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ORIGINAL ARTICLE - NEUROSURGERY GENERAL

The predisposing and precipitating risk factors for delirium in neurosurgery: a prospective cohort study of 949 patients

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Abstract

Background Delirium is the most common neuropsychiatric presentation during hospitalization. In neurosurgery, studies on predisposing and precipitating risk factors for the development of delirium are rare but required for the individual risk estimation.

Methods Prospective cohort study in a tertiary university center. In total, 949 neurosurgical patients, 307 with and 642 without delirium, were included. Demographic factors, neurosurgery-related, neurological, and medical clusters were tested as predictors of delirium in multiple logistic regression analyses.

Results The incidence of delirium in this cohort of neurosurgical patients was 32.4%. Compared to patients without delirium, those with delirium were significantly older, more cognitively and neurologically impaired, transferred from hospitals and nursing homes, admitted as emergencies, longer hospitalized (16.2 vs. 9.5 days; $p < 0.001$), in greater need of intensive care management, and more frequently transferred to rehabilitation. Predisposing factors of delirium were stroke (OR 5.45, CI 2.12–14.0, $p < 0.001$), cardiac insufficiency (OR 4.59, CI 1.09–19.26, $p = 0.038$), cerebral neoplasm (OR 1.53, CI 0.92–2.54, $p = 0.019$), and age ≥ 65 years (OR 1.47, CI 1.03–2.09, $p = 0.030$). Precipitating factors of delirium were acute cerebral injury (OR 3.91, CI 2.24–6.83, $p < 0.001$), hydrocephalus (OR 3.10, CI 1.98–4.87, $p < 0.001$), and intracranial hemorrhage (OR 1.90, CI 1.23–2.94, $p = 0.004$).

Conclusions Delirium in acute neurosurgical patients was associated with longer hospitalization. Whereas common etiologies of delirium like infections and dementia, did not predict delirium, pre-existing neurovascular and traumatic diseases, as well as surgery-related events seem important risk factors contributing to delirium in neurosurgery.

Keywords Delirium · Predisposing factors · Precipitating factors · Risk factors · Interaction · Impact · Neurosurgery

This article is part of the Topical Collection on *Neurosurgery general*

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Abbreviations

OR	Odds ratio
CI	Confidence interval
ICU	Intensive care unit
DOS	Delirium Observation Screening Scale
LOS	Length of stay
CCI	Charlson Comorbidity index
ICD	International Classification of Diseases

Introduction

Delirium is a neuropsychiatric syndrome with disturbances in consciousness and cognition—with the core domains of inattention and impairment of higher order thinking—as well as a range of non-cognitive domains. These are alterations in psychomotor activity, the sleep-wake cycle, and emotionality [3].

The course of delirium is characterized by an abrupt onset and fluctuations. Medical etiologies that underlie delirium are manifold [2, 12, 16, 35].

In the general hospital setting, delirium rates vary between 10 and 60% [38] and reach 80% in certain intensive care setting. In neurosurgery, previous studies reported an overall incidence of delirium between 10 and 13.2% [21, 36]. When investigated at the neuro-ICU, the incidence may increase to over 40% [39].

Predisposing risk factors in general medical patients include advanced age and cognitive and physical impairment such as dementia and renal insufficiency. The precipitating factors are represented by severity of illness, infections, medications, and surgeries [5, 11, 18]. The sequelae of delirium are severe, including short-term consequences such as increased morbidity and mortality, and prolonged hospitalization, as well as long-term consequences such as increased rates of cognitive decline, deterioration in functionality, and institutionalization [14, 15].

Beyond the categorization of risk factors into predisposing and precipitating ones, another approach favors a categorization into modifiable factors (e.g., infections), potentially modifiable factors (e.g., critical illness) and non-modifiable factors (e.g., dementia) [5, 14, 16, 18]. Predisposing and precipitating factors interact with each other. At high predisposition such as in elderly patients or in those with dementia, minor precipitating factors such as infections can trigger delirium. In contrast, in patients at low predisposition, such as the healthy younger ones, major precipitation such as intracranial hemorrhage or sepsis are required. Several neurosurgical conditions causing delirium were investigated in detail. Delirium was observed in around 30% of patients undergoing elective surgery of brain tumors [9]. An important precipitating condition for delirium is intracranial hemorrhage (16–27% of patients) [7, 22]. Furthermore, an even higher incidence of delirium has been reported in patients undergoing brain surgery (43%) [33].

However, the role of predisposing factors in the development of delirium in neurosurgical patients remains unclear. Additionally, although the incidence of delirium in neurosurgery has been investigated previously, precipitating factors other than the neurological condition have not yet been evaluated.

This study sought to determine the predictive value of predisposing and precipitating factors for delirium in a sample of 949 neurosurgical patients, a population at high risk for delirium.

Materials and methods

Patients and procedures

All data in this prospective cohort study were collected at the University Hospital Zurich, a tertiary care center, from January 1 to December 31, 2014 from a quality improvement initiative aiming to improve the detection and management of delirium for all hospitalized patients, the DelirPath.

In 2014, 39,442 patients were admitted and registered in the DelirPath. Exclusion criteria were age < 18, length of stay (LOS) < 1 day, the combination of age and LOS and missing data, resulting in 29,278 eligible patients. In total, 947 patients were admitted to the acute neurosurgical service and included in this analysis (Fig. 1).

The DelirPath implements a screening algorithm with the Delirium Observation Screening Scale (DOS) [30] administered routinely three times daily during the first 3 days of admission in patients 65 years or older and based on clinical evidence of incident delirium for all patients, i.e., in those < 65 years. Trained nursing staff performed the DOS. The training was conducted in a 4-h course with mandatory preceding eLearning and literature research with control of success. The participants were educated with case-reports, state-of-the-art lectures on epidemiology, as well as the diagnostic criteria of delirium, and trained in obtaining delirium scores. Additionally, the involved departments were supported by the delirium task force during the study's initiation period and continuously on-demand throughout the study. In all patients with a DOS ≥ 3 additional delirium scores—Bedside Confusion Scale (BCS) [32], Mental Status Questionnaire (MSQ) [19], Confusion Assessment Method (CAM) [17]—were performed to improve accuracy of the delirium diagnosis. When delirium scores were positive, the assessment was continued three times per day.

In all patients, the Charlson Comorbidity index (CCI), a predictor of 10-year survival in patients with multiple comorbidities, was calculated [8].

All reporting followed the STROBE statement [37]. This study was approved by the ethics committee of the Canton of Zurich (KEK-ZH-Nr. 2012-0263). A waiver of informed consent was obtained from the KEK.

Classification of diagnoses and surgical interventions

The respective neurological and somatic diagnoses were automatically retrieved from the electronic medical chart (Klinikinformationssystem, KISIM, CisTec AG, Zurich) and, for the purpose of the analysis, described as diagnostic clusters according to their ICD-10 classification [25], reported in Table 1.

To achieve the most correct description of clusters, redundant clusters in different chapters were collapsed, e.g., ischemic insults G46 cerebral vascular syndromes and I63 cerebral insult. In addition, diagnostic clusters were collapsed, e.g. J12–15 to pneumonias or F10–19 to substance use disorders. In total, 21 clusters were created. The grouping of predisposing and precipitating clusters is shown in Table 1. Neoplastic

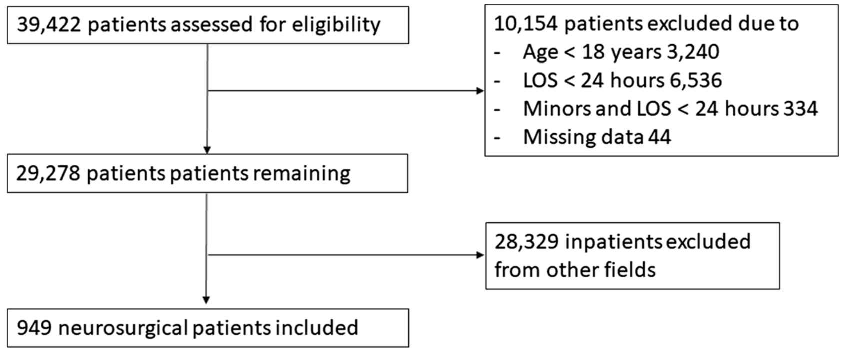

Fig. 1 Flowchart of patient recruitment and attrition; LOS (length of stay)

brain disease, epilepsy (i.e., seizure not as the admission diagnosis), and past ischemic stroke were assigned to the predisposing factors based on the assumption that these are chronic conditions that did not acutely trigger delirium. Hydrocephalus was assigned to the precipitating factors based on the assumption that the incidence of a hydrocephalus was the triggering event. Cardiac insufficiency/heart failure was diagnosed according to the 2016 European Society for Cardiology Guidelines [27].

Surgical interventions were based on the SWISS CHOP (Swiss (CH) Operations Classifications) codes. The CHOP codes consider surgical interventions by organ systems, e.g., the nervous system (01–05), in addition to individual surgical interventions performed, e.g., incision and excision at the skull, brain and meninges (01), or craniotomy and craniectomy (01.2). Thus, the number of surgical procedures refers to the sum of sequential procedures.

Table 1 ICD-10 diagnostic clusters and respective diagnoses representing the predisposing and precipitating factors for delirium

Diagnostic clusters	Respective ICD-10 diagnoses
Dementias and degenerative cerebral disorders	F00 Alzheimer's disease
	F01 vascular dementias
	F02 Dementia due to elsewhere defined disorders
	F03 Dementia ned
	G30 Alzheimer's disease
	G31–.0 localized atrophies (frontal temporal dementia)
	G31–.1–2 senile and alcohol-induced degenerations
	G31.8–9 Degenerations ned
	G32 degenerations due to elsewhere defined disorders
Cerebral neoplasm	C71
Epilepsies	G30–31
Ischemic insults	G46 cerebral vascular syndromes
	I63 cerebral insults / strokes
Hydrocephalus	G91, 94
Cerebral edema	G93.6
Intracerebral hemorrhage	I61–2
Subarachnoidal hemorrhage	I60
Cerebral injury	S06
Substance use disorders	F10–19
Cystitis	N30
Electrolyte imbalances	N87
Pneumonia	J12–15
Cardiac insufficiency	I50
Acute renal failure	N17
Chronic kidney disease	N18
Pulmonal disorders of cardiac disease and circulation	I26–28

Selection of diagnostic clusters for the regression model

In this study, diagnostic clusters were chosen according to the target population of the study—neurosurgical patients—and included relevant neurosurgical and neurological clusters, as well as medical and/-related clusters,

Determination of delirium

The presence and absence of delirium based on the Delirium Observation Screening scale. The DOS is a 13-item scale validated to indicate delirium according to DSM-IV criteria. Items include disturbances of consciousness (1), attention (2–4), thought processes (5 and 6), orientation (7 and 8), memory (9), psychomotor behavior (10, 11 and 13), and affect (12). Symptoms are rated on a scale (0–1) as not existent (0), sometimes to always existent (1), and unable to assess (−). The cut-off score for delirium is ≥ 3 and values were aggregated throughout recordings.

Due to the nature of the delirium screening algorithm, patients younger than 65 years were not routinely screened, but only upon clinical evidence of incident delirium. As a result, out of the 949 neurosurgical patients, only 782 were routinely screened. Two approaches were considered and the latter chosen: (1) excluding all patients with missing DOS scores—without clinical evidence for delirium—biasing the sample towards the elderly who were routinely screened and the delirious screened upon clinical suspicion or (2) including patients without screening in the assumption that those were not screened because there was no clinical suspicion for delirium, whereby accepting the risk of including a few false negatives.

Statistical methods

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 25 and R statistical software version 3.5.0 for Windows. Characteristics of the sample are summarized using means and standard deviations or medians and interquartile ranges for continuous variables depending on their parametric properties and percentages for categorical variables. The data was dichotomized according to the presence or absence of delirium. Further dichotomizations were by age (< 65 versus ≥ 65 years old) and by the median of surgical interventions (< 10 versus ≥ 10).

The data was tested with Shapiro-Wilk's for distribution of normality. Inter-group differences for continuous variables were computed using Student's *t* test and Mann-Whitney *U* test depending on their parametric properties, and for categorical variables with Pearson's-χ^2 or Fisher's Exact test depending on the sample size.

We calculated multiple logistic regressions to evaluate the impact of individual diagnostic clusters for delirium. Clusters relevant to delirium were included in the model, even if they did not reach significance and excluded only in instances of weakening the model, which was verified with the respective Cox-Snell's and Nagelkerke's r^2. For all inferential tests, two-tailed tests were chosen and the significance level alpha (α) was set at $p < 0.05$. The CCI was not considered in the further analysis because the model was not valid. Univariate analyses were performed with chi-square testing; the odds ratios, *p*-values, and confidence intervals for the risk factors are summarized in Table 2.

Results

Baseline characteristics of the neurosurgical patients

The rate of delirium was 32.4% in our cohort. Table 2 shows that patients with delirium were older than those without, with a similar gender distribution in both these groups. Apparently, delirious patients were more acutely ill and functionally impaired, as they were more commonly admitted as emergency cases, and more often transferred from other hospitals and nursing homes. Also, based on the neurological disease profile, delirious patients were neurologically more severely impaired, suffering more often from dementias/degenerative disorders, epilepsies, ischemia, hydrocephalus, subarachnoid bleeding, intracranial hemorrhage, and cerebral injury. Notably, rates of cerebral neoplasm and cerebral edema were similar in both groups.

More surgical interventions were performed in delirious patients who were more often transferred to the intensive care setting post-surgically where they also more often met requirements for ventilation (34.9 versus 6.4%).

Whereas in-hospital mortality was the same in both groups, the duration of hospitalization was about 1 week longer in delirious versus non-delirious patients (16.2 versus 9.5 days). About half of the delirious patients were transferred to rehabilitation, whereas almost three fourths of the non-delirious patients were able to return home.

Predisposing factors for delirium

In terms of sociodemographic factors, age 65 years or older increased the odds of becoming delirious by 47%. Among the neurological clusters, patients with prior cerebral ischemia were at least five times more likely to experience a delirium, followed by those with cerebral neoplasm showing a 53% increase in relative risk. Pre-existent dementia, substance use disorder, and epilepsy did not emerge as significant predisposing factors for delirium.

Of the medical factors predisposing to delirium, chronic cardiac insufficiency predicted an almost five times increased relative risk for delirium, whereas chronic kidney disease did

Table 2 Baseline sociodemographic and medical characteristics of the neurosurgical patients

	Delirium (N=307)	No delirium (n=642)	P (OR, CI)
Age*	61.4, 16.7	55.1, 16.6	<0.001
Gender in %			
Male	55.7	54.2	0.676
Female	44.3	45.8	
Residence prior admission in %			
Home	60.9	79.6	<0.001
Hospital / Nursing	29.3	18.6	
Other	9.8	1.9	
Mode of admission in %			
Emergency	80.9	43.8	<0.001
Elective	11	51.2	
Other	8.1	5	
in %			
Dementias or degenerative CNS disorders	4.9	1.1	<0.001 (4.5, 2.9-7.2)
Epilepsies	24.1	15.9	<0.001 (2.6, 2.0-3.4)
Ischemic insults / strokes	10.4	1.1	<0.001 (1.8, 1.4-2.3)
Hydrocephalus	30	9.3	0.066 (2.4, 1.0-5.8)
Subarachnoid hemorrhage	16.3	5.3	0.368 (2.4, 0.5-10.7)
Intracerebral hemorrhage	30.9	13.1	<0.001 (5.0, 3.1-7.9)
Cerebral Injury	15.3	5.6	0.543 (1.6, 0.5-4.7)
Cerebral edema	4.9	3.7	0.236 (1.9, 0.7-5.3)
Cerebral neoplasm	10.7	12.1	0.008 (2.1, 1.2-3.6)
Number of surgical interventions**	12.6, 9.6 / 10, 10	8, 4.8 / 8, 5	<0.001
Intensive care management	92.5	82.1	<0.001
Requirement for ventilation	34.9	6.4	<0.001
Length of stay***	16.2, 12.6	9.5, 6.5	<0.001
in %			
Discharged to			
Home	28.7	72.4	<0.001
Nursing home	2.9	0.9	
Other hospital	13	4	
Psychiatric hospital	0.3	0.5	
Rehab	49.8	18.7	
Deceased	3.6	3.1	
Other	1.6	0.3	

*mean years, SD; **mean number, SD / median, interquartile range (IQR). The number of interventions refers to each single operation step, e.g. skin incision and craniotomy, according to the CHOP. ***mean days, SD

not emerge as a significant risk factor (Table 3). Predisposing factors are illustrated in Fig. 2. Of the statistically significant factors in the univariate analyses—epilepsies and dementia—were not significant in the multivariate analysis.

Precipitating factors for delirium

Acute and traumatic neurological disorders predicted an increase in the relative risk for delirium. Specifically, cerebral injury caused an almost fourfold increased risk, hydrocephalus a more than threefold increased risk, and intracranial hemorrhage a twofold increased risk. Neither cerebral edema nor subarachnoid hemorrhage was significantly associated with delirium. Cerebral neoplasm reached significance in the multivariate analysis first and was not relevant in the univariate analysis.

Neither of the common medical risk factors—pneumonia, cystitis, acute renal failure, nor electrolyte imbalances—were significant precipitating factors for delirium. Conversely, several surgery-related events predicted a relatively increased risk of delirium, including multiple surgical interventions, intensive care management, and the requirement for ventilation, by 64% and 95%, respectively. Precipitating factors are illustrated in Fig. 2.

Table 3 Predisposing and precipitating factors for delirium in neurosurgical patients. The reported odds are illustrated in figure 2

	B (SE)	Exp(B)	CI lower-upper	P
Predisposing				
Age >65 years	0.39 (0.18)	1.47	1.03-2.09	0.030
Dementia/degenerative cerebral disorders	0.61 (0.53)	1.84	0.65-5.22	0.251
Cerebral neoplasm	0.43 (0.26)	1.53	0.92-2.54	0.019
Epilepsies	-0.56 (0.34)	0.57	0.29-1.12	0.103
Ischemic insults / strokes	1.70 (0.48)	5.45	2.12-14.02	<0.001
Chronic kidney disease	0.56 (0.35)	1.75	0.88-3.45	0.110
Cardiac insufficiency	1.52 (0.73)	4.59	1.09-19.26	0.038
Substance use disorders	0.33 (0.43)	1.39	0.60-3.25	0.447
Precipitating				
Cerebral edema	-0.52 (0.44)	0.59	0.25-1.41	0.235
Intracranial hemorrhage	0.64 (0.22)	1.90	1.23-2.94	0.004
Subarachnoid hemorrhage	0.57 (0.30)	1.70	0.97-3.21	0.061
Cerebral injury	1.36 (0.29)	3.91	2.24-6.83	<0.001
Hydrocephalus	1.13 (0.23)	3.10	1.98-4.87	<0.001
Pneumonia	1.04 (0.98)	2.82	0.41-19.22	0.290
Cystitis	-0.35 (0.26)	0.70	0.43-1.16	0.169
Electrolyte imbalances	-0.16 (0.36)	0.88	0.44-1.78	0.727
Acute renal failure	2.21 (1.15)	9.12	0.96-86.60	0.054
Pulmonal disorders	1.79 (1.15)	5.97	0.62-57.1	0.121
Number of surgical interventions	0.49 (0.18)	1.64	1.15-2.34	0.007
Intensive care management	0.68 (0.28)	1.95	1.13-3.38	0.013
Requirement for ventilation	0.67 (0.28)	1.95	1.15-3.34	0.015
Constant	-2.61 (0.28)	0.73		<0.001

Cox-Snell and Nagelkerke r^2 = 0.24 and 0.33

Discussion

Summary of the main findings

The novelty of this study is the systematic assessment of predisposing and precipitating factors for delirium in neurosurgical patients in a large sample. Compared to patients without delirium, those developing delirium were older, more often admitted as emergencies and transferred from other hospitals or nursing homes, and cognitively and neurologically more impaired. They were hospitalized 7 days longer and required more frequently subsequent rehabilitation. Advanced age, ≥ 65 years, increased the relative risk for delirium by 47%.

Among neurological predisposing factors investigated in our study, relevant diagnostic clusters were cerebral neoplasm, increasing the risk by 53%, and cerebral ischemia, increasing the risk at least fivefold. Neither dementia nor degenerative cerebral disorders affected delirium incidence. Dementia does typically not increase the risk for developing delirium in the presence of other factors, which likely explains the significance reached in univariate, but not in multivariate analyses. Similarly, epilepsy did not reach significance in the multivariate but in the univariate analysis.

Of the medical diagnostic clusters, only cardiac insufficiency increased the odds for delirium almost fivefold. Conversely, chronic kidney disease was not relevant as a risk factor.

Of the precipitating factors for delirium, the neurological ones, acute cerebral injuries quadrupled, hydrocephalus tripled, and intracranial hemorrhages almost doubled the odds for delirium. Medically ones, including pneumonia, cystitis, or electrolyte imbalances did not contribute to delirium. Of the surgical parameters indicating severity of interventions and complications, both intensive care management and requirement for ventilation increased the odds by 95%, and more than ten surgical procedures by 64%.

Comparisons with the existing literature

To date, predisposing and precipitating factors for delirium have been determined in various settings, including medical patients, surgical patients differentiated as non-cardiac and

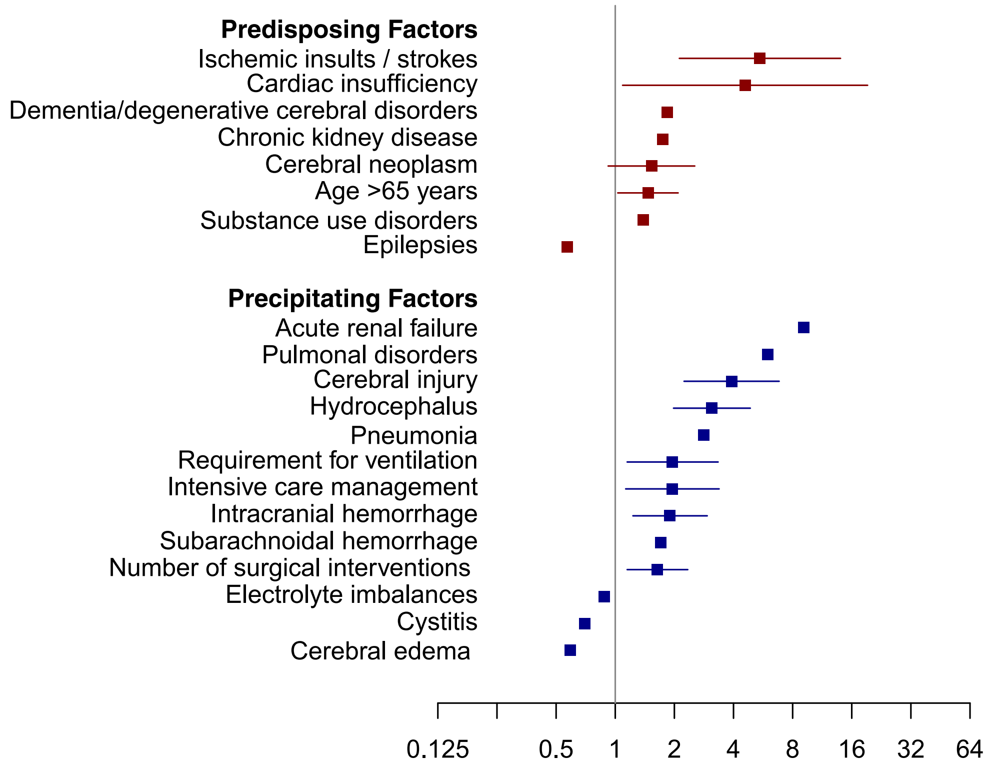

Fig. 2 Graphical representation of the predisposing and precipitating factors for delirium in neurosurgical patients. Error bars are stated for significant values only. The graphical representation in the figure refers to the statistics in Table 3

cardiac surgery, and intensive care patients; however, studies in neurosurgical patients are rare.

The incidence of delirium in the neurosurgical patients was higher than previously reported (32.4 versus 10–13.2%) [21], which likely reflects the routine delirium assessment in our study. Our findings confirm previous reports in non-cardiac surgery patients regarding advanced age and higher incidence of delirium, whereas dementia was not identified as a risk factor [18]. However, the contribution of age was lower in our study than previously reported, which might reflect the lower cut-off in our study, versus a cut-off of ≥ 75 years in previous reports. Our findings in neurovascular conditions, acute ischemic strokes, subarachnoid hemorrhage, and intracranial hemorrhage confirmed previous reports [6, 20, 28].

A history of ischemic stroke as a predisposing factor for neurosurgical patients is novel. This might be related to vascular cognitive impairment following stroke, which might induce higher vulnerability to delirium [26]. Hydrocephalus similarly increased the odds for developing delirium, particularly for the hyperactive motor subtype, as reported previously [7, 29].

In at-risk patients for developing delirium *preventive* strategies are recommended. Standard procedures follow the concept of reality orientation and general supportive measures are beneficial [34], e.g., pain management and clearly structured daily schedule, whereas routine preventive administration of antipsychotics is not recommended [24]. Current *treatment* guidelines emphasize the application of supportive measures in delirious patients; antipsychotics are reserved for severely distressed and anxious patients, and those at risk to harm themselves or their surroundings [23]. Recent randomized controlled trials contradict an effect of antipsychotics on delirium duration [1, 13].

Study implications

This study confirmed most precipitating risk factors previously described while contributing novel findings on predisposing risk factors. Patients and their relatives may be informed better on the individual risk of delirium and potential consequences. Preventive action may reduce days of hospitalization in vulnerable patients. As a novelty, our results encourage further research on the association of previous stroke on post-operative delirium. Future studies that investigate delirium in neurosurgery may address the impact of specific operational procedures on the incidence of delirium, which was not the aim of this study. In patients undergoing brain tumor surgery, there is considerable data available [4, 10].

Study strengths and limitations

This study had several strengths but also its limitations. The novelty of our study is a systematic assessment of the predisposing and precipitating factors for delirium in a large sample of neurosurgical patients, representative of a tertiary care center. All patients older than 65 years were routinely assessed for delirium three times daily in addition to assessments for all patients on clinical suspicion of incident delirium. All data were automatically retrieved from the electronic patient chart and relevant sociodemographic and medical parameters were included. Yet, baseline cognition and function, as well as illness severity, could not be recorded. Although of high relevance, motor subtypes of delirium were not systematically assessed. Due to the automated data retrieval, compromises were required. Owing to the screening algorithm, DOS scores were not performed on all patients. However, excluding the non-screened patients would have biased the sample towards the elderly routinely screened patients and delirious patients screened on suspicion. In addition, the representative nature of the sample would have been lost. ICD-10 includes more than 13,000 codes and those had to be reduced to diagnostic clusters. Clusters may be heterogenous based on the subheadings and not all codes could be included; rather, a selection of delirium-relevant codes was chosen. Information may have been lost in this process, e.g., hypothetically, specific differences of delirium in atypical versus typical pneumonia cannot be estimated. In line with previous studies, we have shown that delirium increases the length of hospital stay. However, due to limited access to details of interventions (e.g., blood loss, duration), we were not able to investigate whether delirium was an independent predictor of length of stay. Of note, the influence of anesthesia was not considered, although it may influence the incidence of delirium [31].

Conclusions

This study systematically assessed the impact of predisposing and precipitating factors for delirium in neurosurgical patients and provided novel findings. In these patients, the incidence of delirium was 32%. Patients were of older age, more severely cognitively impaired, transferred from institutions and admitted as emergencies, their hospitalization was prolonged—with higher rates of intensive care management including mechanical ventilation—and at discharge, commonly transferred to rehabilitation. Relevant predisposing factors were cerebral ischemia, neoplastic brain disease, and advanced age. Relevant precipitating factors were acute cerebral injuries, intracranial hemorrhage and hydrocephalus, as well as surgery-related factors, multiple operations, requirement for intensive care management, and mechanical ventilation. Neurosurgery departments may want to be alert in terms of these risk factors to possibly improve patient care and to lower costs.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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