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Review article

Hyperactive and hypoactive psychomotor subtypes of delirium in demented and nondemented elderly patients with hip fractures: systematic review and meta-analysis

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Background: The occurrence of delirium superimposed on dementia (DSD) in patients with hip fracture may have many life-threatening complications, especially if unrecognized and untreated.
Objectives: To estimate the prevalence and outcomes of DSD in hospitalized elderly adults with dementia and hip fracture, and clinical symptoms of delirium with and without dementia.
Methods: The review process followed guidelines consisting of 5 steps suggested for systematic reviews. Relevant studies between January 2000 to December 2014 were obtained from electronic databases, and 2 trained reviewers independently analyzed them. Comprehensive Meta-Analysis software (Biostat) was used to assess and combine the data across studies.
Results: We identified 15 articles for meta-analysis. Prevalence of DSD after hip fracture was 69.7% (95% confidence interval [CI] = 60.4%-77.7%). People with dementia after hip fracture had a 6.03 times higher likelihood of sustaining delirium than those without dementia (95% CI = 3.63%-10.04%). The symptoms of delirium in a person without dementia was more often any hyperactivity (ES = 2.27, 95% CI = 1.17-4.41, $P = 0.015$), but those lacking dementia were more often hypoactive (ES = 2.22, 95% CI = 1.15-4.56, $P = 0.018$). There was limited evidence of publication bias, and there was substantial selective reporting bias in articles.
Conclusions: The review demonstrates the high prevalence of DSD and highlights the differences in motor subtypes of delirium between delirium with and without dementia, but there is concern about these results given the high risk of bias.

Keywords: Delirium, dementia, hip fracture

Increasing numbers of older adults diagnosed with dementia are hospitalized with hip fractures [1] and have an increased risk of developing delirium. Delirium occurs in over half of hip fracture patients with dementia. Furthermore, delirium may accelerate the clinical course and speed of cognitive decline. It may also be associated with worse long-term outcomes, including worsening of the severity of dementia, further deterioration of cognitive and physical function [2], and prolonged length of hospitalization and rehospitalization within 30 days; nursing home placement; death, and associated costs [3-5]. The occurrence of delirium superimposed on dementia (DSD) may result in life-threatening complications, especially if unrecognized and untreated.

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Delirium is superimposed on dementia when an acute change in mental status (characterized by a fluctuating course, inattention, and disorganized thinking or altered levels of consciousness) are added to preexisting dementia [6]. These conditions can easily be under-diagnosed when patients with dementia experience an acute change in their cognition, it may be missed, misattributed to dementia alone, or labeled as sundowning [7]. The evidence highlights that delirium in older adults with dementia is less likely to be recognized or treated by nurses and physicians than delirium without dementia [8, 9]. Even if nurses are at the bedside and in a key position to label delirium, it is difficult to differentiate between DSD, dementia alone, and delirium alone [10]. The actual diagnosis of delirium and dementia may be missed in 50%-70% of cases [11]. Disruptive dementia-related behavior may be the result of underlying delirium, and medications may only serve to mask or worsen the

problem [6]. Nurses may call a physician to request psychoactive medication for a patient with hypoactive delirium alone (32%) and are more likely call for psychoactive medication for patients with hyperactive DSD (63%) [10]. Consequently, medicating a patient for inappropriate behavior without recognizing DSD may make the problem worse.

The objectives of this systematic review were to estimate the prevalence of DSD in hospitalized older adults with dementia and hip fracture, to identify the common clinical symptoms of delirium in elderly patients with hip fracture with and without dementia, and to describe the outcomes associated with the development of DSD.

Methods

This study followed 5 steps suggested for a systematic review [12]. Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA) was used to combine the data across studies [13].

Framing of questions

Our key study questions were devised using the PICO acronym (patient, intervention or exposure, comparator, and outcome). They met the following criteria: (a) elderly patients (aged 65 years or over) with hip fracture; subgroups included those with delirium and/or those with dementia (e.g., dementia, Alzheimer disease). Elderly patients were considered as living with dementia if their average Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score was ≥3.6, IQCODE-SF (short form) score ≥3.44, Blessed Dementia Scale score ≥4, Mini–Mental State Examination (MMSE) score ≤24 (b) intervention or exposure: DSD, (c) comparator: delirium, and (d) outcome: outcomes related to psychomotor subtypes, duration and/or severity, length of hospital stay, physical and/or cognitive recovery, mortality as shown in **Table 1**. The main research question was therefore, what are the psychomotor subtypes for delirium with and without dementia in elderly patients with hip fracture?

Identifying relevant publications

Predefined criteria were applied to select the final list of articles to be included in the review. The articles had to describe a study that provided the prevalence and/or incidence of DSD in older adults with hip fracture. Prevalence is the number of cases existing at a given time in a given population, usually expressed as a percentage. Incidence is the number of instances of illness commencing during a given period in a specific population.

We considered studies for inclusion if they included delirium being detected at the time of admission and if the delirium newly occurred during the course of a stay. We included studies measuring delirium, if delirium symptoms persisted and motor subtypes of delirium were classified into 5 different types: (1) pure hyperactive delirium characterized by increased psychomotor activity with agitated behavior; (2) pure hypoactive delirium characterized by reduced psychomotor activity with lethargy; (3) mixed subtype of delirium characterized by alternating between a hyperactive and hypoactive manifestation [14]; (4) any hyperactive delirium characterized by pure hyperactive and mixed delirium, and (5) any hypoactive is characterized by pure hypoactive and mixed delirium [15].

We excluded studies if they only explored the incidence of delirium in elderly patients with hip fractures. We excluded reviews, editorials, single cases and case series, studies that were published only as abstracts, letters, or commentaries, or if they were part of duplicate populations.

Table 1. PICO (patient, intervention or exposure, comparator, and outcome): eligibility criteria for considering studies for this review

Population:	Older adults (≥65 years old) with hip fracture; subgroups include those with delirium and/or those with dementia (e.g., dementia, dementia with Lewy bodies, Alzheimer disease) Older adults were consider as living with dementia if Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score was ≥3.6, IQCODE-Short Form score was ≥3.44, Blessed Dementia Scale score was ≥4, or Mini–Mental State Examination score ≤24
Intervention or exposure:	Delirium superimposed on dementia
Comparator group:	Delirium
Outcome or endpoint:	Symptom profile, duration and/or severity, length of hospital stay, physical and/or cognitive recovery, mortality

Selection of relevant databases and search terms

We performed a search of the literature published in English from January 2000 to December 2014. An electronic database search was conducted using the following databases: PubMed, Ovid MEDLINE, CINAHL plus with full text, EBSCO host, Scopus, ScienceDirect, and Web of Science.

A variety of key words were used to conduct multiple searches. We started by searching the terms in each column of the PICO question, linked by "OR," and then combined the results of each search and retrieved only articles that contained Medical Subject Headings (MeSH) terms, Cumulative Index to Nursing and Allied Health Literature (CINAHL) headings, Title-Abstr-Key, and Topic. Two reviewers independently evaluated the study quality and extracted relevant data.

Assessing the quality of studies

We located 243 articles and 147 duplicates were removed. Studies were examined starting with an appraisal of titles and abstracts. In the next stage, printed copies of the remaining publications were read by either author (S.S. or S.Y). A consensus was made on those that met the aforementioned criteria. A further 39 studies were excluded, and 57 papers remained. An additional 40 studies were excluded after examining them carefully. The methodological quality of the 17 included articles was assessed using the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist [16]. STROBE is a reporting guideline that includes a checklist of 22 items that are considered essential for good reporting of observational studies.

Data regarding the study settings, study period, design and purpose, selection of cases, methods, outcomes, and results were extracted by the lead author. The information was independently checked against full-text articles by the second author, and consensus agreement was reached concerning the accuracy of all studies. Study quality was assessed on a scale from 0 to 22, where higher = better. For the purpose of the present review, studies with score of <60% were considered to have poor methodological quality, and therefore 2 other studies were excluded because of inconsistent methodology. The final number of studies meeting our inclusion criteria was 15. The flow of information through the systematic review is outlined in a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram (**Figure 1**) [17].

Data extraction strategy

All methodology data and results from each study were extracted using a data extraction form by 2 reviewers (S.S. and S.Y). Information about the study's location and population was recorded, the sources used to identify the participants, and the methods used to include the participants in the study. Numbers and main characteristics of patients, nature of delirium, and outcomes of delirium were noted. Decisions to include or exclude a study and the information retrieved were compared between the 2 authors. Discrepancies were discussed and agreement was achieved by consensus.

Risk of bias in individual studies

Outcome reporting bias within eligible studies was reported quantitatively using a Quality Assessment Tool for Quantitative Studies [18]. Data were extracted by the lead author for selection bias, study design, confounders, blinding, data collection methods, and withdrawals, and drop-outs. The information was independently checked against full-text articles by the second author and agreement for the accuracy of all studies was reached. Study bias was assessed on a scale from 1 to 3 [1 = strong, 2 = moderate, 3 = weak]. Higher score on the Quality Assessment Tool for Quantitative Studies (Effective Public Health Practice Project [EPHPP]) of the selected articles suggest they were more likely to represent bias than a lower score.

Summary measures and synthesis of results

We considered 3 issues: the prevalence and/or incidence, motor subtypes and outcomes of delirium in hip fractures of older patients with dementia during hospitalization. We had a plan for analysis of each of these issues. We used Comprehensive Meta-Analysis software to combine the data across studies for meta-analysis [13]. A fixed-effects model was used initially in this systematic review because we found homogeneity across the study population. A random-effects model was applied only if statistical heterogeneity existed. We assessed statistical heterogeneity using a Cochran Q test and by calculating squared and I^2 values ($I^2 > 75\%$ considered high level of heterogeneity) [19]. When heterogeneity was substantial ($I^2 > 75\%$), we investigated the sources of heterogeneity by determining the effect of important modiûers: sample details (type and quantity), study design and risk for bias, and the effect of the imputed data.

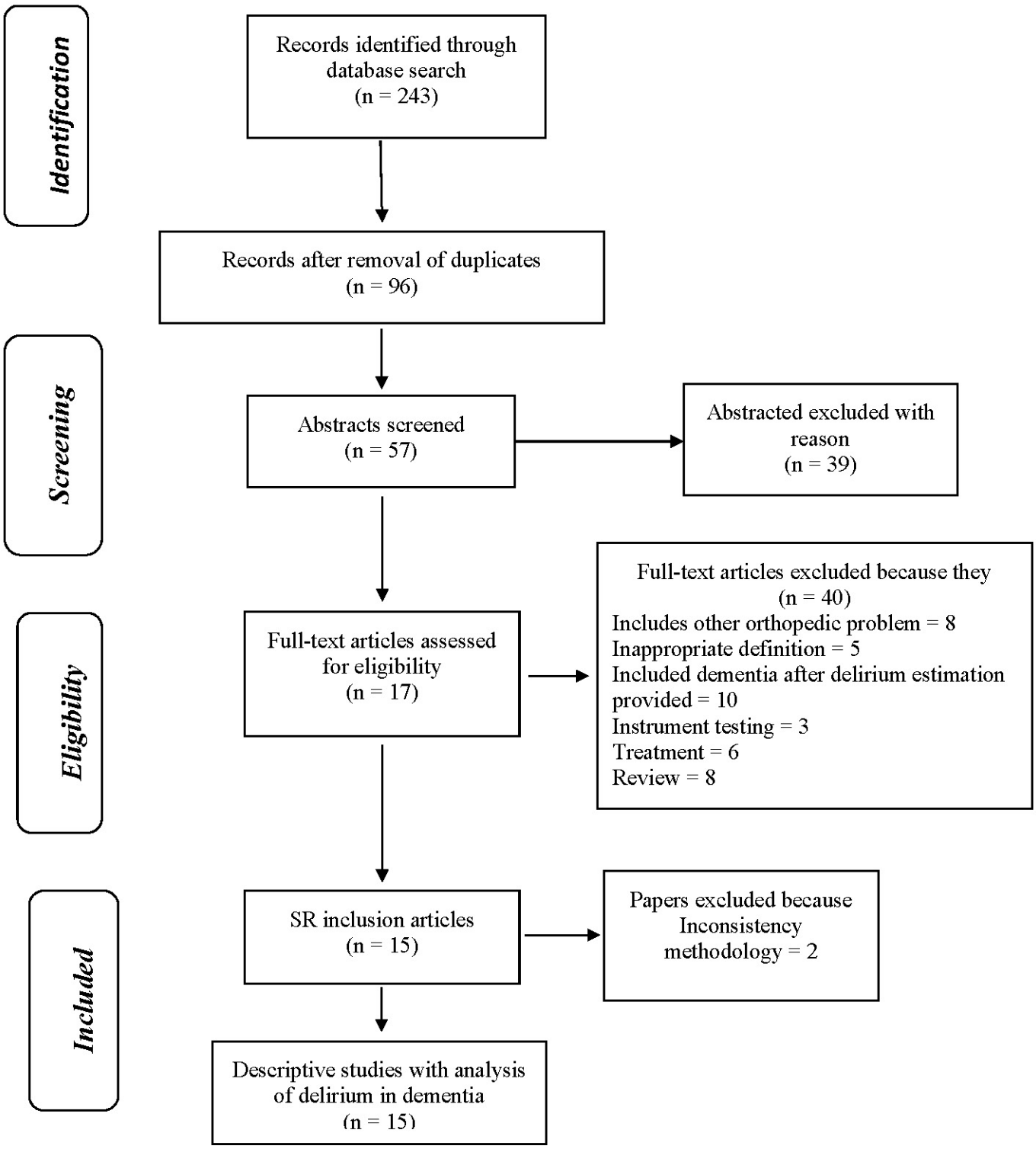

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Risk of bias across studies

Publication bias was assessed by the use of a funnel plot (Funnel Plot Generator [alpha] at *http://funnelplots.anna.ps/*), which is used primarily as a visual aid for detecting bias or systematic heterogeneity. A symmetric inverted funnel shape arises from a 'well-behaved' data set, in which publication bias is unlikely. An asymmetric funnel indicates a relationship between treatment effect and study size. This suggests the possibility of either publication bias or a systematic difference between smaller and larger studies.

Results

Study selection

The initial search identified 243 articles, of which 57 were retained for full review after examination of titles and abstracts. The search criteria and total numbers of articles identified in these steps are shown in **Figure 1**. After full text review, we excluded a further 40 studies.

Study characteristics

Of the 15 studies retained, 14 had a prospective cohort design, while only 1 had a longitudinal design. Fourteen were from Europe and the United States, while only 1 was from Asia. None of the studies used medical records alone to identify the incidence of dementia or delirium cases in cohorts and 4/15 had population sizes above 300. Almost half (9/15) had a follow-up of more than 1 month. Furthermore, 14/15 identified cases using questionnaires with some form of clinical examination, while 1/15 of the studies used medical records. In two-thirds of the studies patients were aged 65 and above, 3/15 aged 70 years or more, and 2/15 aged 75 years or more.

Together the studies included 3455 patients, with a mean age ranging from 82.7 to 85.3 years. Most participants were women (76%) (**Table 2**).

Risk of bias within studies

Based on the STROBE checklist, the quality of included studies was high with a mean of 19 ± 0.10 (ranging between 17 and 20). More than half of the studies did not clearly state how the sample size was determined. Almost all of the studies failed to describe any effort to address sources of bias. Studies did not check for statistical violations such as a normal distribution or linear relationships. The studies used measurements whose validity had been previously mentioned. More than half lacked diagnostic criteria for DSD.

The included studies were identified as having a low bias (73%) and moderate bias (27%) according to the Quality Assessment Tool for Quantitative studies [18]. Over two-thirds of the studies were only somewhat likely to be representative of the target population suggesting selection bias. They were referred from a source, and 33% of the studies (5/15) failed to describe any effort to address the sources of cofounders. About 27% of the studies (4/15) did not employ blinding of outcome assessors. Checking for statistical violation, such as a normal distribution and linear relationships, was lacking. The studies used measurements whose validity had been previously mentioned.

Results of individual studies

Delirium superimposed on dementia assessment instrument

Five tools were used to assess DSD. The most widely-used general diagnostic test was the Confusion Assessment Method (CAM) [20, 23-28, 31-33] (**Table 2**). The other instrumentation used to assess delirium with dementia included the Organic Brain Syndrome Scale or modified Organic Brain Syndrome Scale (OBS scale) [15, 22, 29, 30], Delirium Symptom Interview (DSI) [20, 27], Delirium Rating Scale (DRS-R-98) [31, 32], Delirium Observation Screening Scale (DOS) [20], and Diagnostic and Statistical Manual of Mental Disorders IV [21].

Prevalence and/or incidence of delirium superimposed on dementia

Eleven of 15 studies (73%) reported incidence of postoperative DSD [15, 22-25, 27-31, 33]. However, the article by Lee et al. reported the incidence of DSD differently; 56% in Wiley Online Library, Dec 20, 2011, but 54% in PMC, Dec 1, 2012. In the present review, incidence of DSD was based on PMC, Dec 1, 2012 [24]. The mean of incidence is 67.58%, ranging from 30% to 83.63%. Three of 15 reported preoperative DSD [22, 25, 30] with a mean prevalence of 56.65% (range from 33.33% to 85.71%). The prevalence of pre- and postoperative DSD in 4 of 15 studies was 66.75% (range from 46.53% to 81.03%) [20, 25, 26, 31] (**Table 2**).

The symptom profile of delirium superimposed on dementia

Four of 15 studies reported motor subtypes of DSD and delirium [15, 28, 32, 33]. Lundström et al. found that 22% DSD was with pure hypo active delirium, 50% with pure hyperactive delirium, 48% with any hypoactive delirium, 76% with any hyperactive delirium, and 26% with mixed profiles of delirium [15]. Marcantonio et al. showed that 61.29% DSD was with pure hypoactive delirium, and 38.71% with no hyperactive delirium [28]. Santos et al. found that 33.33% DSD was with hypoactive, 44% with hyperactive, and 22.22% with mixed profiles of delirium [33]. Slor et al. indicated that 16.67% DSD was with hypoactive, 23.33% with hyperactive, and 20% with mixed profiles of delirium [32] (**Table 2**).

Table 2. Study of delirium in elderly patients with and without dementia during hospitalization after hip fracture

Authors	n	Diagnostic instruments		Prevalence		Outcomes
		Dementia	Delirium	Delirium	DSD	
de Jonghe et al. 2012 [20]	140	IQCODE-SF	CAM, DOS, DSI	51%	81.0%	
Edelstein et al. 2004 [21]	921	DSM-IV	DSM-IV	5.1%	Postop: 30.0%	
Edlund et al. 2001 [22]	101	DSM-IV criteria for organic brain disorders	Modified OBS scale	48.5%	Preop: 85.7%	
Lee, Ha et al. 2011 [23]	232	MMSE	CAM	30.2%	Postop: 70.0%	Prolonged delirium*
Lee, Mears et al. 2011 [24]	425	MMSE Clinically diagnosed Dementia	CAM	35.1%	Postop: 54.0%	Risk factors for DSD: Age Sex BMI Comorbidities Duration of surgery Lag time from emergency room to operating room* Length of stay Length of delirium duration*
Lundström et al. 2012 [15]	199	Former dementia diagnosis	Modified OBS	64.8%	Postop: 85.0%	Length of delirium duration Length of stay Hip luxation* Depression Mortality Subtypes of delirium*
Juliebø et al. 2009 [25]	364	IQCODE-SF	CAM	32.4%	46.5% Preop: 33.3% Postop: 54.7%	
Juliebø et al. 2010 [26]	331	IQCODE	CAM	43.2%	66.9%	Mortality*
Marcantonio et al. 2000 [27]	126	Blessed Dementia Rating scale	CAM, DSI	41.0%	Postop: 66.0%	
Marcantonio et al. 2002 [28]	122	Blessed Dementia Rating scale	CAM MDAS	40.2%		Subtypes of delirium* Severity of delirium*
Olofsson et al. 2005 [29]	61	MMSE	The modified OBS	62.3%	Postop: 80.0%	
Olofsson et al. 2009 [30]	180	MMSE	OBS	65.0%	Preop: 50.9% Postop: 83.6%	One year functional ability* Depression Mortality QOL
Slor, Witlox et al. 2013 [31]	157	MMSE IQCODE	CAM DRS-R-98	36.3%	72.6%	Length of delirium duration* Severity of delirium
Slor, Adamis et al. 2013 [32]	169	MMSE IQCODE	CAM DRS-R-98	44.4%	Postop: 67.7%	Subtypes of delirium
Santos et al. 2005 [33]	34	MMSE	CAM	54.9%	Postop:81.8%	Length of delirium duration Subtypes of delirium

*Significant at the 0.05 level (2-tailed). IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE-SF = IQCODE–Short Form, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV, CAM = Confusion Assessment Method, DOS = Delirium Observation Screening Scale, DSI = Delirium Symptom Interview, OBS = Organic Brain Syndrome Scale, DSD = Delirium superimposed on dementia, DRS-R-98 = Delirium Rating Scale, Postop = postoperative, Preop = preoperative, BMI = body mass index, QOL = quality of life.

The outcomes of delirium superimposed on dementia

Four of 15 studies reported the length of delirium duration [15, 24, 31, 33], while 2 of 4 studies indicated the difference of length of hospital stay between older adults with and without dementia [15, 24]. Mortality rate comparing DSD and delirium was explored in 3 of 15 studies with follow-up at 3, 4, and 12 months [15, 26, 30]. Finally, 2 of 15 studies examined the difference of severity between patients with and without dementia [28, 31] (**Table 2**).

DSD may be associated with a longer duration of delirium, length of hospital stay, and increased mortality. However, it is not possible to draw a conclusion because of inconsistency in the results and the numbers of the studies was limited. Preexisting dementia was associated with prolonged duration of delirium [15, 23, 31]. We found that delirium lasting more than 4 weeks was associated with a poor functional outcome and increased mortality [23]. In addition to severity of delirium, the study by Marcantonio et al. indicated that patients that had severe delirium (average MDAS 12.44) were more likely to have preexisting dementia than those with mild delirium (average MDAS < 12.44) [28]. Surprisingly, the length of stay was shorter for patients with dementia (30.70 ± 29.60 days) than for patients without dementia (47.30 ± 37.10 days). However, this difference was not significant ($P = 0.07$). One study showed that mortality rates between hospitalization and 1-year follow-up did not differ significantly between patients with delirium with or without dementia [15]. Further, the variation in postoperative delirium in patients with and without dementia did not differ (10.20 ± 15.0 vs 6.30 ± 7.40 days) [15]. Also, there were no differences in mortality between patients with pure hypoactive and pure hyperactive delirium [15, 26, 32]. Finally, the length of stay was shorter for patients with hypoactive delirium (9.4 ± 4.6 days) than for patients with hyperactive (11.90 ± 6.20 days), or with mixed profiles of delirium (23.80 ± 15.90 days), but this difference was not significant ($P = 0.07$) [32] (**Table 2**).

Synthesis of results

From all studies, we concluded that the prevalence of dementia in elderly patients with hip fracture was 31.6% (95% CI = 26.4-37.3%, $P < 0.001$) and the prevalence of delirium in patients with or without dementia was 44.2% (95% CI = 38.3-50.1%, $P = 0.056$). This estimated prevalence of delirium in dementia group at 69.7% (95% CI = 60.4%-77.7%, $P < 0.001$) including postoperatively delirium was 66.7% (95% CI = 55.8%-76.1%, $P = 0.003$) and preoperatively was 66.8% (95% CI = 38.7%-86.5%, $P = 0.238$). Unsurprisingly, individuals with dementia had a 6.03 times (95% CI = 3.63-10.04, $P < 0.001$) higher likelihood of sustaining delirium than those who were cognitively intact. The variability in those estimates is attributable to the unexplained between-study heterogeneity for hip fracture in older adults with dementia ($I^2 > 75\%$).

To assess the psychomotor types in patients with and without dementia, we compared the difference of pure hypoactive delirium and any hyperactive delirium between those groups (**Table 3**). The review found that the motor subtype in the participants with dementia was often characterized by significantly greater hyperactive delirium (ES = 2.27, 95% CI = 1.72-4.41, $P = 0.015$) with nonsignificant heterogeneity (**Figures 2 and 3**). Participants without dementia were often characterized by hypoactive delirium (ES = 2.22, 95% CI = 1.15-4.27, $P = 0.018$) with nonsignificant heterogeneity as seen in **Figures 4 and 5**.

Table 3. The psychomotor types of delirium in patients with and without dementia

Motor subtypes of delirium	Delirium superimposed on dementia			Delirium only		
	Pool OR (95% CI)	Model of meta-analysis	*P*	Pool OR (95% CI)	Model of meta-analysis	*P*
Any hyperactive	2.27 (1.72-4.41)	Fix effect	0.015*	0.86 (0.48-1.53)	Fix effect	NS
Hypoactive	0.45 (0.23-0.87)	Fix effect	0.018*	2.22 (1.15-4.27)	Fix effect	0.018*

*Significant at the 0.05 level (2-tailed); OR = odds ratio

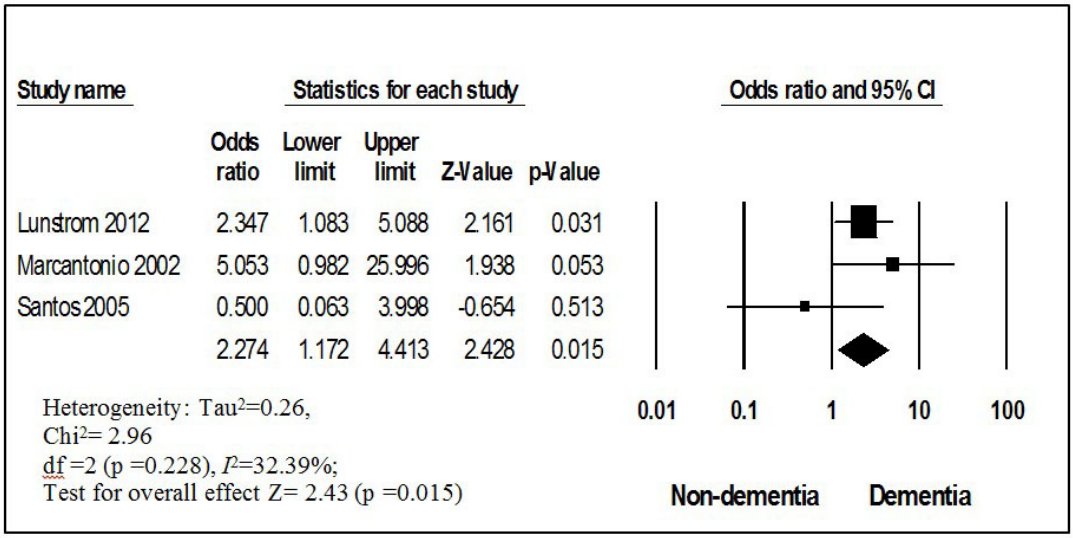

Figure 2. Any hyperactive type of delirium of hip fracture surgery patients with and without dementia.
CI = confidence interval, df = degrees of freedom.

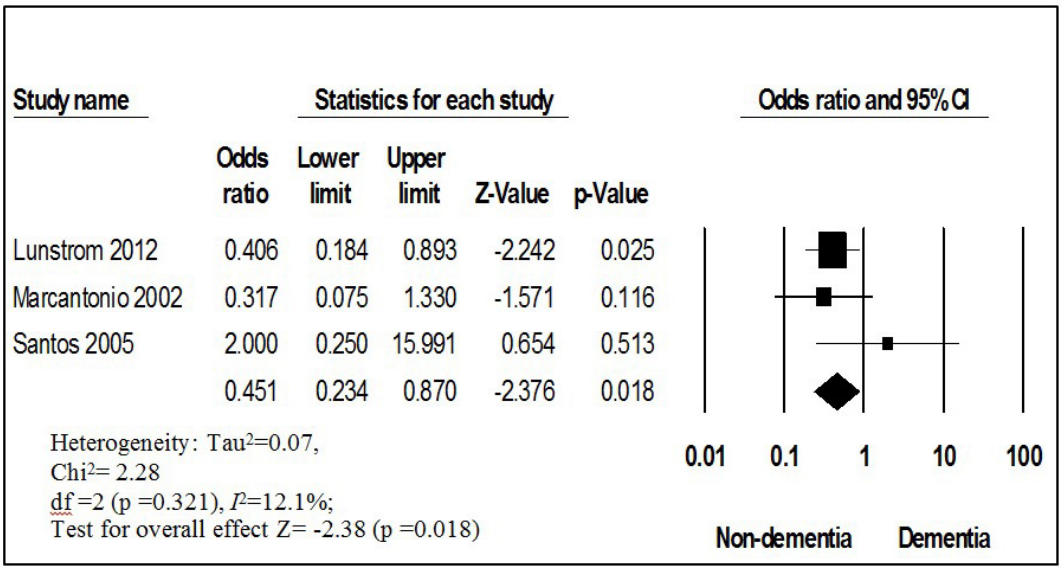

Figure 3. Hypoactive type of delirium of hip fracture surgery patients with and without dementia
CI = confidence interval, df = degrees of freedom.

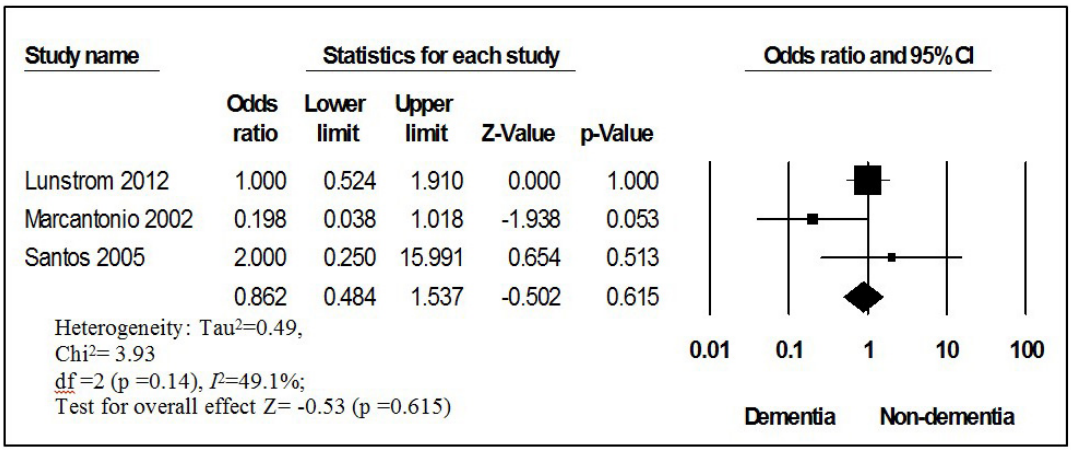

Figure 4. Any hyperactive type of delirium of hip fracture surgery patients without and with dementia
CI = confidence interval, df = degrees of freedom.

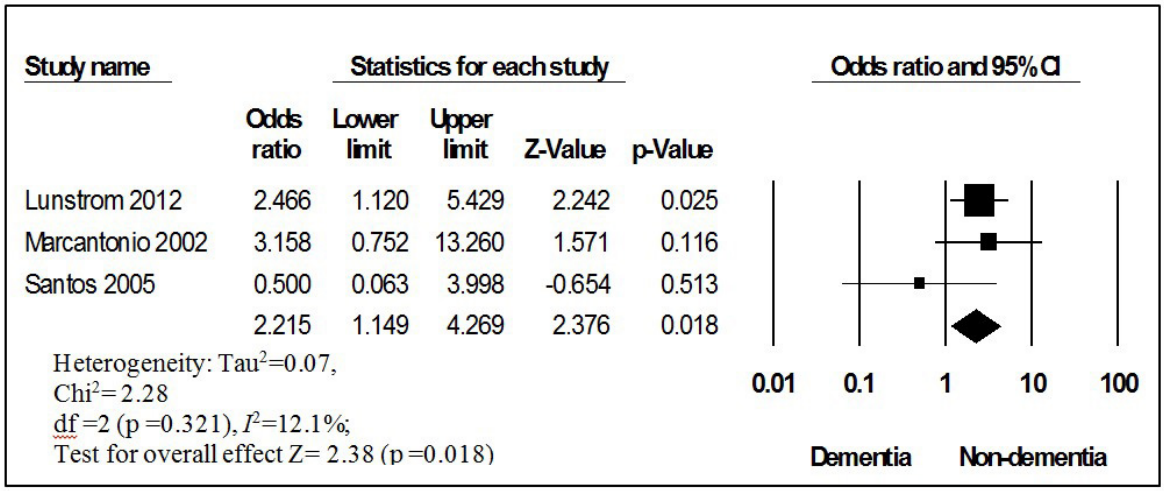

Figure 5. Hypoactive type of delirium of hip fracture surgery patients without and with dementia
CI = confidence interval, df = degrees of freedom.

Risk of bias across studies

The analysis showed evidence of heterogeneity in delirium (I^2 > 75%). The sources of heterogeneity may be the consequence of a wide range of ages, sample sizes, nondifferentiated mild forms of moderated dementia, and methods of data collection. Moreover, the variations may be explained by the difficulty in diagnosing the motor subtypes of delirium with the presence of dementia. Therefore, some episodes of delirium could have been estimated inaccurately.

Publication bias was assessed by the use of a funnel plot, which illustrates the relationship between sample size and ES. Publication bias is found. There is selective reporting of small studies with positive results. The plot takes into account the increased variability of the small unit.

Interpreting findings

Dementia is very common in elderly patients admitted to a hospital and extremely common in those with hip fracture. In older patients with a hip fracture, we found that patients with existing dementia represented 31.6%, ranging from 26.4%-37.3%. This finding may be explained by the cognitive impairment of patients with dementia and administration of medications such as cholinesterase inhibitors to people with dementia, resulting in gait disturbance [34, 35]. Two studies found that most elderly patients with hip fracture and dementia were prescribed such drugs [15, 22]. This prescription was associated with falls. Therefore, special attention should focus on fall prevention programs for every older adult living with dementia because of the high incidence of hip fracture in this group.

Delirium occurs among hip fracture patients with dementia at an incidence of 69.7%, ranging from 60.4%-77.7%. This incidence was higher than with others, such as outpatients (19.74%) [36], normal elderly people (18.8%) [37], and the community-dwelling population (13%) [38]. Patients that are surgically treated may be more at risk of complications and iatrogenic conditions than medically-ill patients without history of surgery. This may be the result of the specific nature of the surgery. Many factors were associated with delirium in hip fracture patients, such as age, being male, BMI, number of medical comorbidities, and duration of surgery longer than 2 hours. However, the lag time from emergency room to operating room was only a significant factor for delirium after hip surgery in patients with dementia (OR: 2.83, 95% CI: 1.24-6.38) [24]. Therefore, prevention strategies 24 hours before surgery may reduce the incidence and severity of delirium in patients undergoing surgery for hip fracture living with dementia.

Hip fracture patients with dementia have an increased incidence of delirium at any time; more than those without dementia. The present review indicated that the occurrence of delirium in an individual with preexisting dementia was 6.03 times greater than in those without dementia. Subjects living with dementia, have greater sensitivity to disturbances in their neurotransmitter systems. They are more likely to have a lower delirium tolerance than those without dementia [39]. The idea was supported by a kynurenine/

tryptophan ratio study. Results of a kynurenine/tryptophan ratio study indicated that the increased activity of the enzyme indoleamine 2,3-dioxygenese (IDO) was associated with lower tryptophan levels, which could lead to a central serotonin deficiency. This might contribute to the development of delirium [20]. Deficiencies in the serotonin and dopamine neurotransmitter systems in patients with frontotemporal dementia have been suggested, while the acetylcholine system appears relatively intact [40]. Thus, serotonergic therapies should have been used through a combination with specific pharmacological interventions for patients with delirium, focusing on the serotonergic system [41]. However, 140 of the 304 eligible patients (46%) were included in this report, so there may have been some uncontrolled bias.

The review shows that the motor symptom profile of delirium differs between hip fracture patients with and without dementia. There are limited data to support this observation (3 studies). There were significant differences in pure hypoactive delirium and any hyperactive delirium between hip fracture patients with and without dementia. Development of any hyperactive delirium is more common with those with dementia, and pure hypoactive delirium is more common among those without dementia. Consistent with previous studies on the associated features of hyperactive delirium with dementia in acute care units [42, 43], 53.52% of participants had hyperactive delirium, and 12.68% of participants had hypoactive delirium [43]. The hyperactive profile was significantly higher in demented patients than with those without delirium. The symptoms included agitation [36], delusion [44], aggressiveness, restlessness, anxiousness, and hallucinations [37]. By contrast, patients with delirium, but without dementia had pure hypoactive delirium, with 67.6% in an intensive care unit [45], 92.0% in an emergency room [46], and 43.5% in an medical intensive care unit setting [47].

There were 2 points (interleukin-6 level and melatonin secretion) possibly explaining the hyperactivity of delirium in patients with dementia. First, the serum interleukin (IL)-6 level of patients in the hyperactive (median 71 pg/mL) was higher than in patients with hypoactive delirium (median 16 pg/mL) [48]. Second, the serum level of IL-6 was significantly elevated among patients with advanced age and dementia [49, 50]. There are positive correlations between serum IL-6 levels and the age and severity of the dementia presented and this plays a role in the hyperactive behavior of delirium. As a result, the delirium in elder patients with dementia may result in more hyperactive profiles than the delirium in elder patients without dementia with changing serum IL-6 levels.

Equally important, hyperactive delirium correlates with lower levels of melatonin metabolites; meanwhile, hypoactive delirium was associated with higher levels of melatonin metabolites [45]. Differences in melatonin levels have been suggested as cause of differences between the subtypes [51]. Previous studies indicated that melatonin levels were diminished in dementia, especially with Alzheimer disease (AD), compared with age-matched controls [52-54], whereas if low doses of melatonin are administered to elderly patients provided a protection against delirium [55] and improved agitated behavior [56]. These may be reasons for the development of hyperactive delirium being more common in those with dementia. Therefore, the motor subtypes of delirium after hip fracture during hospitalization may differ between elderly patients with and without dementia.

The current knowledge of motor subtypes was derived from cross-sectional studies, including motor subtype occurrences at least once from the 3rd to 5th day after surgery [15], or from the 3rd day to the 5th day after surgery [33], or admission time until the 5th day after surgery [31]. Consequently, instead of a motor subtype categorization by cross-sectional study, there was a longitudinal design for the dominant motor subtype across the delirium episode. The variability of motor subtype expression was assessed in patients who had a minimum of 2 days delirium. The results indicated that the dementia group (IQCODE-N score >3.6) did not differ significantly among motoric profiles [32]. Based on this longitudinal data, the most patients had a variability of motor subtype expression, while few patients had a consistent motor profile throughout their delirium episode. By contrast, Lundström et al. indicated that the variation of days of delirium in patients with and without dementia did not differ (10.2 ± 15.0 vs 6.3 ± 7.4 days) [15]. This emphasizes the importance of the effects different data collection related to motor symptoms of delirium. Either the variability or stability of symptoms over the time period of presentation should be considered before selection of the study design.

Limitations

The motor subtypes existing in older adults

with and without dementia may be different. Any hyperactive type may be the most common subtype of delirium in elderly patients with hip fracture and dementia, whereas the hypoactive type was most prevalent in elderly patients with hip fracture, but without dementia, in the present review. However, special attention should be paid to methodological differences between each study, for example, study design, periods of recruitment and data collection, methods of selecting participants, and DSD measurement.

Methodological differences may have led to study bias and variability of the results. Moreover, most research is limited by publication bias; for example, a systematic and extensive search was performed excluding non-English language databases, and there was no blinding of the data collectors to the data sources.

A weakness of the studies reviewed is that the data collectors were not blinded to the rating of delirium evaluations on the day of surgery. This research needs to be expanded to improve early clinical identification of DSD to allow early more specific management.

Recommendations

This systematic review highlights the differences in psychomotor subtypes of delirium in patients with and without dementia after hip fracture in a meta-analysis. Delirium may be considered a natural part of dementia (hyperactive) and the underlying causes of delirium may not be sought and treated. The common prescribing of psychoactive medication for patients with hyperactive DSD may worsen their condition, or at least delay the recognition of delirium. Early discovery of signs and symptoms of delirium in patients with prior dementia may be helpful in better management. Additionally, the challenges of determining motor subtype differences will lead to determination of the validity of existing tools and perhaps newly-developed tools for understanding these common conditions. Tests of the discriminatory value of the level of psychomotor features is a promising area for future study. Moreover, there is evidence suggesting that the subtypes of delirium could be related to different causes and may have different treatment requirements. Evaluating the description of the differences in treatment responses for hypoactive or hyperactive delirium in demented elderly patients with hip fracture may be of clinical benefit.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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