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Contents lists available at ScienceDirect

## Archives of Gerontology and Geriatrics

journal homepage: [www.elsevier.com/locate/archger](http://www.elsevier.com/locate/archger)

# Dementia and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: A systematic review and meta-analysis

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## ARTICLE INFO

## Keywords:

Coronavirus disease 2019  
Covid-19  
Dementia  
Memory disturbance  
Neurologic disease

## ABSTRACT

**Background:** The number of positive and death cases from coronavirus disease 2019 (COVID-19) is still increasing until now. One of the most prone individuals, even in normal situations is patients with dementia. Currently, no study provides clear evidence regarding the link between dementia and COVID-19. This study aims to analyze the relationship between dementia and poor outcomes of COVID-19 infection.

**Materials and Methods:** We systematically searched the PubMed and Europe PMC database using specific keywords related to our aims until October 25th, 2020. All articles published on COVID-19 and dementia were retrieved. The quality of the study was assessed using the Newcastle Ottawa Scale (NOS) tool for observational studies. Statistical analysis was done using Review Manager 5.4 software.

**Results:** A total of 24 studies with 46,391 dementia patients were included in this meta-analysis. This meta-analysis showed that dementia was associated with composite poor outcome [RR 2.67 (95% CI 2.06 – 3.47),  $p < 0.00001$ ,  $I^2 = 99%$ , random-effect modeling] and its subgroup which comprised of risk of COVID-19 infection [RR 2.76 (95% CI 1.43 – 5.33),  $p = 0.003$ ,  $I^2 = 99%$ , random-effect modeling], severe COVID-19 [RR 2.63 (95% CI 1.41 – 4.90),  $p = 0.002$ ,  $I^2 = 89%$ , random-effect modeling], and mortality from COVID-19 infection [RR 2.62 (95% CI 2.04 – 3.36),  $p < 0.00001$ ,  $I^2 = 96%$ , random-effect modeling].

**Conclusions:** Extra care and close monitoring should then be provided to patients with dementia to minimize the risk of infections, preventing the development of severe and mortality outcomes.

## 1. Introduction

World Health Organization (WHO) first declared coronavirus disease 2019 (COVID-19) as a pandemic in March 2020, and now, seven months after that, the number of positive and death cases are still increasing. This global pandemic has caused a significant impact on health, social, and economic aspects around the world. Thus, identification of the risk factors that contribute to the development of severe infections is important to enabling risk stratification, optimizing the hospital resources reallocation, and guiding public health recommendations and interventions. (T. I. Hariyanto & Kurniawan, 2020) Several comorbidities have been demonstrated to be associated with severe COVID-19 outcomes such as hypertension, diabetes, dyslipidemia, anemia, cardiovascular disease, thyroid disease, and pulmonary disease. (T. I.

Hariyanto & Kurniawan, 2020, 2020; Huang et al., 2020; Kwenandar et al., 2020) During normal times, individuals with dementia are the most vulnerable persons as they depend on other people for their day to day survival. In a previous study, it has been shown that dementia increases the risk of morbidity and mortality among hospitalized patients, including the severity of the respiratory disease. (Liao et al., 2015) Unfortunately, until now, no study provides clear evidence regarding the link between dementia and COVID-19. This article aims to explore the potential association between dementia and poor outcomes of COVID-19 infection.

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<https://doi.org/10.1016/j.archger.2020.104299>

Received 4 November 2020; Received in revised form 14 November 2020; Accepted 17 November 2020

Available online 19 November 2020

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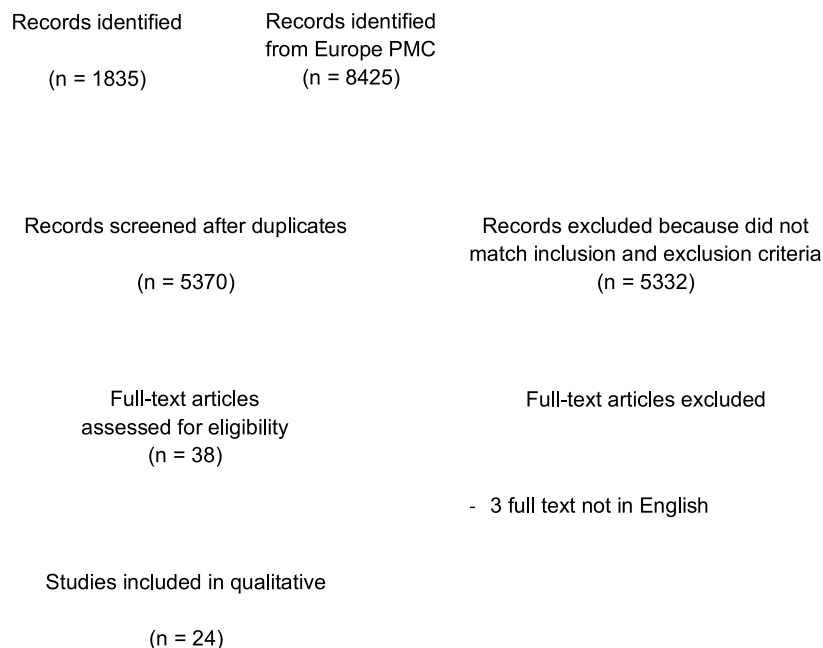


Fig. 1. PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

## 2. Materials and methods

### 2.1. Eligibility criteria

Studies were included in this review if met the following inclusion criteria: representation for clinical questions (P: positive/confirmed cases of COVID-19; I: a group of patients with dementia as their comorbidity; C: a group of patients without dementia; O: composite poor outcomes which comprise of risk of COVID-19 infection, severe COVID-19, and mortality), type of study was a randomized control trial, cohort, clinical trial, case-cohort, and cross-over design, and if the full-text article was available. The following types of articles were excluded: articles other than original research (e.g., review articles, letters, or commentaries); case reports; articles not in the English language; articles on research in pediatric populations (17 years of age or younger); and articles on research in pregnant women.

### 2.2. Search strategy and study selection

A systematic search of the literature was conducted on PubMed and Europe PMC using the keywords "dementia" OR "major cognitive impairment" OR "clinical characteristics" OR "comorbidities" OR "risk factors" AND "coronavirus disease 2019" OR "COVID-19", between 2019 and present time (October 25th, 2020) with language restricted to English only. The title, abstract, and full text of all articles identified that matched the search criteria were assessed, and those reporting the rate of dementia in COVID-19 patients with a clinically validated definition of "severe disease" and "mortality" were included in this meta-analysis. The references of all identified studies were also analyzed (forward and backward citation tracking) to identify other potentially eligible articles. The study was carried out per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (Moher, Liberati, Tetzlaff & Altman, 2009)

### 2.3. Data extraction and quality assessment

Data extraction was performed independently by two authors, we used standardized forms that include author, year, study design, number of participants, age, gender, number of patients with dementia, and proportion of patients with each outcome of COVID-19.

The outcome of interest was the composite poor outcome that comprised of risk of COVID-19 infection, severe COVID-19, and mortality. The risk of COVID-19 infection was defined as the likelihood of someone getting contracted by COVID-19. Severe COVID-19 was defined as patients who had any of the following features at the time of, or after, admission: (1) respiratory distress ( $\geq 30$  breaths per min); (2) oxygen saturation at rest  $\leq 93\%$ ; (3) ratio of the partial pressure of arterial oxygen (PaO<sub>2</sub>) to a fractional concentration of oxygen inspired air (fIO<sub>2</sub>)  $\leq 300$  mmHg; or (4) critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) or admission into ICU. Mortality outcome from COVID-19 was defined as the number of patients who were dead because of COVID-19 infection.

Two investigators independently evaluated the quality of the included cohort and case-control studies using the Newcastle–Ottawa Scale (NOS). (Margulis et al., 2014) The selection, comparability, and exposure of each study were broadly assessed and studies were assigned a score from zero to nine. Studies with scores  $\geq 7$  were considered of good quality.

### 2.4. Statistical analysis

A meta-analysis was performed using Review Manager 5.4 (Cochrane Collaboration) software. Dichotomous variables were calculated using the Mantel-Haenszel formula with a random-effects model regardless of heterogeneity. The effect estimate was reported as risk ratio (RR) along with its 95% confidence intervals (CIs) for dichotomous variables, respectively. P-value was two-tailed, and the statistical significance was set at  $\leq 0.05$ . Subgroup analysis was performed for each component of composite poor outcomes. We performed Begg's funnel-plot analysis to qualitatively assess the risk of publication bias.

## 3. Results

### 3.1. Study selection and characteristics

A total of 10,260 records were obtained through systematic electronic searches. After the removal of duplicates, 5370 records remained. A total of 5332 records were excluded after screening the titles/abstracts because they did not match our inclusion and exclusion criteria. After evaluating 38 full-texts for eligibility, 6 full-text articles were excluded

**Table 1**  
Characteristics of included studies.

Study	Sample size	Design	Outcome	Age (years)	Dementia patients n (%)	Non-dementia patients n (%)
Atkins et al. (2020)	269,070	Retrospective cohort	Risk of infection	73.1 ± 4.4	888 (0.3%)	268,182 (99.7%)
Bianchetti et al. (2020)	627	Retrospective cohort	Mortality	70.7 ± 12.9	82 (13.1%)	545 (86.9%)
Covino et al. (2020)	69	Retrospective cohort	Mortality	85 ± 5.1	8 (11.6%)	61 (88.4%)
Docherty et al. (2020)	20,133	Prospective cohort	Mortality	70.9 ± 17.7	2360 (13.5%)	15,099 (86.5%)
Giorgi Rossi et al. (2020)	2653	Prospective cohort	Mortality	54.7 ± 18.3	107 (4%)	2546 (96%)
Harrison et al. (2020)	31,461	Retrospective cohort	Mortality	49.3 ± 20.7	1031 (3.3%)	30,430 (96.7%)
Hong et al. (2020)	98	Retrospective cohort	Severity	55.4 ± 17.1	3 (3.1%)	95 (96.9%)
Hwang et al. (2020)	103	Retrospective cohort	Mortality	67.6 ± 15.3	11 (10.6%)	92 (89.4%)
Jang et al. (2020)	110	Retrospective cohort	Severity	56.9 ± 17	4 (3.6%)	106 (96.4%)
Ji et al. (2020)	7341	Case-control	Severity	47 ± 19	368 (5%)	6973 (95%)
Kabarriti et al. (2020)	5902	Retrospective cohort	Mortality	48.3 ± 20.4	303 (5.1%)	5599 (94.9%)
Knights et al. (2020)	108	Retrospective cohort	Mortality	68.7 ± 1.5	16 (15%)	92 (85%)
Kokoszka-Bargiel et al. (2020)	53	Retrospective cohort	Mortality	62.4 ± 10.4	12 (22.6%)	41 (77.4%)
Lee et al. (2020)	694	Retrospective cohort	Severity	52.1 ± 18.2	10 (1.4%)	684 (98.6%)
Miyashita et al. (2020)	2071	Retrospective cohort	Mortality	68.5 ± 12.7	98 (4.7%)	1973 (95.3%)
Mohamed et al. (2020t)	144,297	Retrospective cohort	Risk of infection	75.8 ± 12.5	23,961 (16.6%)	120,336 (83.4%)
Moon et al. (2020)	352	Retrospective cohort	Mortality	55.6 ± 25.1	35 (9.9%)	317 (90.1%)
Nystad et al. (2020)	4118,831	Retrospective cohort	Risk of infection	53.8 ± 15.1	15,190 (0.4%)	4103,641 (99.6%)
Poblador-Plou et al. (2020)	4412	Retrospective cohort	Mortality	63.3 ± 18.1	468 (10.6%)	3944 (89.4%)
Rozenfeld et al. (2020)	34,503	Retrospective cohort	Risk of infection	61.5 ± 13.4	1039 (3%)	33,464 (97%)
Sapey et al. (2020)	2217	Retrospective cohort	Mortality	71.6 ± 19.2	326 (14.7%)	1891 (85.3%)
Sung et al. (2020)	3060	Retrospective cohort	Severity	42 ± 22.9	65 (2.5%)	2621 (97.5%)
Wan et al. (2020)	30	Retrospective cohort	Mortality	64.2 ± 14.7	5 (16.6%)	25 (83.4%)
Yang et al. (2020)	52	Retrospective cohort	Mortality	59.7 ± 13.3	1 (1.9%)	51 (98.1%)

**Table 2**  
Newcastle-Ottawa quality assessment of observational studies.

First author, year	Study design	Selection	Comparability	Outcome	Total score	Result
Atkins et al. (2020)	Cohort	***	**	***	8	Good
Bianchetti et al. (2020)	Cohort	**	**	***	7	Good
Covino et al. (2020)	Cohort	***	**	***	8	Good
Docherty et al. (2020)	Cohort	****	**	***	9	Good
Giorgi Rossi et al. (2020)	Cohort	***	**	***	8	Good
Harrison et al. (2020)	Cohort	***	**	***	8	Good
Hong et al. (2020)	Cohort	**	**	***	7	Good
Hwang et al. (2020)	Cohort	***	**	***	8	Good
Jang et al. (2020)	Cohort	***	**	***	8	Good
Ji et al. (2020)	Case-control	***	**	***	8	Good
Kabarriti et al. (2020)	Cohort	***	**	***	8	Good
Knights et al. (2020)	Cohort	**	**	***	7	Good
Kokoszka-Bargiel et al. (2020)	Cohort	***	**	***	8	Good
Lee et al. (2020)	Cohort	**	**	***	7	Good
Miyashita et al. (2020)	Cohort	**	**	***	7	Good
Mohamed et al., 2020t)	Cohort	**	**	***	7	Good
Moon et al. (2020)	Cohort	**	**	***	7	Good
Nystad et al. (2020)	Cohort	***	**	***	8	Good
Poblador-Plou et al. (2020)	Cohort	***	**	***	8	Good
Rozenfeld et al. (2020)	Cohort	***	**	***	8	Good
Sapey et al. (2020)	Cohort	****	**	***	9	Good
Sung et al. (2020)	Cohort	***	**	***	8	Good
Wan et al. (2020)	Cohort	***	**	***	8	Good
Yang et al. (2020)	Cohort	***	**	***	8	Good

because they do not have the control/comparison group, 5 full-text articles were excluded because they do not have the outcome of interest (risk of COVID-19 infection, severe COVID-19, and mortality), 3 full-text articles were excluded because the articles were not in English, and finally, 24 studies (Atkins et al., 2020; Bianchetti et al., 2020; Covino et al., 2020; Docherty et al., 2020; Giorgi Rossi et al., 2020; Harrison, Fazio-Eynullayeva, Lane, Underhill & Lip, 2020; Hong et al., 2020; Hwang, Kim, Park, Chang & Park, 2020; Jang et al., 2020; Ji et al., 2020; Kabarriti et al., 2020; Knights et al., 2020; Kokoszka-Bargiel, Cyprius, Rutkowska, Madowicz & Knapik, 2020; Lee et al., 2020; Miyashita et al., 2020; Mohamed et al., 2020t; Moon et al., 2020; Nystad et al., 2020; Poblador-Plou et al., 2020; Rozenfeld et al., 2020; Sapey et al., 2020; Sung et al., 2020; Wan et al., 2020; Yang et al., 2020) with a total of 4648,247 sample size and 46,391 dementia patients were included in the meta-analysis (Fig. 1). Of a total of 24 included studies, 21 were

retrospective cohort, 2 studies were prospective cohort, while the remaining 1 study was a case-control study. The essential characteristics of the included studies are summarized in Table 1.

### 3.2. Quality of study assessment

Studies with various study designs including cohort and case-control were included in this review and assessed accordingly with the appropriate scale or tool. Newcastle Ottawa Scales (NOS) were used to assess the cohort and case-control studies (Table 2). All included studies were rated 'good'. In conclusion, all studies were seemed fit to be included in the meta-analysis.

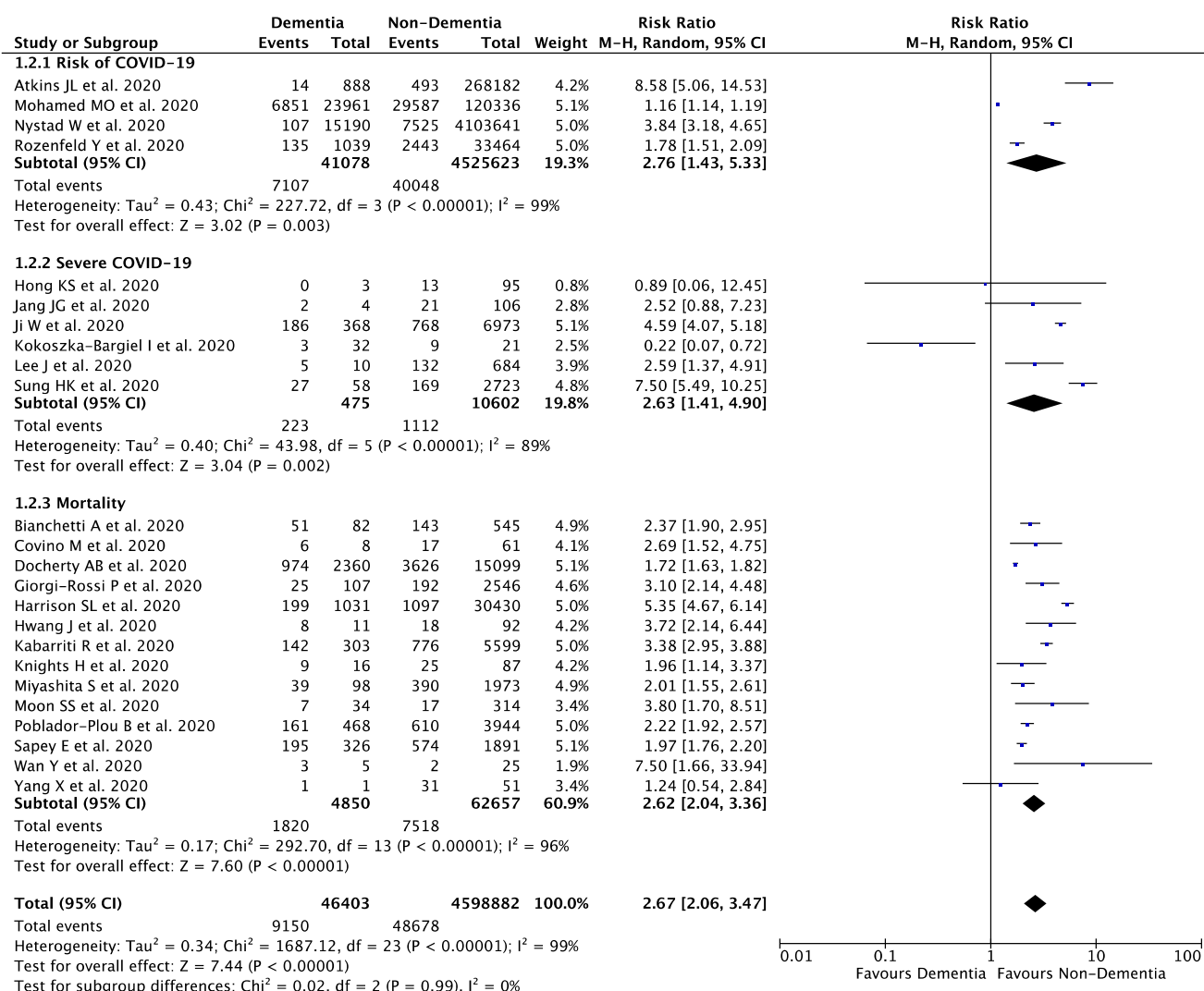


Fig. 2. Forest plot that demonstrates the association of dementia with composite poor outcome and its subgroup which comprises of risk of COVID-19 infection, severe COVID-19, and mortality.

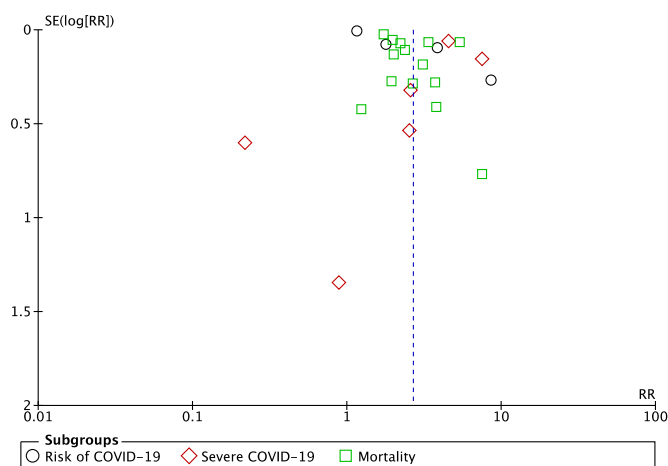


Fig. 3. Funnel plot analysis for the association of dementia with composite poor outcome of COVID-19.

### 3.3. Dementia and outcomes

Our pooled analysis showed that dementia was associated with composite poor outcome [RR 2.67 (95% CI 2.06 – 3.47),  $p < 0.00001$ ,  $I^2 = 99%$ , random-effect modeling] (Fig. 2). Subgroup analysis showed that dementia was associated with higher risk of COVID-19 infection [RR 2.76 (95% CI 1.43 – 5.33),  $p = 0.003$ ,  $I^2 = 99%$ , random-effect modeling], severe COVID-19 [RR 2.63 (95% CI 1.41 – 4.90),  $p = 0.002$ ,  $I^2 = 89%$ , random-effect modeling], and mortality from COVID-19 infection [RR 2.62 (95% CI 2.04 – 3.36),  $p < 0.00001$ ,  $I^2 = 96%$ , random-effect modeling].

### 3.4. Publication bias

The funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot for the association between dementia and composite poor outcome (Fig. 3), showing no indication of publication bias.

## 4. Discussion

Based on our pooled analysis of available data, dementia seems to be associated with an enhanced risk of severity and mortality from COVID-19 infection. Several reasons can be proposed to explain this result. First, most of the patients with dementia were old and have other comorbid

medical conditions that could increase the severity of infections. Older patients with COVID-19 infection tend to present with atypical symptoms. They may be afebrile with non-respiratory symptoms, such as delirium or isolated functional decline without any obvious physical symptoms. (D'Adamo, Yoshikawa & Ouslander, 2020) These atypical presentations of COVID-19 may impede the early recognition of the disease, increase COVID-19 spread, and mortality. Moreover, in a meta-analysis of 611,583 COVID-19 patients, age over 60 years was found to be a risk factor for disease progression. (Bonanad et al., 2020) This fact could be influenced by both the physiological aging process and, especially, the greater prevalence in older adult patients of frailty and comorbidities that contribute to a decrease in functional reserve that reduces intrinsic capacity and resilience and hinders the fight against infections. (Bonanad et al., 2020) Older people will have a condition called "immune senescence" which consist of (1) decreased neutrophil phagocytosis and oxidative burst; (2) decreased macrophages chemotaxis and phagocytosis; and (3) decreased number of peripheral naïve T and B cells which will lead to a reduced ability to respond to new antigen. (Aiello et al., 2019) Not only that, comorbidities such as cardiovascular disease, hypertension, and diabetes are highly prevalent in older adults and have been associated with worse outcomes in COVID-19. (Bonanad et al., 2020) Second, patients with dementia were associated with the ApoE e4 genotype. (Kuo, Pilling, Atkins, Kuchel & Melzer, 2020) ApoE itself has lipoprotein function and modulates the macrophage pro/anti-inflammatory phenotypes (Tudorache, Trusca & Gafencu, 2017) and is expressed by many cell types in the lung, including macrophages, type I and type II alveolar epithelial cells (Gordon et al., 2019), therefore it is possible that having one or two copies of ApoE4 can increase the risk of having severe COVID-19 infection by robust innate immune response and cytokine storm that results in acute respiratory distress syndrome (ARDS). Third, inflammation also plays an important role in the pathogenesis of dementia. In addition to amyloid protein, inflammatory molecules, including acute inflammatory reactants and inflammatory cytokines, have been found in the cerebrospinal fluid of dementia patients. (Kinney et al., 2018; Simone & Tan, 2011) These persistent inflammatory state of dementia patients may be the cause of the increased peripheral blood white blood cells (WBC) and neutrophil counts in dementia patients with COVID-19. (Harrison et al., 2020) On the other side, a meta-analysis study has shown that a high level of leukocyte counts and the high neutrophil-lymphocyte ratio was associated with a higher risk of developing severe COVID-19 and mortality from COVID-19. (Elshazli et al., 2020) Finally, people with dementia, due to the nature of their cognitive decline, would require the care and support of carers such as dementia caregivers in order to be able to follow healthcare and preventive measures such as wearing face masks and washing their hands with water and soap or hand sanitizers. (Suzuki et al., 2020) However, during this COVID-19 pandemic, the availability of caregivers becomes limited which may cause dementia patients unable to follow healthcare and preventive measures therefore making them posed a higher risk of contracting an infection from COVID-19. (Dang et al., 2020)

The limitation of this study is that the presence of confounding factors such as patients' age, other comorbid conditions, nutritional status, and daily medication that can affect the relationship between dementia and mortality from COVID-19 should still be considered. However, with this study, we hope that dementia can further be considered as an important factor and comorbidity in COVID-19 patients.

## 5. Conclusions and implications

Hence, patients with dementia should be given extra care and monitoring to minimize exposure to the virus. Physicians can use the telemedicine-based practice to provide care and evaluations for dementia patients to minimize their visit to the hospitals. Physicians and caregivers should also be engaged in close monitoring of dementia patients with suspected COVID-19, for early diagnosis and treatment to

avoid severe infections. The hospitals can provide Special Care Geriatric COVID-19 units for dementia and elderly patients who contract with COVID-19, which is filled with a team of mental health professionals (doctors, nurses, and psychological counselors), to give better care, more strict monitoring, and enable the healthcare providers in that units to focus only on the management of dementia patients so that the morbidity and mortality from COVID-19 can be reduced. Finally, dementia should be regarded as an important factor in future risk stratification models for COVID-19.

## Funding

None.

## CRediT authorship contribution statement

**Timotius Ivan Hariyanto:** Conceptualization, Data curation, Methodology, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Cynthia Putri:** Conceptualization, Data curation, Methodology, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jessie Arisa:** Conceptualization, Data curation, Methodology, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Rocksy Fransisca V. Situmeang:** Conceptualization, Visualization, Resources, Supervision, Writing - original draft, Writing - review & editing. **Andree Kurniawan:** Conceptualization, Visualization, Resources, Supervision, Writing - original draft, Writing - review & editing.

## Declaration of Competing Interest

None.

## Acknowledgement

None.

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