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# Impact of intraoperative blood pressure, blood pressure fluctuation, and pulse pressure on postoperative delirium in elderly patients with hip fracture: A prospective cohort study

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ABSTRACT

*Aim:* Postoperative delirium (PD) is a frequent complication of hip fracture surgery, but its pathophysiology remains poorly understood. We investigated the impact of a single episode of intraoperative hyper/hypotension, blood pressure (BP) fluctuation (ΔMAP), and pulse pressure (PP) on hyper/hypoactive PD in elderly patients undergoing surgery for hip fracture. We also assessed the effect of PD on clinical outcomes.

*Methods:* This was a prospective 1-year follow-up study of patients over 60 years of age with a primary diagnosis of acute low-energy hip fracture. Perioperative delirium was assessed using the Confusion Assessment Method (CAM); the development of PD and the type, hyperactive or hypoactive PD, were recorded. Cognitive assessment was evaluated using the Short Portable Mental Status Questionnaire (SPMSQ). The lowest and highest BP values were extracted from the patients' anaesthesia charts. Postoperative complications, reinterventions and 1-month mortality were recorded.

*Results:* PD occurred in 148 (53%) patients during the first postoperative week, with 75% of the cases diagnosed as hypoactive PD. Patients developing PD of any type were older, had a lower body mass index, higher SPMSQ and Charlson scores, more severe systemic diseases, a lower lowest intraoperative BP, a higher ΔMAP, a lower PP, and a higher postoperative pain score. They also took more drugs and received more blood transfusion intraoperatively. Multivariate logistic regression analyses showed that a higher MAP min had a protective effect on the occurrence of any type of PD, as well as hypoactive and hyperactive. PD had negative effect on outcomes.

*Conclusion:* Our results provide evidence of an association between maximal hypotension, the lowest intraoperative mean blood pressure (MAP), ΔMAP, PP, and PD. A progressive decrease in MAP during surgery was associated with the increased odds of developing either type of PD.



## Introduction

Postoperative delirium (PD) occurs at a very high incidence (10–55%) among elderly patients following surgical treatment of hip fracture [1]. This potentially devastating complication carries a high risk for adverse outcomes and is associated with a longer hospital stay, further cognitive decline, high morbidity and mortality rates, and a prolonged return to mobility [1–5]. Although multiple studies have investigated the risk factors for PD associated with hip fracture surgery, the pathophysiology remains poorly understood [4,5]. One of the hypothesised mechanisms is a deficit in brain perfusion caused by intraoperative hypotension [6,7].

However, whether intraoperative blood pressure management should be included among the risk factors for a postoperative cognitive decline remains controversial [7,8,9,10]]. One large observational study recently showed a high prevalence of hypotension during hip fracture surgery, occurring in 66–85% of

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patients [8]. Other studies have suggested that intraoperative hypertension and the use of vasopressors are equally important in the occurrence of PD 10,11]. Thus, the relationship between intraoperative blood pressure control and PD is controversial [5,9,10]. Although blood pressure fluctuation is very common in elderly patients, little is known about its effect on PD in this population. In addition, a recent study showed a close relationship between a low pulse pressure (PP) and high cardiovascular mortality rates in patients with moderate to advanced heart failure; however, it has yet to be determined if PP is associated with PD in older hip-fracture patients. A possible strategy for preventing PD may be to optimise the intraoperative haemodynamic status such as by avoiding intraoperative hyper/hypotension, blood pressure fluctuation, or a low PP. According to the literature, PD most often develops on the second postoperative day (POD), which suggests a link between intraoperative haemodynamic events and PD during the early postoperative period. However, whether intraoperative hyper/hypotension, blood pressure fluctuations, and a low PP have prolonged effects on either type of PD is unknown. A literature review suggested that both patient-related (*e.g.*, age, comorbidities and preoperatively prescribed medications) and surgery-related (*e.g.*, type of anaesthesia, type of surgery, blood transfusion therapy and pain) factors can interfere with haemodynamic events during surgery and lead to PD [11–15].

We examined the effects of the lowest intraoperative MAP (MAP min), MAP fluctuations, and PP on the early (day 2) and late (day 7) incidence of hyper/hypoactive PD after hip fracture surgery in elderly patients. We also examined patient-related and perioperative factors, including type of anaesthesia, associated with PD. Furthermore, we analyzed whether development of PD affected clinical outcomes).

## Methods

This prospective cohort study was approved by the Ethics Committee of the Medical Faculty of Belgrade (No. 29/V-9). Patients with a primary diagnosis of acute low-energy hip fracture, age >60 years, and who were treated at a tertiary orthopaedic centre were screened for 1 year. Written informed consent was obtained from participants who met the inclusion criteria. Exclusion criteria were non-operative treatment, inability to participate in a face-to-face interview, severe cognitive disability, end-stage malignancy, and delirium symptoms on admission to the hospital.

### *Assessment*

#### *Preoperative evaluation*

Patients were preoperatively screened regarding their cognitive ability according to the 10-item Short Portable Mental Status Questionnaire (SPMSQ) [16]. Higher scores (0–10) are indicative of a worse cognitive function. The confusion assessment method (CAM) was used to screen for delirium preoperatively and during 7 days postoperatively [17]. It targets four features: 1) acute change in mental status with fluctuating course, 2) inattention, 3) disorganised thinking, and 4) altered level of consciousness. Delirium onset was defined at any point of hospitalisation when a patient exhibited features (1) and (2) or (3) or (4). Patients underwent delirium assessments multiple times a day by trained research nurses during their daily and nightly rounds. All records of delirium were validated by one investigator (KR). The type of delirium according to motor presentation (hyperactive or hypoactive) was also recorded. Patients with hypoactive delirium presented with decreased motor activity, unawareness, lethargy, and approaching stupor, and those with hyperactive delirium presented with agitation, hypervigilance, restlessness, and irritability [18,19]. Data on basic patient characteristics (age, body mass index [BMI] and type of fracture) were obtained from the patients' anaesthesia charts. The classification system of the American Association of Anesthesiologists (ASA) was used to assess physical status before surgery (1=healthy to 4=poor physical status) [20]. For the purpose of this study, two rating categories were used: 1 or 2, and 3 or 4. The comorbidity burden was defined by the Charlson Comorbidity Index score according to the presence of concurrent chronic diseases as recorded in the patients' medical charts [21]. The number of preoperatively prescribed medications was also determined from the medical charts. For the purpose of data analysis, the use of more than three medications preoperatively was defined as polypharmacy.

#### *Surgical and anaesthetic techniques*

Patients with femoral-neck fractures and trochanteric fractures underwent bipolar hemiarthroplasty and a compression hip screw procedure, respectively. Spinal or general anaesthesia was administered depending on the anaesthetist's preference. General anaesthesia was performed with propofol (1.2–2 mg/kg), fentanyl (3 μg/kg), and rocuronium bromide (0.6 mg/kg) induction to facilitate endotracheal intubation. Anaesthesia was maintained using sevoflurane combined with oxygen and air. Fentanyl boluses were used for general analgesia. Spinal anaesthesia was performed with a pencil-point needle (Becton, Dickinson and Company) placed at the L3–4 or L4–5 interspace using 0.5% isobaric bupivacaine in doses of 15 mg.

The vital signs monitored during surgery included heart rate, three-lead electrocardiography, pulse oximetry, non-invasive blood pressure, and end-tidal carbon dioxide. Blood pressure was monitored before anaesthesia induction and then every 5 min during the operation until the end of surgery. Systolic blood pressure (SBP), diastolic (DBP), and MAP were measured using oscillometry in 5-min intervals and recorded manually on an anaesthetic chart. PP was calculated as the difference between the SBP and DBP. The highest (PP 1), and lowest (PP 2) pulse pressures were extracted from the patients' anaesthesia charts. The highest (MAP max) and lowest (MAP min) MAP determined intraoperatively were recorded, and the difference between the two values was defined as the blood pressure fluctuation (ΔMAP). The volume of intraoperative blood transfusions and the duration of anaesthesia were also recorded.

#### *Postoperative evaluation*

Analgesic postoperative therapy was standardised based on the WHO's "analgesic ladder." Acute postoperative pain was assessed by trained nurses using a numeric pain scale (NPS) (0 = no pain, 10 = the most severe pain imaginable) within the first hour after arrival at the post-anaesthesia care unit [22]. An NPS cut-off $\geq$ 7 was considered severe postoperative pain, as previously described [22].

### *Outcomes*

The incidence of any, hypoactive, or hyperactive delirium during PODs 2 or 7 was the primary outcome.

#### *Secondary outcomes were: in-hospital acquired complications, reintervention, length of hospital stay (LOS) and 1-month mortality*

In-hospital acquired complications were: luxation of the hip prothesis, wound infection, urinary tract infection, acute renal failure, duodenal ulcer, hematemesis, diarrhea, colitis, melena, deep venous thrombosis, pulmonary embolism, myocardial infraction, pneumonia and sepsis.) Reintervention was defined

as a need for reoperation. LOS data were extracted from medical notes. The 1-month mortality rate was obtained through the contact with the responsible surgeon. As the number of reinterventions was small and forasmuch that patients were affected by significant surgical stress during reoperation, we analyzed reintervention and 1-month mortality after hip fracture together.

*Statistical analyses*

The arithmetic mean ± standard deviation or the median and range was used to describe the numerical data depending on the data distribution. Mathematical and graphical methods were used to test the criteria of a normal distribution. If the conditions of at least one mathematical and one graphical method were met, the data were considered normal. Categorical data are presented as absolute and relative numbers. A *t*-test or Mann–Whitney test was used to assess the differences in numerical data between groups, and a chi-square test was used for categorical data. Univariate and multivariate logistic regression analyses (enter method) adjusted for age, BMI, SPMSQ, ASA physical status, preoperative diagnosed hypertension, Charlson index, polypharmacy, type of operation, type of anaesthesia, PP1 and/or PP2, blood transfusion during surgery, duration of anaesthesia and NPS were applied to identify predictors of the event of interest (any type, hyperactive or hypoactive delirium). A p-value < 0.05 was considered statistically significant. The figures were constructed in STATA 13. The *x* axis was defined as MAP min, and the *y* axis was defined as the probability of any type, hyperactive or hypoactive PD. Kernel-weighted local polynomial regression was used to examine the relationship between MAP min and the probability of PD occurrence, any type or the hyperactive or hypoactive type.

In order to test the effect of delirium on outcomes, regression analyses were applied in two models: unadjusted and adjusted for age, gender, BMI, type of operation, type of anesthesia, Charlson index, MAPmax, MAPmin. For each model, categorical outcomes (postoperative complications and reinterventions plus 1-month mortality) were tested using logistic regression analysis. The continuous outcome LOS was assessed using linear regression analysis.

All analyses were performed using IBM SPSS ver. 21 software (IBM Corp., Armonk, NY, USA).

**Table 1**
Baseline characteristics of patients without, with any, hyperactive (type 1), and hypoactive (type 2) delirium after hip fracture surgery.

| Characteristics | Delirium | | | | | |
|---|---|---|---|---|---|---|
| | No n = 129 | Yes | | | | |
| | | Any type n = 148 | p[a] | Type 1 n = 37 | p[b] | Type 2 n = 111 | p[c] |
| Age, $\bar{x} \pm sd$ | 74.67 ± 8.11 | 80.95 ± 7.12 | **0.001** | 80.19 ± 8.28 | **0.001** | 81.20 ± 6.71 | **0.001** |
| BMI, n (%) | | | | | | | |
| <20 | 5 (3.9) | 22 (14.9) | **0.002** | 6 (16.2) | **0.050** | 16 (14.4) | **0.003** |
| 20-25 | 85 (65.9) | 102 (68.9) | | 23 (62.2) | | 79 (71.2) | |
| 26-30 | 29 (22.5) | 17 (11.5) | | 5 (13.5) | | 12 (10.8) | |
| >30 | 10 (7.8) | 7 (4.7) | | 3 (8.1) | | 4 (3.6) | |
| HTA preop, n (%) | 100 (77.5) | 115 (77.7) | 0.971 | 28 (75.7) | 0.814 | 87 (78.4) | 0.923 |
| SPMSQ, $\bar{x} \pm sd$ | 1.53 ± 0.64 | 2.86 ± 0.90 | **0.001** | 2.84 ± 0.83 | **0.001** | 2.86 ± 0.93 | **0.001** |
| ASA (3.4), n (%) | 91 (70.5) | 134 (90.5) | **0.001** | 32 (86.5) | 0.051 | 102 (91.9) | **0.001** |
| Polypharmacy, med (min-max) | 3 (0-7) | 4 (0-10) | **0.001** | 3 (0-7) | 0.114 | 4 (0-10) | **0.001** |
| Charlson score, $\bar{x} \pm sd$ | 5.15 ± 1.60 | 6.29 ± 1.42 | **0.001** | 6.26 ± 1.45 | **0.001** | 6.30 ± 1.42 | **0.001** |
| **Surgery factors** | | | | | | | |
| Type of surgery, n (%) | | | | | | | |
| ORIF[†] | 42 (32.6) | 49 (33.1) | 0.923 | 16 (43.2) | 0.229 | 33 (29.7) | 0.696 |
| Hemiratroplastika | 87 (67.4) | 99 (66.9) | | 21 (56.8) | | 78 (70.3) | |
| Type of anesthesia | | | | | | | |
| Total | 78 (60.5) | 78 (52.7) | 0.194 | 20 (54.1) | 0.485 | 58 (52.3) | 0.255 |
| Regional | 51 (39.5) | 70 (47.3) | | 17 (45.9) | | 53 (47.7) | |
| **Intraoperative hemodynamic** | | | | | | | |
| SBP max | 152.40 ± 20.53 | 151.01 ± 15.29 | 0.520 | 148 ± 13.46 | 0.218 | 151.8 ± 15.79 | 0.763 |
| DBP max | 90.47 ± 14.19 | 90 ± 7.74 | 0.731 | 89.14 ± 7.02 | 0.553 | 90.09 ± 7.92 | 0.730 |
| SBP min | 128.22 ± 13.21 | 122.26 ± 14.80 | **0.001** | 122.14 ± 13.79 | **0.015** | 121.98 ± 15.11 | **0.001** |
| DBP min | 78.91 ± 5.76 | 76.72 ± 7.93 | **0.010** | 77.71 ± 6.46 | 0.240 | 76.17 ± 8.09 | **0.002** |
| MAP max[‡], $\bar{x} \pm sd$ | 111.11 ± 15.50 | 110.34 ± 9.08 | 0.608 | 108.76 ± 8.37 | 0.361 | 110.66 ± 9.26 | 0.726 |
| MAP min[§], $\bar{x} \pm sd$ | 95.35 ± 7.41 | 91.68 ± 9.76 | **0.001** | 92.52 ± 7.50 | **0.038** | 91.44 ± 9.78 | **0.001** |
| ΔMAP[¶], med (min-max) | 13.3 (-6.67-106.67) | 16.67 (-1.67-56.67) | **0.007** | 16.67 (-1.67-33.33) | 0.253 | 16.67 (0-56.67) | **0.004** |
| PP1 med (min-max) | 60 (30-110) | 60 (30-110) | 0.478 | 60 (40-80) | 0.208 | 60 (30-110) | 0.796 |
| PP2 med (min-max) | 50 (20-80) | 45 (20-80) | **0.007** | 40 (10-70) | 0.053 | 45 (20-80) | **0.013** |
| Transfusion during surgery in ml, $\bar{x} \pm sd$ | 377.94 ± 147.61 | 437.08 ± 160.13 | **0.001** | 438.92 ± 177.65 | **0.008** | 436.47 ± 154.72 | **0.002** |
| Duration of anesthesia in min, $\bar{x} \pm sd$ | 92.21 ± 23.05 | 93.11 ± 23.37 | 0.748 | 100.00 ± 23.45 | 0.073 | 90.81 ± 22.99 | 0.601 |
| **Postoperative factor** | | | | | | | |
| NPS (≥7), n (%) | 11 (8.5) | 52 (35.1) | **0.001** | 15 (40.5) | **0.001** | 37 (33.3) | **0.001** |

SBP (systolic blood pressure).
DBP (diastolic blood pressure).
PP (pulse pressure).
PP1 (the maximum value of pulse pressure during operation).
PP2 (the minimum value of pulse pressure during operation).
[†] ORIF (open reduction and internal fixation).
[‡] MAP1 (the maximum value of mean arterial blood pressure during surgery).
[§] MAP2 (the minimum value of mean arterial blood pressure during surgery).
[¶] ΔMAP (MAP1-MAP2).
[a] Statistical significance for comparison between patients without and with any type of delirium.
[b] Statistical significance for comparison between patients without and with type 1 delirium.
[c] Statistical significance for comparison between patients without and with type 2 delirium.

## Results

During the 1-year study period, 346 patients presented at the Institute for Orthopaedic Surgery and Traumatology, Clinical Centre of Serbia, with an acute low-energy hip fracture. Of these, 59 (17%) patients did not meet the inclusion criteria for the following reasons: high operative risk (n = 14, 4%), inability to participate in a face-to-face interview (n = 8, 2%), end-stage malignancy (n = 5, 1%), or presence of delirium symptoms on admission to the hospital (n = 32, 9%). Ten patients were lost to follow-up, leaving 277 patients for analyses.

Incident delirium during the first postoperative week was present in 148 (53%) patients. Of these, 37 (25%) had symptoms of hyperactive and 111 (75%) had symptoms of hypoactive delirium. At POD 2, delirium was present in 97 (35%) patients. Of these, 17 (18%) had symptoms of hyperactive and 80 (82%) of hypoactive delirium. Descriptive characteristics and surgical factors were compared between the group of patients without delirium and with any type of delirium as well as with hyperactive *versus* hypoactive delirium (Table 1). Patients with any type of delirium were older ($p < 0.001$), had a lower BMI ($p = 0.002$), higher SPMSQ (cognitive decline) ($p < 0.001$), higher ASA physical score ($p < 0.001$), and higher Charlson score ($p < 0.001$), took more drugs ($p < 0.001$), received more blood transfusions during surgery ($p < 0.001$), and had a higher ΔMAP ($p = 0.007$) and higher NPS postoperatively ($p < 0.001$) than the group without delirium. In the group of patients with any type of delirium, SBP min, DBP min, MAP min, and PP2 were statistically lower than in those without delirium ($p = 0.001$, $p = 0.010$, $p = 0.001$, $p = 0.007$, respectively).

*We also analyzed whether MAP max and MAP min were different between the group of patients who received general and spinal anesthesia. There was no statistically significant difference between MAP max for each type of anesthesia (MAP max general vs. spinal anaesthesia 111.09 ± 13.37 vs. 110.19 ± 11.24 mmHg, t*-test $p = 0.554$). Patients who received general anesthesia had higher MAP min than patients who received spinal anesthesia (96.67 ± 6.55 mmHg vs. 89.43 ± 9.4 mmHg, *t*-test $p < 0.001$).

Patients with hyperactive delirium differed from those without delirium with regard to higher age ($p < 0.001$), lower BMI ($p = 0.050$), higher SPMSQ (cognitive decline) ($p < 0.001$), higher Charlson index ($p < 0.001$), lower SBP min ($p = 0.015$), lower MAP min ($p = 0.038$), more blood transfusions ($p = 0.008$), and more severe postoperative pain ($p < 0.001$). The same variables differed between patients with hypoactive delirium and those without delirium, but additional variables were also identified including higher ASA score (severe systemic diseases) ($p < 0.001$), polypharmacy ($p < 0.001$), lower DBP min ($p = 0.002$), higher Δ MAP ($p = 0.004$), and lower PP2 ($p = 0.013$).

After adjusting for age, BMI, SPMSQ, ASA physical status, preoperatively diagnosed hypertension, Charlson index, polypharmacy, type of operation, type of anaesthesia, PP1 and/or PP2, blood transfusion during surgery, duration of anaesthesia and NPS, multivariate logistic regression analyses showed that a higher MAP min had a protective effect on the occurrence of any type of delirium, both at POD 2 and POD 7 (odds ratio [OR] = 0.947, 95% confidence interval [CI] = 0.90–0.99, $p = 0.045$ at POD 2, and OR = 0.940; 95% CI = 0.89–0.99, $p = 0.015$ at POD 7). A higher MAP min had a protective effect on the occurrence of hyperactive delirium at POD 2 and POD 7 (OR = 0.834, 95% CI = 0.73–0.96, $p = 0.010$ at POD 2, and OR = 0.883; 95 CI = 0.80–0.97, $p = 0.010$ at POD 7). A higher MAP min also had a protective effect on the occurrence of hypoactive delirium, at both POD 2 (OR = 0.938; 95% CI = 0.89–0.99, $p = 0.021$) and POD 7 (OR = 0.921; 95% CI = 0.87–0.97, $p = 0.002$) (Table 2).

The probability of occurrence of any PD type, hyperactive PD, or hypoactive PD as a function of MAP min for 0, 1st and 2nd postoperative days was also examined. The risk for any type delirium was higher with a lower MAP min value progressively from around 80 mmHg until it reached a plateau at MAP min around 75 mmHg (Fig. 1). The risk for the hyperactive type of PD was mostly constant for all MAP min values except for MAP min values under 75 mmHg (Fig. 2). The probability of occurrence of the hypoactive form of delirium was higher progressively with a lower MAP min value from around 80 mmHg until it reached a plateau at a MAP min from around 75 mm Hg (Fig. 3). These results show that

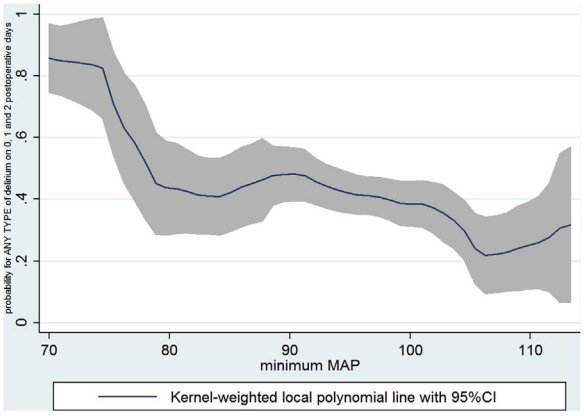


**Fig. 1.** The likelihood of occurrence of any type of delirium during 2 PODs in relationship to the minimum MAP.

**Table 2**
Haemodynamic predictors for **any type, type 1 (hyperactive), and type 2 (hypoactive) of postoperative delirium** after hip fracture (adjusted for age, BMI, SPMSQ, ASA physical status, preoperative diagnosed hypertension, Charlson index, polypharmacy, type of operation, type of anaesthesia, PP1 and/or PP2, blood transfusion during surgery, duration of anaesthesia, and NPS).

| TYPE OF DELIRIUM | Factor | 2 postoperative days | | | | One whole week | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | B | OR | 95%CI | p | B | OR | 95%CI | p |
| **ANY TYPE** | MAP max[a] | 0.003 | 1.003 | 0.97-1.03 | 0.830 | −0.007 | 0.993 | 0.96-1.02 | 0.645 |
| | MAP min[b] | **−0.055** | **0.947** | **0.90-0.99** | **0.045** | **−0.063** | **0.940** | **0.89-0.99** | **0.015** |
| | ΔMAP[c] | 0.014 | 1.014 | 0.98-1.04 | 0.365 | 0.008 | 1.008 | 0.98-1.04 | 0.588 |
| **TYPE 1** | MAP max[a] | −0.027 | 0.974 | 0.89-1.07 | 0.574 | −0.013 | 0.987 | 0.93-1.04 | 0.652 |
| | MAP min[b] | **−0.182** | **0.834** | **0.73-0.96** | **0.010** | **−0.125** | **0.883** | **0.80-0.97** | **0.010** |
| | ΔMAP[c] | 0.025 | 1.026 | 0.98-1.08 | 0.305 | 0.023 | 1.024 | 0.98-1.07 | 0.303 |
| **TYPE 2** | MAP max[a] | 0.005 | 1.005 | 0.97-1.04 | 0.761 | −0.008 | 0.992 | 0.96-1.02 | 0.619 |
| | MAP min[b] | **−0.064** | **0.938** | **0.89-0.99** | **0.021** | **−0.082** | **0.921** | **0.87-0.97** | **0.002** |
| | ΔMAP[c] | 0.014 | 1.014 | 0.99-1.04 | 0.324 | 0.012 | 1.012 | 0.98-1.04 | 0.418 |

[a] additional covariate is PP2 (because PP1 is in correlation with MAP1).
[b] additional covariate is PP1 (because PP2 is in correlation with MAP2).
[c] additional covariates are PP1 and PP2.

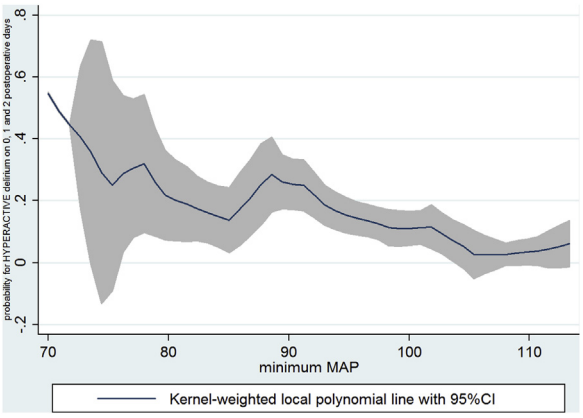


**Fig. 2.** The likelihood of occurrence of hyperactive type of delirium during 2 PODs in relationship to the minimum MAP.

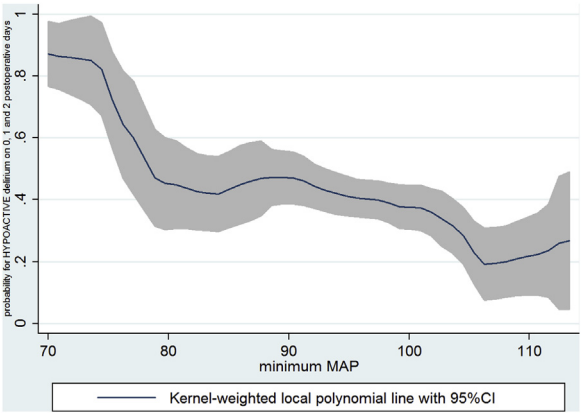


**Fig. 3.** The likelihood of occurrence of hypoactive type of delirium during 2 PODs in relationship to the minimum MAP.

the cut-off value for PD was a MAP min of about 80 mmHg; however, the exact point cannot be defined with certainty.

The effects of delirium on the outcomes (postoperative complications, reintervention plus mortality, and LOS) were analyzed in two models: unadjusted and adjusted for age, gender, BMI, type of operation, type of anesthesia, Charlson index, MAP max and MAP min (Table 3).

In unadjusted model we showed that patients with any type of delirium and patients with hypoactive type were at higher risk of postoperative complications (OR 4.73, 95% CI 2.79–8.04, P < 0.001, and OR 2.94, 95% CI 1.78–7.84, P < 0.001, respectively), reinterventions and death (OR 3.37, 95% CI 1.47–7.73, P = 0.004, and OR 2.53, 95% CI 1.23–5.23, P = 0.012, respectively) and a longer LOS (B = 5.759, 95% B 3.17–8.35, P < 0.001, and B = 4.174, 95% CI 1.49–6.86, P = 0.002, respectively). In adjusted model we showed that patients with any type of delirium and patients with hypoactive type were at higher risk of postoperative complications (OR 2.95, 95% CI 1.63–5.33, P < 0.001, and OR 2.94, 95% CI 1.78–7.84, P < 0.001, respectively) and a longer LOS (B = 5.194, 95% CI 2.25–8.14, P = 0.001, and B = 3.377, 95% CI 0.46–6.29, P = 0.023, respectively). Patients with hyperactive type of delirium were at higher risk for postoperative complications according to both models, unadjusted and adjusted (OR 2.86, 95% CI 1.37–5.95, P = 0.005, and OR 2.28, 95% OR 1.03–5.05, P = 0.043, respectively.

## Discussion

Our study showed a very high incidence of PD (53%), mostly of the hypoactive type (75%), after hip fracture surgery in elderly patients. The distribution of the incidence of PD according to motor type (hypoactive and hyperactive) was in accordance with the results in the literature [18,19,23]. Hypoactive PD is the most common PD subtype in elderly patients. Khurana et al. reported a high prevalence (65%) of the hypoactive form in elderly, delirious hospitalised patients [18]. This type of PD may be associated with a worse outcome, as determined in the study of Meagher et al., who reported that these patients are significantly more likely to die within 1 month of study entry [23].

Risk factors for any type of PD identified in our study were older age, low BMI, preoperative cognitive decline, higher Charlson index, polypharmacy, higher ASA score, low MAP, higher ΔMAP, greater need for blood transfusion and severe postoperative pain. These covariates have also been identified in other studies. For example, “frail elderly patients” with hip fracture tend to be vulnerable to surgery and to the risks of anaesthesia [13,14,24]. We have shown that type of anesthesia has no influence on PD. This finding is in line with the study of Neerland et al. [25]. Our study adds to the growing body of evidence that type of anesthesia does not increase delirium risk.

Our results showed that even the slight difference in MAP values between the group of patients without delirium and those with any type of delirium was significant. We also found that even a single hypotensive episode during hip fracture surgery can lead to PD in the early or late postoperative period. Thus, in clinical settings, changes in MAP in the vulnerable elderly and a single episode of hypotension during surgery should be interpreted as a warning sign for the development of PD.

Our results showed that patients with a lower SBP, DBP and PP2 during hip fracture surgery are at higher risk of developing any type of PD. Older individuals with increased vascular stiffness as the result of atherosclerosis usually have wider PP ranges. After the fifth decade of life, PP values markedly increase

**Table 3**
Multivariate logistic and linear regression analysis of predictors for delirium on clinical outcomes.

| Type of delirium | Outcomes | | |
|---|---|---|---|
| | Postoperative complications n = 112 | Reinterventions plus death n = 35 | Length of hospital stay (LOS) |
| Any | **1.555, 4.73, 2.79-8.04, <0.001**[a]**1.081, 2.95, 1.63-5.33, <0.001**[b] | **1.216, 3.37, 1.47-7.73, 0.004**[a]0.527, 1.77, 0.69-4.53, 0.233[b] | **5.759, 0.255, 3.17-8.35, <0.001**[a]**5.194, 0.230, 2.25-8.14, 0.001**[b] |
| Hyperactive type | **1.050, 2.86, 1.37-5.95, 0.005**[a]**0.823, 2.28, 1.03-5.05, 0.043**[b] | 0.418, 1.52, 0.58-3.97, 0.393[a]0.118, 1.13, 0.40-3.15, 0.821[b] | 3.447, 0.102, -0.55-7.45, 0.091[a]2.595, 0.077, -1.46-6.65, 0.209[b] |
| Hypoactive type | **1.077, 2.94, 1.78-7.84, <0.001**[a]**0.616, 1.85, 1.06-3.24, 0.031**[b] | **0.930, 2.53, 1.23-5.23, 0.012**[a]0.146, 1.52, 0.68-3.40, 0.312[b] | **4.174, 0.182, 1.49-6.86, 0.002**[a]**3.377, 0.147, 0.46-6.29, 0.023**[b] |

For postoperative complications and reinterventions plus death logistic regression was applied (B, OR, 95% CI for OR, and p are presented), whilst for LOS linear regression was used (B, beta, 95% CI for B, and p are presented).

[a] unadjusted model.

[b] adjusted model for age, gender, BMI, type of operation, type of anesthesia, Charlson index, MAPmax, MAPmin.

due to the decreased arterial compliance that occurs with increasing age. A recent study suggested that a lower PP is an independent predictor of a higher risk for cardiovascular mortality in patients with mild to advanced heart failure [26]. Several studies have suggested a positive and independent association between a low PP and a low left ventricular ejection fraction [27–29]. Voors and co-authors proposed that a low PP is indicative of decreased cardiac function [28]. To the best of our knowledge there have been no reports of the clinical use of PP as a predictor of PD. In our study population, most of the patients were classified as ASA 3 or 4, which suggests a high incidence of impaired cardiac function in elderly patients and therefore a low PP. A decreased cardiac function in the elderly may therefore contribute to low brain perfusion and thus PD occurrence. PP is easily calculated and enables the prediction of cardiovascular death but, as demonstrated in our study, it can also be used with equal reliability to predict PD occurrence in elderly patients undergoing hip fracture surgery.

Among the risk factors for PD are those that are patient-related, such as advanced age, low BMI, preoperative cognitive deficit, high Charlson index and polypharmacy, but also others, such as intraoperative blood pressure (MAP and PP) control, blood transfusion and postoperative pain management can be adjusted in-hospital and thus potentially prevented.

After adjusting for potential confounders, a higher MAP min was found to have a protective effect on the occurrence of any type of delirium, hyperactive PD and hypoactive PD, both on POD 2 and POD 7. However, on POD 2, perioperative factors were related to PD occurrence, and on POD 7, postoperative factors were related to factors such as long-lasting pain, immobilisation, unfamiliar surroundings, and infections. Our results suggest that a continuous increase in the odds of PD of any type, hyperactive or hypoactive type, is associated with an intraoperative decrease in the MAP to about 80 mmHg. As this value cannot be defined as hypotension, it suggests that our patients were mainly hypertensive and that their organs, including the brain, were perfused at a high BP, such that a pressure of 80 mmHg may effectively have been hypotension, which would have increased the probability of PD occurrence. Accordingly, the management of relative intraoperative hypotension may contribute to optimising cognitive function in elderly patients with surgery for hip fracture. However, our results remain to be confirmed in a study designed to optimise MAP perioperatively. Nonetheless, there is cause for concern as they suggest that even a single episode of hypotension increases the probability of PD.

While we were unable to determine a cut-off point of MAP during hip fracture surgery below which the probability of PD occurrence increased, a more pronounced reduction in MAP, to within the range of about 80 mmHg to 75 mmHg, was associated with a significantly higher risk for in-hospital PD. As discussed above, this can be explained by the excessive drop in blood pressure, resulting in an imbalance in cerebral autoregulation and cerebral perfusion, as reported in other studies [5,6]. Although the cerebral perfusion pressure threshold varies among individuals, higher MAP values during surgery may have a protective effect with respect to PD, such that an optimised haemodynamic balance is essential for cognitive function. Wang et al. also reported that patients with an average MAP of <80 mmHg, or MAP > 80 mmHg intraoperatively are at significantly greater risk for PD on POD 2 [12]. We also identified fluctuations in blood pressure during hip fracture surgery as a risk factor of PD, as reported by Hirsch et al [15]. The underlying causes for blood pressure fluctuation include factors already measured individually in this study including cardiovascular disease, diabetes, stress, pain, and anxiety. Because blood pressure fluctuations can be easily calculated, this parameter is a useful predictor of PD.

We have shown that PD is associated with adverse clinical outcomes. Patients with any type of delirium and with hypoactive type were at higher risk of occurrence of postoperative complications, reintervention plus death, and LOS in unadjusted and adjusted model while controlling for potentional confounders (age, gender, BMI, type of operation, type of anesthesia, Charlson index, MAP max, MAP min).

The current study suggests that intraoperative hypotension, defined as a low intraoperative MAP, is an independent predictor for any type, hyperactive and hypoactive PD. To the best of our knowledge, this is the first report on the independent risk factors for the different types of PD. According to our study and others in the literature, hypoactive PD is the more frequently occurring type of PD in elderly hospitalised patients. However, hypoactive PD can be difficult to recognise. According to our study, more perioperative factors contribute to hypoactive than to hyperactive delirium. Furthermore, our findings should stimulate further research on the different types of PD.

The strength of our study is its large and homogeneous cohort, representative of elderly patients with hip fracture, and the prospective follow-up of this population. Validated and highly sensitive and specific diagnostic tools were used to assess cognitive dysfunction. In addition, the results were interpreted while controlling for numerous confounding factors to avoid potential bias.

Nonetheless, there were also a few limitations. The results remain to be confirmed also in different patient populations and hospital setting. For example, compliance with anti-hypertensive therapy, the treatment of diabetes and the general physical activity level may be different in developed countries. However, the number of patients worldwide with a haemodynamic profile similar to that of our patients is likely to be large. In addition, we did not register the duration of hypotensive episodes or blood pressure in the post-anaesthesia care unit. These factors may have additionally contributed to the incidence, severity and duration of PD. Although our primary aim was to analyse the effects of intraoperative blood control on PD, the collection of postoperative data could have increased the significance of the results. While blood pressure fluctuation can be used in hospitals with modest resources, it can also be quantified by several dynamic parameters, including pulse pressure variation and stroke volume variation when mechanical ventilation is applied intraoperatively. However, these parameters are used to help determine the probability that hypotension will respond to fluid therapy and that was not the primary aim of our study. Because hypertension can also contribute to PD, its identification as a contributing factor to PD was not unexpected.

Spinal and general anaesthesia were administered in similar proportions in our patient population. Although MAP min was significantly lower during the spinal anaesthesia, type of anaesthesia had no effect on the incidence of PD in multivariate analysis.

We also did not have data on the duration or severity of PD. Instead, we focused on the PD subtype. Finally, only in-hospital outcomes were evaluated and the results do not provide insights into the association between intraoperative BP values and the long-term symptoms of delirium.

Our results indicate that higher minimum MAP values have a protective effect on the occurrence of hyperactive delirium on PODs 2 and 7. Intraoperative hypotension, MAP min, $\Delta$MAP, and a low PP were associated with PD, both during the early postoperative phase as well as 1 week postoperatively. A progressive decrease in MAP during surgery is associated with increased odds of a cognitive decline. Our findings suggest the negative effect of a single hypotensive episode during surgery on the risk for PD of any type, as well as hyperactive and hypoactive PD. Furthermore, we

showed negative independent effects of PD on postoperative clinical outcomes in elderly hip-fracture patients. Further studies are needed in different patients populations.

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