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Dementia as a Mortality Predictor among Older Adults with COVID-19: A Systematic Review and Meta-analysis of Observational Study

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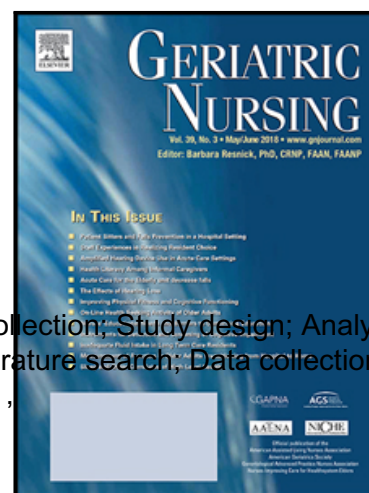
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Highlights

- Older adults with dementia who become infected with COVID-19 are at a higher risk of mortality in the short term
- Dementia patients are more likely to be immunocompromised and vulnerable to having diseases such as hypertension, diabetes, and pneumonia, especially dementia patients infected with COVID-19.
- Dementia is a strong predictor of mortality among older adults infected with COVID-19.

Journal Pre-proof

**Dementia as a Mortality Predictor among Older Adults with COVID-19: A Systematic Review and
Meta-analysis of Observational Study**

Running Head: Dementia and mortality among older adults with COVID-19

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Abstract

The purpose of this study was to systematically examine the association between dementia and mortality among older adults with COVID-19. To do so, we conducted a search of 7 databases for relevant full-text articles. A cohort study and case-control study were included. A meta-analysis was performed to synthesize the pooled odds ratio with a random-effects model. We identified studies that reported mortality among older adults with dementia and non-dementia who have COVID-19. The pooled mortality rates of dementia and non-dementia older adults infected with COVID-19 were 39% (95% CI: 0.23 – 0.54%, $I^2= 83.48\%$) and 20% (95% CI: 0.16 – 0.25%, $I^2= 83.48\%$), respectively. Overall, dementia was the main factor influencing poor health outcomes and high rates of mortality in older adults with COVID-19 infection (odds ratio 2.96; 95% CI 2.00 – 4.38, $I^2= 29.7\%$), respectively. Our results show that older adults with dementia with COVID-19 infection have a higher risk of mortality compared with older adults without dementia. This current study further highlights the need to provide focused care to the older adults with dementia or cognitive impairment who have COVID-19.

Introduction

It has been more than a year since COVID-19 was discovered in Wuhan, China, in late 2019. The COVID-19 pandemic has led in turn to approximately 68,055,468 cases globally and 1,553,150 deaths worldwide as of December 8, 2020 ¹. The disease continues to remain highly infective and to spread rapidly around the globe, resulting in relatively poor outcomes among older adults, those with comorbidities, and those who are immunocompromised. Older adults with dementia face difficulties in accessing and remembering accurate information about the disease, including information about protective measures to prevent COVID-19 infection such as wearing a mask and social distancing, thus putting them at a higher risk of becoming infected ².

Epidemiological evidence has shown that dementia and communicable diseases are significantly associated with higher rates of death³⁻⁵. Furthermore, a previous meta-analysis showed that pneumonia patients with dementia are twice as likely to die as pneumonia patients without dementia⁶. Relatedly, patients infected with COVID-19 who also have dementia have exhibited poor clinical outcomes, including increased rates of hospitalization, prolonged hospital stays, and increased risk of death^{7,8}.

There is still only limited evidence, however, on dementia as a predictor of the risk of COVID-19 infection or COVID-19-related outcomes. Given the relatively high prevalence of dementia, we thus conducted a systematic review and meta-analysis of relevant studies in order to evaluate the mortality risk among older adults with dementia and COVID-19 infection.

Material and Methods

We prospectively registered this review in the International Prospective Register of Systematic Review (PROSPERO): CRD42020223007.

Search strategy

The existing literature published from December 1st, 2019 to November 29th, 2020 and included in the Academic Search Complete, CINAHL, EMBASE, Google Scholar, MEDLINE, PubMed, and Web of Science databases was systematically searched. The MeSH terms used in the search included the following: "dementia" OR "Alzheimer" OR "cognitive impairment" OR "memory loss" AND "older adults" OR "older people" OR "seniors" OR "elderly" OR "older patients" OR "geriatric" AND "COVID-19" OR "coronavirus disease 2019" OR "cov-19" OR "sars-cov-2" OR "coronavirus" OR "novel coronavirus" AND "mortality" OR "survival" OR "death" OR "deceased". The list of terms used was first developed in one database and then continuously modified as appropriate for use in the other databases

(Table 1). The process of study selection is illustrated in the Preferred Reporting Items for Systematic Review and Meta-analyses⁹ flow diagram in Figure 1.

Eligibility criteria

The PICOS (Population, Intervention/issue of interest, Comparison, Outcome, and Study design) method was used to determine the study inclusion criteria¹⁰. The eligibility criteria ultimately used were as follows: a) studies including older adults with dementia who have COVID-19; b) studies reporting clinical outcomes including mortality; c) studies consisting of cohort studies, case-control studies, or cross-sectional studies; and d) studies published in the English language. The last date searched was November 27th, 2020. Studies that were not within the scope of PICOS-determined criteria or were not available as full texts were excluded. Two authors (IDS, ISS) were involved in screening the abstracts of potentially relevant studies against the inclusion and exclusion criteria. Any disagreements were resolved through mutual consensus.

Data extraction

Two authors (IDS, ISS) performed independent data extraction for each included study, with the extracted data including the authors/year, country, study design, sample with COVID-19, percentage of male subjects, mean age of the participants, scales used, total number of cases of dementia, total number of cases of mortality with dementia, total number of cases without dementia who have COVID-19, and total number of cases of mortality in patients without dementia with COVID-19 infection.

Quality assessment

Accurately judging and choosing the appropriate tool for each included study was an important step in analyzing the methodological quality (risk of bias) of the study and exploring whether the study was of low quality or had a high risk of bias^{11,12}. Two authors (IDS, ISS) independently evaluated each included

study for methodological quality using the 12-item JBI Critical Appraisal Checklist for cohort studies and the 8-item JBI Critical Appraisal Checklist for case-control studies, assessing the methodological quality of each study as high, moderate, low, or very low^{13,14}. Each question in the 12-item list was scored as 0 (high risk of bias) or 1 (low risk of bias), with a total score of ≤ 6 points indicating low quality and a total score of >6 points indicating high quality. Meanwhile, each question in the 8-item list was scored as 0 (high risk of bias) or 1 (low risk of bias), with a total score of ≤ 4 points indicating low quality and a total score of >4 points indicating high quality.

Statistical analysis

A pooled odds ratio of mortality in older adult with dementia who have COVID-19 versus non-dementia and a pooled prevalence of mortality in dementia versus non-dementia were estimated using a random effects model because of the presence of heterogeneity between studies using the Higgins I^2 statistic. In terms of the proportions of I^2 , 25% indicated low heterogeneity, 50% indicated moderate heterogeneity, and $>75\%$ indicated high heterogeneity¹⁵. Data were displayed using forest plots, and publication bias was assessed using Egger's regression test and funnel plots^{16,17}. When Egger's regression test was significant ($p < 0.05$), the trim-and-fill procedure was performed to estimate an actual effect size without the influence of potential publication bias¹⁸. Furthermore, funnel plots and forest plots were plotted using metaprop. Meta-analyses were conducted using the metaprop command in STATA 16.

Results

Study selection

A total of 167 potentially relevant studies were identified in the different databases, of which 95 studies were subsequently excluded because the Endnote software indicated that they were duplicates. Hence, we screened a total of 72 studies based on their titles and abstracts, of which 28 were excluded because they

did not meet the following inclusion criteria as following; the study population was not in older adults with dementia who have COVID-19 (n=15), did not provide outcome of mortality (n=11), and was not original article (n=2). A total of 44 full-text sources were screened against the full text eligibility criteria. A total of 8 studies were further removed because they were not original articles, 2 studies were removed because the population was not in older adults with dementia who have COVID-19, 19 studies were removed because they didn't provide the result of the mortality, and 2 studies were removed because they didn't provide full-text article. Finally, 15 studies were included in the systematic review¹⁹⁻³³. The selected studies are presented in Figure 1.

Studies characteristics

The characteristics of the selected studies are summarized in Table 3, which indicates that the included studies came from 7 different countries. Six of the studies were conducted in Italy¹⁹⁻²², 4 were conducted in Spain^{27, 28, 32, 33}, and 1 study per country was conducted in Belgium²³, France²⁴, South Korea²⁵, Turkey²⁶, and Japan²⁹.

A total of 27,952 confirmed COVID-19 patients were included in the 15 studies included in our review. The majority of them were women (55.37%). The mean age of these study participants ranged from 67.62 to 86.3 years old. Almost of all of the included studies (12/15) used clinical history to define dementia in hospitalized older adults with COVID-19, while the rest of the studies used the CDR scale to define dementia, with a CDR score of 0 defined as non-dementia and a CDR score ≥ 0.5 defined as dementia, or used the DSM-5 scale or ICD-10-CM code F00 with the criteria ≥ 2 points defined as dementia. The range of follow-up periods was from 23 days³¹ to 153 days³³. Furthermore, all of the included studies provided the prevalence of mortality in older adults with dementia (15/15) and older adults without dementia (7/15). The prevalence of mortality among the hospitalized older adults with

dementia ranged from 12.50%²² to 72.73%²⁵, and the prevalence of mortality among hospitalized older adults without dementia ranged from 11.48%²² to 84.17%²⁰.

A meta-analysis of 7 selected studies

Mortality among older adult dementia patients versus non-dementia patients with COVID-19

A total of 7 studies were analyzed to estimate the pooled prevalence rates and pooled odds ratios of mortality among older adult with dementia who have COVID-19 as compared to those without dementia with COVID-19 infection^{19, 20, 22, 23, 27, 29, 32}. Among older adults who have COVID-19, the pooled prevalence of mortality was higher in the patients with dementia than in the patients without dementia (39%; $p < 0.001$ vs. 20%; $p < 0.01$) (Fig. 2 and Fig. 4). Furthermore, the pooled odds ratios determined with a random effects model indicated that the older adults with dementia infected with COVID-19 had a significantly higher rate of mortality than the older adults without dementia infected with COVID-19 (odds ratio: 2.96; 95% CI 2.00 – 4.38, $p = 0.0224$, $I^2 = 29.7\%$) (Fig. 6). The Egger's regression test confirmed that there was no statistical evidence of publication bias ($t = -2.00$; $p = 0.184$). The funnel plots are presented in Figures 3, 5, and 7.

Quality assessment for methodology

A high level of quality for each study included in this review was found. The JBI (Joanna Briggs Institute) tool for cohort studies and case-control studies was used to analyze 15 studies included in this review. All of the included cohort studies scored ≥ 6 , and all of the included case-control studies scored ≥ 4 , indicating high levels of quality that in turn indicated a low risk of bias. Generally, the question in the JBI tool regarding the strategies used in a cohort study to address incomplete follow-up was responsible for lower scores. Hence, another limitation for some analyses was that they showed asymmetry, which in turn indicated that there was publication bias presented in the funnel plots. Consequently, we used the

trim and fill method to indicate the bias. Using this approach, we found the influence of publication bias was small. The results of the quality assessment of the included cohort studies and case control studies are presented in Table 2.

Discussion

To the best of our knowledge, this systematic review constitutes an up-to-date study that specifically analyzed the influence on mortality of older adults with dementia who have COVID-19. The prevalence of mortality among older adults with dementia has been partially explored in recent publications. However, our findings are in accordance with the preliminary results of recent investigations and can be used to help predict mortality in older adult with dementia, especially those infected with COVID-19. The 15 studies included in the current analysis included a total of 27,952 older adults confirmed to have COVID-19. Even though the number of older adults with dementia was not reported by all of the included studies, a total of 7,204 dementia cases was found, with 1551 deaths among those cases (21.53%). Meanwhile, the total number of non-dementia was 5591, with 2966 deaths among those cases (53.05%). However, quantitatively, our findings with a random effect models showed that dementia was the main factor influencing mortality among older adults with COVID-19.

Various studies have confirmed that older adults with COVID-19, especially those with dementia, are experiencing higher rates of mortality compared to other populations. Our analyses showed that the pooled odds ratio of mortality in older adults with dementia who have COVID-19 was 2.96 in comparison to older adults without dementia. Furthermore, the pooled prevalence rates of these two groups were 39% and 20%, respectively. Our findings thus confirmed that dementia is a strong predictor of mortality among older adults infected with COVID-19. Higher mortality among hospitalized dementia patients in the UK compared to those without dementia was found (odds ratio = 3.07, 95% CI: 1.71 to 5.50)³⁴. Likewise, an original study which analyzed similar cases from the same country found that the prevalence

of mortality among older adults with dementia (62.2%) was higher than that among older adults without dementia (26.2%)³⁵.

Our analyses specifically predicted mortality among older adults with dementia versus without dementia who have COVID-19, finding that those with a confirmed clinical history or diagnosis of dementia had relatively poor health outcomes and high rates of mortality. Older adults with dementia are a vulnerable population in terms of possible exposure to COVID-19 infection because of their age, comorbidities, difficulties in adhering to and maintaining physical distancing recommendations, and difficulties in understanding, following, and remembering other COVID-19 prevention measures³⁶. Compared to non-dementia, older adults with dementia are more likely to be immunocompromised and vulnerable to having diseases such as hypertension, diabetes, and pneumonia, especially those with dementia infected with COVID-19, and this population remains highly infective with fatal adverse prognosis in general³⁷. Furthermore, human immune functions also play an important role in fighting against COVID-19. Relatedly, older adults with dementia may experience neuroinflammation, placing this population at higher risk of having excessive inflammation when infected with COVID-19 due to the presence of brain inflammatory neurodegeneration, which in turn makes them more vulnerable to severe poor outcomes after SARS-CoV-2 infection³⁸.

Our study has several limitations and strengths. First, this study only reviewed studies published in the English language. Significant findings of studies conducted in other languages were thus omitted from this review. Hence, as new reviews continue to be published, the estimated numbers of individuals with COVID-19 and dementia might change. The strengths of our study were that it used updated literature regarding mortality among older adults with dementia who have COVID-19 and calculated the pooled odds ratio and pooled prevalence rates, making it of greater value compared to earlier published reports

which only reported the prevalence of survival versus death in older adult with dementia who have COVID-19³⁹⁻⁴¹.

Conclusion

In summary, our results show that older adults with dementia with COVID-19 infection have a higher risk of mortality as compared with patients without dementia. This current study further highlights the need to provide focused care to the older adults with dementia or cognitive impairment who have COVID-19. Due to their cognitive frail, older adults with dementia may experience difficulties in adhering to and maintaining physical distancing recommendations, and difficulties in understanding, following, and remembering other COVID-19 prevention measures. Given the multidimensional relationship of age, Multimorbidity, severity of dementia and its impact on neurodegeneration and immune system, further studies should provide a comprehensive assessment of mechanisms underlying poor outcomes among older adults with dementia who have COVID-19.

Credit Author Statements

- Literature search: IDS, ISS
- Data collection: IDS, ISS
- Study design: IDS, ISS
- Analysis of data: IDS, ISS
- Manuscript preparation: IDS, ISS
- Review of manuscript: IDS, ISS, CJL, SOB

Ethical approval

Not required because this study was a review study.

Declaration of interest

None.

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PRISMA 2009 Flow Diagram

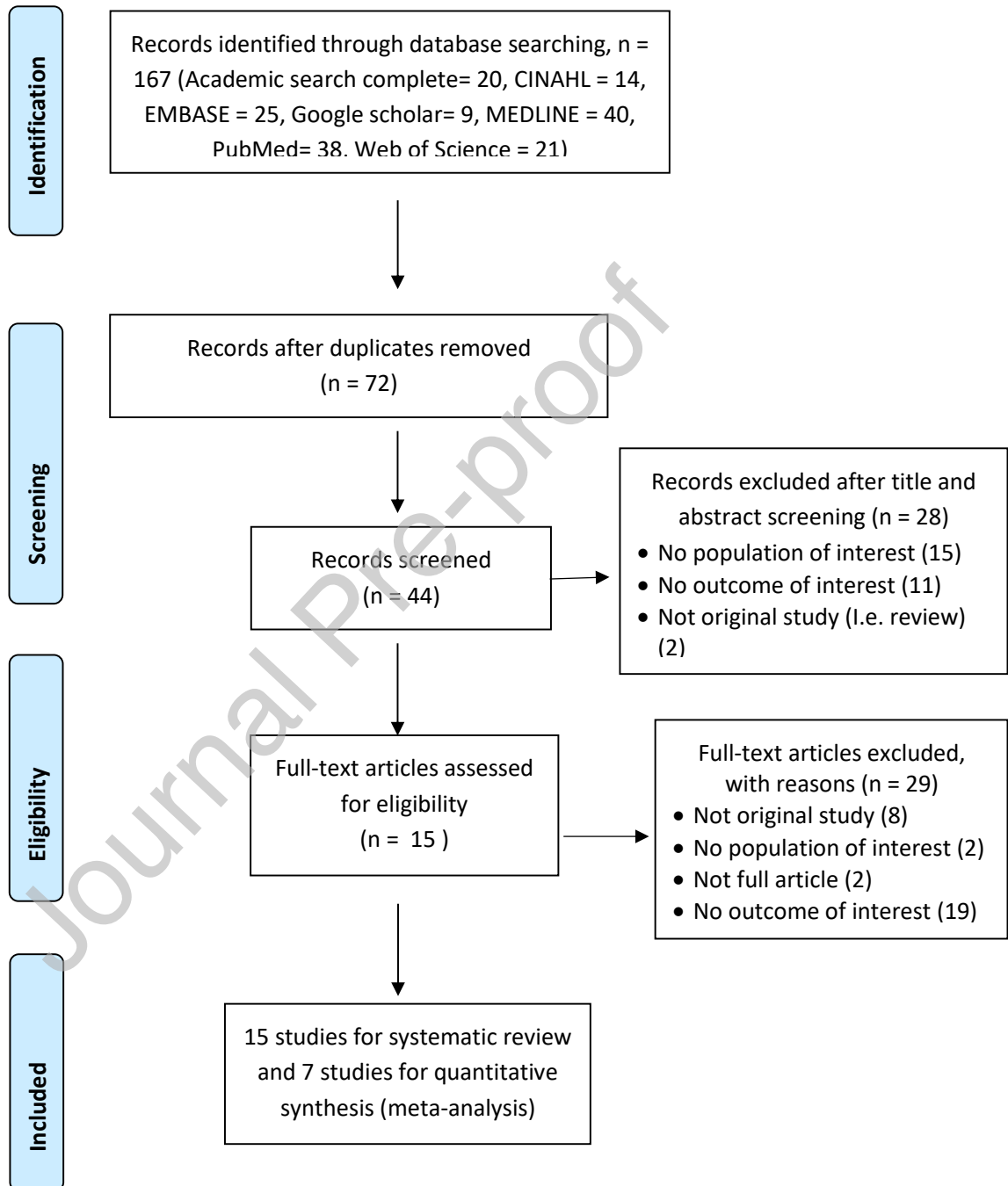


Figure 1 PRISMA Diagram – process of study selection

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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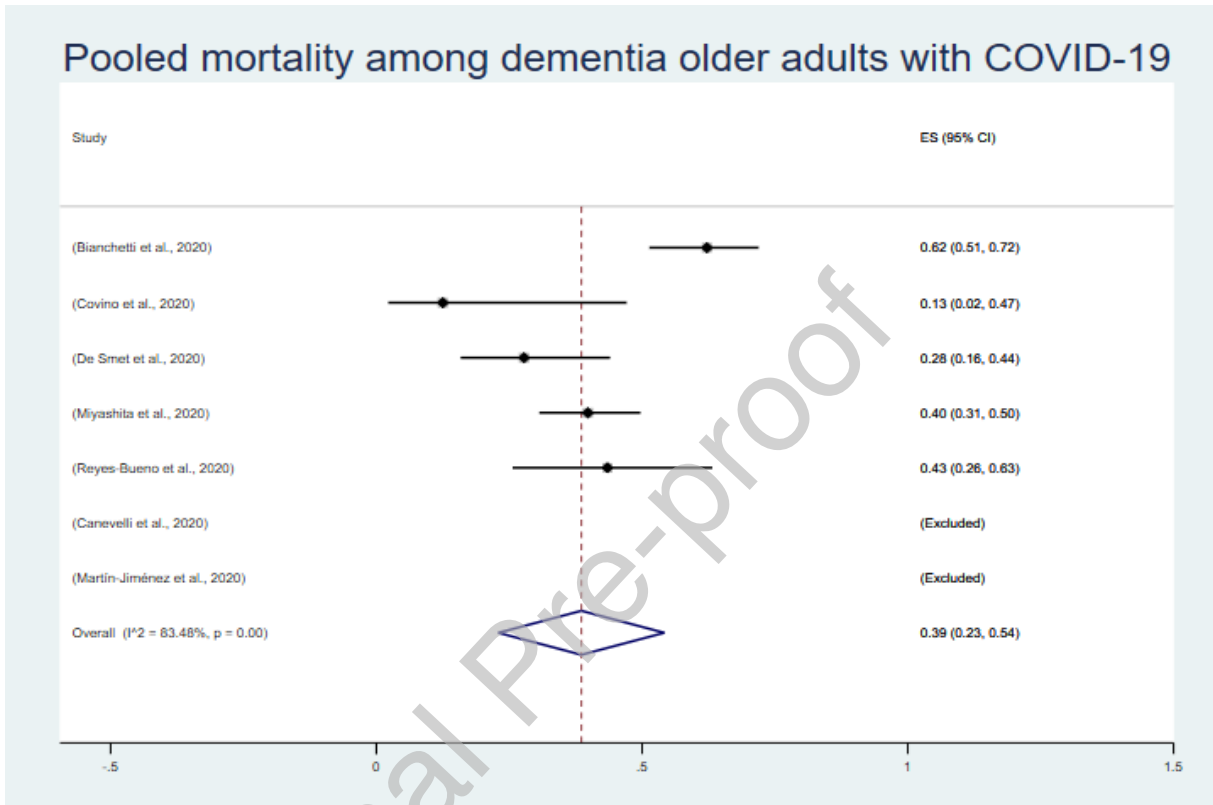


Fig 2: Prevalence of mortality among non-dementia older adults with COVID-19

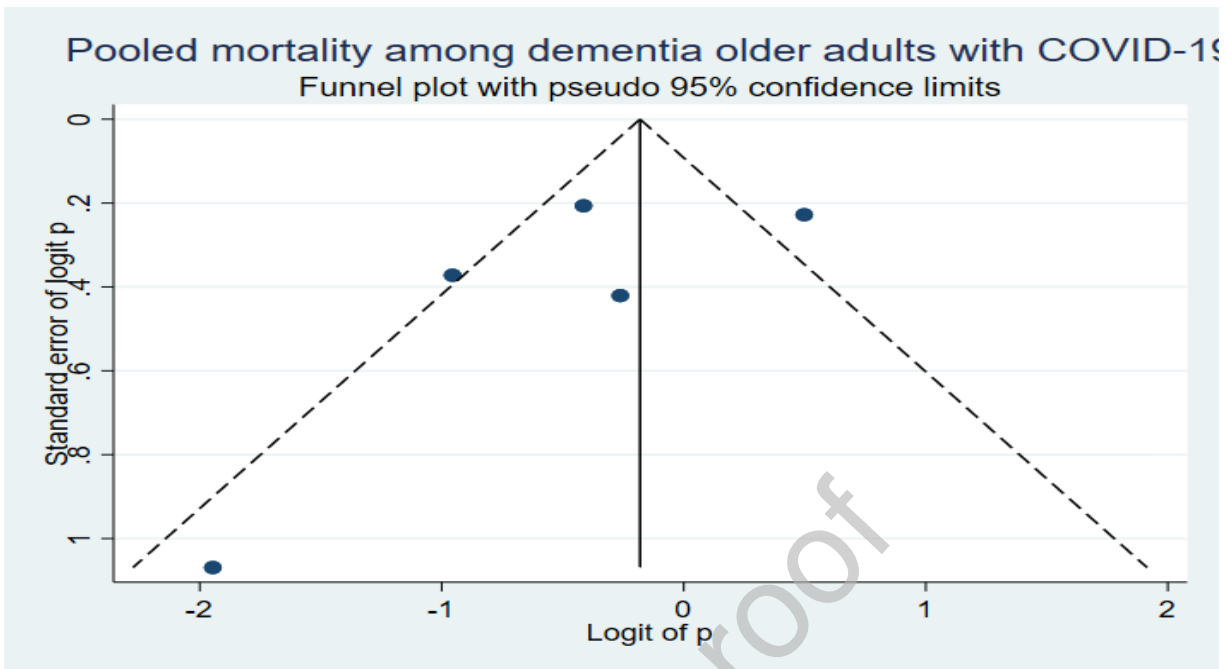


Fig 3: Funnel plot of prevalence of mortality among dementia older adults with COVID-19

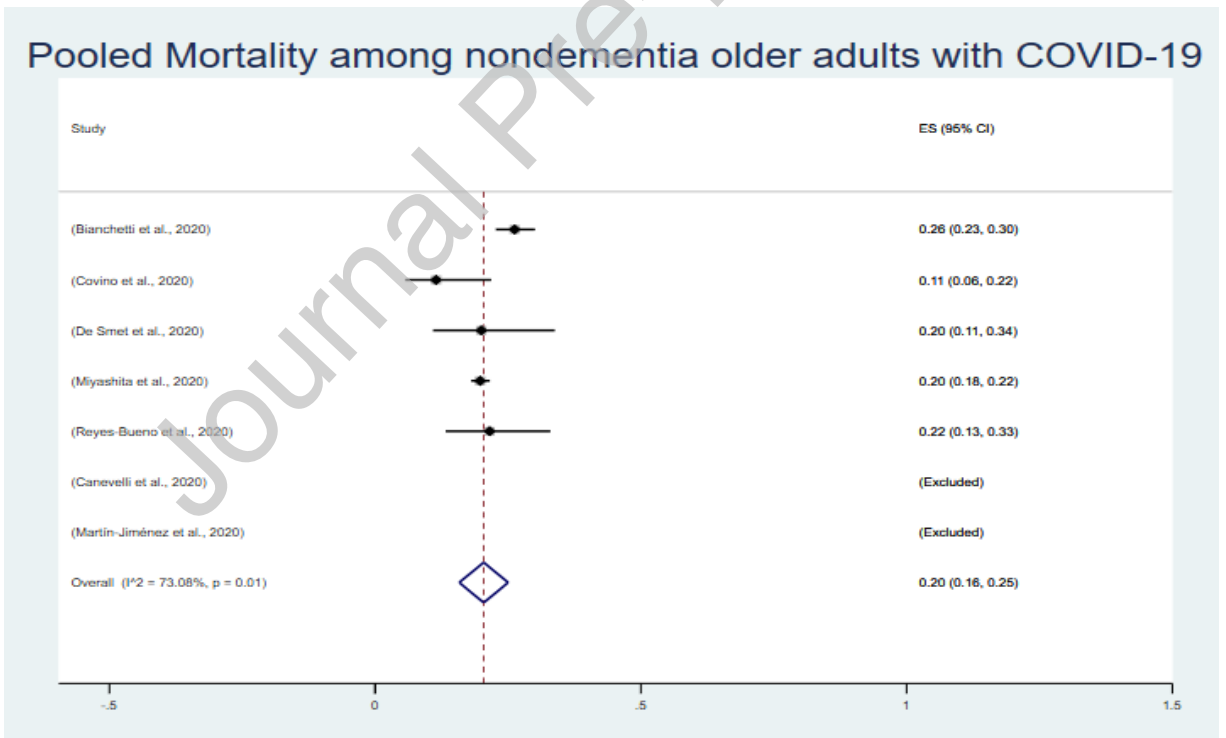


Fig 4: Prevalence of mortality among non-dementia older adults with COVID-19

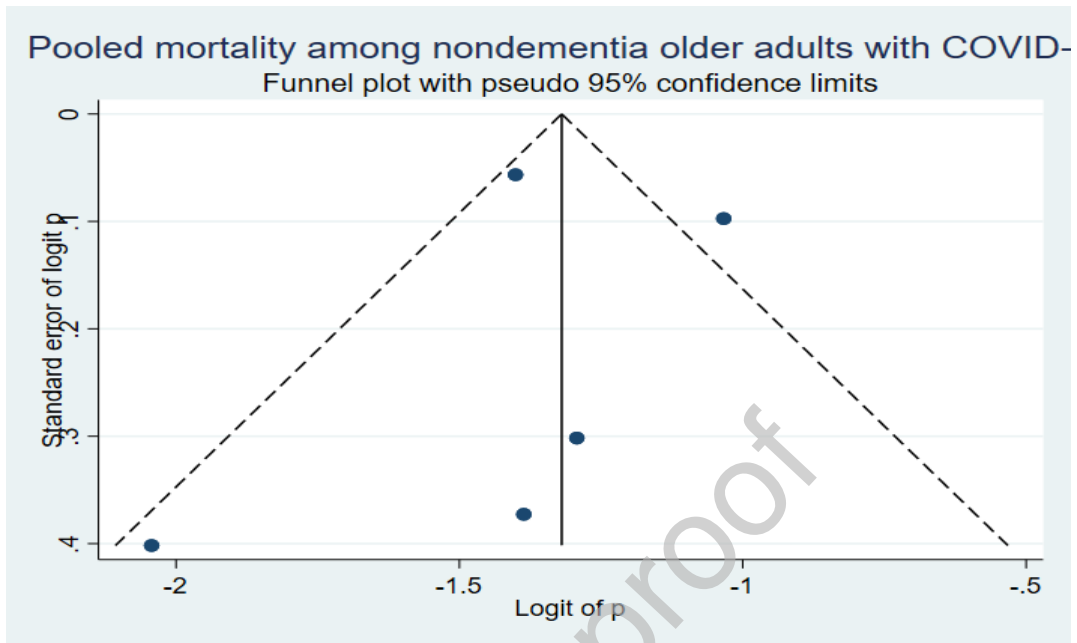


Fig 5: Funnel plot of prevalence of mortality among non-dementia older adults with COVID-19

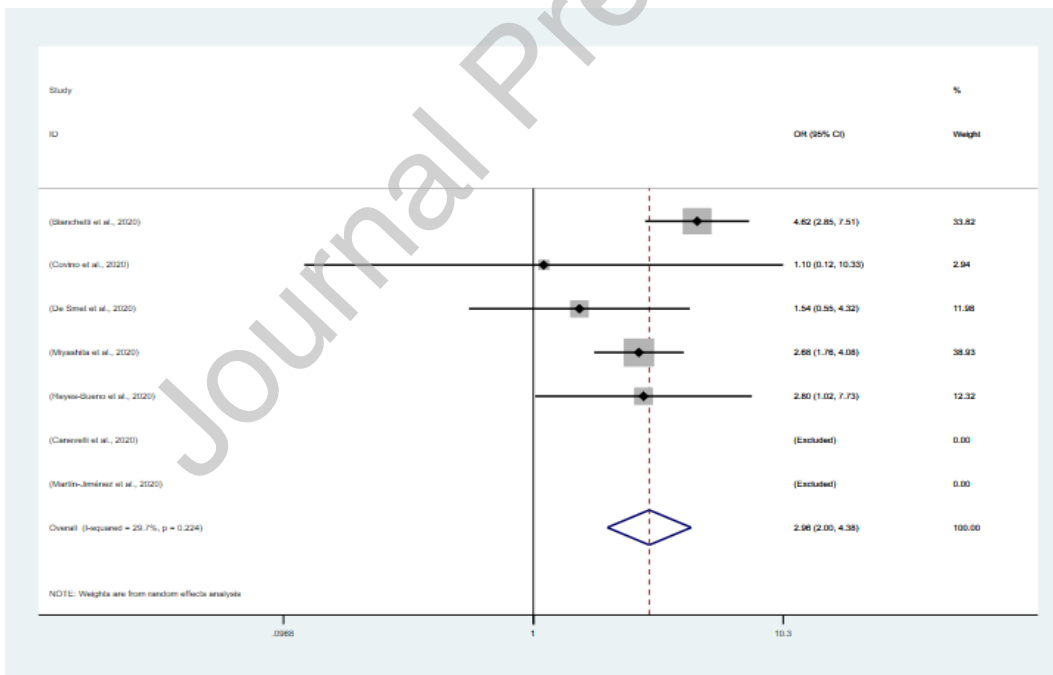


Fig 6: Mortality among dementia vs non-dementia older adults with COVID-19

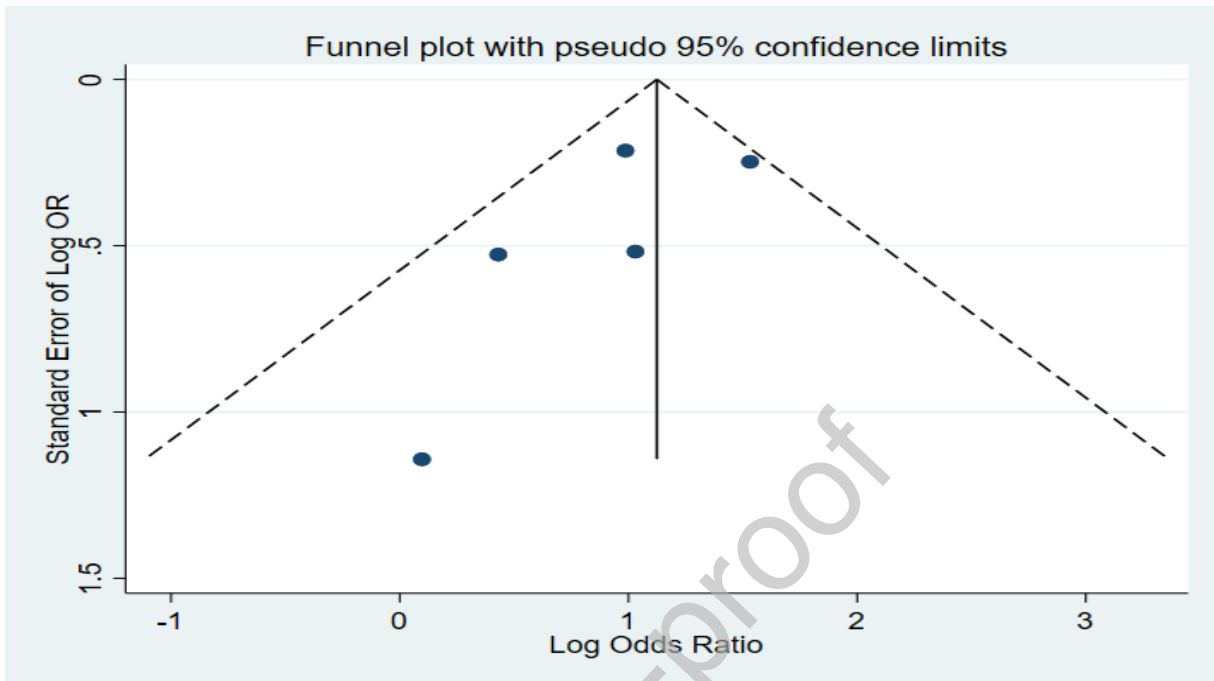


Fig 7: Funnel plot of mortality among dementia vs non-dementia older adults with COVID-19

Table 1 PICO of dementia as a mortality predictor in older adults with COVID-19

Items	Object	Keywords
Population	Older dementia patients infected with COVID-19	Dementia, Alzheimer, cognitive impairment, memory loss. Older adults, older people, seniors, elderly, older patients, geriatric. COVID-19, coronavirus disease 2019, cov-19, sars-cov-2, coronavirus, novel coronavirus.
Intervention/ Issue of interest	None	None
Comparative	None	None
Outcome	Survival	Mortality, survival, death, deceased

Table 2 a. Quality assessment of the included cohort studies

No	JBI Checklist	Bianchetti et al., 2020	Canevelli et al., 2020	Caratozzolo et al., 2020	Covino et al., 2020	De Smet et al., 2020	Genet et al., 2020	Hwang, Kim, Park, Chang, & Park, 2020
1	Were the two groups similar and recruited from the same population?	1	1	1	1	1	1	1
2	Were the exposures measured similarly to assign people?	1	1	1	1	1	1	1
3	to both exposed and unexposed groups?	1	1	1	1	1	1	1
4	Was the exposure measured in a valid and reliable way?	1	1	1	1	1	1	1
5	Were confounding factors identified?	1	1	1	1	1	1	1
6	Were strategies to deal with confounding factors stated?	1	1	1	1	1	1	1
7	Were the groups/ participants free of the outcome at the start of the study (or at the moment exposure)?	1	1	1	1	1	1	1
8	Were the outcomes measured in a valid and reliable way?	1	1	1	1	1	1	1
9	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	1	1	1	1	1	1	1

10	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	1	1	1	1	1	1	1
11	Were strategies to address incomplete follow up utilized?	0	0	0	0	0	0	0
12	Was appropriate statistical analysis used?	1	1	1	1	1	1	1
	Overall Appraisal	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1
	Level of evidence	3.b cohort study	3.b cohort study	3.b cohort study	3.b cohort study	3.b cohort study	3.b cohort study	3.b cohort study

No	JBIChecklist	Kundi et al., 2020	Martín-Jiménez et al., 2020	Matias-Guiu, Pytel, & Matías-Guiu, 2020	Miyashita et al., 2020	Palmieri et al., 2020	Poloni et al., 2020
1	Were the two groups similar and recruited from the same population?	1	1	1	1	1	1
2	Were the exposures measured similarly to assign people?	1	1	1	1	1	1
3	to both exposed and unexposed groups?	1	1	1	1	1	1

4	Was the exposure measured in a valid and reliable way?	1	1	1	1	1	1
5	Were confounding factors identified?	1	1	1	1	1	1
6	Were strategies to deal with confounding factors stated?	1	1	1	1	1	1
7	Were the groups/ participants free of the outcome at the start of the study (or at the moment exposure)?	1	1	1	1	1	1
8	Were the outcomes measured in a valid and reliable way?	1	1	1	1	1	1
9	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	1	1	1	1	1	1
10	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	1	1	1	1	1	1
11	Were strategies to address incomplete follow up utilized?	0	0	0	0	0	0
12	Was appropriate statistical analysis used?	1	1	1	1	0	1
	Overall Appraisal	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 11 Exclude: 1	Include: 10 Exclude: 2	Include: 11 Exclude: 1
	Level of evidence	3.b cohort	3.b cohort study	3.b cohort study	3.b cohort study	3.b cohort	3.b cohort

study

study

study

Table 2 b. Quality assessment of the included case-control studies

No	JBIChecklist	Reyes-Bueno et al., 2020	Sainz-Amo et al., 2020
1	Were the criteria for inclusion in the sample clearly defined?	1	1
2	Were the study subjects and the setting described in detail?	1	1
3	Was the exposure measured in a valid and reliable way?	1	1
4	Were objective, standard criteria used for measurement of the condition?	1	1
5	Were confounding factors identified?	1	1
6	Were strategies to deal with confounding factors stated?	1	1
7	Were the outcomes measured in a valid and reliable way?	1	1

8	Was appropriate statistical analysis used?	1	1
	Overall Appraisal	Include: 8 Exclude: 0	Include: 8 Exclude: 0
	Level of evidence	4.c case series	4.c case series

Table 3 Summary of selected studies on dementia as predictor of mortality among older adults with COVID-19

No.	Authors/year	Country	Study design	Sample size with COVID-19	Men	Age	Scale	Dementia outcome	Effect of measure	Follow-up period (days)	JBI tool
1	(Bianchetti et al., 2020)	Italy	Retrospective study	627	292	82.6	Clinical history	Dementia	OR, Prev	47	11/12
2	(Canevelli et al., 2020)	Italy	Retrospective study	2621	1771	84.3	Clinical history	Dementia	OR, Prev	69	11/12
3	(Caratozzolo et al., 2020)	Italy	Observational Study	95	36	79.2	CDR	CDR 0 'no dementia', CDR	OR, Prev	70	11/12

								≥0.5 'dementia')			
4	(Covino et al., 2020)	Italy	Retrospective study	69	37	84	Clinical history	Dementia	OR, Prev	31	11/12
5	(De Smet et al., 2020)	Belgium	Retrospective study	81	33	85	Clinical history	Dementia	OR, Prev	50	11/12
6	(Genet et al., 2020)	France	Retrospective study	201	66	86.3	DSM-5		OR, Prev	33	11/12
7	(Hwang, Kim, Park, Chang, & Park, 2020)	South Korea	Retrospective study	103	52	67.62	Clinical history	Dementia	OR, Prev	54	11/12
8	(Kundi et al., 2020)	Turkey	Cohort Study	18234	8498	74.1	ICD-10-CM codes-F00	≥ 2 points "dementia"	OR, Prev	104	11/12
9	(Martín-Jiménez et al., 2020)	Spain	Retrospective study	477	273	80.5	Clinical history	Dementia	OR, Prev	31	11/12
10	(Matias-Guiu, Pytel, & Matias-Guiu, 2020)	Spain	Observational Study	204	85	78.02	Clinical history		OR, Prev	29	11/12
11	(Miyashita et al., 2020)	Japan	Retrospective study	2071	1099	≥60	Clinical history	Dementia	OR, Prev	33	11/12
12	(Palmieri et al., 2020)	Italy	Retrospective study	2664		≥ 65	Clinical	Dementia	OR, Prev	61	11/12

13	(Poloni et al., 2020)	Italy	Retrospective study	57	19	82.8	history Clinical history	Dementia	OR, Prev	23	10/12
14	(Reyes-Bueno et al., 2020)	Spain	Case control study	88	53	79	history Clinical history	Dementia	OR, Prev	62	8/8
15	(Sainz-Amo et al., 2020)	Spain	Case control study	39	23	75.9	history Clinical history	Dementia	OR, Prev	153	8/8

CDR = Clinical Dementia Rating Scale; DSM-5= Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ICD-10-CM codes-F00= International Statistical Classification of Diseases and Related Health Problems, 10th revision

Continued.

No.	Authors/year	Mortality					
		Dementia	Total	Prevalence (%)	Non-dementia	Total	Prevalence (%)
1	(Bianchetti et al., 2020)	51	82	62.20	143	545	26.24
2	(Canevelli et al., 2020)	415	2621	15.83	2206	2621	84.17

29

3	(Caratozzolo et al., 2020)	32	95	33.68			
4	(Covino et al., 2020)	1	8	12.50	7	61	11.48
5	(De Smet et al., 2020)	10	36	27.78	9	45	20.00
6	(Genet et al., 2020)	61	178	34.27			
7	(Hwang, Kim, Park, Chang, & Park, 2020)	8	11	72.73			
8	(Kundi et al., 2020)	333	990	33.64			
9	(Martín-Jiménez et al., 2020)	84	281	29.89	197	281	70.11
10	(Matias-Guiu, Pytel, & Matías-Guiu, 2020)	14	31	45.16			

11	(Miyashita et al., 2020)	39	98	39.80	390	1973	19.77
12	(Palmieri et al., 2020)	468	2664	17.57			
13	(Poloni et al., 2020)	14	57	24.56			
14	(Reyes-Bueno et al., 2020)	10	23	43.48	14	65	21.54
15	(Sainz-Amo et al., 2020)	11	29	37.93			