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Abstract

This retrospective cohort study aimed to determine the incidence, and preoperative, intraoperative and postoperative risk factors for postoperative delirium in older patients undergoing surgical fixation of a hip fracture. Electronic medical records were examined of

260 patients who underwent a surgical fixation of a hip fracture between June 2017 and October 2018 at a university-affiliated tertiary care hospital in Victoria, Australia. Demographic, clinical and perioperative data were examined for potential risk factors for postoperative delirium.

Of the 260 patients, 63 patients (24.2%) developed delirium postoperatively. Univariate logistic regression analysis indicated that advanced age, comorbidity, cognitive impairment, dementia, American Society of Anaesthesiologist score, antipsychotic usage were significant risk factors for delirium while doses of paracetamol, fentanyl and diazepam showed complex associations. Multivariate logistic regression analysis determined comorbidity and cognitive impairment as independent risk factors for the development of delirium.

This study demonstrates the importance of evaluation of medications prescribed in the perioperative period as modifiable risk factors, in order to identify patients at high risk of delirium and enable targeted monitoring and treatment during patients' hospitalisation.

KEYWORDS: postoperative delirium; hip fracture; incidence; risk factors.

1 | INTRODUCTION

Delirium is an acute state of mental confusion characterised by a sudden disturbance in attention and cognition (Inouye, Westendorp, & Saczynski, 2014). According to the American

Psychiatric Association (APA) (2013), a definitive diagnosis of delirium can be made when a patient presents with a disturbance in attention and level of consciousness, and disorganised thinking, which develop over a short period and fluctuate during the course of the day. While delirium can occur at any age (Kearney et al., 2015), older patients, aged 65 years and above, are especially at risk (Saller et al., 2019). Delirium is a common complication among patients undergoing surgical fixation of a hip fracture as these patients are typically older, commonly present to the emergency department with multiple comorbidities and have poorer baseline functional status (Morrison et al., 2003). Delirium is associated with immediate and long-term negative outcomes that affect patients, their family members and healthcare providers (Bruera et al., 2009). These outcomes include poor functional recovery, long term cognitive impairment, increased treatment costs, longer length of hospital stay and increased need for nursing home placements (Lee et al, 2011c; MacLulich, Beaglehole, Hall, & Meagher, 2009; Mosk et al, 2017).

Concern about the negative outcomes associated with delirium has led to widespread investigations, which have resulted in a growing body of knowledge related to clinical characteristics and risk factors of postoperative delirium. The reported incidence of postoperative delirium among patients with a hip fracture ranges from 14 to 56 per cent (Lee et al., 2011a; Morrison et al., 2003). These reported differences are mainly due to variations in patient populations and in scales used to diagnose delirium (Inouye et al., 2014).

Despite the significant impact of delirium, it remains under-recognised, and often misdiagnosed (Inouye et al., 2014). While the clinical presentation of delirium is consistent

across patient populations, risk factors for the development of delirium may be different across clinical settings (Inouye et al., 2014). According to Travers et al (2013), it is difficult to predict the development of delirium among patients in different settings without first investigating the causes and risk factors associated with these surroundings. Causes of delirium are usually multifactorial, and often result due to the interactions between predisposing and precipitating risk factors (Inouye et al., 2014).

Predisposing (preoperative) risk factors include factors that are present on admission to hospital. These risk factors are patient demographics, age, gender, cognitive impairment, dementia, functional decline and severe comorbidities, such as stroke and pulmonary failure (Inouye, 2006; Mazzola et al., 2017; Oh, Sieber, Leoutsakos, Inouye, & Lee, 2016). Although these risk factors can be used to identify patients at risk of developing delirium, there is often limited scope to intervene (Tabet & Howard, 2009). Common predisposing risk factors for postoperative delirium include older age and cognitive impairment (Lee et al., 2011a; Mazzola et al., 2017). As a result of an ageing population, surgical fixation of hip fractures has increased in frequency, placing growing importance on complications specifically related to postoperative delirium (Vasilian, Tamasan, Poenaru, & Lungeanu, 2017).

In a review of postoperative delirium, other predisposing risk factors, including comorbidity, frailty status, and dementia, have been identified (Freter et al., 2015; Leung, Tsai & Sands., 2011; Mazzola et al., 2017). Furthermore, preoperative delirium has been identified as a risk factor of postoperative delirium. In a prospective cohort study that investigated preoperative

delirium as a risk factor of postoperative delirium, Juliebø et al. (2009) found, of the 50 patients identified with preoperative delirium, 49 patients remained delirious postoperatively.

Precipitating factors are defined as an insult or medical or surgical treatment that is instigated during hospitalisation, and is associated with the context of delirium. These factors are differentiated from predisposing factors by being potentially modifiable (Siddiqi et al., 2016). Precipitating risk factors that have been identified in the surgical population include medications, indwelling catheter use, pneumonia, deep surgical site infection, urinary tract infection, and metabolic and electrolyte abnormalities (Bo et al., 2019; Bush & Lawlor., 2015; de Jong et al., 2019). Surgical factors including waiting time for surgery, type of surgery, such as hemiarthroplasty, and duration of the surgical procedure, have been identified as risk factors for postoperative delirium (Lee et al., 2011a; Lee et al., 2011c).

When medications were identified as a precipitating risk factor, researchers have explored the association between the total number of medications, different types of medications and delirium development amongst medical and surgical patients. For example, a significant association between delirium and patients who were taking two or more anticholinergic drugs was found in a retrospective cohort study involving Australian veterans (relative risk=2.58, 95% CI=1.91-3.48) (Ellett, Pratt, Ramsay, Barratt, & Roughead, 2014). In another study, involving an audit of 346 neurological patient medical files, diuretics and dopaminergic drugs were found to be associated with 19% of all delirium diagnoses (Hufschmidt, Shabarin, & Zimmer, 2009). However, studies examining medications, including sedatives, opioid and non-opioid analgesics and anaesthetic agents administered during patients' hospitalisation, did not

identify associations with postoperative delirium. Moreover, to our knowledge, no study has specifically examined time spent in the Post Anaesthetic Care Unit (PACU) and its relationship with the development of postoperative delirium in patients with a hip fracture.

Having an understanding of the clinical presentation and risk factors of postoperative delirium would guide clinicians in detecting this condition during the early stages of the surgical admission, and guide the implantation of an appropriate treatment plan to reduce complications (Dubljanin-Raspopović et al., 2012).

1.1 | Aim

The aim of this study was to determine the incidence of postoperative delirium and identify preoperative, intraoperative and postoperative risk factors for postoperative delirium in patients undergoing surgical fixation of a hip fracture.

2 | METHODS

2.1 | Study design and participants

This retrospective cohort study was conducted using data from electronic medical records at a tertiary care university hospital in Victoria, Australia. Three hundred and sixty patients were admitted to the tertiary hospital for treatment of a hip fracture between 1 June 2017 and 1 October 2018. To detect differences between delirium and non-delirium groups of patients with a hip fracture, and to achieve a statistical power of 80%, the number of patients needed for this cohort study was 250.

The researchers collected data by auditing patients' medical records using deidentified information from the electronic medical records. Study subjects were identified for the audit through the Business Intelligence Unit at the study site. The inclusion criteria specified patients aged 65 years or older who were admitted for a primary repair of a hip fracture. Patients diagnosed with delirium or confusion prior to admission, as confusion is often used as an alternate term for delirium by some health care professionals, or those who demonstrated delirium during admission, were excluded. Patients presenting with multiple fractures, including a hip fracture caused by a motor vehicle accident, as well as those undergoing conservative treatment for a hip fracture (non-surgical), or a revision of a hip fracture, were also excluded.

2.2 | Data collection

Patients' demographic, clinical and perioperative information was collected from the hospital information system registers, Inpatient Manager (IPM) and Electronic Content Manager (ECM) patient medical records. Data were extracted using a structured abridged version of the incidence of delirium clinical records audit tool (Tropea, Slee, Holmes, Gorelik and Brand, 2009) with permission to use the tool obtained prior to data collection. Although not previously validated, the tool was developed using the Clinical Practice Guidelines for the Management of Delirium in Older People (Clinical Epidemiology and Health Service Evaluation Unit and Delirium Clinical Guidelines Expert Working Group, 2006). With the focus on medication administration as a risk factor of delirium, the tool was considered appropriate for use in this study.

Two authors checked patients' demographic, clinical and perioperative data; the first author (RA) reviewed the medical records of all included patients, and gathered data related to preoperative, intraoperative and postoperative variables. The second author (PN) independently verified the accuracy of the collected data for a randomly selected sample of 5% of all included patients. Any discrepancies were decided by the third author (EM).

2.3 | Outcomes

Patients were classified into two groups based on the presence or absence of postoperative delirium. For the analysis of risk factors, variables were organised into three categories. First, patient demographic and clinical characteristics, including age, gender, cognitive impairment, comorbidity and presence of dementia were grouped. Comorbidity was assessed using the modified Charlson comorbidity index, which was calculated by totalling points allocated for disease conditions, with a total possible score ranging from 0 to 15, where a higher score indicates a poorer health condition (Charlson, Pompei, Ales & Mackenzie, 1987). Cognitive impairment was assessed using the recorded value of the 4 'A's tool (4AT) in medical records. This tool consists of four items (Alertness, Attention, Acute Medical Test 4, and Acute changes for fluctuation course), with a total possible score of 12. A score of 0 indicates cognitive impairment is unlikely, whereas a score between 1 and 3 indicates possible cognitive impairment. A score of 4 and above is suggestive of delirium (Bellelli et al., 2014). Assessment of cognitive impairment is completed on admission, and preoperatively as a routine nursing practice in the orthopaedic ward and emergency department at the research site.

The diagnosis of delirium was based on information obtained from electronic medical records. This diagnosis of delirium was determined postoperatively in the orthopaedic ward by experienced geriatricians who reviewed patients presenting with delirium signs, such as poor orientation. The incidence, onset time and frequency of postoperative delirium were also obtained. Surgery-related variables included the American Society of Anaesthesiologist (ASA) score, type of anaesthesia, waiting time for surgery, surgery type, duration of surgery and time spent in the PACU. Medication-related factors were extracted, including chronic use of antipsychotics such as olanzapine and haloperidol, and perioperative medication use (sedatives, analgesic and anaesthetic agents).

2.4 | Data Analysis

Statistical analyses were performed using IBM SPSS 22.0.0 (IBM SPSS Inc., IL, US). Data were analysed using univariate and multivariate logistic regression analyses. Descriptive statistics (frequencies, percentage, mean and median) were used to analyse age, gender and other demographic variables. Chi-square or Fisher's exact tests were used to analyse categorical variables. An independent sample t-test was used to analyse continuous variables. Statistical significance was established at $p < 0.05$. Variables that had a significant association with delirium were entered into logistic regression models to establish independent risk factors associated with postoperative delirium.

2.5 | Ethical considerations

This study was conducted in adherence with the ethical guidelines of the National Statement on Ethical Conduct in Human Research (National Health and Medical Research Council, 2007 [updated 2015]). For confidentiality purposes, numerical codes representing patient identification numbers were used. To re-identify records from which data were extracted, patient identification numbers were stored in a separate file with corresponding numerical codes. This process helped when going back to records in cases where information was missing.

Ethics approval was sought and obtained from the Human Research Ethics Committee at the study site (QA2018094), and from the Human Research and Ethics Committee at Deakin University (2018–375). Waivers of consent from the study site were sought and granted from the ethics committee, as the study utilised a retrospective design that made it impractical to seek consent from all patients to review their medical records (Zeps, Iacopetta, Schofield, George, & Goldblatt, 2007).

3 | RESULTS

3.1 | Sample characteristics

Two hundred and sixty patients were included in the study. The mean age of the group was 82.1 years (SD = 8.7) and included more women (68%) than men. Thirty-eight patients (14.6%) were reported as having cognitive impairment on admission to hospital (4AT $\geq$ 1), with a mean score of 1.5 (SD = 1.0). On admission, 49 patients (18.9%) were reported as having dementia. The mean number of pre-existing comorbidities was 5.3 (SD = 2.2).

The median waiting time for surgery from admission to hospital to commencement of surgery was 17.3 hours (interquartile range [IQR]:11.3-28.2 hours). In terms of perioperative factors, the mean ASA score was 3.0. For the type of anaesthesia 227 patients (87%) had a general anaesthetic, 23 patients (8%) had regional anaesthesia and 10 patients (4%) had a combined general and regional anaesthesia.

More than half of patients had a surgical procedure involving intramedullary nailing of the femur (53%), followed by a hemiarthroplasty (32%), with smaller numbers reported for other fractured hip repair procedures. Baseline patient demographics and perioperative clinical characteristics are displayed in Table 1.

[Insert Table 1 here]

3.2 | Incidence of postoperative delirium

The incidence of postoperative delirium was 24.2% (63/260). The mean age of patients with postoperative delirium was 86.2 (SD = 6.6) years. The first onset of delirium was reported as occurring on the same day of surgery (11.11%) to day 5 postoperatively (3.17%), with the highest incidence occurring on day 1 postoperatively (49.21%) (Table 2).

[Insert Table 2 here]

3.3 | Patients' demographic and perioperative risk factors for postoperative delirium

The age of individuals in the delirium group was significantly older than those in the non-delirium group ($M = 86.2$, $SD = 6.6$ vs $M = 80.8$, $SD = 8.8$; $p < 0.0001$). Patients who presented with delirium as compared with those with no delirium had a higher 4AT score for cognitive impairment ($M = 3.9$, $SD = 4.0$ vs $M = 0.9$, $SD = 2.1$; $p < 0.0001$). There was a significant difference between patients with dementia (51%) and those with no dementia (18%) and the development of postoperative delirium ($p < 0.0001$). In addition, patients who developed delirium had a higher score on the modified Charlson comorbidity index ($M = 6.2$, $SD = 2.0$ vs $M = 5.0$, $SD = 2.2$; $p = 0.002$) and a higher score on the ASA ($M = 3.3$, $SD = 0.7$ vs $M = 2.9$, $SD = 0.7$; $p = 0.001$). There were no statistical differences with regards to gender, waiting time for surgery, duration of surgery, type of anaesthesia or time spent in the PACU between the two groups (Table 3).

[Insert Table 3 here]

3.4 | Medication-related factors for postoperative delirium

To assess the association between medications administered pre, intra, and postoperatively, and the development of postoperative delirium, the mean daily doses of antipsychotics, sedatives, analgesics (opioid and non-opioid) and anaesthetic drugs were included in the analyses. While chronic use of antipsychotics was a risk factor for postoperative delirium, the association between preoperative opioid analgesics, including oxycodone, morphine and fentanyl, and the development of postoperative delirium was non-significant ($p = 0.805$; 0.379 ; 0.239) respectively. Further, patients who received lower doses of preoperative non-opioid analgesic of paracetamol were at higher risk of postoperative delirium. In the intraoperative

phase, while the total dose of intraoperative anaesthetic agents, including propofol, ketamine and ropivacaine was not significant in relation to the development of postoperative delirium, a lower dose of intraoperative analgesics of fentanyl was associated with the development of postoperative delirium ($p = 0.006$). The cumulative dose of preoperative and intraoperative fentanyl was analysed, with a non-significant result found in relation to the development of postoperative delirium ($p = 0.519$). Furthermore, in the postoperative phase, higher doses of diazepam were significantly associated with the development of postoperative delirium ($p = 0.017$) (Table 4).

[Insert Table 4 here]

Multivariate logistic regression analysis was performed using variables showing statistical significance in the univariate analysis. Results of this analysis identified comorbidity (OR: 1.19, 95% CI 1.0–1.4, $p=0.032$) and cognitive impairment (OR: 4.3, 95% CI 2.4–7.72, $p<0.0001$) as independent risk factors for development of postoperative delirium (Table 5).

[Insert Table 5 here]

4 | DISCUSSION

In the current study, the incidence of postoperative delirium among patients who underwent surgical fixation of a hip fracture was 24.2%, a finding that is consistent with those previously reported (16–56%) (Lee et al., 2011a; Morrison et al., 2003). Although delirium may develop at any time during hospitalisation, results of the current study indicate that delirium developed between the same day of surgery and day 5 postoperatively, with the majority reported within

the first 48 hours. These findings suggest that assessment of delirium in the early stages of hospitalisation, specifically the first 48 hours following surgery, is crucial in order to reduce onset and severity of delirium and prevent complications associated with postoperative delirium (Lundstrom et al., 2005).

Cognitive impairment was identified as a strong independent risk factor for postoperative delirium. Similarly, recent studies have found an increased incidence of postoperative delirium in patients with cognitive impairment (Freter, Dunbar, Koller, MacKnight, & Rockwood., 2016; Mazzola et al., 2017). Therefore, it is important to conduct a cognitive assessment as soon as possible after admission with regular assessments conducted throughout the patient's hospitalisation.

Data from the current study suggest that comorbidity, with an odds ratio of 1.2 was identified as a strong risk factor for postoperative delirium. Recent studies have revealed similar findings with respect to the relationship between comorbidity and delirium, further supporting our findings (Mosk et al., 2017; Neerland et al., 2017; Wu et al., 2017).

Although dementia was not a significant predictor in the multivariate logistic regression analysis, the incidence of postoperative delirium was notably higher in patients with dementia in the univariate analysis. Patients with dementia had 4.7 times the odds of having postoperative delirium compared with patients without dementia. The results of the current study with respect to dementia are not surprising, given that a considerable amount of research has identified dementia as a risk factor for delirium (Chrispal et al., 2010; Mazzola et al., 2017; Oh et al., 2015). Advanced age was another important risk factor for the development of

postoperative delirium in the current study, which is consistent with other studies (Lee et al., 2011b; Muangpaisan et al., 2015; Oh et al., 2015). One possible explanation is that as the brain ages, it is associated with changes including loss of nerve cells, increased level of cortisol, and decreased level of acetylcholine. These changes can alter the sleep cycle, and cause difficulties in memory and perception, which can be observed as a sign of delirium (Oh et al., 2015). Although these factors are important in identifying patients at risk, there is limited scope of intervening to reduce the risk of developing delirium (Oh et al., 2015).

Regarding the surgical variables in the current study, waiting time for surgery was not a risk factor. This finding is different from a previous study in which waiting time for surgery was identified as a risk factor for postoperative delirium (Freter et al., 2015), although the waiting time was significantly longer (96.6 hours) when compared to the 22.6 hours in this study, which could explain the difference.

Another factor explored in this study included the type of surgery. This was not found to be risk factor, which is different to the study by Lee et al (2011c). A possible explanation for the difference in results could be that of the patients included in Lee et al's study (2011c), 59% of patients underwent a hemiarthroplasty (open reduction) surgical procedure which is more invasive than a surgical fixation with a nail (closed reduction). Other surgical variables, including type of anaesthesia and longer surgery duration, were also not found to be risk factors for delirium, a result that is similar to the findings from more recent studies (Mosk et al., 2017; Neerland et al., 2017).

The ASA score was an important risk factor for postoperative delirium. Patients with an ASA score of 3 or more had 1.9 times the odds of developing postoperative delirium compared with patients who had a score of less than 3. This finding is supported by other studies (Juliebo et al., 2009; Mosk et al., 2017; Wu et al., 2017).

The current study found no evidence that time spent in the PACU was associated with postoperative delirium. With a lack of studies examining the issue involving patients with a hip fracture further work needs to be done to explore time spent in the PACU in the context of delirium development.

Regarding the extent of medication prescribed, chronic use of antipsychotics was significantly associated with postoperative delirium. This finding is consistent with a recent prospective observational study that found patients who are administered antipsychotics had double the risk of developing postoperative delirium (Mazzola et al., 2017). In relation to the medications administered in the perioperative period, there were no statistical differences found between preoperative opioid analgesics, including oxycodone, morphine and fentanyl, and development of postoperative delirium. These findings concur with other studies demonstrating an insignificant association between morphine and development of postoperative delirium (Freter et al., 2015; Muangpaisan et al., 2015; Wang et al., 2015). Lower doses of paracetamol were associated with a higher risk of postoperative delirium in both pre and postoperative periods. Considering pain is a risk factor of delirium (Nie et al., 2019), the relationship in this study could be explained as patients who received lower doses of paracetamol maybe attributable as having inadequate pain management. The use of analgesia is a marker of painful state (Vaurio

et al., 2006). Therefore, in this study, patient with delirium may have been unable to verbalise pain effectively, and therefore may have received lower doses of paracetamol.

The study showed lower doses of intraoperative fentanyl were associated with the development of postoperative delirium, which is an unexpected finding. Fentanyl is a strong opioid, which is highly lipophilic and has strong binding to plasma proteins. This opioid shows wide variability between individuals and between situations in which it is used, and several complex factors influence pharmacokinetic variability for absorption, distribution, metabolism and excretion. Patient age, pharmacogenomics, drug interactions and different dose forms used can affect responses to fentanyl use (Kuip, Zandvliet, Koolen, Mathijssen & Van der Rijt, 2017).

The combination of these complex factors may explain the non-significant relationship between the cumulative doses of preoperative and intraoperative fentanyl and the development of postoperative delirium. In the postoperative phase, there was no statistical difference found between postoperative fentanyl and development of postoperative delirium. The limited number of patients who received fentanyl in the postoperative period could explain this finding relating to postoperative fentanyl use. Hence, further work is needed to determine how varying doses of fentanyl and other factors associated with its use can affect delirium.

There were no statistical differences found between intraoperative anaesthetic agents, including, propofol, ketamine and ropivacaine and development of postoperative delirium. Due to a lack of studies examining intraoperative and postoperative opioid analgesics, and intraoperative anaesthetic agents, it is difficult to compare our findings. Therefore, to examine this association in greater depth, further research is necessary. In regard to sedatives, patients

receiving higher doses of diazepam postoperatively were significantly associated with the development of delirium. This expected finding concurs with another study (Muangpaisan et al., 2015).

The combination of the study findings suggests that the use of perioperative medications, including analgesics, anaesthetic agents and sedatives, may serve as a potential precipitating factor for postoperative delirium. This combination highlights the importance of evaluating the medications administered in perioperative period, as it may be possible to intervene to reduce the risk of postoperative delirium. Our results indicate that preventing delirium occurrence may require multimodal therapy, including the use of alternative or reduce opioid analgesics or sedatives. Furthermore, it is not sufficient to focus on one medication that could precipitate patients to delirium. It is important to review all medications administered during the patients' hospitalisation in an attempt to prevent postoperative delirium.

The best strategy of delirium management is prevention. The first step therefore includes identification and avoidance of possible precipitating factors. Reviewing perioperative medication needs to be considered in any intervention program in order to prevent or reduce the incidence of delirium. Anaesthetists, surgeons, and perioperative nurses therefore play a significant role in reviewing medications administered during the perioperative period.

There are several limitations in the current study. First, the study data were collected by a retrospective medical records audit. Therefore, some cases of delirium may have been missed. Second, the study was limited to patients with a single hip fracture who underwent a primary surgical procedure on a hip fracture, so the applicability of the study findings to patients who

had multiple fractures or who underwent revision of hip fracture surgery is unclear. Third, as this was a single-site study, the generalisability of the study findings to other health settings may be limited.

The study has also strengths, such as inclusion of patients with dementia, which has often been an exclusion criterion in other studies (Saller et al., 2019). The study involved an exploration of the association between time spent in the PACU and development of postoperative delirium in patients with a hip fracture. Additionally, the evidence about the type of medications administered perioperatively known to precipitate postoperative delirium in older patients undergoing surgical fixation of a hip fracture has also been expanded.

5 | CONCLUSION

Delirium remains a serious and poorly recognised disorder in patients presenting with a hip fracture. The first 48 hours following surgery is a key period in identifying postoperative delirium. Pre, intra, and postoperative risk factors were identified in this study. Findings have extended the knowledge on previous research and provided new insights into risk factors relating to the perioperative period, which may allow for early detection of vulnerable patients with a hip fracture for postoperative delirium. Health professionals need to focus attention on the dosages of paracetamol, fentanyl and diazepam prescribed to older patients during the perioperative period. Finally, future prospective large-scale studies are needed to emphasise risk prediction tools for postoperative delirium in patients with a hip fracture.

6 | RELVANCE TO CLINICAL PRACTICE AND NURSING EDUCATION

Nurses are often the first health professionals to recognise changes in cognition, attention and behaviours among patients in health care settings. Therefore, they need to be aware of medications administered during the perioperative period, including opioids, non-opioids analgesics and sedatives may impact delirium development. It is important that nurses monitor those patients during medications administration. Moreover, the importance of pain management has been highlighted in this study. Thus, improving nurses' skills in assessing pain in patients with delirium and possibly reducing the incidence of postoperative delirium, is an important factor in improving patients' overall outcomes.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interests

AUTHORS CONTRIBUTIONS:

Study design: R.A, E.M and P.N

Data collection: R.A and P.N

Data analysis: R.A, E.M and P.N

Manuscript writing: R.A, E.M and P.N

REFERENCES

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorder. DSM-5. (5th ed), pp 595, Washington. DC, American Psychiatric Publishing.
- Bellelli, G., Morandi, A., Davis, D. H. J., Mazzola, P., Turco, R., Gentile, S., MacLulich, A. M. J. (2014). Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age and Ageing*, 43(4), 496-502.
- Bo, M., Porrino, P., Di Santo, S. G., Mazzone, A., Cherubini, A., Mossello, E., & Filippini, C. (2019). The association of indwelling urinary catheter with delirium in hospitalized patients and nursing home residents: an explorative analysis from the "delirium Day 2015". *Aging Clinical and Experimental Research*, 31(3), 411-420.
- Bruera, E., Bush, S. H., Willey, J., Paraskevopoulos, T., Li, Z., Palmer, J. L., Elsayem, A. (2009). Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers, *Cancer*, 115(9), 2004-2012
- Bush, S. H., & Lawlor, P. G. (2015). Five things to know about delirium, *Canadian Medical Association Journal*, 187(2), 129-129.
- Charlson, M. E., Pompei, P., Ales, K. L., Mackenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*, 40(5), 373-383.
- Chrispal, A., Mathews, K. P., & Surekha, V. (2010). The clinical profile and association of delirium in geriatric patients with hip fractures in a tertiary care hospital in India. *The Journal Of The Association Of Physicians Of India*, 58 (1), 15-19.
- Clinical Epidemiology and Health Service Evaluation Unit and Delirium Clinical Guidelines Expert Working Group. (2006). Clinical Practice Guidelines for the Management of Delirium in Older People, Victorian Government Department of Health Services, retrieved 1st May 2019, <http://www.health.vic.gov.au>.
- de Jong, L., van Rijckevorsel, V. A. J. I. M., Raats, J. W., Klem, T. M. A. L., Kuijper, T. M., & Roukema, G. R. (2019). Delirium after hip hemiarthroplasty for proximal femoral fractures in elderly patients: risk factors and clinical outcomes. *Clinical Interventions in Aging*, 14, 427-435. doi: 10.2147/CIA.S189760

- Dubljanin-Raspopović, E., Grajić, M., Vujadinović, S. T., Bumbaširević, M., Denić, L. M., & Marinković, J. (2012). Use of early indicators in rehabilitation process to predict one-year mortality in elderly hip fracture patients. *HIP International*, 22(6), 661-667. doi: 10.5301/HIP.2012.10142
- Ellett, L. M. K., Pratt, N. L., Ramsay, E. N., Barratt, J. D., & Roughead, E. E. (2014). Multiple Anticholinergic Medication Use and Risk of Hospital Admission for Confusion or Dementia, 62(10), 1916-1922.
- Freter, S., Dunbar, M., Koller, K., MacKnight, C., & Rockwood, K. (2016). Prevalence and Characteristics of Pre-Operative Delirium in Hip Fracture Patients. *Gerontology*, 62(4), 396-400. doi: 10.1159/000442385
- Freter, S., Koller, K., MacKnight, C., Rockwood, K., & Dunbar, M. (2015). Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. *Canadian Geriatrics Journal*, 18(4), 212-216. doi: 10.5770/cgj.18.185
- Hufschmidt, A., Shabarin, V., & Zimmer, T. (2009). Drug-induced confusional states: the usual suspects? *Acta Neurologica Scandinavica*, 120(6), 436-438. doi: 10.1111/j.1600-0404.2009.01174.x
- Inouye, S. K. (2006). Delirium in older persons. *The New England Journal of Medicine*, 354(11), 1157-1165.
- Inouye, S. K., Westendorp, R. G. J., & Saczynski, J. S. (2014). Delirium in elderly people. *The Lancet*. 388(9920), 911-922. doi: 10.1016/S0140-6736(13)60688-1
- Juliebo, V., Krogseth, M., Wyller, T. B., Bjørø, K., Skovlund, E., & Ranhoff, A. H. (2009). Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *Journal of the American Geriatrics Society*, 57(8), 1354-1361. doi: 10.1111/j.1532-5415.2009.02377.x
- Kearney, J., Silver, G., Traube, C., Greenwald, B., Gerber, L. M., Sun, X., . . . Patel, A. (2015). Pediatric Delirium and Associated Risk Factors: A Single-Center Prospective Observational Study. *Pediatric critical care medicine. Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, 16(4), 303 .

- Kuip, E. J., Zandvliet, M. L., Koolen, S. L., Mathijssen, R. H., & Van der Rijt, C. C. D. (2017). A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients. *British Journal of Clinical Pharmacology*, 83(2), 294-313
- Lee, H. B., Rosenberg, P. B., Leoutsakos, J. M. S., Mears, S. C., Gottschalk, A., & Sieber, F. E. (2011a). Predisposing factors for postoperative delirium after hip fracture repair in individuals with and without dementia. *Journal of the American Geriatrics Society*, 59(12), 2306-2313. doi: 10.1111/j.1532-5415.2011.03725.x
- Lee, H. J., Wang, S. K., Chee, I. S., Baeg, S., Kim, J. L., & Hwang, D. S. (2011b). Early assessment of delirium in elderly patients after hip surgery. *Psychiatry Investigation*, 8(4), 340-347. doi: 10.4306/pi.2011.8.4.340
- Lee, K. H., Lee, Y. K., Koo, K. H., Ha, Y. C., & Kang, H. (2011c). Frequency, risk factors, and prognosis of prolonged delirium in elderly patients after hip fracture surgery. *Clinical Orthopaedics and Related Research*, 469(9), 2612-2620. doi: 10.1007/s11999-011-1806-1
- Leung, J. M., Tsai, T. L., Sands, L. P. (2011). Preoperative frailty in older surgical patients is associated with early postoperative delirium. *Anesthesia and Analgesia*, 112(5), 1199
- Lundstrom, M., Edlund, A., Karlsson, S., Brannstrom, B., Bucht, G., & Gustafson, Y. (2005). A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *Journal of American Geriatric Society*, 53(4), 622-628.
- MacLulich, A. M. J., Beaglehole, A., Hall, R. J., & Meagher, D. J. (2009). Delirium and long-term cognitive impairment. *International Review Of Psychiatry (Abingdon, England)*, 21(1), 30-42. doi: 10.1080/09540260802675031
- Mazzola, P., Zazzetta, S., Brogini, V., Anzuini, A., Bellelli, G., Annoni, G., . . . Pasinetti, G. M. (2017). Association Between Preoperative Malnutrition and Postoperative Delirium After Hip Fracture Surgery in Older Adults. *Journal of the American Geriatrics Society*, 65(6), 1222-1228. doi: 10.1111/jgs.14764
- Morrison, R. S., Magaziner, J., Gilbert, M., Koval, K. J., McLaughlin, M. A., Orosz, G., . . . Siu, A. L. (2003). Relationship between pain and opioid analgesics on the

- development of delirium following hip fracture. *The Journals of Gerontology, Series* 58(1), 68-74.
- Mosk, C. A., Mus, M., Vroemen, J. P. A. M., Ploeg, T. v. d., Vos, D. I., Elmans, L. H. G. J., & Laan, L. v. d. (2017). Dementia and delirium, the outcomes in elderly hip fracture patients. *Clinical Interventions in Aging*, 421. doi: 10.2147/CIA.S115945
- Muangpaisan, W., Wongprikron, A., Srinonprasert, V., Suwanpatoomlerd, S., Sutipornpalangkul, W., & Assantchai, P. (2015). Incidence and risk factors of acute delirium in older patients with hip fracture in Siriraj Hospital. *Journal Of The Medical Association Of Thailand = Chotmaihet Thangphaet*, 98(4), 423-430.
- Neerland, B. E., Krogseth, M., Juliebø, V., Hylen Ranhoff, A., Engedal, K., Frihagen, F., . . . Watne, L. O. (2017). Perioperative hemodynamics and risk for delirium and new onset dementia in hip fracture patients; A prospective follow-up study. *PLOS ONE*, 12(7), 1-18. doi: 10.1371/journal.pone.0180641
- Nie, H., Zhao, B., Zhang, Y.-Q., Jiang, Y.-H., & Yang, Y.-X. (2012). Pain and cognitive dysfunction are the risk factors of delirium in elderly hip fracture Chinese patients. *Archives of Gerontology and Geriatrics*, 54(2), 172-174.
- Oh, E. S., Li, M., Fafowora, T. M., Inouye, S. K., Chen, C. H., Rosman, L. M., . . . Puhan, M. A. (2015). Preoperative risk factors for postoperative delirium following hip fracture repair: a systematic review. *International Journal of Geriatric Psychiatry*, 30(9), 900-910. doi: 10.1002/gps.4233
- Oh, E. S., Sieber, F. E., Leoutsakos, J.-M., Inouye, S. K., & Lee, H. B. (2016). Sex Differences in Hip Fracture Surgery: Preoperative Risk Factors for Delirium and Postoperative Outcomes. *Journal of the American Geriatric Society*, 64(8), 1616-1621.
- Robinson, S., Vollmer, C., Jirka, H., Rich, C., Midiri, C., & Bisby, D. (2008). Aging and delirium: too much or too little pain medication? *Pain Management Nursing*, 9(2), 66-72.
- Saller, T., MacLulich, A. M. J., Schäfer, S. T., Crispin, A., Neitzert, R., Schüle, C., Von-Dossow, V & Hofmann-Kiefer, K. F. (2019). Screening for delirium after surgery: validation of the 4 A's test (4AT) in the post-anaesthesia care unit. *Anaesthesia*, 74(10), 1260-1266.

- Siddiqi, N., Harrison, J. K., Clegg, A., Teale, E. A., Young, J., Taylor, J., & Simpkins, S. A. (2016). Interventions for preventing delirium in hospitalised non-ICU patients. *The Cochrane Database Of Systematic Reviews*, 3, CD005563. doi: 10.1002/14651858.CD005563.pub3
- Tabet, N., & Howard, R. (2009). Non-pharmacological interventions in the prevention of delirium. *Age and Ageing*, 38(4), 374-379.
- Travers, C., Byrne, G., Pachana, N., Klein, K., Gray, L. (2013). Prospective observational study of dementia and delirium in the acute hospital setting. *Internal Medicine Journal*, 43(3), 262-269.
- Tropea, J., Slee, J., Holmes, A. C. N., Gorelik, A., & Brand, C. A. (2009). Use of antipsychotic medications for the management of delirium: an audit of current practice in the acute care setting. *International Psychogeriatrics*, 21(1), 172-179.
- Vasilian, C. C., Tamasan, S. C., Poenaru, D. V., & Lungeanu, D. (2017). Clock-Drawing Test as a Bedside Assessment of Post-operative Delirium Risk in Elderly Patients with Accidental Hip Fracture. *World Journal of Surgery*, 42(5), 1340-1345. doi: 10.1007/s00268-017-4294-y
- Vaurio, L. E., Sands, L. P., Wang, Y., Mullen, E. A., & Leung, J. M. (2006). Postoperative delirium: the importance of pain and pain management. *Anesthesia & Analgesia*, 102(4), 1267-1273.
- Wang, J., Li, Z., Yu, Y., Li, B., Shao, G., & Wang, Q. (2015). Risk factors contributing to postoperative delirium in geriatric patients postorthopedic surgery. *Asia-Pacific Psychiatry*, 7(4), 375-382. doi: 10.1111/appy.12193
- Wu, X. M., Xu, W. C., Yu, Y. J., Han, L., Zhang, J., & Yang, L. J. (2017). Postoperative serum thioredoxin concentrations correlate with delirium and cognitive dysfunction after hip fracture surgery in elderly patients. *Clinica Chimica Acta*, 466, 93-97. doi: 10.1016/j.cca.2017.01.009
- Zeps, N., Iacopetta, B. J., Schofield, L., George, J. M., & Goldblatt, J. (2007). Waiver of individual patient consent in research: when do potential benefits to the community outweigh private rights? *The Medical Journal Of Australia*, 186(2), 88-90.

Table 1. Baseline Characteristics of Patients Who Underwent Surgical Fixation of Hip Fracture

Variables	Total (N = 260) Mean / count	SD or %
Age (years)	82.1	± 8.7
Gender:		
Male	83	32%
Female	177	68%
Dementia	49	19%
4AT score	1.5	± 1.0
Charlson comorbidity index score	5.34	± 2.2
Perioperative variables		
ASA score	3.0	±0.8
Type of anaesthesia:		
General anaesthesia	227	87%
Regional anaesthesia	21	8.1
Combination of general and regional	10	3.8
Type of surgery:		
Hemiarthroplasty	84	32%
DHS	17	6.5%
IM nail femur	138	53%
Cannulated screws	21	8%
Waiting time for surgery (hours)	24.9	± 26.7
Duration of surgery (minutes)	84.7	± 40.6

Time spent in the PACU (minutes) 122.3 ± 89.3

Notes: ASA = American Society of Anaesthesiologists; SD = standard deviation; 4AT = 4 A test; IM nail femur = intramedullary nailing of femur.

Table 2. Onset, Frequency and Percentage of Delirium Diagnosis

Day of diagnosis (postoperatively)	Frequency (n = 63)	%
Same day as surgery	7	11.11
1	31	49.21
2	15	23.81
3	6	9.52
4	2	3.17
5	2	3.17

Table 3. Summary Statistics of Demographic and Perioperative Features of Delirious and Non-Delirious Patients Who Underwent Surgical Fixation of Hip Fracture

Variables	Non-delirium (n = 197) mean /count	SD / %	Delirium (n = 63) mean /count	SD / %	Univariate p-value
Age (years)	80.7	± 8.9	86.2	± 6.6	<0.0001
Gender					
Male	62	74%	21	25%	0.783
Female	135	76%	42	23%	
Dementia	25	18%	38	51%	<0.0001
4AT score	0.9	± 2.1	3.9	± 4.0	<0.0001
Charlson comorbidity index score	5.0	± 2.1	6.2	±2.0	0.002
Perioperative variables					
ASA	2.9	± 0.7	3.3	± 0.7	0.001
Type of anaesthesia:					
General anaesthesia	172	75%	55	24%	0.886
Regional anaesthesia	15	71%	6	28%	
Combination of general and regional	8	80%	2	20%	
Type of surgery:					
Hemiarthroplasty	61	72%	23	27%	0.328
DHS	14	82%	3	17%	
IM nail femur	103	74%	35	25%	
Cannulated screws	19	90%	2	9%	
Waiting time for surgery (hours)	25.7	± 27.6	22.6	± 23.8	0.436
Duration of surgery (minutes)	82.0	± 41.3	92.8	± 37.2	0.066

Time spent in the PACU (minutes)	118.8	± 88.3	133.1	± 91.7	0.276
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IM Nail Femur = intramedullary nailing of femur; SD = standard deviation; ASA = American Society of Anaesthesiologists; DHS = dynamic hip screw; 4AT = 4 A test.

Table 4. Univariate Analysis of Medications as Risk Factors for Delirium in Patients Who Underwent Surgical Fixation of Hip Fracture

Variables	Non-delirium (n = 197) mean/count	SD / %	Delirium (n = 63) mean /count	SD / %	Univariate p-value
Antipsychotic drug use (yes/no)	11	42%	15	57%	<0.001
Total preoperative opioid analgesics:					
Oxycodone (Endone), mg	10.6	± 7.9	10.9	±8.2	0.805
Morphine, mg	5.5	± 3.9	6.3	± 4.6	0.379
Fentanyl, mcg	57.4	± 45.9	81.2	± 78.4	0.239
Total dose of preoperative non-opioid analgesic:					
Paracetamol, mg	1606	± 1003	1290	± 628	0.030
Total intraoperative analgesics dose:					
Morphine, mg	7.8	± 4.2	4.7	± 3.1	0.374
Fentanyl, mcg	250	± 127	199	± 87.5	0.006
Total dose of intraoperative anaesthetic agents:					
Propofol, mg	64.4	± 39.4	55.3	± 40.4	0.128
Ketamine, mg	14.1	± 13	25	±21.2	0.364
Ropivacaine, mg	144	± 52.4	139	± 61.3	0.675
Postoperative opioid analgesics:					
Fentanyl, mcg	39	±17	70	± 26	0.458

Oxycodone (Endone), mg	7.5	±3.8	6.3	±3.2	0.556
Total postoperative non-opioid analgesic:					
Paracetamol, mg	1548	± 512	1315	± 555	0.006
Postoperative sedative dose:					
Diazepam, mg	5.4	± 1.9	10.1	± 1.6	0.017

Note: SD = standard deviation, mg= milligram, mcg=microgram

Table 5. Multivariate Logistic Regression Analysis of Risk Factors for Postoperative Delirium

Risk factors	Odds ratio	
	(95% CI)	p-value
Charlson comorbidity index score	1.19 (1.0–1.4)	0.032
The 4 ‘A’s test	4.3 (2.4–7.72)	0.001

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