Predisposing and precipitating risk factors for delirium in palliative care patients

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Abstract

Objective. Delirium is a common complication in palliative care patients, especially in the terminal phase of the illness. To date, evidence regarding risk factors and prognostic outcomes of delirium in this vulnerable population remains sparse.
Method. In this prospective observational cohort study at a tertiary care center, 410 palliative care patients were included. Simple and multiple logistic regression models were used to identify associations between predisposing and precipitating factors and delirium in palliative care patients.
Results. The prevalence of delirium in this palliative care cohort was 55.9% and reached 93% in the terminally ill. Delirium was associated with prolonged hospitalization ($p < 0.001$), increased care requirements ($p < 0.001$) and health care costs ($p < 0.001$), requirement for institutionalization (OR 0.11; CI 0.069–0.171; $p < 0.001$), and increased mortality (OR 18.29; CI 8.918–37.530; $p < 0.001$). Predisposing factors for delirium were male gender (OR 2.19; CI 1.251–3.841; $p < 0.01$), frailty (OR 15.28; CI 5.885–39.665; $p < 0.001$), hearing (OR 3.52; CI 1.721–7.210; $p < 0.001$), visual impairment (OR 3.15; CI 1.765–5.607; $p < 0.001$), and neoplastic brain disease (OR 3.63; CI 1.033–12.771; $p < 0.05$). Precipitating factors for delirium were acute renal failure (OR 6.79; CI 1.062–43.405; $p < 0.05$) and pressure sores (OR 3.66; CI 1.102–12.149; $p < 0.05$).
Significance of results. Our study identified several predisposing and precipitating risk factors for delirium in palliative care patients, some of which can be targeted early and modified to reduce symptom burden.

Introduction

Delirium is an acute neurocognitive disorder in medically ill patients, characterized by disturbances in consciousness or attention and cognition, caused by different underlying etiologies. Typically, delirium is characterized by an abrupt onset and fluctuating course (Meagher et al., 2008).

The etiology of delirium is complex and usually multifactorial, resulting from a combination of risk factors, typically termed either "predisposing" or "precipitation factors" (Inouye et al., 2014). Predisposing factors refer to medical conditions and comorbidities that pre-exist in a patient — like male gender, older age, as well as hearing, visual, and cognitive impairment — and increase a patient's risk of developing delirium. In contrast, precipitating factors are contributing risk factors that are critical in the activation of a delirium episode (Bush et al., 2018). Precipitating factors affect neurotransmitter, neuroendocrine, and/or neuroinflammatory pathways and cause endocrine, metabolic, and electrolyte derangements that contribute to delirium (Kang et al., 2013; Bush et al., 2017). The most common precipitating risk factors for delirium can be roughly categorized into environmental factors, iatrogenic factors, medications (e.g., polypharmacy, psychoactive drugs, sedatives, and hypnotics), neurological disease, comorbid illness, organ failure, metabolic syndromes, including electrolyte and endocrine abnormalities, and surgery (Bush et al., 2017, 2018).

Delirium is prevalent in palliative care patients and can cause high levels of distress among patients, caregivers, and clinicians (Lawlor et al., 2000; Finucane et al., 2017; Lawlor et al., 2019). Incidence and prevalence rates for delirium in palliative care patients are high, ranging from 13% to 85% and from 3% to 45%, respectively (Hosie et al., 2013; Ryan et al., 2013; Lawlor et al., 2014; de la Cruz et al., 2015; Mercadante et al., 2017), depending on the diagnostic tool used, health care environment and disease stage. Moreover, the prevalence of

delirium in terminally ill patients can increase up to 90% (Casarett and Inouye, 2001; Hosie et al., 2013). Delirium is associated with an unfavorable short- and long-term prognosis, including prolonged hospital length of stay (LOS), cognitive decline, and increased morbidity, need for long-term care institutionalization, and mortality (Lawlor et al., 2014; Boettger et al., 2015; Dani et al., 2017; Diwell et al., 2018; Tosun Tasar et al., 2018; Harris et al., 2019). In addition, delirium in palliative care patients is associated with a lower median overall survival relative to those without delirium (de la Cruz et al., 2015). Furthermore, delirium in the medically ill is highly correlated with increased healthcare requirements and cost (Schubert et al., 2018). For the purposes of this study, the term "palliative care patients" refers to patients with terminal diseases that are unlikely to be cured or controlled with treatment and are likely to cause death (with a prognosis of weeks to 6 months) (Hui et al., 2014; National Cancer Institute, 2019).

Despite the high prevalence of delirium in palliative care patients and its prognostic importance, little is known about risk factors, early detection, prevention, management, and prognostic outcomes of delirium in this vulnerable patient population. In view of the adverse impact of delirium on the quality of life of the patients and the substantial burden for caregivers, as well as the severe economic consequences, it is necessary to understand palliative care patients' risk factors for and outcomes of delirium to improve prevention, detection, and management of hospital-acquired delirium at the end of life. Identifying predisposing and precipitating risk factors for delirium in palliative care patients is an important step for the development of more effective delirium treatments and preventative strategies in palliative care patients.

This study sought (1) to examine the prevalence of delirium in palliative care patients; (2) to assess for differences with respect to predisposing and precipitating factors in delirious vs. non-delirious palliative care patients; and (3) to identify the most relevant predisposing and precipitating risk factors as predictors of delirium in palliative care patients.

Methods

Study design, patients, and procedures

The present study is a sub-analysis of the *Delir-Path*, a large prospective observational project which aimed to improve the prevention and facilitate the early detection and management of hospital-acquired delirium in surgical and intensive care patients (Schubert, 2013–2015). In the *Delir-Path project*, patients were recruited across 43 departments at the University Hospital Zurich, Switzerland, a tertiary care center with 900 beds. During the period between January 2014 and December 2014, 39,432 patients with clinical evidence of incident delirium were considered eligible for inclusion. The following exclusion criteria — i.e., (1) age <18 years; (2) LOS <1 day; and (3) missing Delirium Observation Screening (DOS) scores — resulted in a total of 29,278 eligible patients [results published elsewhere (Schubert et al., 2018)]. Out of these, 410 patients were managed at the Competence Center for Palliative Care (Figure 1). Demographic and medical information was retrieved via the electronic medical chart (Klinikinformationssystem, KISIM, CisTec AG, Zurich).

The DOS tool was used to screen patients for delirium and was routinely administered thrice daily by trained study nurses during the first three days of admission to all patients ≥65 years and to patients younger than 65 years on clinical suspicion of incident delirium. Once delirium was detected, DOS was continued three times daily until delirium remission. The training of nursing staff was conducted within a 4-h session with mandatory preceding eLearning and literature research, with an assessment of training success. The nurses were educated with case-reports and state-of-the-art lectures on epidemiology, as well in the diagnostic criteria for delirium, and trained to obtain delirium scores.

All study procedures performed were in accordance with the World Health Organization's Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of the Canton Zurich (KEK), Switzerland (KEK-ZH-Nr. 2012-0263). A waver of informed consent was obtained from the KEK. Data were collected and reported in accordance with guidelines set by the strengthening the reporting of observational studies in epidemiology (STROBE) statement (STROBE, 2009).

Characterization of predisposing and precipitating factors for delirium in palliative care patients

A number of predisposing and precipitating factors have been described for palliative care patients (Kang et al., 2013; Inouye et al., 2014; Hosker and Bennett, 2016; Bush et al., 2018; Schubert et al., 2018; Zipser et al., 2019). For the purpose of this study, characterization of the predisposing and precipitating factors for delirium in palliative care patients was based upon the formation of diagnostic clusters, according to the 10th revision of the International Statistical Classification of Diseases (ICD-10) (World Health Organization, 1992) and related health problems (Table 1). Frailty is a common syndrome in palliative care patients and characterized by a decline in physiological functioning, reduced strength and endurance, and impaired mobility (Moorhouse and Rockwood, 2012). For the purposes of this study, frailty was assessed across the component "mobility" (impaired vs. not impaired).

Determination of delirium

The assessment of delirium was based on the DOS scale and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) delirium construct "disturbances in alertness and attention" (European Delirium and American Delirium, 2014). Indebted to the screening algorithm, only 10,906 out of 28,806 patients were screened, and the DOS detected 91% of patients diagnosed with delirium by psychiatrists. For the unscreened patients, a DSM-5-based construct — alertness or inattention and cognitive impairment — was created from the respective daily nursing assessment ePA-AC (Hunstein et al., 2012). This construct was added to the DOS and accurately identified 97% of the patients diagnosed with delirium according to DSM-IV-TR.

Measures

DOS scale

For the purposes of this study, the 13-item Delirium Observation Screening (DOS-13) scale was used (Schuurmans et al., 2003). The scale was originally designed to facilitate the early recognition of delirium, according to the criteria of the Diagnostic and Statistical Manual IV (DSM-IV) (American Psychiatric Association, 2000). 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). Each item is rated as normal (0) or abnormal
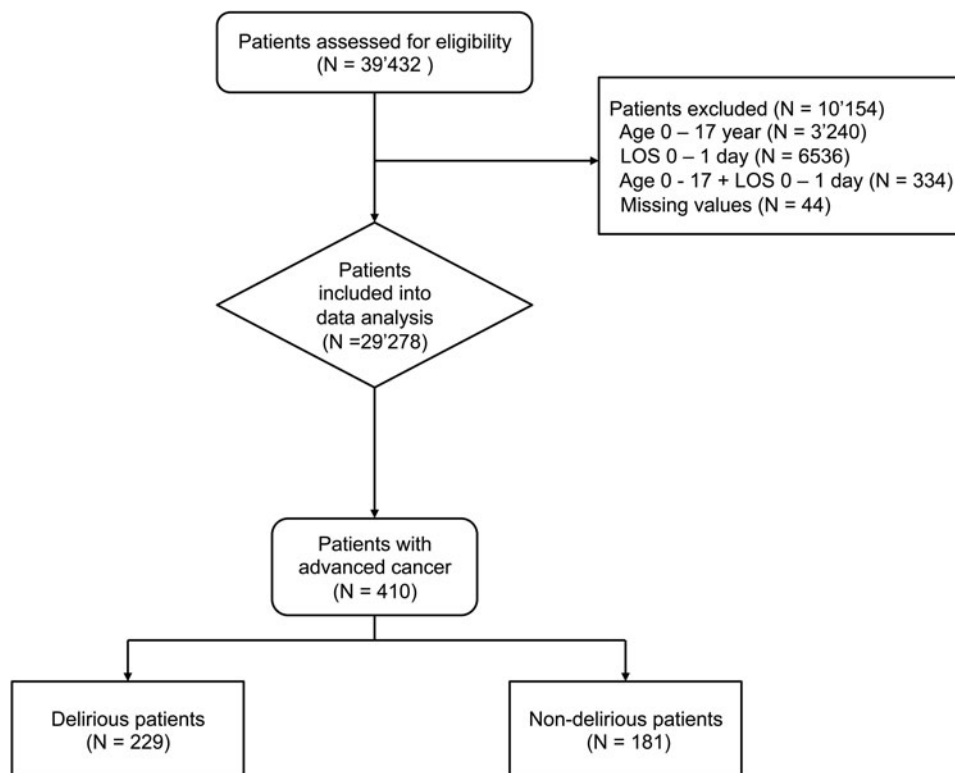
Fig. 1. Screening algorithm for the *Delir-Path*.

(1). Items were aggregated throughout recordings. Any score ≥3 indicates delirium.

Charlson Comorbidity Index

To assess multimorbidity and frailty, the Charlson Comorbidity Index (CCI) was applied (Charlson et al., 1987). The CCI aggregates multiple medical conditions, including age, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia or paraplegia, renal disease, malignancy, and AIDS/HIV. The medical conditions are weighted on a scale from 1 to 6 with total scores ranging from 0 to 37. A total comorbidity score can be computed from the weighted conditions. The CCI shows good reliability and is strongly correlated with mortality and progression-free survival (Williams et al., 2016).

Statistical methods

All analyses were performed with the Statistical Package for the Social Sciences SPSS 25.0 software (IBM Corp., Released 2017) and R. All tests were two-tailed, and the significance level α was set at <0.05. Descriptive statistics were reported as means/standard deviations or medians, interquartile ranges or as counts and percentages, as appropriate. Dichotomizations were chosen for age (<65 vs. ≥65 years), the CCI (<2 vs. ≥2), frailty (mobility impaired vs. not impaired), and residence status prior to admission (institution vs. home). All continuous data were tested for normality using Shapiro–Wilk's test. Continuous outcomes were compared using Student's t-tests or Mann–Whitney U tests for parametric and non-parametric data, respectively, and categorical variables with Pearson's χ^2 or Fisher's exact test, where appropriate.

For the purpose of analysis evaluating the predisposing and precipitating factors for delirium, the data were dichotomized according to the presence or absence of delirium. Subsequently, simple logistic regression models were used to determine effect sizes of socio-demographic and medical characteristics, as well as the prevalence rates for delirium among palliative care patients expressed as odds ratios (OR) with 95% confidence intervals (CIs). As the last step, multiple logistic regression models were used to determine associations between predisposing and precipitating risk factors and delirium in palliative care patients. Multiple regression models were computed with their respective ORs and CIs, based on the results of the simple logistic regressions models, by entering variables with a p-value <0.15. The model was verified with its Cox–Snell's and Nagelkerke's r^2.

Results

Demographics and medical characteristics

Detailed patient demographics and clinical characteristics are summarized in Table 2. The majority of the palliative care patients were cancer patients with predominantly gynecological or lung cancers. In this palliative care patient cohort, the prevalence rate of delirium was 55.9%. Palliative care patients with delirium were primarily males (two-thirds of the sample), who had a twofold increase in risk for delirium. The delirious patients were significantly more commonly admitted as emergencies (OR = 2.14) and less likely to be discharged home (OR = 0.11), and had a hospitalization time twice as long as those who were not delirious. Patients with intracranial neoplasms had a 3.5-fold higher risk

Table 1. Diagnostic clusters with their respective included diagnoses according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

	ICD-10 chapters
Cancer classification	
Head and neck	C00–C14
Lung	C30–C39
Skin	C43–C44
Breast	C50
Gynecological	C51–C58
Hematological	C81–C96
Brain	C70–C72
Secondary neoplasms	C79
Medical disorders	
Sepsis-related disorders	
Streptococcal septicemia, other septicemia	A40–A41
Herpetic sepsis	B00.7
Systemic inflammatory response syndrome	R65
Malnutrition	E40–E46
Electrolyte imbalances	E87
Vascular syndromes of brain in cerebrovascular diseases	
Cerebral vascular syndromes	G46
Cerebral infarction	I63
Cerebral edema	G93.6
Diseases of the circulatory system	
Ischemic heart disease	I20–I25
Diseases of the respiratory system	
Viral Pneumonia	J12–J15
Lung edema	J81
Pleural effusion	J90
Diseases of the liver	
Hepatic failure	K72
Diseases of the skin and subcutaneous tissue	
Pressure sores	L89
Diseases of the genitourinary system	
Acute renal failure	N17
Chronic renal failure	N18
Cystitis	N30
Cachexia	R64
Pain	R52
Neurological disorders	
Organic, including symptomatic, mental disorders	
Alzheimer's disease	F00
Vascular dementias	F01

(Continued)

Table 1. (Continued.)

	ICD-10 chapters
Dementia due to elsewhere defined disorders	F02
Dementia unspecified	F03
Other degenerative diseases of the nervous system	
Alzheimer's disease	G30
Localized atrophies (frontal temporal dementia)	G31
Senile and alcohol-induced degenerations	G31.1–G31.2
Degenerations unspecified	G31.8–G31.9
Degenerations due to elsewhere defined disorders	G32
Episodic and paroxysmal disorders: Epilepsies	G40–G41
Psychiatric disorders	
Substance use disorders	F10–F19

of developing delirium. Generally insured patients developed delirium almost twice as often as semi-privately and privately insured patients. Palliative care patients with delirium had twice the care needs and accounted for twice the health care cost per case. Importantly, delirious patients had a substantial increase in their risk of in-hospital mortality (OR = 18.29). Of those who died in the hospital, 92.6% suffered from terminal delirium. The median time to death did not differ significantly between the groups of delirious and non-delirious patients. No group differences were found for age, number of comorbidities, stay prior to admission, type of facility following hospital discharge, or time to death.

Determination of predisposing and precipitating factors for delirium in palliative care patients

Simple logistic regression identified the following predisposing factors as relevant for delirium: frailty (OR = 31.48), impaired hearing and vision (OR = 7.53 and 6.33, respectively), suffering from epilepsy (OR = 5.68), the presence of brain metastases (OR = 3.55), and male gender (OR = 1.52). No significant group differences were found in terms of older age and the prevalence of degenerative cerebral disorders, stroke, ischemic heart disease, chronic renal failure, cachexia, malnutrition, or substance use disorder.

The most relevant precipitating factors identified by simple logistic regression were acute renal failure (OR = 7.64), pressure sores (OR = 5.92), sepsis (OR = 4.70), and experiencing pain (OR = 1.95). No intergroup differences were found for electrolyte imbalances, cerebral edema, pneumonia, lung edema, pleural effusion, or liver failure. Details on group differences in predisposing and precipitating factors between delirious and non-delirious patients are summarized in Table 3.

Multiple regressions analysis for predisposing and precipitating factors for delirium

Table 4 summarizes the multiple regression analyses examining the relationship between predisposing and precipitating risk factors and delirium in palliative care patients. On multivariate

Table 2. Socio-demographic, medical, and neurological characteristics of the delirious vs. non-delirious palliative care patients

	Delirious patients (DOS ≥ 3) N = 229	Non-delirious patients (DOS < 3) N = 181	OR (95% CI)	*p*-value
Age in years M (SD)	66.4 (14.1)	64.5 (12.4)		0.155
Gender (%)				
Male	64	54	1.52 (1.024; 2.267)	<0.05
Female	36	46	0.65 (0.441; 0.997)	<0.05
CCI[a]	2.3 (1.5); 3 (3)	2.5 (1.3); 3 (1)		0.360
Neoplastic disease	201	177	0.162 (0.056; 0.472)	<0.001
Tumor type (%)				
Gynecological	19	17		0.490
Lung	18	21		0.501
Brain	9	3	3.55 (1.313; 9.619)	<0.01
Head and neck	9	25	0.30 (0.169; 0.519)	<0.001
Skin	7	6		0.712
Hematological	1	3		0.929
Breast	1	2		0.485
Secondary neoplasm	56	59		0.513
Mode of admission N (%)				
Emergency	72	54	2.14 (1.418; 3.220)	<0.001
Elective	26	43	0.46 (0.302; 0.696)	<0.001
Other	2	3		
Stay prior admission N (%)				
Home	78	85		0.083
Assisted/nursing	10	6		0.246
Hospital	10	7		0.216
Other	2	2		0.789
Hospital health insurance (%)				
General health insurance	89	78	2.14 (1.249; 3.682)	<0.01
Semiprivate health insurance	7	14	0.5 (0.261; 0.958)	<0.05
Private health insurance	4	8		0.129
Discharge to N (%)				
Home	25	76	0.11 (0.069; 0.171)	<0.001
Assisted living	15	12		0.431
Other hospital	3	2		0.362
Rehabilitation	8	5		0.312
Other	0	1		0.867
Length of stay in days	23.2 (20.1; 20)	15.2 (13.2; 13)		<0.001
Care requirements per case in h[a]	186 (283); 117 (139)	63 (68); 45 (56)		<0.001
Medical costs per case (CHF)[a]	51,832 CHF (70,417 CHF)	23,457 CHF (22,505 CHF)		<0.001
	34,971 CHF (35,163 CHF)	17,246 CHF (17,377 CHF)		
Death N (%)	49	4	18.29 (8.918; 37.530)	<0.001
Time to death (days)[a]	20 (17); 16 (17)	18 (16); 12 (20)		0.523
Delirium in deceased patients (%)	92.6	7		<0.001

CCI, Charlson Comorbidity Index; M, mean; SD, standard deviation; Md, median; IQR, interquartile range.
[a]Mean, standard deviation; median, interquartile range.

Table 3. Predisposing and precipitating factors in delirious vs. non-delirious palliative care patients

	Delirious (%) (*N* = 229)	Non-delirious (%) (*N* = 181)	OR (95% CI)	*p*-value
Predisposing factors				
Older age (≥65 years)	54	49		0.266
Male gender	64	54	1.52 (1.024; 2.267)	<0.05
Frailty	97	54	31.48 (13.294; 74.532)	<0.001
Impaired hearing	45	10	7.53 (4.338; 13.084)	<0.001
Impaired sight	68	25	6.33 (4.092; 9.792)	<0.001
Neoplastic disease	88	97	0.16 (0.056; 0.472)	<0.001
Brain neoplasm	9	3	3.55 (1.313; 9.619)	<0.01
Degenerative cerebral disorders	2	0		0.07
Stroke	0	0		0.559
Epilepsy	9	2	5.68 (1.660; 19.422)	<0.01
Ischemic heart disease	18	12		0.095
Chronic renal disease	11	7		0.123
Cachexia	6	2		0.087
Malnutrition	19	24		0.227
Substance use disorder	5	5		0.903
Precipitating factors				
Sepsis	10	2	4.70 (1.591; 13.905)	<0.01
Electrolyte imbalances	7	9		0.453
Cerebral edema	4	1		0.074
Pneumonia	2	1		0.172
Lung edema	1	1		0.813
Pleural effusion	3	1		0.271
Liver failure	2	0		0.074
Pressure sores	12	2	5.92 (2.030; 17.231)	<0.001
Acute renal failure	8	1	7.64 (1.748; 33.353)	<0.01
Cystitis	22	23		0.812
Pain	90	83	1.95 (1.083; 3.492)	<0.05

OR, Odds Ratio; CI, Confidence Interval.

regression, the most relevant predisposing risk factor was frailty, with a 15-fold increased risk of delirium. Impaired hearing and the presence of brain neoplasms increased the risk for delirium by a factor of four and impaired vision by a factor of three. Male gender increased the risk of delirium by a factor two. Contrarily, the neoplastic disease was not associated with an increased risk for delirium, although most patients had cancer. No significant associations with delirium in palliative care patients were identified for epilepsy, ischemic heart disease, chronic renal disease, or cachexia.

The most relevant precipitating factors for developing delirium were acute renal failure, increasing the risk of developing delirium by a factor of seven, and pressure sores, increasing the risk of delirium fourfold. Sepsis, cerebral edema, and pain were not predictive of delirium in palliative care patients. Predisposing and precipitating factors for delirium are depicted in Figure 2.

Discussion

This prospective observational study sought to identify predisposing and precipitating risk factors for delirium in palliative care patients that can be targeted early and either modified or eliminated. The prevalence of delirium in palliative care patients was 55.9%, which is consistent with other prevalence rates reported in the current literature (Hosie et al., 2013; de la Cruz et al., 2015; Bush et al., 2017). This finding underscores the need for systematic delirium screening in palliative care patients. The development of delirium is particularly prevalent in patients near the end of life and considered a poor prognostic sign (Bush et al., 2017). In this study, 93% of patients had terminal delirium in their last days of life. Our results corroborate the previous research, including palliative care patients, for which a delirium rated of up to 88% in the terminal phase of life has been reported (Lawlor et al., 2000). Overall, delirium in palliative

Table 4. Summary of a multiple regression model for the predisposing and precipitating factors for delirium in palliative care patients with estimated coefficients (B, SE), 95% CIs, and *p*-values

	B (SE)	Exp (B)	95% CI lower–upper	*p*-value
Predisposing factors				
Gender (male)	0.79 (0.29)	2.19	1.251–3.841	<0.01
Frailty	2.73 (0.49)	15.28	5.885–39.665	<0.001
Hear impaired	1.26 (0.37)	3.52	1.721–7.210	<0.001
See impaired	1.15 (0.30)	3.15	1.765–5.607	<0.001
Neoplastic disease	−1.60 (0.75)	0.20	0.047–0.876	<0.05
Brain tumor	1 .29 (0.64)	3.63	1.033–12.771	<0.05
Epilepsy	1.27 (0.74)	3.55	0.833–15.128	0.087
Ischemic heart diseases	−0.74 (0.41)	0.48	0.211–1.073	0.073
Chronic renal disease	−0.21 (0.58)	0.81	0.260–2.531	0.720
Cachexia	1.18 (0.75)	3.24	0.747–14.096	0.116
Precipitating factors				
Sepsis	1.38 (0.75)	3.99	0.921–17.263	0.064
Cerebral edema	0.38 (0.90)	1.46	0.250–8.559	0.674
Pressure sores	1.30 (0.61)	3.66	1.102–12.149	<0.05
Acute renal failure	1.92 (0.95)	6.79	1.062–43.405	<0.05
Pain	0.89 (0.48)	2.42	0.945–6.225	0.066
Constant	−2.83 (0.93)	0.06		<0.01

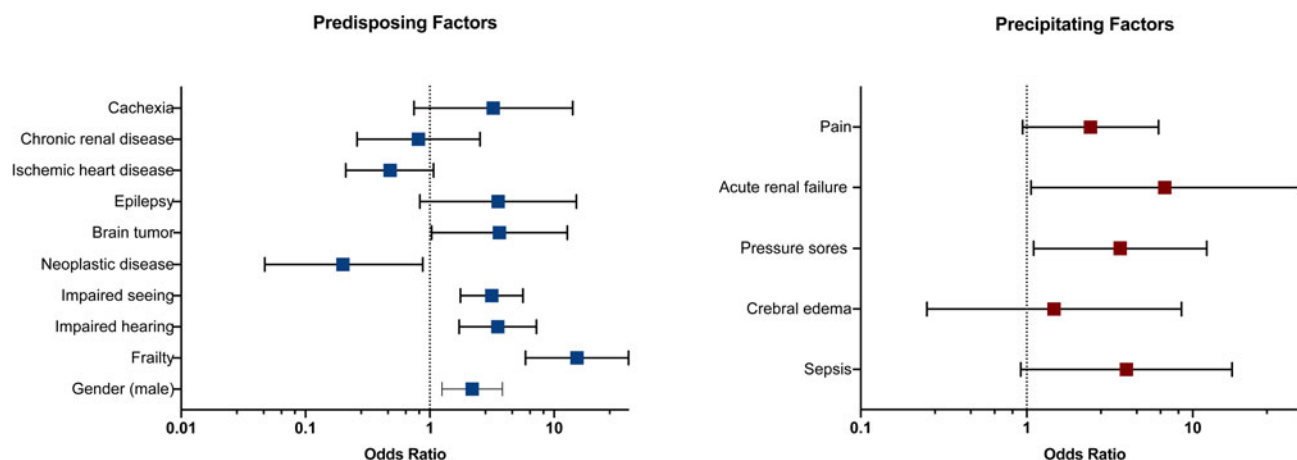Cox–Snell and Nagelkerke r^2 = 0.238 and 0.357. SE, standard error; CI, confidence interval.

Fig. 2. Forest plots of predisposing and precipitating factors for delirium. ORs and 95% CIs are reported for each delirium risk factor. The edges of the polygon represent the 95% CI. The graphical representation in the figure refers to the statistics in Table 4.

care patients was associated with increased healthcare requirements, prolonged hospital stays, increased health care costs, the need for specialized care homes, and increased mortality, reflecting outcomes in the acute hospital setting (Schubert et al., 2018). Contradicting to the current literature, in which age and comorbidities have been claimed as significant risk factors for delirium (Bush et al., 2018), we were unable to identify older age (≥65 years) or comorbidities as contributory. Notably, the palliative care patients had multiple terminal medical conditions more relevant to the outcome than either age or comorbidities. It is reasonable to assume that, in terminally ill patients, factors other than older age have a greater impact on the development of delirium, due to the high degree of systemic inflammation and/or organ dysfunction.

The etiology of the delirium syndrome in terminally ill patients is complex and multidimensional, involving many potentially contributing predisposing and precipitating factors (Bush et al., 2018). Of note, palliative care patients are at particular risk of delirium due to a number of contributing factors in the pathogenesis of delirium, like the advanced disease (e.g., malignancy) itself, the presence of metastases, hematological conditions (e.g., anemia), high-level systemic inflammation, organ dysfunction,

infections/sepsis, impaired functional status, poor nutritional status, adverse effects of radiation/chemotherapy, and treatment with certain medications (e.g., opioids, corticosteroids, and benzodiazepines) (Kang et al., 2013; Hosker and Bennett, 2016; Bush et al., 2017, 2018). In the current palliative care literature, there is limited evidence about socio-demographic or disease-related predictive factors for delirium in palliative care patients (Bush et al., 2018). In addition, studies, including palliative care patients, have traditionally focused predominantly on delirium prevalence, delirium management, and outcomes rather than investigating risk factors predicting delirium in this vulnerable population (Maltoni et al., 2012; de la Cruz et al., 2015; Boettger and Jenewein, 2017; Hui et al., 2017; Hosie et al., 2019; Lawlor et al., 2019).

Considering these findings, in a second analytical step, we sought to identify differences between delirious and non-delirious palliative care patients including a number of delirium risk factors that have been identified in medically ill patients (Schubert et al., 2018; Zipser et al., 2019). Contributory predisposing factors for delirium in palliative care patients included male gender, frailty, hearing and visual impairment, and epilepsy, as well as brain metastases. Contributory precipitating factors included sepsis, pressure sores, acute renal failure, and pain. Neoplastic disease by itself was not associated with an increased delirium risk but even with an 80% decrease. It is notable that cancer itself might not be as relevant to delirium as complications caused by the terminal illness.

Lastly, we explored potential predictors of delirium in palliative care patients. On multivariate analysis, the most relevant predisposing risk factors for delirium were male gender, frailty, hearing and visual impairment, and brain neoplasms, while the most important precipitating risk factors were the presence of pressure sores and acute renal failure. There is scant literature that has systematically investigated predisposing and/or precipitating risk factors for delirium in palliative care patients. One study found that delirium was precipitated by opioids and other psychoactive medications, dehydration, hypoxic encephalopathy, metabolic factors, and non-respiratory infection (Lawlor et al., 2000). Another study explored predisposing risk factors for delirium in terminally ill patients and identified hepatic failure, medications, prerenal azotemia, hyperosmolality, hypoxia, disseminated intravascular coagulation, organic damage to the central nervous system, infections, and hypercalcemia as the main contributing predisposing risk factors for delirium (Morita et al., 2001). In a prospective observational study, including oncological patients with different cancer stages, factors significantly associated with the occurrence of delirium were advanced age, cognitive impairment on admission, hypoalbuminemia, the presence of bone metastases, and the diagnosis of a hematological malignancy (Ljubisavljevic and Kelly, 2003). These inconsistent findings might be best explained by methodological differences. Furthermore, a number of studies suggest that underlying pathologies of delirium in palliative care patients are usually multifactorial and commonly unspecified (Stiefel et al., 1992; Bush et al., 2017; de la Cruz et al., 2017; Diwell et al., 2018). Moreover, the identification of risk factors for delirium in palliative care patients may be complicated by high systemic inflammation and iatrogenic conditions. Furthermore, the distinction between predisposing and precipitating factors for delirium in palliative care patients can be fairly arbitrary, due to the complex and multifactorial etiology of delirium and considerable multimorbidity in terminally ill patients (Lawlor et al., 2000; Ljubisavljevic and Kelly, 2003).

A multifactorial model of delirium has been proposed for hospitalized patients age ≥70 years (Inouye et al., 2014), assuming that patients with multiple predisposing conditions for delirium (high baseline vulnerability) seem to be more vulnerable to precipitating factors or noxious insults than patients with only one predisposing factor. Thus, the accumulation and synergy of predisposing and precipitating factors may potentiate the severity of delirium (Laurila et al., 2008). Correspondingly, in older, frail patients with less advanced disease, relatively little comorbidity is often sufficient to promote delirium, whereas in younger individuals, multiple comorbidities and more severe illness might be necessary (Bush et al., 2018).

Typically, delirium in palliative care patients is an indicator of some acute change in the patient's medical condition (Hosie et al., 2013). In particular, hyperactive delirium — commonly referred to as "terminal agitation" or "terminal restlessness" — can cause high distress among family members (Namba et al., 2007). Given the substantial burden of delirium for palliative care patients and their caregivers, it is clinically important to prevent, recognize, and manage early the symptoms of delirium and identify contributory causes. One key strategy to prevent delirium is the treatment of potentially reversible predisposing and acute precipitating factors (e.g., providing hearing and vision aids, treating pain, infections and electrolyte abnormalities, reducing polypharmacy, and regulating the sleep–wake cycle) (Bush et al., 2018).

In many acute care hospital settings, delirium is frequently underdiagnosed (Elsayem et al., 2016). The early detection of clinical signs of delirium in palliative care patients can be improved by the routine use of screening tools and monitoring by the nursing staff (Bush et al., 2018). In this study, a combined approach using the DOS tool and the DSM-5 diagnostic criteria for delirium achieved diagnostic sensitivity of 97%, and thus, proved to be superior to using the DOS instrument alone or the combined DOS/Intensive Care Delirium Screening Checklist (ICDSC) (Schubert et al., 2018). A similar approach has been utilized to diagnose delirium among elderly medical inpatients, in whom applying the DSM-IV diagnostic criteria for delirium exhibited high sensitivity and specificity (Cole et al., 2003).

Pharmacological and non-pharmacological treatments are available for delirium management. However, most of these guidelines are based on the knowledge of delirious symptom management in medically ill patients (Schubert et al., 2018) or elderly individuals (Inouye et al., 2014). Although delirium in palliative care patients can potentially be reversed in approximately 50% of cases, the decision to initiate pharmacological treatment depends on the estimated prognosis and objectives of care (e.g., management of delirium to reduce morbidity and improve the quality of life vs. palliative sedation for refractory delirium and expected survival of hours to days) (Kang et al., 2013; Bush et al., 2017). Although eliminating delirium is not always feasible, symptomatic management of potentially reversible causes of delirium, particularly multicomponent non-pharmacological strategies (e.g., training nursing staff and improving the patients' environment) should be provided to all palliative care patients and complemented with pharmacological interventions, where indicated (Bush et al., 2018).

Strengths and limitations

Important strengths of our study include its rigorous methodology, utilization of an innovative delirium-screening approach,

combining the DOS score and the DSM-5 diagnostic criteria for delirium, and systematic assessment of precipitating and predisposing risk factors for delirium in a select group of palliative care patients known to be extremely vulnerable to delirium. On the other hand, the study had several limitations. First, data collection was limited to a single center, which may limit the generalizability of results. Second, certain uncommon factors for delirium, like endocrine disorders, were not investigated, and brain imaging was not routinely performed. Third, clinical features of delirium were assessed only cross-sectionally. Finally, conducting research in delirious patients at the end of life includes many ethical challenges (e.g., decision-making capacity in delirious patients at the end of life) (Casarett, 2005). In accordance with the Declaration of Helsinki, Article 29, a waiver of consent was granted by the ethics committee because the majority of our studied population was physically and mentally unable to give consent (delirious patients), and the condition (delirium) that causes this inability was a necessary characteristic of our research population (World Medical Association, 2013). This prospective observational study was considered to produce not more than a minimal risk to the study subjects and involved no procedure for which written informed consent was required. Proxy assessments were conducted by well-trained and experienced nurses, and medical information was retrieved through medical record retrieval. Finally, this study sought to improve the quality of delirium assessments in an acute hospital setting by proposing a novel delirium-screening construct, an effort that should be of benefit for future patients.

Conclusions

Delirium is a prevalent complication in palliative care patients, especially in the end-of-life context. Combining the DOS instrument and the DSM-5 diagnostic criteria for delirium appeared to screen for delirium with high sensitivity and specificity. Our study also identified several predisposing and precipitating risk factors for delirium in palliative care patients, some of which can be targeted early and either modified or eliminated to reduce symptom burden and improve clinical outcomes. At present, limited evidence exists with respect to predisposing and precipitating risk factors for delirium in palliative care patients. Continued research is warranted to strengthen the reliability of our findings and to better understand risk factors for delirium and their potential reversibility with the ultimate aim of improving the management of delirium in palliative care patients (Hui, 2019).

Conflict of interest. The authors do not have any conflicts of interest to declare.

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