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## Review article

# Risk factors of delirium in elderly patients with hip fracture

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**Background:** Delirium is a leading cause of death and disability in the elderly with hip fracture. Identifying reliable risk factors for delirium is critical to support optimal outcomes for prevention and reducing delirium.

**Objective:** To quantify the reported factors associated to delirium for patients with hip fracture.

**Methods:** Electronic databases were searched (including Medline, Pub Med, CINAHL, EMBASE, Evidence Based Medicine Reviews, Cochrane Review, Web of Science, and PsycINFO) to identify all studies, published in English language that evaluated the risk factors of delirium hospitalized people with hip fracture. Two reviewers independently assessed methodology quality and extracted relevant data. The data from the included studies were summarized, and pooled estimates were calculated for 12 risk factors.

**Results:** Thirty-seven studies were included in the review and 25 in the meta-analysis. The incidence of delirium was 32.4% (95% confidence interval [CI] = 25.9%–39.5%). Six predisposing and four precipitating factors predicted delirium among older patients with hip fracture confirmed. The predisposing factors included advanced age (ES = 1.06, 95% CI = 1.03–1.09), male sex (ES = 1.34, 95% CI = 1.08–1.68), impairment of cognition (ES = 2.91, 95% CI = 1.91–4.42), and function (ES = 1.75, 95% CI = 1.39–2.2), comorbidity (ES = 1.59, 95% CI = 1.30–1.96), and health problems (ES = 2.64, 95% CI = 2.04–3.42). Precipitating factors were hypo- or hypernatremia (ES = 1.73, 95% CI = 1.14–2.64), depression (ES = 4.07, 95% CI = 1.95–8.49), more than three prescribed drugs (ES = 1.28, 95% CI = 1.10–1.49), and drugs including opioids (ES = 2.13, 95% CI = 1.42–3.18) and anticholinergic agents (ES = 2.10, 95% CI = 1.60–2.75).

**Conclusion:** This meta-analysis result provides evidence that these risk factors have a significant impact on delirium in elders with hip fracture during hospitalization. Developing formal screening, and effective preventive and management strategies for delirium is important.

**Keywords:** Delirium, elderly, hip fracture, risk factors, systematic review

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Delirium is a severe neuropsychiatric syndrome that is common and serious in older patients with hip fracture. A systematic review that identified 12 studies of interventional and analysis of pathogenic factors of postoperative delirium for hip fracture found that the occurrence of delirium varied between 16% and 62% [1]. Delirium is defined conceptually as “a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hour to days) and fluctuates over time” [2]. Episodes of delirium are associated with longer hospital stays and greater morbidity and mortality [3], cause considerable distress to patients and families, and is expensive [4].

A useful predictive model for the development of delirium in elderly hospitalized patients [5] suggests that delirium is precipitated when the sum of predisposing and precipitating factors crosses a certain threshold. In such a model, the greater the predisposing factors, the fewer precipitating factors are required to initiate delirium [6]. This would explain why elderly hip fracture patients develop delirium in the face of stressors that are much less severe than those that can cause delirium in healthy adults. Understanding the predisposing and precipitating factors in cases of delirium provides the critical first step to identifying patients at high risk of developing the condition and for developing effective preventive and management strategies.

Systematic reviews have assessed studies investigating risk factors in medical and surgical patients. The reviews are limited by variation in quality

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and heterogeneity of the constituent studies [7], 84.4% of the evidence was obtained from observational studies or expert opinions [8]. Thus, convincing data to prepare guidelines for prevention or attenuation of delirium associated with hip fracture is insufficient. Our objectives are to complete a systematic review and meta-analysis of the incidence of delirium in elderly patients with hip fracture, and risk factors for delirium during hospitalization.

## Materials and methods

### *Data sources and search strategy for identification of studies*

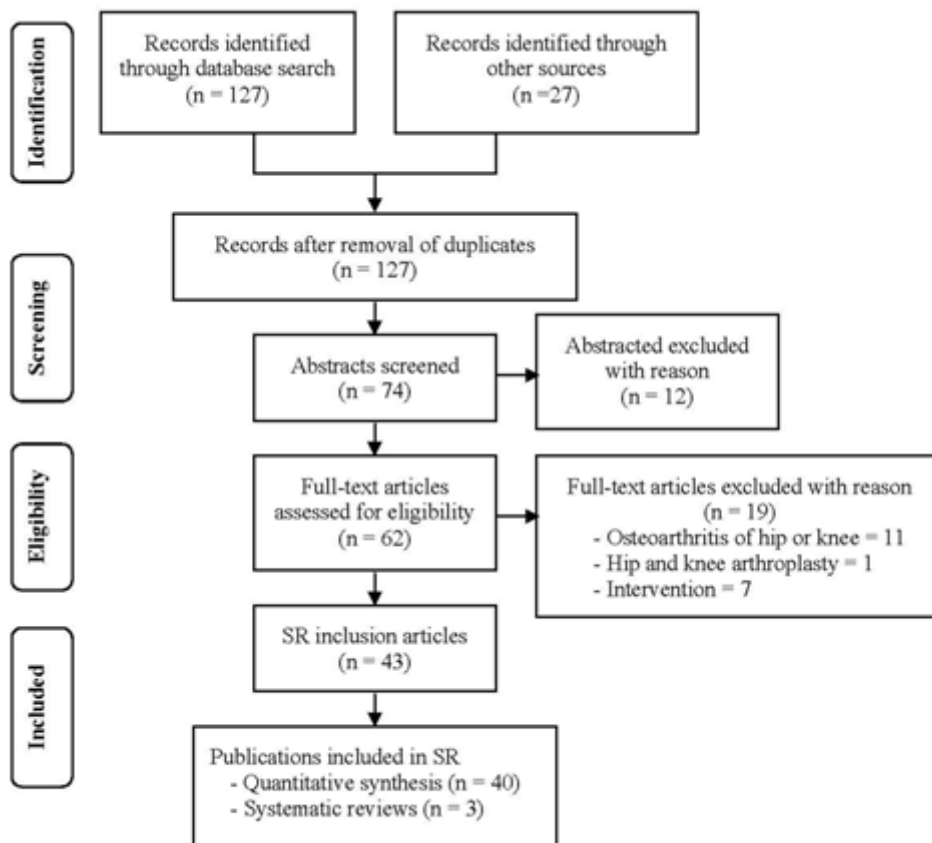
We searched databases for primary research published in English, from 1990 to 2012. An electronic database search was carried out using the following databases: Medline, Pub Med, CINAHL, EMBASE, Evidence Based Medicine Reviews, Cochrane Review, Web of Science, and PsycINFO. We also searched the studies from references of full-text articles. Duplicates were removed. We excluded research published before 1990 because of the different names used to define and describe delirium. Searches were undertaken using keywords including

‘delirium’, ‘acute confusion’, ‘cognitive dysfunction’, ‘decline in cognitive function’, ‘hip fracture’, ‘femoral neck fracture’, ‘intertrochanteric fracture’, and ‘subtrochanteric fracture’ and an English language restriction was applied. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [9] were followed and fulfilled in this review.

### *Criteria for considering studies*

PICO specifies patients selection, intervention, comparison, and outcomes [10]. This definition then determined criteria for including articles in the analysis. Two reviewers assessed the studies independently using the following inclusion criteria:

1. The majority of study participants were patients (aged 60 years or over) who sustained a hip fracture during hospitalization.
2. The factors included risk factors of delirium, pathogenic factors of delirium predictors of delirium, precipitating factors, and predisposing factors of delirium could have started preoperatively and postoperatively. Incidence of delirium also was included.



**Figure 1.** PRISMA flow diagram

3. Delirium outcome pertaining to patients with history of risk factors, pathogenic factors or predictors was compared with those with no history of these factors.

4. Outcomes reflecting incidence, duration and severity of delirium, acute confusion, cognitive dysfunction, and decline in cognitive dysfunction were reported.

**Data collection and quality assessment**

All of the steps were conducted independently by 2 reviewers (SS and DP). The full texts of fifty articles were read and examined independently by two authors and there was consensus that twelve articles did not meet the inclusion criteria and they were eliminated. The methodological quality of the included articles was assessed using the Strengthening the Reporting of Observation Studies in Epidemiology [STROBE] criteria [11]. The lead author extracted data for study settings, study period, design and purpose, selection of cases, methods, outcomes, and results. The information was independently checked against the full-text articles by the second author and an agreement was reached for the accuracy of all studies. Studies quality was assessed on a scale from 0 to 10. For this review, studies score of <60% was considered to have poor methodological quality and, therefore, were excluded. Thus, the final number of studies meeting our inclusion criteria was 25 [11].

**Data synthesis, analysis, and assessment of heterogeneity**

We considered two issues: incidence of delirium and risk factors for delirium during hospitalization by

pooling data. We had a specific analysis plan for each of these issues. An odds ratio was estimated for most of the studies that compared the delirium group with the nondelirium group. We estimated the DerSimonian and Laird fixed and random effects pooled log odd ratio of all studies, conducted a  $\chi^2$  test for heterogeneity, and calculated the *p* statistic and its 95% uncertainty interval. This was also done for analysis of incidence rate ratios.

We used Comprehensive Meta-analysis software (version 2, Biostat, Englewood, NJ, USA) [12] to combine data across studies. A fixed-effects model was initially used in this systematic review because we found the homogeneity across the studies population. A random-effects model was applied only if statistical heterogeneity existed. We assessed statistical heterogeneity using the Cochran Q test and by calculating  $\gamma$ -squared and *p* values (*p* > 75% were considered to indicate a high level of heterogeneity) [13]. When heterogeneity was substantial (*p* > 75%), we investigated sources of heterogeneity by determining the effect of important modifiers: sample details (type and quantity), study design and risk for bias, and effect of imputed data.

**Results**

Twenty-five studies met the inclusion criteria for review. The studies had a total of 4484 patients, with the mean age of the study participants ranging from 74.9 to 84 years. Most participants were female (74.36%). Almost one-third of the studies (n = 8) excluded participants with cognitive impairment or delirium. The hip fracture studies that met the inclusion criteria are presented in **Table 1**.

**Table 1.** Incidence and risk factors of delirium in hip fracture surgery

Study	Incidence	Factors
Marcantonio et al. 2000 [14], N = 126	41.3%	Age*, gender*, cognitive and functional* impairment, comorbidity
Edlund et al. 2001 [15], N = 101	49% 30% preop 19% Postop	Age, gender*, dementia*, Parkinson*, previous delirium*constipation*creatinine*, depression, anticholinergic agents*, Neuroleptic*
Galanakis et al. 2001 [16], N = 105	24%	Age*, gender, cognitive*, vision*, hearing* impairment, comorbidity, more than 3 prescribed drugs, sodium*, potassium, depression*, low education*,psychotropic drug use, number of medications
Marcantonio et al. 2002 [17], N = 122	40%	Age, gender, cognitive*, functional impairment*, comorbidity*
Zakriya et al. 2002 [18], N = 168	28%	Age, gender, health problem, sodium, BUN, creatinine, albumin

**Table 1.** Incidence and risk factors of delirium in hip fracture surgery (Continue)

Study	Incidence	Factors
Morrison et al. 2003 [19], N = 541	16%	Age, gender, cognitive impairment, heart failure*
	12% preop	comorbidity, opioids*, meperidine*, poor controlled
	14% postop	pain*
Kagansky et al. 2004 [20], N = 102	12%	Age, preexisting cognitive* and function impairment, comorbidity, health problem*, more than 4 prescribed drugs*, hemoglobin, WBC
Zakriya et al. 2004 [21], N = 92	28%	
	21% preop	
	28% postop	
Olofsson et al. 2005 [22], N = 61	62%	Age, male, vision, hearing impairment, dementia*, antidepressant (anticholinergic agent), depression*, poly medicine
Santos et al. 2005 [23], N = 34	56%	Age, gender, dementia*, hemoglobin, health problem, opioids*, midazolam*, length of stay
Sharma et al. 2005 [24], N = 47	36%	health problem*
Furlaneto & Garcez-Leme 2006 [25], N = 103	13%	Age, gender, cognitive* and functional impairment, health problem*, comorbidity, malnutrition, hemoglobin, creatinine, education level
	17% preop	
	13% postop	
Goldenberg et al. 2006 [26], N = 77	48% postop	Age*, pre-existing cognitive* impairment, multiple medications*, hematocrit*, albumin*
de Jonghe et al. 2007 [27], N = 101	16%	Age, gender*, cognitive* and vision* impairment, health problem*, BUN/Cr ratio, anticholinergic agent (haloperidol)
van Munster et al. 2008 [28], N = 98	50%	Age, gender, cognitive*, function* impairment, polymedicine, IL-6*, IL-8*, IL-12*, length of stay
van Munster et al. 2009 [3], N = 120	52%	Age, gender, cognitive*, physical impairment, polymedicine, IL-6, IL-8, length of stay
Juliebo et al. 2009 [29], N = 364	58%	Age, gender*, cognitive*, function* impairment, comorbidity, health problem, BMI*, hemoglobin*
	21% preop	sodium, potassium, BUN/Cr ratio, polypharmacy*, Arrhythmia, medication use (psychotropic, selective serotonin reuptake inhibitor, zopiclone, aspirin, beta-blocker, diuretic, statin) fentanyl*
	36.4% postop	
Juliebo et al. 2010 [30], N = 331	43.2%	
Kat et al. 2011 [31], N = 603	12.3% postop	
Bisschop et al. 2011 [32], N = 143	34%	Age*, gender, preexisting cognitive* and functional* impairment, comorbidity*, laboratory abnormalities*, glucose
Lee et al. 2011 [33], N = 232	30.2%	Age, gender, comorbidity, health problem*, BMI
Vochteloo et al. 2011 [34], N = 378	27%	Age*, gender*, dementia, health problem*, psychotropic drug use*, length of stay*
Sieber et al. 2011 [35], N = 236		Age, gender*, dementia*, comorbidity*, opioids
Witlox et al. 2011 [36], N = 76	40%	Age*, cognitive* and functional impairment
Nie et al. 2012 [37], N = 123	13%	Age, gender, cognitive impairment, education

\*Statistically significant  $p < 0.05$

### *Quality of the studies*

It was considered that 11% (4/37) were of high level of quality, 57% (21/37) were moderate level, and 32% (12/37) were low level. For internal validity, over half of the studies had unclear information regarding how the sample size was determined or if outcomes were objective. Almost all studies failed to describe any efforts to address sources of bias. Some studies used invalidated methods to describe delirium or terms such as ‘confusional state’ without a clear definition of term. Furthermore, studies did not check for statistical violation, such as a normal distribution or linear relationships. Sixty-seven percent of the studies used measurements whose validity had been previously reported. More than 40% did not provide diagnostic criteria of delirium. In relation to the analysis, almost all of the studies used logistic linear and/or linear regressions. Only a few studies reported how they handled missing data. Most studies failed to exclude confounders that might have a significant influence on predicting incidence of delirium. An issue for the meta-analysis showed the evidence of heterogeneity in incidence of delirium and cognitive impairment ( $p > 75\%$ ). The sources of heterogeneity might be the result of a wide range of sample size, exclusion or inclusion of elderly with cognitive impairments, and methods of data collection. For example, the hypoactive form of delirium in patients with cognitive impairment was often overlooked in studies. Moreover, the variation may be explained by the difficulty in diagnosing delirium in the presence of cognitive impairment whereas when cognitive ability is intact, it is easier to recognize symptoms of delirium. Therefore, some episodes of delirium and the effect of risk factors might have been estimated inaccurately.

### *Delirium assessment*

The most widely-used general diagnostic test was the Confusion Assessment Method (CAM) [38], which is a standard screening protocol consisting of an orientation–memory–concentration test and a delirium algorithm. However, the current ‘gold standard’ for assessing delirium are the diagnostic criteria set by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [39]. Other less commonly used diagnostic tools that feature different use of DSM criteria include the Organic Brain Syndrome Scale (OBS scale) [40] and the Delirium Symptom Interview (DSI) [41]. Severity scales designed for use by experts with significant

professional training were the delirium Rating Scale (DRS-R-98) [42] and Memorial Delirium Assessment Scale (MDAS) [43]. Screening scale developed by nurses are the Delirium Observation Screening Scale (DOS) [44] and The NEECHAM Confusion Scale (NEECHAM) [45]. Bearing this in mind, all of the studies reviewed used one or more of these tools to define delirium and identify patients for studying.

### *Incidence of delirium in elderly with hip fracture during hospitalization*

In elderly patients with a hip fracture, the incidence of delirium was 32.4% (95% CI = 25.9%–39.5%) with significant heterogeneity ( $p < 0.001$ ). The incidence of delirium in the sample including cognitive impairment was 35.2% (95% CI = 27.7%–43.5%,  $p < 0.001$ ) and the incidence of delirium in the sample excluding cognitive impairment was 24.7% (95% CI = 15.8%–36.4%,  $p < 0.001$ ). The reported incidence of preoperative delirium was 19.2% (95% CI = 13.7%–26.3%,  $p < 0.001$ ) and the postoperative delirium was 22.3% (95% CI = 13.9%–33.7%,  $p < 0.001$ ).

### *Risk factors*

The etiology of delirium is usually multifactorial [48]. It can, however, be caused by a single factor. The review of 25 studies identified 12 risk factors of delirium, which are classified into two groups: predisposing and precipitating factors. The predisposing factors included age, gender, the impairment of cognition, function, and sensory impairment (vision and hearing), comorbidity, health problems, more than three prescribed drugs, and malnutrition. Precipitating factors were laboratory abnormalities, anemia and hypo- or hypernatremia, depression, and drugs (opioids and anticholinergic). Ten of twelve different risk factors were proven to have significant pooling of results. However, deficient nutrition as defined by albumin level and body mass index and sensory impairment were not statistically significant when data was pooled.

The results indicated that each year of age increases the risk for delirium, with effect size (ES) 1.06 (95% CI = 1.03–1.09,  $p < 0.001$ ). Men were at a higher risk than women. Men with hip fracture were 1.34 times more likely to face delirium than women with hip fracture (95% CI = 1.08–1.68,  $p = 0.01$ ). Patients with dementia and cognitive impairment had 2.90 times more delirium than those who were

cognitively intact (95% CI = 1.91–4.42,  $p < 0.001$ ). The review indicated that functional impairments such as ambulatory and walking impairment, lower Activity Daily Living (ADL), and Instrument Activities of Daily Living (IADL), significantly increased risk factors for delirium (ES = 1.75, 95% CI = 1.39–2.20,  $p < 0.001$ ). Patients who had a greater number of comorbidities were more likely to have delirium (ES = 1.59, 95% CI = 1.30–1.96,  $p < 0.001$ ). Health problems were also identified as being significantly predictive of delirium, with ES = 2.64 (95% CI = 2.04–3.42,  $p < 0.001$ ). More than three prescribed drugs also significantly increased risk factors for delirium (ES = 1.28, 95% CI = 1.10–1.49,  $p < 0.001$ ).

Among the three precipitating factors, nine laboratory blood values were tested as possible risk factors for delirium. Hypo- or hypernatremia (ES = 1.73, 95% CI 1.14–2.64,  $p = 0.01$ ) was the only one reported as significant risk factors. Drugs including anticholinergic agents, levodopa, hypnotics, and sedatives were noted to be a precipitating risk factor in developing delirium. The probability of developing delirium among patients who received anticholinergic drugs was more than two times that of nonusers (ES = 2.01, 95% CI = 1.60–2.75,  $p < 0.001$ ). The administration of opioids (morphine and meperidine) also influenced the presence of postoperative delirium (ES = 2.13, 95% CI = 1.42–3.18,  $p < 0.001$ ). When meperidine and morphine were compared, the findings indicated that patients receiving meperidine had a higher risk of delirium than those receiving morphine (RR = 1.93, 95% CI = 1.27–2.94,  $p < 0.001$ ). We also found that the elderly who were depressed at the time of hip fracture are at 4 times higher risk for delirium than those who were not depressed with ES = 4.07 (95% CI = 1.95–8.49,  $p < 0.001$ ).

## Discussion

Delirium is a common and serious condition among the elderly, particularly in hospitalized patients with hip fracture. We found that the incidence of delirium after hip fracture ranged from 25.9% to 39.5%. The variance can be explained by methodological differences and measurement tools used in previous studies. The variable exclusion criterion used reflects the large differences in the incidence of delirium. We found studies that excluded patients with cognitive dysfunction and had lower incidences of delirium than other studies that did not exclude them (25% vs. 35%).

The results supported the hypothesis that delirium is difficult to diagnose among patients with cognitive dysfunction, but when excluding these patients, the incidence of delirium may only represent a minimum risk subjects given that high-risk patients have been excluded.

Our findings demonstrate convincing evidence of the predictive value of both predisposing and precipitating factors for delirium. The results of the studies included showing clinically important effects of similar magnitude. The risk factors for delirium in the elderly with hip fracture were advanced age, male sex cognitive impairment, functional impairment, and history of comorbidity such as cardiovascular disease, congestive heart failure, and stroke. Depression, health status during admission, more than three prescribed drugs and using anticholinergic agents and opioids also were contributing factors. This analysis supports the hypothesis that delirium after surgery has procedure-related and patient-related risk factors [46] that differ from those identified in geriatric studies [47]. In elderly patients with hip fracture who are highly vulnerable to delirium, such as those with dementia and multiple coexisting conditions, it may develop as a result of relatively benign insults, such as one dose of a sleeping medication or premedication. Conversely, in patients who are not vulnerable to delirium, it develops only after exposure to multiple noxious insults, such as major surgery and psychoactive medications. Addressing just one contributing factor is unlikely to resolve delirium in an older patients with hip fracture; all contributors should all be addressed when possible [6].

These findings have practical implications for management of elderly patients with hip fracture during hospitalization. However, one of the 10 risk factors influencing delirium—cognitive impairment—may be affected by heterogeneity. Health care providers are encouraged to use comprehensive assessment of the patient based on screening and identifying early signs of delirium. For example, careful reviews of prescribed drugs, laboratory testing, and identification of frail patients should be completed. This should make it possible to prevent delirium and treat patients [16, 27]. Specific screening should be incorporated in admission evaluation. The patients at high risk should also be monitored closely and consistently for early signs of delirium [48].

Based on these findings, minimizing time spent in bed should be promoted. Mobilization should be implemented as soon as possible. Attempts should be

made to provide a comfortable and familiar environment such as a quiet, well-lit room with easily-visible clocks and a calendar. The patients' awareness and interaction with the environment should be optimized through use of visual aids, hearing aids, and frequent reorientation. Prescribed drugs should be reviewed with avoidance where possible of anticholinergic agents. Meperidine should be avoided or used sparingly. The anticholinergic drugs include antipsychotics and sedative-hypnotics. They should be reduced or replaced with medications that have no central effects. Particularly, reduction of anti-Parkinson drugs should be conducted in close collaboration with the Parkinson's team. The adoption of a standardized protocol for pain assessment and management, appropriate fluid replacement and nutrition are needed to prevent electrolyte imbalances. Consideration should be made for geriatric and psychiatric consultation to evaluate and treat of cognitive impairment, depression and comorbidity when indicated.

Our study has limitations and strengths. First, the heterogeneity in risk factors such as cognitive impairment could be explained by different time of delirium assessment, which included or excluded cognitive impairment during recruitment. Second, it is important to keep in mind that most participants were selected from one unit or one hospital, in a teaching institution. It is therefore possible that these patients had more complicated cases. Thirdly, results were not adjusted for confounders known to influence delirium development. As a result, our studies may overestimate the incidence of delirium in elderly patients with hip fracture. Despite these limitations, our study provides useful information to understand incidence and associated risk factors in elderly hip fracture patients with and without delirium. We included the most commonly investigated risk factors influencing care. Finally, this information may help facilitate the most effective strategy for reducing incidence by orientation protocols, better fluid balance, mobility enhancement, better selection and dosing of pain medications.

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