Aging and Health Research 3 (2023) 100125

Contents lists available at ScienceDirect

Aging and Health Research

journal homepage: www.elsevier.com/locate/ahr

Risk factors and outcomes of delirium in hospitalized older adults with COVID-19: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
COVID-19
Delirium
Older adults
Hospitalized
Risk factors

ABSTRACT

Background: Older adults with COVID-19 are more likely to present with atypical symptoms, notably delirium. The main objective of this meta-analysis is to identify risk factors for delirium and outcomes of delirium in hospitalized older adults (65 years or above) with COVID-19.

Methods: Comprehensive literature search of Embase, CINAHIL, Medline and Web of Science was performed for published literature until 31st August 2021. Two independent researchers evaluated study eligibility and assessed study quality using the Newcastle Ottawa Scale (NOS) for cohort studies and Joanna Briggs Institute (JBI) critical appraisal tools for case series. The association of various predisposing factors with delirium in this cohort was reported as odds ratio (OR) and its 95% confidence interval (CI).

Results: A total of 31 studies from 11 countries were included in this review. Most of the included studies investigated patients from non-ICU settings (n = 24; 77.4%). Frailty (OR 3.52, 95% CI: 1.96–6.31, p<0.0001, I^2=71.63%), cognitive impairment including dementia (OR 6.17, 95% CI: 2.92–13.07, p<0.00001, I^2=88.63%) and being nursing home residents (OR 1.72, 95% CI: 1.31–2.24, p<0.0001, I^2=0) were significantly associated with increased likelihood of developing delirium in older adults with COVID-19. The presence of delirium also significantly increases mortality risk in hospitalized older adults with COVID-19 (OR 2.51, 95% CI: 1.51–4.17, p<0.0001, I^2=89.3%).

Conclusion: Our review identifies key factors associated with increased risk of developing delirium in hospitalized older adults with COVID-19. Identification of patients at risk of delirium and attention to these factors early during admission may improve outcomes for this vulnerable cohort.

1. Introduction

Older adults with COVID-19 are more likely to present with atypical symptoms, notably delirium [1]. Such atypical presentations may delay recognition of COVID-19 [2], leading to poorer outcomes in this cohort.

Delirium is an acute neuropsychiatric syndrome characterized by altered levels of arousal and fluctuating cognition and is considered a harbinger of severe illness in older adults [3]. Older adults are particularly vulnerable to developing severe COVID-19, probably due to immunosenescence and higher burden of comorbidities [4,5]. Evidence from mixed age studies shows that up to 1 in 3 COVID-19 patients develop delirium with an even higher prevalence in patients requiring intensive care [6–8]. Delirium is associated with poor outcomes in COVID-19; increased length of stay (LOS), higher mortality rates and accelerated functional and cognitive decline [9,10].

In the past year, there has been an increase in the volume of literature on delirium in COVID-19. Many of these studies have focussed on mixed age cohorts. Existing evidence points towards higher rates of delirium and poorer outcomes in older adults. Few studies have focussed exclusively on hospitalized older adults. Identification of the risk factors for delirium in this cohort may improve risk stratification for clinicians and enable a more personalised approach of care. Also, exploring vulnerability factors in this subgroup which predispose them to delirium may provide useful entry points towards understanding the underlying mechanisms and pathological processes that result in varying clinical presentations in COVID-19.

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https://doi.org/10.1016/j.ahr.2023.100125
Received 18 August 2022; Received in revised form 30 January 2023; Accepted 1 February 2023
Available online 3 February 2023

This review aims to analyze the existing data on delirium in COVID-19 in hospitalized older adults (65yrs and older) and identify risk factors for delirium and outcomes of delirium in this cohort.

2. Methods

2.1. Protocol and registration

The protocol for this study is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the ID number CDR42021277723. The study adheres to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) reporting guidelines [11] [Supplementary Table 1. Prisma 2020 Checklist].

2.2. Eligibility criteria

Inclusion criteria for articles in this study were: Observational studies (including case series, cohort studies, cross-sectional and case-control studies) reporting outcomes of interest for delirium in hospitalized older adults (65 years or above) with Covid-19.

Articles were excluded if they fulfilled one of the following criteria 1) Publications not in English Language 2) Pre-prints 3) Abstract-only publications 4) Duplicate report with same study patients 5) Reviews, comments, opinions, guidelines and editorials 6) Where data for only 65 years and above hospitalised older adults cannot be extracted.

2.3. Information sources and search strategy

Systematic literature searches of Embase, Medline, CINAHIL and Web of Science were performed for published literature until 31st August 2021 using appropriate MeSH or Emtree terms related to Covid-19, delirium and confusion. The detailed search strategy devised in consultation with the librarian is presented in *Supplementary Table 2*. The reference lists of the articles included in the final review were also hand searched to identify potential eligible studies.

2.4. Selection process

After removing duplicates from the database bibliographic search results, the references were imported into Covidence [12] for screening and team collaboration. Two researchers (N.M and M.C) independently screened the title/abstracts of the records. Any conflicts were advanced to full text screening. Full text review of the potentially eligible studies was also undertaken independently by the two researchers (N.M and M. C) and discrepancies were resolved by consensus following discussion with the senior author (E.G).

2.5. Data extraction

Data extraction was performed by two independent researchers (N.M and R.S) . An extraction form was developed in Covidence to list the baseline study characteristics, patient characteristics and outcomes of interest. Information on study characteristics including the first author, year of publication, study design, setting, region, data collection period, Covid-19 confirmation procedure were collected. Population characteristics (number of participants, age, sex [male], criteria for delirium, number of patients with and without delirium) and number of patients with each risk factor and outcomes of interest were also recorded. The outcomes of interest were in-hospital mortality, length of hospital stay and discharge destination. The checklist of potential risk factors was developed using factors listed in previous delirium guidelines and reviews. Disagreements were resolved by consensus discussion.

The variables of interest extracted from each study are included in *Supplementary Table 3*. The most commonly used instrument in the eligible studies to assess frailty was the Clinical Frailty Scale (CFS) [13]. Most eligible studies used categorization for grouping patients for frailty by CFS. For this review, CFS $>$ 5 was used to study assosciation between frailty and risk of delirium.

Variables that were initially planned to be extracted from each study and later not included in the final dataset as they were only investigated in one or two studies included history of Parkinson's disease, heart disease, stroke, cancer, obesity, mental illness, polypharmacy including psychotropic medications, severity of COVID-19, need for invasive ventilation, length of hospital stay and discharge destination. They have been mentioned briefly in the text later.

2.6. Quality assessment

Methodological quality of the included studies was independently assessed by two researchers (N.M and M.C). Studies with various study designs were included in the review and were assessed using appropriate tools. Studies classified as case series were evaluated using Joanna Briggs Institute (JBI) Critical Appraisal Tool for case series [14]. Newcastle-Ottawa Quality Assessment scale [NOS] was used to evaluate included cohort studies [15]. Discrepancies were resolved through consensus by discussion with the senior author (E.G) on a case-by-case basis.

2.7. Statistical analysis

Meta-analysis was used to combine effect estimates of the variables when they were reported in more than 2 studies to produce an overall summary of a factor's effect. PyMeta software [16] was used to perform the statistical analysis. Inverse Variance formula with random-effects model was used to calculate the association of different variables with delirium in hospitalised older adults. The effect size was reported as odds ratio (OR) for each variable with categorical data (numbers/counts) and its 95% confidence interval, and the pooled results were presented in Forest plots. Pooled mean difference was calculated for age (continuous data) using inverse variance method. Cochran's Q test with the *P-value* and the I^2 test were used to measure the extent of heterogeneity among included studies. An effect estimate was considered as significant for heterogeneity if the value was $>$50% or p-value$<$0.05. To assess for publication bias, funnel plot analysis and Egger's test was performed.

3. Results

3.1. Study selection and study characteristics

A total of 31 studies were included in the final qualitative synthesis and meta-analyses (Fig.1). There were only 7 studies among the 135 advanced to full text review that required discussion among the two researchers (N.M and M.C) to deem suitability for inclusion in the final review. The percentage agreement between the two screening researchers was estimated to be 94.8%. No additional articles were identified for inclusion after screening the reference list of the included studies.

The baseline characteristics of the included studies can be seen in *Supplementary Table 3*.The included studies were from UK (n = 7), Italy (n = 8), USA (n = 4), Spain (n = 2), Denmark (n = 2), France (n = 3), Belgium (n = 1), Ireland (n = 1), Canada (n = 1), Turkey (n = 1), Switzerland (n = 1). The sample size ranged from 4 to 821 COVID-19 positive hospitalized older adults in each study. The median age of the participants ranged from 76.2 to 86 years. All studies reported sex (total 6,767participants), however, in one study [17] it was not possible to extract the sex distribution for those above 65 years old. In the other 30 studies there were 3307 (49.6%) males and 3357 (50.4%) females.

Different approaches were used to identify delirium in the studies. 13 studies used tools to diagnose delirium such as the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), Confusion Assessment Method (CAM), Richmond Agitation-Sedation Scale (RASS)

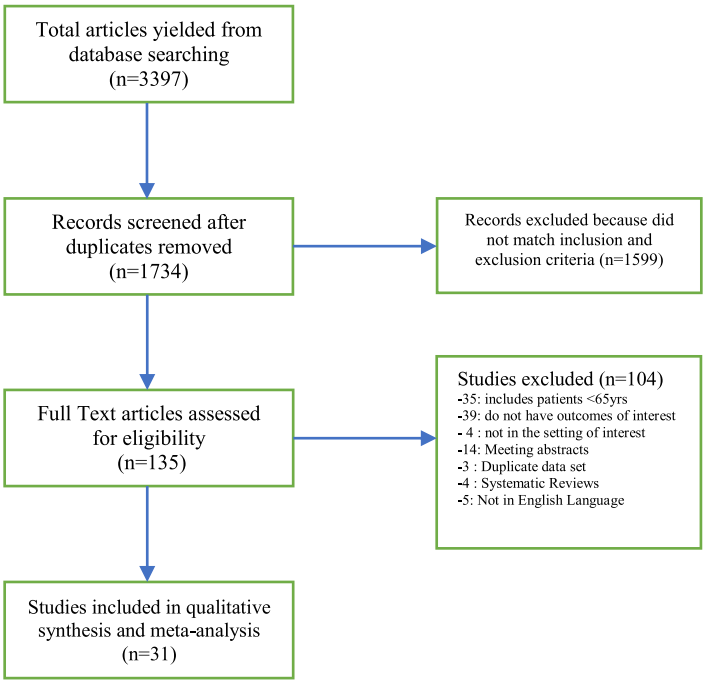

Fig. 1. PRISMA Diagram for study selection and inclusion.

and 4AT. Delirium was identified in 8 studies through medical records review searching for the terms "confusion" or "delirium". In 10 studies there was no mention of the criteria used to identify delirium. Most studies included patients from non-ICU settings ($n = 24$; 77.4%), others analysed patients from both ICU and non-ICU ($n = 3$), ED ($n = 2$), ICU ($n = 1$) and dementia special care unit ($n = 1$). Among these studies 6 were judged to be of moderate quality and 25 of high quality using the appraisal tools described above (*Supplementary Table 4: Quality Assessment of included studies)*.

We were able to estimate the pooled OR for eight risk factors and pooled mean difference for age (Table 1). *See Appendix 1 published as supplemtary material for forest plots.*

3.2. Demographic factors

We identified 7 studies which reported patients with and without delirium according to sex ($n = 1708$) . There was no association between sex and odds of developing delirium with COVID-19. Four studies reported mean age for patients with and without delirium ($n = 439$). Pooled analysis showed a trend towards an association between older age and increased delirium risk in hospitalized older adults with COVID-19, however the association was not statistically significant; mean difference 4.45 (95% CI: 0.85–8.05; $p = 0.016$).

3.3. Co-morbidities and delirium

Four studies ($n = 1049$) explored the association between hypetension and delirium, five studies ($n = 1866$) explored diabetes and four studies ($n = 1631$) reported data on chronic pulmonary disease and delirium. There was no association between these co-morbidities and delirium, both on univariate analysis and pooled statistical analysis. Three studies ($n = 1574$) reported data on smoking in patients with and without delirium however there was no association between smoking status and delirium.

3.4. Cognitive impairment

The review identified 8 studies that reported delirium in patients with cognitive impairment (including dementia). Poloni et al. [18] and Agathe et al. [19] exclusively studied cohorts of 57 and 125 patients with dementia, respectively. 36.9% (21/57) had delirium in Poloni et

Table 1
Meta-analysis of risk factors for delirium in hospitalized older adults with COVID-19.

Risk Factor	Studies	Total sample (n)	Pooled OR or MD* (95% CI)	Heterogeneity I^2 (%)
Demographic factors				
Age	4	439	4.45 [0.85, 8.05]*	82
Male sex	7	1708	1.08 [0.71, 1.63]	54
Female sex	7	1311	0.92 [0.56, 1.52]	65
Hypertension	4	1049	1.09 [0.73, 1.61]	21
Diabetes	5	1866	1.18 [0.86, 1.60]	23
Chronic Pulmonary Disease	4	1631	0.89 [0.66, 1.20]	0
Smoking	3	1574	0.82 [0.51, 1.31]	0
Nursing Home Resident	4	1288	1.72 [1.31, 2.24]	0
Frailty (CFS>5)	6	1663	3.52 [1.96, 6.31]	72
Cognitive Impairment (including dementia)	5	2205	6.17 [2.92, 13.07]	88

* indicates that the mean difference is reported.

al's study and 82.4% (103/125) developed delirium in Agathe et al's study. The latter did not mention the diagnostic guidelines employed to assess delirium in the cohort with dementia. Pooled analysis of data from the other studies showed that COVID-19 patients with pre-existing cognitive impairment are more likely to develop delirium and the association was statistically significant (OR 6.17, 95% CI: 2.92–13.07, $P<0.00001$, $I^2=88.63\%$).

3.5. Nursing home residents

Hospitalized older adults with COVID-19 admitted from care homes are more likely to experience delirium with COVID-19. Three of four studies concluded residential care prior to hospital admission as a significant risk factor for developing delirium with COVID-19 in univariate anlysis that remained statistically significant in pooled analysis (OR 1.72, 95% CI:1.31–2.24, $P<0.0001$, $I^2=0$).

3.6. Frailty and delirium

Six studies were identified (n = 1663) from which data can be extracted for pooled analysis to determine the association between frailty (CFS>5) and risk of delirium with COVID-19.

Frailty in hospitalized older adults with COVID-19 was significantly associated with increased delirium risk (OR 3.52, 95% CI:1.96–6.31, $p<0.0001$, $I^2=71.63\%$).

3.7. Miscellaneous factors

Other risk factors reported to be significantly associated with increased risk of delirium in this cohort were explored in only one study [20]. This study identified prior use of psychoactive medication, vision impairment, hearing impairment, stroke and Parkinson Disease as being significantly associated with delirium in hospitalized older adults with COVID-19. Another study [21] reported a significant association of heart failure with delirium in this cohort.

3.8. Delirium and outcomes

Pooled analysis of data from 16 studies showed that delirium significantly increases the mortality risk in hospitalized older adults with COVID-19 (Fig 2.) Mortality in this review refers to in-hospital mortality. The pooled odds ratio for unadjusted mortality with delirium was 2.51 (95% CI: 1.51–4.17, p = 0.0001, $I^2=89.3\%$).

A funnel plot of the included studies did not show evidence of publication bias. Egger's test for a regression intercept gave a p-value of 0.580 and it was somewhat symmetrical in appearance (Fig 3).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that explores the risk factors associated with delirium in hospitalized older adults with COVID-19. Based on our pooled analysis, delirium is a common occurrence in this cohort. The prevalence of delirium in hospitalized older adults with COVID-19 in the studies included ranged from 11% to 87%. There are a number of factors which could account for the wide variation in prevalence of delirium. Diverse study settings and differences in methods for diagnosing delirium alone could contribute. These rates are significantly higher than those reported in pre-pandemic studies of hospitalized older adults where rates of delirium of 11–25% were found [22]. Lack of visitors who know the

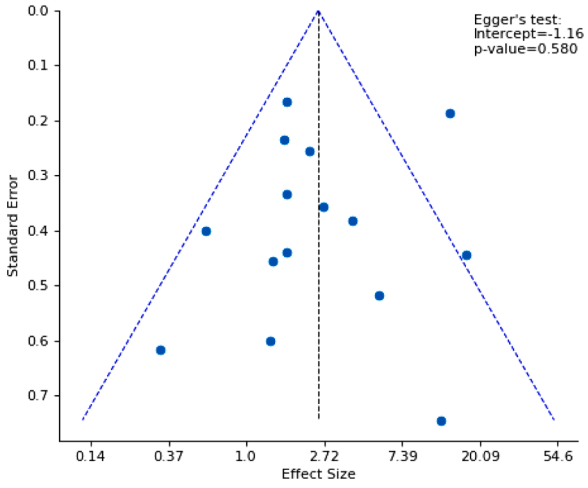

Fig. 3. Funnel plot analysis for association of delirium in COVID-19 with mortality.

Study ID	Patients with Delirium event	Patients with Delirium number	Patients without Delirium event	Patients without Delirium number
DeSmet2020	8	34	11	47
Poloni2020	11	21	3	36
Marengoni2020	18	25	21	66
Kennedy2020	84	226	154	591
Lozano-Montoya2021	105	201	6	99
Morandi2021	20	39	57	202
Forget2021	36	62	17	65
BağSoytaş2021	8	27	44	191
Rebora2021	38	73	145	443
Zerah2021	200	330	50	491
Karlsson2021	15	30	27	72
Agathe2021	24	103	4	22
Mendes2021	20	48	56	187
Covino2021	41	82	246	647
Steinmeyer2020	7	41	10	53
Maniero2021	14	58	23	66

OR,IV,Random Study ID	n	Effect(95% CI)	Weight(%)
DeSmet2020	81	1.01 [0.36, 2.85]	5.70
Poloni2020	57	12.10 [2.81, 52.08]	4.63
Marengoni2020	91	5.51 [2.00, 15.21]	5.77
Kennedy2020	817	1.68 [1.21, 2.33]	7.26
Lozano-Montoya2021	300	16.95 [7.10, 40.50]	6.14
Morandi2021	241	2.68 [1.33, 5.39]	6.56
Forget2021	127	3.91 [1.85, 8.27]	6.44
BağSoytaş2021	218	1.41 [0.58, 3.43]	6.09
Rebora2021	516	2.23 [1.35, 3.68]	6.98
Zerah2021	821	13.57 [9.41, 19.58]	7.21
Karlsson2021	102	1.67 [0.71, 3.94]	6.17
Agathe2021	125	1.37 [0.42, 4.43]	5.35
Mendes2021	235	1.67 [0.87, 3.21]	6.66
Covino2021	729	1.63 [1.03, 2.58]	7.05
Steinmeyer2020	94	0.89 [0.31, 2.57]	5.64
Maniero2021	124	0.59 [0.27, 1.31]	6.35
Total	**4678**	**2.51 [1.51, 4.17]**	**100.00**

16 studies included (N=4678)
Heterogeneity: Tau²=0.899, Q=140.16 (p=0.000), I²=89.3%
Overall effect test: z=3.55, p=0.000

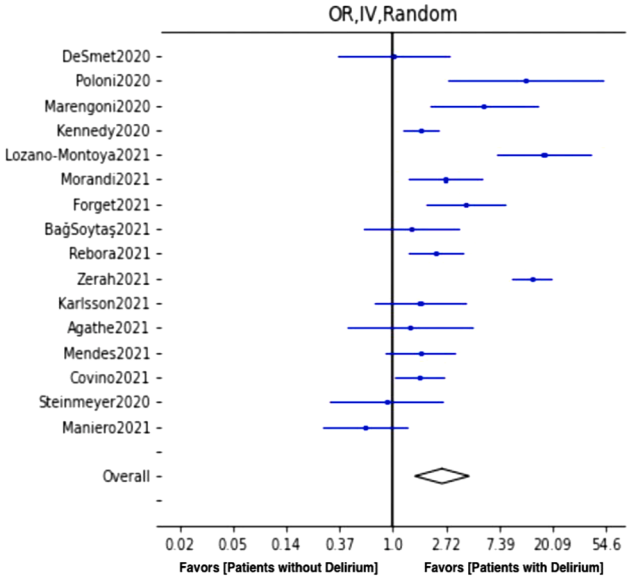

Fig. 2. Forest plot that demonstrates the association of delirium in hospitalised older adults with COVID-19 and mortality. *Each study's effect includes a 95% confidence interval (95% CI) line and central block (position for effect and size for weight). Overall effect is denoted by the diamond. OR: Odds ratio; IV: Inverse variance.*

true baseline of the hospitalized patient and limited staff-patient interaction due to isolation and personal protective equipement may mean that subtle changes in hospitalized older adults may go unnoticed resulting in higher incidence of delirium. Higher rates of delirium have been reported in patients with COVID-19 in the ICU. This may be due to prolonged mechanical ventilation and the use of sedatives [23]. This does not account for our elevated rates as most of the studies included in our review (28/31) recruited patients from non-ICU settings. Additionally, anecdotally, older adults were more likely to be cared for in non-ICU settings during the pandemic.

The association between sex and delirium is well described. Being male is a recognized predisposing factor for delirium in pre-pandemic studies [24]. Our study found no association between sex and delirium in this cohort. Illness severity is a well known precipitating risk factor for delirium. Some studies have shown an association between male sex and severe forms of COVID-19. Diabetes, hypertension and chronic pulmonary disease are linked with severe forms of COVID-19 [25,26]. Our review found no significant association between these predisposing factors and delirium in hospitalized older adults with COVID-19. It can be argued that these comorbidities were not significantly associated with increased risk of delirium despite having an association with a severe form of COVID-19. This may be due to small number of studies and sample size inadequate to derive a meaningful association. Most studies included in our review involved hospitalized older adults from non-ICU settings and patients with severe COVID-19 are more likely to be cared for in ICU settings.

Our pooled analysis showed that patients with a vulnerable brain, manifested by cognitive impairment or dementia, were 5–6 times more likely to develop delirium. The risk of delirium in cognitively impaired older adults is well documented. Inherent genetic vulnerabilities, pro-inflammatory states and direct invasion of the vulnerable brain by the COVID-19 virus have all been implicated in the pathogenesis of delirium in this cohort [27,28].

Frailty is described as a health state that predisposes older adults to develop severe COVID-19, increases the odds of developing delirium and risk of mortality due to COVID-19 [29,30]. This has been confirmed in our findings.Our study has found that frail, older adults with COVID-19, those admitted to hospital from nursing homes and those with pre-existing cognitive impairment were at the highest risk of developing delirium with COVID-19. This vulnerable cohort of patients may present with only delirium and lack the typical COVID-19 symptoms of fever and cough [31]. Delirium in this patient population should raise the suspicion of COVID-19, prompting early interventions to avoid poor outcomes. It can be argued that nursing home residents are more likely to be frail and have cognitive impairment compared to community-dwelling older adults [32]. Due to the lack of studies exploring these factors together in the same cohort of patients, in our review, it was not possible to undertake a multivariable analysis and assess each factor's independent influence on the outcome.

Not surprisingly, we found that delirium significantly increases mortality risk, almost 2 fold, in older adults with COVID-19. The pooled results show high heterogeneity. A sensitivity analysis by sequential omission of each individual study shows that the high heterogeneity persists. High heterogeneity can be attributed to pooled data analysis not being adjusted for severity of COVID-19, length of delirium, geographical variation, frailty and presence of co-morbidities. Subgroup analysis was initially planned, however, was not performed due to insufficient number of studies per group and uneven covariate distribution among the groups.

It is important to note the strengths and limitations of the study when interpreting the results of the analysis. The protocol was pre-registered and the rules for the review process were transparently set out. The first limitation is that there was considerable variation in the criteria used for delirium diagnosis across all studies and eight studies did not document the criteria they used. Secondly, most of the studies were retrospective observational studies, increasing the risk of bias. Thirdly, the study populations included are geographically and clinically heterogenous (e.g. COVID-19 severity, burden of comorbidities and duration of delirium). Another limitation of the review is excluding studies not in English. Also, the review did not yield enough data for the 2 of the 3 prespecified outcomes (length of hospital stay and discharge destination) to be considered. Notwithstanding these limitations, our analysis highlights the impact of delirium in this cohort and the importance of early identification and intervention to improve outcomes. Due to visiting restrictions, now more than ever, delirium detection tools should be used at the time of admission and during times of transfer between wards. Staff should be educated about delirium and collateral histories should be encouraged so that delirium is less likely to be missed. Preventive measures such as pain management, good hydration, ensuring regular bowel movements and paying attention to sensory deficits should be instituted early in the course of admission along with regular mental state assessments.

5. Conclusion

The findings from the review suggest frailty, cognitive impairment including dementia and being nursing home residents to be significantly associated with increased likelihood of developing delirium in older adults with COVID-19. The presence of delirium also significantly increases mortality risk in hospitalized older adults with COVID-19.

Further research correlating inflammatory markers, laboratory parameters of organ function and co-morbid illnesses is needed to understand the risk factors and pathogenic basis of delirium in COVID-19.

CRediT authorship contribution statement

Nida Munawar: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. **Rubab Syed:** Data curation, Formal analysis, Software. **Maria Costello:** Data curation, Formal analysis. **David Robinson:** Writing – review & editing. **Colm Bergin:** Conceptualization, Writing – review & editing. **Elaine Greene:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of Conflicts of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NONE

Funding

None

Acknowledgements

We would like to thank David Mockler, Trinity College Dublin librarian, for his assistance with literature searching.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahr.2023.100125.

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