Prevalence, incidence and mortality of delirium in patients with COVID-19: A systematic review and meta-analysis

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Abstract

Background

Attention should be paid to delirium in COVID-19 patients, especially older people, since advanced age poses increased risk of both delirium

and COVID-19-related death.

Objective

This study aims to summarize the evidence on prevalence, incidence and mortality of delirium in COVID-19 patients.

Methods

We conducted a comprehensive literature search on Pubmed and Embase from inception to December 1, 2020. Three independent reviewers evaluated study eligibility and data extraction, and assessed study quality. Outcomes were analyzed as proportions with 95% confidence interval (CI). We also compared mortality differences in COVID-19 patients using odds ratio.

Results

In total, we identified 48 studies with 11,553 COVID-19 patients from 13 countries. Pooled prevalence, incidence and mortality rates for delirium in COVID-19 patients were 24.3% (95% CI: 19.4-29.6%), 32.4% (95% CI: 20.8-45.2%) and 44.5% (95% CI: 36.1-53.0%), respectively. For patients aged over 65yrs, prevalence, incidence and mortality rates for delirium in COVID-19 patients were 28.2% (95% CI: 23.5-33.1%), 25.2% (95% CI: 16.0-35.6%) and 48.4% (95% CI: 40.6-56.1%), respectively. For patients under 65yrs, prevalence, incidence and mortality rates for

delirium in COVID-19 patients were 15.7% (95% CI: 9.2-23.6%), 71.4% (95% CI: 58.5-82.7%) and 21.2% (95% CI: 15.4-27.6%), respectively. Overall, COVID-19 patients with delirium suffered higher risk of mortality, compared to those without delirium (OR: 3.2, 95% CI: 2.1-4.8).

Conclusion

Delirium developed in almost 1 out of 3 COVID-19 patients, and was associated with 3-fold overall mortality. Our findings suggest that first-line healthcare providers should systematically assess delirium and monitor related symptoms among COVID-19 patients.

Keywords

COVID-19, delirium, prevalence, incidence, mortality, meta-analysis

Key points

- This systematic review and meta-analysis of 48 studies summarizes the epidemiological data associated with prevalence, incidence and mortality of delirium in 11,553 COVID-19 patients.
- It is common for COVID-19 patients to develop delirium with the reported prevalence and incidence rates being 24.3% and 32.4%, respectively.

- The occurrence of delirium in COVID-19 patients is significantly associated with 3-fold higher mortality, compared to those without delirium.
- First-line healthcare providers should systematically assess delirium, monitor related symptoms and optimize treatment in COVID-19 patients.

Introduction

Since the emergence of coronavirus 2019 (COVID-19) disease in China in December 2019, it has affected over 1.2 billion people worldwide, causing more than 2.7 million deaths up to March 22, 2021 [1]. Among the different age groups, older people are at particular risk of developing or dying from COVID-19 infections, probably because of weaker immune response and frailty [2-5]. For example, mortality was found to be 6-times higher in patients with COVID-19 aged over 65 years old, compared to those younger than 65 [6, 7]. To date, only limited treatment options are available specifically for COVID-19 [8], so early identification and management of complications related to COVID-19 infections (e.g., venous thromboembolism, catheter-related bloodstream infections, pressure ulcers, falls and delirium) are critical to prevent mortality in the geriatric population [9].

The increased neuropsychiatric complication risk in COVID-19 patients, especially in older people, may be on account of viral factors (e.g., direct central nervous system invasion, induction of central nervous system inflammatory mediators), treatment factors (e.g., medication, such as cortisone, analgesics and antibiotics, prolonged mechanical ventilation, deep sedation with immobilization), disease factors (e.g., fever, dehydration and hypoxia) and environmental factors (e.g., isolation and separation from family) [10, 11]. Among the various neuropsychiatric complications, delirium, a transient but reversible disturbance of consciousness and inattention triggered by an acute event (e.g. medical illness) [12], is associated with an increased risk of adverse outcomes, such as longer stays in hospitals and death during admission [13]. Early studies indicate that 20–30% of COVID-19 patients will present with or develop delirium or mental status changes during the course of their hospitalization, with rates of 60–70% in cases of severe illness [14-16].

Understanding the epidemiological features of delirium and COVID-19 is an urgent research priority, especially in older people, where age increases the risk of both developing delirium and COVID-19-related death. Recently, there has been an increase in the volume of published literature on delirium in patients with COVID-19. Therefore, a comprehensive synthesis of existing evidence investigating prevalence, incidence and mortality of delirium in COVID-19 patients is necessary to inform clinical care and public health policy. Specifically, we aimed to identify mortality differences in COVID-19 patients with and without delirium.

Methods

We have registered this study protocol with the International Prospective Register of Systematic Reviews (PROSPERO) under the ID number ANONYMISED, and this study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines **(Appendix Table 1)**.

Search strategy

We conducted a systematic review and meta-analysis of published studies extracted from Pubmed and Embase up to December 1, 2020. We used free-text search with appropriate MeSH or Emtree terms related to COVID-19, delirium, confusion, incidence, prevalence and mortality in these biographic databases. The detailed search strategy devised by the pharmacist in consultation with a librarian is presented in **Appendix Table 2**.

Study inclusion and exclusion criteria

For inclusion, studies were required to provide information on prevalence (e.g., initial symptoms with delirium during hospital admission), incidence (e.g., new occurrences of delirium during hospitalization) or all-cause mortality of delirium in COVID-19 patients. We only included

retrospective or prospective observational studies, while other publication types (e.g., review, editorial, commentary, case reports, treatment consensus or guidelines) were excluded. Studies without full-text availability were also excluded.

Literature selection

After removing duplicate studies from the bibliographic database search results, three independent researchers (ANONYMISED) reviewed remaining titles and abstracts to identify potentially eligible studies for full-text review. The reference lists of thus included articles were also hand-searched. Any disagreements were resolved by discussion after review of original data and consultation with another researcher (ANONYMISED).

Data extraction

Data extraction was completed and re-checked by the same researchers. The extracted information included study characteristics (e.g., region, study design and settings), patient characteristics (e.g., age, sex, comorbidity, and dependent status), treatment characteristics (e.g., COVID-19 treatment) and outcome data of study interest (e.g., prevalence, incidence and mortality). Specifically, we defined dependent status of patients as having reached a clinical frailty score above 5 points. All disagreements were resolved through discussion.

Study quality

Methodological quality of the included studies was independently assessed by three researchers (ANONYMISED). For case series consisting of a collection of patients with COVID-19 and lacking a comparison group, we followed the 10-item checklist for critical appraisal sheets, published by the Joanna Briggs Institute (JBI) [17]. Every item of the checklist affirmed with 'yes' by the researchers attracted a score of one point, while checklist items described as 'no' or 'unclear' attracted a 0 point score. Studies that scored a total of over 7 points, 5-6 points and less than 4 points were categorized as good, moderate and low quality, respectively [18, 19]. For the cohort studies evaluating COVID-19 patients with and without delirium, to report the mortality risk difference, we followed the Newcastle-Ottawa Quality Assessment Scale (NOS)[20, 21]. Studies with 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain were judged as good quality; studies with 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain were judged as moderate quality; studies with 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 star in the outcome/exposure domain were judged as low quality [19, 22]. Studies where the researchers differed in their assessments of study quality were resolved on a case-by-case basis by bringing an additional researcher (ANONYMISED) into the discussion to help reach a conclusion.

Statistical analysis

The reported prevalence, incidence and mortality rates (with 95% confidence intervals (CI)) for delirium in COVID-19 patients underwent meta-analysis based on random-effects models. Odds ratios (OR) were calculated to detect differences in mortality of COVID-19 patients with and without delirium, and the pooled results were presented in Forest plots. Cochran's Q test with p-value and the I^2 test were used to measure the extent of statistical heterogeneity among the included studies. Subgroup analyses were conducted on groupings derived from age (mean or median age < 65 or ≥ 65 years old), geographical region (Asia, Europe, America and others), clinical settings (intensive care units; ICU and non-ICU), specific population (yes, e.g., dementia or other indications; otherwise no), results of validated delirium assessment tools (Memorial Delirium Assessment Scale (MDAS), Revised Delirium Rating Scale (DRS-R-98), Confusion Assessment Method (CAM), Delirium Observation Screening Scale (DOSS), Diagnostic and Statistical Manual (DSM) [23]), study size (< 100 or ≥ 100 patients) and study quality (high, moderate and low quality). Any potential publication bias was determined using Egger's test with $p<0.05$. All statistical analyses were conducted using MedCalc for Windows, Version 19.4 (MedCalc Software, Ostend, Belgium).

Results

Study selection and study characteristics

We identified 350 relevant published literatures, of which 37 were retrospective studies and 11 were prospective studies, from a total of

48 records in Pubmed, Embase and from the reference lists of the included studies, which reported prevalence, incidence or mortality of delirium covering 11,553 COVID-19 patients (**Figure 1**). We described the definitions of prevalent and incident delirium cases in included studies in the **Appendix Table 3**. The included studies were from China (n=4), USA (n=4), Brazil (n=1), Spain (n=2), France (n=8), Italy (n=9), United Kingdom (n=11), Switzerland (n=2), Scotland (n=1), Norway (n=2), Sweden (n=1), Belgium (n=1), Tunisia (n=1) and multi-nation (n=1). The sample size ranged from 10 to 1379 COVID-19 patients in each study, whereby the majority of the studies (66.0%) included patients with mean or median ages over 65 years old. Most of the studies (89.6%) analyzed data from non-ICU settings, and some studies were related to dementia (n=8) or other specific indications (e.g., palliative care, n=3; rheumatic diseases, n=2; neurological diseases, n=1; cancer, n=1). Among these studies, 4 (8.3%), 10 (20.8%) and 34 (70.8%) were judged to be of low, moderate and high methodological quality, respectively. The characteristics of the included studies are presented in **Appendix table 8**, and the details about the risk of bias in included studies are presented in **Appendix Table 4-5**.

Prevalence and incidence of delirium in COVID-19 patients

We found 39 studies reporting the prevalence of delirium, ranging from 2.8% to 77.4%, in a total of 9,031 COVID-19 patients. Meta-analysis of these studies showed that the prevalence of delirium in COVID-19 patients was 24.3% (95% CI: 19.4-29.6%; I^2: 96.8%, p<0.01; Egger's test: p<0.01) (**Figure 2A**). Compared to the pooled prevalence, a higher prevalence of delirium was found in COVID-19 patients with

underlying dementia (45.3%). The pooled incidence of delirium was 32.4% (95% CI: 20.8-45.2%; I^2: 98.4%, p<0.01; Egger's test: p=0.58) derived from 16 studies covering a total of 3,923 COVID-19 patients, with the incidence rates ranging from 4.0% to 80.2% (**Figure 2B**). For patients aged over 65 years old, the prevalence and incidence rates for delirium in COVID-19 patients were 28.2% (95% CI: 23.5-33.1%) and 25.2% (95% CI: 16.0-35.6%), respectively. For patients aged under 65 years old, the prevalence and incidence rates for delirium in COVID-19 patients were 15.7% (95% CI: 9.2-23.6%) and 71.4% (95% CI: 58.5-82.7%), respectively. Subgroup analyses showed no substantial changes in statistical heterogeneity **(Appendix Table 6)**, whereby the results remained consistent with the overall analyses.

Mortality in COVID-19 patients with and without delirium

We identified 17 studies reporting mortality in 6,457 COVID-19 patients with or without delirium. The reported mortality rates in COVID-19 patients with delirium ranged from 10.0% to 88.0%, and the pooled mortality rate was 44.5% (95% CI: 36.1-53.0%; I^2: 93.1%, p<0.01; Egger's test: p=0.42). The mortality rates were 48.4% (95% CI: 40.6-56.1%) and 21.2% (95% CI: 15.4-27.6%) in COVID-19 patients aged over 65 and under 65, respectively. Overall, the meta-analysis of these studies showed that the mortality rate of COVID-19 patients with delirium was higher than of those without delirium (OR: 3.2, 95% CI: 2.1-4.8) (**Figure 3**). We observed substantial statistical heterogeneity (I^2: 86.1%, p<0.01) without evidence of publication bias (Egger's test: p=0.83) among the included studies. Statistical heterogeneity was reduced after the subgroup analyses, but there was no significant change in the pooled OR estimate, compared to the overall analyses **(Appendix Table 6)**.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to point out that COVID-19 patients frequently experience delirium, and may be at high risk of mortality as a result. Our study found that prevalence, incidence and mortality of delirium in COVID-19 patients were 24.3% (95% CI: 19.4-29.6%), 32.4% (95% CI: 20.8-45.2%) and 44.5% (95% CI: 36.1-53.0%), respectively. In addition, mortality in COVID-19 patients with delirium increased 3-fold, compared to those without delirium. Different subgroup analyses by age groups, geographic area, clinical settings, specific populations, the results of validated delirium assessment tools, study size and quality of study (high, moderate or low) revealed consistent findings. Specifically, our results also indicated higher prevalence of delirium among people with dementia and COVID-19, probably due to patients with dementia being more likely to develop behavioral disturbances [24].

COVID-19 patients are known to develop various clinical manifestations involving many organs [25-27], but most are related to fever, cough, shortness of breath, fatigue, nausea/vomiting, diarrhea and myalgia [28]. Psychiatric and neuropsychiatric presentations have been also reported in COVID-19 patients; for example, early studies reported the occurrence of confusion in 26 (65%) out of 40 COVID-19 patients from two intensive care units (ICU) in France [15]. However, critically ill patients in the ICU frequently develop ICU delirium due to the effect of

sedative strategies, prolonged mechanical ventilation or multiple organ failure [29, 30], so previous study focused on ICU settings may have overestimated the incidence of delirium in COVID-19 patients. Our findings, indicating that nearly 1 out of 2 COVID-19 patients in ICU settings develop delirium, higher than in non-ICU settings (26.3%), could provide the evidence to better understand the epidemiology of delirium after COVID-19 infections in different clinical settings.

Delirium, a clinical manifestation of many diseases, is known to be a significant risk factor for poor outcomes [31, 32]. Previous meta-analysis has indicated that delirium increased the risk 2-fold for mortality in older patients [33], but the impact on COVID-19 patients has remained unclear. Our study indicated that mortality in COVID-19 patients with delirium was 44.5%, three times higher than in those without delirium. The pathophysiology of this excess mortality in COVID-19 patients with delirium is likely to be multifactorial [34], but it is suggested that brain involvement of COVID-19, rather than the worsening of pre-existing comorbidities is to blame [35]. In addition, delirium might reflect disease severity, since COVID-19 patients with delirium have frequently developed more severe symptoms during hospitalization, including abundant bronchial secretions, severe hypotension, poorly controlled hyperpyrexia, pulmonary edema, persistently low SpO2, stupor or seizures [36]. Regular assessment and early management of delirium-related symptoms in COVID-19 patients are suggested in clinical practice [10].

The COVID-19 mortality rate is low for children and younger adults but increases progressively with age [37, 38]. Due to this increased vulnerability to COVID-19 and the strict isolation requirements that have been imposed during the current pandemic, older adults are experiencing greater stress levels and mental health challenges [39, 40], and it is important to understand the relative magnitude of delirium prevalence, incidence and mortality in older people and younger groups [41]. However, there is a paucity of evidence about delirium in younger patients with COVID-19. In this study, we present the prevalence and mortality of delirium in COVID-19 patients to be lower but the incidence of delirium with COVID-19 are higher in younger, compared to older people. COVID-19 patients, whether older or younger, share the same major risk factors for developing delirium, namely those associated with longer lengths of hospital stay and higher mortality [29]. Based on our findings, we suggest closely monitoring and promptly treating delirium not only in older people, but also importantly in younger COVID-19 patients.

Global differences in the approach taken to timing and intensity of testing and social distancing may affect COVID-19 epidemiology or complications in different countries [42, 43]. For example, governments in Asia (China, Hong Kong, Taiwan, Singapore, South Korea, Australia and New Zealand) took action early and decisively toward the COVID-19 pandemic, compared to the European and American countries [43]. As a result, comparisons between Asian and non-Asian countries are useful to better understand the clinical impact of delirium in COVID-19 patients. In our subgroup analyses, we found the impact of delirium (prevalence, incidence and mortality) is more predominant in COVID-19

patients from non-Asian countries than in those from Asian countries. Possible reasons may be found in the significant variations in clinical characteristics of patients with COVID-19 across the globe; for example, we found COVID-19 patients with delirium in America and Europe were older compared to their Asian counterparts.

To date, there have been no randomized clinical trials investigating delirium treatment or prevention in COVID-19 patients [44]. To prevent delirium, timely avoidance of important reversible contributors in COVID-19 patients is crucial. Rapid investigation and management of the contributory etiologies and concomitant implementation of non-pharmacological methods (e.g., re-orientation, provision of sensory aids and early mobilization) are suggested if COVID-19 patients begin to develop delirium [45, 46]. Several literatures of expert consensus also suggest that the primary management of delirium in COVID-19 patients should be to implement preventative measures (e.g., pain management, avoiding urinary retention, avoiding physical restraints, avoiding anticholinergic medications, benzodiazepines and opioids) whenever possible. Finally, effective vaccines have been available since December 2020, but COVID-19 is not likely to be eliminated in the near future and will probably continue to affect the world [47]. Our findings suggest first-line healthcare providers should always remain vigilant and monitor delirium while considering all available treatment or prevention options mentioned above to prevent death in COVID-19 patients with delirium.

Some limitations should be noted when interpreting the results of the presented analyses. First, not all studies included in the analysis

aimed initially to investigate delirium in the context of COVID-19, so several studies did not report details regarding diagnostic tools for the assessment of delirium [48]. In addition, it should be noted that the studies included in this review are clinically heterogeneous, possibly reflecting the heterogeneity of the study populations (e.g, co-morbidities and COVID-19 severity) and varying sensitivities and specificities of the different assessment tools employed to identify delirium [23]. Only 29.2% of the studies examined in this systematic review and meta-analysis used validated instruments, such as CAM, DOSS, DRS-R-98, MDAS or DSM-5 to identify delirium. Some COVID-19 cases of delirium may not have been recognized in the included studies, but our subgroup analyses on the results of validated delirium assessment tools showed results consistent with the overall analyses. Third, since most of the included studies were from hospitals, we suggest further research based on the community to investigate delirium in COVID-19 patients. Despite these limitations, our systematic review and meta-analysis is clinically relevant to provide comprehensive evidence of overall high delirium rates in COVID-19 patients and the associated significant increase in mortality odds.

Conclusion

In this systematic review and meta-analysis involving 11,553 COVID-19 patients worldwide, we found that nearly 1 out of 3 COVID-19 patients developed delirium associated with 3-fold higher mortality. Our findings underscore the need for first-line healthcare providers to

systematically assess delirium and monitor related symptoms in COVID-19 patients. Future studies are suggested to evaluate the effectiveness of intervention strategies to prevent delirium in COVID-19 patients.

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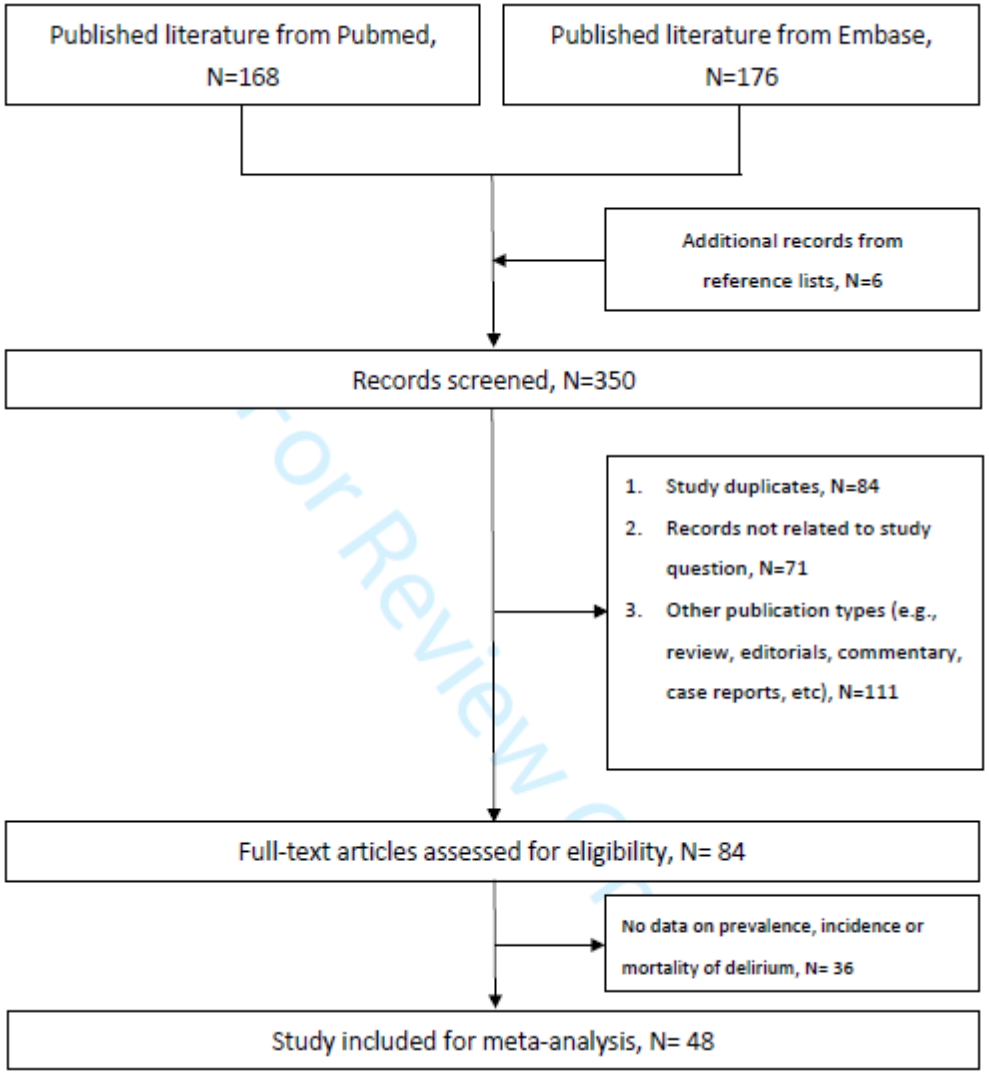


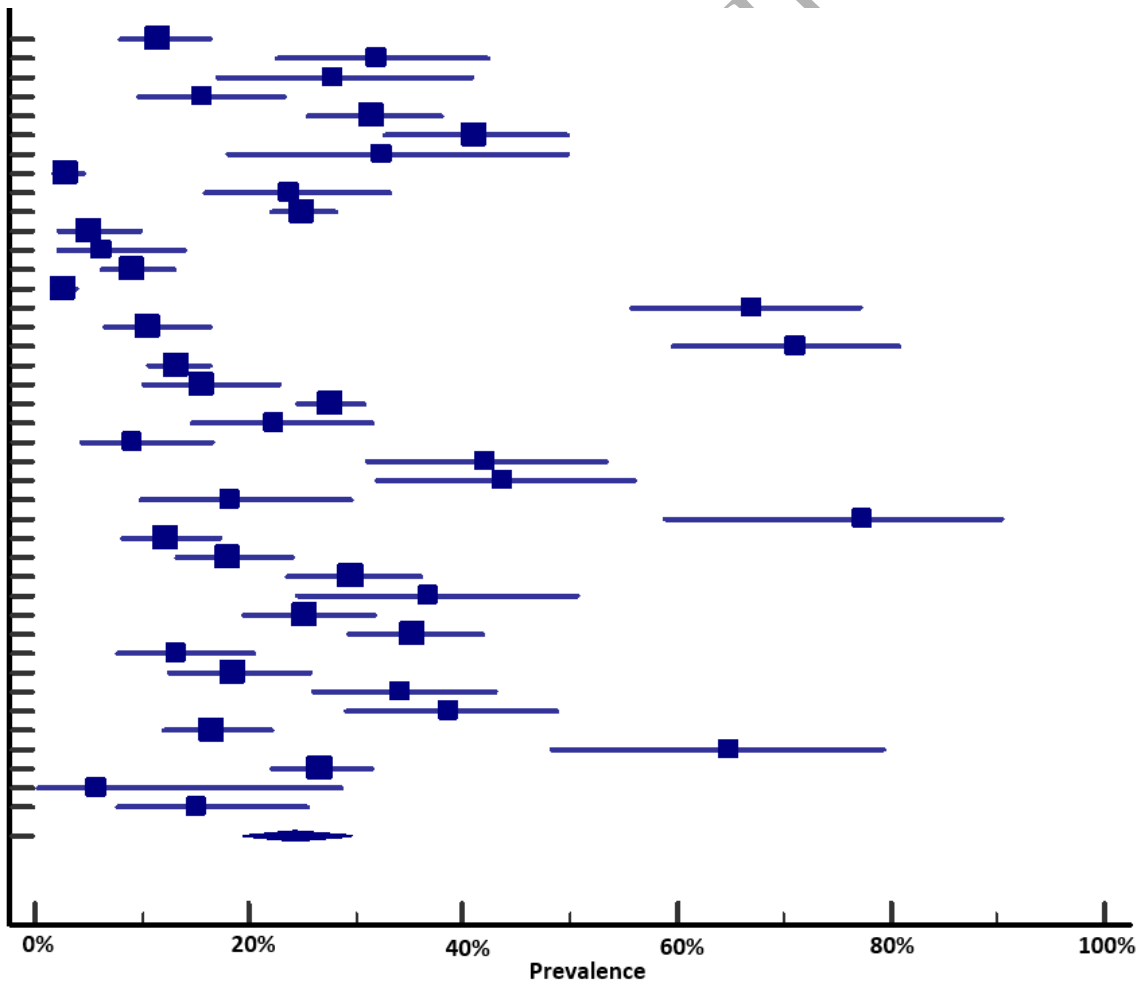
Figure 1. Study selection based on PRISMA diagram

Figure 2. (a) Prevalence and (b) Incidence rate of delirium in COVID-19 patients

a. Prevalence rate

First author	COVID-19 patients, n	Prevalence, %	(95 % CI)	weight, %	Study quality
Garcia Clemente MM	249	11.6	(7.9 - 16.3)	2.5	Good
Steinmeyer Z	94	31.9	(22.7 - 42.3)	2.4	Good
Alderman B	61	27.9	(17.1 - 40.8)	2.3	Good
Gan JM	122	15.6	(9.6 - 23.2)	2.5	Good
Davis P	222	31.5	(25.5 - 38.1)	2.5	Good
Rawle MJ	134	41.0	(32.6 - 49.9)	2.5	Good
Kremer S	37	32.4	(18.0 - 49.8)	2.2	Good
Liu D	599	2.8	(1.7 - 4.5)	2.6	Moderate
Lovell N	101	23.8	(15.9 - 33.3)	2.4	Moderate
Zerah L	821	25.0	(22.0 - 28.1)	2.6	Good
D'Silva KM	156	5.1	(2.2 - 9.9)	2.5	Good
Cao Z	80	6.3	(2.1 - 14.0)	2.4	Good
Vena A	317	9.1	(6.2 - 12.9)	2.6	Good
Martín-Sánchez FJ	1379	2.8	(2.0 - 3.8)	2.6	Good
Bianchetti A	82	67.1	(55.8 - 77.1)	2.4	Poor
Hetherington L	169	10.7	(6.4 - 16.3)	2.5	Good
Vrillon A	76	71.1	(59.5 - 80.9)	2.4	Good
Mansella G	572	13.3	(10.6 - 16.3)	2.6	Good
Helms J	140	15.7	(10.1 - 22.8)	2.5	Moderate
Kennedy M	817	27.7	(24.6 - 30.9)	2.6	Good
Liguori C	103	22.3	(14.7 - 31.6)	2.4	Poor
Chen N	99	9.1	(4.2 - 16.6)	2.4	Good
De Smet R	81	42.0	(31.1 - 53.5)	2.4	Good
Mcloughlin BC	71	43.7	(31.9 - 56.0)	2.4	Good
Myrstad M	66	18.2	(9.8 - 29.6)	2.4	Good
Heath L	31	77.4	(58.9 - 90.4)	2.1	Moderate
Mendes A	220	12.3	(8.2 - 17.4)	2.5	Good
Pinato DJ	204	18.1	(13.1 - 24.1)	2.5	Good
Knopp P	217	29.5	(23.5 - 36.0)	2.5	Good
Poloni TE	57	36.8	(24.4 - 50.7)	2.3	Good
Zazzara MB(1)	210	25.2	(19.5 - 31.7)	2.5	Good
Zazzara MB(2)	238	35.3	(29.2 - 41.7)	2.5	Good
Maguire D	122	13.1	(7.7 - 20.4)	2.5	Good
Shi SM	146	18.5	(12.6 - 25.8)	2.5	Good
Graham NSN	126	34.1	(25.9 - 43.1)	2.5	Poor
Strang P(1)	101	38.6	(29.1 - 48.8)	2.4	Good
Strang P(2)	228	16.7	(12.1 - 22.2)	2.5	Good
Helms J	40	65.0	(48.3 - 79.4)	2.2	Good
Annweile C	353	26.6	(22.1 - 31.6)	2.6	Poor
Mathian A	17	5.9	(0.1 - 28.7)	1.9	Moderate
Ihle-Hansen H	73	15.1	(7.8 - 25.4)	2.4	Moderate
Total (random effects)	9031	24.3	(19.4 - 29.6)	100.0	

Heterogeneity: Q=1266.7, DF=40 (P<0.01); I^2=96.8%



b. Incidence rate

First author	COVID-19 patients, n	Incidence, %	(95 % CI)	weight, %	Study quality
Steinmeyer Z	94	11.7	(6.0 - 20.0)	6.3	Good
Alderman B	61	55.7	(42.4 - 68.5)	6.2	Good
Lombardi CM	396	4.0	(2.3 - 6.5)	6.5	Good
Zerah L	821	40.2	(36.8 - 43.6)	6.5	Good
Benussi A	56	26.8	(15.8 - 40.3)	6.2	Poor
Garcez FB	707	33.1	(29.6 - 36.7)	6.5	Moderate
Helms J	140	68.6	(60.2 - 76.1)	6.4	Moderate
Ticinesi A	852	11.0	(9.0 - 13.3)	6.5	Moderate
Khan SH	268	80.2	(74.9 - 84.8)	6.5	Moderate
D'Ardes D	56	25.0	(14.4 - 38.4)	6.2	Good
Myrstad M	66	16.7	(8.6 - 27.9)	6.2	Good
Fan S	86	12.8	(6.6 - 21.7)	6.3	Good
Shi SM	146	56.8	(48.4 - 65.0)	6.4	Good
Marengoni A	91	27.5	(18.6 - 37.8)	6.3	Moderate
Saida IB	10	50.0	(18.7 - 81.3)	4.9	Good
Ihle-Hansen H	73	24.7	(15.3 - 36.1)	6.2	Moderate
Total (random effects)	3923	32.4	(20.8 - 45.2)	100.0	

Heterogeneity: Q=952.7, DF=15 (P<0.01); I^2=98.4%

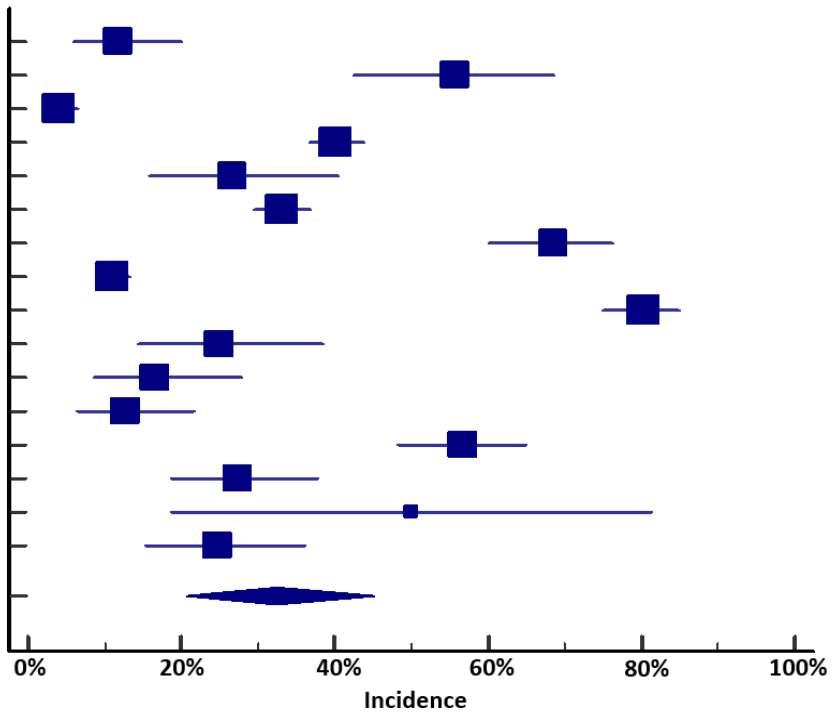


Figure 3. Mortality risk in COVID-19 patients with and without delirium

First author	Death / COVID-19 patients with delirium, n	Death / COVID-19 patients without delirium, n	Odds ratio	(95 % CI)	weight, %	Study quality
García Clemente MM	17/29	17/220	16.9	(7.0 - 41.2)	5.4	Good
Steinmeyer Z(1)	3/30	14/64	0.4	(0.1 - 1.5)	4.2	Good
Steinmeyer Z(2)	4/11	13/83	3.1	(0.8 - 12.0)	4.1	Good
Liu D	5/17	78/582	2.7	(0.9 - 7.9)	4.9	Moderate
Zerah L(1)	81/205	169/616	1.7	(1.2 - 2.4)	6.9	Good
Zerah L(2)	200/330	50/491	13.6	(9.4 - 19.6)	6.8	Good
Vena A	22/25	98/250	11.4	(3.3 - 39.0)	4.4	Good
Vrillon A	17/54	5/22	1.6	(0.5 - 4.9)	4.7	Good
Garcez FB	129/234	144/473	2.8	(2.0 - 3.9)	6.9	Moderate
Helms J	19/118	2/22	1.9	(0.4 - 8.9)	3.7	Moderate
Ticinesi A	432/758	28/94	3.1	(2.0 - 5.0)	6.6	Moderate
Kennedy M	84/226	154/591	1.7	(1.2 - 2.3)	6.9	Good
Khan SH	50/215	8/53	1.7	(0.8 - 3.9)	5.7	Moderate
De Smet R	8/34	11/47	1.0	(0.4 - 2.9)	5.0	Good
Mendes A	15/27	55/193	3.1	(1.4 - 7.1)	5.6	Good
Poloni TE	11/14	10/43	12.1	(2.8 - 52.1)	3.9	Good
Maguire D	10/16	29/106	4.4	(1.5 - 13.3)	4.8	Good
Marengoni A	18/25	21/66	5.5	(2.0 - 15.2)	5.1	Moderate
Ihle-Hansen H	8/26	6/47	3.0	(0.9 - 10.0)	4.5	Moderate
Total (random effects)	1133/2394	912/4063	3.2	(2.1 - 4.8)	100.0	

Heterogeneity: Q=129.0, DF=18 (P<0.01); I^2=86.1%