ORIGINAL RESEARCH

Factors for Timely Identification of Possible Occurrence of Delirium in Palliative Care: A Prospective Observational Study

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ABSTRACT

Delirium occurs in 50–80% of end-of-life patients but is often misdiagnosed. Identification of clinical factors potentially associated with delirium onset can lead to a correct early diagnosis. To this aim, we conducted a prospective cohort study on patients from an Italian palliative care unit (PCU) admitted in 2018–2019. We evaluated the presence of several clinical factors at patient admission and compared their presence in patients who developed delirium and in those who did not develop it during follow-up. Among 503 enrolled patients, after a median follow-up time of 16 days (interquartile range 6–40 days), 95 (18.9%) developed delirium. Hazard ratios (HR) and corresponding 95% confidence intervals were computed using Cox proportional hazard models. In univariate analyses, factors significantly more frequent in patients with delirium were care in hospice, compromised performance status, kidney disease, fever, renal fail-

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ure, hypoxia, dehydration, drowsiness, poor well-being, breathlessness, and "around the clock" therapy with psychoactive drugs, particularly haloperidol. In multivariate analyses, setting of care (HR 2.28 for hospice versus home care, 95% CI 1.45–3.60; $p < 0.001$), presence of breathlessness (HR 1.71, 95% CI 1.03–2.83, $p = 0.037$), and administration of psychoactive drugs, particularly haloperidol (HR 2.17 for haloperidol, 95% CI 1.11–4.22 and 1.53 for other drugs, 95% CI 0.94–2.48; $p = 0.048$) were significantly associated with the risk of developing delirium. The study indicates that some clinical factors are associated with the probability of delirium onset. Their evaluation in PC patients could help healthcare professionals to identify the development of delirium in those patients in a timely manner.

Keywords: Causality; Clinical predisposing factors; Delirium; Palliative care

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Abbreviations

CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CNS	Central nervous system
ESAS	Edmonton Symptoms Assessment System
HR	Hazard ratio
IQR	Interquartile range
KPS	Karnofsky Performance Status
PC	Palliative care
PCU	Palliative care unit
SD	Standard deviation

Key Summary Points

Delirium is frequent in terminal care patients

Its early diagnosis is not easy

This paper aims to find signs and symptoms that could help in the early detection of delirium in terminal patients

The results obtained are encouraging. In fact, using the studied questionnaire and following the reported criteria, the delirium may be detected early in terminal patients

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14697003

INTRODUCTION

According to the *Diagnostic and Statistical Manual of Mental Disorders 5th Edition*, delirium is defined as an acute change in mental status, with a fluctuating course, inattention, disturbance of consciousness, and disorganized thinking [1]. Delirium is also associated with

serious short- or long-term clinical morbidities, falls, increased risk of institutionalization, decline of physical and social functions, and high risk of death [2]. The overall prevalence of delirium varies widely, between 9% and 80%, the variability depending on many factors, such as age, multimorbidity, dementia, organ functional deficits, ongoing therapies, setting of care, and other factors [3–7]. In particular, 18–35% of elderly people present delirium at the moment of hospital admission or during hospital stay [3–5, 7–9]. In a retrospective review of 319 patients admitted to two hospices and one hospital ward, the prevalence of delirium was higher, being 36–39% among 319 patients [10]. The prevalence of patients with delirium in palliative care (PC) and hospice wards is generally higher, varying from 50% to 80% [11–13]. A recent systematic review estimated a high variability in delirium prevalence in the PC setting (between 6% and 74%, rising during follow-up and reaching with the highest values prior to death) [14].

Delirium has merely a clinical diagnosis, as currently there are no biomarkers or laboratory tests with high sensitivity and specificity to confirm its presence. Especially in the PC setting—both hospice and home care—clinical evaluation is crucial and constitutes the exclusive way to make a diagnosis of delirium. Nevertheless, delirium is often misdiagnosed. In all situations, early recognition of meaningful signs and symptoms may be important to anticipate the onset of delirium and to contain its clinical manifestations and associated complications. In the PC context, given the high prevalence of delirium [11–13], a specific alertness/attention of the healthcare professionals and caregivers in observing the patients can have a relevant preventive value.

To this aim, we conducted a prospective cohort study set up by the health professionals of an Italian PC unit (PCU) and other experts in PC to identify relevant clinical factors that could be related to the risk of delirium onset.

MATERIALS AND METHODS

A prospective, single-center, cohort study was conducted at the specialist PCU of Giussano, ASST Brianza (MB), Lombardy Region, Italy, between October 2018 and December 2019. The PCU treats both patients at home and in hospice, with the same staff and clinical protocols, thus ensuring homogeneity of care. We screened all consecutive patients and included those who satisfied the following inclusion criteria: presence of a chronic progressive disease needing specialist PC intervention; age 18 years or over; ability to comprehend and speak Italian; informed consent to the processing of personal data and participation in the study. Patients with a state of coma, diagnosis of a psychiatric pathology, dementia, or substance abuse and/or dependence, current or lasting for at least 3 months, were excluded. Moreover, patients with delirium in progress at the time of admission were excluded.

Within 24 h from patients' admission to the PCU, we collected several pieces of clinical information—selected within a previous literature search as potential risk factors linked to the onset of delirium [15–17]—such as age, sex, education, marital status, primary pathology for which admission to the PCU had been required, Karnofsky Performance Status (KPS), presence of comorbidities considered in the Cumulative Illness Rating Scale (CIRS), presence of fever, renal and/or liver failure, hypoxia, dehydration, nutritional deficiency, cerebral radiotherapy, and systemic chemotherapy during the last 3 months. Besides, we recorded prevalence and severity of patients' symptoms measured at the time of patients' admission to PCU by the Edmonton Symptoms Assessment System (ESAS) [18, 19], and the "around the clock" therapeutic scheme.

Patients were followed up from the date of admission to the PCU to the date of delirium onset, death, transfer outside the PCU, or end of follow-up (October 28, 2020), whichever came first. During this period, attention was paid to recognizing patients who developed delirium and those who did not develop it. The diagnosis of delirium was carried out by means of the

Italian version of 4AT, a frequently adopted tool for rapid delirium screening, which has been proven to have a good diagnostic test accuracy [20–22]. The 4AT test included four questions to investigate the patient's state of supervision, orientation, and attention, and the presence of acute change or fluctuating courses. A score is assigned to each question and the final score ranges from 0 to 12; patients with a 4AT total score ≥ 4 were considered to be suffering from delirium. The 4AT was assessed by health workers of the PCU (medical doctors in 44.6% of cases and nurses in 55.4%, in most cases different from those who collected the baseline patient data), in every situation in which the patient showed symptoms possibly linked to a delirium state.

The study protocol was approved by the Ethics Committee of the ASST of Vimercate (MB), Italy on June 18, 2018 (project no. 2824). Written informed consent for participation in the study and processing personal data was collected from all recruited patients before any study-related activity was carried out.

Statistical Analysis

Descriptive statistics were used to summarize the patients' demographic and clinical characteristics. Sociodemographic factors and prevalence of potential risk factors, symptoms, and drug use were compared between patients who developed delirium and those who did not develop it, to understand which factors were significantly related to the development of delirium. Differences between patients with and without delirium were analyzed using the t test and chi-square test, respectively for continuous and categorical variables. We used Cox proportional hazards models to estimate the hazard ratio (HR) of delirium for various exposure factors and their corresponding 95% confidence intervals (CIs). In the multivariate model, we included all factors with a p value ≤ 0.10 in the univariate analyses. For all statistical analyses, we used the software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among 780 patients admitted to the PCU, 35.5% were excluded since they did not satisfy the inclusion criteria; one-third were excluded because of delirium in progress.

Table 1 shows the general characteristics of 503 patients enrolled in the study at the moment of admission to PCU. After a median follow-up time of 16 days (interquartile range, IQR, 6–40), 95 (18.9%) patients developed delirium. The characteristics of 95 patients who developed delirium and 408 patients who did not develop it are listed separately. Fifty-six percent of patients were male, mean age was 76 years; 49.8% of them had primary education or less, 54.7% of patients were married, 90.3% had a diagnosis of cancer (of whom about 87% metastasized). Over 64% of patients were initially cared for at home and 35.8% in hospice. The distribution of characteristics was similar in patients who did and did not develop delirium, although significant differences were observed in relation to age and setting of care. Patients who developed delirium were on average almost 3 years older than those who did not develop it (mean age 78.2 and 75.4, respectively), and were less frequently treated at home (49.5% and 67.6%, respectively). Median survival time was 9 days (IQR 2–22) in patients with delirium and 19 days (IQR 8–42) in those without delirium (data not shown).

Table 2 presents the distribution of comorbidities included in the CIRS and the KPS, overall and according to the presence of delirium. Prevalence of comorbidities was not significantly different between patients with and without delirium; moreover, no significant difference was found according to levels of the CIRS score and KPS, although values of CIRS ≥ 8 were found more frequently in patients who developed delirium (20.0%) than in those who did not develop it (13.5%), and general conditions were more severe in patients with delirium than in those without delirium (KPS ≤ 30 in 33.7% and in 24.5% of patients, respectively).

The prevalence of clinical factors in all patients and in the two sub-groups of patients

Table 1 Main baseline characteristics among 503 patients admitted to palliative care, overall and according to the presence of delirium

Characteristics	All patients (%) (N = 503)	Presence of delirium (%)		p value [a]
		Yes (N = 95)	No (N = 408)	
Sex, male	280 (55.7)	58 (61.1)	222 (54.4)	0.241
Age (years)				
≤ 70	141 (28.0)	21 (22.1)	120 (29.4)	
71–80	177 (35.2)	30 (31.6)	147 (36.0)	
> 80	185 (36.8)	44 (46.3)	141 (34.6)	
Mean (SD)	76.0 (11.4)	78.2 (11.0)	75.4 (11.5)	0.036
Education				0.341
Primary school or less	251 (49.8)	50 (52.6)	201 (49.2)	
Middle school	149 (29.6)	24 (25.3)	125 (30.6)	
High school or university degree	103 (20.5)	21 (22.1)	82 (13.5)	
Marital status				0.628
Single	39 (7.8)	7 (7.4)	32 (8.6)	
Married	275 (54.7)	52 (54.7)	223 (54.7)	
Widow/widower	167 (33.2)	33 (34.7)	134 (32.8)	
Divorced	9 (1.8)	0 (0.0)	9 (2.2)	
Separate	11 (2.2)	2 (2.11)	9 (2.2)	
Cohabiting	2 (0.4)	1 (1.1)	1 (0.2)	
Primary disease				0.150
Cancer	454 (90.3)	82 (86.3)	372 (91.2)	
Other diseases	49 (9.7)	13 (13.7)	36 (8.8)	
Respiratory	3 (0.6)	0 (0)	3 (0.7)	
Heart	9 (1.8)	2 (2.1)	7 (1.7)	
Liver	15 (3.0)	3 (3.2)	12 (2.9)	
Vascular	3 (0.6)	0 (0)	3 (0.7)	
Kidney	7 (1.4)	2 (2.1)	5 (1.2)	
Other	12 (2.4)	6 (6.3)	6 (1.5)	
Setting of care				0.001
Home care	323 (64.2)	47 (49.5)	276 (67.6)	
Hospice	180 (35.8)	48 (50.5)	132 (32.4)	

SD standard deviation

[a] Differences between the two groups were tested using chi-square or *t* tests

Table 2 History of comorbidities included in the Cumulative Illness Rating Scale (CIRS) and Karnofsky Performance Status (KPS) among 503 patients admitted to palliative care, overall and according to the presence of delirium

Comorbidities	All patients (%) (N = 503)	Presence of delirium (%)		p value[a]
		Yes (N = 95)	No (N = 408)	
Heart disease	218 (43.3)	39 (41.1)	179 (43.9)	0.617
Hypertension	297 (59.0)	53 (55.8)	244 (59.8)	0.474
Vascular disease	227 (45.1)	38 (40.0)	189 (46.3)	0.265
Respiratory disease	257 (51.1)	54 (56.8)	203 (49.8)	0.213
Otolaryngology or eye disease	59 (11.7)	13 (13.7)	46 (11.3)	0.511
Gastrointestinal disease	209 (41.6)	38 (40.0)	171 (41.9)	0.734
Liver disease	238 (47.3)	37 (39.0)	201 (49.3)	0.070
Kidney disease	124 (24.7)	29 (30.5)	95 (23.3)	0.140
Genitourinary system disease	146 (29.0)	30 (31.6)	116 (28.4)	0.543
Musculoskeletal-cutaneous disease	207 (41.2)	41 (43.2)	166 (40.7)	0.659
Neurologic disease	66 (13.1)	11 (11.6)	55 (13.5)	0.621
Endocrine-metabolic disease	184 (36.6)	38 (40.0)	146 (35.8)	0.442
Psychiatric or behavioral problem	60 (11.9)	14 (14.7)	46 (11.3)	0.348
Oncologic disease[b]	435 (86.1)	80 (84.2)	355 (87.0)	0.472
CIRS score				0.298
≤ 3	88 (17.5)	19 (20.0)	69 (16.9)	
4–7	341 (67.8)	57 (60.0)	284 (69.6)	
≥ 8	74 (14.71)	19 (20.0)	55 (13.5)	
KPS				0.060
≤ 30	132 (26.2)	32 (33.7)	100 (24.5)	
30–50	163 (32.4)	30 (31.6)	133 (32.6)	
≥ 50	208 (41.4)	33 (34.7)	175 (42.9)	

[a] Differences between the two groups were tested using chi-square tests
[b] During the last 10 years

who developed and did not develop delirium is given in Table 3. No significant differences were found for most clinical factors; however, the presence of hypoxia and the total number of simultaneously present clinical factors were significantly more frequent in patients who developed delirium than in those who did not develop it (24.2% versus 14.7% respectively with hypoxia, and 58.9% and 47.5% respectively with at least two clinical factors). Only 17.7% of patients (12.6% of those with delirium and 18.9% of those without delirium) had no clinical factors (data not shown).

In relation to symptoms, the presence of breathlessness and poor well-being was significantly higher in patients who developed

Table 3 Baseline risk clinical factors among 503 patients admitted to palliative care, overall and according to the presence of delirium

Risk factors	All patients (%) (N = 503)	Presence of delirium (%)		p value[a]
		Yes (N = 95)	No (N = 408)	
Fever	24 (4.8)	7 (7.4)	17 (4.2)	0.187
Renal failure	85 (16.9)	22 (23.2)	63 (15.4)	0.071
Liver failure	114 (22.7)	19 (20.0)	95 (23.3)	0.491
Hypoxia	83 (16.5)	23 (24.2)	60 (14.7)	0.025
Dehydration	129 (25.6)	30 (31.6)	99 (24.3)	0.142
Nutritional deficiency	192 (38.2)	41 (43.2)	151 (37.0)	0.267
Cerebral radiotherapy[b]	35 (7.0)	4 (4.2)	31 (7.6)	0.243
Chemotherapy[b]	173 (34.4)	29 (30.5)	144 (35.3)	0.378
Number of clinical factors				0.041
0	89 (17.7)	12 (12.6)	77 (18.9)	
1	164 (32.6)	27 (28.4)	137 (33.6)	
≥ 2	250 (49.7)	56 (58.9)	194 (47.5)	

[a] Differences between the two groups were tested using chi-square tests
[b] During the last 3 months

delirium (79.0% and 63.2%, respectively) than in those who did not develop it (64.5% and 46.1%; Table 4). Conversely, for other symptoms, such as pain, fatigue, anxiety, and depression the prevalence was similar in patients with and without delirium.

The relationship between the severity of symptoms (measured by ESAS) and risk of developing delirium is shown in Table 5. For most symptoms, the severity was similar in patients who developed and in those who did not develop delirium. Only for drowsiness, poor well-being, and breathlessness, was the presence of moderate/severe degree symptoms higher in the former (17.9%, 26.3%, and 17.9%, respectively) than the latter group (9.6%, 18.4%, and 12.0%, respectively).

Table 6 shows the distribution of the main classes of drugs prescribed as "around the clock" therapy in all patients, and separately according to the presence of delirium. Use of haloperidol and other drugs acting on the central nervous systems (CNS; tricyclic and SSRI

antidepressants, antiepileptics, antiparkinsonians, antipsychotics, barbiturates, and benzodiazepines) was more frequent in patients who developed delirium (24.2% and 31.6%, respectively) than in those who did not develop it (14.5% and 26.2%, respectively). For other drugs considered, the prevalence of use was similar in the two groups of patients.

The univariate and multivariate analyses of the 18 factors with a p value < 0.1 in univariate analysis are shown in Table 7. Factors that were significantly related to delirium in univariate analyses were care in hospice, compromised performance status, kidney disease, fever, renal failure, hypoxia, dehydration, drowsiness, poor well-being, breathlessness, "around the clock" treatment with haloperidol and other drugs acting on the CNS, cardiovascular drugs, anticoagulants, gastroprotective drugs, and morphine. After adjustment for each of these factors, setting of care, presence of breathlessness, and administration of CNS active drugs, particularly haloperidol were significantly

Table 4 Prevalence of selected symptoms among 503 patients admitted to palliative care, overall and according to the presence of delirium

Symptoms	All patients (%) (N = 503)	Presence of delirium (%)		p value[a]
		Yes (N = 95)	No (N = 408)	
Pain	321 (63.8)	61 (64.2)	260 (63.7)	0.929
Fatigue	469 (93.2)	87 (91.6)	382 (93.6)	0.474
Nausea	165 (32.8)	29 (30.5)	136 (33.3)	0.600
Depression	224 (44.5)	41 (43.2)	183 (44.9)	0.765
Anxiety	257 (51.1)	45 (47.4)	212 (52.0)	0.420
Drowsiness	346 (68.8)	73 (76.8)	273 (66.9)	0.060
Loss of appetite	396 (78.7)	79 (83.2)	317 (77.7)	0.241
Poor well-being	338 (67.2)	75 (79.0)	263 (64.5)	0.007
Breathlessness	248 (49.3)	60 (63.2)	188 (46.1)	0.003

[a] Differences between the two groups were tested using chi-square tests

associated with the development of delirium: the HR was 2.28 for hospice versus home care (95% CI 1.45–3.60, $p < 0.001$), 1.71 for presence versus no presence of breathlessness (95% CI 1.03–2.831.74), and 2.17 for haloperidol administration versus no administration of any CNS drugs (95% CI 1.11–4.22, $p = 0.0248$).

DISCUSSION

Delirium is often undetected or misdiagnosed. In one study, nursing staff anticipated delirium onset in only 31% of patients that subsequently manifested it [23]. Other studies confirmed these difficulties in making a timely diagnosis of delirium [24, 25]. These difficulties are likely due to the limited experience and lack of specific skills of the healthcare professionals to diagnose this syndrome and to make a differential diagnosis from other neuropsychiatric conditions. For this reason, we tried to identify a priori relevant clinical factors which can anticipate delirium onset and help the healthcare workers to make a diagnosis of this condition in a timely manner.

Investigating various clinical factors in all enrolled patients, we found that some of them were significantly more frequent in patients who subsequently developed delirium than in those who did not. In particular, 15 factors were significantly related in univariate analyses, i.e., care in hospice, compromised performance status, kidney disease, fever, renal failure, hypoxia, dehydration, drowsiness, poor well-being, breathlessness, "around the clock" treatment with haloperidol and other drugs acting on the CNS, cardiovascular drugs, anticoagulants, gastroprotective drugs, and morphine. Multivariate analyses stressed the role of care in hospice, breathlessness, and administration of CNS active drugs (particularly haloperidol), as relevant "delirium-predisposing factors" in advanced (cancer) patients.

Our data indicate that the risk of developing delirium is higher in patients in hospice than those cared for at home, suggesting that the relevant factor seems to be the hospitalization. This is consistent with previous studies which reported that old patients requiring hospital admission have a prevalence of delirium between 18% and 35% [3, 16, 17, 26]. The sudden departure from their own habitat to a different environment plays an important role in delirium onset, especially in elderly patients with serious health conditions.

As already reported, we also observed that respiratory activity is important in predicting

Table 5 Edmonton Symptom Assessment System (ESAS) grade of symptoms among 92 patients admitted to palliative care who experienced delirium

Symptoms, grade	Presence of delirium (%)		p value for trend[a]
	Yes (N = 95)	No (N = 408)	
Pain			0.701
None	34 (35.8)	148 (36.3)	
Mild	41 (43.2)	185 (45.3)	
Moderate/severe	20 (21.1)	75 (18.4)	
Fatigue			0.636
None	8 (8.4)	26 (6.4)	
Mild	49 (51.6)	240 (58.8)	
Moderate/severe	38 (40.0)	142 (34.8)	
Nausea			0.764
None	66 (69.5)	272 (66.7)	
Mild	24 (25.3)	118 (28.9)	
Moderate/severe	5 (5.3)	18 (4.4)	
Depression			0.712
None	54 (56.8)	225 (55.2)	
Mild	36 (37.9)	158 (38.7)	
Moderate/severe	5 (5.3)	25 (6.1)	
Anxiety			0.464
None	50 (52.6)	196 (48.0)	
Mild	39 (41.1)	184 (45.1)	
Moderate/severe	6 (6.3)	28 (6.9)	
Drowsiness			0.010
None	22 (23.2)	135 (33.1)	
Mild	56 (59.0)	234 (57.4)	
Moderate/severe	17 (17.9)	39 (9.6)	
Loss of appetite			0.507
None	16 (16.8)	91 (22.3)	
Mild	59 (62.1)	229 (56.1)	
Moderate/severe	20 (21.1)	88 (21.6)	
Poor well-being			0.006

Table 5 continued

Symptoms, grade	Presence of delirium (%)		p value for trend[a]
	Yes (N = 95)	No (N = 408)	
None	20 (21.1)	145 (35.5)	
Mild	50 (52.6)	188 (46.1)	
Moderate/severe	25 (26.3)	75 (18.4)	
Breathlessness			0.004
None	35 (36.8)	220 (53.9)	
Mild	43 (45.3)	139 (34.1)	
Moderate/severe	17 (17.9)	49 (12.0)	

ESAS = 0, none; ESAS $\leq$ 5, mild; ESAS > 5, moderate/severe

[a] Differences between the two groups were tested using chi-square tests for trend

delirium: patients with breathlessness had an approximately twofold risk of developing delirium. Furthermore, we found an increase of over twofold in the risk of delirium onset in patients who used haloperidol and of more than 70% in those administered other CNS-acting drugs as "around the clock" therapy. This is not surprising, since the role of CNS-active drugs in inducing delirium has been often debated in recent years. Anticholinergics, antidopaminergics, sedative/hypnotics, antipsychotics, opioids, and relaxants, in particular, have been considered as drugs that may cause delirium [26]. It should be also noticed that haloperidol has been considered for years as the gold standard treatment in case of agitation conditions, including delirium [27–29]. Recently, a randomized clinical trial highlighted that the administration of risperidone or haloperidol among patients with delirium in palliative care resulted in lower control of symptoms, greater extrapyramidal effects, and lower median survival than in those receiving placebo [30].

In our study, no association was found between level of education or marital status and

Table 6 Prescribed drugs, as around the clock therapy, among 503 patients admitted to palliative care, overall and according to the presence of delirium

Drugs	All patients (%) (N = 503)	Presence of delirium (%)		p value[a]
		Yes (N = 95)	No (N = 408)	
Haloperidol	82 (16.3)	23 (24.2)	59 (14.5)	0.015
Other drugs for the central nervous system	137 (27.2)	30 (31.6)	107 (26.2)	
Drugs for other symptoms	337 (67.0)	65 (68.4)	272 (66.7)	0.743
Anti-infective drugs	58 (11.5)	11 (11.6)	47 (11.5)	0.987
Anticancer drugs	12 (2.4)	0 (0.0)	12 (2.9)	0.091
Cardiovascular drugs	192 (38.2)	28 (29.5)	164 (40.2)	0.053
Anticoagulants	152 (30.2)	21 (22.1)	131 (32.1)	0.056
Antidiabetic drugs	25 (5.0)	3 (3.2)	22 (5.4)	0.367
Gastroprotective drugs	312 (62.0)	53 (55.8)	259 (63.5)	0.164
Preventive drugs	24 (4.8)	4 (4.2)	20 (4.9)	0.776
Drugs for respiratory system	6 (1.2)	1 (1.1)	5 (1.2)	0.889
Drugs for genitourinary system	220 (43.7)	41 (43.2)	179 (43.9)	0.899
Drugs for pain	373 (74.2)	71 (74.7)	302 (74.0)	0.847
Opioids	360 (96.5)	67 (94.4)	293 (97.0)	0.273
Morphine	116 (32.2)	28 (41.8)	88 (40.0)	0.063
Other drugs	37 (7.4)	6 (6.3)	31 (7.6)	0.666

[a] Differences between the two groups were tested using chi-square tests

risk of delirium; this suggests that delirium is related to the patients' severe clinical condition at the end of life—able to trigger delirium pathogenetic mechanisms—rather than the patients' cultural and socio-familial background. We also found no association with age, although some previous studies suggested an increased risk of delirium with advancing age [3, 31].

Moreover, the role of the primary pathology and concomitant diseases was not relevant for the onset of delirium. However, it should be considered that in this study the population of the patients was quite clinically homogeneous, since 90% of them had a diagnosis of neoplasm.

Although various risk factors for the onset of delirium have previously been investigated [15–17, 32], most studies considered retrospectively these factors in patients who already presented an episode of delirium. In this study, we investigated a number of possible risk factors at the time of admission to the PCU, when the delirium episode had not yet happened, allowing us to identify potentially "delirium-predisposing factors". Recent data have shown the importance of physical activity on the well-being of PC patients [33]. It would be interesting to explore whether this would also affect the appearance of delirium, and this might be a topic for a future research on those difficult and fragile patients.

This study presents some limitations. In particular, we did not achieve the expected sample size calculated at the moment of planning the project. Given the initial difficulties in undertaking the study and the selection of

Table 7 Univariate and multivariate associations between selected "delirium-predisposing factors" among 503 patients admitted to palliative care

Risk factors	HR[a] (95% CI)	p value[a]	HR[b] (95% CI)	p value[b]
Setting of care				
Home care	1.00[c]	< 0.001	1.00[c]	< 0.001
Hospice	2.98 (1.96–4.51)		2.28 (1.45–3.60)	
KPS				
≥ 50	1.00[c]	< 0.001	1.00[c]	0.128
40	3.01 (1.82–4.97)		1.77 (1.00–3.14)	
≤ 30	1.22 (0.75–2.00)		1.14 (0.68–1.92)	
Respiratory disease				
No	1.00[c]	0.058	1.00[c]	0.759
Yes	1.48 (0.99–2.23)		1.08 (0.68–1.71)	
Kidney disease				
No	1.00[c]	0.027	1.00[c]	0.692
Yes	1.64 (1.06–2.54)		0.88 (0.47–1.64)	
Oncologic disease				
No	1.00[c]	0.083	1.00[c]	0.420
Yes	0.61 (0.35–1.07)		0.78 (0.43–1.43)	
Fever				
No	1.00[c]	0.049	1.00[c]	0.328
Yes	2.18 (1.01–4.72)		1.50 (0.67–3.40)	
Renal failure				
No	1.00[c]	0.005	1.00[c]	0.126
Yes	1.98 (1.23–3.12)		1.69 (0.86–3.29)	
Hypoxia				
No	1.00[c]	0.001	1.00[c]	0.308
Yes	2.22 (1.38–3.57)		1.38 (0.74–2.56)	
Dehydration				
No	1.00[c]	0.009	1.00[c]	0.255
Yes	1.78 (1.15–2.75)		1.32 (0.82–2.13)	
Drowsiness				
No	1.00[c]	0.009	1.00[c]	0.292
Yes	1.90 (1.18–3.07)		1.16 (0.67–2.03)	
Poor well-being				

Table 7 continued

Risk factors	HR[a] (95% CI)	p value[a]	HR[b] (95% CI)	p value[b]
No	1.00[c]	0.001	1.00[c]	0.856
Yes	2.29 (1.39–3.75)		1.06 (0.57–1.99)	
Breathlessness				
No	1.00[c]	< 0.001	1.00[c]	0.037
Yes	2.22 (1.46–3.37)		1.71 (1.03–2.83)	
Lack of appetite				
No	1.00[c]	0.065	1.00[c]	0.748
Yes	1.66 (0.97–2.85)		0.90 (0.48–1.70)	
Drugs for central nervous system				
No	1.00[c]	< 0.001	1.00[c]	0.048
Haloperidol	3.79 (2.24–6.41)		2.17 (1.11–4.22)	
Other drugs	1.57 (0.98–2.51)		1.53 (0.94–2.48)	
Cardiovascular drugs				
No	1.00[c]	0.002	1.00[c]	0.052
Yes	0.49 (0.32–0.77)		0.61 (0.37–1.00)	
Anticoagulants				
No	1.00[c]	0.027	1.00[c]	0.261
Yes	0.58 (0.36–0.94)		0.74 (0.44–1.25)	
Gastroprotective drugs				
No	1.00[c]	0.049	1.00[c]	0.528
Yes	0.67 (0.44–0.99)		1.16 (0.73–1.83)	
Morphine				
No	1.00[c]	< 0.001	1.00[c]	0.313
Yes	2.15 (1.37–3.37)		0.72 (0.38–1.37)	

95% CI 95% confidence interval, *HR* hazard ratio, *KPS* Karnofsky Performance Status

[a] Estimates from a univariate Cox regression model

[b] Estimates from a multivariate Cox regression model adjusted for all variables in the table

[c] Reference category

patients according to eligibility criteria, the final number of recruited patients was 503 (about 63% of the expected sample size). We examined a number of risk factors evaluated at baseline visit, but there are likely many other risk factors, which could occur during the course of a patient's admission, and might be considered as precipitants for delirium, and which were not considered in our analysis. Moreover, the incidence of patients with

delirium in our study was lower (about 19%) compared with previous study populations [11–13]. This is probably because patients enrolled in our study were at a very advanced stage of disease with a short survival time (average 16 days), reflecting the Italian situation where the delay in sending terminally ill patients to PC is very frequent [34]. Furthermore, it may be also due to the criteria for patient selection and, in particular, to the decision to exclude baseline delirium cases, limiting analysis to cases that occurred during follow-up. Consequently, for some clinical factors, the association with occurrence of new cases of delirium did not reach statistical significance, even in the presence of a high HR.

CONCLUSIONS

This study identified a few factors which are relevant for the onset of delirium in terminally ill patients treated in a PCU. At the time of admission, the presence of main "delirium-predisposing factors", namely hospice care, breathlessness, and CNS drugs consumption, must alert caregivers and healthcare professionals that the patient could run into delirium in the near future. Additional data and a future active sharing experience with other PCUs would be worthwhile to confirm these finding and usefulness in the clinical practice.

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