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▶ **To cite this version:**

Bastien Genet, Tina Lamy, Judith Cohen-Bittan, Pauline Glasman, Marc Verny, et al.. Lack of Association Between Perioperative Medication and Postoperative Delirium in Hip Fracture Patients in an Orthogeriatric Care Pathway. Journal of the American Medical Directors Association, 2021, S1525-8610 (21), pp.00857-4. 10.1016/j.jamda.2021.09.022 . hal-03385940

HAL Id: hal-03385940

https://hal.sorbonne-universite.fr/hal-03385940

Submitted on 19 Oct 2021

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Lack of association between perioperative medication and postoperative delirium in hip fracture patients in an orthogeriatric care pathway

Running title: Perioperative drugs and postoperative delirium

Bastien Genet MD [1], Tina Lamy MD [1], Judith Cohen-Bittan MD [1], Pauline Glasman MD [2], Marc Verny MD, PhD [1,3], Bruno Riou MD, PhD[4], Jacques Boddaert MD, PhD [1,5], Lorène Zerah MD, PhD [1,6]

1. Assistance Publique Hôpitaux de Paris (APHP), Hôpital la Pitié-Salpêtrière, Department of Geriatric medicine, Unit of Peri-Operative Geriatric care, Paris, France
2. Assistance Publique Hôpitaux de Paris (APHP), Hôpital la Pitié-Salpêtrière, Department of Anesthesiology and Critical Care, Paris, France
3. Sorbonne Université, UMR CNRS 8256, Team Neuronal Cell Biology & Pathology, Paris 75005, France
4. Sorbonne Université, UMRS INSERM 1166, IHU ICAN, APHP, Hôpital la Pitié-Salpêtrière, Department of Emergency Medicine and Surgery, Paris, 75013, France
5. Sorbonne Université, UMR INSERM 1135, Paris, 75013, France
6. Sorbonne Université, UMRS INSERM 1136, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, 75013, France

Correspondence to: Dr Bastien Genet

Assistance Publique Hôpitaux de Paris (APHP), Hôpital la Pitié-Salpêtrière, Department of Geriatric medicine, Unit of Peri-Operative Geriatric care, Paris, France. 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France

Mail: bastien.genet@aphp.fr

Tel: +33 1 42 16 41 17

Fax: +33 1 42 16 06 26

Keywords: postoperative delirium, hip surgery, perioperative drugs, orthogeriatric care, older person

Funding statement: This work was supported only by institutional sources

Word count: Abstract: N = 307, Text: N =2335, **references:** N = 37 **and graphics count:** Tables: N = 4, Figures: N = 1

Brief summary

- No significant association was found between therapeutics administered pre, intra and postoperatively and postoperative delirium.
- Efforts to reduce postoperative delirium should focus on patients at risk (advanced age, with dementia, depression, etc).

ACKNOWLEDGMENTS

- Laura Smales: English editing (BioMedEditing, Toronto, Canada)
- Sponsor's role: no sponsor's role

ABSTRACT

Objectives: Units for perioperative geriatric care are playing a growing role in the care of older patients after hip fracture surgery. Postoperative delirium is one of the most common complications after hip fracture, but no study has assessed the impact of therapeutics received during a dedicated orthogeriatric care pathway on the incidence of postoperative delirium. Our main objective was to assess the association between drugs used in emergency, operating and recovery departments and postoperative delirium during the acute stay.

Design: Retrospective cohort study

Setting and Participants: All patients ≥ 70 years old admitted for hip fracture to the emergency department and hospitalized in our unit for perioperative geriatric care after hip fracture surgery under general anesthesia between July 2009 to December 2019 in an academic hospital in Paris.

Methods: Demographic, clinical, biological data and all medications administered pre-, peri- and postoperatively were prospectively collected by 3 geriatricians. Postoperative delirium in the unit for perioperative geriatric care was assessed by using the confusion assessment method scale. Logistic regression analysis was used to assess variables independently associated with postoperative delirium in the unit for perioperative geriatric care.

Results: 490 patients were included (mean [SD] age 87 [6] years); 215 (44%) had postoperative delirium. The occurrence of postoperative delirium was not associated with therapeutics administered during the dedicated orthogeriatric care pathway. Probability of postoperative delirium was associated with advanced age (>90 years, odds ratio [OR] 2.03, 95% confidence interval [CI] [1.07 to 3.89], dementia (OR 3.51, 95% CI [2.14 to 5.82]), depression (OR 1.85, 95% CI [1.14 to 3.01]), and preoperative use of beta-blockers (OR 1.75, 95% CI [1.10 to 2.79]).

Conclusions and implications: No emergency or anesthetic drugs were significantly associated with postoperative delirium. Further studies are needed to demonstrate a possible causal link between preoperative use of beta-blockers and postoperative delirium.

INTRODUCTION

In older people, a common but avoidable complication in the first postoperative days after hip fracture surgery is postoperative delirium, characterized by an acute onset and fluctuating course of inattention and either disorganized thinking or altered level of consciousness. A specialized geriatric intervention can lead to a 30% reduction in risk of postoperative delirium[1–4]. Postoperative delirium, which is distressing to patients, family members and clinicians, is associated with poor cognitive and functional recovery, increased use of health care resources, and increased mortality [1,5]. The UK National Institute for Health and Care Excellence, American Geriatric Society, American College of Surgeons, and American Society of Anesthesiologists have all identified the prevention of postoperative delirium as a public health priority [1,3,5].

Risk factors for postoperative delirium can be classified by the timing of their occurrence, as pre-, intra-, and postoperative[1]. Advanced age, preoperative cognitive impairment and comorbidities are the most frequent preoperative recognized risk factors[1–3,5–7]. Postoperative risk factors include severe pain, chronic administration of benzodiazepine (or benzodiazepine withdrawal) and anticholinergic drugs, and several postoperative complications (i.e., atrial fibrillation, infectious diseases, and urinary retention)[1,5]. Intraoperative risk factors are debated; whether different regimens of anesthesia may affect postoperative delirium occurrence is unclear[1]. Beyond anesthesia, all therapeutics received pre- and postoperatively may represent additional postoperative delirium risk factors. Because dedicated orthogeriatric care pathways, including units for perioperative geriatric care, are playing a growing role for patients with hip fracture, one cannot consider postoperative delirium occurrence restricted to geriatric factors without considering management in other settings. However, to the best of our knowledge, no study has assessed the impact of all drugs used before, during, and after hip fracture surgery on postoperative delirium occurrence.

Our main objective was to assess the association between all drugs used in emergency, operating, and recovery departments in older people with hip fracture and the occurrence of in-hospital postoperative delirium during the acute stay in an unit for perioperative geriatric.

METHODS

The database was declared to the French National Commission on Computing and Liberty (CNIL) of the Assistance Publique-Hôpitaux de Paris (APHP) for this study (no. 20190822165316). This report follows the STROBE recommendations[8].

Study design, study setting and eligibility criteria

A retrospective cohort study was conducted in the unit for perioperative geriatric care of an academic hospital. The unit for perioperative geriatric care is part of a dedicated orthogeriatric care pathway including coordination between the department of emergency medicine and surgery, department of anesthesiology and critical care, department of orthopaedic surgery and the department of rehabilitation. This dedicated orthogeriatric care pathway is defined as 1) early alert from the emergency department (ED), 2) considering hip fracture as requiring surgery as soon as feasible (i.e., 24 hr/day), 3) rapid transfer to the unit for perioperative geriatric care after surgery, and 4) rapid transfer of stable patients to a dedicated rehabilitation unit[9,10].

The management strategy in this unit for perioperative geriatric care, previously described[10], focused on early mobilization with the aim of chair-sitting and walking within 24 and 48 hours after arrival respectively, pain management, the provision of air-filled mattresses for patients with pressure sores or a high risk of pressure sores, swallowing disorders detected using a systematic medical survey, detection of stool impaction and urinary retention using bedside ultrasound, correction of anemia with transfusion of packed red blood cells (usually

when the hemoglobin level was <8 $g.L^{-1}$), detection of delirium and malnutrition.

From July 2009 to December 2019, all consecutive patients with hip fracture admitted to the unit for perioperative geriatric care were evaluated for eligibility. Patients were included if they were ≥70 years old and their primary presentation was due to hip fracture (first hospitalization after surgery in the unit for perioperative geriatric care). We excluded patients with multiple or metastatic or periprosthetic fractures, patients with missing data (missing anesthesia records, missing data from the ED), patients with surgery under exclusive loco-regional anesthesia, and patients with delirium before surgery (in the ED). We excluded patients whose admission to the unit for perioperative geriatric care was > 24 hr after the operating room (due to in-hospital organizational reasons) because we could not to retrieve information about all the treatments they had received in orthopedics. Patients were followed until death or the end of hospitalization in the unit for perioperative geriatric care. Some patients had been included in previous studies[10–17].F

Outcomes

Our main outcome measure was the occurrence of in-hospital postoperative delirium during the acute stay in the unit for perioperative geriatric care, identified by using the confusion assessment method scale[2], assessed on arrival in the unit for perioperative geriatric care and then once a day consistently by one of 2 physicians (JCB, JB). To prevent and manage the postoperative delirium occurrence, we used the recommendations proposed by Inouye et al. (non-pharmacological and pharmacological acute treatment strategies) [2].

Data collection methods

Since the opening of unit for perioperative geriatric care in 2009, we have created a dedicated research database that is prospectively supplemented by 3 senior geriatricians (J.B.,

J.C.B., L.Z.), experts in orthogeriatric, and that integrates all the data from the orthogeriatric care pathway for each patient.

The following variables were collected prospectively by interviewing patients, their family members or their physicians and pharmacists during the hospital stay and were defined as baseline characteristics before hip fracture: age, sex, home or nursing home living conditions, walking ability, previous medical history including cognitive status and depression (with or without antidepressants), chronic medications, and type of fracture (radiological definition by an orthopedic surgeon). Co-morbidity severity was assessed with the Cumulative Illness Rating Scale[18], because all comorbidity scores are equivalent in predicting mortality in this population[13]. Functional status was evaluated with an activities of daily living scale[19]. Obesity was defined as body mass index > 30 $kg.m^2$, repeated falls as ≥ 2 falls in the previous year, chronic renal failure as Cockcroft creatinine clearance < 60 ml/min, and anemia as haemoglobin level < 12 $g.dL^{-1}$ for women and 13 $g.dL^{-1}$ for men.

During the perioperative period, we prospectively recorded the surgical treatment, the delay and duration of surgery, and the anesthetic drugs used. All drugs and transfusions administered from the ED to the unit for perioperative geriatric care were recorded, including those administered in the operating room and recovery room.

After surgery, delays to first sitting and first walking, destination at discharge of unit for perioperative geriatric care (home or rehabilitation) and length of stay in acute care were recorded. All postoperative complications during the acute care period were prospectively recorded.

Delirium in the ED was the only variable that was classified retrospectively, before any statistical analysis (exclusion criteria). It was adjudicated by 2 geriatricians (BG, LZ) who independently reviewed medical charts (K = 0.88, 95% CI [0.70 to 0.99]). In case of disagreement, consensus was reached with a third independent senior expert (JB).

Statistical considerations

The statistical plan of the study was established before the statistical analysis. Because the database was prospectively supplemented, all authors were "blinded" to the research question at the time of data collection. The study is based on all available patients during the study period, and thus no a priori power calculation was conducted. Data are presented as mean (SD) or median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. Comparison of quantitative variables involved unpaired Student *t* test or Mann-Whitney test depending on the normal distribution of data. Normality was assessed by graphical representation of the distribution. Comparison of categorical variables involved chi-square or Fisher's exact test, as appropriate.

Logistic regression analysis was used to assess variables independently associated with in-hospital postoperative delirium during the acute stay, and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated. To avoid overestimation, a conservative approach was used:[20,21] all variables with $P < .20$ on univariate analyses and all clinically relevant variables were included[1]. Correlation between continuous variables was considered significant with Spearman correlation coefficient >.50. The choice between 2 correlated variables was based on their respective clinical relevance.

We assessed missing data and their distribution between the 2 groups (with and without postoperative delirium). Because missing values represented < 3% of the data and were balanced between the 2 groups, no specific treatment strategy was necessary.

Statistical analyses were performed with R v4.0.0. All p-values were two-tailed and $p \leq .05$ was considered statistically significant.

RESULTS

Demographic data and patients baseline characteristics of patients

We included 490 patients **(Figure)**; 215 (44%) had postoperative delirium **(Table 1)**. Patients excluded (N = 775, 61%) had similar characteristics (demographics, comorbidities, in-hospital mortality, postoperative complications including delirium) as patients included (**Appendix 1)**.

Baseline characteristics are reported in **Table 1**. The mean (SD) age was 87 (6) years, 383 (78%) patients were female; the median Cumulative Illness Rating Scale score was 9 [IQR 6–12], median number of drugs per day was 5 [3–8], and 15% were living in a nursing home before the hip fracture. Patients with postoperative delirium were older, had more comorbidities (especially dementia), were less autonomous and more frequently lived in a nursing home than patients without postoperative delirium. They were more likely to use neurological medication, beta-blockers and angiotensin-converting enzyme–angiotensin II receptor blockers before surgery than patients without postoperative delirium (**Table 1**).

Patients with and without postoperative delirium did not differ in type of hip fracture or surgery. The median time to surgery was 24 hr [IQR 16-46] and was higher in patients with than without postoperative delirium (**Table 1**).

Main outcome and post-operative complications

On univariate analysis, 2 anesthetic drugs, etomidate and droperidol, were significantly used differently between patients with and without postoperative delirium (**Table 2**). The groups did not significantly differ regarding drugs prescribed in the ED, recovery room, or unit for perioperative geriatric care, with the exception of transfusion (more prevalent in patients with than without postoperative delirium). Anemia, stool impaction, bladder retention and infection were more frequent in patients with than without postoperative delirium (**Table 3**).

On multivariable logistic regression analysis, after controlling for potential confounders

(all variables detailed in **Table 4, Appendix 2**), no anesthetic drug use was associated with postoperative delirium. The factors associated with in-hospital postoperative delirium were advanced age, dementia, depression and preoperative use of beta-blockers (**Table 4**). Among the 145 patients with a medical history of depression, 76 (52%) were treated with antidepressant.

DISCUSSION

To the best of our knowledge, this is the first study considering the association between all therapeutics received during a dedicated orthogeriatric care pathway and in-hospital postoperative delirium after hip fracture surgery in a cohort of older patients. The incidence of postoperative delirium was high (44%), but no emergency or anesthetic drugs were significantly associated with postoperative delirium. Advanced age, dementia, depression and preoperative beta-blocker use were associated with postoperative delirium.

The wide variance in postoperative delirium incidence between our cohort and the literature[4,22] is probably a result of the considerable heterogeneity in definitions and methods used to identify postoperative delirium, the study populations, and the settings. By selecting only studies specific to older patients with hip fracture surgery [23–25], the incidences were comparable (30% to 42%).

We found no association between anesthetic drugs used and postoperative delirium despite potential pathophysiological hypotheses (gamma-aminobutyric acid activation[26,27], anticholinergic action[28]). Only one prospective observational study, analysing the incidence of emergence delirium after anesthesia, reported an association between etomidate and postoperative delirium (12.6% of patients receiving etomidate vs 3.8% receiving propofol, $p < .001$),[29] but patients were younger (mean age < 60 years) and were admitted for elective surgery. The most-described anesthetic predictor of postoperative delirium remains general

anesthesia regarding local anesthesia but is still debated[1,30]. All patients in this cohort had general anesthesia.

The preoperative risk factors we found (advanced age, dementia, depression) agreed with factors described in the literature[1,31–33]. Surprisingly, we found a significant association between preoperative use of beta-blockers and postoperative delirium. This association has never been observed in hip fracture surgery. Controversial data have been published for vascular and cardiologic surgeries[34]. In 582 patients (mean age 68 years) who underwent vascular surgical procedures, the postoperative delirium incidence was 26.5% in patients who received preoperative beta-blockers versus 17.4% in patients who did not ($p = .032$)[35]. Patients who started and did not start beta-blocker therapy postoperatively did not differ in incidence of postoperative delirium [35]. However, in 455 patients (mean age 66 years) undergoing cardiac surgery, the incidence of hypoactive presentation of postoperative delirium after cardiac surgery was decreased by > 3 times with preoperative beta-blockers ($p < .01$)[34]. This association could be due to 1) reduced cerebral perfusion pressure and potentially reduced cerebral oxygen supply[35], 2) an interaction with the beta-adrenoceptors and serotonin (5-HT) receptors[35,36], and 3) the abolishment of nocturnal secretion of melatonin[37].

Median length of stay was only one day longer in the group with postoperative delirium compared to patients without. Discharge to home can alleviate postoperative delirium. In the group with postoperative delirium, 25% lived in an institution before surgery, often because of preexisting neurocognitive disorders, and could therefore return “home” despite the delirium because of the medical and paramedical staff in these structures. Similarly, if the home environment allowed it, discharge home was also organized. This could explain why the median length of stay was close between the 2 groups.

Our study has several strengths. We included all consecutive patients ≥ 70 years old with hip fracture and excluded only patients with complicated fractures, which suggests that

our population was representative of most older patients with hip fracture. Second, outcomes were closely monitored by only 3 highly trained physicians who prospectively collected the data, which allowed for a homogeneous description of complications and particularly postoperative delirium. Lastly, we reported all treatments administered from the ED to discharge, which allowed for a precise analysis of the association between all therapeutics received during a dedicated orthogeriatric care pathway and the occurrence of postoperative delirium.

Our study has several limitations. First, it was an observational study, and causality cannot be demonstrated. Second, many patients had to be excluded because of missing anesthesia records or because of > 24 hr for transfer to the unit for perioperative geriatric care. However, these patients had the same characteristics as included patients. We excluded all patients with a diagnosis of delirium established in the ED before surgery to ensure as much as possible a temporal link between drugs received and postoperative delirium. Nevertheless, some forms of hypoactive delirium may not have been diagnosed in the ED and some patients could have been wrongly included. Third, we did not differentiate subtypes of postoperative delirium or severity and duration of delirium. Fourth, we had no data on the dosage or depth of anesthesia nor on hemodynamics recordings during surgery. Finally, our study was conducted in a highly specialized environment (department of emergency medicine and surgery, department of anesthesiology and critical care, department of orthopaedic surgery, unit for perioperative geriatric care and department of rehabilitation) because each step of care pathway may represent a new risk of delirium and our results may not be extrapolated to conventional or other orthogeriatric models previously reported. However, in outside institutions without a geriatric perioperative unit in a dedicated care pathway, previous studies have shown the benefit of one-off geriatric interventions in non-surgical conditions and the intervention of the orthogeriatrician in perioperative hip fracture conditions[38–40]. This is why we believe that

multimorbid older patients with hip fracture should be hospitalized in a geriatric environment and that an interdisciplinarity and pathway should be encouraged.

Our study has revealed several perspectives. One is the need for external validation using another cohort of multimorbid older patients (in particular, the association between preoperative use of beta-blockers and in-hospital postoperative delirium). However, only a randomized control trial could provide a definite demonstration of a causality link. Also, according to this study and the literature, patient characteristics and geriatric management seem to be the main factors associated with postoperative delirium occurrence after hip fracture surgery in older patients. Physicians and health policy decision-makers should focus actions to minimize risk of postoperative delirium on patients at risk (advanced age, with dementia, depression, etc.) and ensure that hip fracture prevention strategies are applied (physiotherapy, nutrition, antiosteoporosis treatment, etc).

CONCLUSION AND IMPLICATIONS

In a cohort of older patients with hip fracture managed in a dedicated orthogeriatric care pathway, we evaluated the incidence of postoperative delirium according to all therapeutics received. The incidence of postoperative delirium was high (44%), with no significant difference between patients with and without postoperative delirium regarding emergency or anesthetic drugs used. In contrast, probability of postoperative delirium was increased after hip fracture surgery for patients with advanced age, dementia or depression and using preoperative beta-blockers. Further studies are needed to demonstrate a possible causal link between preoperative use of beta-blockers and postoperative delirium.

Tables and Figures

Figure: Flow of participants in the study.

Table 1: Demographic data and baseline characteristics of older patients with and without postoperative delirium in the unit for perioperative geriatric care

Table 2: Perioperative drugs of older patients with and without postoperative delirium in the unit for perioperative geriatric care

Table 3: Postoperative complications of older patients with and without postoperative delirium in the unit for perioperative geriatric care

Table 4: Logistic regression analysis of factors associated with probability of in-hospital postoperative delirium during hospitalization in the unit for perioperative geriatric care

Appendices:

Appendix 1: Comparison between included and excluded patients in the perioperative geriatric unit

Appendix 2: Correlation matrices guiding variable selection for logistic regression

Competing interests: No conflict of interest to declare

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Table 1: Demographic data and baseline characteristics of older patients with and without postoperative delirium in the unit for perioperative geriatric care

	All patients N = 490	With delirium N = 215	Without delirium N = 275	p value
Age (years)	87 (6)	88 (6)	86 (6)	<.001
<85	155 (32)	50 (23)	105 (38)	<.001
85 to 90	203 (41)	93 (43)	110 (40)	
>90	132 (27)	72 (33)	60 (22)	
Sex				.99
Male	107 (22)	47 (22)	60 (22)	
Female	383 (78)	168 (78)	215 (78)	
Medical history				
CIRS	9 [6-12]	10 [6-13]	8 [6-11]	<.001
Dementia	186 (38)	128 (60)	58 (21)	<.001
Parkinson disease	24 (5)	15 (7)	9 (3)	.09
Depression	145 (30)	82 (38)	63 (23)	<.001
Stroke	75 (15)	35 (16)	40 (15)	.60
Hypertension	334 (68)	143 (67)	191 (69)	.49
Diabetes	66 (13)	30 (14)	36 (13)	.78
Obesity*	34 (7)	13 (6)	21 (8)	.49
Atrial fibrillation	127 (26)	60 (28)	67 (24)	.37
Coronary artery disease	83 (17)	41 (19)	42 (15)	.27
Cardiac failure	77 (16)	33 (15)	44 (16)	.84
Thromboembolic disease	39 (8)	18 (8)	21 (8)	.77
COPD	37 (8)	16 (7)	19 (7)	.83
Chronic renal failure†	328 (67)	158 (73)	170 (62)	.006
Cancer	99 (20)	42 (20)	57 (21)	.74
Number of drugs per day	5 [3-8]	5 [3-8]	5 [3-8]	<.001
Cardiovascular drugs				
Oral anticoagulant	86 (18)	36 (17)	50 (18)	.68
Platelet inhibitors	173 (35)	81 (38)	92 (33)	.33
Amiodarone	59 (12)	28 (13)	31 (11)	.55
Digoxin	9 (2)	4 (2)	5 (2)	.99
Beta-blocker	137 (28)	73 (34)	64 (23)	.01
ACE inhibitor or ARB	191 (39)	73 (34)	118 (43)	.04
Statin	117 (24)	51 (24)	66 (24)	.94
Calcium channel blockers	123 (25)	45 (21)	78 (28)	.06
Diuretic	138 (28)	55 (26)	83 (30)	.26
Neurologic drugs				
Cholinesterase inhibitor	35 (7)	25 (12)	10 (4)	<.001
Serotonin reuptake inhibitor	110 (22)	61 (28)	49 (18)	.008
Benzodiazepine	87 (18)	50 (23)	37 (13)	.007
Antipsychotic	23 (5)	16 (7)	7 (3)	.02
Autonomy before surgery				
ADL	5.5 [3.5-6]	5 [3-6]	6 [5-6]	<.001
Living in institution	75 (15)	53 (25)	22 (8)	<.001
Living at home with assistance	406 (83)	190 (88)	216 (79)	.004

Table 1 (Follow-up)

	All patients N = 490	With delirium N = 215	Without delirium N = 275	p value
Walking and falls				
Walking	478 (98)	206 (96)	272 (99)	.04
Walking with assistance	269 (55)	132 (61)	137 (50)	.01
Repeated falls‡	240 (49)	132 (61)	108 (39)	<.001
Missing values	*1*	*1*	*0*	
Biologic factors				
Albumin ($g.L^{-1}$)	29.4 (4.3)	29 (4.2)	29.7 (4.4)	.10
Missing values	*19*	*12*	*7*	
Haemoglobin < 10 g.dL-1 before surgery	33 (7)	10 (5)	23 (8)	.87
Missing values	*5*	*1*	*4*	
Fracture				
Intertrochanteric fracture	264 (54)	115 (53)	149 (54)	.88
Femoral neck fracture	224 (46)	99 (46)	125 (45)	.90
Surgery				
Time to surgery (hr)	24 [16-46]	27 [17-50.5]	24 [15-42]	.05
Time to surgery > 48 hr	104 (21)	56 (26)	48 (17)	.02
Duration of surgery (min)	135 (39)	134 (35)	135 (42)	.74
Time to UPOG (h)§	41.4 (27)	42 (29)	41 (25)	.70
Type of surgery				.36
Gamma nail	259 (53)	116 (54)	143 (52)	
Dynamic hip screw	25 (5)	8 (4)	17 (6)	
Unipolar prosthesis	190 (39)	86 (40)	104 (38)	
Bipolar prosthesis	9 (2)	2 (1)	7 (3)	

Data are mean ± SD, median (interquartile range), or number (percentage). Missing values are detailed only when they exist. ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blocker; CIRS: Cumulative Illness Rating Scale; COPD: chronic obstructive pulmonary disease; Chronic renal failure: creatinine clearance < 60 ml/min; Oral anticoagulant: vitamin K antagonists or direct oral anticoagulant. ADL: activities of daily living, UPOG: unit for perioperative geriatric care

*Obesity: body mass index > 30 $kg.m^2$

† Chronic renal failure: Cockcroft creatinine clearance < 60 ml/min

‡ Repeated falls: ≥ 2 falls in the previous year

§ Delay between emergency department and UPOG

Table 2: Perioperative drugs of older patients with and without postoperative delirium in the unit for perioperative geriatric care

	All patients N = 490	With delirium N = 215	Without delirium N = 275	p value	Missing data n (%)
EMERGENCY DEPARTMENT (ED)					
Paracetamol	197 (40)	85 (40)	112 (41)	.27	3 (0.6)
Tramadol	245 (50)	102 (47)	143 (52)	.30	3 (0.6)
Nefopam	45 (9)	23 (11)	22 (8)	.31	3 (0.6)
Morphine	165 (34)	68 (32)	97 (35)	.38	3 (0.6)
NSAIDs	2 (0)	1 (0)	1 (0)	.99	3 (0.6)
ANAESTHESIA					
Sufentanil	430 (88)	186 (87)	244 (89)	.47	2 (0.4)
Remifentanil	58 (12)	26 (12)	32 (12)	.87	2 (0.4)
Propofol	439 (90)	186 (87)	253 (92)	.07	1 (0.2)
Etomidate	103 (21)	54 (25)	49 (18)	.05	2 (0.4)
Sevoflurane	239 (49)	102 (47)	137 (50)	.84	31 (6.3)
Desflurane	83 (17)	32 (15)	51 (19)	.35	31 (6.3)
Ketamine	88 (18)	33 (15)	55 (20)	.18	2 (0.4)
Muscular relaxant	474 (97)	207 (96)	267 (97)	.95	2 (0.4)
Prostigmine	26 (5)	12 (6)	14 (5)	.81	4 (0.8)
Atropine	42 (9)	17 (8)	25 (9)	.66	3 (0.6)
Corticoids	280 (57)	122 (57)	158 (57)	.93	3 (0.6)
Droperidol	125 (26)	42 (20)	83 (30)	.008	3 (0.6)
Ondansetron	20 (4)	8 (4)	12 (4)	.82	3 (0.6)
All cardiovascular drugs	409 (83)	178 (83)	231 (84)	.90	8 (1.6)
Phenylephrine	130 (27)	54 (25)	76 (28)	.54	4 (0.8)
Ephedrine	327 (67)	141 (66)	186 (68)	.60	3 (0.6)
Norepinephrine	64 (13)	33 (15)	31 (11)	.18	1 (0.2)
Paracetamol	474 (97)	209 (97)	265 (96)	.34	3 (0.6)
Tramadol	222 (45)	90 (42)	132 (48)	.18	2 (0.4)
Nefopam	111 (23)	46 (21)	65 (24)	.56	2 (0.4)
Morphine	276 (56)	125 (58)	151 (55)	.42	3 (0.6)
NSAIDs	39 (8)	13 (6)	26 (9)	.18	3 (0.6)
Local anesthetics (femoral block)	123 (25)	101 (47)	122 (44)	.59	1 (0.2)
TRANSFUSION (ED + anaesthesia)					
RBC transfusion	63 (13)	40 (19)	23 (8)	<.001	1 (0.2)
Unit for perioperative geriatric care					
Paracetamol	456 (93)	199 (93)	257 (93)	.24	17 (3.5)
2nd-level analgesics	10 (2)	3 (1)	7 (3)	.53	17 (3.5)
Morphine	455 (93)	205 (95)	250 (91)	.06	0 (0)
RBC transfusion	175 (36)	82 (38)	93 (34)	.35	2 (0.4)
RBC transfusion (in all units)	238 (49)	121 (56)	117 (43)	.002	2 (0.4)
Total packed RBC per patient transfused*	2 [1-3]	2 [1-3]	2 [1-3]	<.001	1 (0.2)

Data are mean ± SD, median (interquartile range), or number (percentage).
NSAIDs = non-steroidal anti-inflammatory drugs; RBC = red blood cell; ED = emergency department
* with at least one transfusion

Table 3: Postoperative complications of older patients with and without postoperative delirium in the unit for perioperative geriatric care

	All patients N = 490	With delirium N = 215	Without delirium N = 275	p value
Anemia*	479 (98)	214 (99)	265 (96)	.03
Pain	473 (97)	210 (98)	263 (96)	.22
Stool impaction	239 (49)	125 (58)	114 (41)	<.001
Bladder retention	126 (26)	67 (31)	59 (21)	.01
Infection	79 (16)	44 (20)	35 (13)	.02
Acute heart failure	70 (14)	33 (15)	36 (13)	.48
Atrial fibrillation	48 (10)	23 (11)	25 (9)	.55
Acute coronary syndrome	46 (9)	22 (10)	24 (9)	.57
Pressure ulcer	37 (8)	19 (9)	18 (7)	.34
Thromboembolic disease	22 (4)	11 (5)	11 (4)	.55
Stroke	4 (1)	3 (1)	1 (0)	.21
In-hospital mortality				
In-hospital mortality	17 (3)	11 (5)	6 (2)	.08
LOS (days)	9 [7–13]	10 [7–13]	9 [7–13]	<.001
Time to first sitting (days)	1 [1–2]	1 [1–2]	1 [1–1]	<.001
Missing values	*2*	*1*	*1*	
Time to first walking (days)	2 [1–3]	2 [1–3]	2 [1–2.75]	<.001
Missing values	*24*	*9*	*15*	
At discharge				
Admission to rehabilitation care	385 (79)	156 (73)	229 (83)	.003
Return to home†	79 (16)	42 (20)	37 (13)	.07

Data are mean ± SD, median (interquartile range), or number (percentage). Missing values are detailed only when they exist.
LOS = length of hospital stay (in days)

* defined as haemoglobin level < 12 $g.dL^{-1}$ for women and 13 $g.dL^{-1}$ for men

† Institution was considered "home" in patients previously living in an institution

Table 4: Logistic regression analysis of factors associated with probability of in-hospital postoperative delirium during hospitalization in the unit for perioperative geriatric care

	Univariate analysis OR (95% CI)	P value	Multivariable analysis* OR (95% CI)	P value
ANAESTHESIA				
Propofol	0.58 (0.32 to 1.04)	.07	0.79 (0.34 to 1.81)	.58
Etomidate	1.55 (1.01 to 2.40)	.05	1.23 (0.65 to 2.35)	.52
Ketamine	0.73 (0.45 to 1.16)	.19	0.92 (0.50 to 1.66)	.78
Droperidol	0.57 (0.37 to 0.86)	.008	0.82 (0.49 to 1.37)	.45
Noradrenaline	1.44 (0.85 to 2.44)	.18	1.26 (0.66 to 2.40)	.48
Tramadol	0.78 (0.54 to 1.12)	.18	0.87 (0.55 to 1.38)	.56
NSAIDs	0.61 (0.30 to 1.21)	.17	0.78 (0.34 to 1.71)	.55
Unit for perioperative geriatric care				
Morphine	2.05 (0.99 to 4.57)	.06	1.81 (0.71 to 4.99)	.23
ALL UNITS				
Transfusion	1.75 (1.22 to 2.51)	.002	1.34 (0.85 to 2.12)	.21
OTHER PREDICTORS				
Age <85 years	1			
85-90 years	1.78 (1.15 to 2.76)	.01	1.69 (0.96 to 2.99)	.07
>90 years	2.52 (1.56 to 4.90)	<.001	**2.03 (1.07 to 3.89)**	**.03**
Male	1.00 (0.65 to 1.54)	.99	1.27 (0.73 to 2.19)	.40
Dementia	5.50 (3.72 to 8.24)	<.001	**3.51 (2.14 to 5.82)**	**<.001**
Parkinson disease	2.22 (0.97 to 5.37)	.07	1.77 (0.66 to 4.95)	.26
Depression	2.07 (1.40 to 3.08)	<.001	**1.85 (1.14 to 3.01)**	**.01**
Chronic renal failure	1.71 (1.53 to 2.16)	.007	0.97 (0.58 to 1.62)	.91
Beta-blockers	1.69 (1.14 to 2.53)	.009	**1.75 (1.10 to 2.79)**	**.02**
Benzodiazepine	1.95 (1.22 to 3.13)	.005	1.06 (0.60 to 1.90)	.83
Antipsychotic drugs	3.08 (1.29 to 8.14)	.02	1.63 (0.57 to 5.19)	.38
ADL (per 1-point increase)	0.67 (0.59 to 0.76)	<.001	0.87 (0.75 to 1.02)	.09
Albumin <30 g/L	1.33 (0.92 to 1.94)	.16	1.09 (0.71 to 1.69)	.68
Time to surgery > 48 hr	1.67 (1.08 to 2.58)	.02	1.27 (0.74 to 2.19)	.38
Duration of surgery (for 1 min)	1.00 (0.99 to 1.00)	.06	1.00 (0.71 to 4.99)	.82
Infection in UPOG	1.76 (1.09 to 2.88)	.02	1.12 (0.62 to 2.03)	.71
Bladder retention in UPOG	1.66 (1.10 to 2.50)	.02	1.56 (0.92 to 2.65)	.10
Stool impaction in UPOG	1.96 (1.37 to 2.82)	<.001	1.37 (0.85 to 2.23)	.20

Notes: N = 464

NSAIDs = non-steroidal anti-inflammatory drugs; ADL = activities of daily living; UPOG: unit for perioperative geriatric care

* Only significant ORs in the multivariate analysis are provided.

Appendix 1: Comparison between included and excluded patients in the perioperative geriatric unit

	All patients N = 1265	Included patients N = 490	Excluded patients N = 775	P Value
Age (years)	86 (6)	87 (6)	86 (6)	0.07
Men	302 (24)	107 (22)	195 (25)	0.20
Medical history				
CIRS	9 [6-12]	9 [6-12]	10 [7-12]	0.04
Dementia	501 (40)	186 (38)	315 (41)	0.32
Parkinson disease	71 (6)	24 (5)	47 (6)	0.37
Depression	378 (30)	145 (30)	233 (30)	0.84
Stroke	214 (17)	75 (15)	139 (18)	0.22
Hypertension	852 (67)	334 (68)	518 (67)	0.67
Diabetes	173 (14)	66 (13)	107 (14)	0.85
Obesity[1]	82 (6)	34 (7)	48 (6)	0.61
Atrial fibrillation	335 (26)	127 (26)	208 (27)	0.70
Coronary artery disease	221 (17)	83 (17)	138 (18)	0.68
Cardiac failure	205 (16)	77 (16)	128 (17)	0.69
Thromboembolic disease	91 (7)	39 (8)	52 (7)	0.41
COPD	100 (8)	35 (7)	65 (8)	0.42
Chronic renal failure[2]	772 (61)	328 (67)	444 (57)	<0.005
Cancer	282 (22)	99 (20)	183 (24)	0.15
Number of drugs per day	5 [3-8]	5 [3-8]	6 [3-8]	0.14
Autonomy before surgery				
ADL	6 [4-6]	6 [5-6]	6 [4-6]	0.09
Living in institution	178 (14)	75 (15)	103 (13)	0.32
Living at home with assistance	1054 (83)	406 (83)	648 (84)	0.65
Walking ability before surgery				
Walking	1226 (97)	478 (98)	748 (97)	0.42
Walking with assistance	728 (58)	269 (55)	459 (59)	0.11
Repeated falls[3]	610 (48)	241 (49)	369 (48)	0.66
Biologic factors				
Albumin (g/l)	28.6 (4.3)	29.4 (4.3)	28.1 (4.1)	<0.005
Haemoglobin < 10 g.dL-1 before surgery	1 (0.2)	1 (0.4)	0 (0)	0.28
Fractures				
Intertrochanteric fracture	625 (49)	264 (54)	361 (46)	0.02
Femoral neck fracture	562 (44)	224 (46)	338 (44)	0.55
Surgery				
Time to surgery (h)	40 (45)	36 (35)	43 (51)	0.01
Time to surgery > 48 hours	296 (24)	104 (21)	192 (25)	0.08
Duration of surgery (min)	140 (49)	134 (39)	144 (55)	0.001
Time to UPOG (h)	68 (94)	41 (27)	86 (115)	<0.001
Gamma nail	612 (49)	259 (53)	353 (46)	0.04
Dynamic hip screw	69 (6)	25 (5)	44 (6)	0.58
Unipolar prosthesis	480 (39)	190 (39)	290 (37)	0.93
Bipolar prosthesis	49 (4)	9 (2)	40 (5)	<0.001

Appendix 1 (Follow-up):

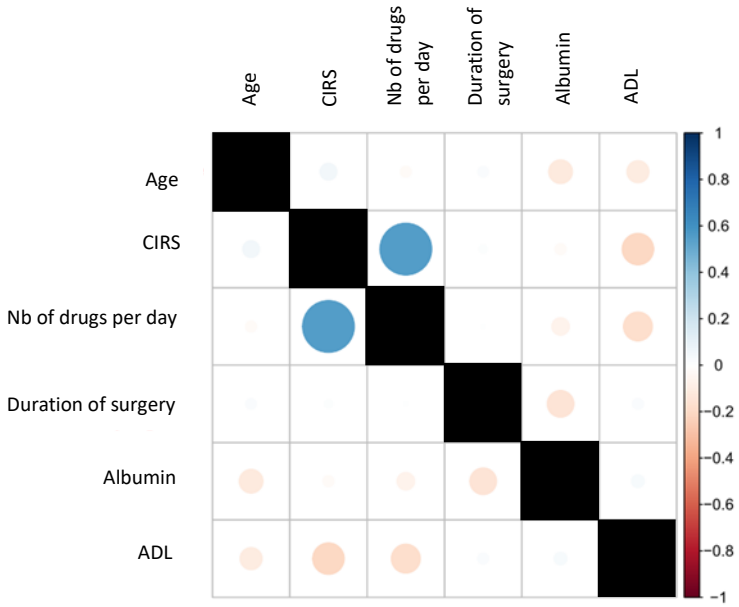
	All patients N = 1265	Included patients N= 490	Excluded patients N= 775	P Value
In hospital complications				
Postoperative delirium	530 (42)	215 (44)	315 (41)	0.27
Atrial fibrillation	102 (8)	48 (10)	54 (7)	0.07
Acute coronary syndrome	99 (8)	46 (9)	53 (7)	0.10
Infection	216 (17)	79 (16)	137 (18)	0.46
Bladder retention	332 (26)	126 (26)	206 (27)	0.71
Stool impaction	587 (46)	239 (49)	348 (45)	0.19
In-hospital mortality	37 (3)	75 (15)	103 (13)	0.36
LOS (days)	9 [7-13]	9 [7-13]	9 [7-13]	0.52
Admission to rehabilitation care	1009 (80)	385 (79)	624 (81)	0.40
Back home[4]	199 (16)	79 (16)	120 (15)	0.76

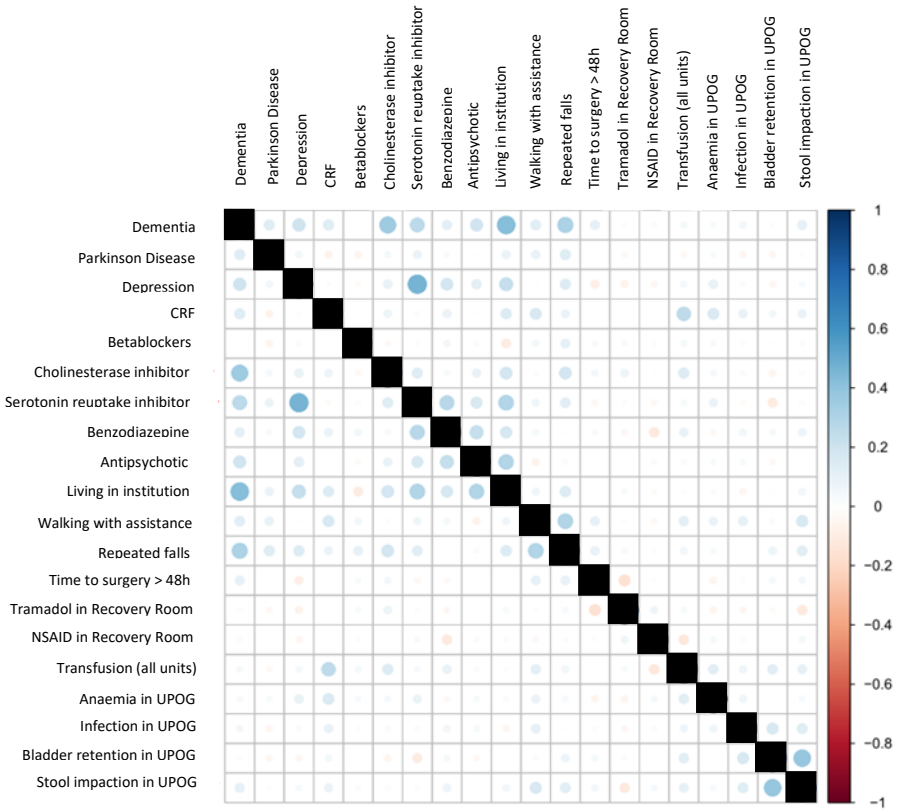
Data are mean ± SD, median (25–75 interquartile range), or number (percentage). Comparison between the two groups by t test or Mann-Whitney U test for quantitative variables and chi-square test or Fisher's exact test for qualitative variables.

[1]Obesity defined as body mass index>30 kg.m^2
[2] Repeated falls : ≥ 2 falls in the previous year
[3] Delay between emergency room and UPOG
[4] Institution was considered as ''home'' in patients previously living in an institution.

Abbreviations: CIRS: Cumulative Illness Rating Scale; COPD: Chronic Obstructive Pulmonary Disease; Chronic Renal Failure: creatinine clearance<60 ml/min. ADL: Activity of Daily Living; UPOG: Unit for Perioperative geriatric care; LOS: Length Of Stay

Appendix 2: Correlation matrices guiding variable selection for logistic regression





Variables selected with p<0.2 in univariate analysis (Table 1,2,3) and clinically relevant. Correlation coefficients calculated by Spearman method.

Abbreviations: NSAID: Non-Steroidal Anti-Inflammatory Drugs, CIRS = Cumulative Illness Rating Scale; CRF = Chronic Renal Failure (creatinine clearance<60 ml/min); UPOG: Unit for Perioperative geriatric care; NSAID: Non-Steroidal Anti-Inflammatory Drugs; Emergency Room = ER, Recovery Room = RR; LOS = Length Of Stay (in days). I- = inhibitor. RR = Recovery Room