



Five-decade prevalence of delirium in pneumonia, risk factors and associated mortality: a systematic review and meta-analysis

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Delirium rates in pneumonia vary widely across studies. This meta-analysis establishes that delirium is common in pneumonia, driven by patient- and care-related factors rather than microbiology, including COVID-19, and consistently associated with mortality. <https://bit.ly/3Gu1wc7>

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Abstract

Background Delirium can occur in patients with pneumonia, but its prevalence is inconsistent across studies. Unreliable estimates and uncertainty regarding the significance of patient-specific *versus* microbiological risk factors hinder delirium management and prognosis. Here, we provide robust estimates of delirium prevalence in patients with pneumonia, associated risk factors and association with mortality.

Methods We searched five databases (Medline, Cochrane Library, Embase, PsycINFO and Scopus), from inception to 6 August 2024. We included studies in adults hospitalised with pneumonia reporting delirium, encephalopathy or altered mental status. Two investigators extracted data and assessed risk of bias. Summary rates were calculated using random-effects models. We performed prespecified analyses for diagnostic methods, microbiologic factors, clinical factors and mortality, with sensitivity analysis among studies at low risk of bias. The review protocol was registered with PROSPERO: CRD42023385571.

Results Delirium prevalence across 126 studies was 22% (95% CI 18–26%) and higher in studies at low risk of bias (40%, 95% CI 24%–58%; $n=11$). Standardised assessments yielded higher rates than symptom- or International Classification of Diseases code-based assessments ($p<0.05$). Surprisingly, delirium rates did not differ by microbiological aetiology ($p=0.63$), including COVID-19, nor by pneumonia origin ($p=0.14$). Predisposing factors included older age and neurologic and systemic comorbidities. Delirium was associated with increased mortality (odds ratio 4.3, 95% CI 3.24–5.76; $p<0.001$), without change over five decades ($p=0.32$).

Interpretation Delirium is highly prevalent and enduring in pneumonia, with nearly double the estimated prevalence when standardised diagnostic methods for both pneumonia and delirium are used. Our results emphasise patient- and care-related factors over microbiological causes, including COVID-19. Delirium's entrenched association with mortality, even considering covariates, reinforces the need to manage delirium as a convergent syndrome in pneumonia.

Introduction

Pneumonia is one of the most frequent causes of hospitalisation in the USA and the leading cause of infectious mortality worldwide [1, 2]. Delirium, an acute neuropsychiatric disorder characterised by disturbances in attention and awareness, is variably observed in patients hospitalised with pneumonia and has been associated with increased length of hospital stay and mortality [3–6]. To date, there is no consensus on delirium prevalence in patients with pneumonia across studies, with reported rates from lower than 10% to as high as 80%, raising concerns for potential under- or overdiagnosis [7–11]. Furthermore, the importance of key risk factors remains largely undetermined, given delirium's



multifactorial origin and the complex interplay between infection-specific *versus* patient-specific risk factors. This lack of consensus hampers efforts to anticipate, prevent and manage delirium effectively in patients with pneumonia.

In general, older age, cognitive impairment and severe illness are known risk factors for delirium across many different clinical conditions [12]. However, for pneumonia specifically, infection-related factors, such as the setting in which pneumonia is acquired, microbiological origin and the extent of lung involvement, may play important roles. Notably, during the COVID-19 pandemic, several studies reported increased rates of delirium in severe COVID-19 infections, suggesting a microbiology-related contribution [13, 14]. However, comparisons of delirium rates between COVID-19 and non-COVID-19 pneumonia aetiologies are wanting. This gap could result in an underappreciation of delirium in non-COVID-19 pneumonia populations.

Establishing reliable prevalence estimates of delirium in patients hospitalised with pneumonia and identifying the key factors influencing its occurrence and recognition are essential to guide healthcare providers in implementing targeted, multimodal strategies within the broader care of patients with pneumonia, to reduce delirium incidence, improve prognosis and mitigate mortality. This systematic review and meta-analysis addresses this knowledge gap by quantifying delirium prevalence across a wide population range, hospital settings and time periods, including the pre- and post-COVID-19 eras, evaluates the relevance of associated predisposing and precipitating risk factors for both infection and patient features, and robustly determines its association with mortality over time, even when accounting for other important clinical covariates.

Methods

We followed the Preferred Reporting in Systematic Review and Meta-Analysis guidance (PRISMA) [15]. The protocol was registered in PROSPERO, the international prospective register of systematic reviews (CRD42023385571).

Search strategy and eligibility criteria

We searched five databases: Medline, Cochrane Library, Embase, PsycINFO and Scopus, without filters or language limits, from inception to August 2024. We used controlled vocabulary and keywords related to the topics of 1) pneumonia, 2) delirium, encephalopathy, altered mental status (AMS) or confusion, and 3) hospitalisation. Multiple terms were used for delirium given fragmentation of nomenclature in the clinical literature [16, 17]. References were downloaded and deduplicated, and unique records were uploaded to Covidence for screening. Search strategies are detailed in table S1 and the numbers of studies initially obtained per database are detailed in table S2.

Our pre-registered inclusion criteria were studies describing adult patients (>18 years old) hospitalised with pneumonia reporting rates of delirium or related keywords. We only included studies from peer-reviewed journals. We *a priori* excluded studies with <20 patients with pneumonia, delirium tremens, chronic or nondelirium-related encephalopathies, and case-control or randomised-controlled designs, as in the former, the prevalence of delirium cannot be estimated from pre-selected populations, while in the latter intervention studies, rates of delirium may be less reflective of natural clinical progression. Two reviewers independently screened records at each stage and discrepancies were resolved through consensus. The PRISMA study flow diagram is shown in figure 1.

Data extraction and management

Two authors independently extracted data from included studies (E.L. Juarez-Martinez, D. Prasad or E.Y. Kimchi). Discrepancies were resolved through consensus. Extracted data fields are presented in the supplementary methods and summarised as follows: general study information; population demographics and comorbidities [18]; pneumonia diagnostic criteria, imaging, infection origin (*e.g.* community *versus* hospital-acquired) and microbiological aetiology; clinical severity indicators (CURB-65 (confusion, urea >7 mmol·L⁻¹, respiratory rate of ≥30 breaths·min⁻¹, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic and age ≥65 years) scores) [19], pneumonia severity index (PSI) scores [20], mechanical ventilation and intensive care unit (ICU) admission); delirium/encephalopathy assessment methods (*Diagnostic and Statistical Manual of Mental Disorders* (DSM)-based assessment [21] and validated delirium scales, *e.g.* the confusion assessment method (CAM) framework [22] or CAM-ICU [23]); nondelirium standardised assessments of mental status (*e.g.* the Glasgow Coma Scale [24], International Classification of Diseases (ICD) codes and nonstructured, symptom-based reports, *e.g.* tracking of individual symptom collections such as confusion, AMS or altered consciousness); and clinical outcomes (length of hospitalisation and stay in the ICU, length of ventilation and mortality). For mortality, we recorded deaths in the hospital, during follow-up and overall (hospital+follow-up). Follow-up deaths were

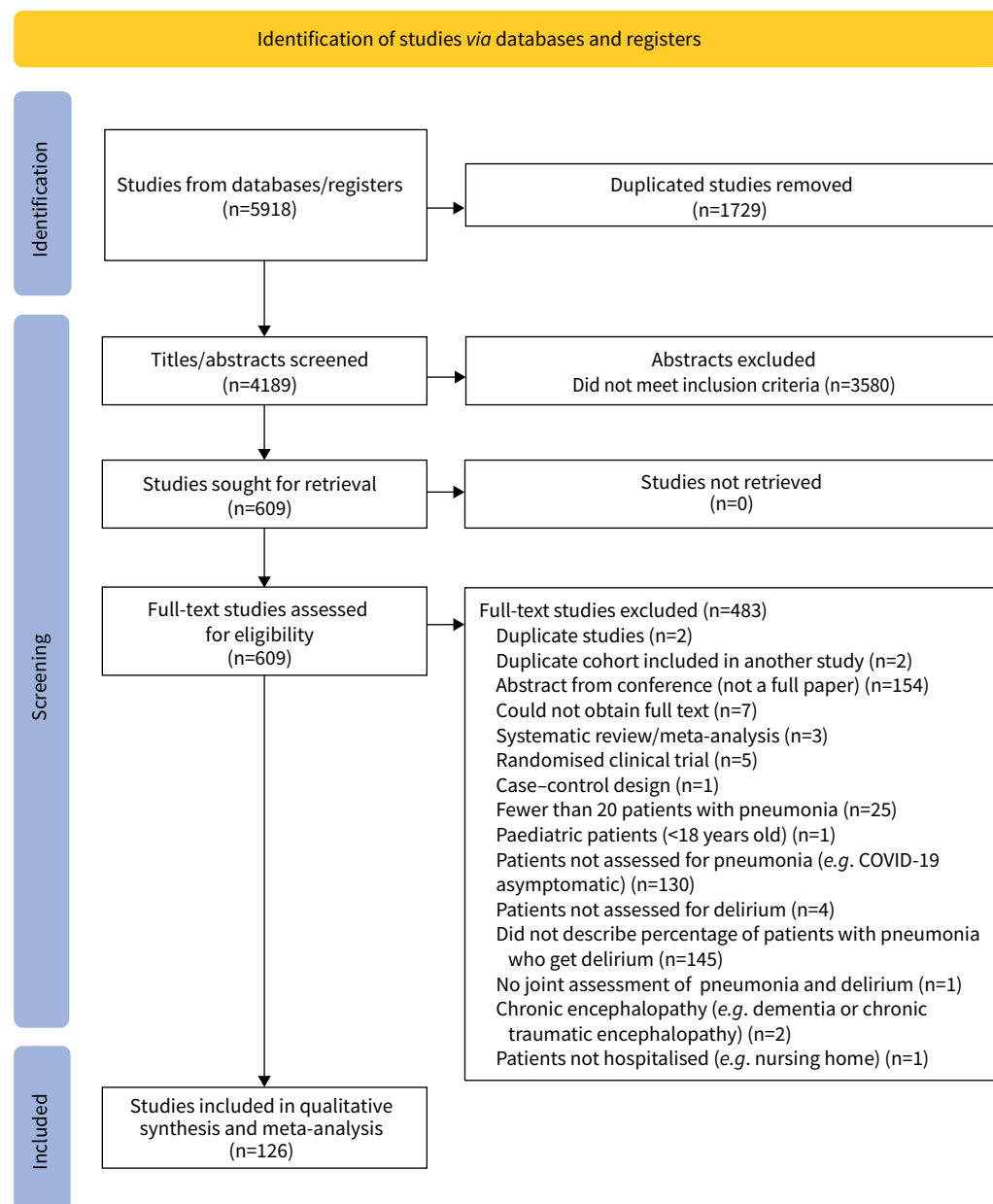


FIGURE 1 Preferred Reporting in Systematic Review and Meta-Analysis (PRISMA) flowchart.

analysed for up to 1 year after hospital discharge. Additionally, we recorded odds ratios from univariate analysis, as well as odds ratios from multivariable analyses when performed while controlling for clinical covariates.

Meta-analysis methods

Meta-analyses were performed in R (4.2.3) using the *metafor* package [25]. All primary analyses included all eligible studies and were performed at the study level, since individual patient data were not available across this broad set of studies. We used random-effects models for summary estimates of delirium prevalence given expected heterogeneity. The restricted maximum likelihood estimator (ReML) [26] was used to calculate the heterogeneity variance τ^2 . We also assessed between-study heterogeneity using the Higgins I^2 index, since it is robust to changes in the number of studies in the analysis, unlike the Cochrane Q test. We used Knapp–Hartung adjustments to calculate the confidence interval around the pooled effect [27]. Effect measures were calculated using the *metaprop*, *metabin* and *metacount* functions and the

metamedian [28] package (Hozo–Wan–Bland method), and were expressed as proportions, odds ratios and difference of means (DOM), respectively. Proportions were logit-transformed automatically in R before they were pooled. We created forest plots of all estimates with 95% confidence intervals. The contribution of each study to the pooled proportion was given by its weight based on the inverse variance of the study's proportion estimate. Publication bias was assessed using funnel plots [29] and supplemented with Eggers' regression test. The effects of publication bias were assessed using Rucker's limit meta-analysis method (*metasens* package) [30].

We performed prespecified subgroup analyses based on infection origin, microbiological agent, clinical care setting and delirium assessment method, including all studies that reported relevant data to minimise potential selection bias. Meta-regression using random-effects models was used to calculate R^2 , *i.e.* the proportion of variance in the dependent variable (delirium rate) explained by each model and subgroup effects. *Post hoc* comparisons were performed to test for subgroup differences compared to a gold standard subgroup when applicable or otherwise to the average proportion across all groups. *p*-values were adjusted for multiple comparisons using Holm's procedure. We ran separate analyses for studies that split cohorts into groups <65 and >65 years old, and cohorts that assessed delirium in groups based on gender, comorbidities, pneumonia severity factors or clinical care measures. *p*-values <0.05 were considered significant and corrected for multiple comparisons where indicated.

Quality and risk of bias assessment

Risk of bias was assessed by two independent reviewers using the JBI manual for evidence synthesis tool (table S3) [31]. Disagreements were resolved through consensus. The overall risk of bias was classified as "low" if studies met $\geq 6/8$ domains, including validated evaluation of both pneumonia and delirium. We conducted sensitivity analyses in studies at low risk of bias.

Results

Included studies

We identified 4189 articles after deduplication, of which 126 met inclusion criteria and were used for synthesis and meta-analysis (figure 1). These studies represent a total of 8 379 648 patients with pneumonia and included cohorts from Africa, Asia, Europe, North America and South America. Paper languages included English (*n*=113), Spanish (*n*=7), Chinese (*n*=2), Dutch (*n*=1), German (*n*=1), Japanese (*n*=1) and Portuguese (*n*=1). Study characteristics are shown in tables S4 and S5, and risk of bias assessments in figure S1.

Summary prevalence

The summary meta-analytic estimate for delirium was 22% (95% CI 18–26%) (figure 2). There was statistical heterogeneity in the results ($I^2=100\%$; $\tau^2=1.62$, 95% CI 1.4–2.4), which was expected and explored below [29]. Funnel plot analysis suggested the presence of true heterogeneity rather than nonreporting bias (figure S2), despite a suggestive Eggers' regression test (test 22.2, 95% CI 18.3–26.1; $\tau=11.1$; $p<0.0001$) [32]. Regardless, addressing publication bias using Rucker's limit meta-analysis method yielded a similar adjusted proportion delirium occurrence estimate of 19% (95% CI 16–23%).

The quality of the studies (risk of bias assessment) influenced delirium rates, explaining 6.2% of delirium rates variance ($R^2=6.21\%$, $F_{2,123}=4.35$, $p=0.015$). 11 studies had a low risk of bias, including both validated pneumonia and delirium assessment (2517 patients). In those studies, the reported occurrence of delirium was 40% (95% CI 24–58%) and higher compared to those at moderate (*n*=44 studies; 16%, 95% CI 12–20%; $p=0.005$) and high risk of bias (*n*=71 studies; 24%, 95% CI 18–31%; $p=0.0002$). Forest plots per risk of bias group with delirium rates, 95% confidence intervals and measures of heterogeneity are provided in figure S3.

Delirium assessment

Given the heterogeneity across studies, we investigated factors that may contribute to reported variability in delirium rates (figures S4–S7). Delirium rates were significantly influenced by assessment method ($R^2=36.7\%$, $F_{4,120}=15.2$, $p<0.0001$) (figure 3a). Compared to gold standard DSM diagnosis (*n*=12 studies; 34%, 95% CI 24–45%), delirium rates were similar when studies used validated delirium scales (*n*=20 studies; 40%, 95% CI 28–53%; $p=0.73$ compared to DSM) or standardised assessments of mental status (AMS scales) (*n*=7 studies; 45%, 95% CI 24–69%; $p=0.73$ compared to DSM). In contrast, compared to DSM diagnosis, delirium rates were lower when studies used nonstandardised symptom assessments (symptom collection) (*n*=78 studies; 18%, 95% CI 15–22%; $p=0.03$) or ICD codes (*n*=8 studies; 3%, 95% CI 2–6%; $p<0.001$). Forest plots for each subgroup analysis, including delirium rates and 95% confidence

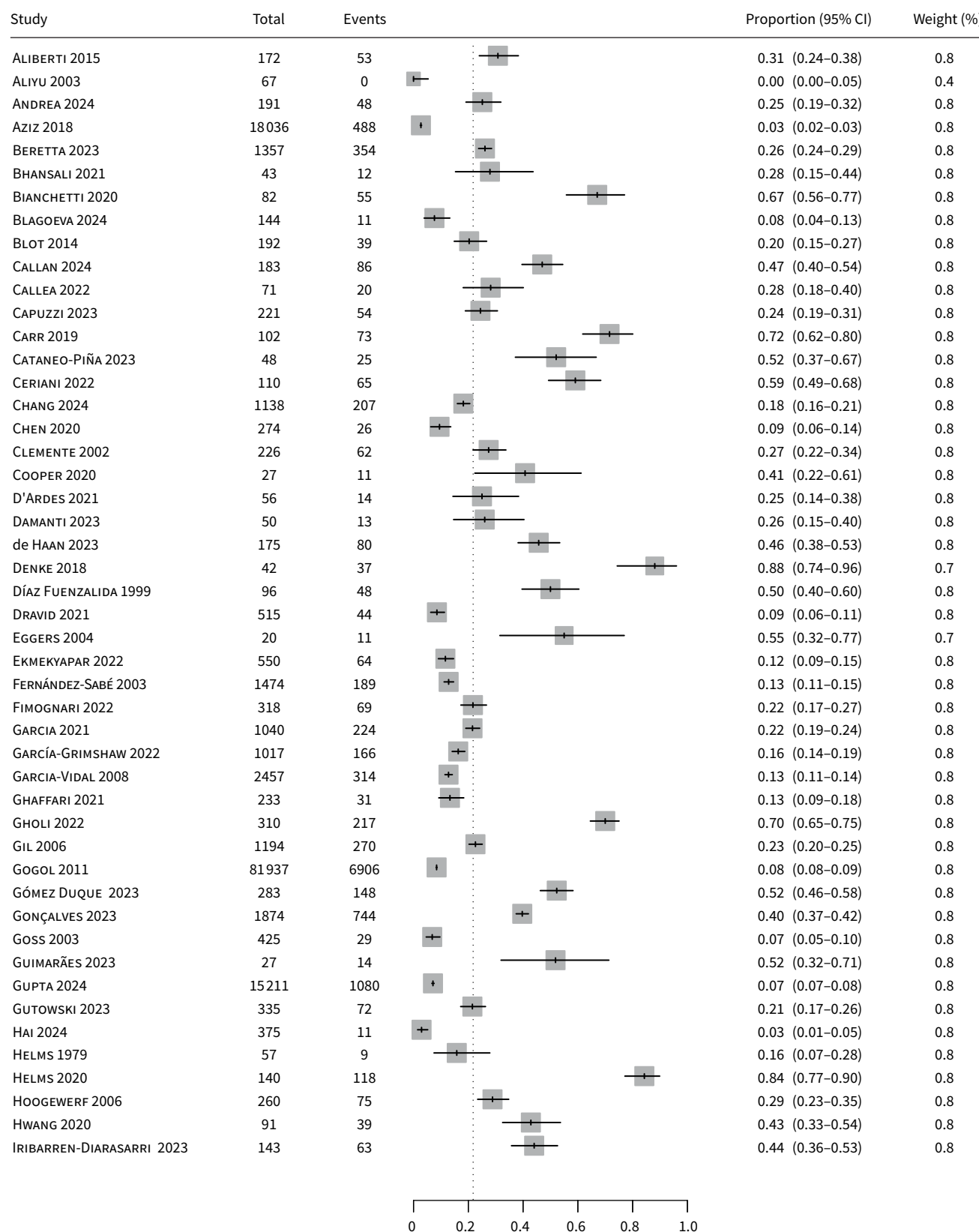


FIGURE 2 Summary estimate for occurrence of delirium in patients hospitalised with pneumonia. Effect measures were calculated using random-effects models and expressed as proportions. 126 studies were included and the overall summary rate was 0.22 (95% CI 0.18–0.26). References for the studies listed are provided in the supplementary material.

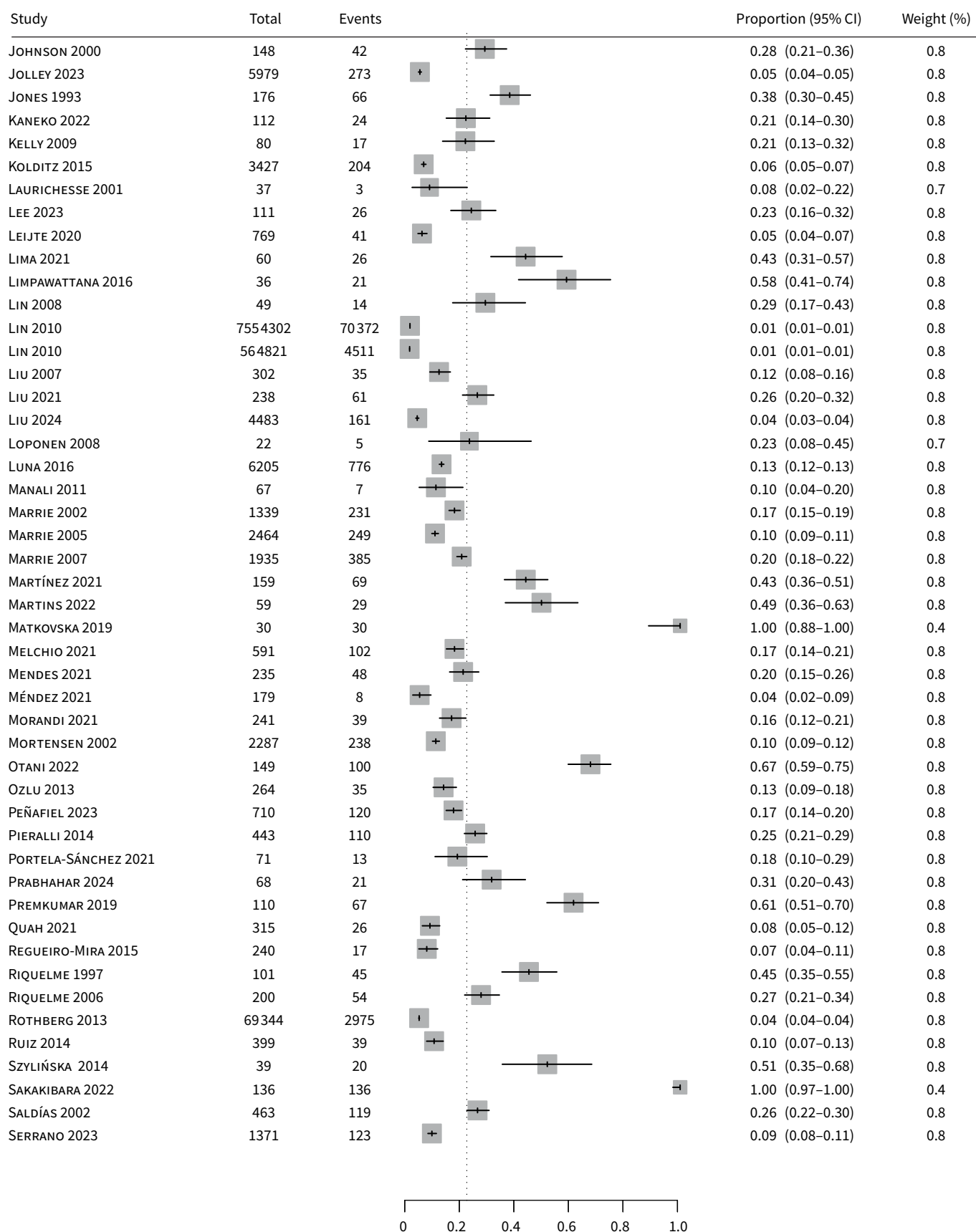


FIGURE 2 Continued.

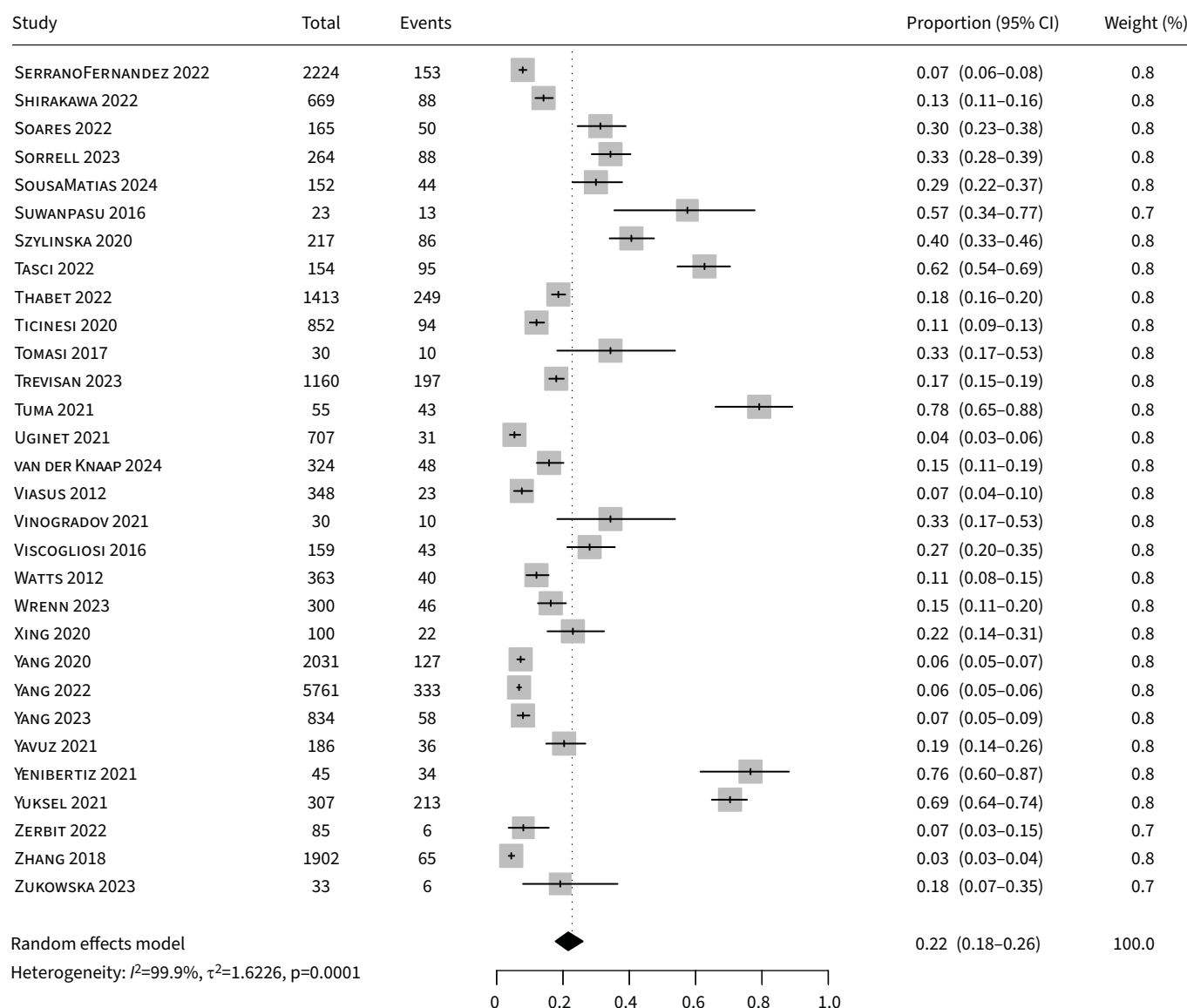


FIGURE 2 Continued.

intervals are shown in figure S4. Sensitivity analysis in studies at low risk of bias (in which ascertainment of delirium through validated methods was a criterion) showed similar results, with no difference in delirium rates when assessed using the DSM ($n=3$ studies; 30%, 95% CI 9–65%), standardised assessments of mental status (AMS scales) ($n=2$ studies; 59%, 95% CI 18–91%) and validated delirium scales ($n=6$ studies; 39%, 95% CI 13–74%) ($R^2=0.0\%$, $F_{2,8}=0.54$, $p=0.60$) (figure S8A). A forest plot for the sensitivity analysis per delirium assessment method is shown in figure S9A.

Hospital care setting

The hospital care setting in which the study was conducted was significantly associated with delirium rate ($R^2=12.1\%$, $F_{3,122}=5.2$, $p=0.002$). *Post hoc* comparisons showed that delirium occurrence was greater than average in studies conducted in the ICU ($n=16$ studies; 47%, 95% CI 33–63%; $p=0.0002$) (figure 3b). Forest plots for subgroup by hospital care setting, delirium rate and 95% confidence interval are shown in figure S5. Sensitivity analysis in studies at low risk of bias showed similar results, with delirium rates varying significantly according to the setting and explaining 68% of the variance ($R^2=68.3$, $F_{1,9}=20.06$, $p=0.0015$). Delirium rates were also higher in the ICU studies ($n=3$ studies; 73%, 95% CI 36–93%; $p=0.001$) than in hospital ward studies ($n=8$ studies; 27%, 95% CI 18–39%) (figure S8B). A forest plot for the sensitivity analysis per hospital study setting is shown in figure S9B.

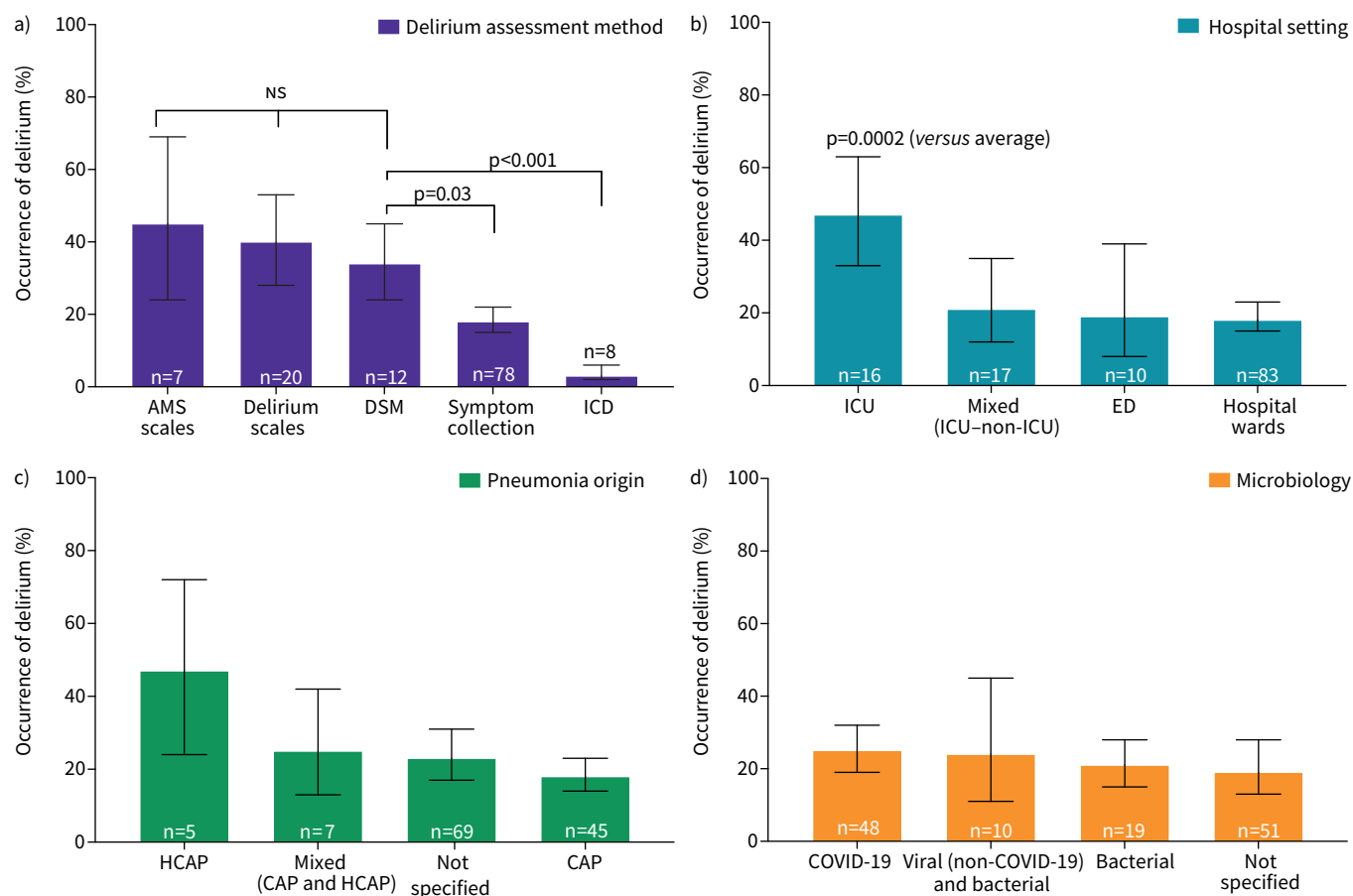


FIGURE 3 Delirium rates differ based on assessment methods and are higher in studies performed in intensive care units, but do not differ based on pneumonia origin or microbiological aetiology. **a)** Delirium rates varied significantly according to the assessment method used, which explained 37% of variance in delirium rates across studies ($R^2=36.8\%$, $p<0.0001$). Given that the assessment outlined in the *Diagnostic and Statistics Manual* (DSM) [21] is considered the gold standard for delirium assessment, we compared delirium rates to those of the DSM. Delirium rates were similar to the DSM assessment for standardised assessments of mental status (altered mental status (AMS) scales, such as the Glasgow Coma Scale or Richmond Agitation Sedation Scale, $p=0.73$) or validated delirium scales (such as the Confusion Assessment Method (CAM), the CAM-Intensive Care Unit, the Intensive Care Delirium Screening Checklist and the Four “A”s Test, $p=0.73$). In contrast, rates of delirium were lower when assessed using nonstructured symptom assessments (i.e., symptom collection, $p=0.03$) or International Classification of Disease (ICD) codes ($p<0.001$). Symptom collection: identification of relevant symptoms, e.g. chart report of AMS. Each bar represents a meta-analytic estimate of delirium rates, with the calculated 95% confidence interval. *Post hoc* p-values in all panels are adjusted for multiple comparisons (Holm). Forest plots of all studies with n data, meta-analytic proportion, confidence intervals and heterogeneity measures for each subgroup analysis are provided in the supplementary material (figure S4). **b)** Delirium rates varied significantly according to study setting, which explained 12% of variance in delirium rates across studies ($R^2=12.1\%$, $p=0.002$). Compared to the average of all studies, delirium rates were significantly higher for studies performed in the intensive care unit (ICU) ($p=0.0002$). Conventions as in **a)**, with forest plots provided in figure S5. **c)** Delirium rates did not vary significantly according to pneumonia origin, which explained only 2.4% of variance in delirium rates across studies ($R^2=2.4\%$, $p=0.15$). Conventions as in **a)**, with forest plots provided in figure S6. **d)** Delirium rates did not vary significantly according to microbiological aetiologies, which explained 0.0% of variance in delirium rates across studies ($R^2=0.0\%$, $p=0.63$). Conventions as in **a)**, with forest plots provided in figure S7. CAP: community-acquired pneumonia; ED: emergency department; HCAP: healthcare-acquired pneumonia; ns: nonsignificant.

Microbiological factors

Delirium rates did not differ significantly based on the origin of the infection (e.g. community-acquired versus healthcare-acquired pneumonia) ($R^2=2.4\%$, $F_{3,122}=1.8$, $p=0.146$) (figure 3c). Delirium rates also did not differ significantly based on the type of microbiological agent causing pneumonia, whether COVID-19 or other viral and/or bacterial causes ($R^2=0.0\%$, $F_{3,124}=0.57$, $p=0.630$) (figure 3d). Forest plots, delirium rates and 95% confidence intervals are shown for infection origin in figure S6 and for microbiological agents in figure S7. Sensitivity analysis in studies at low risk of bias showed similar results, with no difference in delirium rates based on infection origin ($R^2=0\%$, $F_{2,8}=0.26$, $p=0.77$) (figure S8C) or the

TABLE 1 Relationship of delirium to clinical factors, including baseline characteristics, comorbidities, measures of pneumonia severity and acute care, mortality, and length of clinical care

	OR	95% CI	p-value
Baseline characteristics			
Female (n=21)	0.93	0.73–1.20	0.578
Age >65 years (n=7)	2.87	2.37–3.47	<0.0001 [#]
Nursing home (n=3)	4.73	0.64–35.04	0.079
Smoking (n=6)	0.82	0.70–0.96	0.021 [#]
Alcohol (n=3)	2.06	1.02–4.16	0.047 [#]
Comorbidities			
Dementia (n=12)	4.13	3.07–5.55	<0.001 [#]
Stroke (n=9)	2.01	1.40–2.91	0.002 [#]
Respiratory disease (n=10)	1.75	1.35–2.27	0.001 [#]
Liver disease (n=5)	1.73	1.23–2.43	0.011 [#]
Kidney disease (n=10)	1.62	1.08–2.43	0.026 [#]
Hypertension (n=13)	1.41	1.04–1.91	0.032 [#]
Heart disease (n=14)	1.33	0.89–1.99	0.154
Diabetes (n=14)	1.19	0.99–1.43	0.063
Cancer (n=8)	1.03	0.51–2.09	0.918
Pneumonia severity and acute care			
ICU admission (n=21)	1.73	0.96–3.10	0.07
Invasive ventilation (n=15)	3.86	1.60–9.33	0.005 [#]
Noninvasive ventilation (n=17)	0.39	0.17–0.92	0.033 [#]
Multilobar pneumonia (n=6)	1.56	0.84–2.90	0.123
Dialysis (n=3)	4.12	2.07–8.17	0.012 [#]
Steroids (n=4)	0.44	0.08–2.52	0.232
Length of clinical care (days)			
	DOM	95% CI	p-value
Length of invasive ventilation (n=4)	+8.81	0.09–17.52	0.047 [#]
Length of ICU stay (n=2)	+7.58	–1.98–17.13	0.120
Length of hospitalisation (n=7)	+4.42	–0.64–9.49	0.087
Mortality			
Overall death (univariate) (n=41) [¶]	4.32	3.24–5.76	<0.001 [#]
Hospital death (n=39)	3.98	2.99–5.31	<0.001 [#]
Death during follow-up (n=4)	2.49	0.80–7.74	0.084
Overall death (multivariable) (n= 23) [¶]	2.92	2.18–3.92	p<0.0001

All comorbidities reflect reports of chronic disease prior to admission. Forest plots and measures of heterogeneity for each of baseline characteristics, comorbidities, pneumonia severity factors and acute care, length of clinical care, and mortality are shown in figures S10–S12, S15 and S17, and figure 4a, respectively. DOM: difference of means; ICU: intensive care unit; OR: odds ratios. [#]: Significant p-value <0.05. [¶]: Overall death=hospital death+death during follow-up.

type of microbiological agent ($R^2=0\%$, F_3 , $\gamma=0.04$, $p=0.98$) (figure S8D). Forest plots for the sensitivity analysis for infection origin are shown in figure S9C and for microbiological agents in figure S9D.

Predisposing factors

Next, we investigated potential predisposing factors for delirium (table 1 and figures S10–S12). Patients with pneumonia and delirium were older than those without delirium (n=18 studies; DOM +6.5 years, 95% CI 4.2–8.7 years; $p<0.0001$) (figure S10A). Studies stratifying patients into those younger and older than 65 years (n=7 studies) found that age >65 years was associated with delirium (OR 2.9, 95% CI 2.4–3.5; $p<0.0001$) (figure S10B). Gender was not associated with delirium, but alcohol intake was (n=3 studies; OR 2.1, 95% CI 1.02–4.16; $p=0.047$) (figure S11). Previous psychoactive treatments (hypnotics, sedatives and antipsychotics) were not significantly associated with delirium occurrence (n=4 studies; OR 2.47, 95% CI 0.72–8.40; $p=0.10$). Surprisingly, delirium was somewhat less likely in patients with a history of smoking (n=6 studies; OR 0.8, 95% CI 0.7–0.96; $p=0.021$).

Multiple comorbidities were associated with delirium (table 1 and figure S12), including neurologic disorders such as dementia (OR 4.1, 95% CI 3.1–5.5; $p<0.001$) and stroke (OR 2.0, 95% CI 1.4–2.9; $p=0.002$), and chronic respiratory disease (COPD) (OR 1.7, 95% CI 1.3–2.3; $p=0.001$). Delirium was also associated with liver disease (OR 1.7, 95% CI 1.2–2.4; $p=0.011$), kidney disease (OR 1.6, 95% CI 1.08–

2.43; $p=0.026$) and hypertension (OR 1.4, 95% CI 1.04–1.91; $p=0.032$). We found no association between delirium and diabetes, heart disease or cancer ($p<0.05$).

Sensitivity analysis in studies at low risk of bias corroborated that patients with delirium were older than those without delirium ($n=5$ studies; DOM +6.2 years, 95% CI 1.5–10.9 years; $p=0.01$) (table S6 with forest plots in figure S13). Neurological comorbidities remained associated with delirium such as dementia ($n=3$ studies; OR 4.1, 95% CI 1.9–8.9; $p=0.015$) and stroke ($n=4$ studies; OR 2.2, 95% CI 1.3–3.7; $p=0.017$), but other systemic comorbidities did not show a significant association (table S6 with forest plots in figure S14).

Pneumonia and acute clinical severity

We next analysed if factors related to pneumonia severity were associated with delirium (table 1 and figure S15). Delirium was more likely in patients treated with invasive ventilation (OR 3.9, 95% CI 1.60–9.33; $p=0.005$) and less likely in patients treated with noninvasive ventilation (OR 0.4, 95% CI 0.17–0.92; $p=0.033$). The association between delirium and ICU admission did not reach statistical significance (OR 1.7, 95% CI 0.96–3.1; $p=0.07$). Delirium was more likely with renal replacement therapy (OR 4.1, 95% CI 2.1–8.2; $p=0.012$). Pneumonia severity scores (*e.g.* PSI or CURB-65) were not consistently reported for patients with and without delirium and none of the identified papers split patients by delirium status for septic shock, acute respiratory distress syndrome (ARDS) or pleural effusion. Sensitivity analysis in studies at low risk of bias did not show a significant association with pneumonia severity factors, albeit very few studies reported them, including ICU admission ($n=3$ studies; OR 2.7, 95% CI 0.57–12.49; $p=0.11$) and invasive ventilation ($n=1$ study; OR 5.3, 95% CI 0.10–272.3; $p=0.41$) (figure S16).

Clinical outcomes

We investigated if there was an association between delirium and clinical outcomes (table 1 and figure S17). Delirium was associated with a significantly increased length of invasive ventilation ($n=4$ studies; DOM +8.8 days, 95% CI 0.1–17.5 days; $p=0.047$), but not ICU stay ($n=2$ studies; DOM +7.6 days, 95% CI –1.9–17.1 days; $p=0.120$) nor length of hospitalisation ($n=7$ studies; DOM +4.4 days, 95% CI –0.6–9.5 days; $p=0.087$). Most importantly, delirium was associated with increased overall mortality ($n=41$ studies; OR 4.3, 95% CI 3.2–5.7; $p<0.001$) (figure 4a) and, specifically, with hospital death ($n=39$ studies; OR 3.98, 95% CI 2.99–5.31; $p<0.001$) (table 1). This association between delirium and mortality remained significant in studies applying multivariable models to control for clinical covariates ($n=23$ studies; OR 2.9, 95% CI 2.2–3.9; $p<0.0001$) (table 1). Sensitivity analysis showed similar results (table S6). Delirium remained associated with increased length of invasive ventilation, though this was available only in one study (DOM +6 days, 95% CI 1.54–10.46 days; $p=0.008$) (figure S18). Importantly, delirium continued to be associated with increased mortality in studies at low risk of bias for both univariate analyses ($n=6$ studies; OR 3.7, 95% CI 1.14–12.05; $p=0.036$) (table S6 and figure S19A) and in studies that controlled for clinical covariates with multivariable analyses ($n=5$ studies; OR 2.16, 95% CI 1.2–3.9; $p=0.023$) (figure S19B).

Delirium prevalence and mortality association over time

Finally, we analysed if there has been a change in delirium prevalence and its association with mortality over time. Meta-regression analysis of delirium prevalence using year of publication as a continuous variable showed no difference in rates of delirium throughout five decades, including the COVID-19 era ($n=126$ studies, $R^2=0.08$, $F_{1,124}=1.45$, $p=0.23$) (figure 4b). Additionally, the association of delirium and mortality over five decades also remained unchanged ($n=126$ studies, $R^2=0.05$, $F_{1,39}=1.01$, $p=0.32$) (figure 4c).

Discussion

To resolve inconsistencies in the occurrence and relationship of delirium with pneumonia, we performed a systematic review and meta-analysis yielding over 100 studies from over five decades of research across multiple continents and languages, diverse hospital settings and varied pneumonia aetiologies, including pre- and post-COVID-19 eras. We provide a robust estimate of delirium, determining that it occurs in approximately one in every five patients with pneumonia (22%). The prior lack of reliable estimates, including uncertainty regarding the roles of patient-specific *versus* microbiological risk factors, has hindered delirium management and prognosis. Included studies displayed an expected amount of heterogeneity; however, our adjusted estimate of delirium occurrence, after accounting for small-study effects and between study heterogeneity, yielded similar rates of delirium (19%). Interestingly, our results are in line with systematic reviews on delirium occurrence in hospitalised patients for other common conditions [33], *e.g.* urinary tract infections [34], surgical and oncological procedures [35–37], and stroke [38] (17%–25%). This suggests that across diverse conditions, delirium might be more strongly associated with patient- and care-specific factors, rather than unique pathologies or infectious aetiologies. The large number of studies in our systemic review allowed us to evaluate these hypotheses directly within patients with pneumonia.

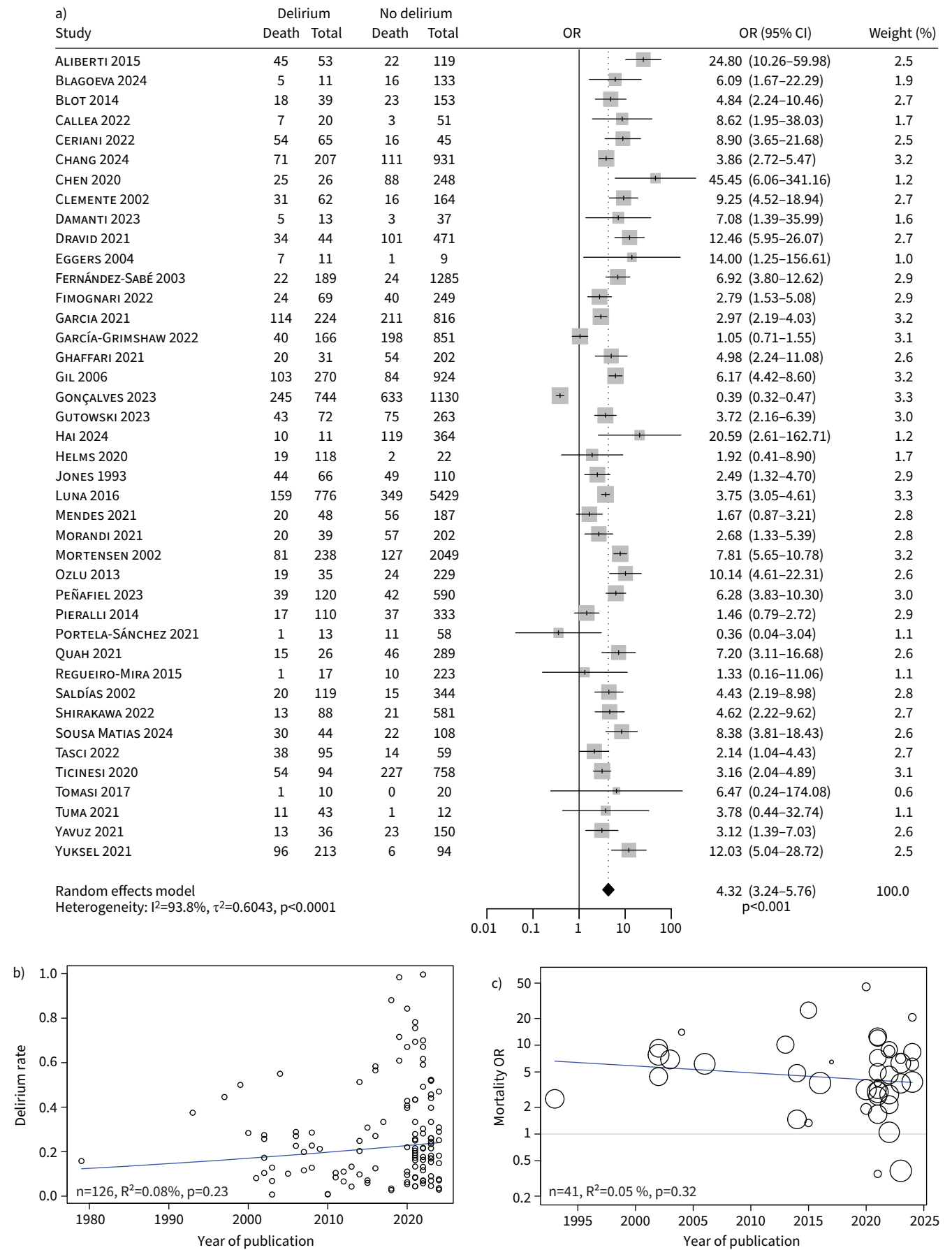


FIGURE 4 Delirium is associated with significantly increased mortality in patients with pneumonia and has not changed over time. **a)** Pooled effect of studies demonstrating the association between delirium and mortality using univariate analysis ($n=41$ studies; OR 4.3, 95% CI 3.24–5.76; $p<0.001$). This association remained significant in studies applying multivariable models to quantify the relationship of delirium and mortality while controlling for clinical covariates (table 1). **b)** Meta-regression analysis measuring the prevalence of delirium in patients hospitalised with pneumonia over time shows steady rates including during the COVID-19 era ($R^2=0.08$, $F_{1,124}=1.45$, $p=0.23$). **c)** Notably, the association of delirium and mortality over time remains unchanged ($R^2=0.05$, $F_{1,39}=1.01$, $p=0.32$). Each circle represents one study and the size of the circles represents the study weight (studies with a higher precision, *i.e.*, with a smaller standard error, receive a greater weight). References for the studies listed in this figure are provided in the supplementary material.

Delirium assessment methods influence delirium rates

There was substantial variation in how studies defined and assessed delirium, which significantly contributed to delirium rates variability. ICD determination of delirium and less formal and less validated symptom assessments likely underestimate delirium compared to gold standard DSM diagnosis, whereas validated delirium or other mental status assessment scales yield similar, higher estimates. Our sensitivity analysis, which showed nearly double the delirium rate (up to 40%) in studies at low risk of bias, reinforces the latter finding and underscores the need for standardised assessments in clinical care. Critically, only 30% of the studies used validated delirium methods or standardised assessments of mental status, being more common in studies conducted in the ICU (70%) than hospital wards (30%). Thus, implementation strategies are needed to ensure that standardised assessments are adopted consistently across all care settings to determine the prevalence and impact of delirium reliably.

Infection-related factors were not associated with delirium rates

We hypothesised that delirium rates might be influenced by pneumonia-specific factors, such as microbiological aetiology or infection origin. Our results showed that microbiological aetiology, including COVID-19, was not significantly associated with delirium rates. While delirium is a highly recognised neuropsychiatric disorder accompanying COVID-19 infection [13, 14], we show that in a broader pneumonia context, other groups of aetiological agents, such as bacteria (*e.g.* *Streptococcus pneumoniae* or *Staphylococcus aureus*) or other viruses (*e.g.* influenza A H1N1), are similarly associated with delirium. Notably, many studies did not document a specific microorganism ($n=52$), which reflects the difficulty in determining pneumonia aetiology using standard culture-based diagnosis. Our findings, however, endorse a mechanism for delirium common to diverse infectious organisms, *e.g.* an exacerbated inflammatory and immune responses, increased procoagulant states or altered cerebral perfusion, or general hypoxia [39–42]. Efforts to shed a light into pathophysiological mechanisms related to delirium in severe illness support a key role of inflammation, reflected by increased levels of interleukin (IL)-6, IL-8, IL-10, tumour necrosis factor (TNF)- α , TNFR1, protein S100 β and pathological pathway convergence [43–47]. Additionally, infection contracted in healthcare settings compared to community acquired pneumonia had similar rates of delirium, suggesting that the clinical impact and severity of pneumonia may drive delirium more than its cause.

Care-specific factors were related to delirium rates

Nonmicrobiologic, case-specific factors significantly influenced delirium rates. Delirium was more common in studies conducted in the ICU setting [48, 49]. Across all studies, care for acute organ failure such as invasive ventilation and dialysis were associated with increased rates of delirium. Unfortunately care information was only provided in a small set of studies at low risk of bias. These data currently cannot determine whether decreased sedation and accelerated weaning from ventilation can decrease delirium [50–52], but highlight the importance of studying clinical support for organ failure in high quality studies of delirium and pneumonia, following the criteria identified (*e.g.* standardised assessment of mental status). Overall, our analysis indicates that delirium in pneumonia is more strongly associated with care-specific factors and illness severity rather than specific infectious aetiologies. Our results suggest opportunities for broadly oriented, system-level delirium prevention and management, which is critical given that up to 40% of delirium could be prevented [50, 53–55]. Such measures are likely to remain important well beyond any particular pandemic (such as COVID-19), given the ongoing evolution of respiratory threats [56].

The role of comorbidities in predisposition to delirium

Delirium is thought to have a multifactorial pathophysiology including predisposing and precipitating factors [57]. In other patient populations, predisposing vulnerabilities include older age, cognitive impairment, critical illness, vision impairment, lower functional status and dehydration [58, 59]. Within the context of pneumonia, older age, dementia and stroke continued to be the strongest predisposing factors for delirium, consistent with the frequent superimposition of delirium on severe brain disorders such as dementia and stroke [38, 60, 61]. Our results highlight that *pre-established* brain disorders, in which

resilience and cognitive reserve are hampered by either neurodegeneration or a localised lesion, increases delirium vulnerability in the context of respiratory infection [62].

Across all studies, the next strongest predisposing risk factor for delirium, among those with pneumonia, was chronic respiratory illness, including COPD [63]. A superimposed lung infection in patients with limited lung function may lead more easily to respiratory failure, mechanical ventilation and ICU admission, suggesting decreased resilience across the organ system most affected by pneumonia. Extensive literature suggests a link between smoking and increased risk of delirium in critically ill or post-operative settings, albeit a direct association remains uncertain [64, 65]. Surprisingly, in our study, smoking instead appeared to be associated with a decreased risk of delirium. Two important factors, however, were not reported in the papers. First, the association between smoking and delirium in prior studies seems linked to acute cessation and nicotine withdrawal [64, 66], but papers did not report whether smoking history was recent or remote. Second, the effects of nicotine replacement therapy, as a cholinergic agonist with plausible protective effects on delirium, are mixed [67–70] and papers did not report what therapies were provided. Given that self-reports of smoking may differ from biochemical measures [64], more research with careful characterisation of smoking and cessation timing, as well as treatments, are needed to understand the link between delirium, smoking and cholinergic networks across clinical contexts.

Other systemic comorbidities were also associated with delirium, including liver disease, kidney disease and hypertension, remarking the importance of close monitoring of three organ systems that can be directly associated with acute metabolic encephalopathy [71–73]. However, studies at lower risk of bias did not routinely report rates of systemic predispositions, suggesting the importance of future work to verify which organ system dysfunction are most reliably associated with delirium in pneumonia. Systemic disorders may play an important role in delirium through diverse mechanisms and delirium should be assessed consistently in studies of other organ interventions. For instance, for hepatic encephalopathy, hyperammonaemia can induce astrocyte and microglia reactivity, a pro-inflammatory state, altered neurotransmission and oxidative stress, contributing to (acute) impairments in cognitive function [71]. Similarly, renal failure may exacerbate delirium through upregulated inflammatory processes that contribute to blood–brain barrier disruption and release of proinflammatory cytokines [72]. Blood pressure variability as seen with hypertension in critical illness has also been associated with delirium and linked to microvascular damage and blood–brain barrier disruption, [74] which may be a modifiable factor that could be incorporated into delirium prevention. These predisposing factors should be added or continue to be integrated into predictive models to identify high-risk patients and implement preventive strategies [75].

Delirium is associated with worse clinical outcomes in patients with pneumonia

Delirium is consistently associated with worse clinical outcomes, including increased mortality across diverse conditions [60]. Here, delirium was associated with increased length of invasive ventilation, though length of ICU stay and hospitalisation were not statistically significantly different. Most importantly, delirium was associated with significantly increased mortality in patients with pneumonia, even in studies controlling for factors that would be independently related to increased death (e.g. age, ventilation status and comorbidities). We corroborated these findings also in studies at low risk of bias. While delirium may reflect illness severity not fully accounted for by covariates, and its causal relationship with mortality remains undetermined, delirium may contribute to increased mortality in at least some cases through complications such as aspiration, inappropriate antipsychotic use and falls [76–78].

The association between delirium and mortality remained unchanged over the past five decades

Despite increased research into delirium's pathophysiology and essential guidelines on its prevention and management [50–55], mortality outcomes have seen little improvement. As we discussed, this persistent gap may stem from fundamental issues, such as under-recognition of delirium, misconceptions about its true prevalence and, thus, its clinical relevance. Our study addresses this gap by providing a reliable estimate of delirium prevalence in pneumonia and key insights into factors influencing its occurrence and recognition. Ultimately, the entrenched link between delirium and mortality underscores the urgent need for renewed efforts in research, implementation and clinical practice to change delirium's prognosis in patients with pneumonia.

Limitations

General limitations inherent to large systematic reviews were the high heterogeneity across studies, reflecting methodological differences, which we accounted for through pre-planned subgroup analyses. Pharmacologic therapies including sedatives and even antibiotics are important factors associated with delirium, but their relationship was not explored in the studies included, possibly due in part to the difficulty of assessing confounding by indication. We identified an association between delirium and

pneumonia severity factors; however, there was surprisingly limited data on the timing of delirium and important complications such as ARDS and lung protective ventilation strategies preventing us from inferring a causal relationship. Further studies are needed to understand the independent relationship between delirium and the risk factors we identified, guided by the above results.

Conclusions

Delirium is highly prevalent and persistent in pneumonia and is identified at nearly twice the rate when standardised diagnostic tools are used for both pneumonia and delirium. Our results emphasise patient- and care-specific factors, over microbiological causes, including COVID-19. Delirium's entrenched association with mortality, even controlling for covariates, reinforces the urgent need of improving its prevention and management as a convergent syndrome in pneumonia.

Points for clinical practice

- Delirium is common in patients with pneumonia, affecting approximately one in five patients.
- Standardised and validated methods to assess delirium are essential for reliable diagnosis, with consistent use necessary across all care settings.
- Delirium in pneumonia is primarily associated with care-specific and illness severity factors rather than infectious aetiologies, endorsing shared mechanisms across multiple causes of pneumonia.
- Our results suggest the importance of broadly oriented, system-level delirium prevention and management beyond the context of any specific respiratory pandemic, such as COVID-19.
- Delirium's persistent association with mortality calls for renewed efforts in research, implementation and clinical efforts to improve delirium prognosis in patients with pneumonia.

Data availability: Data are available upon request from qualified investigators.

Provenance: Submitted article, peer reviewed.

The systematic review protocol was registered with PROSPERO (<https://www.crd.york.ac.uk/prospero/>) with identifier: CRD42023385571.

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