BMJ Open Diabetes Research & Care

In-hospital hyperglycemia but not diabetes mellitus alone is associated with increased in-hospital mortality in community-acquired pneumonia (CAP): a systematic review and meta-analysis of observational studies prior to COVID-19

Rahul D Barmanray ,[1,2] Nathan Cheuk,[1] Spiros Fourlanos ,[1,3] Peter B Greenberg,[4] Peter G Colman,[1,3] Leon J Worth[2,5]

To cite: Barmanray RD, Cheuk N, Fourlanos S, *et al*. In-hospital hyperglycemia but not diabetes mellitus alone is associated with increased in-hospital mortality in community-acquired pneumonia (CAP): a systematic review and meta-analysis of observational studies prior to COVID-19. *BMJ Open Diab Res Care* 2022;**10**:e002880. doi:10.1136/bmjdrc-2022-002880

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2022-002880).

Received 4 April 2022
Accepted 8 June 2022

Linked

► http://dx.doi.org/10.1136/bmjdrc-2022-003011

Check for updates

For numbered affiliations see end of article.

Correspondence to
Dr Rahul D Barmanray; rahul.barmanray@mh.org.au

ABSTRACT

The objective of this review was to quantify the association between diabetes, hyperglycemia, and outcomes in patients hospitalized for community-acquired pneumonia (CAP) prior to the COVID-19 pandemic by conducting a systematic review and meta-analysis. Two investigators independently screened records identified in the PubMed (MEDLINE), EMBASE, CINAHL, and Web of Science databases. Cohort and case–control studies quantitatively evaluating associations between diabetes and in-hospital hyperglycemia with outcomes in adults admitted to hospital with CAP were included. Quality was assessed using the Newcastle-Ottawa Quality Assessment Scale, effect size using random-effects models, and heterogeneity using I^2 statistics. Thirty-eight studies met the inclusion criteria. Hyperglycemia was associated with in-hospital mortality (adjusted OR 1.28, 95% CI 1.09 to 1.50) and intensive care unit (ICU) admission (crude OR 1.82, 95% CI 1.17 to 2.84). There was no association between diabetes status and in-hospital mortality (adjusted OR 1.04, 95% CI 0.72 to 1.51), 30-day mortality (adjusted OR 1.13, 95% CI 0.77 to 1.67), or ICU admission (crude OR 1.91, 95% CI 0.74 to 4.95). Diabetes was associated with increased mortality in all studies reporting >90-day postdischarge mortality and with longer length of stay only for studies reporting crude (OR 1.50, 95% CI 1.11 to 2.01) results. In adults hospitalized with CAP, in-hospital hyperglycemia but not diabetes alone is associated with increased in-hospital mortality and ICU admission. Diabetes status is associated with increased >90-day postdischarge mortality. Implications for management are that in-hospital hyperglycemia carries a greater risk for in-hospital morbidity and mortality than diabetes alone in patients admitted with non-COVID-19 CAP. Evaluation of strategies enabling timely and effective management of in-hospital hyperglycemia in CAP is warranted.

INTRODUCTION

Diabetes mellitus increases the risk of developing multisystem complications predominantly through hyperglycemia-mediated adverse effects on the vasculature, immune system, and end organs. Among these complications is an increased risk of infections[1] contributing to an increased frequency of hospitalization for infectious diseases in people with diabetes.[2] Community-acquired pneumonia (CAP) contributes significantly to the burden of infection-related hospitalization, with significant consequential healthcare expenditure.[3] As the prevalence of diabetes continues to increase, it is expected that hospitalizations due to CAP will also increase.[4] Better understanding and quantification of the morbidity and mortality of patients with diabetes requiring hospitalization for CAP might alleviate the burden of diabetes on communities and healthcare systems.

While several studies have considered the relationship between diabetes and CAP, contextual and temporal heterogeneities prevent estimations of the contribution of diabetes to CAP morbidity and mortality in hospitalized patients. Given the marked discrepancies between clinical definitions employed in prior studies, it is also unclear on a prima facie basis what proportion of diabetes-related morbidity in CAP can be attributed to inpatient hyperglycemia, an important distinction given that this may be a potentially modifiable risk factor. Furthermore, hyperglycemia in the absence of diagnosed diabetes as a contributor to CAP hospital outcomes is seldom reported and thus incompletely understood.

Since the onset of the COVID-19 pandemic, multiple studies considering the relationship between diabetes, glycemia, COVID-19 infection, and pneumonia have been published. Both diabetes and new hyperglycemia have been associated with increased risk of adverse

outcomes in patients hospitalized with COVID-19 in international cohorts (although not universally), with ORs for mortality conferred by pre-existing diabetes ranging from 1.49 to 3.64.[5–9] The increased morbidity and mortality conferred by hyperglycemia independent of the contribution of diabetes are less well characterized. One study found hyperglycemia in those without previously diagnosed diabetes to confer an HR of 5.38 (95% CI 3.46 to 8.35) for intensive care unit (ICU) admission compared with those without hyperglycemia or diabetes.[8]

During the COVID-19 pandemic, there was a reduction in non-COVID-19 CAP, likely through infection control measures such as mask wearing and social distancing reducing CAP of viral etiology.[10 11] Bacterial etiologies were thought to have remained largely unaffected by these measures. However, as rising vaccination rates and public health measures begin to reduce the burden and severity of COVID-19 infections leading to hospitalization, and non-vaccine infection control measures are relaxed, endemic causes of CAP may re-emerge as precipitants of hospitalization for those with CAP. In this context, prepandemic data establishing the associations between diabetes and hyperglycemia with CAP outcomes will again become relevant. We therefore conducted a systematic review and meta-analysis to determine the impact of both diabetes alone and of hyperglycemia on outcomes in hospitalized patients with CAP.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for design, conduct, and reporting.[12 13] The review protocol was not registered.

Eligibility criteria

This review sought published studies that quantitatively assessed associations between both 'diabetes' and 'in-hospital hyperglycaemia' on outcomes in adults admitted to hospital with CAP. Outcomes considered included mortality, length of stay, and ICU admission. Cohort studies and case-control studies were eligible while case reports and series were excluded. Cross-sectional studies also were excluded due to uncertain temporal relationships between exposures and outcomes. Included studies assessed participants aged 18 years or older, as the management of pneumonia in children and young adolescents differs from that in adults. Eligible studies were reported in English, with full text available.

Definitions

Standard definitions of CAP included either a clinical diagnosis comprising clinical features and consistent radiological findings, with onset prior to or within 48 hours of hospitalization in the absence of recent inpatient healthcare contact, or discharge coding consistent with CAP. Standard definitions of diabetes mellitus included treatment with glucose-lowering medications, biochemical diagnosis consistent with prevalent guidelines, discharge coding, and patient self-report. It should be noted that there are issues with each of these definitions, for example, treatment with glucose-lowering medications may be instituted for conditions other than diabetes including pre-diabetes, while patient self-report is subject to recall bias. However, few studies use only a single definition. Given the marked heterogeneity in definitions of hyperglycemia, included definitions were glucose concentrations of 7.0 mmol/L (126 mg/dL) or greater. Studies of admitted patients with hyperglycemia were included regardless of whether participants had or did not have a diagnosis of diabetes.

Search strategy and data sources

The following databases were searched from inception (1950) to 4 June 2019: PubMed (MEDLINE), EMBASE, CINAHL, and Web of Science. MeSH and free-text terms were used to search PubMed. We searched for the MeSH headings 'Pneumonia', 'Diabetes Mellitus', 'Hyperglycemia' and the text strings 'pneumoni*', 'diabet*', 'hyperglyc*'. MeSH headings were exploded and text strings were searched for in titles, abstracts, subject headings, and keyword headings. EMTREE and free-text terms were used to search EMBASE. Free-text terms were used to search CINAHL and Web of Science. The strategies sought publications referring to both pneumonia and either diabetes mellitus or hyperglycemia, or derivations thereof.

Study selection

Title and abstract screening was performed independently by two investigators (RDB, NC), who then reviewed full-text publications. Review-specific eligibility forms were created in PRISMA-compliant review software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) for each step of the review process with forms available on request. Discordance was resolved by case review with both investigators seeking consensus and a third investigator (LJW) consulted when this was not achieved.

Data extraction

Publication data were extracted independently by two investigators (RDB, NC) who then performed simultaneous comparisons to verify the accuracy of extracted data. Extracted data included first author, journal citation, year of publication, study location, funding, study design, data source, duration, population characteristics, and study-specific data including: inclusion and exclusion criteria, definitions, measures of association, and statistical methods.

Quality assessment

Quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS)[14] according to recommended procedures by two investigators (RDB, NC). Discordance was resolved by case review with both investigators seeking consensus and a third investigator consulted when this

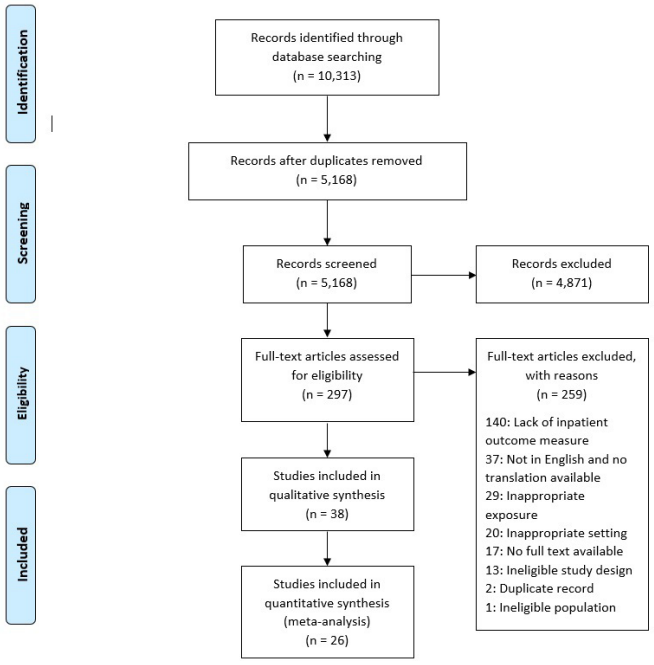


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

was not achieved. The NOS allocates a maximum of nine stars across three domains: participant selection (four stars); group comparability (two stars); and ascertainment of either the exposure or outcome (three stars). If any item is not reported, a zero score is applied. We classified study quality according to the study score into low (score 0–3), moderate (score 4–6) and high quality (score 7–9).

Data synthesis and analysis

Characteristics of included studies were described in multiple publication and data-related domains. Where equivalence of measures allowed, meta-analysis was performed. Crude and adjusted results were pooled separately. Crude data meta-analyses use the Mantel-Haenszel method and the DerSimonian-Laird random-effects model with Hartung-Knapp adjustment. Adjusted measures included were the most adjusted statistical model from each study (covariates vary and are described in online supplemental tables 2 and 3). Adjusted data meta-analyses use the inverse variance method and the DerSimonian-Laird random-effects model. Summary measures were reported as ORs. Heterogeneity was assessed with Higgins and Thompson's I^2.[15]

To account for variability in definitions of hyperglycemia, published study data were categorized with data-derived cut-points. Category A was defined as a study-defined hyperglycemia cut-point of ≤7.8 mmol/L, category B as 7.9–11.0 mmol/L, category C as ≥11.1 mmol/L and category D as not defined. Where a study defined hyperglycemia as a range with an upper boundary and lower boundary, the lower boundary was used to define the category. Studies with multiple grades of definitions of hyperglycemia, for which outcome data were reported separately, were thus able to contribute data to more than one hyperglycemia category.

All statistical analyses were performed in R V.3.6.0 (R Project for Statistical Computing). Non-base packages used for the analyses included meta version 4.15-1 and metafor version 2.4-0.

RESULTS

Study selection in PRISMA format is shown in figure 1 with 38 studies included: 36 cohort studies and 2 case–control studies. Study characteristics including NOS quality assessment summary score are described in online supplemental table 1. Studies were conducted in a variety of contexts with a mean duration of 4.8 years (median: 4.0 years, range: 0.3–15.5 years).

Diabetes studies

The relationship between diabetes status and CAP outcomes was reported in 31 studies. Study details are described in online supplemental table 2.

Mortality

Mortality was reported in various ways: in-hospital mortality was assessed in 14 studies, 30-day mortality in 10 studies, 90-day mortality in 1 study, 1-year mortality in 2 studies, and end-of-trial mortality in 4 studies.

When considering all studies reporting in-hospital mortality there was no association shown for diabetes status. The pooled crude OR for in-hospital mortality with diabetes was 1.17 (95% CI 0.95 to 1.44, I^2=89%) while the adjusted OR was 0.92 (95% CI 0.91 to 0.94, I^2=0%) (figure 2A,B). Two studies used discharge coding data only to establish a diagnosis of diabetes. While this is a valid definition of diabetes it is likely to identify fewer and a substantively different subset of patients to clinical definitions, especially in more contemporary data sets,[16 17] which can affect comparisons between studies using coding or clinical definitions. These studies also contributed the largest numbers of patients to the analyses. To explore their contributions to the results, analyses were repeated with these two studies removed. Meta-analysis of the remaining studies yielded both an increased crude OR of 1.50 (95% CI 1.11 to 2.01, I^2=0%) and an increased adjusted OR of 1.04 (95% CI 0.72 to 1.51, I^2=10%) (figure 2C,D).

Diabetes status was not associated with 30-day mortality (pooled crude OR 1.37, 95% CI 0.92 to 2.04, I^2=41%; pooled adjusted OR 1.13, 95% CI 0.77 to 1.67, I^2=62%) (online supplemental figure S1). One study reported this outcome as an HR of 1.29 (95% CI 1.01 to 1.65, p<0.001) and was not included in the meta-analysis.[18]

Other mortality outcomes were reported in a manner or with frequency unsuitable for meta-analysis. Ninety-day mortality was found by one study to be associated with diabetes (HR 2.47, 95% CI 2.05 to 2.98, p<0.001)[18] as was 1-year mortality (OR 2.13, 95% CI 1.28 to 3.54, p=0.004[19] and HR 1.3, 95% CI 1.03 to 1.65, p=0.02[20]). An association

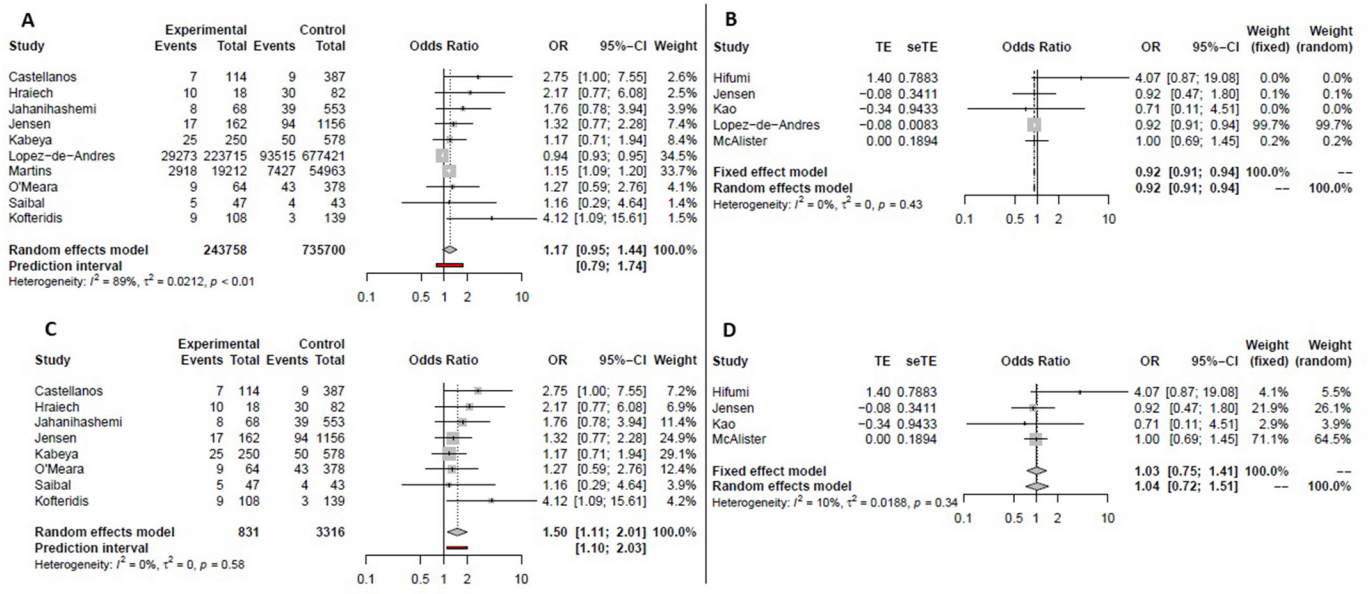


Figure 2 Meta-analyses of the association between diabetes and in-hospital mortality in hospitalized patients with community-acquired pneumonia. Pooled crude (A) and adjusted (B) ORs including all eligible studies. Pooled analyses after removal of studies that used coding data only in establishing a diagnosis of diabetes for crude (C) and adjusted (D) ORs.

between diabetes and end-of-trial mortality was found, with HR of 2.84 (95% CI 1.35 to 5.99, p=0.006),[21] 1.26 (95% CI 1.04 to 1.54, p=0.02),[18] and a relative risk of 1.5 (95% CI 1.05 to 2.14, p=not reported) but was not quantified in a study that reported crude event numbers.[22]

ICU admission

ICU admissions were no different between those with and without diabetes. The pooled crude OR for this outcome in those with diabetes for the five studies reporting it was 1.91 (95% CI 0.74 to 4.95, I^2=84%) (online supplemental figure S2, panel A). The OR for ICU admission in those with diabetes was elevated in two studies, and not significantly different in three studies.

Length of stay

Length of hospital stay was generally longer for those with diabetes. Variable reporting of summary measures and crude continuous data or significance testing alone notwithstanding, of the six studies that assessed this, five found a statistically significant longer length of stay in those with diabetes versus those without[23–27] while the last found no difference.[28] Two studies reported a test of difference, being an HR of 0.68 (95% CI 0.51 to 0.89) for discharge in patients with diabetes compared with those without[25] and an incidence rate ratio for longer length of stay in patients with diabetes of 1.19 (95% CI 1.06 to 1.33).[27]

Clinical outcomes

There was no association between diabetes status and the development of pleural effusion with a pooled crude OR from the three studies that assessed this outcome of 2.91 (95% CI 0.17 to 48.5, I^2=83%) (online supplemental figure S2, panel B).

In individual studies, diabetes was found to be associated with both cardiovascular events during follow-up (HR 1.92, 95% CI 1.18 to 3.14, p=0.009)[22] and a lower likelihood of weaning from mechanical ventilation (OR 0.23, 95% CI 0.05 to 0.92, p=0.048).[29]

'Complicated hospitalization' and a 'severe outcome' were reported by five and three studies, respectively, with various definitions precluding meaningful meta-analysis. None of these showed a statistically significant association between diabetes and defined study outcomes.

Hyperglycemia studies

The relationship between hyperglycemia and pneumonia outcomes was reported in 17 studies. Study details are described in online supplemental table 3. One study was found to be a clear outlier in terms of effect size and its results were removed from the primary analyses reported.[30] Analyses retaining this study are included in the online supplemental figures S5, S6 and S8. Of the 16 hyperglycemia studies, 12 included patients with and without diabetes, 2 were limited to patients with diabetes, while 2 only included patients without a diagnosis of diabetes.

Mortality

Similar to the studies assessing diabetes, mortality was reported in multiple ways: in-hospital mortality was assessed in seven studies, 30-day mortality in three studies, 90-day mortality in two studies, 1-year mortality in two studies, and end-of-trial mortality in one study.

Hyperglycemia was associated with in-hospital mortality both for those studies reporting crude ORs (pooled crude OR 1.42, 95% CI 1.06 to 1.88, I^2=0%) and adjusted ORs (pooled adjusted OR 1.28, 95% CI 1.09 to 1.50, I^2=36%)

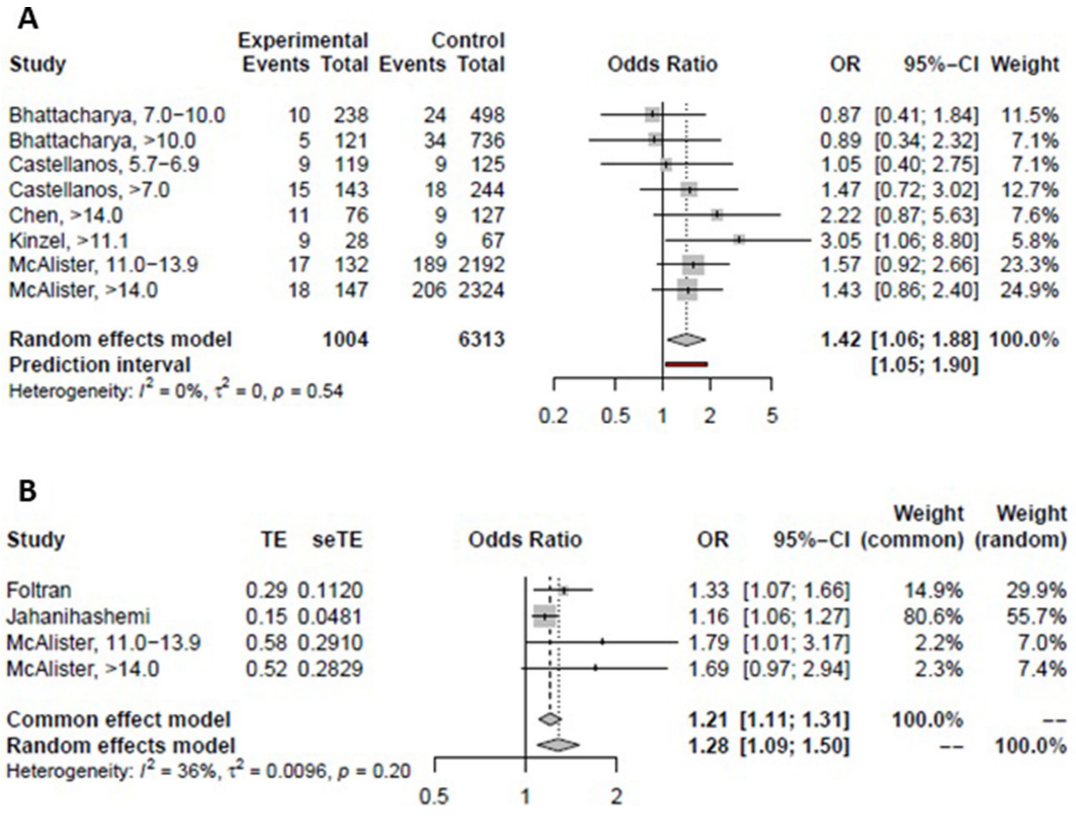


Figure 3 Meta-analyses of the association between hyperglycemia and in-hospital mortality in hospitalized patients with community-acquired pneumonia. Pooled crude (A) and adjusted (B) ORs.

(figure 3). When stratified by hyperglycemia cut-point categories using the mixed-effects model, there was no relationship seen between any individual cut-point category and in-hospital mortality point estimate for the crude OR. All but one category showed a relationship with in-hospital mortality for the adjusted OR; however, each category consisted of data from only a single study (online supplemental figure S3).

It is of interest to the clinician to differentiate the contribution of hyperglycemia to in-hospital mortality in patients with and without diabetes. Most studies[31–35] included patients regardless of diabetes status and did not report the contribution of hyperglycemia to mortality separately in both of these groups. When studies including only patients with or without diabetes were excluded (relevant only to the pooled crude analysis), results were unchanged. The two studies to consider just patients with diabetes found hyperglycemia to not be associated with increased in-hospital mortality when hyperglycemia was defined as glucose >14.0 mmol/L (OR 2.22, 95% CI 0.87 to 5.63, p=0.18)[36] or when risk was assessed per 1 mmol/L increase in glucose (OR 1.05, 95% CI 0.99 to 1.12, p=0.11).[37] Similarly, both studies assessing the relationship between in-hospital mortality and hyperglycemia only in patients without diabetes found no association when hyperglycemia was defined as a glucose of ≥7.0 mmol/L (OR 1.98, 95% CI 0.32 to 12.4, p=0.46),[38] or when assessing risk per 1 mmol/L increase in glucose (OR 1.10, 95% CI 0.99 to 1.23, p=0.09).[37]

Other mortality outcomes were reported in a manner unsuitable for meta-analysis. Hyperglycemia was not found to be associated with 30-day mortality in three studies,[28 39 40] with 90-day mortality in one study,[41] or with 1-year mortality in two studies.[20 41] One study, the largest of the hyperglycemia-reporting studies, found 90-day mortality to be associated with an admission glucose of either 6.0–10.9, 11.0–13.9, or ≥14.0 mmol/L, with a progressively greater OR for each group respectively.[18] Another study found new postprandial hyperglycemia in patients without diabetes to be associated with end-of-trial mortality (median surveillance duration of 5 years and 11 months) with an adjusted HR of 2.56 (95% CI 1.04 to 6.32).[21]

ICU admission

Three studies reported ICU admission, which was found to be associated with hyperglycemia (pooled crude OR 1.82, 95% CI 1.17 to 2.84, I^2=16%) (online supplemental figure S4). In general, a higher glucose was associated with a greater OR of ICU admission, but this was not universally reported. One additional study found an association with hyperglycemia ≥11.1 mmol/L and ICU admission in those without diabetes,[37] while another found none.[40]

Length of stay

Length of hospital stay was either longer or no different in those with hyperglycemia compared with those without.

Of the six studies reporting this outcome, three found a statistically significant longer length of stay in those with hyperglycemia compared with those without,[32 36 42] while the others reported no difference.[31 33 38] The combination of summary measures and crude continuous data precluded meta-analysis.

Clinical outcomes

'Complicated hospitalization' was reported by three studies and variably defined. One study found hyperglycemia ≥14.0 mmol/L in patients with diabetes to be associated with complicated hospitalization, defined as a composite of 11 outcomes including in-hospital mortality.[36] Another showed an association with hyperglycemia ≥11.0 mmol/L regardless of diabetes status, where complicated hospitalization was defined all inclusively as death, any non-metabolic complications, cardiac complications, and nosocomial infections.[33] A third found complicated hospitalization, defined as an increase in oxygen requirements after 24 hours of admission or broadened antibiotic coverage, to be associated with glucose values >5.7 mmol/L in those without diabetes, but only for participants aged ≥65 years.[38]

A 'severe outcome' of the hospitalization was reported by three studies, with some definitions including mortality. Two studies found hyperglycemia to be associated with a severe outcome regardless of diabetes status for glucose values ≥11.1 mmol/L.[37 40] A further study only found hyperglycemia of 5.7–6.9 mmol/L in those without diabetes and aged ≥65 years to be associated with a severe outcome, but in that same subset there was no association for hyperglycemia >7.0 mmol/L.[38]

Study quality and publication bias

Included studies were generally of high quality (7–9 points) on the NOS with two of moderate quality.

Funnel plots for the studies contributing data to the meta-analyses of in-hospital mortality, the most commonly reported outcome of pneumonia hospitalization, revealed significant publication bias for studies associating this outcome with both diabetes (figure 4) and hyperglycemia (online supplemental figure S7). Small studies (higher SE) with a small effect size (lower Hedges' g) were missing in both cases. On the basis of clear outlier status in terms of effect size, one study reporting on hyperglycemia and pneumonia outcomes was removed (online supplemental figure S9).[30]

Inter-rater reliability

For title and abstract screening, proportionate agreement between investigators was 0.94, random agreement 0.87, and Cohen's kappa 0.56. For full-text review, proportionate agreement was 0.89, random agreement 0.73, and Cohen's kappa 0.61.

CONCLUSIONS

While there is a clear pathological relationship between diabetes, hyperglycemia, and infection risk, patient and health service impacts of infection in diabetes and hyperglycemia are not well understood. Our review clarifies the nature of these relationships in a pre-COVID-19 pandemic context and identifies hyperglycemia as a stronger risk factor than diabetes for poor in-hospital outcomes in those admitted with CAP although diabetes is a greater risk factor for postdischarge mortality.

Individual studies revealed length of stay to be either no different or longer with both the presence of diabetes alone and with hyperglycemia. For both ICU admission and in-hospital mortality, however, on meta-analysis there appears to be a clear increase in risk associated with hyperglycemia but not with diabetes status. It is thus probable that hyperglycemia, at least in part, mediates the increased in-hospital mortality seen with diabetes in some individual studies assessing diabetes and mortality, especially as in-hospital hyperglycemia was reported in fewer than one-third of these studies. Indeed, the one study that reported adjusted ORs for both diabetes and hyperglycemia with in-hospital mortality found hyperglycemia but not diabetes to carry increased risk. Similarly, risks for composite outcomes termed complicated hospitalization and severe outcome, though variably defined,

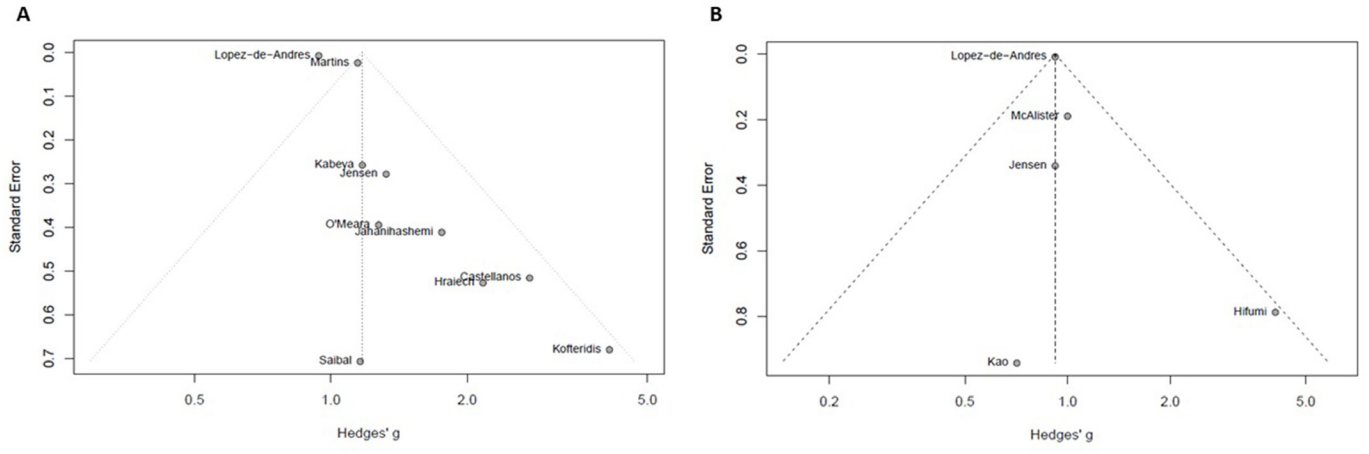


Figure 4 Funnel plots of the association between diabetes and in-hospital mortality in hospitalized patients with community-acquired pneumonia for studies reporting crude (A) and adjusted (B) ORs.

were universally increased with hyperglycemia but unchanged with diabetes status. These findings concur with the long-established increased risk for in-hospital adverse outcomes attributable to hyperglycemia in both those with and without diabetes.[43 44]

In contrast, postdischarge mortality outcomes were more strongly associated with diabetes than hyperglycemia, although heterogeneity precluded quantification of these effects through meta-analysis. For mortality reported as ≥90 days after discharge, diabetes was universally associated with increased risk in the six evaluable studies. In contrast, only two of five studies found hyperglycemia to increase the risk of ≥90-day mortality and in one of these studies it was new hyperglycemia in patients without previously diagnosed diabetes that was considered, which could thus represent diabetes newly detected during the admission for pneumonia. By 90 days after discharge, it is likely that any complications resulting from admission have been experienced and the risk of adversity stemming from hospitalization, amplified by acute hyperglycemia or not, has largely returned to baseline. These results are consistent with the known contribution of diabetes to mortality risk in ambulatory settings.[45]

The clear implications of these findings to clinicians managing adults hospitalized with pneumonia are that hyperglycemia during the hospital stay is a greater risk factor for in-hospital morbidity and mortality than diabetes status alone. Hyperglycemia is mechanistically linked to infection through immune dysfunction at multiple levels including impaired cytokine production,[46] pathogen recognition,[47] neutrophil function,[48] and macrophage function.[49] There is also long-standing evidence that in-hospital hyperglycemia is associated with a greater in-hospital mortality risk than diabetes.[44] Our findings thus suggest that the effects of acute hyperglycemia are more important over the course of a hospital admission than the non-glycemic effects of the chronic condition of diabetes. These effects appear limited to the admission, however, and following discharge there does not appear to be a significant legacy effect of inpatient hyperglycemia, with medium-term outcomes such as mortality at ≥90 days associated to a greater degree with diabetes status.

This is noteworthy as while diabetes itself is not modifiable over the course of a hospital admission, hyperglycemia is. In patients admitted with CAP, outcomes may therefore potentially be improved through the identification and timely management of elevated plasma glucose concentrations, consistent with general hospital glucose management guidelines.[50] A trial published in 2019 of proactive care to improve inpatient glycemia in the non-critical care setting showed reduced hyperglycemia and hospital-acquired infections, including pneumonia, in the intervention arm.[51] The same intervention applied to adults hospitalized with pneumonia could similarly improve outcomes and is worthy of study, particularly to determine optimal glucose levels for prevention of CAP-related morbidity and mortality in admitted patients. This is especially important in our current context of different glycemic targets being recommended by different international groups.[52 53]

Methodological strengths of this review include a comprehensive search strategy and good inter-rater reliability suggesting consistent application of criteria. That the studies meeting the inclusion criteria were predominantly of high quality and represented a wide selection of geographic and temporal contexts is a further strength and confirms the reliability and broad applicability of the review findings. This review is limited by the observational nature of the source studies, which are by design necessarily susceptible to bias and confounding. Definitional heterogeneity of both diabetes and hyperglycemia is a source of error that is partially but not completely accounted for using random-effects model meta-analysis. Similarly, the reporting of different outcomes of CAP hospitalization resulted in a few data points for each, precluding meta-analysis for some outcomes. While it would be of interest to clinicians to differentiate the contribution of hyperglycemia to in-hospital mortality in patients with and without diabetes, most studies reporting on hyperglycemia outcomes pooled patients with and without diabetes and did not report on these associations separately. The presence of publication bias, as evidenced by the relative paucity of small studies with small effect size, may also impact on the strength of any conclusions drawn.

Future observational studies could improve the current state of knowledge summarized in this review by adopting standardized definitions for both hyperglycemia in patients admitted to hospital and clinical outcomes, which will enable direct comparisons between published studies. Studies considering the contribution of hyperglycemia to outcomes should additionally separately report on the effects of hyperglycemia on risk in patients with and without diabetes. Findings of our review highlight the need to evaluate whether early identification and treatment of hyperglycemia in individuals hospitalized with CAP can improve patient outcomes. Such an approach has shown promise for improved outcomes in a general population in a trial context.[51] Future interventional studies, including randomized controlled trials, assessing the relationships between diabetes, hyperglycemia and CAP, offer the possibility of establishing euglycemia as a target for therapy, alongside appropriate antimicrobial therapy, as standardized treatment of CAP in hospitalized patients.

Author affiliations
[1]Department of Diabetes and Endocrinology, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[2]Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
[3]Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne, Melbourne, Victoria, Australia
[4]Department of General Medicine, The Royal Melbourne Hospital, Parkville, Victoria, Australia

[5]National Centre for Infections in Cancer (NCIC), Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia

Contributors RDB, NC, SF, and LJW conceived the study and wrote the research protocol. RDB and NC performed the search, study selection, data extraction, and quality assessment. RDB performed the data synthesis and statistical analysis. RDB and LJW wrote the initial manuscript. NC, SF, PBG, and PGC reviewed and edited the manuscript and contributed to the discussion. All authors reviewed the final manuscript and approved it for submission.

Funding RDB was supported by the Australian Government Research Training Program Scholarship.

Disclaimer The funders had no role in the study design, recruitment, data collection, analysis, interpretation, or writing of the report.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

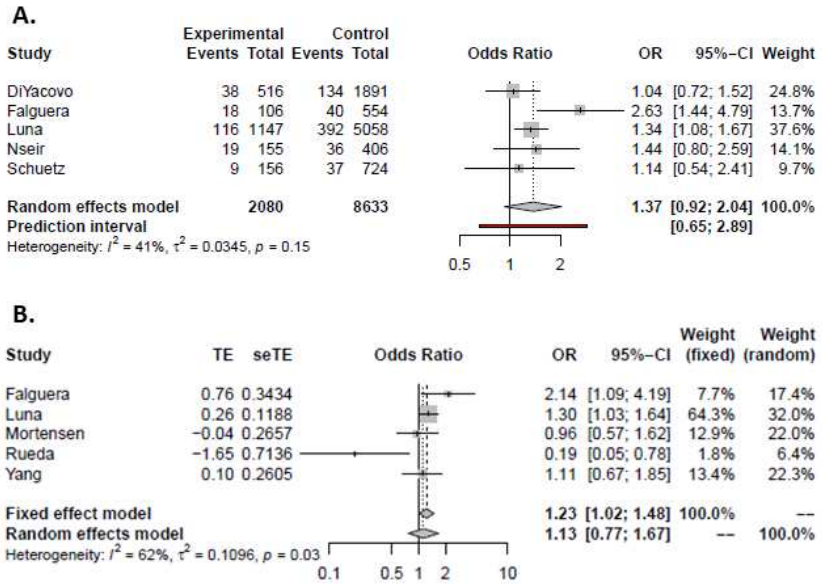
ORCID iDs
Rahul D Barmanray http://orcid.org/0000-0002-1433-2239
Spiros Fourlanos http://orcid.org/0000-0002-5153-8324

REFERENCES

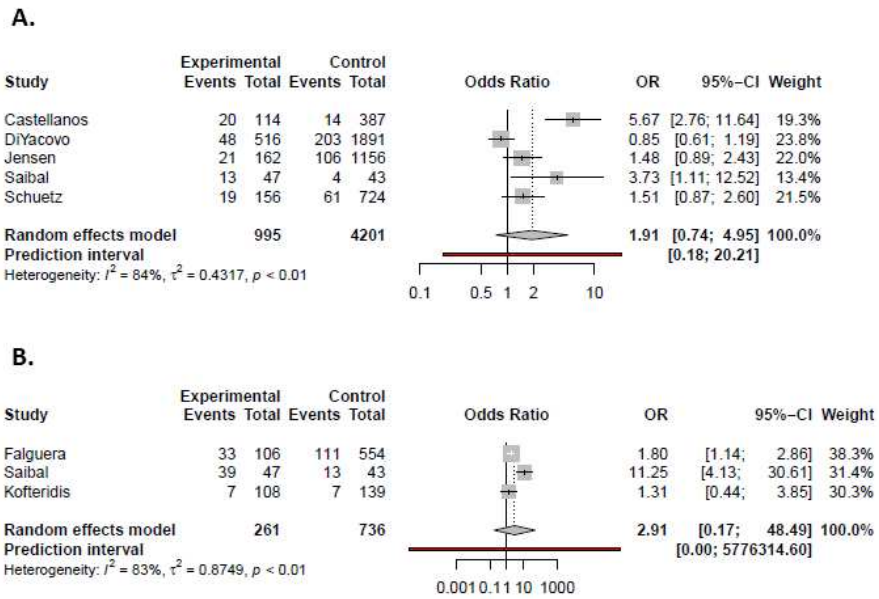
1 Abu-Ashour W, Twells L, Valcour J, *et al*. The association between diabetes mellitus and incident infections: a systematic review and meta-analysis of observational studies. *BMJ Open Diabetes Res Care* 2017;5:e000336.
2 Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003;26:510–3.
3 Fry AM, Shay DK, Holman RC, *et al*. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. *JAMA* 2005;294:2712–9.
4 Korbel L, Spencer JD. Diabetes mellitus and infection: an evaluation of hospital utilization and management costs in the United States. *J Diabetes Complications* 2015;29:192–5.
5 Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. *Diabetes Metab* 2020;46:265–71.
6 Cariou B, Hadjadj S, Wargny M, *et al*. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020;63:1500–15.
7 Apicella M, Campopiano MC, Mantuano M, *et al*. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020;8:782–92.
8 Wang W, Chai Z, Cooper ME, *et al*. High fasting blood glucose level with unknown prior history of diabetes is associated with high risk of severe adverse COVID-19 outcome. *Front Endocrinol* 2021;12:791476.
9 Bode B, Garrett V, Messler J, *et al*. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol* 2020;14:813-821.
10 Yamamoto T, Komiya K, Fujita N, *et al*. COVID-19 pandemic and the incidence of community-acquired pneumonia in elderly people. *Respir Investig* 2020;58:435–6.
11 Mandell LA, Zhanel GG, Rotstein C, *et al*. Community-acquired pneumonia in Canada during coronavirus disease 2019. *Open Forum Infect Dis* 2022;9:ofac043.
12 Moher D, Liberati A, Tetzlaff J. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ Clinical research* 2009;339:b2535.
13 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (moose) group. *JAMA* 2000;283:2008–12.
14 The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2014. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
15 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
16 Campbell SE, Campbell MK, Grimshaw JM, *et al*. A systematic review of discharge coding accuracy. *J Public Health Med* 2001;23:205–11.
17 Burns EM, Rigby E, Mamidanna R, *et al*. Systematic review of discharge coding accuracy. *J Public Health* 2012;34:138–48.
18 Lepper PM, Ott S, Nüesch E, *et al*. Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. *BMJ* 2012;344:e3397.
19 Adamuz J, Viasus D, Jiménez-Martínez E, *et al*. Incidence, timing and risk factors associated with 1-year mortality after hospitalization for community-acquired pneumonia. *J Infect* 2014;68:534–41.
20 Yende S, van der Poll T, Lee M, *et al*. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. *Thorax* 2010;65:870–7.
21 Koskela HO, Salonen PH, Romppanen J, *et al*. Long-term mortality after community-acquired pneumonia-impacts of diabetes and newly discovered hyperglycaemia: a prospective, observational cohort study. *BMJ Open* 2014;4:e005715.
22 Cangemi R, Calvieri C, Falcone M, *et al*. Relation of cardiac complications in the early phase of community-acquired pneumonia to long-term mortality and cardiovascular events. *Am J Cardiol* 2015;116:647–51.
23 Martins M, Boavida JM, Raposo JF, *et al*. Diabetes hinders community-acquired pneumonia outcomes in hospitalized patients. *BMJ Open Diabetes Res Care* 2016;4:e000181.
24 Saibal MAA, Rahman SHZ, Nishat L, *et al*. Community acquired pneumonia in diabetic and non-diabetic hospitalized patients: presentation, causative pathogens and outcome. *Bangladesh Med Res Counc Bull* 2012;38:98–103.
25 Suter-Widmer I, Christ-Crain M, Zimmerli W, *et al*. Predictors for length of hospital stay in patients with community-acquired pneumonia: results from a Swiss multicenter study. *BMC Pulm Med* 2012;12:21.
26 Kofteridis DP, Giourgouli G, Plataki MN, *et al*. Community-acquired pneumonia in elderly adults with type 2 diabetes mellitus. *J Am Geriatr Soc* 2016;64:649–51.
27 Kabeya Y, Shimada A, Tsukada N, *et al*. Diabetes affects length of stay and hospital costs for elderly patients with pneumonia: an analysis of a hospital administrative database. *Tokai J Exp Clin Med* 2016;41:203–9.
28 Di Yacovo S, Garcia-Vidal C, Viasus D, *et al*. Clinical features, etiology, and outcomes of community-acquired pneumonia in patients with diabetes mellitus. *Medicine* 2013;92:42–50.
29 Falguera M, Pifarre R, Martin A, *et al*. Etiology and outcome of community-acquired pneumonia in patients with diabetes mellitus. *Chest* 2005;128:3233–9.
30 Iroezindu MO, Isiguzo GC, Chima EI, *et al*. Predictors of in-hospital mortality and length of stay in community-acquired pneumonia: a 5-year multi-centre case control study of adults in a developing country. *Trans R Soc Trop Med Hyg* 2016;110:445–55.
31 Bhattacharya RK, Mahnken JD, Rigler SK. Impact of admission blood glucose level on outcomes in community-acquired pneumonia in older adults. *Int J Gen Med* 2013;6:341–4.
32 Kinzel T, Smith M. Hyperglycemia as a predictor for mortality in veterans with pneumonia. *Exp Aging Res* 1988;14:99–102.
33 McAlister FA, Majumdar SR, Blitz S, *et al*. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes Care* 2005;28:810–5.
34 Foltran F, Gregori D, Caropreso A, *et al*. Is blood glucose on admission a predictor of mortality in adult acute pneumonia? *Clin Respir J* 2013;7:276–80.
35 Jahanihashemi H, Babaie M, Bijani S, *et al*. Poverty as an independent risk factor for in-hospital mortality in community-acquired pneumonia: a study in a developing country population. *Int J Clin Pract* 2018;72:e13085.

36 Chen P-C, Liao W-I, Wang Y-C, *et al*. An elevated glycemic gap is associated with adverse outcomes in diabetic patients with community-acquired pneumonia. *Medicine* 2015;94:e1456.
37 Jensen AV, Egelund GB, Andersen SB, *et al*. The impact of blood glucose on community-acquired pneumonia: a retrospective cohort study. *ERJ Open Res* 2017;3. doi:10.1183/23120541.00114-2016. [Epub ahead of print: 19 06 2017].
38 Castellanos MR, Szerszen A, Saifan C, *et al*. Fasting hyperglycemia upon hospital admission is associated with higher pneumonia complication rates among the elderly. *Int Arch Med* 2010;3:16.
39 Rueda AM, Ormond M, Gore M, *et al*. Hyperglycemia in diabetics and non-diabetics: effect on the risk for and severity of pneumococcal pneumonia. *J Infect* 2010;60:99–105.
40 Schuetz P, Friedli N, Grolimund E, *et al*. Effect of hyperglycaemia on inflammatory and stress responses and clinical outcome of pneumonia in non-critical-care inpatients: results from an observational cohort study. *Diabetologia* 2014;57:275–84.
41 Eurich DT, Gamble JM, Marrie TJ, *et al*. Dysglycaemia and 90 day and 1 year risks of death or readmission in patients hospitalised for community-acquired pneumonia. *Diabetologia* 2010;53:497–503.
42 Godar DA, Kumar DR, Schmelzer KM, *et al*. The impact of serum glucose on clinical outcomes in patients hospitalized with community-acquired pneumonia. *WMJ* 2011;110:14–20.
43 Bruno A, Gregori D, Caropreso A, *et al*. Normal glucose values are associated with a lower risk of mortality in hospitalized patients. *Diabetes Care* 2008;31:2209–10.
44 Umpierrez GE, Isaacs SD, Bazargan N, *et al*. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87:978–82.
45 Li S, Wang J, Zhang B, *et al*. Diabetes mellitus and cause-specific mortality: a population-based study. *Diabetes Metab J* 2019;43:319–41.
46 Reinhold D, Ansorge S, Schleicher ED. Elevated glucose levels stimulate transforming growth factor-beta 1 (TGF-beta 1), suppress interleukin IL-2, IL-6 and IL-10 production and DNA synthesis in peripheral blood mononuclear cells. *Horm Metab Res* 1996;28:267–70.
47 Gupta S, Maratha A, Siednienko J, *et al*. Analysis of inflammatory cytokine and TLR expression levels in type 2 diabetes with complications. *Sci Rep* 2017;7:7633.
48 Stegenga ME, van der Crabben SN, Blümer RME, *et al*. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. *Blood* 2008;112:82–9.
49 Restrepo BI, Twahirwa M, Rahbar MH, *et al*. Phagocytosis via complement or Fc-gamma receptors is compromised in monocytes from type 2 diabetes patients with chronic hyperglycemia. *PLoS One* 2014;9:e92977.
50 Pasquel FJ, Lansang MC, Dhatariya K, *et al*. Management of diabetes and hyperglycaemia in the hospital. *Lancet Diabetes Endocrinol* 2021;9:174–88.
51 Kyi M, Colman PG, Wraight PR, *et al*. Early intervention for diabetes in medical and surgical inpatients decreases hyperglycemia and hospital-acquired infections: a cluster randomized trial. *Diabetes Care* 2019;42:832-840.
52 American Diabetes Association. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020;43:S193–202.
53 JBDS-IP. *Management of hyperglycaemia and steroid (glucocorticoid) therapy*, 2021.

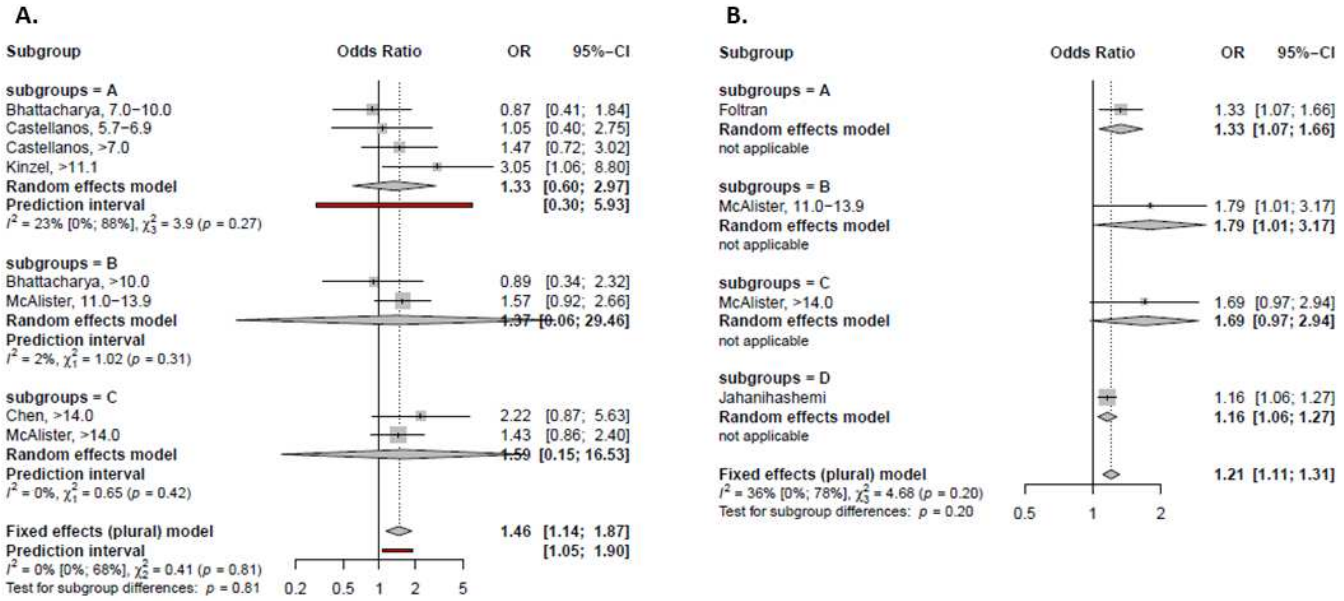
Supplementary Figures



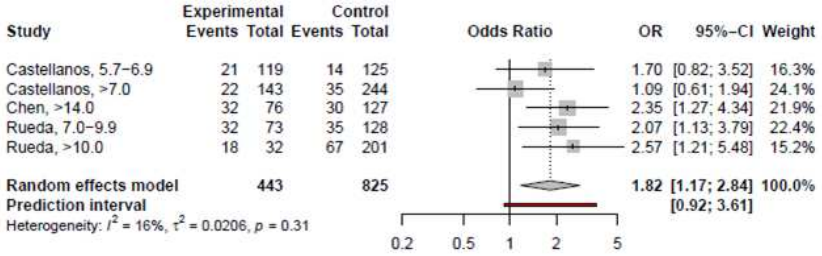
Supplementary figure S1: Meta-analyses of the association between diabetes and 30-day mortality in hospitalized patients with community-acquired pneumonia. Pooled crude (**A**) and adjusted (**B**) odds ratios.



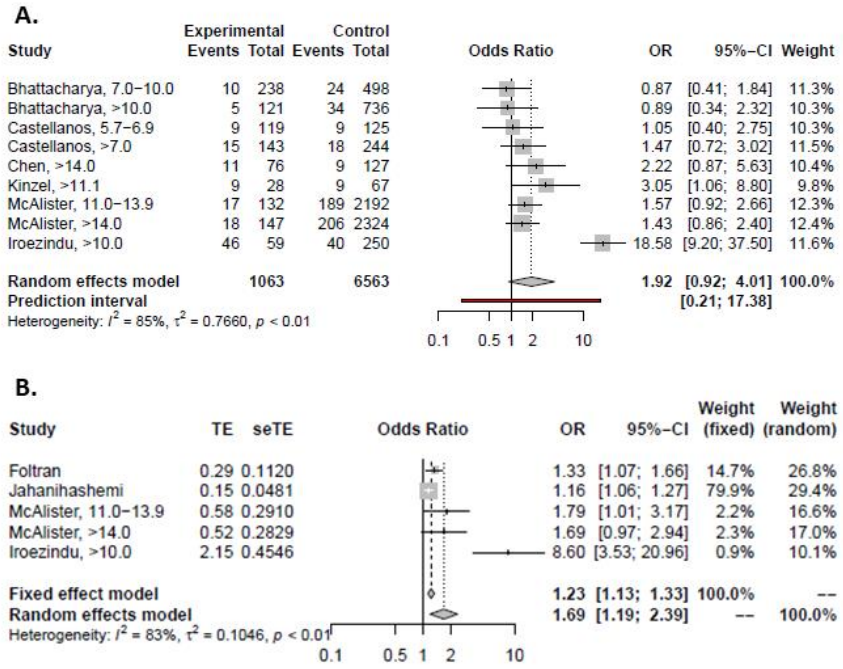
Supplementary figure S2: Meta-analyses of the association between diabetes and intensive care unit (ICU) admission (**A**) and pleural effusion (**B**) in hospitalized patients with community-acquired pneumonia, reported as crude odds ratios.



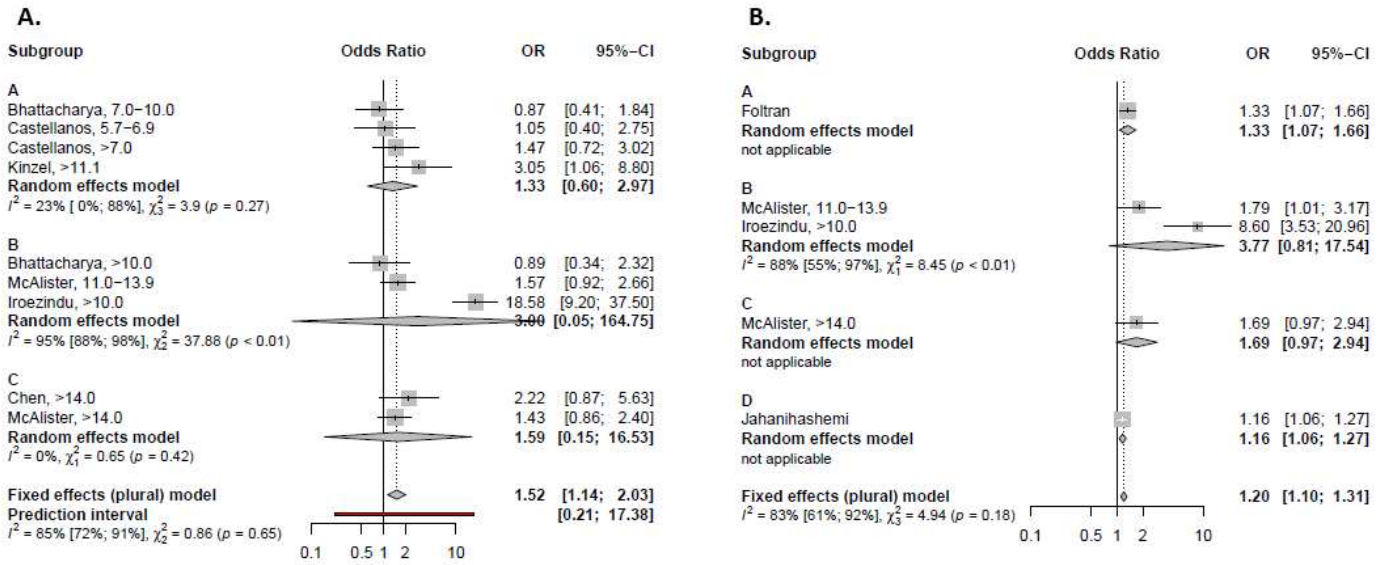
Supplementary figure S3: Meta-analyses of the association between hyperglycaemia and in-hospital mortality in hospitalized patients with community-acquired pneumonia stratified by subgroup. Pooled crude (**A**) and adjusted (**B**) odds ratios by glycaemic cut-off category using the mixed-effects model. Hyperglycaemia subgroup cut-offs = A: ≤ 7.8 mmol/L, B: 7.9-11.0 mmol/L, C: ≥ 11.1 mmol/L, D: not defined.



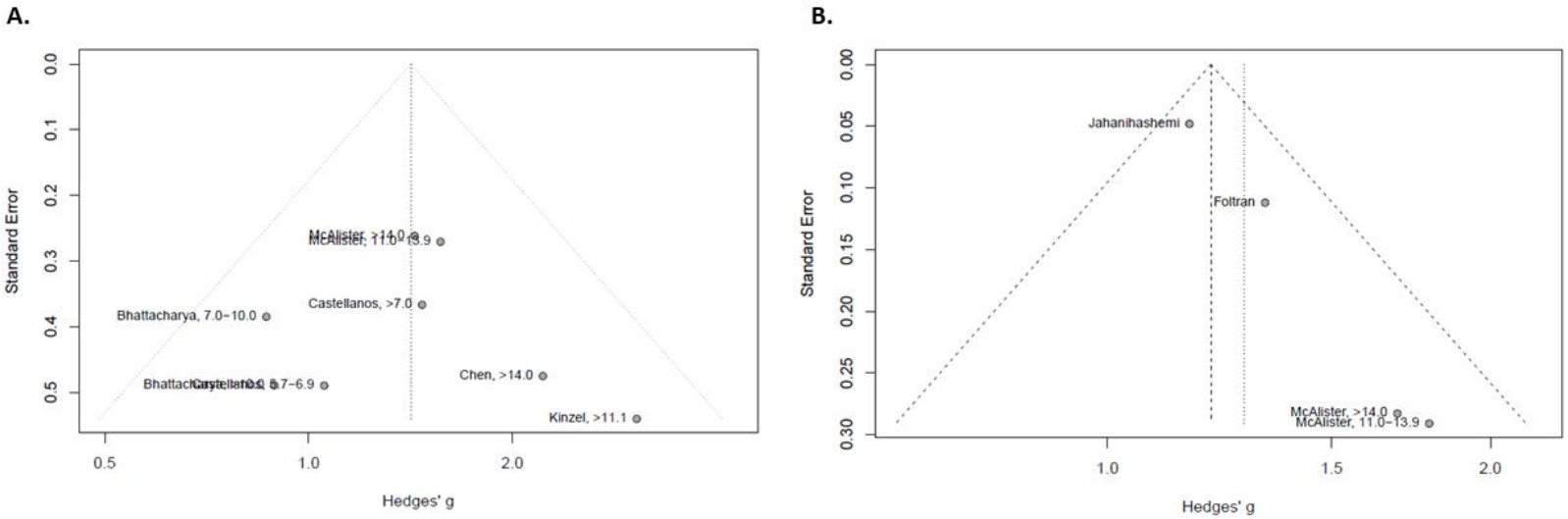
Supplementary figure S4: Meta-analysis of the association between hyperglycaemia and intensive care unit (ICU) admission in hospitalized patients with community-acquired pneumonia for studies reporting crude odds ratios.



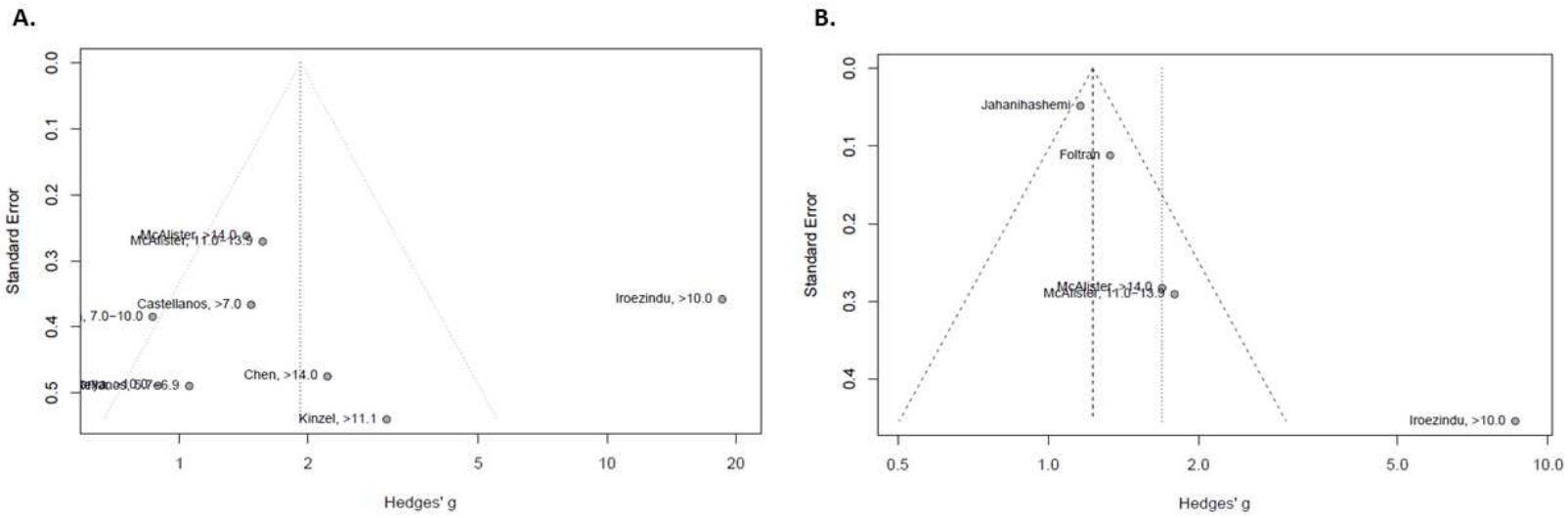
Supplementary figure S5: Meta-analyses of the association between hyperglycaemia and in-hospital mortality in hospitalized patients with community-acquired pneumonia including the study with outlier results by Iroezindu et.al. (24). Pooled crude (**A**) and adjusted (**B**) odds ratios.



Supplementary figure S6: Meta-analyses of the association between hyperglycaemia and in-hospital mortality in hospitalized patients with community-acquired pneumonia stratified by subgroup including the study with outlier results by Iroezindu et.al. (24). Pooled crude (**A**) and adjusted (**B**) odds ratios by glycaemic cut-off category using the mixed-effects model. Hyperglycaemia subgroup cut-offs = A: ≤ 7.8 mmol/L, B: 7.9-11.0 mmol/L, C: ≥ 11.1 mmol/L, D: not defined.



Supplementary figure S7: Funnel plots of the association between hyperglycaemia and in-hospital mortality in hospitalized patients with community-acquired pneumonia for studies reporting crude (A) and adjusted (B) odds ratios.



Supplementary figure S8: Funnel plots of the association between hyperglycaemia and in-hospital mortality in hospitalized patients with community-acquired pneumonia including the study with outlier results by Iroezindu et.al. (24) for studies reporting crude (**A**) and adjusted (**B**) odds ratios.

Supplementary Tables

First author, year, country	Funding source	Study design	Quality (NOS Score)	Data source	Primary outcome	Inclusion Criteria	Exclusion Criteria	Length (yrs), period
Adamuz, 2014, Spain(19)	Fondo de Investigacion Sanitaria de la Seguridad Social and others	Cohort: Prospective	8: High	Hospital records and the SAP Healthcare Database of the Catalan Health Service	1-year mortality after hospital discharge	Adult patients >17 years of age with CAP admitted to hospital	Immunosuppression, in-hospital mortality.	5.0, 2007-2011
Benfield, 2007, Denmark(52)	Danish Heart Foundation; Danish Medical Association Research Fund and others	Cohort: Retrospective	9: High	Copenhagen City Heart Study, Danish National Hospital Discharge Register, Danish Civil Registration System National Register of Causes of Death	Risk of infectious disease hospitalization; secondary outcome of mortality after hospitalization for given infectious disease (e.g. pneumonia)	Patients >16 years of age with a diagnosis of pneumonia admitted to hospital	Unclear	11.0, 1991-2001
Bhattacharya, 2013, United States of America(38)	None reported	Cohort: Retrospective	9: High	Hospital records	In-hospital mortality, length of stay, and readmission for community-acquired pneumonia within 30 days	Age ≥ 40 years with CAP admitted to hospital	Missing glucose measures, disposition code, or race data.	3.0, 2008-2010
Biteker, 2016, Turkey(53)	None reported	Cohort: Prospective	6: Moderate	Prospective collected data on admission to ED	Complicated hospitalization (CH) defined as intensive care unit admission, need for mechanical ventilation, or in-hospital mortality	Age ≥ 18 years with CAP admitted to hospital	Age < 18 years, active pulmonary TB, hospital-acquired pneumonia, pregnancy, immunosuppression, chronic dialysis.	0.3, 2015-2015
Biteker, 2018, Turkey(54)	None reported	Cohort: Prospective	9: High	Prospectively collected	Complicated hospitalization (CH) defined as intensive care unit admission, need for mechanical ventilation, or in-hospital mortality	Age ≥ 18 years with CAP admitted to hospital	Age < 18 years, active pulmonary TB, hospital-acquired pneumonia, pregnancy, immunosuppression, chronic dialysis.	1.0, 2015-2016
Cangemi, 2015, Italy(22)	Grant from the Sapienza University of Rome	Cohort: Prospective	7: High	Prospectively collected; Follow-up data from review of hospital databases, medical records, death certificates, or telephone interviews	Death from any cause at long-term follow-up	Age ≥ 18 years with CAP admitted to hospital	Pre-existing radiologic infiltrates, immunosuppression, malignancy, pregnancy or breastfeeding, health care-associated pneumonia, antibiotic allergy, no consent.	4.0, 2011-2014
Castellanos, 2010, United	None reported	Cohort: Retro-	8: High	Hospital records	Pneumonia complications, defined as “Mild” or “Severe”	Age ≥ 18 years with CAP admitted to hospital and	Hospital-acquired pneumonia, admission to critical care unit.	1.0, Unclear

States of America(39)		spective				early morning fasting blood glucose level drawn within 24 hours of admission		
Chen, 2015, Taiwan(35)	None reported	Cohort: Retro-spective	7: High	Hospital records	Adverse outcomes including mortality during admission, ARDS, bilateral pulmonary infiltrates on CXR consistent with oedema, and others	Patients with diabetes and CAP with plasma glucose levels at presentation and HbA1c within 1 month of admission (before or after)	Concurrent infections, steroid use, hypoglycaemia (<70mg/dL), anaemia requiring blood transfusion.	5.3, 2007-2012
DiYacovo, 2013, Spain(28)	Ministerio de Ciencia e Innovacion and others	Cohort: Pros-pective	9: High	Prospectively collected using computer-assisted protocol	Pneumonia outcomes included mortality, length of stay and in-hospital complications, all assessed separately	Age ≥ 18 years with CAP admitted to hospital	Immunosuppression, corticosteroid therapy (20 mg prednisone/day or equivalent) at admission.	8.6, 2002-2010
Eurich, 2010, Canada(33)	None reported	Cohort: Pros-pective	9: High	Prospectively collected using standardized abstraction forms, linkage to provincial administrative databases	Death from any cause within 90 days following hospital admission	Age ≥ 18 years with CAP admitted to hospital, casual blood glucose measurement on admission	Diabetes, admission glucose < 4mM or > 20mM, ICU admission, aspiration pneumonitis, TB, cystic fibrosis, pregnancy, breastfeeding, immunosuppression.	3.0, 2000-2002
Falguera, 2005, Spain(29)	None reported	Cohort: Pros-pective	8: High	Prospectively collected, hospital records	30-day mortality and pleural effusion	Age ≥ 18 years with CAP admitted to hospital	Misdiagnosis, nosocomial pneumonia, no consent, TB, opportunistic infections.	5.0, 1998-2002
Foltran, 2013, Italy(55)	None reported	Cohort: Retro-spective	9: High	Hospital administrative data, laboratory measurement dataset	In-hospital mortality	Patients with CAP admitted to hospital and glucose recorded on admission	Lack of admission glucose record.	3.0, 2003-2006
Godar, 2011, United States of America(36)	None reported	Cohort: Retro-spective	9: High	Hospital records	LOS, 30-day hospital readmission, ICU transfer, 365-day mortality	Age > 17 years at diagnosis, radiologic evidence and symptoms of CAP, at least 1 fasting glucose measure within 6 hours of presentation, admission to hospital	ICU admission, transfer from another hospital, left hospital against medical advice, hospital discharge <30 days pre-admission, pneumonia diagnosed ≥ 48 hours after admission, history of or suspected: aspiration, fungal, or viral pneumonia, pulmonary TB or pneumocystis carinii pneumonia, immunosuppression, tracheostomy.	15.5, 1992-2007
Hifumi, 2015, japan(56)	None reported	Cohort: Retro-spective	9: High	Hospital records	Percentage weaned successfully from mechanical ventilation	Age ≥ 65 years, received mechanical ventilation for CAP in the ED	Recent ICU admission, nursing home or long-term care resident, recent intravenous antibiotics,	7.0, 2006-2012

							chemotherapy, or wound care, attended a hospital or haemodialysis clinic.	
Hraiech, 2013, France(57)	None reported	Cohort: Pros-pective	9: High	Previous prospective cohort study	In-hospital mortality	Age ≥ 18 years with CAP admitted to medical ICU requiring invasive mechanical ventilation	No invasive ventilation, suspected aspiration pneumonitis, TB, or cystic fibrosis, intubation for ≥12 hours, referred from another hospital.	5.0, 2007-2011
Jahanihashemi, 2018, Iran(58)	None reported	Cohort: Pros-pective	9: High	Prospectively performed interview with patients and their companions	In-hospital mortality	Age ≥ 12 years with CAP admitted to hospital	Lung cancer, history of TB or HIV, admitted to hospital within last month, structural respiratory tract damage.	1.0, 2014-2015
Jensen, 2017, Denmark(34)	The Christenson–Cesons Family Foundation and others	Cohort: Retro-spective	9: High	CAP-NORTH Cohort, Hospital records	Severe outcome, defined as: ICU admittance, in-hospital mortality, or combined risks (ICU admittance and/or in-hospital mortality)	Age ≥ 18 years with CAP admitted to hospital	Recent pneumonia admission, active TB, missing data, immunosuppression.	1.5, 2011-2012
Kabeya, 2016, Japan(27)	None reported	Cohort: Retro-spective	9: High	Inpatient administrative claims database	Length of stay, hospital costs	Age ≥ 65 years with CAP admitted to hospital	Admissions subsequent to the initial admission.	4.0, 2010-2013
Kao, 2017, Taiwan(59)	None reported	Cohort: Retro-spective	9: High	Hospital records	All-cause in-hospital mortality	Admitted for community-acquired Legionnaires' disease and pneumonia	Unclear	4.8, 2012-2017
Kinzel, 1988, United States of America(37)	None reported	Cohort: Retro-spective	8: High	Hospital Records	Mortality and length of stay	Age ≥ 60 years with CAP admitted to hospital	Patients not fulfilling criteria for pneumonia.	2.0, 1982-1984
Koskela, 2014, Finland(21)	Hospital District of Northern Savo	Cohort: Pros-pective	8: High	Prospectively collected	Mortality from 30 days after pneumonia to the end of follow-up	Age ≥ 18 years with CAP admitted to hospital	ICU admission, no consent, antibiotic treatment commenced elsewhere.	1.6, 2006-2008
Lepper, 2012,Germany (18)	German Ministry of Education and Research	Cohort: Pros-pective	8: High	Prospectively collected data from CAPNETZ database	Mortality (28, 90 and 180 days)	Age ≥ 18 years with CAP admitted to hospital	Recent hospital admission, immunosuppression, and active TB.	7.5, 2002-2009
Lopez-de-Andres, 2017, Spain(60)	Fondo de Investigaciones Sanitarias- Health Research Fund	Cohort: Retro-spective	9: High	Spanish National Hospital Discharge Database (Conjunto Mínimo Básico de Datos (CMBD))	Readmission, in-hospital mortality, length of hospital stay	Age ≥ 40 years with CAP admitted to hospital	Type 1 diabetes mellitus	10.0, 2004-2013
Luna, 2016, 17 countries(61)	None reported	Cohort: Retro-spective	9: High	Community-Acquired Pneumonia Organization (CAPO) study database	30-day hospital mortality	Age ≥ 18 years with CAP admitted to hospital	Residence in a nursing home, HIV infection, suspected influenza A H1N1 2009 infection.	10.3, 2001-2011
Martins, 2016, Portugal(23)	Pfizer Grant	Cohort: Retro-	8: High	National Hospital Discharge Database	Mortality and length of stay	Age 20-79 years with CAP admitted to hospital	Recent admission, day cases, hospitalized > 90 days,	4.0, 2009-

		spective					immunosuppression.	2012
McAlister, 2005, Canada(40)	Alberta Heritage Foundation for Medical Research and others	Cohort: Pros-pective	9: High	Prospectively collected	Mortality, non-metabolic complications, cardiac complications, nosocomial infections	Age ≥ 18 years with CAP admitted to hospital	No glucose at presentation, diagnosed or suspected aspiration pneumonia, TB, cystic fibrosis, immunosuppression, pregnant or breastfeeding, ICU admission.	2.0-2000-2002
Mortensen, 2010, United States of America(62)	Department of Veteran Affairs Veterans Integrated Service grant and others	Cohort: Retro-spective	8: High	Hospital records	30-day mortality	Age ≥ 18 years with CAP admitted to hospital	Recent admission, transfer from another hospital, palliative status, subsequent hospitalizations.	4.0, 1999-2002
Nseir, 2019, Israel(63)	None reported	Cohort: Retro-spective	8: High	Hospital records	30-day all-cause mortality	Age ≥ 18 years admitted with CAP and underwent an abdominal ultrasound examination	Hospital-acquired pneumonia, structural lung disease, asthma, empyema, stroke, aspiration pneumonia, pneumonia severity index class I and V, cirrhosis or significant hepatic disease, significant renal disease, alcohol intake > 20 g/day, immunosuppression, malignancy, intravenous drug use, active autoimmune disease, pregnancy.	4.2, 2013-2017
O'Meara, 2005, United States of America(64)	National Heart, Lung, and Blood Institute	Cohort: Pros-pective	9: High	Cardiovascular Health Study (CHS) records, follow-up clinics annually, phone calls, HCFA Medicare utilisation files	Mortality (in-hospital, total mortality after hospitalization)	Age ≥ 65 years with CAP admitted to hospital	Institutionalized, not ambulatory at home, in hospice care, cancer therapy, likely to move in 3 years, no consent, concurrent cardiovascular events.	12.5, 1989-2001
Parrott, 2017, Japan(65)	None reported	Cohort: Retro-spective	9: High	Hospital records	Pathogens, risk factors, and disease outcomes	Age ≥ 18 years with CAP admitted to hospital	Unclear	3.0, 2011-2013
Rueda, 2010, United States of America(31)	Department of Veterans Affairs Merit Review Program and others	Cohort: Pros-pective (Case Control element exclude d)	8: High	Prospectively collected	ICU admission within 72h, mortality at 7 and 30 days	Age ≥ 18 years with CAP due to pneumococcal pneumonia admitted to the hospital	Unclear	7.5, 2000-2007

Saibal, 2012, Bangladesh(24)	None reported	Cohort: Prospective	6: Moderate	Prospectively collected	Pathogens and disease outcomes	Age ≥ 18 years with CAP admitted to hospital	Acid fast bacilli in sputum, bronchial carcinoma, chronic renal disease stage 4 or 5, heart failure, pregnancy.	0.8, 2009-2009
Schuetz, 2014, Switzerland(32)	Swiss National Research Foundation and others	Cohort: Prospective	8: High	ProHOSP study records	Inflammatory response and adverse clinical course (30 day all-cause mortality, ICU)	Age ≥ 18 years with CAP admitted to hospital and blood glucose level taken on admission	Included during earlier hospitalizations, not fluent in German, no consent, immunosuppression, concomitant infection, drug abuse, hospital-acquired pneumonia, palliative status.	1.5, 2006-2008
Suter-Widmer, 2012, Switzerland(25)	Swiss National Science Foundation and others	Cohort: Prospective	9: High	ProHOSP study records	Length of stay	Age ≥ 18 years with CAP admitted to hospital, survived to discharge	Active intravenous drug use, immunosuppression other than corticosteroid use, palliative status, hospital acquired pneumonia, chronic infection needing antibiotic treatment.	1.5, 2006-2008
Yang, 2018, Taiwan(66)	Ministry of Science and Technology, Taiwan and others	Cohort: Retrospective	8: High	Hospital records	30-day mortality	Age ≥ 18 years with CAP and concomitant mono-microbial bacteraemia admitted to hospital	Contaminated blood cultures, incomplete records, hospital-onset bacteraemia, bacteraemia diagnosed prior to ED visit, poly-microbial bacteraemia, uncertain outcome 30 day after bacteraemia onset.	6.0, 2008-2013
Yende, 2010, United States of America(20)	GenIMS funded by NIGMS R01 GM61992 and others.	Cohort: Prospective	7: High	GenIMS study records	All-cause mortality within the first year	Age > 18 years with CAP admitted to hospital	Transfer from another hospital, discharge from hospital in past 10 days, diagnosis of pneumonia in past 30 days, mechanical ventilation, cystic fibrosis, active pulmonary TB, palliative status, prior enrolment, incarceration, or pregnancy.	3.0, 2001-2003
Iroezindu, 2016, Nigeria(30)	Pan-African Thoracic Society Methods in Epidemiologic and others	Case Control	8: High	Hospital records	Predictors of mortality and length of stay	Age ≥ 18 years with CAP admitted to hospital	Hospital-acquired pneumonia, no chest x-ray, findings suggestive of TB, malignancy, or pulmonary oedema.	5.0, 2008-2012
Kofteridis, 2016,	None reported	Case Control	6: Moderate	Hospital records	Mortality and length of stay	Age ≥ 65 years with CAP admitted to hospital	Immunosuppression, malignancy, hospitalized for	7.0, 2005-

Greece(26)							≥ 2 days during the previous 90 days.	2011

Supplementary table 1: General characteristics of the thirty-eight studies identified in the review. NOS = Newcastle-Ottawa Scale. CAP = community-acquired pneumonia. ED = emergency department. ICU = intensive care unit. TB = tuberculosis. HIV = human immunodeficiency virus.

First author, year	Diabetes definition	Numbers			Mortality measure	Other outcomes
		Total	DM	No DM		
Adamuz, 2014	Unclear	1,284	325	959	1-year	N/A
Benfield, 2007	Answering 'yes' to the question: 'Do you have diabetes?'	586	Unc.	Unc.	30-day	N/A
Biteker, 2016	Unclear	111	22	89	N/A	Complicated hospitalization
Biteker, 2018	Unclear	154	33	121	N/A	Complicated hospitalization
Cangemi, 2015	As per European guidelines on cardiovascular disease prevention in clinical practice (version 2012)	301	81	220	End-of-trial	CV events in follow-up
Castellanos, 2010	Unclear	501	114	387	In-hospital	Complicated hospitalization, ICU admission, length of stay
DiYacovo, 2013	Fasting glucose ≥ 7.0 mmol/L (126 mg/dL) on 2 or more occasions, random glucose ≥ 11.1 mmol/L (200 mg/dL), previous clinical and/or biochemical diagnosis, or treatment with oral antidiabetic agents or insulin.	2,407	516	1,891	In-hospital, 30-day	ICU admission, length of stay
Falguera, 2005	Previous clinical and/or biochemical diagnosis, or treatment with oral antidiabetic agents or insulin, fasting glucose ≥ 126 mg/dL (7.0 mmol/L), or random glucose ≥ 200 mg/dL (11.1 mmol/L) on 2 or more occasions.	660	106	554	30-day	Pleural effusion

Hifumi, 2015	Unclear	71	13	58	In-hospital	Weaning from mechanical ventilation
Hraiech, 2013	Unclear	100	18	82	In-hospital	N/A
Jahanihashemi, 2018	ADA criteria	621	68	553	In-hospital	N/A
Jensen, 2017	Self-reported diabetes, attending physician diagnosis, or treatment with either oral or injectable anti-diabetes medication.	1,318	162	1,156	In-hospital	Severe outcome, ICU admission
Kabeya, 2016	Diabetes on discharge coding or registered in the medical record	828	250	578	In-hospital	Length of stay, hospital costs
Kao, 2017	Unclear	32	11	21	In-hospital	N/A
Koskela, 2014	Doctor's diagnosis of diabetes before the current pneumonia episode and verified from the patient files	153	22	131	End-of-trial	N/A
Lepper, 2012	Self-report or drug use, including long term use of glucose lowering drugs	6,891	1,114	5,756	30-day, 90-day, End-of-trial	N/A
Lopez-de-Andres, 2017	ICD-9-CM codes: 250.x0 and 250.x2	901,136	223,715	677,421	In-hospital	N/A
Luna, 2016	Unclear	6,205	1,147	5,058	30-day	N/A
Martins, 2016	ICD-9-CM 250 on discharge coding	74,175	19,212	54,963	In-hospital	Length of stay

McAlister, 2005	Unclear	2,471	401	2,070	In-hospital	Complicated hospitalization
Mortensen, 2010	Unclear	787	230	557	30-day	N/A
Nseir, 2019	Unclear	561	155	406	30-day	N/A
O'Meara, 2005	Fasting glucose of at least 126 mg/dL or the use of insulin or oral hypoglycaemic medications	442	64	378	In-hospital, End-of-trial	N/A
Parrott, 2017	Unclear	97	9	88	N/A	Length of stay
Rueda, 2010	Diagnosis before admission, during admission, or in the 1 year after admission, based on ADA criteria.	233	53	180	30-day	N/A
Saibal, 2012	Current or previous biochemical diagnosis according to WHO definition	90	47	43	In-hospital	Pleural effusion, ICU admission, length of stay
Schuetz, 2014	Self-report or medical record documentation	880	156	724	30-day	Severe outcome, ICU admission
Suter-Widmer, 2012	Self-report or medical record documentation	875	107	768	N/A	Length of stay
Yang, 2018	Unclear	278	93	185	30-day	N/A
Yende, 2010	Self-report and review of medications	1,895	384	1,511	1-year	Severe outcome
Kofteridis, 2016	ADA criteria	247	108	139	In-hospital	Complicated hospitalization, pleural effusion, length of stay

Supplementary table 2: Details of the thirty-one studies associating diabetes status with hospitalized community-acquired pneumonia outcomes. DM = diabetes mellitus. Unc. = unclear. ADA = American Diabetes Association. WHO = World Health Organisation. CV = cardiovascular. ICU = intensive care unit.

First author, year	Hyperglycaemia definition	Numbers			Mortality measure	Other outcomes
		Total	HG	No HG		
Bhattacharya, 2013	Admission glucose: normal glycemia < 126 mg/dL (< 7.0 mmol/L), mild hyperglycemia 126–180 mg/dL (7.0-10.0 mmol/L) [A], and uncontrolled hyperglycemia ≥ 180 mg/dL (≥ 10 mmol/L) [B]	857	A: 238 B: 121	498	In-hospital	Length of stay
Castellanos, 2010	Admission glucose: normal glycemia ≤ 100 mg/dL (≤ 5.6 mmol/L), mild hyperglycemia 101–125 mg/dL (5.7-6.9 mmol/L) [A], severe hyperglycemia > 126 mg/dL (> 7.0 mmol/L) [B], and known diabetes	387	A: 119 B: 143	125	In-hospital	Severe outcome, ICU admission, complications, length of stay
Chen, 2015	Admission glucose ≥ 252 mg/dL (≥ 14.0 mmol/L)	203	76	127	In-hospital	ICU admission, complications, length of stay
DiYacovo, 2013	Admission glucose > 198 mg/dL (> 11.0 mmol/L) [A] or > 252 mg/dL (> 14 mmol/L) [B], only assessed within the cohort with diabetes	516	A: 228 B: 141	288	30-day	N/A
Eurich, 2010	Admission glucose: 72-109 mg/dL (4.0-6.0 mmol/l); 110-139 mg/dL (6.1-7.7 mmol/l); 140-199 mg/dL (7.8-11.0 mmol/l) [A]; and 200-360 mg/dL (11.1 to 20.0 mmol/l) [B]	2,366	A: 535 B: 129	778	90-day, 1-year	N/A
Foltran, 2013	Continuous variable, each 10 mg/dL (0.6 mmol/L) below and above 86 mg/dL (4.8 mmol/L)	1,018	Unc.	Unc.	In-hospital	N/A

Godar, 2011	Admission glucose ≥ 140 mg/dL (≥ 7.8 mmol/L)	969	370	599	1-year	Length of stay
Jahanihashemi, 2018	Not defined	621	Unc.	Unc.	In-hospital	N/A
Jensen, 2017	Admission glucose ≥ 200 mg/dL (≥ 11.1 mmol/L)	1,318	97	1,221	In-hospital	Severe outcome, ICU admission
Kinzel, 1988	Fasting BGL > 140 mg/dL (> 7.8 mmol/L) on at least two occasions or random BGL > 200 mg/dL (> 11.1 mmol/L)	95	28	67	In-hospital	Length of stay
Koskela, 2014	Hyperglycaemia in first 24 hours of hospitalization without a prior diagnosis of diabetes. Fasting hyperglycaemia defined as glucose > 127 mg/dL (> 7.05 mmol/L) between 0300-0700 pre-breakfast. Postprandial hyperglycaemia defined as glucose > 194 mg/dL (> 10.75 mmol/L) during the day or in the evening	131	43	88	End-of-trial	N/A
Lepper, 2012	Admission glucose: < 72 mg/dL (< 4.0 mmol/L), 72-107 mg/dL (4.0-5.9 mmol/L), 108-197 mg/dL (6.0-10.9 mmol/L) [A], 198-251 mg/dL (11.0-13.9 mmol/L) [B], ≥ 252 mg/dL (≥ 14 mmol/L) [C]	6,016	A: 2,768 B: 303 C: 217	2,728	90-day	N/A
McAlister, 2005	Admission glucose: ≤ 109 mg/dL (≤ 6.0 mmol/L), 110-198 mg/dL (6.1-11.0 mmol/L), 199-251 mg/dL (11.0-13.9 mmol/L) [A], ≥ 252 mg/dL (≥ 14.0	2,471	A: 132 B: 147	2,192	In-hospital	Complications, length of stay

	mmol/L) [B]					
Rueda, 2010	Admission glucose: 60-125 mg/dL (3.3-6.9 mmol/L), 126-179 mg/dL (7.0-9.9 mmol/L) [A], ≥ 180 mg/dL (≥ 10.0 mmol/L) [B]	233	A: 73 B: 32	128	30-day	ICU admission
Schuetz, 2014	Admission glucose: < 108 mg/dL (< 6.0 mmol/L), 108-198 mg/dL (6.0-11.0 mmol/L) [A], > 198 mg/dL (> 11.0 mmol/L) [B]	880	A: 571 B: 93	216	30-day	Severe outcome, ICU admission
Yende, 2010	Admission glucose > 200 mg/dl (> 11.1 mmol/L)	1,795	Unc.	Unc.	1-year	N/A
Iroezindu, 2016	Random blood glucose > 180 mg/dL (> 10.0 mmol/L)	309	59	250	In-hospital	N/A

Supplementary table 3: Details of the seventeen studies associating hyperglycaemia with hospitalized community-acquired pneumonia outcomes. Total numbers are those in whom hyperglycaemia as per the study definition was assessed and may thus be lower than the total number of participants reported in the study. HG = hyperglycaemia. Unc. = unclear. CV = cardiovascular. ICU = intensive care unit. Hyperglycaemia cut-offs = A: ≤ 7.8 mmol/L, B: 7.9-11.0 mmol/L, C: ≥ 11.1 mmol/L, D: not defined.