 doi:10.20944/preprints202103.0445.v1

Article

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

Oscar Corli [1]*, Claudia Santucci [2,3], Sara Uggeri [1], Cristina Bosetti [2], Matteo Cattaneo [4], Daniela Ermolli[5], Giustino Varrassi [6], Dariusz Myrcik [7], Cristiana Gerosa [4], Martina Ornaghi [4], Alessandra Roccasalva [4], Paola Santambriogio [4] and Matteo Beretta [4]

[1] Department of Oncology, Pain and Palliative Care Research Unit, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 20156 Milano, Italy. Email: OC, Oscar.corli@marionegri.it, SU, sara.uggeri@marionegri.it
[2] Department of Oncology, Laboratory of Methodology for Clinical Research, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 20156 Milano, Italy. Email: CS, claudia.santucci@marionegri.it; CB, cristina.bosetti@marionegri.it
[3] Department of Clinical Sciences and Community Health, University of Milano, Milano, Italy
[4] Palliative Care Unit, ASST Vimercate, 20871 Vimercate (MB), Italy Email: MC, matteo.cattaneo@asst-brianza.it; CG, cristiana.gerosa@asst-brianza.it; MO, martina.ornaghi@asst-brianza.it; AR, roccasalva.psicologa@gmail.com; PS, paola.santambrogio@asst-brianza.it; MB, matteo.beretta@asst-brianza.it
[5] Hospice "Fondazione Mantovani", 20093 Cologno Monzese (MI), Italy. Email: DE, daniela.ermolli@gmail.com
[6] Paolo Procacci Foundation, Via Tacito 7, 00193 Roma, Italy. Email: giuvarr@gmail.com
[7] Department of Internal medicine, Medical University of Silesia in Katowice, Piekarska 18, 42-600 Bytom, Poland. Email: dariuszmyrcik@me.com
* Correspondence: Dr. Oscar Corli. Oscar.corli@marionegri.it; Tel.: +39 02 3901 4654

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 an observational prospective study on patients from an Italian Palliative Care Unit (PCU) in 2018-2019 and evaluated the presence of clinical factors at patient' admission. We then compared their presence in patients who developed delirium and in those who did not develop it during follow-up. On 503 enrolled patients, 95 (18.9%) developed delirium. In univariate analyses, factors significantly more frequent in patients with delirium were advanced age, care in hospice, very compromised performance status, hypoxia, high number of simultaneous clinical factors, presence of breathlessness, poor well-being, severe drowsiness, and background therapy with haloperidol and psychiatric drugs. In multivariate analyses, setting of care (odds ratio, OR, 1.68 for hospice versus home care, 95% confidence interval, CI 1.02-2.75; p=0.040), and administration of psychiatric drugs (OR 1.74 for administration versus no administration, 95% CI 1.08-2.81; p=0.023) were significantly associated with the risk of developing delirium, while the associations with age (OR 1.82 for >80 years versus ≤ 70 years, 95% CI=0.98-3.36; p=0.046) and presence of breathlessness (OR 1.70, 95% CI 0.99-2.89, p=0.053) were of borderline significance. The study indicates that some clinical factors are associated with the probability of delirium onset. Their evaluation in PC patients could help the healthcare professionals to timely identify the development of delirium in those patients.

Keywords: Causality; Clinical Predisposing Factors; Delirium; Palliative Care

List of abbreviations

CI, confidence interval; **CIRS**, Cumulative Illness Rating Scale; **CNS**, central nervous system; **ESAS**, Edmonton Symptoms Assessment System; **IQR** interquartile range; **KPS**, Karnofsky performance status; **OR**, odds ratio; **PC**, palliative care; **PCU**, Palliative Care Unit; **SD**, standard deviation.

 doi:10.20944/preprints202103.0445.v1

1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders-V, 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% to 35% of elderly people presents 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 lower, 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].

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, a project was 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.

2. Materials and Methods

An observational, prospective, single center study was conducted at the specialist PCU of Giussano, ASST Vimercate (MB), Lombardy Region, Italy, between October 2018 and December 2019. We screened all consecutive patients and included those who satisfied the following inclusion criteria: presence of a chronic progressive disease needing the specialist PC intervention; age 18 or over; comprehension and speaking the Italian language; informed consent to the processing of personal data and participation in the study. Patients with a state of coma, diagnosis of a psychiatric pathology, or substance abuse and/or dependence, current or lasting for at least three months, were excluded.

Within 24 hours from patients' admission to the PCU, we collected several clinical information - selected within a previous literature search as potential risk factors linked to the onset of delirium [14-16] -, such as age, sex, education, marital status, primary pathology for which admission to the PCU had been required, Karnofky 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 three months. Besides, we recorded prevalence and severity of patients' symptoms measured by the Edmonton Symptoms Assessment System (ESAS) [17, 18], and the background therapeutic scheme.

After the baseline visit, patients were followed-up throughout the whole stay at the PCU. During this period, attention was paid on recognizing patients who developed delirium and those who did not develop it. The diagnosis of delirium was carried out by means of 4AT, a frequently adopted tool for rapid delirium screening [19-21].

 doi:10.20944/preprints202103.0445.v1

The study protocol was approved by the Ethics Committee of the ASST of Vimercate (MB), Italy in June 18, 2018 (project n. 2824). Written informed consent for participation in the study and processing personal data were collected from all recruited patients before any study-related activity was carried out.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 March 2021 doi:10.20944/preprints202103.0445.v1

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 of them 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 then run univariate and multivariate logistic regression models to estimate the odds ratios (ORs) of delirium for various exposure factors and their corresponding 95% confidence intervals (CIs). For all statistical analyses, we used the software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.1 (R Development Core Team, 2017)..

3. Results

After a median follow-up time of 16 days (interquartile range, IQR, 6-39), 95 (18.9%) patients developed delirium. **Table 1** shows the general characteristics of 503 consecutive patients enrolled in the study at the moment of admission to PCU. Separately, there are the characteristics in 95 patients who developed delirium and 408 patients who did not develop it. 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 at home and 35.8% in hospice. 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 three 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 18 days (IQR 6-36) in patients with delirium and 18 days (IQR 8-42) in those without delirium (Data not shown).

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

Characteristics	All patients (%)	Presence of delirium (%)		p-value [a]
	(N=503)	Yes (N=95)	No (N=408)	
Sex, male	280 (55.7)	58 (61.1)	222 (54.4)	0.241
Age (years)	76.0 (11.4)	78.2 (11.0)	75.4 (11.5)	0.037
≤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)	

 doi:10.20944/preprints202103.0445.v1

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 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, 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%). Conversely, general conditions were significantly more severe in patients with delirium than in those without delirium (KPS ≤3 0 in 33.7% and in 24.5% of patients, respectively).

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 (%)	Presence of delirium (%)		p-value[a]
	(N=503)	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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 March 2021 doi:10.20944/preprints202103.0445.v1

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 behavioural 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)	
40	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.

The prevalence of clinical factors in all patients and in the two sub-groups of patients 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 ≥ 2 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).

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 (%)	Presence of delirium (%)		p-value[a]
	(N=503)	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 risk 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 three months.

 doi:10.20944/preprints202103.0445.v1

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

Table 4. Prevalence of selected symptoms among 503 patients admitted to Palliative Care, overall and according to the presence of delirium.

Symptoms	All Patients (%)	Presence of delirium (%)		p-value[a]
	(N=503)	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.

The relationship between the severity of symptoms (measured by ESAS) and risk of developing delirium was 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, the presence of moderate/severe degree symptoms was 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 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=92)	No (N=411)	
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)	

 doi:10.20944/preprints202103.0445.v1

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
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)	

None: ESAS=0; Mild: ESAS ≤5; Moderate/severe: ESAS >5.

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

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 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 47.4%, respectively) than in those who did not develop it (14.5% and 32.6%, respectively). For other drugs considered, the prevalence of use was similar in the two groups of patients.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 March 2021 doi:10.20944/preprints202103.0445.v1

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 (%)	Presence of delirium (%)		p-value[a]
	(N=503)	Yes (N=95)	No (N=408)	
Haloperidol	82 (16.3)	23 (24.2)	59 (14.5)	0.021
Drugs for central nervous system	178 (35.4)	45 (47.4)	133 (32.6)	0.007
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
Anti-cancer 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
Anticoagulation drugs	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
Other	37 (7.4)	6 (6.3)	31 (7.6)	0.666
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

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

The univariate and multivariate analyses of the ten factors found to be significantly associated with delirium onset in univariate analysis are shown in **Table 7**. After taking it into account for each factor, multivariate analyses showed that setting of care and administration of CNS active drugs were significantly associated with the development of delirium: OR 1.68 for hospice versus home care, 95% CI 1.02-2.75, p=0.040, and OR 1.74 for CNS administration versus no administration, 95% CI 1.08-2.81, p=0.023), while the associations with age (OR1.82 for >80 years versus ≤ 70 years, 95% CI=0.98-3.36; p=0.046) and the presence of breathlessness (OR 1.70 for presence versus absence, 95% CI 0.99-2.89, p=0.053) were of borderline significance.

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

Risk factors	OR[a] (95% CI)	p-value[a]	OR[b] (95% CI)	p-value[b]
Age				
≤70	1.00[c]	0.038	1.00[c]	0.046
71-80	1.67 (0.64-2.14)		1.19 (0.63-2.25)	
>80	1.78 (1.00-3.17)		1.82 (0.98-3.36)	
Setting of care				
Home care	1.00[c]	0.001	1.00[c]	0.040
Hospice	2.14 (1.36-3.36)		1.68 (1.02-2.75)	

 doi:10.20944/preprints202103.0445.v1

KPS				
≥ 50	1.00[c]	0.060	1.00[c]	0.567
40	1.70 (0.98-2.93)		0.79 (0.41-1.51)	
≤ 30	1.20 (0.70-2.06)		0.94 (0.52-1.68)	
Hypoxia				
No	1.00[c]	0.026	1.00[c]	0.745
Yes	1.85 (1.08-3.19)		1.11 (0.59-2.09)	
Number of risk clinical factors[d]				
0	1.00[c]	0.042	1.00[c]	0.165
1	1.27 (0.61-2.64)		1.35 (0.62-2.90)	
≥ 2	1.85 (0.94-3.65)		1.68 (0.80-3-52)	
Drowsiness severity				
No	1.00[c]	0.010	1.00[c]	0.248
Mild	1.47 (0.86-2.51)		1.05 (0.57-1.94)	
Moderate/severe	2.68 (1.29-5.53)		1.74 (0.74-4.07)	
Poor well being				
No	1.00[c]	0.007	1.00[c]	0.528
Yes	2.07 (1.21-3.52)		1.23 (0.65-2.35)	
Breathlessness				
No	1.00[c]	0.003	1.00[c]	
Yes	2.01 (1.26-3.18)		1.70 (0.99-2.89)	0.053
Haloperidol				
No	1.00[c]	0.022	1.00[c]	0.444
Yes	1.89 (1.10-3.26)		1.28 (0.68-2.39)	
Drugs for central nervous system				
No	1.00[c]	0.007	1.00[c]	0.023
Yes	1.86 (1.18-2.93)		1.74 (1.08-2.81)	

95% CI: 95% confidence interval; OR: odds ratio. KPS: Karnofsky Performance Status.

[a] Estimates from a univariate logistic regression model. [b] Estimates from a multivariate logistic regression model adjusted for all variables in the Table. [c] Reference category. [d] Including fever, renal failure, liver failure, hypoxia, dehydration, nutritional deficiency, cerebral radiotherapy, and chemotherapy.

4. Discussion

Delirium is often undetected or misdiagnosed. In one study, nursing staff anticipated delirium onset in only 31% of patients that subsequently manifested it [22]. Other studies confirmed these difficulties in making a timely diagnosis of delirium [23, 24]. 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 timely make a diagnosis of this condition.

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, ten factors were significantly related in univariate analyses, i.e., advanced age, care in hospice, very compromised performance status, hypoxia, high

 doi:10.20944/preprints202103.0445.v1

number of simultaneous clinical factors, presence of breathlessness, poor well-being, severe intensity drowsiness, and around the clock treatment with haloperidol and drugs acting on the CNS. Multivariate analyses stressed the role of care in hospice, and administration of CNS active drugs, and possibly age and breathlessness as relevant "delirium predisposing factors" in advanced (cancer) patients.

Among demographic aspects, only age seems to be a relevant predictor for delirium diagnosis: our data indicate in fact a progressive increase in the prevalence of delirium for increasing age of the patients. This is consistent with what has been reported in previous studies [3, 25]. In particular, a review of the literature described a four-fold increased risk of developing delirium in hospitalized patients aged 75 years or more, when compared to younger individuals [3].

Our data indicate that the risk of developing delirium is higher in patients in hospice than those cared 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, 15, 16, 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 [26], we also observed that respiratory activity is important in predicting delirium: patients with breathlessness had an approximately two-fold risk of developing delirium. Furthermore, we found an increase of more than 70% in the risk of delirium onset in patients who used CNS acting drugs administered as background 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, relaxants, in particular, have been considered as drugs that may cause delirium [26]. It should be also noticed that haloperidol, considered for years as the golden treatment in case of delirium [27-29], in univariate analysis was associated with an about 90% increased risk of delirium onset when prescribed as around the clock therapy, though the increase was only by 30%, not significant, in the multivariate analysis.

In our study, no association was found between level of education or marital status and risk of delirium, this suggests that delirium is related to the severe patients' clinical condition at the end-of-life – able to trigger delirium pathogenetic mechanisms – rather than the patients' cultural and socio-familial background. 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 [14-16], 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 palliative care patients [30]. It would be interesting to explore whether this would also the appearance of delirium, and this might be the topic for a future research on those difficult and fragile patients.

However, this study presents some limitations. In particular, we did not achieve the expected sample size calculated at the moment of planning the project, due to some difficulties in conducting the study in the setting of terminally ill patients. Moreover, the proportion of patients with delirium in our study was lower (about 19%) compared with previous study populations [11-13].This is probably due to the fact that patients enrolled in our study were at a very advanced stage of disease with a short survival time (average 18 days), reflecting the Italian situation where the delay in sending terminal patients to PC is very frequent [31]. Consequently, for some clinical factors, the association with delirium occurrence did not reach the statistical significance, even in the presence of high OR.

5. Conclusions

In conclusion, the study identified some factors which are relevant for the onset of delirium in terminally ill patients treated in a PCU. The identification of specific delirium predisposing factors may bring an advantage to patients, caregivers and healthcare professionals. Additional data and a future active sharing experience with other PCUs would be worthwhile to confirm these finding and usefulness in the clinical practice.

Acknowledgments:

The authors are grateful to all the personnel who has honorarily contributed to the research. Their support was indispensable.

Funding

This research was supported by Associazione ARCA Onlus Desio (MB), Italy. The authors are also grateful to the Paolo Procacci Foundation, Roma, Italy, for the editorial support.

Contribution

OC has conceived the study and prepared the draft of the manuscript. All the authors have equally contributed to the research, have ameliorated the manuscript and accepted its final version for publication.

Declaration of Conflict Interest

The authors have no conflict of interest to declare.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition Washington (DC): American Psychiatric Association. 2013.

2. Murray AM, Levkoff SE, Wetle TT, Beckett L, Cleary PD, Schor JD, et al. Acute delirium and functional decline in the hospitalized elderly patient. J Gerontol. 1993;48:M181-6. DOI: 10.1093/geronj/48.5.m181.

3. Inouye SK, Westendorp RG, Saczynski JS, Kimchi EY, Cleinman AA. Delirium in elderly people--authors'reply. Lancet. 2014;383:2045. DOI: 10.1016/S0140-6736(14)60994-6.

4. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35:350-64. DOI: 10.1093/ageing/afl005.

5. Brummel NE, Jackson JC, Pandharipande PP, Thompson JL, Shintani AK, Dittus RS, et al. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. Crit Care Med. 2014;42:369-77. DOI: 10.1097/CCM.0b013e3182a645bd.

6. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008;168:27-32. DOI: 10.1001/archinternmed.2007.4.

7. van den Boogaard M, Schoonhoven L, van der Hoeven JG, van Achterberg T, Pickkers P. Incidence and short-term consequences of delirium in critically ill patients: A prospective observational cohort study. Int J Nur Stud. 2012;49:775-83. DOI: 10.1016/j.ijnurstu.2011.11.016.

8. Qian X, Russell LB, Valiyeva E, Miller JE. "Quicker and sicker" under Medicare's prospective payment system for hospitals: new evidence on an old issue from a national longitudinal survey. Bull Econ Res. 2011;63:1-27. DOI: 10.1111/j.1467-8586.2010.00369.x.

9. Hill TE, Osterweil D, Bakerjian D, Lam A. "Post-Acute Care 2.0" Regarding Burke RE, Whitfield EA, Hittle D, et al. Hospital Readmission From Post-Acute Care Facilities: Risk Factors, Timing, and Outcomes. J Am Med Dir Ass. 2016;17:368-9. DOI: 10.1016/j.jamda.2016.01.009.

10. Hey J, Hosker C, Ward J, Kite S, Speechley H. Delirium in palliative care: Detection, documentation and management in three settings. Palliat Support Care. 2015;13:1541-5. DOI: 10.1017/S1478951513000813.

11. Grassi L, Caraceni A, Mitchell AJ, Nanni MG, Berardi MA, Caruso R, et al. Management of delirium in palliative care: a review. Curr Psychiat Rep. 2015;17:550. DOI: 10.1007/s11920-015-0550-8.

12. Breitbart W, Strout D. Delirium in the terminally ill. Clin Geriat Med. 2000;16:357-72. DOI: 10.1016/s0749-0690(05)70061-6.

13. Moyer DD. Review article: terminal delirium in geriatric patients with cancer at end of life. American J Hosp Palliat Care. 2011;28:44-51. DOI: 10.1177/1049909110376755.

14. Lauretani F, Ceda GP, Maggio M, Nardelli A, Saccavini M, Ferrucci L. Capturing side-effect of medication to identify persons at risk of delirium. Aging Clin Exp Res. 2010;22:456-8. DOI: 10.1007/BF03324944.

15. Han JH, Zimmerman EE, Cutler N, Schnelle J, Morandi A, Dittus RS, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. Acad Emerg Med. 2009;16:193-200. DOI: 10.1111/j.1553-2712.2008.00339.x.

16. Collins N, Blanchard MR, Tookman A, Sampson EL. Detection of delirium in the acute hospital. Age Ageing. 2010;39:131-5. DOI: 10.1093/ageing/afp201.

17. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991;7:6-9. PMID: 1714502

18. Moro C, Brunelli C, Miccinesi G, Fallai M, Morino P, Piazza M, et al. Edmonton symptom assessment scale: Italian validation in two palliative care settings. Support Care Cancer. 2006;14:30-7. DOI: 10.1007/s00520-005-0834-3.

19. Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing. 2014;43:496-502. DOI: 10.1093/ageing/afu021.

20. Jeong E, Park J, Lee J. Diagnostic Test Accuracy of the 4AT for Delirium Detection: A Systematic Review and Meta-Analysis. Int J Env Res Pub Health. 2020;17. DOI: 10.3390/ijerph17207515.

21. Tieges Z, Maclullich AMJ, Anand A, Brookes C, Cassarino M, O'Connor M, et al. Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. Age Ageing. 2020. DOI: 10.1093/ageing/afaa224.

22. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM, Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Arch Intern Med. 2001;161:2467-73. DOI: 10.1001/archinte.161.20.2467.

23. Clegg A, Westby M, Young JB. Under-reporting of delirium in the NHS. Age Ageing. 2011;40:283-6. DOI: 10.1093/ageing/afq157.

24. Steis MR, Fick DM. Are nurses recognizing delirium? A systematic review. J Gerontol Nurs. 2008;34:40-8. DOI: 10.3928/00989134-20080901-12.

25. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354:1157-65. DOI: 10.1056/NEJMra052321.

26. Setters B, Solberg LM. Delirium. Prim Care. 2017;44:541-59. DOI: 10.1016/j.pop.2017.04.010.

27. Prommer E. Role of haloperidol in palliative medicine: an update. Am J Hosp Pall Care. 2012;29:295-301. DOI: 10.1177/1049909111423094.

28. Crawford GB, Agar MM, Quinn SJ, Phillips J, Litster C, Michael N, et al. Pharmacovigilance in hospice/palliative care: net effect of haloperidol for delirium. J Pall Med. 2013;16:1335-41. DOI: 10.1089/jpm.2013.0230.

29. [29] Lindqvist O, Lundquist G, Dickman A, Bukki J, Lunder U, Hagelin CL, et al. Four essential drugs needed for quality care of the dying: a Delphi-study based international expert consensus opinion. J Pall Med. 2013;16:38-43. DOI: 10.1089/jpm.2012.0205.

30. Myrcik D, Statowski W, Trzepizur M, et al. Influence of physical activity on pain, depression and quality of life of patients in palliative care: A proof-of-concept study. J Clin Med. 2021;10(5):1012. DOI: 10.3390/jcm10051012

31. Corli O, Pellegrini G, Bosetti C, Riva L, Crippa M, Amodio E, et al. Impact of Palliative Care in Evaluating and Relieving Symptoms in Patients with Advanced Cancer. Results from the DEMETRA Study. Int J Env Res Pub Health. 2020;17(22):8429. DOI: 10.3390/ijerph17228429.