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ORIGINAL RESEARCH

The Impact of Comorbid Dementia and Diabetes Mellitus on Hospital Patients' Outcomes: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Previous reviews have demonstrated that dementia and diabetes mellitus, separately, can worsen the hospital outcomes of patients. Unfortunately, there are no systematic evaluations regarding the hospital outcomes of patients with dementia and diabetes mellitus as a comorbidity. Therefore, our review aimed to determine any differences in hospital length of stay, hospital mortality, and hospital readmission between patients with the comorbidity and patients without.

Methods: Searches were conducted of Medline, CINHAL, EMBASE, PsychINFO, Web of Science and Google Scholar for original studies. All studies were quality assessed using the Joanna Briggs Institute critical appraisal tools. Where possible, studies were pooled in a meta-analysis to generate odds ratios (OR) with 95% confidence intervals (CI).

Results: Sixteen studies were included in this review. When comparing patients with the comorbidity to patients with dementia, the difference in length of stay was inconclusive, and there was no difference in the odds of hospital mortality (OR = 0.98, 95% CI 0.91–1.06). However, patients with the comorbidity had increased odds of 30-day readmission compared to patients with dementia alone (OR = 1.20, 95% CI 1.14–1.26). When comparing patients with the comorbidity to patients with diabetes, those with the comorbidity had a longer length of stay and but no difference in the odds of hospital mortality (OR = 1.48, 95% CI 0.84–2.62). Additionally, those with the comorbidity may have worse readmission outcomes than those with diabetes alone.

Conclusions: Our findings suggest that patients with comorbid dementia and diabetes mellitus may have worse hospital outcomes. Therefore, we recommend further research to assess these

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patients' hospital outcomes to resolve the discrepancies found.

Keywords: Diabetes; Dementia; Hospitalised patients; Readmission; Length of stay; Hospital mortality

Key Summary Points

Why carry out this study?

Separately, dementia and diabetes mellitus can increase a patient's risk of hospitalisation and patients with either condition can have worse outcomes when admitted to hospital

However, these two conditions are not separate issues—diabetes mellitus is a well-established risk factor for dementia development

Our review aimed to answer, 'Is there any difference in the hospital outcomes between patients with the comorbidity and patients with a single diagnosis of either dementia or diabetes mellitus?'

What was learned from the study?

Hospital patients with comorbid dementia and diabetes mellitus can have worse hospital outcomes than those with a singular diagnosis

Additional research should be conducted on this inpatient group regarding risk factors and causes of poor hospital outcomes which can lead to the development of evidence-based practices and guidelines

INTRODUCTION

Background

Diabetes mellitus is a common chronic metabolic condition with ~ 422 million people worldwide living with the condition and an increasing projected prevalence [1]. Over time, complications develop from the damage caused by high blood glucose [2]. This includes cardiovascular disease, renal disease, neuropathy, retinopathy, foot disease, and importantly dementia [2].

Dementia is a cognitive syndrome resulting in a decline in brain functioning with Alzheimer's disease being the most common cause [3]. Primarily, it is a condition of old age, mainly affecting those over 65 years old [3], with an estimated 55 million people living with dementia worldwide [3]. Consequently, it is the seventh leading cause of death worldwide and a major cause of disability and dependency [3].

Importantly, dementia and diabetes mellitus are not separate issues. Diabetes mellitus is a well-established risk factor for dementia development [4]. The potential mechanisms behind this are unclear and complex but there is evidence that brain atrophy and protein deposition forming plaques in the brain in dementia can be increased by having diabetes [5]. Some have even called Alzheimer's disease 'type three diabetes mellitus' [6]. Patients with both dementia and diabetes mellitus diagnoses will be referred to as patients with the comorbidity throughout this review.

Separately, dementia and diabetes mellitus can increase a patient's risk of hospitalisation [7, 8]. Additionally, patients with either condition can have worse outcomes when admitted to hospital [9–11]. This includes longer hospital stays and an increased risk of mortality during their admission [11, 12]. Currently, there is limited research and systematic evaluation regarding hospital patients with comorbid dementia and diabetes mellitus. Previous systematic reviews have only established the outcomes of hospital patients with dementia and diabetes mellitus separately [13, 14]. No systematic reviews have evaluated the impact of the comorbidity on hospital outcomes for this group of inpatients.

This systematic review aimed to fill this gap to advance our knowledge of the comorbidity and its implication for hospital patients. Understanding the hospital outcomes of these patients can shed light on the challenges and complexities associated with the comorbidity. At the same time, providing a valuable insight into these patients' overall care during their hospital admission [15]. Potentially assessing whether current practices and guidelines

are adequate for the hospital management of patients with comorbid dementia and diabetes mellitus.

Specifically, our review aimed to answer, 'Is there any difference in the hospital length of stay, hospital mortality and hospital readmission between patients with the comorbidity and patients with a single diagnosis of either dementia or diabetes mellitus?'.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [16]. Before conducting this review, the protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO, CRD42023421514).

Literature Search

The following databases were originally searched on the 18th of January 2023: Ovid Medline (1946 to present), Ovid Embase (1974 to present), EBSCOhost CINAHL, EBSCOhost PsychINFO, Web of science. A further search was conducted on Google Scholar, with only the first 100 articles, sorted by relevance, being screened. No date or language restrictions were applied to the searches. An updated search on the 1st August 2023 was also conducted.

The search strategy was developed based on three concepts: dementia, diabetes, and hospitalisation. A university research librarian reviewed the search strategy. Review outcomes were not included in the search strategy to increase the number of records retrieved for screening. See Supplementary Table S1 for the search strategy.

The results from the searches were exported onto EndNote (version 20) before de-duplication by the first reviewer (KGD).

Study Selection

Title and Abstract Screening

The first reviewer (KGD) initially screened the titles and abstracts of the exported studies against three questions: (1) Is the study primary research? (2) Does the study include a population diagnosed with comorbid dementia and diabetes mellitus? (3) Is the study population hospital inpatients? If the study answered yes or unclear to all these questions, it would proceed to full-text screening.

Full-Text Screening

Full texts of the potentially eligible studies were obtained. The first reviewer (KGD) screened the full texts against the eligibility criteria (Supplementary Table S2). Primary quantitative studies of any design were eligible if they assessed at least one hospital outcome (length of stay, mortality, readmission) on inpatients with comorbid dementia and diabetes mellitus. Based on the eligibility criteria, studies were categorised as included, excluded or unclear.

The second reviewer (NG) checked 10% of the included studies, 10% of the excluded studies and 100% of the unclear studies. The first reviewer (KGD) and the second reviewer (NG) discussed the unclear studies to decide on their eligibility. Any discrepancies were resolved by the third reviewer (MH). Due to time constraints, two reviewers could not fully screen the studies independently. However, inter-rater reliability between the first and second reviewers was assessed with Cohen's kappa statistic (k) to determine the level of agreement and reliability in this screening process [17].

If full texts were not initially available, corresponding authors were contacted to gain full access and given four weeks to respond otherwise the study was excluded.

Study Categorisation

All included studies were categorised by the first reviewer (KGD) into three groups based on

the primary outcomes of this review. The three primary outcomes of this review were hospital length of stay, hospital mortality and hospital readmission for inpatients. Hospital length of stay was defined as the duration between hospital admission and discharge. Hospital mortality was defined as if patients died during their hospitalisation. Hospital readmission was defined as when a discharged patient gets readmitted again within a specified timeframe. Any result and effect measure compatible with each outcome was sought for comprehensive insight.

Data Extraction

Data extraction was completed by the first reviewer (KGD) on a data extraction template designed by the first reviewer (KGD). Where available, data collected from each study included:

- Study details: author, title, publication year, aims, country, setting, study duration.
- Population details: total number, age range, percentage of men.
- Comorbidity population details: total number, age range, percentage of men.
- Comparator group population details: diagnosis (dementia alone or diabetes mellitus alone), total number, age range, percentage of men.
- Hospital length of stay: definition, median, mean, odds ratio, confidence intervals, *p* values.
- Hospital mortality: definition, number of deaths, percentages, odds ratio, confidence intervals, *p* values.
- Hospital readmission definition, number of readmissions, percentages, odds ratio, confidence intervals, *p* values.
- Additional notes: comments for other important aspects of the study, including results that do not fit into any section in the extraction form.

After completing data extraction, the second reviewer (NG) checked 100% of the results to assess for accuracy. Any discrepancies or uncertainties in the data extraction process were discussed with the third reviewer (MH). If necessary, corresponding authors were contacted to clarify or provide missing data for the studies and given four weeks to respond.

Quality Assessment

All included studies were quality assessed using the validated Joanna Briggs Institute (JBI) critical appraisal tool [18] by the first reviewer (KGD). The JBI tools contain questions that generally focus on the study population, exposures, confounding factors, outcomes, and statistical analysis [18]. Questions could be answered yes, no, unclear or not applicable. The quality of studies was rated based on the percentage of yes answers, with those scoring higher than 70% being described as high quality, those between 50% and 69% being medium quality and those lower than 50% being low quality. The second reviewer (NG) checked 100% of the quality assessment results for accuracy.

Synthesis of Results

The included studies' results are presented in three tables according to outcome (length of stay, hospital mortality, hospital readmission). Where appropriate, odds ratios, confidence intervals and *p* values were calculated from available data within the study using RevMan software (version 5.4).

To answer this review's question, where possible, meta-analyses were conducted to provide a better estimate of the differences in the hospital outcomes between patients with the comorbidity and those without the comorbidity [19]. Before meta-analysis, an assessment of clinical and methodological heterogeneity took place. Only studies which were sufficiently similar were pooled to provide a meaningful result [20]. Odds ratios were pooled using an inverse-variance method and random effects model. The random effects model was selected to accommodate the expected heterogeneity present both within and between studies, which can be attributed to variations in comorbidity profiles and study designs. An assessment of statistical heterogeneity was carried out using Higgins I^2 statistic [21]. A value

of more than 75% was classified as considerable heterogeneity [20]. The meta-analysis was carried out using RevMan (version 5.4). Studies that were not sufficiently similar to be combined in a meta-analysis were eligible for narrative synthesis, which summarised the differences in the hospital outcomes.

Ethics

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection

The results from the complete search can be seen in the PRISMA flowchart (Fig. 1). After database searching, 4679 records were identified. Of these, 16 studies met the inclusion criteria and were included in the review [22–37]. Cohen's kappa statistic indicates perfect agreement between the two reviewers in our screening process ($k = 1$). See Supplementary Table S3 for Cohen's kappa calculation table. The updated search found no additional studies that met our inclusion criteria.

Study Characteristics

The characteristics of all the included studies [22–37] are summarised in Table 1. The 16 included studies [22–37] took place between 2011 and 2022 across eleven countries in four different continents. Most of the studies included were observational in design, including cross-sectional ($n = 11$) [22, 23, 26, 27, 29, 31–36], cohort ($n = 3$) [24, 25, 28], and case–control ($n = 1$) [37] studies. However, one randomised control trial [30] was also eligible for inclusion. Across the studies, there were 252,490 hospital inpatients reported with the dementia and diabetes mellitus comorbidity. However, the sizes of the studies varied, ranging from a population of just 16 patients with the comorbidity [29] to the largest population of 143501 [35] (median = 337). The outcomes reported were hospital length of stay ($n = 6$) [23, 25, 29, 32, 35, 36], hospital mortality ($n = 11$) [22, 23, 26–28, 31–35, 37], and hospital readmission ($n = 6$) [24, 25, 30, 32, 35, 36]. However, no study was excluded based on missing data.

Quality Assessment

The appraisal tools for cross-sectional, cohort, case–control studies and randomised control trials were used to accommodate for the different study designs. See Supplementary Table S4 for the respective questions used from each tool. A summary of the quality assessment results can be seen in Supplementary Table S5. No studies were excluded based on quality assessment, as low-quality studies can still provide valuable insight.

Eleven studies [22, 23, 26, 27, 29, 31–36] were assessed by the cross-sectional tool. Of these, three were medium quality [22, 23, 27] and eight were high quality [26, 29, 31–36]. Generally, the studies performed well regarding questions relating to sampling, reducing confounding, outcome measures and statistical analysis. However, nine studies [22, 23, 26, 27, 31–33, 35, 36] either had no description or used the International Classification of Diseases (ICD) to identify conditions. The ICD is descriptive and not objective, which can introduce information bias.

Three studies [24, 25, 28] were assessed by the cohort tool. Of these, one was low quality [24] and two were high quality [25, 28]. All three studies performed well in reducing selection bias and information bias, but only two studies [25, 28] recorded and adjusted for confounders.

The one case–control study was assessed as medium quality [37]. There was no description of how the exposures were measured, introducing information bias. The cases and controls were not appropriately matched at baseline however, it did attempt to reduce confounding by statistical analysis.

The one randomised control trial study was assessed as high quality [30]. There was true randomisation and allocation concealment reducing selection bias. Outcomes were recorded

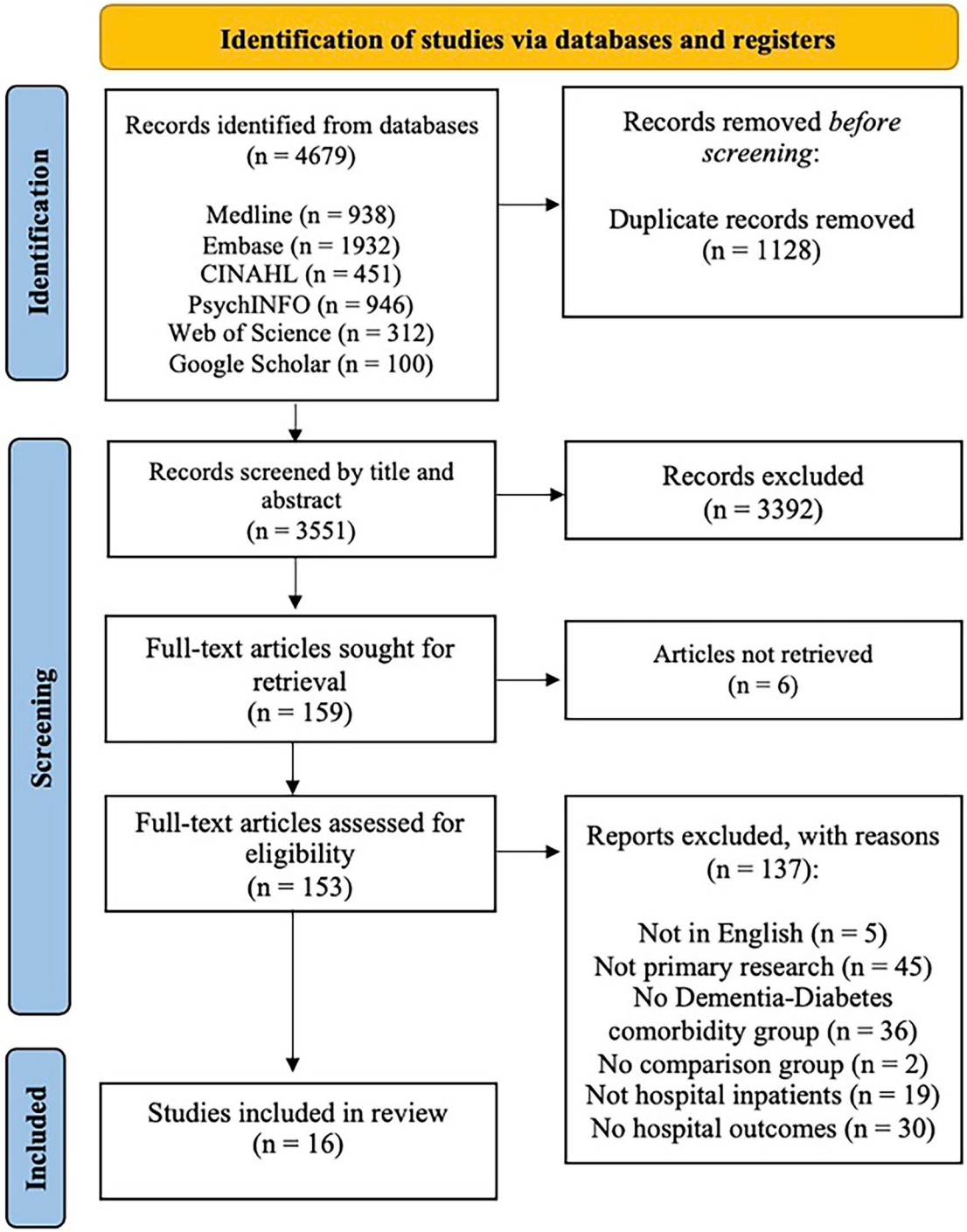

Fig. 1 Flowchart of the literature search and study selection with the number of studies at each stage (*n*)—4679 studies were identified through database searches conducted on 18 January 2023. After screening 16 studies were eligible

Table 1 Characteristics of included studies–study details and key aspects of the study design for all 16 included studies

Author, year	Country, setting	Study design	Comorbidity[a] group			Comparison group(s)				Outcomes[c] (units)
			Number of participants	Sex (% male)	Age (years)	Diagnosis[b]	Number of participants	Sex (% male)	Age (years)	
Albaladejo-Vicente et al. [22], 2020	Spain, hospital records	Cross-sectional	6270	–	> 40	DM	56,692	–	> 40	HM (OR)
Beydoun et al. [23], 2016	United States, nationwide inpatient sample	Cross-sectional	–	–	> 60	DE	–	–	> 60	LOS (LR), HM (OR)
Caughey et al. [24], 2017	Australia, Department of Veterans	Retrospective cohort	20	–	–	DM	828	–	–	HR (%)
Chang et al. [25], 2015	Taiwan, hospital Neurology Department	Retrospective cohort	67	–	> 65	DE	136	–	> 65	LOS (OR), HR (OR)
Chen et al. [26], 2022	China, Sichuan University	Cross-sectional	–	–	> 65	DE	–	–	> 65	HM (OR)
Corrao et al. [27], 2022	Italy, REPOSI registrar	Cross-sectional	125	–	> 65	DM	1253	–	> 65	HM (OR)
Erdemir et al. [28], 2021	United States, insurance claims	Retrospective cohort	1152	–	> 18	DM	4111	–	> 18	HM (OR)
Fraser et al. [29], 2021	United States, Kentucky	Cross-sectional	16	68.7	> 18	1) DM 2) DE	1) 567 2) 29	1) 48.9 2) 71	> 18	LOS (M)

Table 1 continued

Author, year	Country, setting	Study design	Comorbidity[a] group			Comparison group(s)				Outcomes[c] (units)
			Number of participants	Sex (% male)	Age (years)	Diagnosis[b]	Number of participants	Sex (% male)	Age (years)	
Gustafson et al. [30], 2018	Sweden, internal medicine wards	Randomised control trial	108	–	> 65	DE	321	–	> 65	HR (%)
Hernandez-Barrera et al. [31], 2020	Spain, hospital discharge records	Cross-sectional	548	–	> 40	DE	2336	–	> 40	HM (%)
Jimenez-Garcia et al. [32], 2017	Spain, national hospital database	Cross-sectional	58,668	44.6	> 70	DE	111,939	46.8	> 70	LOS (Mdn), HM (OR), HR (%)
Laskey et al. [33], 2014	United States, nationwide inpatient sample	Cross-sectional	35,178	–	> 18	DM	400,087	–	> 18	HM (OR)
Manabe et al. [34], 2017	Japan, hospital autopsies	Cross-sectional	27	–	–	DE	177	–	–	HM (OR)
Miguel-Yanes et al. [35], 2017	Spain, national hospital database	Cross-sectional	143,501	31.6	> 70	DE	398,357	33.5	> 70	LOS (Mdn), HM (%), HR (%)
Prinz et al. [36], 2016	Germany and Austria, diabetes patient's database	Cross-sectional	6770	43	> 40	DM	209,162	51.7	> 40	LOS (M), HR (%)
Schoepf et al. [37], 2011	United Kingdom, university hospital	Case–control	40	–	> 70	DE	594	–	> 70	HM (%)

Table 1 continued

[a]Refers to patients who have a dementia and diabetes mellitus diagnosis

[b]Those with only a dementia (DE) diagnosis or diabetes mellitus (DM) diagnosis as a comparison

[c]Outcomes are length of stay (LOS), hospital mortality (HM), or hospital readmission (HR). The units can be median (Mdn), mean (M), linear regression (LR) percentage (%), odds ratio (OR)

reliably by a group of blinded experts. However, the participants and those delivering the intervention could not be blinded, introducing performance bias.

Hospital Length of Stay

Six studies [23, 25, 29, 32, 35, 36] reported the length of stay of patients with the dementia and diabetes mellitus comorbidity. Five studies [23, 25, 29, 32, 35] reported results that compared the patients to those with dementia alone, and two [29, 36] compared them to diabetes mellitus alone. Due to high methodological heterogeneity in the outcomes reported, no studies were pooled for a meta-analysis. See Supplementary Table S6 for the individual results of these studies.

Comorbidity Versus Dementia

Five studies [23, 25, 29, 32, 35] reported this outcome; however, there was a mixture of findings. Two studies showed that those with the comorbidity stay longer in hospital than those with dementia alone [25, 29]. One study [35] found that patients with the comorbidity stay less time in hospital than patients with dementia. Two studies [23, 32], found that both groups had no difference in hospital length of stay. One study [23] was assessed as medium quality but five studies [25, 29, 32, 35] were of high quality. Therefore, due to the inconsistencies between the studies, an overall conclusion regarding the differences between the groups' length of stay was unable to be determined.

Comorbidity Versus Diabetes Mellitus

Two studies [29, 36] reported this outcome, and both indicated that those with the comorbidity have a longer length of hospital stay than patients with diabetes. One study [36] indicated that patients with the comorbidity have a mean length of stay of nearly two days longer than those with diabetes mellitus. The second study [29] suggests those with the comorbidity stay 1.83 days compared to 1.71 days

(log-transformed). The studies [29, 36] were deemed high in quality.

Hospital Mortality

Eleven studies [22, 23, 26–28, 31–35, 37] reported the hospital mortality of patients with comorbid dementia and diabetes mellitus. Seven studies [23, 26, 31, 32, 34, 35, 37] reported results that compared patients to those with dementia alone, and four [22, 27, 28, 33] compared them to patients with diabetes alone. See Supplementary Table S7 for the individual results of these studies.

Comorbidity Versus Dementia

Seven studies [23, 26, 31, 32, 34, 35, 37] reported this outcome. The results from six studies [26, 31, 32, 34, 35, 37] were sufficiently similar methodologically and reported odds ratios of in-hospital mortality, so they were combined in a meta-analysis (Fig. 2). No significant difference in the odds of hospital mortality was found between those with the comorbidity and patients with dementia (OR = 0.98, 95% CI 0.91–1.06). There was considerable statistical heterogeneity (I^2 = 89%). Five of these studies [26, 31, 32, 34, 35] were deemed high quality, and one [37] as medium quality.

One study [23] was not included in the meta-analysis due to it reporting of different participant characteristics compared to the other included studies. This study [23] reported hospital mortality in those with the comorbidity either with or without complications and compared them to patients with dementia. It showed there was no difference in the odds of hospital mortality between these groups of patients, regardless of whether patients with the comorbidity had complications. This study [23] was assessed as medium quality due to its risk of selection bias.

Comorbidity Versus Diabetes Mellitus

Four studies [22, 27, 28, 33] reported this outcome. All studies were sufficiently similar methodologically and reported odds ratios, so they were combined in a meta-analysis (Fig. 2).

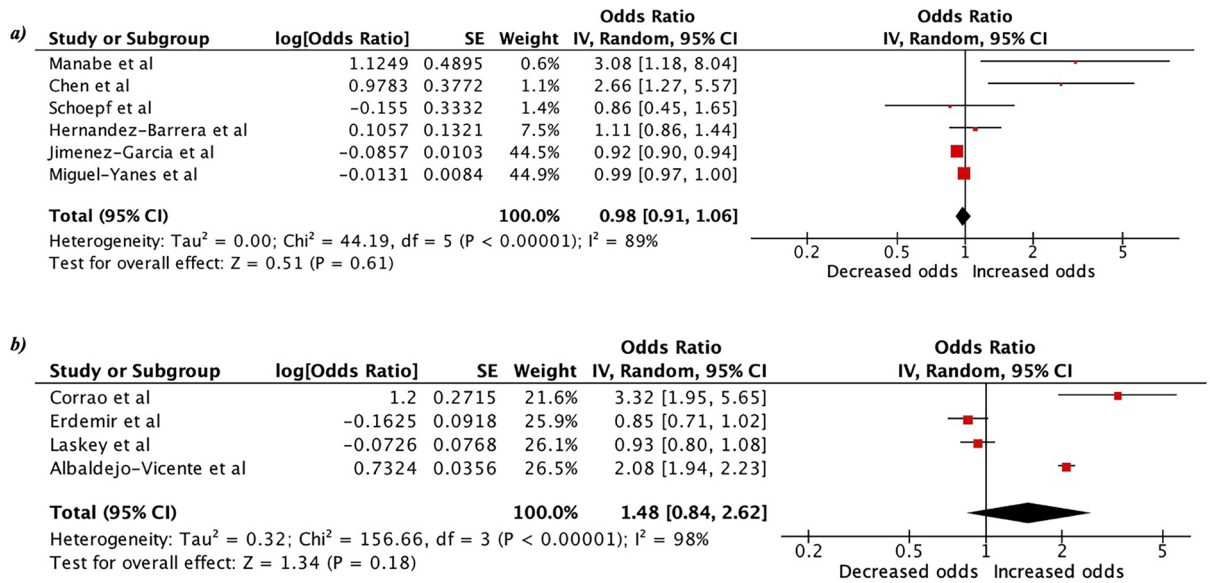

Fig. 2 **a** Forest plot for the results of the meta-analysis assessing the odds of hospital mortality of patients with the comorbidity compared to patients with dementia. **b** Forest plot for results of meta-analysis assessing the odds of hospital mortality of patients with the comorbidity compared to patients with diabetes. *CI* confidence interval, *IV* inverse variance, *SE* standard error

The pooled result suggests no difference in the odds of hospital mortality for patients with the comorbidity compared to those with diabetes alone (OR = 1.48, 95% CI 0.84–2.62). There was considerable statistical heterogeneity (I^2 = 98%). Two studies [28, 33] were high quality and two [22, 27] were medium quality.

Hospital Readmission

Six studies [24, 25, 30, 32, 35, 36] reported the hospital readmission of patients with comorbid dementia and diabetes mellitus. Four studies [25, 30, 32, 35] reported results that compared these patients to those with dementia alone, and two [24, 36] compared them to patient with diabetes alone. See Supplementary Table S8 for the individual results of these studies.

Comorbidity Versus Dementia

Four studies [25, 30, 32, 35] reported this outcome. Two studies [32, 35] were sufficiently similar methodologically and reported the odds ratio for 30-day readmission, so they were combined in a meta-analysis (Fig. 3). The pooled odds ratio suggests those with the comorbidity have 20% higher odds of 30-day readmission compared to those with dementia alone (OR = 1.20, 95% CI 1.14–1.26). Both studies [32, 35] were rated as high in quality. However, there was considerable statistical heterogeneity (I^2 = 88%).

Two studies [25, 30] reported different outcomes, so they were not included in the meta-analysis. One study [25] indicated no difference in the odds of having more than four readmissions within 4 years between those with the comorbidity and those with dementia alone (OR = 1.67, 95% CI 0.42–6.69). However, the second study [30] indicated that patients with the comorbidity have 23% higher odds of having drug-related readmissions within 180 days than those with dementia alone (OR = 2.23, 95% CI 1.41–3.81). Both studies [25, 30] were rated as high quality.

Comorbidity Versus Diabetes Mellitus

Two studies [24, 36] reported this outcome but could not be combined in a meta-analysis due to the different outcomes reported. One study [24] reported a non-significant odds ratio comparing the odds of 30-day readmission between patients with the comorbidity and those with diabetes alone (OR = 1.02, 95% CI 0.37–2.84). This study [24] was assessed as low in quality due to the risk of confounding (Supplementary Table S5). Whereas the second study [36] suggested, patients with the comorbidity have 49% higher odds of having more than two readmissions within 1 year compared to those with diabetes (OR = 1.49, 95% CI 1.40–1.59). This study [36] was deemed as high quality.

DISCUSSION

Our review suggests no difference in hospital mortality but an increased odds of readmission for patients with the comorbidity compared to patients with only a dementia diagnosis. However, the difference in length of stay between these two groups is uncertain. Whereas there is an increased length of stay and increased odds of readmission for those with the comorbidity compared to patients with diabetes mellitus

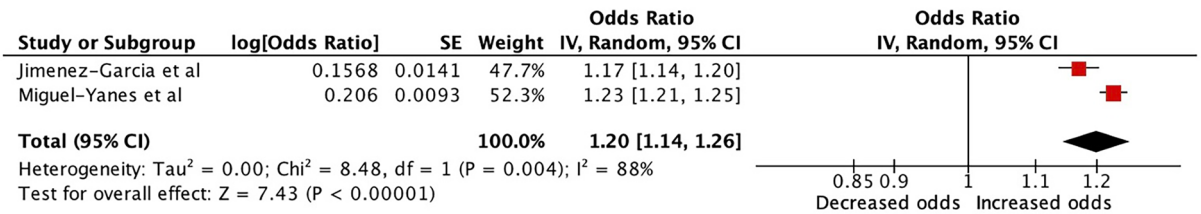

Fig. 3 Forest plot for the results of the meta-analysis assessing odds of 30-day readmission of patients with the comorbidity compared to patients with dementia. *CI* confidence interval, *IV* inverse variance, *SE* standard error

alone. There may be an increased hospital mortality risk for patients with the comorbidity compared to those with diabetes alone, but this was non-significant.

When comparing the length of stay between those with the comorbidity and dementia alone, the evidence is inconsistent. Some included studies suggest those with the comorbidity have an increased hospital length of stay [25, 29], with one study suggesting patients with both diagnoses are up to nearly three times more likely to stay longer [25]. Other included studies suggest patients with dementia stay longer instead [35], or that there is no difference in hospital stay between the two groups [32]. Unfortunately, as the studies reported a mixture of outcomes, it was impossible to combine the findings to generate one reliable pooled result and to derive an overall conclusion regarding the differences between the groups. Although it seems plausible that the addition of a diabetes diagnosis could prolong the length of stay, compared to having dementia alone, as some previous studies suggest patients with dementia stay longer if they have comorbidities, albeit these studies did not specifically look at the role of a diabetes mellitus comorbidity [38–40]. However, the hospital length of stay for patients with the comorbidity was found to be longer by up to about two days compared to patients with diabetes alone [36]. However, only two studies [29, 36] were found to report this outcome in this review, so this is supported by limited evidence. Despite this, pre-existing literature can potentially explain the findings. Patients with dementia are more at risk of functional decline during hospitalisation [14]. Additionally, these patients have 49% higher odds of developing postoperative complications in hospitals than those without dementia [41]. Ultimately these factors could delay discharge and negatively affect those with the dementia and diabetes mellitus comorbidity compared to those with only diabetes mellitus.

There was a non-significant difference in hospital mortality between those with the comorbidity and those with dementia alone. The one study not included in the meta-analysis also reported a non-significant odds ratio [23]. There are several possible explanations for why a comorbid diabetes mellitus diagnosis does not significantly impact hospital mortality for patients with dementia. This can include the anti-inflammatory effects of insulin treatment [42], the reduced risk of acute lung injury during infections [43, 44] or the obesity paradox in patients with diabetes [45]. However, our findings should be interpreted with caution. As there was considerable statistical heterogeneity in the meta-analysis ($I^2 = 89\%$), two studies [32, 35] contributed to over 90% of the weighting, and several studies contradict this finding for community patients [46, 47]. In the community, patients with both diagnoses have an 85% increased risk of mortality compared to those with dementia alone [47]. Therefore, why this review did not find this result in hospital patients is unclear. Again, we found a non-significant difference in the odds of hospital mortality between patients with the comorbidity and those with diabetes mellitus alone. Although not significant and has a high statistical heterogeneity ($I^2 = 98\%$), the 48% higher odds of hospital mortality in patients with the comorbidity may have potential clinical significance. This is due to the consistent alignment with community-based studies suggesting increased mortality rates for patients with the comorbidity compared to those with diabetes alone [48–50]. There is up to 46% higher mortality risk for those with the comorbid dementia and diabetes mellitus in the community [49]. An increased hospital mortality risk can potentially be explained by patients with dementia having a greater risk of life-threatening infections [34, 51], acute organ dysfunction [52] and severe sepsis [53] during their admission.

Furthermore, this review indicated that those with the comorbidity have 20% higher odds of 30-day readmission than those with dementia alone. Studies not pooled in the meta-analysis also support the increased readmission risk for patients with both diagnoses but over a longer timeframe of up to 4 years [25, 30]. This result can potentially be explained by the increased risk of hypoglycaemia hospitalisations in those with the comorbidity [36, 54]. Similar research aligns with this indicating that patients with the comorbidity are up to 12% more likely to be readmitted to psychiatric hospitals than

those with dementia alone [55]. Although, it should be noted that the reasons for psychiatric hospital readmissions are likely to differ from those for general hospital readmissions. Although the results reached statistical significance, they should be interpreted with caution due to the considerable statistical heterogeneity ($I^2 = 88$) and only two studies being used to generate one overall result in the meta-analysis. Additionally, those with the comorbidity may have an increased readmission risk compared to those with diabetes mellitus alone. However, the two included studies reported different outcomes and one [24] was low in quality so should be interpreted with caution due to the limited high-quality statistically significant evidence. Additionally, it becomes difficult to determine the timeframe for which readmission most likely occurs due to the varying outcomes reported. Despite this, pre-existing literature assessing hospitalisation risk can support the potential increased readmission risk for patients with the comorbidity. It has been found that patients with diabetes have over double the hospitalisation rate if they have comorbid dementia, compared to if they do not have dementia [54]. A possible explanation for this is that patients with the comorbidity are less likely to follow recommended blood glucose monitoring regimes compared to those without dementia due to poor self-care [54, 56]. Therefore, patients are at risk of diabetes-related complications that can lead to re-hospitalisation [54].

The results from this review highlight the negative impact the comorbidity can have on hospital outcomes for patients. However, some variations between the studies and inconclusive findings made it challenging to derive some definitive conclusions. Therefore further research needs to assess all three hospital outcomes (length of stay, mortality, and readmission) on the same cohort as this provides a better overall evaluation of the hospital care this group of inpatients are receiving [15]. Only two studies in this review did this [32, 35]. In particular, further research should compare hospital mortality in patients with the comorbidity compared to those with diabetes alone and to compare length of stay and hospital mortality in patients with the comorbidity to those with dementia alone. This is due to our review finding studies that report both positive and negative effect sizes in each of these comparisons. Although the poorer outcomes we found could suggest that patients with both diagnoses have more complexities that need managing when admitted to hospital, which are not currently being addressed effectively. Guidelines for managing these hospital inpatients have been released, but they are often non-specific and based on limited evidence [57]. Therefore, additional research should be conducted on these inpatients which will lead to developing and improving current guidelines and practices, ensuring they are sufficiently evidence-based. This should include research that identifies the causes and predictors of poor hospital outcomes. For example, identifying risk factors for readmission in this group of inpatients can change and improve discharge planning and follow-up. Additionally, the role of specific management and monitoring regimes should be investigated such as the use of closed-loop diabetes monitoring systems. These systems have shown promise for diabetes mellitus inpatients [58], but more research is needed to understand its role in those inpatients with the comorbidity.

The studies included in this review have several limitations. Firstly, most studies used the International Classification of Diseases (ICD) [59] to identify cases of dementia and diabetes mellitus. The ICD classification system is not diagnostic criteria, so it can be subjective. Therefore, the reliability of the classification relies on the healthcare provider, which can introduce information bias [60]. It is important to note that ICD codes are particularly poor at accurately reflecting inpatient diabetes mellitus diagnoses [61]. Secondly, dementia is difficult to diagnose and is often underdiagnosed prior to hospital admission [62]. Consequently, this could result in underreporting of dementia in these hospital patients further, introducing information bias [60]. Thirdly, many studies could not measure and account for all important factors, such as disease duration, severity, laboratory results, complications, and medication regimes. This results in important covariates not being examined, which could have a confounding effect on hospital outcomes. Fourthly, several studies were large national databases that lacked patient-level

identifiers; therefore, it could not be determined if multiple admission data were from the same person. This results in the potential overestimation of sample size and can affect the conclusions derived from the study. Lastly, few studies [32, 35] measured the hospital length of stay, hospital mortality, and readmission for the same group of patients. All three, in combination, are needed to evaluate the overall care a patient receives, compared to only using one of these outcomes [15]. In addition, most of the included studies assessing hospital length of stay did not report sufficient results to determine if there were statistical differences between the groups. This made it harder to derive overall conclusions.

Although every attempt was made to create an accurate and reliable systematic review, there are some limitations to be considered. One issue is that due to time constraints, full-text screening could not be completed by two independent reviewers as recommended [20]. This increases the risk of errors and the possibility that the results are influenced by a single reviewer's own biases [20]. To minimise this risk, a second reviewer checked a sample of results during the full-text screening, generating a Cohen's kappa score that suggested perfect inter-rater agreement between the first and second reviewers. This provides greater confidence in the review process, despite this limitation [17]. It was not possible for a second reviewer to be involved in the title and abstract screening stage. However, the first reviewer erred on the side of over-inclusion at this stage to mitigate the risk of missing eligible studies. However, the second reviewer fully checked data extraction and quality assessment to confirm accuracy. Additionally, due to the accessibility of resources, only English-language databases were searched, and there was insufficient time to translate non-English studies [20]. Grey literature was also not searched. As a result, there is the possibility that eligible studies meeting the inclusion criteria were not included in this review. Furthermore, this increases the risk of publication bias, which can skew the results towards a positive effect [20]. Studies are more likely to be published if they report significant results compared to non-significant results [20]. Due to the limited number of studies in each meta-analysis, publication bias could not be formerly assessed [20].

All three meta-analyses had high I^2 values ranging from 88 to 98%, suggesting considerable statistical heterogeneity [20]. There was also heterogeneity in the direction of the results in individual outcomes of the included studies. Potential reasons for this include variations in design, geographical setting, healthcare systems, patient demographics, and their comorbidity profiles between studies. Ultimately, this means that the results of the meta-analyses need to be interpreted cautiously. Although speculative, geographical variation could have an impact. Two studies [26, 34] conducted in Asia were the only studies to show that those with the comorbidity have a significant increase in odds of hospital mortality compared to those with dementia alone. All the other studies [23, 31, 32, 35, 37] conducted in Europe and North America indicate no difference in hospital mortality between the two groups. Additionally, another included study [25] conducted in Asia indicated that those with the comorbidity have 179% increased odds of staying longer in the hospital compared to those with dementia alone. This is in contrast to the other included studies conducted in non-Asian countries, which had inconsistent results with smaller directions of effect. These differences could arise from the variations in healthcare [63]. However, subgroup analysis was not conducted to explore this heterogeneity as there were not enough studies to produce a meaningful result [20].

CONCLUSIONS

In conclusion, this systematic review indicated that hospital patients with comorbid dementia and diabetes mellitus can have worse hospital outcomes than those with a singular diagnosis. However, the findings varied depending on the patient group used for comparison. Patients with the comorbidity had a longer length of stay, a non-significant increase in hospital mortality odds and an increased readmission odds compared to those with diabetes mellitus. Whereas, compared to patients with

dementia, there was only an increased odds of readmission for patients with the comorbidity. Differences in length of stay and hospital mortality between these two groups were inconclusive or non-significant, respectively. These findings suggest a need for the improved care and management of hospital patients with the dementia and diabetes mellitus comorbidity. This includes further research assessing specific predictors of the poor outcomes and assessing current diabetes management regimes, such as closed-loop diabetes monitoring, in this patient group. It should be noted that the included studies had some limitations, such as subjective diagnosis classification and poor adjustment for important covariates.

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Data Availability. The data for this study are available within the article and its supplementary materials. Additional data generated or analysed during this study, including search strategies and quality assessment checklists, are included in the supplementary files. Any other relevant data are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest. Ketan Dhatariya is an Editorial Board member of Diabetes Therapy. Ketan Dhatariya was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. All other authors (Kieran Gadsby-Davis, Nikki Garner, Busra Donat Ergin, Michael Hornberger) have no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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