Biomarkers and clinical features of delirium in elderly individuals with hip fracture surgery.

Paul Thisayakorn MD[1], Sookjaroen Tangwongchai MD[1], Saran Tantavisut MD PhD[2], Yanin Thipakorn MD[1], Siree Sukhanonsawat MD[1], Tanya Wongwarawipat MD[3], Sunee Sirivichayakul Ph.D[4], Michael Maes, MD Ph.D[1,5,6].

1. Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Thailand

2. Department of Orthopedics, Faculty of Medicine, Chulalongkorn University, Thailand

3. Nan District Hospital, Nan, Thailand.

4. Department of Medicine, Faculty of Medicine, Chulalongkorn University, Thailand

5. Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria.

6. Impact Research Center, Department of Psychiatry, Geelong, VIC, Australia.

Corresponding author: Paul Thisayakorn, MD

Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, 1873 Rama 4 Road, Pathumwan Bangkok 10330, Thailand

Tel. +66 0-22564298, +66 0-22564346

E-mail: paul.thi@chula.ac.th

Abstract

Background: Post-operative delirium in elderly with hip fracture is associated with various adverse clinical outcomes. Nevertheless, the pathophysiological processes underpinning delirium have remained elusive. The aim of this study is to explore the associations between delirium and its features and immune-inflammatory and blood gas biomarkers.

Methods: In this prospective study we examined 65 patients who underwent a hip fracture surgery and assessed the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Richmond Agitation-Sedation Scale (RASS), and Delirium Rating Scale Revised-98 (DRS-R-98) before and during 4 days after the surgery. Complete Blood Count (CBC) and venous blood gas markers were obtained at the same time points.

Results: Delirium was observed in 19 patients and was accompanied by significantly increased pO2, number of white blood cells, neutrophil percentage, and neutrophil/lymphocyte ratio, and lower mean platelet volume (MPV) (after adjusting for age, central nervous system (CNS) disease, blood loss during surgery, sleep disorders, and body mass index. The severity of delirium was associated with lowered number of platelets and MPV. Psychomotor disorders were associated with lower bicarbonate levels. The requirement of physical restraint of the patients was predicted by increased percentages of neutrophils and lymphocytes. Prior CNS disease was together with these biomarkers a significant predictor of delirium and severity of delirium.

Conclusion: Delirium and psychomotor disorders following hip fracture and surgery may be caused by immune-inflammatory and oxidative stress pathways probably attributable to an aseptic inflammatory process. Oxygen administration may aggravate these pathways.

Key words: delirium, inflammation, neuro-immune, biomarkers, oxidative stress

Introduction:

One third of elderly undergoing surgery or admitted to the intensive care unit suffer from delirium[1]. Delirium symptoms appear between one to twelve days after surgery, most often occurring in the following 4 days.[2, 3] Age and surgery increase delirium incidence, with post-surgery elderly patients showing an incidence of 15-53% and critically ill patients show a delirium incidence up to 70%[4, 5]. Delirium is multicausal in origin with various etiological, risk and trigger factors precipitating, or contributing to, delirium, including age, surgery, type of surgery, infection, anemia, dehydration, hypovolemia, nutritional deficits, medications, smoking, and alcohol use[1, 6, 7].

Hip fracture is a common orthopedic condition in elderly population which, when complicated with delirium, may associate with post-surgical complications including medical morbidities, increased length of hospitalization, and increased mortality at one year[8, 9]. A systematic review and meta-analysis reported that the incidence of delirium following hip fracture surgery was around 24%[10]. Early detection in high-risk patients is one of the most important factors in the prevention of delirium.

Recently, we were the first to report that the onset of delirium is strongly predicted by lower bicarbonate levels[11]. We found that lowered bicarbonate levels together with attenuated rises in bicarbonate levels from admission to three days post-surgery predict delirium some days later. This suggests that deficits in the bicarbonate buffer system may underpin delirium onset. However, metabolic acidosis, which may explain lowered bicarbonate levels in the postoperative period, is associated with delirium onset[6, 12]. Postoperative acidosis is frequent after inhalation anesthesia

and abdominal surgery and is related to lactatemia and hyperchloremic acidosis[13, 14] indicating that intraoperative hypercapnia is a risk factor for delirium. Most importantly, we found that supplementary oxygen therapy significantly increased bicarbonate levels, suggesting that the beneficial effects of oxygen therapy on delirium incidence may be related to effects on the acid-base equilibrium and that oxygen therapy is indicated in patients with lower bicarbonate levels[11]. Nevertheless, there are no data whether bicarbonate itself or related factors affect the onset of delirium, including O2 saturation or changes in acid-base equilibrium. Venous blood measurements of HCO3-, pO2, pCO2 and pH are reliable substitutes for the same measurement made in arterial blood[15]. Moreover, we found that lowered bicarbonate levels were inversely associated with increased white blood cell (WBC) number[11], suggesting that immune-inflammatory processes may play a role in lowered bicarbonate levels.

Recently, there were some reports that delirium is associated with increased immune-inflammatory biomarkers including increased interleukin (IL)-1 and soluble tumor necrosis factor receptor (sTNFR) levels[16]. Another study reported an inflammatory signature in delirium involving IL-6 and other cytokines[17]. A recent review concludes that immune-inflammatory biomarkers are increased in delirium suggesting that neuro-immune pathways play a role in delirium[18].

Previous studies detected that delirium is predicted by age, sex, blood loss during surgery, duration of surgery, and insomnia[12, 14, 19]. Nevertheless, there are no data whether a) immune-inflammatory biomarkers and blood gas measurements are associated with the onset of delirium, delirium severity, and psychomotor agitation and retardation, and b) these biomarker effects occur

beyond and above the effects of possible risk factors such as blood loss during surgery, surgery duration, premorbid neuro-psychiatric disoders, sleep disturbances, education, and pain symptoms.

Hence, the aim of the present study is to delineate whether increases in the neutrophil/lymphocyte ratio (NLR) or increased white blood cell (WBC) number or monocytes, and blood gas assessments (HCO3-, O2, pH, pCo2) are associated with delirium and severity of delirium and related psychomotor disturbances above and beyond the effects of the above-mentioned putative trigger factors.

5. Method

Participants

We included 65 patients admitted to the hip fracture pathway of the orthopedic surgery department of Chulalongkorn Hospital, Bangkok, Thailand between April 2019 and May 2020. Inclusion criteria were male and female patients, aged ≥ 65 years, with an understanding of the Thai language. Participants underwent hip fracture surgery and were postoperatively transferred to the surgery intensive care unit (SICU) or orthopedic units. Exclusion criteria were coma or premorbid severe dementia (Thai Mental Status Examination-TMSE score ≤ 10), a life-time history of neuro-inflammatory disease including multiple sclerosis, or psychiatric illness such as schizophrenia, bipolar disorder, and an acute phase of major depressive disorder.

Design.

This is a prospective cohort study, which examined 65 hip fracture patients during 4 consecutive days after admission into the orthopaedic service. Baseline clinical data were collected

12 - 24 hours before hip fracture surgery and included general demographic characteristics as well as the underlying medical diagnoses, and number of hospitalizations over the past year. We registered a) common central nervous system illness including ischemic or hemorrhagic cerebrovascular disorders, traumatic brain injury, epilepsy, and intracranial malignancy, b) previous psychiatric history including psychotic, mood, anxiety, and substance use disorders, and prior delirium history, c) use of medications with high anticholinergic activity, benzodiazepines, opiates, and psychotropic drugs prior to hospitalization, d) relevant peri/post-operative clinical data including operative time, blood loss, restraint requirement due to psychomotor agitation, as well as a pain score. We performed postoperative clinical assessments twice daily for 4 consecutive days or until the day the delirium occurred. Preoperative delirium cases also underwent a similar clinical data collection process.

To make the diagnosis of delirium, a senior psychiatrist assessed the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) twice a day, namely in the morning between 6.00 – 8.00 a.m. and in the evening between 4.00 – 6.00 p.m. and this during the study period. The CAM-ICU is a clinician-rated delirium screening instrument for ICU settings and is validated showing good interrater reliability, sensitivity, and specificity [20]. The scale is translated and validated into Thai language with adequate inter-rater reliability and internal consistency reliability (Cohen's k = 0.81 with 95% confidence interval =0.64-0.99) and with an adequate sensitivity of 92.3% (95% CI=64.0-99.8%) and specificity of 94.7% (85.4-98.9) for delirium [21].

The Delirium Rating Scale Revised-98 (DRS-R-98) was measured in the evenings to assess severity of delirium and sleep quality. The Thai DRS-R-98 has good validity, reliability and inter-rater reliability; the sensitivity of this scale is 100% and specificity 97.0% when compared with the clinical neuro-psychiatric diagnosis[22]. We used item one of the Thai DRS-R-98 to assess sleep-wake cycle (SWC) disturbances over the last 24 hours and to grade the severity of the sleep-wake cycle from normal to severe disturbance. The Richmond Agitation-Sedation Scale (RASS) was developed and validated in 2003[23] and demonstrates a good face/construct/criterion validity and interrater reliability (weighted κ 0.91). It has an ability to measure the changes in sedation and agitation status correlated with the level of consciousness and the content of consciousness of delirium in ICU. We assessed the RASS by observing the patients at bedside and graded the objective verbal and behavioral expression into the scores ranged between -5 to +4. The minus side of the RASS represents decreased levels of consciousness from drowsiness to unarousable, while the score above 0 reflects the agitated type of consciousness ranging from restlessness to combativeness. We used the RASS scores in the statistical analyses and an adapted RASS score with both the agitation and retardation scores being rated positively, thus assessing severity of psychomotor disorders, either agitation or retardation. Once the patients developed delirium, we discontinued all the assessments. All delirium diagnoses were confirmed by the senior psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[24].

Approval for the study was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (registration number 528/61), in compliance with the International Guideline for Human Research protection, as required by the

Declaration of Helsinki, was conducted according to Thai and international ethics and privacy laws. Written informed consent was obtained before the study from the patients or their gardians (first-rank family members).

Analyses

All blood for the assays of venous blood gas and CBC were sampled daily at 7 a.m. except the first blood sample which was obtained on day 1 in the operative room by the anesthesiology team just before surgery. The specific parameters of venous blood gas assays were pH, pO2, pCO2, and HCO3-. While total WBC, platelet count, neutrophil/lymphocyte ratio, as well as neutrophil, lymphocyte, monocyte, eosinophil, basophil percentage were analyzed from the CBC results. The blood tests were collected for 4 consecutive days after the operation. However, it was discontinued once the individual patient developed postoperative delirium. Thus, two to four blood samples were obtained from each patient. All laboratory samples were promptly sent to the central laboratory unit at the same hospital.

All CBC values were assayed by XN-10 (Sysmex, Kobe, Japan) using the flow cytometry method with semiconductor laser except the platelet count and MPV which used the sheath flow DC detection method. Blood gas data were analyzed by Nova Stat Profile pHOx series (Nova Biomedica, MA, USA) by using ion-selective electrode. The analytical inter-assay coefficients of variation are as follows: WBC 1.6%, Neutrophils 1.8%, Lymphocytes 4.1%, Monocytes 8.1%, Eosinophils 7.5%, Basophils 2.2%, Platelet count 1.9%, MPV 1.2%, pH 0.6%, pO2 9.4%, pCO2 5.3%, and HCO3- 7.1%. The NLR was computed as a z unit based composite score as z neutrophil percentage – z lymphocyte percentage.

Statistics

Analysis of contingency tables (X^2-test) was used to assess associations between sets of categorical variables, and analysis of variance (ANOVA) was employed to check between-group differences in scale variables. The primary outcome measurement is the diagnosis of delirium, as assessed with the CAM-ICU and DSM-IV-TR, while the second outcome variable is the DRS-R-98 scale score. Generalized estimating equations (GEE) was used as the primary statistical analysis to examine the effects of biomarkers and background variables (predictors) on the outcome (delirium as binary variable or severity of delirium as scale variable). Background variables were age, sex, time to surgery, estimated blood loss during surgery, duration of surgery, use of deliriogenic medications, insomnia, nasal cannula oxygen, and physical restraint. The secondary statistical approach is a repeated measurement design ANOVA with the time points as dependent variable and delirium (yes/no) as factor while examining the time x group interaction. Tests are 2-tailed and a p-value of 0.05 was used for statistical significance. All statistical analyses are performed using IBM SPSS windows version 25. Power analysis showed that using an effect size of 0.2, alpha=0.05, power=0.85, 2 groups (delirium versus non delirium) and 4 repeated measurements, the sample size should be around n = 60 (repeated measurements design ANOVA with within-between interaction). Consequently, we recruited 65 hip frature patients accounting for a possible drop out rate of 10%.

Results

Table 1 shows the demographic data of the hip fracture patients included in the present study. We observed that 19 hip fracture patients developed delirium during the study. Eight of these developed delirium before hip surgery. Patients with delirium were somewhat older than those without delirium. There were no significant differences in sex, education, duration of surgery, blood loss during surgery, premorbid medical disorders, prior use of delirogenic medications, a lifetime history of psychiatric disoders, and smoking between patients who developed a delirium and those who did not. Patients with delirium showed significantly higher incidence of premobid CNS disoders especially stroke.

Table 2 shows the differences in clinical scores between patients with and without delirium. The DRS score was significantly higher in patients with delirium than in those without. There were no significant differences in pain score between both groups. There were significantly more delirium patients who has increased SWC scores as compared with non delirium patients. Significantly more patients with delirium needed to be restrained as compared with patients who did not develp delirium. There were no differences in the RASS score between subjects with and without delirium (Wald=0.97, df=1, p=0.324) although the adapted RASS score was significantly higher in delirium patients than in those without delirium.

Table 3 shows that there were no significant differences in WBC number between both study groups. The NLR was significantly higher in patients with delirium and this was determined by a significantly increased neutrophil and lowered lymphocyte percentage. There were no significant differences in percentage of monocytes and eosonophils between patients with and

without delirium. The percentage of basophils was significantly lower in delirium patients than in those without delirium. The number of platelets was not significantly different between both groups, but MPV was significantly reduced in patients with delirium. There were no significant differences in HCO3-, pCO2 and pH between both groups and pO2 was significantly higher in delirium patients than in those without.

Table 4 shows the results of GEE analyses, which examined the associations between the clinical diagnosis or scale scores (entered as dependent variables) and the biomarkers and demogropahic data (entered as explanatory variables). The CAM-ICU diagnosis and the requirement to be restrained were entered as a binary response variables, SWC as an ordinal variable, and the DRS, pain, and RASS scores as scale variables. We found (GEE CAM #1) that the CAM-ICU diagnosis was significantly associated with number of WBC, neutrophil percentage, age, blood loss during surgery, prior CNS disease (all positively) and MPV (inversely). GEE CAM #2 shows an alternative prediction of the CAM-ICU diagnosis, namely after removing age we found that neutrophil percentage, pO2, prior CNS disease, and SWC were significantly and positively associated with CAM-ICU diagnosis, whereas BMI was inversely associated. The necessacity to be restrained was predicted by higher neutrophil and lymphocyte percentage. The DRS score was significantly predicted by prior CNS disease and age (both positively) and basophil percentage and MPV (both inversely). The RASS score (thus assessing psychomotor agitation) was associated with NLR and the adapted RASS score (assessing severity of any psychomotor disorder) was significantly predicted by lowered HCO3- levels and by incrased SWC scores.

Discussion

The first major finding of this study is that the onset of delirium due to hip fracture and the severity of delirium were associated with increased white blood cell counts, NLR, neutrophil precentage, and lowered MPV and basophil percentage, and that psychomotor disturbances are associated with lowered HCO3- levels. Our white blood cell count findings extend the results of previous papers showing abnormal immune-inflammatory responses including increased NLR levels in patients with delirium (see Introduction). For example, Egberts and Mattace-Raso in 2017[25], Kotfis et al in 2019[26], and He et al 2020[27] reported significant positive correlations between an elevated NLR and the emergence of delirium in various patient settings. NLR is relevant index which is useful in surgical emergencies, postoperative complications, and inflammatory conditions[28-30]. In critical care patients, an increased NLR indicates a systemic inflammatory response[31, 32]. In our study, we found that a higher NLR was associated with psychomotor retardation and increased neutrophil percentage with the severity of delirium symptoms. Interestingly, increased percentages of neutrophils and lymphocytes were associated with the necessity to be restrained. Increased numbers of WBC predicted delirium after considering the effects of other biomarkers and relevant clinical variables. All in all, these findings indicate that increased immune-inflammatory biomarkers are accompanied by an increased risk of delirium and more severe delirium symptoms.

Interestingly, the results of our study showed a significant lower basophil percentage and MPV values in delirious patients. Chen et al. reported lower basophil levels in Alzheimer's disease patients when compared with matched normal controls[33]. One prior study found an inverse

correlation between age and basophil percentage in an elderly with hip fracture but this study did not include a diagnosis of delirium[34]. Low basophil levels may be observed during inflammatory conditions as a consequence of releasing its granules[35]. Some previous studies demonstrated an association between decreased MPV and mild cognitive impairment and dementia[36, 37]. In some disease models, decreased or increased mean platelet volume may reflect platelet activation occurring during the inflammatory state[38]. Low number of platelets may appear in inflammatory conditions due to adherence of thrombocytes to WBC[39] and lowered MPV can be observed in immune-inflammatory and infectious disease[38].

The associations between delirium symptoms and immune variables may indicate that at least part of the patients developed delirium due to the effects of aseptic inflammation. Indeed, hip fracture patients do not suffer from an infectious state in the pre- and post-operative period. Aseptic trauma as a consequence of surgery may trigger an injurious-inflammatory cascade from the traumatic site to a peripheral immune-inflammatory response which may then translate into neuro-inflammation in the brain with consequent delirium symptoms[40-42]. Interestingly, this aseptic immune-inflammatory process may not only emerge after the surgery but could, in theory, start directly after the traumatic event. In elderly subjects, aseptic inflammatory processes may develop at the fracture site soon after the accident [43]. Overall, our findings in hip fracture patients support the theory that immune-inflammatory processes [44-46] play a role in the pathophysiology of delirium.

The second major finding of this study is that changes in blood gas parameters may affect delirium. Firstly, pO_2 was significantly increased in elderly subjects with delirium as compared with those without. These findings extend those of Lopez et al.[47] who reported an association

between intraoperative hyperoxic cerebral reperfusion and a higher incidence of postoperative delirium. On the other hand, perioperative hypoxia is a well-known risk factor of delirium [48]. Therefore, it is possible that not the hypoxemic events during or post-surgery per se, but rather the oxygen supplementation leading to a hyperoxic state induces delirium. Nevertheless, both hypoxic and hyperoxic states are involved in free oxygen radical production and oxidative stress toxicity and consequent neuronal dysfunctions or injuries, which cause delirium [49]. Second, HCO_3^- levels were inversely associated with psychomotor disturbances (either agitation or retardation), although no significant association was found with the diagnosis of delirium. In a previous study we found that low bicarbonate levels predict delirium onset in surgical ICU patients [5]. However, the pathophysiology of delirium in the patients included in the latter report may be quite different because the authors included patients with abdominal surgery which is more associated with septic inflammation [50]. Prior studies reported abnormal blood gas parameters in delirium including metabolic acidosis [12, 51] and hypercapnia [14]. These discrepant results may be explained by a number of factors including patient population, surgical and medical settings, time of blood gas analysis, delirium etiologies, and oxygen treatment therapy. It is important to note that O2 consumption may cause reactive oxygen species generation and increased oxidative stress toxicity [52, 53]. In rat models, increasing oxygen concentrations increase oxidative stress toxicity to red blood cells [54]. These effects could further aggravate the oxidative stress associated with delirium [49, 55] and with inflammatory conditions [56].

The third major finding of this study is that age, neurological degenerative and neuro-inflammatory diseases, especially stroke, are together with the above-mentioned biomarkers

significant risk factors of delirium and that they contribute to severity of delirium when coupled with these biomarkers. Our findings extend those of previous reports which showed significant associations of neurological disease with consequent delirium following several trigger factors including hip fracture [9,10,57,58]. Phrased differently, aseptic inflammation due to hip fracture or the consequent surgery may aggravate the existing neurocognitive deficits in neurodegenerative and neuro-inflammatory disease thereby triggering delirium symptoms and the onset of full-blown delirium. In contrast, other known predisposing factors of delirium such as the operative time[59], pre-admission deliriogenic drugs and polypharmacy[60, 61], and postoperative pain[62, 63] were not correlated with the diagnosis of delirium. On the other hand, the current study showed that increased blood loss during surgery may further increase the severity of delirium. These findings are in agreement with previous results.[64,65]

Other clinical findings are worth mentioning including that delirium due to hip fracture and surgery was associated with increased psychomotor retardation and agitation (and consequent necessity to be restrained), more sleep disorders as assessed with the SWC and aberrations in the sleep-wake cycle as assessed with the DRS-R-98. These are all important features of the delirium phenome which are described in the diagnostic criteria. Restraint is a frequent manageable care method but potentially harmful consequence, especially when used in elderly population[66].

The results of the present study should be interpreted with regard to its limitations. First, it would have been more interesting if we had assessed other clinical and laboratory data which are involved with the onset of delirium including the APACHE II severity score, baseline nutritional status, albumin levels, anesthetic events during the operation (hypotension, hypoxemia), as well as

time of ambulation. Second, preoperative delirium was reported to be highly prevalent in hip fracture populations, namely between 12.7-58%[67, 68]. Third, we obtained venous rather than arterial blood samples to assess the acid base and blood gas biomarkers of delirium. Although, there is evidence that venous and arterial blood gas analysis show comparative results[16], venous blood gas may not completely represent the gold standard arterial blood gas levels.

In conclusion, this study found that delirium is accompanied by significantly increased NLR, neutrophil percentage, WBC numbers, and pO2 levels, and lowered MPV and that the severity of delirium symptoms (severity of delirium, psychomotor disorders) is significantly associated with higher NLR levels, lowered basophil percentage, MPV, and bicarbonate levels. These findings support the theory that the onset of delirium as well as delirium severity are in part caused by immune-inflammatory and oxidative stress pathways. Further research should examine immune-inflammatory biomarkers including cytokine and chemokine levels and oxidative stress pathways to further elucidate the pathophysiology of delirium due to hip fracture and consequent surgery.

Acknowledgement

We gratefully acknowledge the works of all nursing staffs, psychiatry/orthopedic/anesthesiology residents who involved and supported this study.

Funding

Conflict of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

Author's contributions

All the contributing authors have participated in the preparation of the manuscript.

References

1.   Collier R. Hospital-induced delirium hits hard. Cmaj 2012;184:23-4.
2.   Horacek R, Krnacova B, Prasko J, Latalova K. Delirium as a complication of the surgical intensive care. Neuropsychiatr Dis Treat 2016;12:2425-34.
3.   Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg 2009;249:173-8.
4.   Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 2009;5:210-20.
5.   Pipanmekaporn T, Chittawatanarat K, Chaiwat O, Thawitsri T, Wacharasint P, Kongsayreepong S. Incidence and risk factors of delirium in multi-center Thai surgical intensive care units: a prospective cohort study. J Intensive Care 2015;3:53.
6.   Aldemir M, Ozen S, Kara IH, Sir A, Baç B. Predisposing factors for delirium in the surgical intensive care unit. Crit Care 2001;5:265-70.

7.   Lawlor PG. Delirium and dehydration: some fluid for thought? Support Care Cancer 2002;10:445-54.

8.   Mosk CA, Mus M, Vroemen JP, van der Ploeg T, Vos DI, Elmans LH, et al. Dementia and delirium, the outcomes in elderly hip fracture patients. Clin Interv Aging 2017;12:421-30.

9.   Arshi A, Lai WC, Chen JB, Bukata SV, Stavrakis AI, Zeegen EN. Predictors and Sequelae of Postoperative Delirium in Geriatric Hip Fracture Patients. Geriatr Orthop Surg Rehabil 2018;9:2151459318814823.

10.   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;29:115-26.

11.   Potharajaroen S, Tangwongchai S, Tayjasanant T, Thawitsri T, Anderson G, Maes M. Bright light and oxygen therapies decrease delirium risk in critically ill surgical patients by targeting sleep and acid-base disturbances. Psychiatry Res 2018;261:21-7.

12.   Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. Crit Care Med 2015;43:40-7.

13.   Park CM, Chun HK, Jeon K, Suh GY, Choi DW, Kim S. Factors related to post-operative metabolic acidosis following major abdominal surgery. ANZ J Surg 2014;84:574-80.

14.   Nazemi AK, Gowd AK, Carmouche JJ, Kates SL, Albert TJ, Behrend CJ. Prevention and Management of Postoperative Delirium in Elderly Patients Following Elective Spinal Surgery. Clin Spine Surg 2017;30:112-9.

15.   Malatesha G, Singh NK, Bharija A, Rehani B, Goel A. Comparison of arterial and venous pH, bicarbonate, PCO2 and PO2 in initial emergency department assessment. Emerg Med J 2007;24:569-71.

16.   Ritter C, Tomasi CD, Dal-Pizzol F, Pinto BB, Dyson A, de Miranda AS, et al. Inflammation biomarkers and delirium in critically ill patients. Crit Care 2014;18:R106.

17.   Vasunilashorn SM, Ngo L, Inouye SK, Libermann TA, Jones RN, Alsop DC, et al. Cytokines and Postoperative Delirium in Older Patients Undergoing Major Elective Surgery. J Gerontol A Biol Sci Med Sci 2015;70:1289-95.

18.   Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. CNS Neurosci Ther 2011;17:506-13.

19.   Simons KS, Laheij RJ, van den Boogaard M, Moviat MA, Paling AJ, Polderman FN, et al. Dynamic light application therapy to reduce the incidence and duration of delirium in intensive-care patients: a randomised controlled trial. Lancet Respir Med 2016;4:194-202.

20.   Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). Jama 2001;286:2703-10.

21.   Pipanmekaporn T, Wongpakaran N, Mueankwan S, Dendumrongkul P, Chittawatanarat K, Khongpheng N, et al. Validity and reliability of the Thai version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Clin Interv Aging 2014;9:879-85.

22.   Bangphichet. A. Reliability and Validity of the Thai version of the Delirium Rating Scale-Revised-98 (DRS-R-98). 2008.

23.   Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). Jama 2003;289:2983-91.

24.   Diagnostic and Statistical Manual of Mental Disorders (DSM‑5). 2013.

25.   Egberts A, Mattace‑Raso FU. Increased neutrophil‑lymphocyte ratio in delirium: a pilot study. Clin Interv Aging 2017;12:1115‑21.

26.   Kotfis K, Ślozowska J, Safranow K, Szylińska A, Listewnik M. The Practical Use of White Cell Inflammatory Biomarkers in Prediction of Postoperative Delirium after Cardiac Surgery. Brain Sci 2019;9.

27.   He R, Wang F, Shen H, Zeng Y, LijuanZhang. Association between increased neutrophil‑to‑lymphocyte ratio and postoperative delirium in elderly patients with total hip arthroplasty for hip fracture. BMC Psychiatry 2020;20:496.

28.   Sarikaya M, Dogan Z, Ergul B, Filik L. Neutrophil‑to‑lymphocyte ratio as a sensitive marker in diagnosis of celiac disease. Ann Gastroenterol 2014;27:431‑2.

29.   Hajibandeh S, Hajibandeh S, Hobbs N, Mansour M. Neutrophil‑to‑lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: A systematic review and meta‑analysis. Am J Surg 2020;219:154‑63.

30.   Vulliamy P, McCluney S, Mukherjee S, Ashby L, Amalesh T. Postoperative Elevation of the Neutrophil: Lymphocyte Ratio Predicts Complications Following Esophageal Resection. World J Surg 2016;40:1397‑403.

31.   Zahorec R. Ratio of neutrophil to lymphocyte counts‑‑rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5‑14.

32.   Liu X, Shen Y, Wang H, Ge Q, Fei A, Pan S. Prognostic Significance of Neutrophil‑to‑Lymphocyte Ratio in Patients with Sepsis: A Prospective Observational Study. Mediators Inflamm 2016;2016:8191254.

33.   Chen SH, Bu XL, Jin WS, Shen LL, Wang J, Zhuang ZQ, et al. Altered peripheral profile of blood cells in Alzheimer disease: A hospital‑based case‑control study. Medicine (Baltimore) 2017;96:e6843.

34.   García‑Alvarez F, González P, Navarro‑Zorraquino M, Larrad L, García‑Alvarez I, Pastor C, et al. Immune cell variations in patients with hip fracture. Arch Gerontol Geriatr 2008;46:117‑24.

35.   Johnson J. Everything you need to know about basophils www.medicalnewstoday.com2019 [Available from: medicalnewstoday.com/articles/324188.

36.   Liang QC, Jin D, Li Y, Wang RT. Mean platelet volume and platelet distribution width in vascular dementia and Alzheimer's disease. Platelets 2014;25:433‑8.

37.   Wang RT, Jin D, Li Y, Liang QC. Decreased mean platelet volume and platelet distribution width are associated with mild cognitive impairment and Alzheimer's disease. J Psychiatr Res 2013;47:644‑9.

38.   Korniluk A, Koper‑Lenkiewicz OM, Kamińska J, Kemona H, Dymicka‑Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm 2019;2019:9213074.

39.   Sonmez O, Sonmez M. Role of platelets in immune system and inflammation. Porto Biomed J 2017;2:311‑4.

40.   Saxena S, Maze M. Impact on the brain of the inflammatory response to surgery. Presse Med 2018;47:e73‑e81.

41.   Vacas S, Degos V, Feng X, Maze M. The neuroinflammatory response of postoperative cognitive decline. Br Med Bull 2013;106:161‑78.

42.   Safavynia SA, Goldstein PA. The Role of Neuroinflammation in Postoperative Cognitive Dysfunction: Moving From Hypothesis to Treatment. Front Psychiatry 2018;9:752.

43.   Lin X, Chen Y, Zhang P, Chen G, Zhou Y, Yu X. The potential mechanism of postoperative cognitive dysfunction in older people. Exp Gerontol 2020;130:110791.

44.   Schreuder L, Eggen BJ, Biber K, Schoemaker RG, Laman JD, de Rooij SE. Pathophysiological and behavioral effects of systemic inflammation in aged and diseased rodents with relevance to delirium: A systematic review. Brain Behav Immun 2017;62:362-81.

45.   Subramaniyan S, Terrando N. Neuroinflammation and Perioperative Neurocognitive Disorders. Anesth Analg 2019;128:781-8.

46.   Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One 2018;13:e0195659.

47.   Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, et al. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med 2017;103:192-8.

48.   Liu Z, Pang X, Zhang X, Cao G, Fang C, Wu S. Incidence and Risk Factors of Delirium in Patients After Type-A Aortic Dissection Surgery. J Cardiothorac Vasc Anesth 2017;31:1996-9.

49.   Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry 2018;33:1428-57.

50.   Gabriel V, Grigorian A, Nahmias J, Pejcinovska M, Smith M, Sun B, et al. Risk Factors for Post-Operative Sepsis and Septic Shock in Patients Undergoing Emergency Surgery. Surg Infect (Larchmt) 2019;20:367-72.

51.   Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for intensive care delirium: a systematic review. Intensive Crit Care Nurs 2008;24:98-107.

52.   Hammond B, Hess ML. The oxygen free radical system: potential mediator of myocardial injury. J Am Coll Cardiol 1985;6:215-20.

53.   Weston C. Oxygen therapy in acute myocardial infarction -- too much of a good thing? Cochrane Database Syst Rev 2010;2011:Ed000006.

54.   Nagatomo F, Fujino H, Kondo H, Ishihara A. Oxygen concentration-dependent oxidative stress levels in rats. Oxid Med Cell Longev 2012;2012:381763.

55.   Oldham MA, Flaherty JH, Maldonado JR. Refining Delirium: A Transtheoretical Model of Delirium Disorder with Preliminary Neurophysiologic Subtypes. Am J Geriatr Psychiatry 2018;26:913-24.

56.   Morris G, Puri BK, Olive L, Carvalho A, Berk M, Walder K, et al. Endothelial dysfunction in neuroprogressive disorders-causes and suggested treatments. BMC Med 2020;18:305.

57.   Yang Y, Zhao X, Gao L, Wang Y, Wang J. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res 2020.

58.   Smith TO, Cooper A, Peryer G, Griffiths R, Fox C, Cross J. Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis. Int J Geriatr Psychiatry 2017;32:386-96.

59.   An YS, Jin Y, Jin T, Hur EY, Lee SM. Operative and anaesthetic factors influencing on delirium in the intensive care unit: An Analysis of electronic health records. J Clin Nurs 2019;28:1327-35.

60.   Kassie GM, Nguyen TA, Kalisch Ellett LM, Pratt NL, Roughead EE. Preoperative medication use and postoperative delirium: a systematic review. BMC Geriatr 2017;17:298.

61.   Hosoya R, Sato Y, Ishida E, Shibamoto H, Hino S, Yokote H, et al. Association between Delirium and Prehospitalization Medication in Poststroke Patients. J Stroke Cerebrovasc Dis 2018;27:1914-20.

62.   Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998;86:781-5.

63. Denny DL, Lindseth GN. Pain, Opioid Intake, and Delirium Symptoms in Adults Following Joint Replacement Surgery. West J Nurs Res 2020;42:165-76.

64. Hong N, Park JY. The Motoric Types of Delirium and Estimated Blood Loss during Perioperative Period in Orthopedic Elderly Patients. Biomed Res Int 2018;2018:9812041.

65. 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;13:186.

66. Pan Y, Jiang Z, Yuan C, Wang L, Zhang J, Zhou J, et al. Influence of physical restraint on delirium of adult patients in ICU: A nested case-control study. J Clin Nurs 2018;27:1950-7.

67. Freter S, Dunbar M, Koller K, MacKnight C, Rockwood K. Prevalence and Characteristics of Pre-Operative Delirium in Hip Fracture Patients. Gerontology 2016;62:396-400.

68. Agrawal S, Turk R, Burton BN, Ingrande J, Gabriel RA. The association of preoperative delirium with postoperative outcomes following hip surgery in the elderly. J Clin Anesth 2020;60:28-33.

Table 1. Socio-demographic and clinical data of patients with and without delirium

Variables	No delirium N=46	Delirium N=19	F/X2/FEPT	df	p
Age (years)	79.7 (7.9)	84.5 (6.3)	5.57	1/63	0.021
Sex (female/male)	36/10	15/4	0.00	1	0.951
Education (years)	7.4 (5.7)	9.4 (6.4)	1.44	1/61	0.235
Duration surgery (minutes)	104.6 (42.8)	97.9 (29.9)	0.38	1/63	0.543
Blood loss during surgery (mL)	199.8 (110.8)	231.6 (138.7)	0.95	1.63	0.333
Diabetes mellitus (Yes/No)	37/7	16/3	-	-	1.0
Hypertension (Yes/No)	13/31	8/11	0.94	1	0.332
Cardiovascular disease (Yes/No)	31/13	13/6	0.03	1	0.872
Respiratory disease (Yes/No)	41/3	18/1	-	-	0.650
Chronic kidney disease (Yes/No)	36/8	17/2	-	-	0.709
Putative deliriogenic drugs (Yes/No)	28/18	12/7	0.03	1	0.863
Admit (Yes/No)	30/14	11/8	-	-	-
Psychiatric history (Yes/No)	37/9	17/2	-	-	0.486
Prior CNS disease (Yes/No)	36/10	7/12	10.30	1	0.001
Prior stroke (Yes/No)	42/4	12/7	7.58	1	0.006
Smoking (Yes/No)	45/1	18/1	0.08	-	0.512

Admit: prior inpatient admission within the past year; CNS disease: underlying central nervous system illnesses such as Parkinson's disease, stroke, traumatic brain injury, mild cognitive impairment, mild dementia; delirogenic drugs: tricyclic antidepressants, newer generation antidepressants, benzodiazepines, Z-drugs, opioid medications, anticholinergics, first generation antihistamines.

Table 2. Clinical differences between patients with and without delirium, results of Generalized Estimating Equations (GEE)

Variables	No delirium	Delirium	Delirium (df=1)	
			Wald	**p**
DRSR-98 [SC]	2.52 (0.24)	7.39 (1.04)	27.13	<0.001
Pain [SC]	2.61 (0.27)	2.33 (0.38)	0.34	0.563
SWC (0/1/>=2) [O]	108/69/3	25/22/17	14.18	<0.001
Being restrained [B]	175/5	62/14	10.27	0.001
Adapted RASS [SC]	0.027 (0.017)	0.591 (0.124)	21.06	<0.001

Results are shown as estimated marginal means (SE)

[SC, O, B]: type of GEE model. SC: scale regression (linear); O: ordinal regression; B: binary logistic. All GEE analyses are adjusted for age,

sex, and prior CNS disease.

DRS-R-98: Delirium Rating Scale, Revised-98; Pain: postoperative pain score; SWC: sleep-wake cycle disturbances; being Restrained:

necessity for postoperative restraint; RASS: Richmond Agitation-Sedation Scale

Table 3. Results of GEE analysis examining differences in biomarkers between hip fracture patients with and without delirium.

Variables	No delirium	Delirium	Delirium (df=1)	
			Wald	p
WBC (x10*3/ul)	9.66 (0.40)	9.22 (0.41)	0.57	0.450
Neutrophils (%)	77.40 (0.87)	82.37 (1.15)	11.92	0.001
Lymphocytes (%)	13.93 (0.70)	10.03 (0.86)	12.35	<0.001
NLR (z scores)	-0.291 (0.192)	0.672 (0.243)	9.58	0.002
Monocytes (%)	6.25 (0.21)	6.02 (0.50)	0.18	0.680
Eosinophils (%)	2.05 (0.23)	1.54 (0.32)	1.65	0.199
Basophils (%)	0.34 (0.03)	0.22 (0.02)	8.31	0.004
Platelets (x10*3/ul)	197.4 (10.8)	204.4 (24.4)	0.07	0.794
MPV (fl)	10.02 (0.17)	9.28 (0.28)	5.04	0.025
HCO3- (mmol/L)	27.61 (0.35)	27.10 (0.72)	0.41	0.523
pO2 (mmol/L)	89.1 (1.0)	93.1 (1.1)	7.09	0.008
pCO2 (mmHg)	40.12 (0.71)	39.95 (2.03)	0.01	0.935
pH	7.445 (0.005)	7.443 (0.007)	0.08	0.773

Results are shown as estimated marginal means (SE)

NLR: neutrophil / lymphocyte ratio (in z scores)

Table 4. Results of generalized estimating equation predicting delirium (CAM), being restrained (restrain), Delirium Rating Scale, revised-

98 (DRS), Richmond Agitation-Sedation Scale (RASS), Sleep-wake cycle disturbance scale of DRS-R-98 (SWC).

Dependent variables	Explanatory variables	B	SE	Wald	P (all df=1)
CAM #1	CNS disease	1.791	0.6804	6.93	0.008
	WBC	0.847	0.3040	7.76	0.005
	Neutrophils	1.123	0.2519	19.85	<0.001
	MPV	-0.857	0.3872	4.89	0.027
	Blood loss	0.705	0.2827	6.23	0.013
	Age	1.034	0.3695	7.83	0.005
CAM #2	CNS disease	1.794	0.7359	5.95	0.015
	pO2	0.634	0.2304	7.33	0.007
	SWC	1.183	0.2260	27.38	<0.001
	BMI	-1.264	0.3954	10.22	0.001
	Neutrophils	0.621	0.2837	4.78	0.029
Being restrained	Neutrophils	2.548	0.8444	9.10	0.003
	Lymphocytes	2.176	0.7930	7.45	0.006
DRS	Age	0.030	0.0054	34.09	<0.001
	CNS disease	0.301	0.1179	6.51	0.011
	Basophils	-0.114	0.0278	16.84	<0.001
	MPV	-0.098	0.0399	6.05	0.014
RASS	NLR	-0.030	0.0.133	5.00	0.025
RASS (all+)	HCO3-	-0.019	0.0086	5.04	0.025
	SWM	0.175	0.0510	11.80	0.001

CNS disease: underlying central nervous system illnesses such as Parkinson's disease, stroke, traumatic brain injury, mild cognitive impairment, mild dementia; BMI: Body Mass Index; WBC: white blood cells; MCV: Mean Corpuscular Volume; MPV: Mean Platelet Volume; HCO3-: Bicarbonate; NLR: Neutrophil-Lymphocyte ratio.