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Review of Postoperative Delirium in Geriatric Patients After Hip Fracture Treatment

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Abstract

Introduction: Postoperative delirium (POD) is a serious complication occurring in 4–53.3% of geriatric patients undergoing surgeries for hip fracture. Incidence of hip fractures is projected to grow 11.9% from 258,000 in 2010 to 289,000 in 2030 based on 1990 to 2010 data. As prevalence of hip fractures is projected to increase, POD is also anticipated to increase. **Signficance:** Postoperative delirium remains the most common complication of emergency hip fracture surgery leading to high morbidity and mortality rates despite significant research conducted regarding this topic. This study reviews literature from 1990 to 2021 regarding POD in geriatric hip fracture management. **Results:** Potentially modifiable and non-modifiable risk factors for developing POD include, but are not limited to, male gender, older age, multiple comorbidities, specific comorbidities (dementia, cognitive impairment, diabetes, vision impairment, and abnormal blood pressure), low BMI, preoperative malnutrition, low albumin, low hematocrit, blunted preoperative cytokines, emergency surgery, time to admission and surgery, preoperative medical treatment, polypharmacy, delirium-inducing medications, fever, anesthesia time, and sedation depth and type. Although the pathophysiology remains unclear, the leading theories suggest neurotransmitter imbalance, inflammation, and electrolyte or metabolic derangements as the underlying cause of POD. POD is associated with increased length of hospital stay, cost, morbidity, and mortality. Prevention and early recognition are key factors in managing POD. Methods to reduce POD include utilizing interdisciplinary teams, educational programs for healthcare professionals, reducing narcotic use, avoiding delirium-inducing medications, and multimodal pain control. **Conclusion:** While POD is a known complication after hip fracture surgery, further exploration in prevention is needed. Early identification of risk factors is imperative to prevent POD in geriatric patients. Early prevention will enhance delivery of health care both pre- and post-operatively leading to the best possible surgical outcome and better quality of life after hip fracture treatment.

Keywords

postoperative delirium, hip fracture, geriatric, geriatric medicine, geriatric trauma

Introduction

Per clinical definition, delirium is a rapid—though often waxing and waning—decline in neurocognitive function, presenting as altered consciousness or changes in attention that cannot be explained by a pre-existing neurocognitive disorder.[1] Three types of delirium exist: hyperactive delirium, hypoactive delirium, and mixed delirium.[1,2] Restlessness, excitability, and agitation are descriptive

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of a hyperactive delirious state, whereas lethargy, inactivity, and disinterest are descriptive of a hypoactive delirious state.[3] Mixed delirium displays a combination of hyperactive and hypoactive delirium features.[4]

While POD can be a complication of both elective and traumatic hip surgeries, it is far more prevalent in traumatic hip fracture patients.[5] This indicates a therapeutic need for deeper understanding of prevention, detection, and management of POD in the scope of non-elective surgeries.[5] Prevention and early recognition are key factors in managing POD.[6,7] Exact incidence of POD in hip fracture patients varies by study and population, ranging from 4 to 53.3%.[5,8-18] A recent research article analyzed patients with hip fracture aged 60 years and older identified in the 2016 and 2017 National Surgical Quality Improvement Program Procedure Targeted Databases.[19] Postoperative delirium was found to be a potentially preventable postoperative adverse outcome and was seen in 18.8% of 18,754 patients with hip fractures.[19] Interestingly, although women have a higher hip fracture incidence,[20] men are more likely to be diagnosed with POD following hip fracture treatment.[9,12] Other risk factors for POD include indoor injury,[18] older age,[21-23] prior dementia diagnosis or cognitive impairment,[18,21] diabetes,[23] multiple comorbidities,[22] American Society of Anesthesiologists classification >2 level,[13,23] vision impairment,[22] low BMI,[18] preoperative malnutrition,[24] low albumin,[21] low hematocrit,[21] and blunted preoperative cytokine levels.[25] Further studies identified risk factors for POD in the perioperative period including patients undergoing emergency surgery,[22] time to admission,[22] preoperative waiting time,[21] preoperative medical treatment,[22] the use of multiple prescription medications,[21] treatment with antibiotics,[22] anesthesia time,[22] use of midazolam,[2] abnormally high or abnormally low blood pressure,[26] fever,[18] and depth and type of sedation.[9,27]

Frailty is recognized as a factor in surgical and geriatric outcomes[28-30] which is defined as a state of diminished physiologic capacity to respond to external stressors such as trauma and infections in vulnerable individuals.[31] It is important to note the association between physical frailty and cognitive function reported by cross-sectional studies.[32,33] Physical frailty may lead to cognitive decline and vice versa.[34-37] Thus, one might expect patients with either physical frailty or cognitive decline to be at risk for delirium. One study examined the relationship between physical frailty and cognitive decline in a single-center retrospective study of older patient who had undergone cardiac surgery.[38] They found that the coexistence of physical frailty and mild cognitive impairment poses the greatest risk of delirium whereas either alone has no significant risk for the incidence of delirium.[38] In addition, another study found the modified frailty index is an independent predictor of mortality for patients undergoing hemiarthroplasty and total hip arthroplasty.[39]

Not only is POD the most common complication of surgical hip fracture treatment but it also significantly contributes to extended length of hospital stay, institutional discharge, and rate of 30-day readmission.[16] POD is a risk factor for multiple short-term and long-term complications, influencing physical recovery,[11,15] cognitive recovery,[15,40] and higher episode-of-care cost.[17] Studies support that incidence of POD may be a large contributor to the high 1-year mortality rate of traumatic hip fractures, reporting that 6-month[41,42] to 1-year[43] mortality is significantly increased in hip fracture patients diagnosed with POD compared to patients not diagnosed with POD.[9,41-45]

Hip fracture repair is commonly associated with postoperative complications including, but not limited to, postoperative delirium (POD), urinary tract infection/retention, dislocation of prosthesis, stroke, deep vein thrombosis, cardiac events, pneumonia, and wound infection.[10] A third of patients experience at least one postoperative complication, with 7.2% experiencing more than one.[10] Of the possible postoperative complications, the most common in traumatic hip fracture patients is POD.[10]

With age comes progressive deterioration of bone mass,[46,47] consequently increasing risk for fracture. Though not the most common fracture site with age, hip fractures have become the most feared fracture site with age—riddled with serious preoperative, short-term postoperative, and long-term postoperative complications,[9,15,48,49] including a 12.7% 1-year mortality rate, according to a prospective cohort study.[50] From 2014 to 2017, the incidence of hip fractures plateaued at approximately 1.77 per 1000-person years and 1.75 per 1000-person years, respectively,[51] but is projected to grow 11.9% from 258,000 in 2010 to 289,000 in 2030 based on 1990 to 2010 data.[52] There is a higher incidence of hip fractures in women (957.3 per 100,000 person years) than men (414.4 per 100,000 person years),[20] likely a result of increased prevalence of osteoporosis in post-menopausal women,[47] though incidence rates rise exponentially in both genders with age.[46] The most common mechanism of hip fracture in the geriatric patients (>65) is an accidental lateral fall from standing,[53] at average ages of 83 years in women and 84 years in men.[54] Limited data are available on hip fracture trends based on ethnic or racial subgroups, and one study describes global hip fracture epidemiology separated by regions and reports increased hip fracture rates in industrialized countries compared to developing countries.[55]

Pathophysiology

There is extensive research that highlights the connection between postoperative hip fractures and delirium in geriatric patients. The exact pathogenesis and physiology of

how this process occurs remains unclear, the leading theories suggest neurotransmitter imbalance, inflammation, and electrolyte or metabolic derangements as the underlying cause of POD[56]

Cortical regions of the brain have been implicated as the site of origin in the pathways leading up to a delirious state.[57] Dysfunctions in the prefrontal cortex, subcortical structures, thalamus, basal ganglia, frontal temporoparietal cortex, fusiform cortex, and lingual gyri have all been found to have some part in causing the state of delirium.[57] Most importantly, with the relevance to hip fractures, delirium has been noted to be influenced and conceived in a state of an inflammatory storm, chronic stress, and/or neurotransmitter chemical alterations.[58] In addition, recent research has linked metabolic alterations (fatty acid and amino acid serum concentration changes) in association with postoperative delirium following hemi-arthroplasty in older patients.[59]

Hip fracture surgery is a known risk factor in itself for delirium.[60] One potential theory to why surgery itself causes delirium[60] is that pain and inflammation, compounded with stress and repair causes inflammatory chemicals to be systemically released throughout the body[57] during the surgical procedure. The pathogenesis of delirium has mostly been attributed to neurotransmission, inflammation, and chronic stress.[58] Cytokines are chemicals secreted by the cells during times of cellular damage and repair. Cytokines such as interleukins (IL), tumor necrosis factor alpha (TNF-α), and interferons (IFN) play an intricate role in the inflammatory process.[61] Likewise, increase levels of cytokines seem to have a connection in causing delirium.[61] Interleukin-1 (IL-1),[57,61] IL-2 (a T-cell activator),[57] IL-6 (pro-pyrogenic molecules),[57] and TNF-α[57,61] have all been suspected of causing delirium.

Cells undergoing a response to stress, inflammation, and tissue damage release cytokines which directly influence the hippocampus and amygdala to secrete neurotransmitters and activate the sympathetic nervous system.[57] As such, the hypothalamic hormonal axis will secrete a large concentration of hormones that will affect the pituitary gland which will subsequently affect the adrenal glands as they [adrenal glands] will secrete adrenocortical hormone in order to minimize the level of stress that is endured by the inflammatory process.[62] A chronic state of high cortisol levels will contribute to vast neurotransmitter processes within the body possibly contributing to the effects of delirium.[57]

Evidence has also pointed to a lack of cholinergic activity in the brain as a contributory factor to the initiation of a delirium state.[58] Abnormally high levels of dopamine have also been linked to delirium as they regulate the release of acetylcholine.[57] Imbalances in other neurotransmitters such as γ-aminobutyric acid, glutamate, and norepinephrine have also been linked to inducing delirium.[57]

Alterations in variables related to metabolism have been associated to causing delirium in postoperative hemi-arthroplasty in geriatric patients.[59] Recent studies have been conducted to measure important metabolic elements pre- and post-surgery in both POD and non-postoperative delirium (NPOD) patients to detect differences among both groups. Data have indicated that deficiencies in Omega-3 and Omega-6 fatty acids exist in POD patients when compared to NPOD patients.[59] Branched-chain amino acid (BCAA)/aromatic amino acid ratio was also measured to being lower in the POD group than in the NPOD group post-surgery.[59] This recent discovery has opened the discussion for other possible mechanisms of postoperative hip surgery delirium in the geriatric population.

Metabolites such as arachidonic acid, hexadecatrienoic acid, and eicosapentaenoic acid (EPA) among others were decreased before and significantly decreased after surgery in POD patients.[59] These and other fatty acids are important for the development of myelination by oligodendrocytes.[59] Thus, a lack of fatty acids causes neurodegenerative effects and is associated with delirium post-hip fracture.[59]

Even though we do not fully understand the process of delirium post-hip fractures in geriatric patients, we understand some basic pathways that have been investigated and later contributed to the state of delirium. We can infer from such pathways the general understanding of how delirium is caused. Overall, the pathogenesis of POD has vast etiologies. The inflammatory response involving cytokines, cortisol, neurotransmitters, and metabolites are all a contributory factor in causing delirium in postoperative surgeries involving complex hip fractures.

Patient Outcomes

Geriatric patients who experience traumatic hip fracture are prone to more postoperative complications compared to patients receiving elective surgery.[63] POD is the most common diagnosed postoperative complication in hip fracture patients, exhibiting a unique presentation of physical and cognitive short-term and long-term outcomes per patient.[10]

Physical Outcomes

Short-term physical outcome trends noted in hip fracture patients diagnosed with POD include worse surgical outcomes,[48] increased difficulty for independent living,[9,48] prolonged length of hospital stay,[9,48,49] elevated incidence of discharge to a care facility rather than to prior dwelling,[14,49] and an increased 30-day readmission rate.[49]

Though a diagnosis of POD does not guarantee the onset of serious long-term physical deficits, negative functional outcomes are common and serious, especially compared to patients never diagnosed with POD following hip fracture repair.[9,14,15] On the milder side of the

spectrum, hip fracture patients with POD were less likely to both recover their pre-fracture level of ambulation[9] and reap optimal rehab results in the months following surgery.[45] The more serious long-term physical outcomes associated with POD in hip fracture patients included higher likelihood of becoming wheelchair bound or bedridden,[14] higher occurrence of severe dependency for basic activities of daily life,[9,15] and increased nursing home placement post-surgery.[8]

The effect of POD on hip fracture patient mortality is of great concern and interest. Considering the short term, the presence or absence of POD did not affect in-hospital mortality.[9] Looking toward the long term, however, there is a general consensus that mortality by 6-month follow-up significantly increases in hip fracture patients diagnosed with POD compared to hip fracture patients without POD,[14,41,42] one study reporting a 28.1% mortality in POD hip replacement patients vs a 13.4% NPOD mortality by 6 months post-procedure.[42] Further trends suggest that there is an increased risk of 6-month mortality for each additional day a patient experiences POD.[42] Persistent delirium, continuing for months after hip fracture repair, is further implicated in a significantly increased 1-year mortality rate, one study concluding that persistent POD rendered patients 2.9 times more likely to die by 1-year post-procedure compared to patients whose delirium quickly resolved.[43]

Cognitive Outcomes

Postoperative delirium itself is a cognitive outcome of traumatic hip fracture, but POD is also associated with a variety of other short-term and long-term cognitive outcomes. The short-term effects of POD are associated with patient-specific presentations of changes in mental status and psychomotor activity—which can be classified as hyperactive delirium, hypoactive delirium, or mixed delirium.[1,2] All subtypes of delirium have been recorded in patients with POD following treatment for a hip fracture, but studies do not agree on which subtype is more common in this population.[2,64] In addition to changes in attention and awareness, patients can present with transient bouts of hallucinations,[14] anxiety,[14] depression,[14] delusions,[14] emotionalism,[14] and/or general cognitive dysfunction.[65] All of these mental status changes can impede trajectory of physical recovery from surgery.

Not only did hip fracture patients with POD acutely experience depressed cognitive function compared to hip fracture patients without POD, but a continuation of significantly blunted cognitive function was found at 38 months post-surgery in POD vs NPOD hip fracture patients.[15] Another study found this same trend in patients at 1-month follow-up and 1-year follow-up.[65] Patients without a history of dementia who experienced POD exhibited an increased risk for future dementia diagnosis compared to non-POD patients, with permanent deficits in memory, spatial orientation, and abstract thinking.[40] Finally, the incidence of POD in patients already diagnosed with Alzheimer disease may cause an accelerated cognitive decline.[66]

Economic Impact

Delirium itself has a high economic impact on healthcare and government spending. POD has been associated with increased time of hospital stay.[17] A study performed at Toronto Western Hospital found that POD in hip fracture patients was associated with an approximate 7.4 day longer stay and an $8286 (Canadian dollars) increase in healthcare fees during this time.[17] In another study conducted at the University of California, Davis, Medical Center, researchers discovered that developing POD or other in-hospital complications and length of time to surgery were predictive of an increased LOS.[67]

Some organizations within certain nations have begun to implement programs and initiatives that encourage incentives for developing assessment protocols for delirium. Hospital Elder Life Program (HELP) is currently practiced in the United States, Australia, and other nations.[68] Components of the HELP program include implementing targeted interventions by a skilled interdisciplinary team to address issues that contribute to cognitive and functional decline during hospitalization.[69] Teams consist of geriatric nurse specialists, specially trained Elder Life Specialists, and trained volunteers.[69] Issues addressed include cognitive orientation and stimulation activities, therapeutic activities, sleep enhancement strategies, exercise and mobilization, hearing and vision aids, feeding assistance and preventing dehydration, pastoral care, family support and education, and individualized discharge planning.[69] This program investigates and assesses both the costs and benefits of implementing such protocols.[70] In one study, a 40-bed unit saved $626,261 in over 6 months for 704 patients after utilizing the HELP protocol.[70] In one hospital utilizing the HELP protocol, over 7000 patients in 6 hospital units were served by the program which resulted in approximately $7.3 million of total savings in 2008.[68]

With the growing costs of health care and the complexities of medicine, physicians need to implement protocols to reduce delirium cases within patients. Delirium, as mentioned above, has a high burden and a great toll on the economy. Cases of delirium are only compounded into more severe cases should the patient be a postoperative hip fracture patient. The high costs of wrap-around treatment in addition to the burden on both the hospitals, long-term care facilities, and caregivers makes the creation of such protocols necessary to better the health outcomes of the patient.

Table 1. Screening and Diagnostic Tools to Diagnose POD and Their Respective Sensitivities and Specificities.

Screening method	Sensitivity	Specificity
Confusion Assessment Method	46–100%[72]	63–100%[72]
DRS/DRS-R-98	91–100%[72]	84–92%[72]
Memorial Delirium Assessment Scale	64.1%[72]	100%[72]
Diagnostic method	**Sensitivity**	**Specificity**
DSM-V (strict criteria compared to DSM-IV)	30% (95% CI 26 to 35)[73]	99% (95% CI 97 to 99)[73]
DSM-V (relaxed criteria compared to DSM-IV)	89% (95% CI 86 to 92)[73]	96% (95% CI 93 to 98)[73]

Screening and Diagnosing

There are various screening tools used to assess delirium with varying sensitivities and specificities (Table 1). The Confusion Assessment Method (CAM)[71] (Appendix Tables A1 and A2) is the most commonly used screening tool to assess delirium.[72] However, a systematic review of delirium screening tools found wide ranges in sensitivity (46–100%) and specificity (63–100%) for CAM likely resulting from variations in user training and comfortability with the method.[72] The Memorial Delirium Assessment Scale had a low sensitivity (64.1%) and a high specificity (100%).[72] In addition, the Delirium Rating Scale (DRS)/Delirium Rating Scale-Revised-98 (DRS-R-98) had a high sensitivity (91-100%) and a relatively lower specificity (84-92%).[72] It is important to note that each of these screening tools is most useful after specific training for optimum performance.[72] For instance, the DRS/DRS-R-98 requires psychiatric training.[72]

There is no standardized, validated tool to diagnose POD, specifically. Diagnosis requires a multi-factorial approach by trained medical professionals, often starting with a perceived cognitive shift by family or a provider. The American Geriatric Society Best Practice statement recommends using Diagnostic and Statistical Manual of Mental Disorders (DSM), ICD-10, or Confusion Assessment Method to diagnose delirium.[74] In addition, they also recommend healthcare personnel be trained to recognize all forms of delirium[74] considering hypoactive delirium may have worse outcomes due to under recognition, diagnosis, and treatment.[75] One study assessed the concordance between DSM-IV and DSM-V criteria to diagnose delirium[73] (Table 1). This study found DSM-V using strict criteria compared to the DSM-IV had a low sensitivity, 30% (95% CI 26 to 35), but a high specificity, 99% (95% CI 97 to 99).[73] Alternatively, the DSM-V using relaxed criteria compared to the DSM-IV showed a higher sensitivity, 89% (95% CI 86 to 92), and a comparable specificity, 96% (95% CI 93 to 98).[73]

Prevention and Treatment

Clinical management of delirium is broadly categorized into non-pharmacologic and pharmacologic approaches. Both approaches aim to address the underlying cause of the delirium in prevention and treatment.

Non-Pharmacologic

In 2015, the American Geriatrics Society published a postoperative delirium in older adults best practice statement which highlights 3 key non-pharmacologic components to prevent and treat postoperative delirium: (1) implementing formal education programs for healthcare systems and hospitals, (2) implementing multicomponent non-pharmacologic interventions to prevent postoperative delirium in high-risk patients which are overseen by an interdisciplinary team, and (3) utilize interdisciplinary teams to deliver multicomponent interventions once a patient has been diagnosed with postoperative delirium.[74] In addition, it states that there is insufficient evidence regarding the use of delirium units for treatment.[74] Multicomponent interventions (Table 2) specifically targeted minimizing delirium risk such as minimizing time to surgery,[76] sensory enhancements (visual aids, hearing aids, etc.),[70,77-80] mobility enhancement,[77,79,81,82] cognitive stimulation,[70,77,79,82] nutritional and fluid repletion enhancement,[70,77,79,81] sleep enhancement,[70,77,79,81] and environmental familiarity.[80]

Non-pharmacologic interventions (Table 2) for prevention of delirium have shown to reduce the incidence by 27–100%.[76,78,80-83] Despite the decrease of incidence of delirium after the implementation of multicomponent interventions, one study found that mortality, length of stay, functional status, and disposition remained similar in both the intervention and non-intervention groups.[83] Other studies identified similar outcomes for those in the intervention group who experienced delirium finding no significant difference in severity, length, and recurrence of episodes of delirium.[77,78]

Table 2. Non-Pharmacologic and Pharmacologic Approaches to Clinically Managing Post-Operative Delirium.

Non-pharmacologic	Pharmacologic
Education on POD • Health care team[78,81,83] • Patient family members[80]	Regional analgesia and multimodal pain control[76,81]
Minimizing the time to surgery[76]	Reduce narcotic use[84]
Utilizing interdisciplinary approach • Multicomponent non-pharmacologic intervention programs[70,81]	Medication review • Reduction of polypharmacy or delirium exacerbating medications[76,78]
Sensory enhancement • Ensuring glasses[77-80]	Avoid the following drugs or drug classes • Drugs with anticholinergic properties[85] • Corticosteroids[86]
• Visual aids and adaptive equipment[70,77-80] • Hearing aids and listening amplifiers[70,77-80]	• Meperidine[87] • Benzodiazepines[87]
Mobility enhancement • Early mobilization[79,81,82] • Ambulating patients daily[77,78,81] • Minimizing immobility equipment (such as restraints or urinary catheter)[77,78,81]	Starting >3 new medications increases the risk of delirium[88,89]
Cognitive stimulation[70,77,79,82]	Supplemental oxygen[76,81]
Nutritional and fluid repletion enhancement[76,79,81,82]	
Sleep enhancement[70,77,79,81] • At bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage. Unit-wide noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures).[77,79]	
Environmental familiarity • Placing familiar objects to the patient in the rooms[80] • Extending visiting hours[80] • Reorientation by family members[80]	

However, multicomponent interventions can reduce complications (Lundstrom 2007), hospital length of stay,[81] days with delirium,[77,81] total number of episodes,[77] the rate of functional decline,[78,82] nutritional status decline,[82] and improve other quality interventions.[78]

Pharmacologic

The 2015 American Geriatrics Society postoperative delirium in older adults best practice statement also highlights 3 key pharmacologic components to prevent and treat postoperative delirium: (1) utilizing regional anesthesia, (2) pain control should be optimized with nonopioid drugs, and (3) cholinesterase inhibitors should not be newly prescribed to a patient to prevent or treat delirium.[74] The statement also addresses that there is insufficient evidence regarding prophylactic use of antipsychotics.[74] Pharmacologic interventions (Table 2) mainly center around the reduction[76,78,84,88,89] or avoidance[85] of using medications to prevent or treat delirium. Certain medications or a combination of multiple medications (Table 2) have been found to increase the incidence of delirium in geriatric patients. Specifically, drugs with anticholinergic properties,[85] corticosteroids,[86] meperidine,[87] and benzodiazepines[87] have been shown to be significantly associated with delirium. Other pharmacologic interventions (Table 2) include providing regional analgesia, multimodal pain control, and supplemental oxygen.[76,81]

Conclusion

Postoperative delirium remains the most common complication of emergency hip fracture surgery despite significant research conducted regarding this topic. Additionally, patients experiencing POD after hip fracture treatment have a high morbidity and mortality rate. This study found that early prevention, recognition, and treatment of POD are important for obtaining the best surgical outcomes for geriatric patients after hip fracture management. Future investigations should focus on application of multimodal interventions in both the prevention and treatment of POD in hip fracture patients as they have been shown to decrease the incidence of delirium.

Appendix 1

Table A1. The Confusion Assessment Method Instrument [71]

Acute onset
Is there evidence of an acute change in mental status from the patient's baseline?
Inattention*
A. Did the patient have difficulty focusing attention, for example, being easily distractable, or having difficulty keeping track of what was being said?
Not present at any time during interview.
Present at some time during interview, but in mild form.
Present at some time during interview, in marked form.
Uncertain.
B. (If present or abnormal) Did this behavior fluctuate during the interview, that is, tend to come and go or increase and decrease in severity?
Yes.
No.
Uncertain.
Not applicable.
C. (If present or abnormal) Please describe this behavior:
Disorganized thinking
Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Altered level of consciousness
Overall, how would you rate this patient's level of consciousness?
Alert (normal).
Vigilant (hyperalert, overly sensitive to environmental stimuli, startled very easily).
Lethargic (drowsy, easily aroused).
Stupor (difficult to arouse).
Coma (unarousable).
Uncertain.
Disorientation
Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?
Memory impairment
Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?
Perceptual disturbances
Did the patient have any evidence of perceptual disturbances, for example, hallucinations, illusions, or misinterpretations (such as thinking something was moving when it was not)?
Psychomotor agitation
Part 1.
At any time during the interview, did the patient have an unusually increased level of motor activity, such as restlessness, picking at bedclothes, tapping fingers, or making frequent sudden changes of position?
Psychomotor retardation
8. Part 2.
At any time during the interview, did the patient have an unusually decreased level of motor activity, such as sluggishness, staring into space, staying in one position for a long time, or moving very slowly?
Alerted sleep-wake cycle
Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?
*The questions listed under this topic were repeated for each topic where applicable.

Table A2. The Confusion Assessment Method (CAM) Diagnostic Algorithm* [71]

Feature 1. Acute onset or fluctuating course
This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2. Inattention
This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3. Disorganized thinking
This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4. Altered level of consciousness
This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy and easily aroused], stupor [difficult to arouse], or coma [unarousable])
*The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4

Author Contributions

AMA and LB: study concept and design; AMA, NR, NG, and LB: preparation of manuscript.

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References

1. Association AP ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
2. Santana Santos F, Wahlund LO, Varli F, Tadeu Velasco I, Eriksdotter Jonhagen M. Incidence, clinical features and subtypes of delirium in elderly patients treated for hip fractures. *Dement Geriatr Cognit Disord*. 2005;20(4):231-237. doi:10.1159/000087311
3. Durst J, Wilson D. Effects of protocol on prevention of delirium in hospitalized hip fracture patients: A quality improvement project. *Int J Orthop Trauma Nurs*. 2020;36:100710.
4. van Velthuijsen EL, Zwakhalen SMG, Mulder WJ, Verhey FRJ, Kempen GIJM. Detection and management of hyperactive and hypoactive delirium in older patients during hospitalization: A retrospective cohort study evaluating daily practice. *Int J Geriatr Psychiatr*. 2018;1133(11):1521-1529. doi:10.1002/gps.4690
5. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. *Int Psychogeriatr*. 2007;19(2):197-214. doi:10.1017/S104161020600425X
6. Bilotta F, Lauretta MP, Borozdina A, Mizikov VM, Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. *Minerva Anestesiol* 2013;79(9):1066-76.
7. Rizk P, Morris W, Oladeji P, Huo M. Review of postoperative delirium in geriatric patients undergoing hip surgery. *Geriatr Orthop Surg Rehabil* 2016;7(2):100-5. doi:10.1177/2151458516641162
8. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc*. 2000;48(6):618-624. doi:10.1111/j.1532-5415.2000.tb04718.x
9. Edelstein DM, Aharonoff GB, Karp A, Capla EL, Zuckerman JD, Koval KJ. Effect of postoperative delirium on outcome after hip fracture. *Clin Orthop Relat Res*. 2004;422(422):195-200. doi:10.1097/01.blo.0000128649.59959.0c
10. Merchant RA, Lui KL, Ismail NH, Wong HP, Sitoh YY. The relationship between postoperative complications and outcomes after hip fracture surgery. *Ann Acad Med Singapore*. 2005;34(2):163-168.
11. Lee KH, Ha YC, Lee YK, Kang H, Koo KH. Frequency, risk factors, and prognosis of prolonged delirium in elderly patients after hip fracture surgery. *Clin Orthop Relat Res*. 2011;469(9):2612-2620. doi:10.1007/s11999-011-1806-1.
12. Yang Y, Zhao X, Dong T, Yang Z, Zhang Q, Zhang Y. Risk factors for postoperative delirium following hip fracture

repair in elderly patients: A systematic review and meta-analysis. *Aging Clin Exp Res*. 2017;29(2):115-126. doi:10.1007/s40520-016-0541-6
13. Zakriya KJ, Christmas C, Wenz JF, Franckowiak S, Anderson R, Sieber FE. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. *Anesth Analg*. Jun 2002;94(6):1628-1632. doi:10.1097/00000539-200206000-00050
14. Edlund A, Lundström M, Lundström G, Hedqvist B, Gustafson Y. Clinical profile of delirium in patients treated for femoral neck fractures. *Dement Geriatr Cognit Disord*. 1999;10(5):325-329. doi:10.1159/000017163
15. Bickel H, Gradinger R, Kochs E, Förstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cognit Disord*. 2008;26(1):26-31. doi:10.1159/000140804
16. Zenilman ME. Delirium: An important postoperative complication. *J Am Med Assoc*. 2017;317(1):77-78. doi:10.1001/jama.2016.18174
17. Zywiel MG, Hurley RT, Perruccio AV, Hancock-Howard RL, Coyte PC, Rampersaud YR. Health economic implications of perioperative delirium in older patients after surgery for a fragility hip fracture. *J Bone Joint Surg Am*. 2015;97(10):829-836. doi:10.2106/JBJS.N.00724
18. Juliebø V, Bjøro K, Krogseth M, Skovlund E, Ranhoff AH, Wyller TB. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *J Am Geriatr Soc*. 2009;57(8):1354-1361. doi:10.1111/j.1532-5415.2009.02377.x
19. Haynes MS, Alder KD, Toombs C, Amakiri IC, Rubin LE, Grauer JN. Predictors and sequelae of postoperative delirium in a geriatric patient population with hip fracture. *J Am Acad Orthop Surg Glob Res Rev*. 2021;5(5):2151459318814823. doi:10.5435/JAAOSGlobal-D-20-00221
20. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *J Am Med Assoc*. 2009;302(14):1573-1579. doi:10.1001/jama.2009.1462
21. Goldenberg G, Kiselev P, Bharathan T, et al. Predicting post-operative delirium in elderly patients undergoing surgery for hip fracture. *Psychogeriatrics* 2006;6(2):43-48.
22. Andersson EM, Gustafson L, Hallberg IR. Acute confusional state in elderly orthopaedic patients: Factors of importance for detection in nursing care. *Int J Geriatr Psychiatry*. 2001;16(1):7-17.
23. Wang CG, Qin YF, Wan X, Song LC, Li ZJ, Li H. Incidence and risk factors of postoperative delirium in the elderly patients with hip fracture. *J Orthop Surg Res*. 2018;13(1):186. doi:10.1186/s13018-018-0897-8
24. Mazzola P, Ward L, Zazzetta S, et al. Association between preoperative malnutrition and postoperative delirium after hip fracture surgery in older adults. *J Am Geriatr Soc*. 2017;65(6):1222-1228. doi:10.1111/jgs.14764
25. Westhoff D, Witlox J, Koenderman L, et al. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. *J Neuroinflammation*. 2013;10:122. doi:10.1186/1742-2094-10-122
26. Wang NY, Hirao A, Sieber F. Association between intraoperative blood pressure and postoperative delirium in elderly hip fracture patients. *PLoS One*. 2015;10(4):e0123892. doi:10.1371/journal.pone.0123892
27. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc*. 2010;85(1):18-26. doi:10.4065/mcp.2009.0469
28. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. *J Am Geriatr Soc*. 2012;60(8):1487-1492. doi:10.1111/j.1532-5415.2012.04054.x
29. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg*. 2010;210(6):901-908. doi:10.1016/j.jamcollsurg.2010.01.028
30. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: A call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397. doi:10.1016/j.jamda.2013.03.022
31. Basic D, Shanley C. Frailty in an older inpatient population: Using the clinical frailty scale to predict patient outcomes. *J Aging Health*. 2015;27(4):670-685. doi:10.1177/0898264314558202
32. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. *J Am Geriatr Soc*. 2009;57(3):453-461. doi:10.1111/j.1532-5415.2008.02136.x
33. Macuco CR, Batistoni SS, Lopes A, et al. Mini-mental state examination performance in frail, pre-frail, and non-frail community dwelling older adults in Ermelino Matarazzo, SP, Brazil. *Int Psychogeriatr*. 2012;24(11):1725-1731. doi:10.1017/S1041610212000907
34. Avila-Funes JA, Carcaillon L, Helmer C, et al. Is frailty a prodromal stage of vascular dementia? Results from the three-city study. *J Am Geriatr Soc*. 2012;60(9):1708-1712. doi:10.1111/j.1532-5415.2012.04142.x
35. Mitnitski A, Fallah N, Rockwood K. A multistate model of cognitive dynamics in relation to frailty in older adults. *Ann Epidemiol*. 2011;21(7):507-516. doi:10.1016/j.annepidem.2011.01.006
36. Raji MA, Al Snih S, Ostir GV, Markides KS, Ottenbacher KJ. Cognitive status and future risk of frailty in older Mexican Americans. *J Gerontol A Biol Sci Med Sci*. 2010;65(11):1228-1234. doi:10.1093/gerona/glq121
37. Doba N, Tokuda Y, Goldstein NE, Kushiro T, Hinohara S. A pilot trial to predict frailty syndrome: The Japanese health research volunteer study. *Exp Gerontol*. 2012;47(8):638-643. doi:10.1016/j.exger.2012.05.016

38. Itagaki A, Sakurada K, Matsuhama M, Yajima J, Yamashita T, Kohzuki M. Impact of frailty and mild cognitive impairment on delirium after cardiac surgery in older patients. *J Cardiol*. 2020;76(2):147-153. doi:10.1016/j.jjcc.2020.02.007
39. Dayama A, Olorunfemi O, Greenbaum S, Stone ME, McNelis J. Impact of frailty on outcomes in geriatric femoral neck fracture management: An analysis of national surgical quality improvement program dataset. *Int J Surg*. 2016;28: 185-190. doi:10.1016/j.ijsu.2016.02.087
40. Wacker P, Nunes PV, Cabrita H, Forlenza OV. Post-operative delirium is associated with poor cognitive outcome and dementia. *Dement Geriatr Cognit Disord*. 2006;21(4): 221-227. doi:10.1159/000091022
41. Mazzola P, Bellelli G, Broggini V, et al. Postoperative delirium and pre-fracture disability predict 6-month mortality among the oldest old hip fracture patients. *Aging Clin Exp Res*. 2015;27(1):53-60. doi:10.1007/s40520-014-0242-y
42. Bellelli G, Mazzola P, Morandi A, et al. Duration of postoperative delirium is an independent predictor of 6-month mortality in older adults after hip fracture. *J Am Geriatr Soc*. 2014;62(7):1335-1340. doi:10.1111/jgs.12885
43. Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc*. 2009; 57(1):55-61. doi:10.1111/j.1532-5415.2008.02092.x
44. Abelha FJ, Luís C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Crit Care*. 2013;17(5):R257. doi:10.1186/cc13084
45. Olofsson B, Lundström M, Borssén B, Nyberg L, Gustafson Y. Delirium is associated with poor rehabilitation outcome in elderly patients treated for femoral neck fractures. *Scand J Caring Sci*. 2005;19(2):119-127. doi:10.1111/j.1471-6712.2005.00324.x
46. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29(11):2520-2526. doi:10.1002/jbmr.2269
47. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359(9319):1761-1767. doi:10.1016/S0140-6736(02)08657-9
48. Zakriya K, Sieber FE, Christmas C, Wenz JF, Franckowiak S. Brief postoperative delirium in hip fracture patients affects functional outcome at three months. *Anesth Analg*. 2004;98(6): 1798-1802. doi:10.1213/01.ane.0000117145.50236.90
49. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of delirium and other major complications on outcomes after elective surgery in older adults. *JAMA Surg*. 2015;150(12): 1134-1140. doi:10.1001/jamasurg.2015.2606
50. Aharonoff GB, Koval KJ, Skovron ML, Zuckerman JD. Hip fractures in the elderly: Predictors of one year mortality. *J Orthop Trauma*. 1997;11(3):162-165. doi:10.1097/00005131-199704000-00004
51. Lewiecki EM, Chastek B, Sundquist K, et al. Osteoporotic fracture trends in a population of US managed care enrollees from 2007 to 2017. *Osteoporos Int*. 2020;31(7):1299-1304. doi:10.1007/s00198-020-05334-y
52. Stevens JA, Rudd RA. The impact of decreasing US hip fracture rates on future hip fracture estimates. *Osteoporos Int*. 2013;24(10):2725-2728. doi:10.1007/s00198-013-2375-9
53. Parkkari J, Kannus P, Palvanen M, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: A prospective controlled hip fracture study with 206 consecutive patients. *Calcif Tissue Int*. 1999;65(3):183-187. doi:10.1007/s002239900679
54. Swift CG. Prevention and management of hip fracture in older patients. *Practitioner*. 2011;255(1743):293-333.
55. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. *Indian J Orthop*. 2011;45(1):15-22. doi:10.4103/0019-5413.73656
56. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383(9920):911-22. doi:10.1016/S0140-6736(13)60688-1
57. Trzepacz P, van der Mast R. *Delirium in Old Age*. Oxford, UK: Oxford University Press; 2002:51-90.
58. Inouye SK. Delirium in older persons. *N Engl J Med*. 2006; 354(11):1157-1165. doi:10.1056/NEJMra052321
59. Guo Y, Li Y, Zhang Y, et al. Post-operative delirium associated with metabolic alterations following hemi-arthroplasty in older patients. *Age Ageing*. 2019;1249(1):88-95. doi:10.1093/ageing/afz132
60. Gleason OC. Delirium. *Am Fam Physician*. 2003;67(5): 1027-1034.
61. Broadhurst C, Wilson K. Immunology of delirium: New opportunities for treatment and research. *Br J Psychiatr*. 2001;179:288-289.
62. Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the Hypothalamic-Pituitary-Adrenal Axis in Demented Patients with Delirium. *Int Clin Psychopharmacol*. 2001;16(1):39-47.
63. Duppils GS, Wikblad K. Acute confusional states in patients undergoing hip surgery. A prospective observation study. *Gerontology*. 2000;46(1):36-43. doi:10.1159/000022131
64. Albrecht JS, Marcantonio ER, Roffey DM, et al. Stability of postoperative delirium psychomotor subtypes in individuals with hip fracture. *J Am Geriatr Soc*. 2015;63(5):970-976. doi:10.1111/jgs.13334
65. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367(1):30-39. doi:10.1056/NEJMoa1112923
66. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology*. 2009; 72(18):1570-1575. doi:10.1212/WNL.0b013e3181a4129a
67. Hecht G, Slee CA, Goodell PB, Taylor SL, Wolinsky PR. Predictive modeling for geriatric hip fracture patients: Early surgery and delirium have the largest influence on length of stay. *J Am Acad Orthop Surg*. 2019;27(6):e293-e300. doi:10.5435/JAAOS-D-17-00447
68. Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK. Sustainability and scalability of the hospital elder life program at

a community hospital. *J Am Geriatr Soc*. 2011;59(2): 359-365. doi:10.1111/j.1532-5415.2010.03243.x

69. Hospital elder life program (HELP) for prevention of delirium. https://www.hospitalelderlifeprogram.org/about/ . 2013
70. Rubin FH, Williams JT, Lescisin DA, Mook WJ, Hassan S, Inouye SK. Replicating the hospital elder life program in a community hospital and demonstrating effectiveness using quality improvement methodology. *J Am Geriatr Soc*. 2006; 54(6):969-974. doi:10.1111/j.1532-5415.2006.00744.x
71. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948. doi:10.7326/0003-4819-113-12-941
72. De J, Wand AP. Delirium screening: A systematic review of delirium screening tools in hospitalized patients. *Gerontol*. 2015;1255(6):1079-1099. doi:10.1093/geront/gnv100
73. Meagher DJ, Morandi A, Inouye SK, et al. Concordance between DSM-IV and DSM-5 criteria for delirium diagnosis in a pooled database of 768 prospectively evaluated patients using the delirium rating scale-revised-98. *BMC Med*. 2014; 12:164. doi:10.1186/s12916-014-0164-8
74. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: Best practice statement from the American geriatrics society. *J Am Coll Surg*. 2015;220(2):136-148. doi:10.1016/j.jamcollsurg.2014.10.019
75. Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT. A longitudinal study of motor subtypes in delirium: Relationship with other phenomenology, etiology, medication exposure and prognosis. *J Psychosom Res*. 2011; 71(6):395-403. doi:10.1016/j.jpsychores.2011.06.001
76. Björkelund KB, Hommel A, Thorngren KG, Gustafson L, Larsson S, Lundberg D. Reducing delirium in elderly patients with hip fracture: A multi-factorial intervention study. *Acta Anaesthesiol Scand*. 2010;54(6):678-688. doi:10.1111/j.1399-6576.2010.02232.x
77. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340(9):669-676. doi:10.1056/NEJM199903043400901
78. Vidán MT, Sánchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *J Am Geriatr Soc*. 2009;57(11):2029-2036. doi:10.1111/j.1532-5415.2009.02485.x
79. Inouye SK, Bogardus ST, Baker DI, Leo-Summers L, Cooney LM. The hospital elder life program: A model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital elder life program. *J Am Geriatr Soc*. 2000;48(12): 1697-1706. doi:10.1111/j.1532-5415.2000.tb03885.x
80. Martinez FT, Tobar C, Beddings CI, Vallejo G, Fuentes P. Preventing delirium in an acute hospital using a non-pharmacological intervention. *Age Ageing*. 2012;41(5): 629-634. doi:10.1093/ageing/afs060
81. Lundström M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: A randomized intervention study. *Aging Clin Exp Res*. 2007; 19(3):178-186. doi:10.1007/BF03324687
82. Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified hospital elder life program: Effects on abdominal surgery patients. *J Am Coll Surg*. 2011;213(2): 245-252. doi:10.1016/j.jamcollsurg.2011.05.004
83. Holt R, Young J, Heseltine D. Effectiveness of a multicomponent intervention to reduce delirium incidence in elderly care wards. *Age Ageing*. 2013;42(6):721-727. doi: 10.1093/ageing/aft120
84. Krenk L, Rasmussen LS, Hansen TB, Bogø S, Søballe K, Kehlet H. Delirium after fast-track hip and knee arthroplasty. *Br J Anaesth*. 2012;108(4):607-611. doi:10.1093/bja/aer493
85. Agostini JV, Leo-Summers LS, Inouye SK. Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. *Arch Intern Med*. 2001;161(17):2091-2097. doi:10.1001/archinte.161.17.2091
86. Wada K, Yamada N, Sato T, et al. Corticosteroid-induced psychotic and mood disorders: Diagnosis defined by DSM-IV and clinical pictures. *Psychosomatics*. 2001;42(6): 461-466. doi:10.1176/appi.psy.42.6.461
87. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272(19):1518-1522.
88. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996; 275(11):852-857.
89. Taipale PG, Ratner PA, Galdas PM, et al. The association between nurse-administered midazolam following cardiac surgery and incident delirium: An observational study. *Int J Nurs Stud*. 2012;49(9):1064-1073. doi:10.1016/j.ijnurstu.2012.03.008
90. Cunningham J and Kim LD. Post-operative delirium: A review of diagnosis and treatment strategies. *Journal of Xiangya Medicine* 2018;3(2).