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Duration of Surgery and Intraoperative Blood Pressure Management Are Modifiable Risk Factors for Postoperative Neurocognitive Disorders After Spine Surgery

Results of the Prospective CONFESS Study

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Study Design. Prospective quasi-experimental observational study.

Objective. The objective of this study was to evaluate whether duration of surgery is a modifiable risk factor for postoperative delirium (POD) after spine surgery and explore further modifiable risk factors. In addition, we sought to investigate the association between POD and postoperative cognitive dysfunction and persistent neurocognitive disorders.

Summary of Background Data. Advances in spine surgery enable technically safe interventions in elderly patients with disabling spine disease. The occurrence of POD and delayed neurocognitive complications (*e.g.* postoperative cognitive dysfunction/persistent neurocognitive disorder) remain a concern since these contribute to inferior functional outcomes and long-term care dependency after spine surgery.

Materials and Methods. This prospective single-center study recruited patients aged 60 years or above and scheduled for elective spine surgery between February 2018 and March 2020. Functional (Barthel Index, BI) and cognitive outcomes [Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery; telephone Montréal Cognitive Assessment] were assessed at baseline, three (V3), and 12 months postoperatively. The primary hypothesis was that the duration of surgery predicts POD. Multivariable predictive models of POD included surgical and anesthesiological parameters.

Results. Twenty-two percent of patients developed POD (n = 22/99). In a multivariable model, duration of surgery [OR_{adj} = 1.61/h (95% CI, 1.20–2.30)], age [OR_{adj} = 1.22/yr (95% CI, 1.10–1.36)], and baseline deviations of intraoperative systolic blood pressure [25th percentile: OR_{adj} = 0.94/mm Hg (95% CI, 0.89–0.99); 90th percentile: OR_{adj} = 1.07/mm Hg (95% CI, 1.01–1.14)] were significantly associated with POD. Postoperative cognitive scores generally improved (V3, ΔCERAD total *z*-score: 0.22 ± 0.63). However, this positive group effect was counteracted by POD [beta: −0.87 (95% CI, −1.31 to 0.42)], older age [beta: −0.03/yr (95% CI, −0.05 to 0.01)], and lack of functional improvement [ΔBI; beta: −0.04/point (95% CI, −0.06 to 0.02)]. Cognitive scores at twelve months remained inferior in the POD group, adjusted for baseline cognition/age.

Conclusions. This study identified distinct neurocognitive effects after spine surgery, which are influenced by perioperative risk factors. Potential cognitive benefits are counteracted by POD, rendering its prevention critical in an aging population.

Key words: spine surgery, complications, demographic change, elderly patients, postoperative delirium, postoperative cognitive

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The proportion of people aged 65 years or above continues to increase at an unprecedented rate.[1] Degenerative spine disease affects about 31% to 36% of these elderly people and accounts for about 10% to 14% of their disability.[2] Advances in spine surgery enable technically safe interventions in patients of advanced age but cannot overcome concerns associated with perioperative neurocognitive disorders (pNCD).[3,4] Postoperative delirium (POD) is a serious pNCD that affects about 25% of patients undergoing noncardiac surgery and has a detrimental impact on functional recovery, complication rates, and health care costs.[5] Postoperative cognitive dysfunction (POCD) develops in about 30% to 50% of patients who endure neurocognitive symptoms for three months or more after surgery.[6] Symptoms persisting ≥12 months indicate a transition from postoperative to persistent neurocognitive disorders, including dementia.[4,7]

The risk of severe pNCD and the need for surgical interventions for spine disease are opposing challenges in an aging population. Precision medicine may alleviate this dilemma by enabling perioperative procedures adjusted to individual risk profiles.[8] Unfortunately, previous studies conducted in spine surgery could either not establish (modifiable) risk factors for POD and POCD, or were unable to disentangle their relationship.[9]

This prospective study aims to enhance the class of evidence concerning factors associated with pNCDs after spine surgery through an evaluation of the dose-response relationship between exposure and outcome, which enables inference of causation.[10,11] The primary hypothesis was that the duration of surgery (dose) is a predictor of POD (response), the confirmation of which could be immediately translated into clinical routine.[9] Further perioperative-/intraoperative parameters were investigated as secondary factors associated with POD in multivariable models.

MATERIALS AND METHODS

Study Registration and Ethical Considerations

This prospective single-center observational study trial was approved by the Institutional Review Board of the University of Greifswald (BB 192/17) and prospectively registered (clinicaltrials.gov, NCT03486288).

Setting and Participants

Patients were recruited through the outpatient clinic of the Department of Neurosurgery at a tertiary care hospital from February 2018 and March 2020, when recruitment stopped due to the triage of nonemergent surgical procedures during the SARS-CoV-2 pandemic.[12] The main inclusion criteria were age 60 years or above and elective spine surgery without opening the dura. Exclusion criteria were any history of neurodegenerative (*e.g.* movement disorders such as Parkinson disease, dementia) or psychiatric disease (*e.g.* depression, anxiety, personality disorders), electronic or displaceable metallic implants, or active neoplasms. Patients taking central nervous system-active medication (*e.g.* antidepressants, antipsychotics, anxiolytics, or tranquilizers) were also excluded. Medication used to treat pain but established to potentially exhibit minor central nervous system effects (*e.g.* gabapentin and tizanidine) was permitted.

Study Design and Delirium Assessment

All patients underwent baseline assessments of their sociodemographic characteristics, medical history, cognitive abilities, pain, quality of life (QoL), frailty and activities of daily living (ADL) prior surgery (V0; Table 1). The perioperative period (V1) included detailed records of vital parameters and anesthesiologic and surgical procedures. The postoperative period (V2) consisted of daily pain and mobility assessments and delirium assessments three times daily (Nursing Delirium Screening Scale, cutoff ≥2; confirmation using *DSM-5* criteria).[13] Cognitive abilities were assessed three (V3, POCD) and twelve months (V4, persistent NCD) postoperatively. QoL and ADL were additionally investigated at V3, which was embedded in a routine follow-up visit at the outpatient clinic of the Department of Neurosurgery. V4 was conducted remotely to reduce the risk of loss to follow-up.

Assessment of Secondary Parameters

Sociodemographic characteristics, substance use, medication, and medical history were recorded as suggested.[14] Disease-specific QoL was assessed using the Oswestry disability index (ODI), frailty through the Groningen frailty indicator, ADL using the Barthel index (BI) and pain using the critical care pain observation tool (CPOT).[15–17] Cognitive abilities were evaluated at baseline and three months postoperatively using the Consortium to Establish a Registry for Alzheimer's Disease Plus test battery (CERAD-NP, summarized in Table 4).[18] There is a substantial one-month within-subject test-retest reliability ($r = 0.85$–0.87) of the CERAD-NP total score (TS; mean z-score of all domains) supporting its repeated use in this study.[19] Cognitive assessments at V4 were conducted using the telephone variant of the Montréal Cognitive Assessment (tMoCA).[20]

Routine Surgical Procedures

Surgical and anesthesiologic procedures adhered to national clinical guidelines and in-house standard operating procedures. Anesthesia started with oral premedication with midazolam (0.1 $mg*kg^{-1}$), if preoperative excitement was present and was induced by intravenous injection of sufentanyl (0.3–0.6 $mg*kg^{-1}$) and propofol (1.5–2.5 $mg*kg^{-1}$). Muscular relaxation was performed by intravenous injection of cisatracurium (1.5 $mg*kg^{-1}$). Procedures were categorized by the amount of spine levels and type of intervention. Anesthesia

TABLE 1. Summary of the Recruitment Process and Visit Plan

		Study period								
	Enrolment	preoperative (V0)	intraoperative (V1)	Postoperative (V2.1, V2.2, etc.)					3-mo follow-up (V3)	1-yr follow-up (V4)
Time point		**−7d ± 7**	**0**	**1d**	**2d**	**3d**	**4d**	***etc.***	**90d ± 14**	**360d ± 14**
Eligibility screen	X	—	—	—	—	—	—	—	—	—
Informed consent	X	—	—	—	—	—	—	—	—	—
Demographic data	—	X	—	—	—	—	—	—	—	—
Medical history	—	X	—	—	—	—	—	—	X	X
Cognitive testing	—	X	—	—	—	—	—	—	X	X
Activities of daily living		X	—	—	—	—	—	—	X	—
Frailty	—	X	—	—	—	—	—	—	—	—
Quality of life	—	X	—	—	—	—	—	—	X	—
Vital parameters	—	—	X	—	—	—	—	—	—	—
Delirium screening	—	X	—	X	X	X	X*	X*	—	—
Medication	—	X	X	X	X	X	X*	X*	X	X
Pain	—	X	—	X	X	X	X*	X*	—	—
Mobilization	—	—	—	X	X	X	X*	X*	—	—

Study visits V0-V4 had to be completed by all participants. V2 included compulsory examinations for the first three days, which were discontinued if the patients did not develop POD.[17]

**Examinations were otherwise continued until POD ended or the patient was discharged.*

TABLE 2. Summary of the Sociodemographic Characteristics and Medical History of the Study Population

	Unit/category	Patients with data at V0-V2 n = 99	Patients with data at V0-V3 n = 57	Patients with data at V0-V4 n = 41	Statistical difference between visits *P*	
					V0 *vs.* V3	V0 *vs.* V4
Age	Years	71.3 ± 7.0	70.3 ± 7.0	72.2 ± 6.7	0.57	0.80
Sex	Male/female	50/49	28/29	24/27	0.67	0.58
Education*	None	5	1	1	0.74	0.40
	Primary school	20	9	8	—	—
	Junior high school	50	33	22	—	—
	High school	16	9	6	—	—
Graduation*	None	6	3	1	0.91	0.43
	Vocational training	67	38	27	—	—
	College/university	7	5	4	—	—
Work status*	Employed	11	8	4	0.95	0.94
	Unemployed	0	0	0	—	—
	Sick leave	2	1	1	—	—
	Disabled	4	2	1	—	—
	Retired	81	45	35	—	—
No. medication taken	—	6.2 ± 4.5	6.9 ± 5.1	6.9 ± 4.4	0.72	0.74
No. diagnoses	—	4.1 ± 2.7	4.3 ± 2.8	4.4 ± 2.5	0.98	0.97
Oswestry disability index	—	40.7 ± 16.3	44.2 ± 16.7	38.6 ± 15.3	0.45	0.97
Barthel index	—	92.4 ± 15.9	91.7 ± 14.5	92.1 ± 16.3	0.82	0.99
Groningen frailty index	—	3.7 ± 2.2	4.1 ± 2.4	3.4 ± 1.9	0.21	0.49

Since there was a substantial drop-out from the inpatient to the follow-up periods, we explored whether patient samples differed at visits, which was not the case.
**Single questions may have been left unanswered by participants, thus the sum of answers may be lower than the sample size.*

was maintained with sevoflurane at a target alveolar concentration of 0.8–1.0× MAC. Blood pressure (BP) was assessed noninvasively every five minutes unless invasive measurement was indicated. Mean values obtained 30 minutes before surgery were considered baseline systolic/diastolic BP. Peaks and troughs of intraoperative BP were quantified by calculating quantiles (10th, 25th, 50th, 75th, and 90th). Hypotensive situations were managed through fluid challenges and continuous medication with norepinephrine at discretion of the anesthesiologist in charge.

Sample Size Considerations and Statistics

Statistical evaluations were performed using MATLAB 2018a (The MathWorks Inc., Natick, USA) and SPSS (v28, IBM, Armonk). The simulation based on published effects sizes [OR = 1.47/h (95% CI, 1.15–1.79), reviewed in[9]] yielded a sample size of n = 200 (10% drop-out rate; power: 80%, $P = 0.05$) was required to test the primary hypothesis that the duration of surgery influences POD. Prespecified secondary analyses included the assessment of sociodemographic characteristics, functional abilities, and perioperative (surgical, anesthesiologic) parameters as factors associated with POD in a generalized linear model (GLM, logit linking function, main effects). A stepwise backward approach based on the Akaike information criterion was used to estimate the best set of influential factors.[21] Prespecified secondary analyses furthermore concerned factors associated with POCD, that is, CERAD-NP TS changes. The GLM (identity linking function and main effects) included POD incidence, sociodemographic characteristics, and changes of functional abilities as initial set of predictors, which was again optimized based on the Akaike information criterion. Paired (CERAD-NP subscales) and unpaired (tMOCA) *t* tests were done for detailed exploratory analyses of postoperative cognitive changes.

RESULTS

Patient Population, Baseline Characteristics, Surgical Intervention, and Outcomes

We screened 565 patients for eligibility, and 124 patients consented to participate in the study. Twenty-five patients withdrew their consent, or their intervention was cancelled. The remaining 99 patients completed baseline examinations

TABLE 3. Summary of the Surgical Characteristics of the Study Population

	Unit/category	Patients with data at V0-V2 n = 99	Patients with data at V0-V3 n = 57	Patients with data at V0-V4 n = 41	Statistical difference between visits *P*	
					V0-V2 *vs.* V0-V3	V0-V2 *vs.* V0-V4
Surgical time	Minutes	192.7 ± 110.7	169.6 ± 94.5	171.4 ± 84.0	0.20	0.22
Surgical type	Lumbar fusion	47	30	23	0.48	0.93
	Lumbar decompression and fusion	32	16	10	—	—
	Cervical decompression and fusion (ventral)	8	6	4	—	—
	Cervical decompression and fusion	4	2	1	—	—
	Kyphoplasty	2	1	1	—	—
	Other	6	2	2	—	—
Surgical complexity	Simple	42	26	18	0.41	0.89
	Intermediate	41	23	18	—	—
	Complex	16	8	3	—	—
Surgical levels	—	1.8 ± 1.2	2.4 ± 1.2	1.7 ± 1.0	< 0.01	0.43
Blood volume in	Milliliter	74 ± 285	57 ± 287	3 ± 22	0.74	0.10
Blood volume out	Milliliter	397 ± 482	289 ± 406	346 ± 482	0.24	0.59
Fluid in	Milliliter	2572 ± 1363	2147 ± 1087	2282 ± 1097	0.06	0.19
Fluid out	Milliliter	231 ± 364	159 ± 293	126 ± 231	0.32	0.14
Fluid balance	Milliliter	2018 ± 802	1756 ± 675	1813 ± 406	0.06	0.23

In line with Table 2, we again explored whether patient samples differed at visits. There were no significant differences between the samples except for more extensive surgery in patients that presented at the three-month outpatient follow-up, i.e. with data from V0-V3, as compared with all initially participating patients, i.e. from V0-V2. Although we did not expect such a substantial drop-out rate, it is plausible that patients with more extensive surgery were more likely to present to their follow-up appointment.

and the postoperative in-hospital period (V0-V2). Three-month follow-up outpatient visits (V3) were scheduled for all but one patient who died during the in-hospital period. There were 57 patients with complete data sets from V0-V3 and 41 patients with complete data sets from V0-V4 available for paired within-subject evaluations. Tabular overviews and comparisons of baseline sociodemographic, medical, and surgical characteristics of these sub-populations are provided in Tables 2 and 3.

Surgical outcomes were generally favorable. The ODI significantly improved from V0 (44.2 ± 16.7) to V3 (23.6 ± 18.0, $P < 0.01$). The BI also improved slightly from V0 (91.7 ± 14.5) to V3 (92.8 ± 13.3), but this was not significant ($P = 0.34$).

Postoperative Delirium

POD occurred in 22% of patients (n = 22/99). Patients with POD were significantly older (75.9 ± 5.4 *vs.* 70.0 ± 6.9 years, $P < 0.01$) but did not differ with respect to sex ($P = 0.51$) or premedication with benzodiazepines ($P = 1.0$). We confirmed the primary hypotheses and found that the POD group underwent significantly longer surgery than patients without delirium (247 ± 120 *vs.* 176 ± 103 min, $P < 0.01$). Multiple logistic regression confirmed duration of surgery as independent factor [$OR_{adj} = 1.61$/h (95% CI, 1.20–2.30), $P < 0.01$] adjusted for age [$OR_{adj} = 1.17$/y (95% CI, 1.06–1.18), $P < 0.01$; illustrated in Figure 1]. We furthermore investigated the impact of other predefined sociodemographic, anesthesiological or surgical characteristics on the incidence of POD. The number of prior medical diagnoses was not a significant factor following multivariable analysis adjusted for age [$OR_{adj} = 1.15$ (95% CI, 0.95–1.39), $P = 0.14$]. Neither Groningen frailty indicator, ODI, BI, sex, educational or work status, prior amount of alcohol consumption or smoking, type of surgery, nor intraoperative fluid or blood turnover, blood oxygenation, temperature, or heart frequency were factors associated with POD (all $P > 0.05$). Stepwise backward optimization of the GLM; however, identified the change of systolic BP in relation to the preoperative period (ΔsBP) as significant. Adjusted for age and duration of surgery, increasing lowest (25th percentile) ΔsBP values was protective [$OR_{adj} = 0.94$/mm Hg (95% CI, 0.89–0.99), $P = 0.03$] while

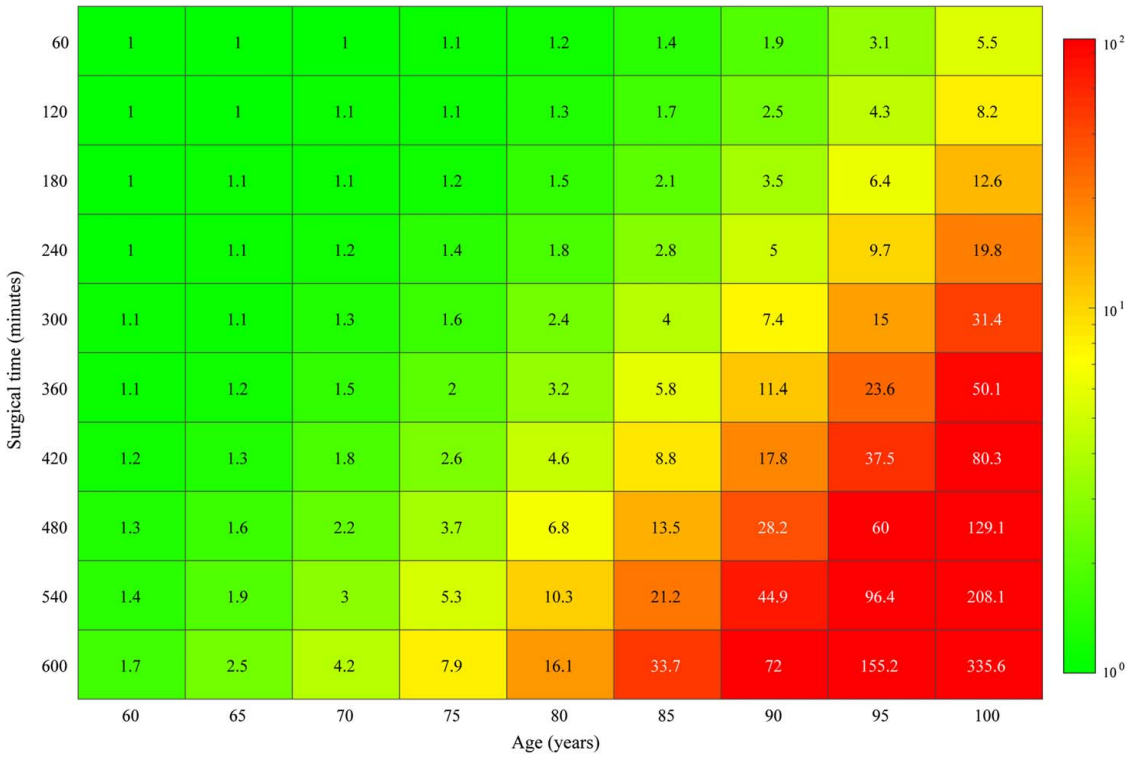

Figure 1. Illustration of how the ORs for developing POD change with age and duration of surgery, which was the primary hypothesis. The odds for a patient being 60 years of age and undergoing surgery for about 60 minutes were defined as baseline, *i.e.* OR = 1. One can see that the risk for a 60-year-old patient being exposed to 600 minutes of surgery equals the risk of a 85-year-old patient undergoing 120 minutes of surgery (both OR = 1.7). The risk increases exponentially with age and duration of surgery.

increasing highest (90th percentile) ΔsBP values increased the odds of POD [OR_{adj} = 1.07/mm Hg (95% CI, 1.01–1.14), $P = 0.01$]. This interplay of age, duration of surgery, and sBP management is illustrated in Figure 2.

Postoperative Cognitive Dysfunction

CERAD-NP TS results (V0: 0.03 ± 0.85, V3: 0.24 ± 0.73, $P = 0.02$) indicated postoperative cognitive improvement (POCI) on a group level. The results of CERAD-NP subscales are summarized in Table 4. Subgroup analyses revealed that POCI was carried by patients that were not delirious (V3 *vs.* V0: +0.30 ± 0.65, $P = 0.02$) while delirious patients did not show any change (V3 *vs.* V0: −0.28 ± 0.87, $P = 0.72$). Since delirious (del+) patients were significantly older than nondelirious (del-) patients (del+: 77.9 ± 6.7 years, del−: 69.4 ± 6.4 yr, $P < 0.01$), we were interested if age-adjusted changes of cognitive scores would differ. Having adjusted for age, nondelirious patients showed no change of cognitive abilities while delirious patients performed significantly worse (V3 *vs.* V0: −0.44 ± 0.86, $P < 0.01$). We were furthermore interested whether postoperative changes of functional abilities (ΔBI) or QoL (ΔODI) would explain POCI on a group level. GLMs adjusted for age and POD revealed that changes of the BI [beta: +0.04 (95% CI, 0.02–0.06)] but not ODI were associated with postoperative CERAD-NP TS. Associations of POD [beta: −0.87 (95% CI, −1.31 to 0.42)] and changes of BI [beta: 0.02 (95% CI, 0.00–0.03)] remained significant even when adjusted for preoperative cognition and age (Figure 3).

Exploratory Analysis of Persistent NCD

Cognitive abilities were assessed in 41 patients 12 months postoperatively and again revealed a significant difference between patients without (n = 33) and with (n = 8) POD (tMoCA Score, del+: 16.8 ± 3.1, del−: 18.5 ± 2.1, $P = 0.03$). These findings remained significant when adjusted for preoperative cognitive function and age ($P < 0.01$) (Figure 4).

DISCUSSION

This prospective study provides evidence that the duration of surgery and intraoperative BP management as modifiable factors associated with the development of POD after spine surgery. Given that even one episode of POD independently influenced postoperative cognitive performance, even when adjusted for preoperative performance, measures to prevent POD are of utmost clinical relevance. Of note, functional improvement after surgery counteracted negative effects of age and POD on cognitive scores in a multivariable model.

Postoperative outcome with regard to functional improvement of gait and pain are in general estimated by the treating physician and discussed with the patient accordingly. Patients should be informed with similar rigor regarding their risk for pNCDs and its consequences. Unanimous risk factors for the development of POD in spine surgery, however, remain elusive so far. We found

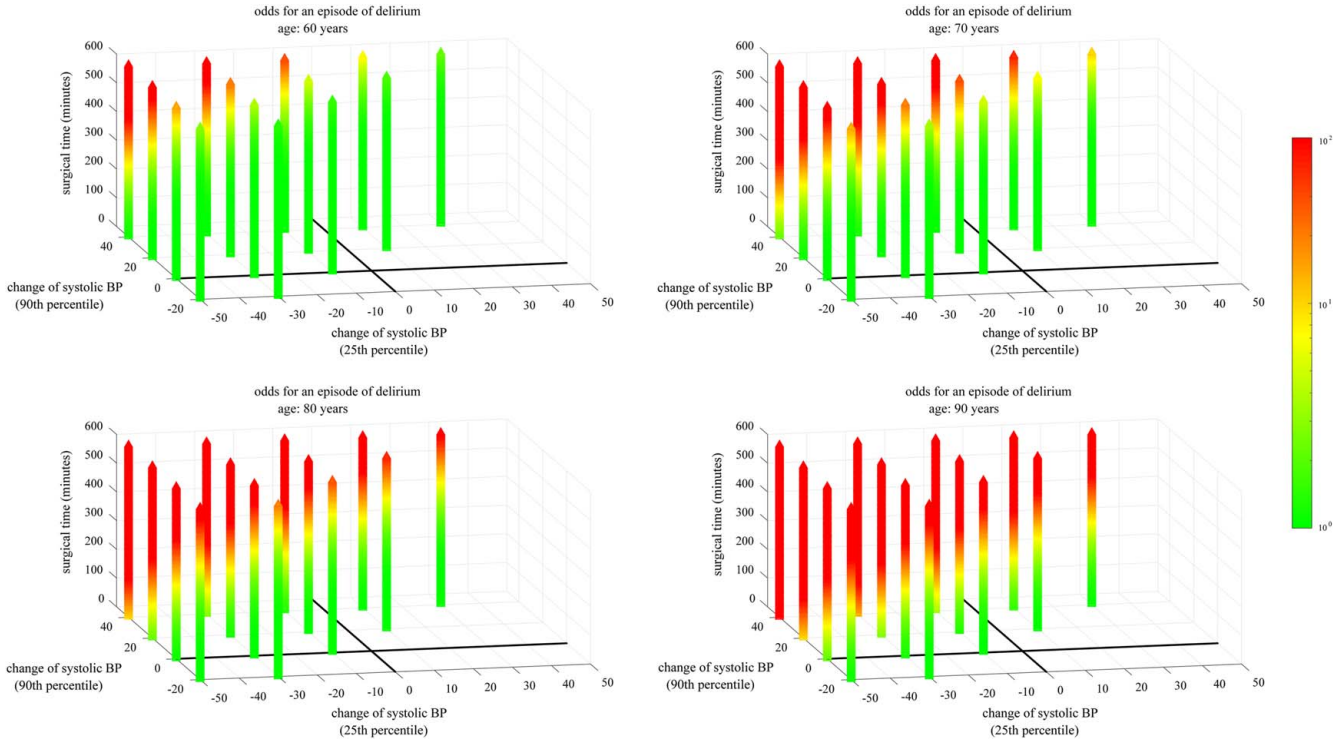

Figure 2. Illustration of how the ORs for developing POD change with age, duration of surgery and intraoperative blood pressure management. Color coding is similar to Figure 1. The illustration of the four-factor multivariable model includes a box for each of four representative age groups. The *z*-axis represents an increasing duration of surgery, and *x*-/*y*-axes depict intraoperative changes of systolic blood pressure (sBP) compared with baseline values before surgery (25th percentile, *i.e.* lowest proportion, and 90th percentile, *i.e.* highest proportion, of intraoperative sBP changes). ORs for an episode increase with age and duration of surgery in line with Figure 1. The model based on this study's data reveals that either lowering or increasing intraoperative sBP beyond baseline sBP values increases the risk for POD, *i.e.* blood pressure management should be even more meticulously taken care of in older patients undergoing longer surgery. BP indicates blood pressure.

that limiting the duration of surgery and meticulous management of intraoperative sBP might substantially decrease the risk for POD. This notion is crucial given that POD was significantly associated with inferior cognitive outcomes at three and 12 months postoperatively, irrespective of age and preoperative cognitive function. Thus, acknowledging these modifiable risk factors may render spine surgery neurocognitively safe, even in patients aged 80 years and older.[22]

It is increasingly acknowledged that preoperative cognitive trajectories affect the development of cognitive abilities after critical illness or surgery.[23] We clearly found that spine surgery *per se* is not necessarily associated with POCD in elderly patients if these have a functional gain (*i.e.* postoperative BI increases) and do not suffer POD. This being said, we confirmed that POD is associated with POCD/persistent NCD.[24] However, it cannot be excluded that POD is merely an epiphenomenon (or surrogate marker) of the brain's susceptibility for POCD/persistent NCD.[25] This hypothesis should be tested in future studies.[26]

Somewhat surprisingly, group analyses revealed postoperative cognitive improvement in multiple domains of the CERAD-NP test battery. POCI was previously noted in other types of surgery, most importantly cardiac surgery, which was attributed to restoration of brain perfusion, an unlikely mechanisms after spine surgery.[27] Another possible explanation might pertain to improved functional abilities, as a result of the surgery, which allows for increased physical activity, which again improves cerebral blood flow and connectivity.[28]

Finally, we cannot rule out that repeated testing accounted for some of the improvement in younger non-delirious individuals that better retained training effects. However, another study revealed that the CERAD-NP TS shows a good retest reliability even when readministered within shorter periods.[19]

Two previous studies evaluated intraoperative BP as a risk factor for POD after spine surgery, and yielded conflicting results.[29,30] Pre-existing hypertension was identified as a risk factor for POD in prior work; however, intraoperative BP values were not monitored.[31] An intriguing synthesis of previous findings is the hypothesis that neither pre-existing hypertension *per se*, nor absolute values of intraoperative BP, are risk factors for POD but rather the inter-relationship between lower intraoperative and higher (*e.g.* due to arterial hypertension) preoperative BP values represent the main driver. Our results clearly support this notion, demonstrating that the deviation from baseline sBP was associated with POD, even when adjusted for age and duration of surgery. Compromised cerebral autoregulation poses a plausible mechanism that renders patients with pre-existing arterial hypertension

TABLE 4. Summary of Cognitive Baseline Characteristics for the Complete Patient Population at V0-V2 and the Subpopulation With Complete Data at V0-V3

	Baseline			Follow-up (only V0-V3 subpopulation)					
				z-scores and p-values		*z*-scores by POD status (unadjusted)		*z*-scores by POD status (adjusted for age)	
CERAD item	*z*-scores (V0-V2) n = 99	*z*-scores (V0-V3) n = 57	Statistical difference V0-V2 vs. V0-V3 *P*	z-scores adjusted by POD status (adjusted for age)	z-scores adjusted by POD status	Del− n = 46	Del+ n = 11	Del− n = 46	Del+ n = 11
Verbal fluency	−0.08 ± 1.21	0.04 ± 1.20	0.56	0.22 ± 1.17	0.07	0.20 ± 1.13	0.22 ± 1.17	0.05 ± 1.07	−0.17 ± 1.25*
Boston Naming Test	0.33 ± 1.16	0.44 ± 1.24	0.55	0.74 ± 1.06	0.01	0.75 ± 0.93*	0.68 ± 1.57	0.00 ± 0.93	−0.11 ± 1.57
Mini Mental State Exam	−0.92 ± 1.98	−0.70 ± 1.75	0.56	−0.41 ± 1.75	0.53	−0.34 ± 1.77	−1.10 ± 1.93	0.15 ± 1.77	−0.67 ± 1.92†
WLL learning	−0.61 ± 1.33	−0.27 ± 1.18	0.13	−0.03 ± 1.43	0.23	0.07 ± 1.40	−1.16 ± 0.68	0.15 ± 1.41	−1.02 ± 0.71†
WLL recall	−0.01 ± 1.66	0.45 ± 1.22	0.09	0.52 ± 1.29	0.39	0.52 ± 1.31	−0.02 ± 1.36	0.08 ± 1.30	−0.32 ± 1.33†
WLL recognition	−0.38 ± 1.26	−0.20 ± 1.42	0.40	0.32 ± 1.23	0.01	0.32 ± 1.33	−0.14 ± 0.98	0.06 ± 1.32	−0.48 ± 1.03
Visuo-construction copy	−0.17 ± 1.53	−0.06 ± 1.40	0.65	−0.12 ± 1.84	0.87	0.11 ± 1.60	−0.86 ± 2.37	0.09 ± 1.60	−0.55 ± 2.33
Visuo-construction recall	−0.25 ± 1.64	−0.17 ± 1.72	0.82	0.11 ± 1.72	0.32	0.20 ± 1.48	−1.23 ± 1.44	0.13 ± 1.47	−1.25 ± 1.47
Trail Making Test A	−0.27 ± 1.18	−0.07 ± 1.27	0.35	0.22 ± 1.02	0.07	0.20 ± 1.01	0.03 ± 1.11	−0.04 ± 1.02	−0.01 ± 1.03
Trail Making Test B	0.22 ± 1.14	0.44 ± 1.11	0.32	0.73 ± 1.22	0.02	0.83 ± 1.28	0.13 ± 1.08	0.11 ± 1.28	−0.33 ± 0.99*
Phonemic fluency	0.16 ± 1.37	0.26 ± 1.46	0.62	0.30 ± 1.23	0.67	0.34 ± 1.21	0.11 ± 1.26	0.01 ± 1.21	−0.06 ± 1.17
Total score (mean)	−0.18 ± 0.91	0.03 ± 0.85	0.18	0.24 ± 0.73	0.02	0.30 ± 0.65*	−0.28 ± 0.87	0.08 ± 0.65	−0.44 ± 0.86†

Baseline z-scores (± SD) of CERAD items did not differ significantly between V0-V2 and V0-V3 samples, which supports that the cognitive trajectory of V0-V3 can be considered representative for the V0-V2 population. Statistical comparisons between visits (V0 vs. V3) were done pairwise in subjects with complete data at both visits (V0-V3 subpopulation; green = improvement, red = deterioration). Interestingly, we did not observe POCD on a group level but rather postoperative cognitive improvement (POCI). Subgroup analyses, however, revealed that this effect was carried by patients that were not delirious (Del−). When results were additionally adjusted for age, we did not find POCI but delirious patients (Del+) performed significantly worse at follow-up. SDs and P-values are not denoted exactly for POD subgroup analyses due to presentational purposes:

**Statistical significance at P < 0.05.*

†Statistical significance at P < 0.01.

WLL indicates word list learning.

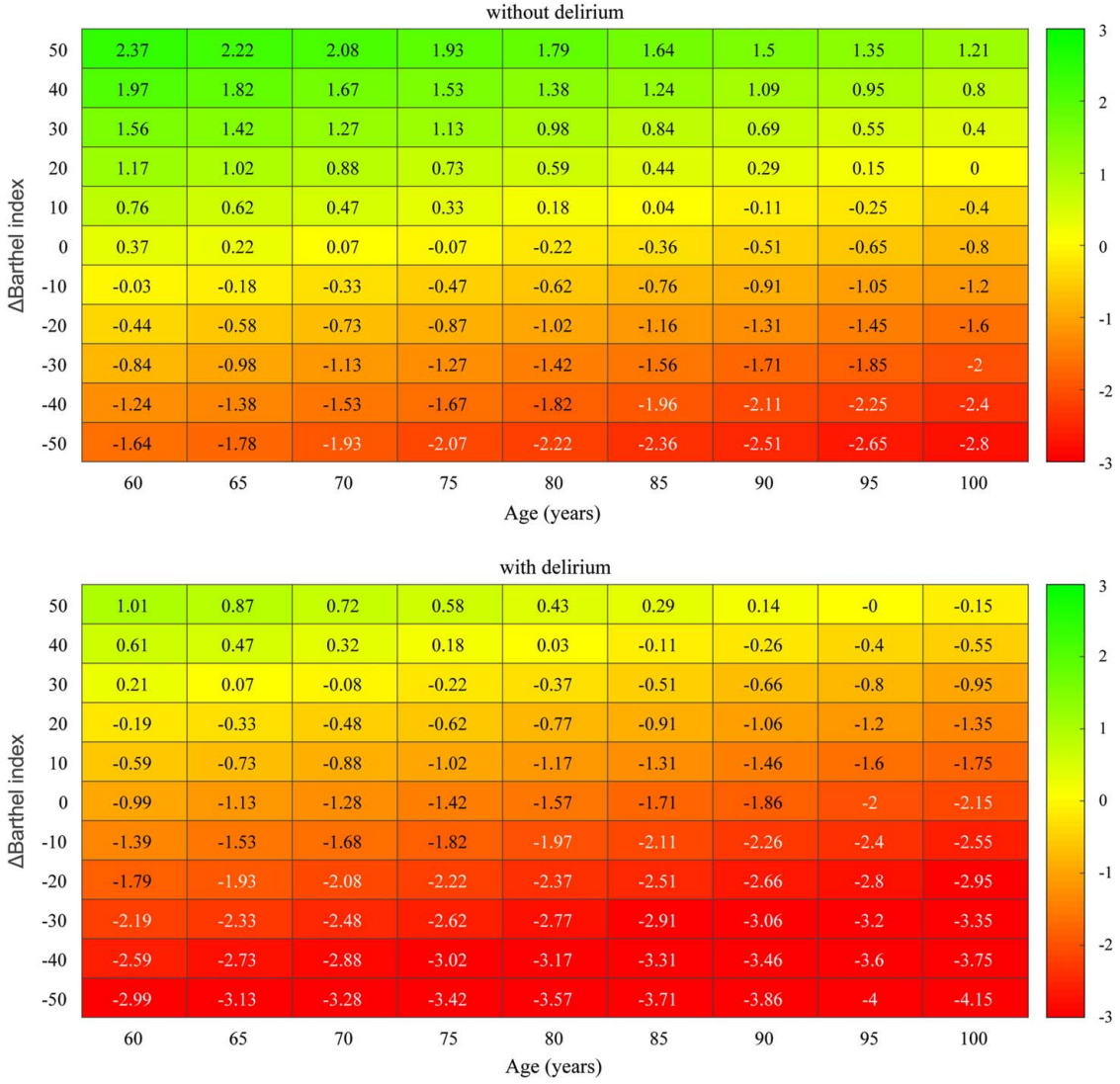

Figure 3. Illustration of how CERAD-NP total scores (*z*-score) change from the preoperative to the postoperative period (V0 *vs.* V3) depending on the delirium status during the postoperative period (top = nondelirious; bottom = delirious), age (*x*-axis) and functional improvement/deterioration after surgery as assessed by the Barthel Index (*y*-axis). Color coding indicates either postoperative cognitive dysfunction (POCD; toward red) or cognitive improvement (POCI; toward green), while yellow indicates no change. The model based on this study's data reveals that no patient, irrespective of age, would be affected by POCD (defined as a *z*-score change of ≤ -1)[4] if neither POD nor deterioration of functional abilities were present. In contrast, almost any age group would develop POCD if they were affected by POD, unless they functionally improved by about 10 (70 years of age or below) to 30 (90 years of age or above) points on the Barthel scale after surgery. The notion of POCI in patients improving by ≥ 1 *z*-score is difficult to interpret and may be either subject to enhanced cognitive abilities due to improved physical abilities or retest training effects (see Discussion for a more elaborate discussion).

particularly susceptible to peaks and troughs of intraoperative sBP.[32]

In a study by Brown *et al*,[31] it was suggested that POD largely accounts for complication and readmission rates in older patients and was associated with level of surgical complexity. In contrast, we found that perceived complexity and extent of spine surgery were not associated with POD (*i.e.* complexity *per se* does not seem to be a concern). However, duration of surgery was associated with POD (*i.e.* interventional approaches with expected shorter duration should be preferred in elderly patients).

Another interesting finding is that a functional gain on the Barthel scale was associated with cognitive improvement three months postoperatively. Thus, the expected functional gain and risk for POD due to longer surgery need to be balanced by the treating surgeon and should be discussed with the patient. Importantly, interventions with little risk for POD and substantial functional gain may even yield an improvement of cognitive abilities irrespective of age and should thus not generally be deferred.[22] This interpretation of secondary outcomes needs to be confirmed in further prospective research.

This observational trial had to be stopped, given the triage of elective surgical procedures due to the SARS-CoV-2 pandemic. Nonetheless, our primary hypothesis was confirmed given the larger than expected effect size (OR), which should be considered valid based on the

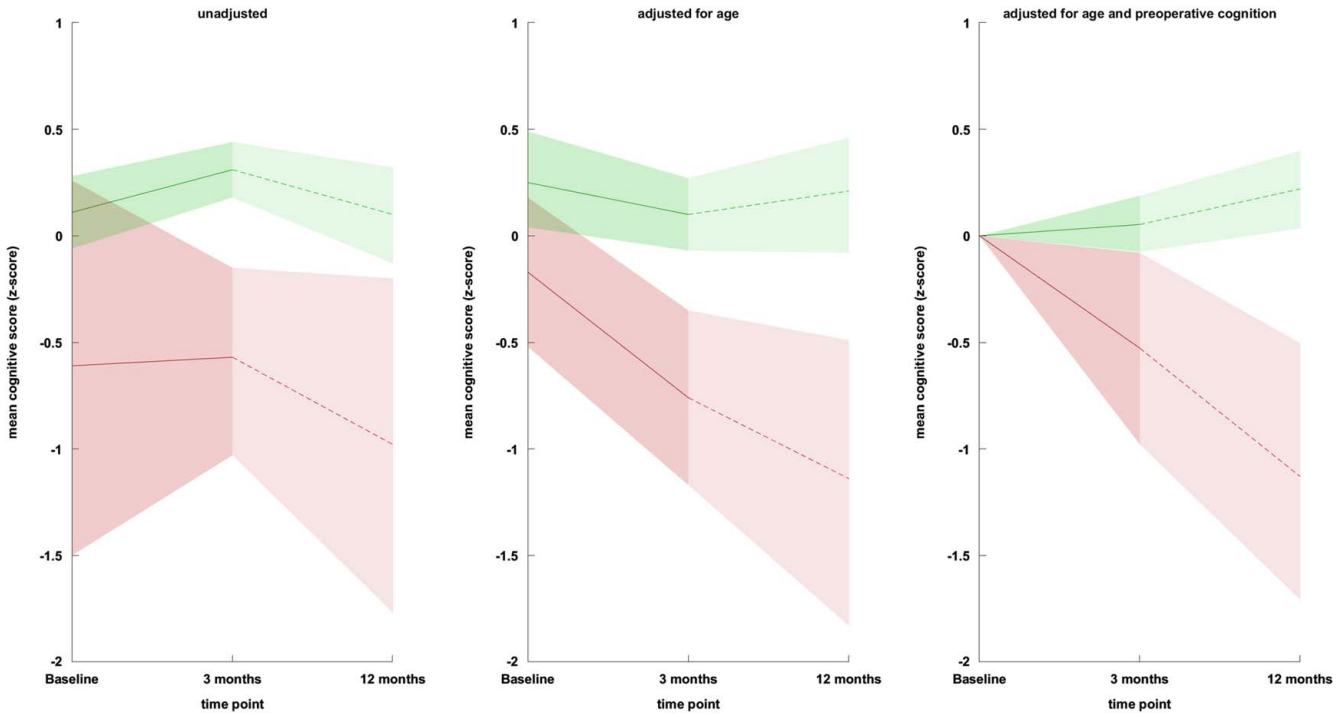

Figure 4. Trajectories of cognitive scores (mean, 95% CI) at baseline, three and 12 months postoperatively. Cognitive scores are normalized (*z*-score) and represent the CERAD-NP total score (baseline, 3 mo; straight line) and telephone MoCA sum score (12 mo; dashed line), respectively. Scores are furthermore given unadjusted (left), adjusted for age at baseline (center), and additionally for baseline cognitive performance (right). Color coding indicates patients without (green) and with an episode of POD (red). Patients suffering an episode of PSD tended to have lower cognitive scores at baseline, which was not significant since 95% CI overlap. Postoperative scores were significantly lower in the POD group at three and 12 months, which was more pronounced in the age-adjusted analysis and remained significant after adjusting for baseline cognitive abilities. full color online

CONSORT statement, which considers early terminations of clinical trials "for reasons apparently independent of trial findings […] are unlikely to introduce bias by stopping."[33] Investigations of secondary endpoints, however, may be affected by the smaller data set. Another limitation is that we screened for POD only for a limited postoperative period. This decision was made since POD is understood to develop within 72 hours postoperatively and later cases of delirium may also be attributed to infectious complications or intensive care delirium.[34] Importantly, risk factors for delirium other than POD may differ and thus confound effects of modifiable perioperative factors, which were the focus of the current investigation. Finally, we cannot clearly distinguish the independent impact of a longer duration of surgery and longer duration of anesthesia on the odds for POD since both are inevitably highly correlated. However, a recent study identified that the amount of systemic inflammation related to surgery was associated with the development of POD, and not the use of sevoflurane, rendering duration of surgery the more plausible driver of this outcome.[35]

In conclusion, this study identified the duration of surgery and intraoperative sBP management as modifiable factors associated with POD after spine surgery. Potential cognitive benefits are counteracted by POD, rendering its prevention critical in an aging population. Undesirable neurocognitive complications of complex spine surgery in elderly patients should be counteracted by limiting duration, enhancing functional gain of surgery, and tight intraoperative BP management.

➢ Key Points

- ❑ Quality surgical care of degenerative spine disease in patients of older age is an increasing challenging in an aging society.
- ❑ Neurocognitive complications, including postoperative delirium and cognitive dysfunction, are a major concern that may be mitigated by adjusting modifiable risk factors in patients over 60 years of age.
- ❑ Surgical interventions of the spine should not be routinely deferred in patients of older age and can lead to a functional gain if neurocognitive complications are avoided.

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