	COVID-19 patients with dementia	Body size COVID-19 patients not with dementia	Mortality	11.612 (4.964-27.855)
8	Topless et al. (2021)	English	Retrospective cohort	473,139	Hospitalized COVID-19 patients	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	1.36 (0.97-1.90)
9	Vlachogiannis et al. (2022)	English	Retrospective cohort	471	COVID-19 confirmed patient	COVID-19 patients with dementia	COVID-19 patients not with dementia	Mortality	2.94 (1.30-6.65)

Table 2. Assessment of the quality of research articles on the influence of dementia on mortality in COVID-19 patients

No	Quetions	Cuumins et al (2021)	Gerwen et al (2020)	Harrison et al (2020)	Kolheet al (2020)	Manuel et al (2021)	Shin et al (2021)	Song et al (2021)	Topless et al. (2021)	Vlachogiannis et al (2022)
1	Can the cohort research method answer the research question?	1	1	1	1	1	1	1	1	1
2	Did the subject matter enough to determine that the findings did not occur by chance?	1	1	1	1	1	1	1	1	1
3	Was the cohort selection based on objective and validated criteria?	1	1	1	1	1	1	1	1	1
4	Is the cohort representative of the defined population?	1	1	1	1	1	1	1	1	1
5	Were the observations made in sufficient time?	1	1	1	1	1	1	1	1	1
6	Are objective and unbiased outcome criteria used?	1	1	1	1	1	1	1	1	1
7	Are effect sizes practically relevant?	1	1	1	1	1	1	1	1	1
8	Is there a belief intervention provided?	1	1	1	1	1	1	1	1	1
9	Have confounding factors been taken into account?	1	1	1	1	1	1	1	1	1
10	Does this research address a clearly focused problem?	1	1	1	1	1	1	1	1	1
11	Can the results be applied to your research?	1	1	1	1	1	1	1	1	1
	Total	11	11	11	11	11	11	11	11	11

Answer: 1=Yes, 0=No.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Cummins 2021	0.7701	0.2212	11.5%	2.16 [1.40, 3.33]	
Gerwen 2020	0.708	0.1682	12.8%	2.03 [1.46, 2.82]	
Harrison 2020	0.2546	0.0954	14.2%	1.29 [1.07, 1.56]	
Kolhe 2020	0.8198	0.2148	11.7%	2.27 [1.49, 3.46]	
Manuel 2021	0.0488	0.1517	13.1%	1.05 [0.78, 1.41]	
Shin 2021	0.9632	0.3018	9.7%	2.62 [1.45, 4.73]	
Song 2021	2.452	0.4336	7.0%	11.61 [4.96, 27.16]	
Topless 2021	0.3075	0.1724	12.7%	1.36 [0.97, 1.91]	
Vlachogiannis 2022	1.0784	0.4164	7.3%	2.94 [1.30, 6.65]	
Total (95% CI)			**100.0%**	**2.02 [1.48, 2.75]**	

Heterogeneity: Tau² = 0.17; Chi² = 45.77, df = 8 (P < 0.00001); I² = 83%
Test for overall effect: Z = 4.44 (P < 0.00001)

0.01 0.1 1 10 100
Not Dementia   Dementia

Figure 3. Forest Plot of the effect of dementia on mortality of COVID-19 patients

Figure 4. Funnel plot of the effect of dementia on mortality of COVID-19 patients

DISCUSSION

Corona Virus or Severe Acute Respiratory Syndrome Coronavirus 2 (SARS Cov-2) is a virus that attacks the respiratory system. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS)-CoV 2 or better known as the Corona virus is a new variant of the virus that is transmitted to humans. This virus can infect everyone, from the elderly, adults, children, even babies, pregnant and lacta- ting women can. The virus can cause respi- ratory problems, both mild to death (Handayani, 2020).

The manifestations of Corona Virus Disease (COVID-19) infection are non-spe- cific and varied, ranging from mild and uncomplicated manifestations, mild-to-se- vere pneumonia, Acute Respiratory Distress Syndrome (ARDS), to Sepsis Shock. The most common symptoms found in hospi- talized patients are fever, dry cough, fatigue

dyspnea, and myalgia. These symptoms are also more experienced by people with morbidity factors that affect the risk of mortality (Chakraborty et al., 2020).

Dementia is a common cause of morbidity and mortality in the elderly population (Munawaroh et al., 2021). Dementia is a syndrome of decreasing a person's cognitive and functional abilities, which can occur later in life due to neurodegenerative and cerebrovascular processes (Killin, 2016). The elderly are more at risk of experiencing more serious COVID-19 symptoms and requiring hospitalization, requiring intensive care, or dying. When sick, older adults with dementia are also more likely to exhibit behavioral disorders, which can make the family more anxious and stressed. In addition, most people with dementia live with one or two additional chronic health conditions. Currently, several studies have shown dementia to be a comorbid factor for COVID-19 (Nelis et al., 2019).

Dementia also causes nerve cell damage in certain parts of the brain. This also affects the communication process between the body's nerve cells which allows bacteria and viruses to more easily access the brain so that they are more easily infected with bacteria, viruses, and fungi (Iadecola et al., 2016). The decline in cognitive abilities can certainly affect the pattern of life and its nature. For example: forgetting to wear a mask, not doing social distancing to people, and not limiting other mobility activities that make a person with dementia more susceptible to viruses and other bacteria.

This study builds on the theme of the influence of dementia on mortality in COVID-19 patients. The variables analyzed consisted of the dependent variable and the independent variable. The dependent variable is the mortality of COVID-19 patients, while the independent variable is dementia. This study uses a systematic review and meta-analysis. Meta-analysis is a type of epidemiological study in which results from different types of independent primary studies are statistically combined on the same test and in the same way to obtain quantitative results. The steps taken followed normal research procedures.

The research design is a systematic study and meta-analysis. Systematic reviews have the advantage of integrating adverse events from independently conducted studies to reduce trends. In this study, a systematic review involves a meta-analysis process. Meta-analysis is a statistical technique used to synthesize data from various qualitative studies so that a summary measure is produced (Uman, 2011). This includes the problem, the quality and diversity of the data analyzed, trends and employment opportunities, and the extent to which research findings can be resolved (Egger & Smith in Murti, 2018).

The purpose of this study was to obtain conclusions from various primary studies regarding the effect of dementia on mortality in COVID-19 patients. This research is considered important considering that the elderly have a high risk of being infected with COVID-19, so the impact on the number of relevant research that can be accessed is still small and has data access problems (data duplication). The most frequently reported statistical results are in percent and bivariate analysis, ie confounding factors are not controlled by the researcher.

Confounding factors that affect the relationship or effect of exposure to the occurrence of a disease by the study are not the same as the actual effect or relationship on the target population, or in other words the results of the study are not true or valid (Murti, 2018). This systematic review and meta-analysis research use research that controls for confounding factors that can be

seen from the inclusion criteria of the multivariate analysis study and the reported systematic results, namely the adjusted odd ratio (aOR). The application used in processing data from various primary studies uses Review manager 5.3 (RevMan 5.3). the results of processing are presented in the form of forest plots and funnel plots.

This study uses an article with an observational design. The forrest plot results showed that COVID-19 patients with dementia experienced a 2.02 times mortality risk and the results were statistically significant (aOR= 2.02; 95% CI= 1.48 to 2.75; p<0.001) compared to COVID-19 patients without dementia.

The results of this study are supported by the research of Gerwen et al. (2020) who conducted a study from March 1 to April 1, 2020 identified through electronic medical record systems throughout the New York City health system, stated that COVID-19 patients with dementia had a mortality risk of 2.03 times compared to COVID-19 patients without dementia (aOR=2.03 95% CI= 1.46 to 2.83).

While the results of the funnel plot indicate that this study has publication bias because the distribution of effect estimates tends to be located on the right side of the average vertical line of effect estimates than on the left. In addition, the distribution of effects on the funnel plot lies to the right of the vertical line in the same direction as the average effect estimate on the forest plot image, so the publication bias indicates an overestimation of the (true effect).

Based on heterogeneity, this study used a statistical random effect model, obtained heterogeneity in this study of $I^2 = 83\%$. Therefore, the heterogeneity in this study is high. In addition, it can also be interpreted that there are various studies used from populations from different countries including New York, the United States,

Spain, 2 from Korea, and 4 from the United Kingdom. The population in this study came from different countries, so the heterogeneity in this study was also influenced by the size and age of the sample used, the results showed that the p value <0.001.

Dementia is a condition that can increase the risk of mortality in COVID-19 patients. Therefore, research that examines the effect of dementia on the risk of mortality in COVID-19 patients can help several health workers and policy makers to improve health care facilities, so that good health services are established so as to prevent the risk of mortality due to COVID-19 in patients. with dementia.

AUTHORS CONTRIBUTION

Ulya Khoirunnisa' Atin is the main researcher who chooses topics, searches for, and collects research data. Bhisma Murti and Hanung Prasetya analyzed and reviewed research documents.

CONFLICT OF INTEREST

There is no conflict of interest in the study.

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