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ORIGINAL COMMUNICATION

Predisposing and precipitating factors for delirium in neurology: a prospective cohort study of 1487 patients

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Abstract

Introduction Predisposing and precipitating factors for delirium are well known; however, their interaction and impact on delirium in neurological patients remains largely unknown. Therefore, those factors were evaluated in hospitalized patients with neurological disorders.

Methods In this prospective cohort study, 1487 neurological patients were included, 356 patients with delirium and 1131 without delirium. Relevant neurological- and medical-related clusters were assessed with multiple regression analyses, prediction models, and cluster analysis evaluating their association with delirium.

Results The 1-year incidence of delirium in this cohort was 23.9%. Delirium developed in 31% of patients with stroke, in 39.5% with epilepsy, and in 58.4% with ICH. The most relevant predisposing factors were substance-use disorders (OR 4.24, 2.28–7.78, $p < 0.001$), advanced age (OR 3.44, CI 2.40–4.92, $p < 0.001$), and neurodegenerative disorders (OR 2.58, CI 1.47–4.54, $p = 0.001$). The most relevant precipitating factors were meningitis (OR 21.52, CI 1.22–379.83, $p = 0.036$), acute renal failure (OR 10.01, CI 1.13–88.73, $p = 0.039$), and intracranial hemorrhage (OR 3.62, CI 2.08–6.30, $p < 0.001$). Delirious patients were hospitalized 6 days longer, had higher in-hospital mortality, and were discharged more often to nursing homes and rehabilitation. Best predictor for delirium was the coexistence of advanced age with epilepsy (58.3%, $p < 0.001$), while patients aged < 65 years without epilepsy and stroke rarely developed delirium (5.1%, $p < 0.001$).

Conclusions Delirium is common in elder neurological patients and associated with worse outcome. Primary cerebral conditions most frequently precipitate delirium in neurology. Neurologists are advised to monitor symptoms of delirium in the presence of risk factors to enable both timely diagnostic work-up and management of delirium.

Keywords Delirium · Neurology · Risk factor · Neuropsychiatry

Abbreviations

CCI Charlson comorbidity index
CNS Central nervous system
DOS Delirium Observation Screening Scale
ICH Intracerebral hemorrhage
ICU Intensive-care unit
LOS Length of stay
SU Stroke unit

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Introduction

Delirium is a neuropsychiatric syndrome characterized by disturbances in consciousness, cognition, the core domain with inattention, and disturbances of higher order thinking, as well as a range of non-cognitive domains, including disturbances in motor behavior, emotionality and sleep–wake cycle as another core domain, an abrupt onset and fluctuating course caused by an underlying etiology, or, more commonly, multiple etiologies [1–3].

In the general hospital setting, delirium rates vary between 10 and 60% [4, 5]. Previous studies revealed a prevalence of 28.5% in general neurological patients [6]. Delirium develops in patients in the presence of risk factors, which are generally divided into predisposing and precipitating, as well as potentially modifiable and non-modifiable factors [7]. Predisposing factors include age, male gender, and cognitive and physical impairment, such as chronic renal illness, poor nutritional status, and frailty, whereas precipitating factors include severity of illness, infections, medications, and surgeries [8, 9]. Delirium superimposed on dementia is highly prevalent, its diagnosis and management are particularly challenging [10]. The sequelae of delirium can be severe and include short-term consequences, such as increased morbidity and mortality, and prolonged hospitalization, as well as long-term consequences, such as cognitive decline, deterioration in functionality, and institutionalization [8]. Furthermore, the economic consequences following longer hospital stay, higher per day costs, and higher need for institutionalization are remarkable; national health costs of delirium might exceed those of diabetes [11].

In neurology, prevention, detection, and nonpharmacologic management of delirium have been defined a core opportunity for quality improvement in patient care [12]. However, most studies focused on stroke, while systematic investigations on predisposing and precipitating factors for delirium in other neurological disorders are rare. Furthermore, most attention has been given to patients in intensive-care units (ICU) and stroke units (SU), while delirium on neurologic wards remains understudied. The identification of risk factors is a prerequisite for the development of preventive measures and management strategies [13–15]. Therefore, we aimed to investigate previously reported risk factors in a subgroup of a hospital-wide study composed of 1487 neurological patients in an acute hospital setting. We previously reported data from neurosurgical patients [16].

Methods

Patients and procedures

All patients in this prospective cohort study were retrieved from the Delir-Path, a Health Service Research and Practice Development Project at the University Hospital Zurich aimed to improve the prevention, early detection, and management of delirium in all hospitalized patients; the cohort included in this study refers to delirium screening data collected between January 1st and December 31st 2014, and reporting followed the STROBE standard [17]. The University Hospital Zurich is one of the eight hospitals providing acute neurological care in the canton of Zurich (Population: ~ 1.5 million), one of four hospitals with a stroke unit, and the only provider of ICU. In this analysis, we present data from neurological non-ICU and non-SU patients.

In the context of the Delir-Path project, a screening algorithm with the Delirium Observation Screening Scale (DOS) [18] has been implemented; the DOS is administered three times daily during the first 3 days of admission for all patients ≥ 65 years and on clinical evidence of incident delirium. The DOS is performed by nursing staff specifically trained in its use.

In 2014, overall, 39,442 patients were enrolled in this single-study center in the Delir-Path Health Service Research Project. Exclusion criteria were age < 18 years, length of stay (LOS) < 1 day, as well as missing data, resulting in 29,278 eligible patients. Out of these, 1487 patients were admitted to the neurology service and included in this study (Fig. 1). Neurological patients with no signs of delirium were used as an internal control group. In all patients, age, gender, the place of residence prior to admission, and after discharge, mode of

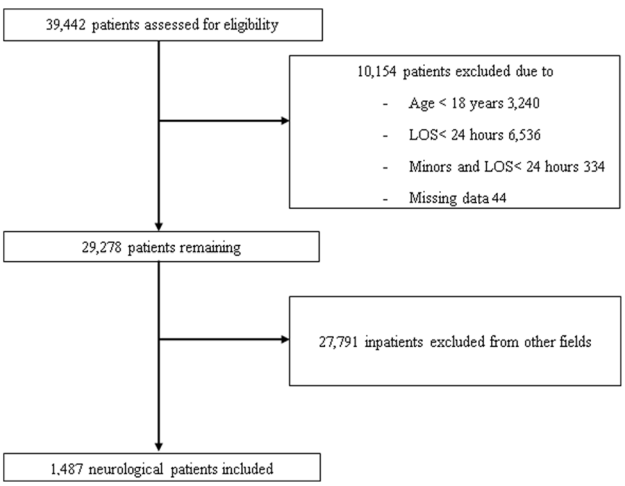

Fig. 1 Flowchart of sample recruitment. LOS (length of stay)

admission, and length of stay were included in accordance with the protocol of the Delir-Path study. The choice of these variables was guided by previously described predisposing and precipitating factors for delirium in general medical patients.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the ethics committee of the Canton of Zurich (KEK) (KEK-ZH-Nr. 2012-0263). A waiver of informed consent was obtained from the KEK.

Classification of diagnoses

The respective neurological and medical diagnoses data, which are particularly of interest for this subgroup, 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 the 10th revision of the International Classification of Diseases (ICD-10) [19] and listed in Table 1. The electronic medical chart reflects the neurological diagnoses as determined by the neurological service.

To achieve the most correct description of clusters representing the predisposing and precipitating factors, redundant

Table 1 ICD-10 diagnostic clusters with their respective included diagnoses

Dementias/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
Inflammatory cerebral disorders	A8x Viral infections of the brain
	A39 Meningococcal meningitis
	B00.3/4 Herpetic meningitis
	G00-09 Cerebral inflammatory disorders
Demyelinating disorders	G35 Multiple sclerosis
	G36 Other acute disseminating demyelinations
	G37 Other demyelinating disorders
Epilepsies	G40
Transitory ischemic attack	G45
Ischemic insults	G46 Cerebral vascular syndromes
	I63 Cerebral insults/strokes
Hydrocephalus	G91, 94
Cerebral edema	G93.6
Myocardial infarction	I21–23
Cardiac insufficiency	I50
Intracerebral hemorrhage	I61–62
Malnutrition	E40–46
Substance-use disorders	F10–19
Cystitis	N30
Electrolyte imbalances	N87
Pneumonia	J12–15
Acute renal failure	N17
Chronic kidney disease	N18
Sepsis-related disorders	A40–41 Other sepsis, streptococcal
	B00.7 Herpetic sepsis
	R65 Systemic inflammatory response syndrome
Decubital ulcers	L89

ICD (International classification of diseases and related health problems)

clusters from different chapters were collapsed, e.g., dementias included the psychiatric F00-03 cluster and the respective neurological—G30–32 other degenerative disorders of the central nervous system (CNS), or sepsis and systemic inflammatory response syndrome (SIRS)—A40 to 41, B00.7, and R65. In total, 20 clusters were created: 9 neurological and 11 medical clusters. In addition, three sociodemographic factors were included in the analysis; age > 65 years, institutionalization prior to admission, and emergency admission. Cardiac insufficiency/heart failure and myocardial infarction were diagnosed according to the 2016 European Society for Cardiology Guidelines [20].

Classification of predisposing and precipitating factors for delirium

The respective diagnostic clusters were classified as predisposing and precipitating risk factors. Predisposing factors included non-modifiable baseline sociodemographic characteristics and chronic medical or neurological conditions which modification and reversibility were limited, whereas precipitating factors include potentially modifiable acute medical or neurological disorders.

Assessment of multimorbidity and malnutrition

The Charlson comorbidity index (CCI) was used to assess multimorbidity [21]. The CCI considers age, diabetes mellitus, liver disease, malignancies, human immunodeficiency virus infection, chronic kidney disease, congestive heart failure, myocardial infarction, chronic obstructive pulmonary diseases, peripheral vascular disease, cerebrovascular accidents or transitory ischemic attacks, dementias, hemiplegia, connective tissue disease, and peptic ulcer disease. Malnutrition was diagnosed with routine Nutrition Risk Screening (NRS) at admission [22, 23].

Determination of delirium

In this large data set, the presence and absence of delirium was based on the DOS. The DOS is a 13-item scale validated to indicate the presence and severity of delirium in accordance with DSM-IV criteria [2]. The cut-off score for delirium was set at ≥ 3 and values were aggregated throughout recordings [18]. Out of the 1487 patients admitted to the neurology service, 985 were *routinely* screened, i.e., those ≥ 65 years. All patients were included in the final analysis in the assumption that younger patients with delirium were detected upon suspicion with a low risk of including few false negatives.

To anticipate falsely positive diagnoses of delirium, every patient with a DOS ≥ 3 was required to be evaluated by a neurologist—as a quality control. Patients suspected to have another etiology for their symptoms than delirium were referred to the respective diagnostic testing, i.e., cranial imaging, blood sampling, cerebrospinal fluid analysis (CSF), and electroencephalography (EEG).

Statistical methods

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 25 for Windows. Characteristics of the sample were summarized using means and standard deviations for continuous variables and percentages for categorical variables. The data set was dichotomized according to the presence or absence of delirium. Further dichotomizations were made on age ≥ 65 versus < 65 years, the CCI ≥ 2 versus < 2, and residence status prior to admission—institution versus home.

Normality of the data distribution was tested with the Shapiro–Wilk test. Between-group differences for continuous variables were computed using Student's t and Mann–Whitney U test depending on their metric properties, and for categorical variables with Pearson's-χ^2 or Fisher's exact test, where appropriate.

For the evaluation of the impact of individual diagnostic clusters, multiple logistic regressions were calculated, with the dependent variable set on the presence or absence of delirium and the respective diagnoses clusters treated as covariates. The model was optimized with Cox–Snell's and Nagelkerke's r^2. To identify symptom constellations rendering patients vulnerable for delirium, we computed decision trees and cluster analysis. Decision trees were created with CHAID growing method and presence of delirium as the dependent variable, and with predisposing and precipitating factors as independent variables. Hierarchical cluster analysis was performed to estimate the relationship between predisposing factors. Average linkage was employed for clustering applying Jaccard measure to account for binary values. The level of significance was set at $p < 0.05$ (two-tailed).

Results

Baseline characteristics of the neurological patients

In this neurological patient cohort, the incidence of delirium was 23.9%. There were 356 patients with delirium and 1131 without delirium. As shown in Table 2, patients with delirium were on average 10 years older than those without and had marginally more comorbidities as measured with the CCI. More patients with delirium were transferred from other hospitals and nursing homes than resided at home prior to admission indicating acute illness and functional impairment. Moreover, patients with delirium stayed about 6 days longer in the hospital, had a higher risk to decease during

Table 2 Sociodemographic, medical, and neurological characteristics of the delirious versus non-delirious patients

	Delirious patients ($n=356$)	Non-delirious patients ($n=1131$)	P
Age in years[a]	71.2, 13.3	61.2, 16.6	<0.001
Gender in %			0.392
Male	54.2	56.9	
Female	45.8	43.1	
Charlson comorbidity index[a,b]	2.4, 1.7/3, 4	2.1, 1.5/2, 2	0.001
Stay prior admission in %			<0.001
Home	70.8	82.4	
Hospital/Nursing	26.3	15.5	
Other	2.8	2.1	
Mode of admission in %			<0.001
Emergency	80.9	65.9	
Elective	11	23.8	
Other	8.1	4.3	
Neurological disorders in %			
Dementias/degenerative CNS disorders	12.4	3	<0.001
Inflammatory CNS disorders	4.8	3.2	0.127
Demyelinating CNS disorders	0.8	6.3	<0.001
Epilepsies	32.3	15.6	<0.001
Ischemia/strokes	48.3	33.8	<0.001
Hydrocephalus	2.5	1.1	0.066
Subarachnoid hemorrhage	0.8	0.4	0.368
Intracerebral hemorrhage	12.6	2.8	<0.001
Cerebral edema	1.7	0.9	0.236
Length of stay in days[a,b]	13.9, 12.1/11, 10	8, 6.1/7, 7	<0.001
Discharged to in %			<0.001
Home	28.4	63.9	
Nursing home	9.6	2.7	
Other hospital	9.8	4.2	
Psychiatric hospital	4.2	1	
Rehabilitation	41.6	20.2	
Deceased	5.9	1.6	
Other	0.6	0.9	

[a]Mean, standard deviation, [b]median, interquartile range, CNS (central nervous system)

hospitalization, and were more often referred for rehabilitation. Out of 70.8% of delirious patients who resided at home before hospitalization, only 28.4% returned home. Of the delirious patients, the largest subgroups were those with stroke, epilepsies, and ICH (Table 3). Regarding single neurological disorders, 31.0% of patients with stroke (total $N=554$), 39.5% with epilepsies (total $N=291$), and 58.4% with ICH had delirium (total $N=77$). The relationship between presence versus absence of delirium, age, and length of stay is illustrated in Fig. 2.

Predisposing factors for delirium

The most relevant predisposing factor was substance-use disorders with a 4.2-fold increased risk of delirium, followed by age over 65 years increased the risk for delirium by the factor 3.4, and pre-existing dementias or degenerative disorders increased this risk by 2.5. In addition, delirious patients resided at an institution almost two times more often. Conversely, the only cluster not contributing to delirium was demyelinating disorders. No significant associations were noted for hydrocephalus, chronic kidney disease, and multimorbidity. Neither a history of cardiac insufficiency nor a history of myocardial infarction predisposed to delirium (Table 2, Fig. 3).

Precipitating factors for delirium

Although inflammatory CNS disorders as a cluster failed to contribute to delirium, meningitis, when separated from

Table 3 Multiple regression model for the predisposing and precipitating factors for delirium in neurological patients

	B (SE)	Exp(*B*)	CI lower–upper	*P*
Predisposing factors				
Age > 65 years	1.23 (0.18)	3.44	2.40–4.92	< 0.001
Institution prior admission	0.66 (0.19)	1.93	1.35–2.75	< 0.001
Dementia/degenerative cerebral disorders	0.95 (0.29)	2.58	1.47–4.54	0.001
Substance use disorders	1.44 (0.32)	4.24	2.28–7.87	< 0.001
Demyelinating cerebral disorders	− 1.67 (0.62)	0.19	0.06–0.64	0.007
Hydrocephalus	0.47 (0.52)	1.61	0.57–4.45	0.365
Malnutrition	1.86 (1.20)	6.43	0.62–66.96	0.119
Chronic kidney disease	0.04 (0.27)	1.04	0.61–1.78	0.891
Charlson comorbidity index	− 0.005 (0.05)	0.99	0.90–1.09	0.917
Myocardial infarction	0.17 (0.22)	1.18	0.76–1.83	0.449
Cardiac insufficiency	0.15 (0.41)	1.17	0.53–2.59	0.702
Precipitating factors				
Admission as emergency	0.29 (0.19)	1.33	0.92–1.93	0.133
Inflammatory CNS disorders	0.21 (0.48)	1.24	0.48–3.16	0.659
Meningitis	3.07 (1.46)	21.52	1.22–379.83	0.036
Transitory cerebral ischemia	− 0.58 (0.34)	0.56	0.29–1.10	0.092
Cerebral edema	0.47 (0.59)	1.59	0.50–5.08	0.431
Epilepsies	1.19 (0.18)	3.28	2.28–4.71	< 0.001
Intracranial hemorrhage	1.29 (0.28)	3.62	2.08–6.30	< 0.001
Ischemic insult/stroke	0.57 (0.17)	1.76	1.25–2.48	0.001
Pneumonia	1.03 (0.68)	2.80	0.73–10.68	0.133
Cystitis	0.16 (0.21)	1.17	0.78–1.78	0.437
Electrolyte imbalances	0.09 (0.30)	1.09	0.60–1.98	0.770
Acute renal failure	2.30 (1.11)	10.01	1.13–88.73	0.039
Sepsis-related disorders	1.26 (0.60)	3.52	1.08–11.43	0.037
Decubital ulcers	1.22 (0.54)	3.40	1.17–9.86	0.025
Constant	− 5.24 (0.45)	0.005		< 0.001

Cox–Snell and Nagelkerke $r^2 = 0.242$ and 0.362, SE (standard error), CI (confidence interval), CNS (central nervous system)

this cluster, was the most relevant factor with a more than 20 times increased risk for delirium, followed by acute renal failure increasing the odds tenfold, whereas intracranial hemorrhage, sepsis-related disorders, and decubital ulcers increased the odds at least threefold. Stroke increased the risk for delirium almost twofold. Among neurological disorders, transitory ischemic attacks and cerebral edema were not associated with an increased risk of delirium. Notably, commonly cited somatic risk factors, pneumonia, cystitis, and electrolyte imbalances, but also emergency admission, were all not relevant for delirium in neurological patients (Table 3).

Prediction models and cluster analysis

With decision tree, the predicted probability (PP) not to develop delirium was highest in patients < 65 years with neither epilepsy nor stroke (PP = 94.9%, $P < 0.001$) (Fig. 4). The probability to develop delirium was highest in patients > 65 years with epilepsy (PP = 58.3%, $P < 0.001$). The second notable constellation was in patients with higher age, epilepsy, and living in an institution prior to admission (PP = 46.4%, $P < 0.001$). The cluster analysis revealed a strong association between age, higher load of comorbidities, and emergency admission. Delirium was strongly associated with this cluster, followed by cystitis and epilepsy to a lesser extent.

Discussion

Summary of main findings

This study systematically assessed the effect or impact of predisposing and precipitating factors on delirium in a large neurological sample of hospitalized non-ICU and non-SU patients. The 1-year incidence of delirium was 23.9%. The delirious inpatients were generally older and more often

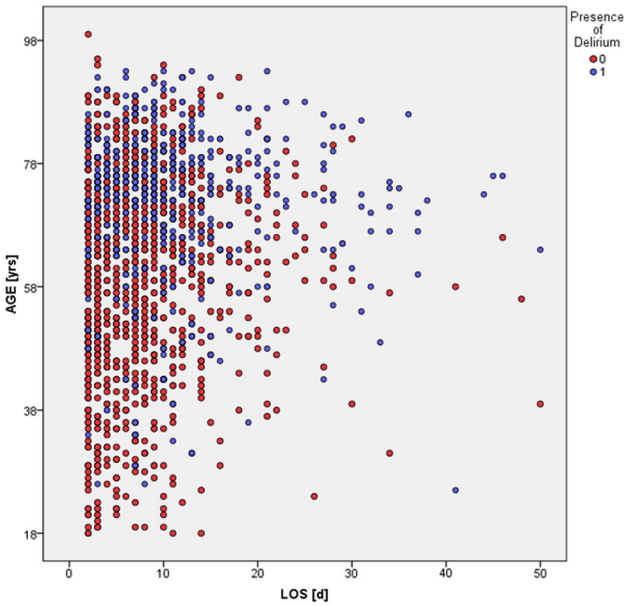

Fig. 2 Relationship between age and length of stay (LOS) in delirious (blue) vs. non-delirious (red) patients. Not depicted: $N=6$ with LOS > 50 days, of those 5 had delirium

multimorbid, transferred from hospitals or nursing homes, were hospitalized longer, and discharged less often home. Out of the precipitating factors for delirium, meningitis increased the odds more than 20-fold and acute renal failure increased the risk almost tenfold. Delirious patients had also more frequently dementias or degenerative CNS disorders, epilepsies, stroke, and ICH. Ischemic insults, ICH, epilepsies, substance-use disorders, sepsis-related disorders, and decubital ulcers caused increases between twofold and fourfold. Elder patients with multiple medical disorders and admitted as an emergency were prone to develop delirium. In those patients, epilepsy was the strongest precipitator for delirium.

Critical appraisal of delirium in neurological disorders

Delirium is associated with primary cerebral disorders [24], such as stroke [25], meningitis [26], and epileptic seizures [27], as well as with secondary conditions, such as sepsis [28], electrolyte disturbances [8], substance withdrawal [29], and surgery [30]. The pathomechanisms leading to delirium are specific to the underlying condition [24, 31, 32]. In any case, the identification and treatment of the underlying causes is the priority in delirium management. Meanwhile, patients benefit from nonpharmacological supportive care [9]. Despite the evidence, for several reasons, the diagnosis of delirium in neurological conditions remains difficult, illustrated by the conflicting use of the terms encephalopathy and delirium, and the use of descriptive terms, such as confusion [33]. In addition, it is challenging to discriminate some neurological disorders from delirium, e.g., coma and aphasia, and delirium superimposed on dementia. These obstacles result in different delirium management strategies across medical professions [34].

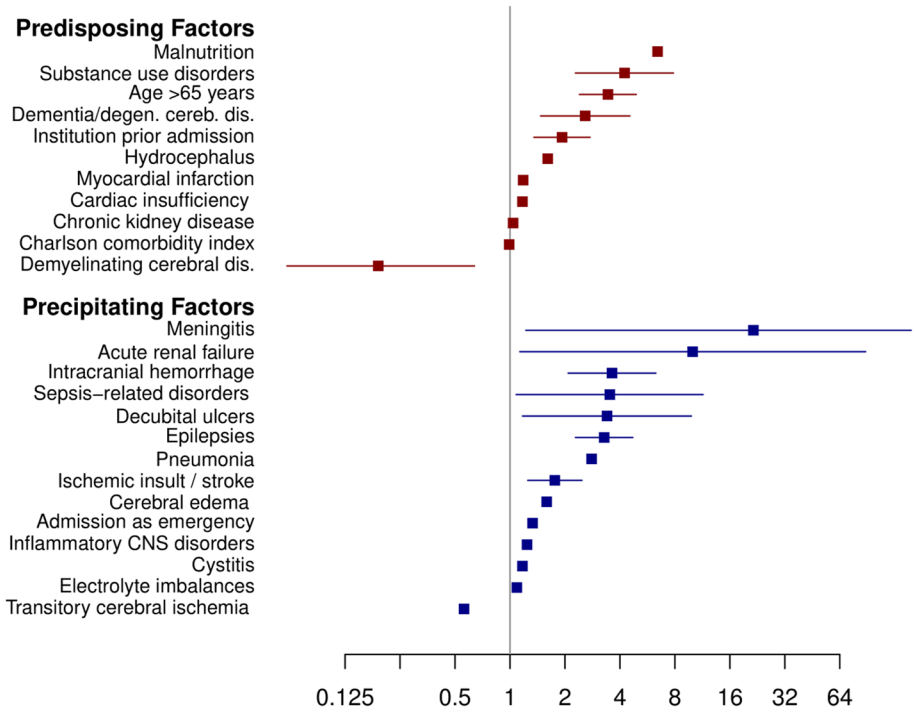

Fig. 3 Graphic representation of the predisposing and precipitating factors for delirium for neurological patients, including odds ratios (ORs) and confidence intervals (CIs). Significant ORs displayed with CIs. CNS (central nervous system)

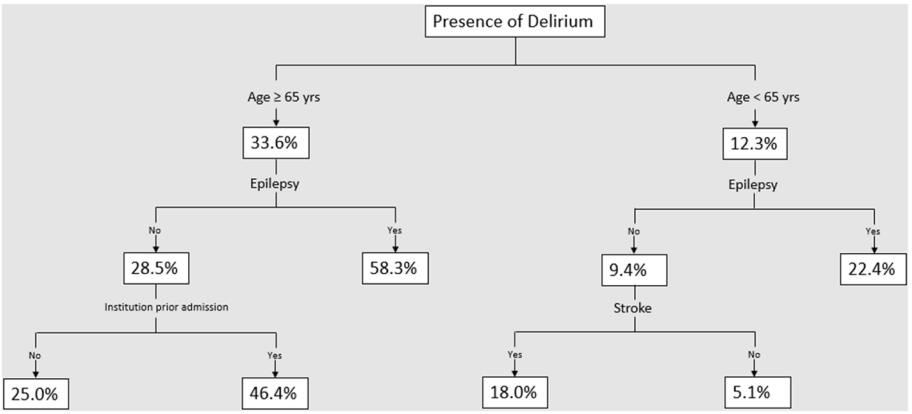

Fig. 4 Prediction tree for the presence of delirium

Comparison of own findings to the literature of delirium in neurological disorders

Overall, the observed incidence of 23.9% for delirium in our study resembles the prevalence of 28.5% in neurology reported by Bellelli and colleagues from a large multicenter study [6]. Of neurological conditions, to this date, post-stroke delirium has been investigated most extensively. Between 13 and 48% of patients on stroke units develop delirium [35, 36], whereas 31% of stroke patients had delirium in our cohort. Our results are in line with previous stroke cohorts that reported longer stay of delirious patients on average (i.e., 9.4 days versus 5.9 in our study), and higher inpatient mortality [25]. Delirium is associated with stroke in specific brain areas [37] and more prevalent in multimorbid patients with lower cognitive function, more severe neurological disability and in those with impaired perception [38, 39]. Previously, we found that neurosurgery patients with a history of stroke are predisposed to experience delirium after brain surgery [16]. Here, we confirmed the association of age and dementia as predisposing factors for delirium in stroke patients [39–41]. The inter-relation of delirium and dementia has been the subject of extensive research, and the mechanisms remain to be elucidated [42–45]. Our study complements previous studies from SU cohorts, because it demonstrates remarkable delirium rates on non-SU wards.

In ICH, a delirium rate of 30% [46] and a longer stay of 3.5 days on average were previously reported [47]. Those studies investigated delirium in ICH patients on the ICU. Again, our results revealed the significance of delirium on non-ICU wards. Regarding hydrocephalus, this study did not replicate a previously reported association with delirium [48, 49], likely related to different study populations, the investigators reported data from patients with subarachnoid hemorrhage-associated hydrocephalus, while in our study, all patients with hydrocephalus—regardless of the etiology, e.g., normal pressure hydrocephalus—were included. We expected higher odds for delirium in sepsis-related disorders [28], and attribute this finding to the study setting, since patients not managed in an ICU setting are less severely affected. For meningitis, showing odds for delirium similarly high as previously reported [50], the confidence interval was large, related to the clustering of different severity and types of meningitis [51]. In demyelinating inflammatory disorders, delirium was rare (< 1%), reflecting that mostly case reports have been published previously [52, 53]. Delirious symptoms occur frequently after epileptic seizures, as confirmed by our study. Of note, in those patients, further work-up and monitoring is mandatory to identify ongoing epileptic activity as a differential diagnosis [54].

Comparison of own findings to previous literature in non-neurological disorders

Compared to general medical patients, relative risks and odds ratios resemble our findings in terms of age, dementia, comorbidities, and substance-use disorder [8]. The odds for delirium in patients with acute renal failure were about four times higher than previously reported, indicating higher vulnerability of patients with primary cerebral disorders [55]. Interestingly, the co-presence of neurological illness, pneumonia, cystitis, and electrolyte imbalances failed to be as relevant precipitating factors for delirium as in the literature on medical populations [56]. The diagnostic clusters for these disorders were specific; therefore, the only conclusion was that these common risk factors for delirium were not relevant for neurological in-patients. This finding is likely caused by the lower incidence of pneumonia, cystitis, and electrolyte imbalances in neurological patients compared to a general medical population. Moreover, in internal medicine, the focus on these conditions allows to identify mild cases. Since patients with acute heart failure, and particularly those with dementia, are prone to develop delirium [57, 58], we investigated cardiac disorders, too. We were able to show that in neurological patients, there was no increased delirium rate associated with heart failure and myocardial infarction. We attribute this finding to the study setting not

being an environment for acute cardiac disease and to fewer comorbidities in our cohort (Mean CCI 2.1, respectively, 2.4 for delirious patients) compared to heart failure cohorts (Mean CCI > 3–4) [59–61]. Regarding malnutrition, previous studies reported an association with delirium in surgery [62] and in general medical populations [6]. Although the odds were increased, malnutrition failed to reach significance, likely due to the heterogeneity of the cohort. Also noteworthy, we found an association of delirium with decubital ulcers, which may reflect that these patients are bedridden due to physical handicap and cognitive dysfunction. However, we were not able to determine the causal direction, i.e., whether patients with delirium are prone to being bedridden or whether bedridden patients are prone to develop delirium.

Strengths and limitations

As a strength, this study systematically assessed predisposing and precipitating factors for delirium in neurological patients with an ample sample size, representative of a tertiary care center. Notably, all patients older than 65 years were rigorously 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 electronic patient charts and relevant sociodemographic and medical parameters as well as comorbidities were recorded. However, baseline cognition and function, as well as severity of illness could not be recorded. Due to the automated retrieval and sample size, compromises were required, e.g., the construct of delirium was based on DOS scores. ICD-10 includes more than 13,000 codes and those had to be reduced with diagnostic clusters. Clusters may be heterogeneous based on the subheadings and not all codes could be included; rather, a selection of delirium-relevant codes was chosen. Information may have been skewed or lost in this process. Of note, diagnosis of dementia was retrieved from the medical chart, although a systematic assessment was not performed. Given high rates of undiagnosed cognitive deficits, the incidence of dementia in this cohort may be higher.

Although many important factors contributing to the development of delirium were considered, others were not investigated. For instance, *frailty* is a concept used in ageing populations to estimate functional impairment [63, 64], and, if present, contributes to the development of delirium and interacts with the outcome [65, 66]. The estimation of frailty helps to discriminate healthy ageing and at-risk populations for geriatric syndromes. Healthy elderly individuals, i.e., those who pursue an active lifestyle and physical activity, may exhibit a lower biological age than their actual chronological age and, therefore, are not at high risk for delirium [67, 68]. *Drug administration* was not recorded in this study; therefore, the association between delirium and sedating medication, e.g., benzodiazepines [69], anticholinergics, and opioids [70, 71], could not be evaluated. Particularly, elder patients are at-risk for drug-induced delirium [72–75]. We did not systematically assess *pain* in our cohort, which has been demonstrated to be associated with the rate of postoperative delirium [76].

Conclusions

The novelty of this study was the systematic assessment of predisposing and precipitating factors for delirium in a large sample of neurological in-hospital non-ICU/SU patients. We demonstrated that most predisposing factors reported in general medical patients are also relevant to neurological patients, while precipitating factor are mostly primary cerebral disorders, but also acute renal failure and sepsis. Clinicians may want to increase awareness for these risk factors and systematically inquire them in neurological wards to identify modifiable risk factors. In risk populations, delirium-inducing drugs should be avoided. Medical complications and prolonged hospitalization call for effective management in risk groups. Future studies on specific preventive and therapeutic strategies for delirium in neurological patients are requested.

Author contributions CMZ: design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content. JD: major role in the analysis and of data and data bank management, and revised the manuscript for intellectual content. JE: interpreted the data; revised the manuscript for intellectual content. MS: Interpreted the data; revised the manuscript for intellectual content. MW: interpreted the data; revised the manuscript for intellectual content. RK: interpreted the data; revised the manuscript for intellectual content. SB: design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.

Compliance with ethical standards

Conflicts of interest None.

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