Prevalence of Delirium in End-of-Life Palliative Care Patients: An Observational Study

Angela Recchia^a Barbara Rizzi^a Alessandra Favero^b Alessandro Nobili^c
Luca Pasina^c

^aFondazione VIDAS, Milano, Italy; ^bAssociazione VIDAS, Milano, Italy; ^cIstituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy

Highlights of the Study

- Delirium is frequently often under-recognized or misdiagnosed in palliative care.
- This study was aimed at assessing the prevalence of delirium in end-of-life patients in palliative care.
- Patients included those with cancer and noncancer life-limiting diseases.
- The results indicate that delirium is quite common in end-of-life patients.

Keywords

Delirium · Prevalence · Palliative care · End of life · Hospice care · Home care

Abstract

Objectives: The aim of this study was to assess the prevalence of delirium, using the Assessment Test for Delirium and Cognitive Impairment (4AT) in end-of-life palliative care patients. **Subjects and Methods:** This retrospective cross-sectional study was conducted on end-of-life patients in a hospice or at home. All patients were evaluated with the 4AT for the presence of delirium. **Results:** Of the 461 patients analyzed, 76 (16.5%) were inpatients and 83.5% (385) outpatients. The median age was 79.5 (72–86) years, and 51.0% were female. According to the 4AT score, 126 patients (27.3%) had delirium (A4T ≥4) at admission, 28 (36.8%) were inpatients, and 98 (25.5%) outpatients. Around 33.8% of the cancer inpatients had delirium, while 20.6% of the cancer outpatients had delirium. The prevalence of delirium varied

according to the setting, clinical condition, and life expectancy. In addition, 55.0% (11) actively dying inpatients, within 3 days, had delirium, and 56.7% (17) outpatients had delirium; while among those with life expectancy longer than 4 days, 30.4% (17) inpatients and 22.8% (81) outpatients were with delirium. **Conclusions:** Our study confirms that delirium is common in cancer and noncancer palliative care patients. Further research on delirium in end-of-life palliative care patients should consider the complexity of palliative care of this population as well as of the characteristics of the settings.

© 2022 The Author(s)
Published by S. Karger AG, Basel

Introduction

Delirium is a neuropsychiatric syndrome arising from acute global brain dysfunction, characterized by disturbances in attention, awareness, cognition, perception, and orientation. Additional disturbances include memo-

ry deficit, disorientation in time and place, visual-spatial disabilities, aphasia, illusions, hallucinations, delusions, altered mood, and persistent agitation. Other hallmark symptoms are sleep disturbances, irritability, restlessness, and anxiety, which are also prodromal symptoms. This complex multifactorial syndrome presents as an acute and fluctuating state of confusion and has multifactorial etiologies [1]. Delirium risk factors are predisposing and precipitating [2]. Predisposing factors are older age, critical illness, cognitive impairment, visual and hearing impairment, poor functional status, malnutrition, and current hip fracture. Precipitating factors include polypharmacy, anticholinergic load, drug intoxication, indwelling catheters, infections, dehydration, hyponatremia, hypercalcemia, hypoxia, metabolic and endocrine abnormalities, organ dysfunction or failure, pro-inflammatory cytokines, paraneoplastic syndromes, and physical restraints [3, 4].

Delirium is associated with increased morbidity and mortality, with longer hospital stay and higher healthcare costs, and appears to worsen preexisting dementia besides increasing the risk of *ex novo* dementia [5]. Delirium is classified in three clinical subtypes according to the type of psychomotor activity: (i) hyperactive, characterized by symptoms like agitation, hyperactivity, delusions, aggressiveness, and perceptual disturbances; (ii) hypoactive, characterized by decreased reactivity and motor and speech retardation; and (iii) mixed, characterized by alternating hyperactive and hypoactive features [6].

Delirium, developing over a short time (hours to days), negatively impacts every aspect of a patient's care, including symptom expression, patient-clinician communication, patient's decision-making, and relationships with family members and healthcare staff [7]. It is distressing both for patients and their families [8]. Delirium in the last days of life is often a refractory symptom and may be a sign of imminent death [9] and is a common medical complication experienced by the terminally ill patient [10], even in palliative care settings [8, 11].

Delirium in palliative care is often under-recognized or misdiagnosed, detected too late, or not detected at all [10, 12–14]; this is particularly true for the hypoactive subtype [15]. The diagnosis of delirium in palliative care patients is interdisciplinary and often made after a global clinical assessment of the patient by experienced clinicians. The core clinical criteria and gold standard for the diagnosis are codified in the DSM-5 and ICD-10. Early recognition of delirium is essential so that the patient's and family's needs can be assessed, and an appropriate goal of care can be defined.

The routine use of observational, cognitive, and attention screening tools may improve the detection of delirium in parallel with the caregivers' reports of any acute changes in mental status and baseline cognitive function. There are 30 or more delirium screening tools, but none are routinely used in palliative care, and there is no consensus on how this assessment should be performed. Some commonly used tools are: Memorial Delirium Assessment Scale (MDAS) and Confusion Assessment Method, both validated in palliative care patients; Delirium Rating Scale Revised 98 (DRS-R-98); Nursing Delirium Screening Scale (Nu-DESC) and 4AT [2, 16, 17]; DSM-5; and ICD-10.

The goals of palliative care for a delirious patient are to reduce distress; maintain function, physical and emotional safety, and well-being; and, if possible, to resolve the delirium. Pharmacologic and nonpharmacologic preventive strategies constitute an integral part of a comprehensive delirium management plan, which remains the best practice in the treatment of delirium [18]. Depending on the precipitating factors, up to 50% of the episodes of delirium in palliative care patients are reversible, and treatment of the cause is the only established strategy to reverse them [18]. The standard management of a delirium episode includes investigation of precipitating and aggravating factors and, where possible, their treatment, followed as necessary by symptomatic drug therapy. Reversibility correlates with the type of precipitating factors identified. There is a greater likelihood of reversing an episode of delirium that is precipitated by medications, electrolyte abnormalities, and infection. However, the evidence base for the management of delirium in palliative care patients is limited by the lack of good quality randomized controlled trials and practitioners' practice.

The prevalence and incidence of delirium in end-of-life patients admitted to palliative care settings have a wide range [19]. Several studies have obtained prevalence and incidence estimates of delirium in different palliative care settings: hospital, hospice and acute palliative care units, or acute medical units, but very few studies are available on home palliative care [20, 21]. Most researchers who assessed delirium in end-of-life patients limited their focus to advanced or terminally ill cancer patients. But, palliative care is also appropriate for patients with noncancer illnesses, and the demand for palliative care for these patients with terminal diseases is increasing.

We analyzed a cohort of Italian end-life patients in hospice and cared for at home finding that was predominantly composed of older adults [22, 23]. The prevalence of delirium increases in the older adults [3], and although

Table 1. Sociodemographic and clinical characteristics of patients with and without delirium

Patients characteristics	All (N = 461)	With delirium (N = 126)	Without delirium (N = 335)	p
Age, median (25–75), years	79.5 (72–86)	82.8 (76–89)	78.1 (71–85)	<0.0001
Sex, n (%)				
Male	226 (49.0)	63 (50.0)	163 (48.7)	0.7971
Female	235 (51.0)	63 (50.0)	172 (51.3)	
Marital status, n (%)				
Never married	31 (6.7)	8 (6.3)	23 (6.9)	0.0979
Married/unmarried	257 (55.7)	59 (46.8)	198 (59.1)	
Separated/divorced	18 (3.9)	6 (4.8)	12 (3.5)	
Widowed	134 (29.1)	48 (38.1)	86 (25.7)	
Unknown	21 (4.6)	5 (4.0)	16 (4.8)	0.0012
Education, mean (±SD), years	9.9 (4.1)	8.9 (4.1)	10.3 (4.1)	
KPS, n (%)				
≤40	330 (72.0)	113 (91.1)	217 (65.0)	<0.0001
≥50	128 (28.0)	11 (8.9)	117 (35.0)	
Life expectancy, median (25–75), days	16 (7–32)	7 (4–18)	20 (10–37)	<0.0001
Up to 3 days, n (%)	50 (10.9)	28 (22.2)	22 (6.6)	<0.0001
More than 4 days, n (%)	411 (89.1)	98 (77.8)	313 (93.4)	
Primary diagnosis, n (%)				
Cancer	403 (87.4)	92 (73.0)	311 (92.8)	<0.0001
Noncancer	58 (12.6)	34 (27.0)	24 (7.2)	
Charlson index (mean ± SD)	2.9 (1.3)	3.0 (1.3)	2.8 (1.2)	0.1145
Dementia, n (%)	18 (3.9)	15 (11.9)	3 (0.9)	<0.0001

SD, standard deviation.

limited data are available for the national palliative care population, our sample is representative of the northern Italian end-of-life patients in hospice or living at home [24]. We aimed to estimate this condition in this fragile population. The aim of this study was to assess the prevalence of delirium, using the Assessment Test for Delirium and Cognitive Impairment (4AT) in end-of-life hospice patients (inpatients) and living-at-home patients (outpatients) – in the whole palliative care population.

Subjects and Methods

Subjects and Study Design

This was a retrospective cross-sectional study conducted in a sample of end-of-life patients in hospice or at home. Between February and August 2019, all end-of-life adults who died in the Casa VIDAS Hospice and all end-of-life adult patients who were cared for by VIDAS home palliative care services and died at home were included in the analysis. Data collection complied fully with Italian laws on personal data protection; the Ethics Committee of the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation approved the study. Sociodemographic information including age, sex, marital status, educational status, and clinical data including diagnosis, life expectancy, Karnofsky Performance Status (KPS), indicating physical

performance ability, and 4AT scores for each patient were collected in a Web-based case report form. The presence of multimorbidity was assessed using the Charlson Comorbidity Index.

Evaluation of Delirium

All patients were evaluated for delirium at admission by the palliative care physician on duty with the 4AT [25], according to the Regione Lombardia Decree XI/1046/2018 [26]. This validated screening tool for delirium diagnosis has good sensitivity and specificity and has been validated in the Italian language to detect delirium [25]. The 4AT is usable in palliative care and can be easily incorporated into the admission visit [13, 16]; it is brief and easy to administer (including in people with visual or hearing impairment) and does not require any special training; thus, it can be performed by any healthcare professionals without a previous specific training session. The test gives an assessment of “untestable” patients (those who cannot undergo cognitive testing or interview because of severe drowsiness or agitation) and patients with fluctuating levels of consciousness, hypoactive delirium, and cognitive impairment. The 4AT scores are 0–12. A score of 0 indicates the absence of dementia or delirium; 1, 2, or 3 suggests possible cognitive impairment but not delirium; while a score ≥4 strongly suggests possible delirium. In this study, delirium was defined as a score of 4 or more in the 4AT. We used in this study the working definitions of an end-of-life, actively dying, refractory symptom or refractory delirium; goals of care; terminal delirium; and palliative sedation suggested by Bush and Hui [7, 9].

Table 2. Sociodemographic and clinical characteristics of inpatients and outpatients with and without delirium

Patients characteristics	Hospice			Home care		
	with delirium (N = 28)	without delirium (N = 48)	<i>p</i>	with delirium (N = 98)	without delirium (N = 287)	<i>p</i>
Age, median (25–75), years	79.3 (67–87)	76.1 (66–83)	0.3140	84.3 (78–89)	78.5 (72–85)	<0.0001
Sex, <i>n</i> (%)						
Male	14 (50.0)	21 (43.7)	0.5980	49 (50.0)	142 (49.5)	0.9288
Female	14 (50.0)	27 (56.3)		49 (50.0)	145 (50.5)	
Marital status, <i>n</i> (%)						
Never married	2 (7.1)	6 (12.5)	0.9290	6 (6.1)	17 (5.9)	0.0753
Married/unmarried	13 (46.4)	20 (41.7)		46 (46.9)	178 (62.0)	
Separated/divorced	3 (10.7)	5 (10.4)		3 (3.1)	7 (2.4)	
Widowed	9 (32.1)	14 (29.2)		39 (39.8)	72 (25.1)	
Unknown	1 (3.6)	3 (6.2)		4 (4.1)	13 (4.5)	
Education, mean (±SD), years	8.3 (2.6)	9.4 (4.1)	0.1284	9.0 (4.4)	10.4 (4.1)	0.0091
KPS, <i>n</i> (%)						
≤40	26 (96.3)	44 (91.7)	0.4404	87 (89.7)	173 (60.5)	<0.0001
≥50	1 (3.7)	4 (8.3)		10 (10.3)	113 (39.5)	
Life expectancy, median (25–75), days	5 (2–15)	12 (5–21)	0.0178	9 (4–20)	21 (11–40)	<0.0001
Up to 3 days, <i>n</i> (%)	11 (39.3)	9 (18.7)	0.0499	17 (17.3)	13 (4.5)	<0.0001
More than 4 days, <i>n</i> (%)	17 (60.7)	39 (81.3)		81 (82.7)	274 (95.5)	
Primary diagnosis, <i>n</i> (%)						
Cancer	23 (82.1)	45 (93.8)	0.1117	69 (70.4)	266 (92.7)	<0.0001
Noncancer	5 (17.9)	3 (6.2)		29 (29.6)	21 (7.3)	
Charlson index (mean±SD)	3 (1.7)	2.6 (1.1)	0.2836	3.0 (1.2)	2.8 (1.2)	0.1875
Dementia, <i>n</i> (%)	3 (10.7)	–	0.0220	12 (12.2)	3 (1.0)	<0.0001

KPS, Karnofsky Performance Status; SD, standard deviation.

Statistical Analysis

Data analysis was done with JMP Pro 14.1.0 (SAS Institute Inc. Cary, NC, USA) statistical package. In the descriptive analysis, the qualitative variables are reported as frequencies and percentages, and the quantitative variables are based on mean and standard deviation for parametric distribution or median and 25th–75th quartiles for nonparametric distribution. Sociodemographic and clinical characteristics of patients with and without delirium were compared using a χ^2 test for categorical variables and Student's *t*-test or Wilcoxon-Mann-Whitney test for continuous variables. The prevalence of delirium on the day of admission was calculated as the number of patients with an 4AT score of 4 or more, by strata of setting. *p* values of <0.05 were considered statistically significant.

Results

Population

Between February and August 2019, 97 patients were admitted and died in the hospice (inpatients), and 426 patients were cared for and died at home (outpatients); 62 patients were excluded for lack of a 4AT evaluation. Of the 461 patients eligible for analysis, 76 (16.5%) were inpatients and 385 (83.5%) outpatients. Sociodemographic and

clinical characteristics of all patients are reported in Table 1. The median age of the whole sample was 79.5 (72–86) years, and 51.0% were female. The mean level of education was 9.9 (4.1) years, and 55.7% were married. The median life expectancy was 16 (7–32) days; 10.9% (50) of actively dying patients had life expectancy of up to 3 days; and 330 (72.0%) patients had a KPS score less than 50%. The most common diagnosis was cancer (87.4%). The main primary cancer sites were digestive organs and peritoneum (39.2%), respiratory and intrathoracic organs (24.6%), genitourinary organs (13.7%), bone (9.2%), connective tissue, skin, and breast. There were 58 (12.6%) nononcologic patients. The main nononcologic diagnoses were cardiovascular diseases (34.5%), neurologic diseases (17.2%), genitourinary diseases (12.1%), respiratory diseases (10.3%), gastrointestinal diseases (10.3%), and others.

Prevalence

In all, 126 (27.3%) patients had delirium (A4T ≥4), 28 (36.8%) were inpatients, and 98 (25.5%) outpatients (*p* = 0.0418). Sociodemographic and clinical characteristics of patients with and without delirium in both settings are

presented in Table 1. There was no significant difference between patients with and without delirium in relation to sex and co-pathologies, measured with the Charlson Index. Patients with delirium were older ($p < 0.0001$), less educated ($p = 0.0012$), and with shorter life expectancy ($p < 0.0001$). The mortality rate in the first 3 days of admission of patients with delirium who died (22.2%) was higher than for patients without delirium (6.6%); in contrast, the mortality rate at 4 days or more for patients without delirium (93.4%) was higher than for patients with delirium (77.8%). More than 50% (198) of subjects without delirium were married, 46.8% (59) with delirium were married, and 38.1% (48) were widowed.

Among 28 inpatients with delirium, 82.1% (23) had cancer and 17.9% (5) did not; similarly, among 48 inpatients without delirium, 93.8% (45) had cancer and 6.2% (3) did not. Among 98 outpatients with delirium, 70.4% (69) had cancer and 29.6% (29) did not; similarly, among 287 outpatients without delirium, 92.7% (266) had cancer and 7.3% (21) did not (Table 2). Nevertheless, there was a significant difference ($p < 0.0001$) between home care patients with and without delirium with a noncancer diagnosis but no significant difference ($p = 0.1117$) between inpatients with and without delirium and a noncancer diagnosis.

Among all inpatients, 93.3% (70) had a KPS ≤ 40 , but 67.9% (260) of all outpatients had a KPS ≤ 40 . There was no significant difference in KPS between inpatients with and without delirium, but there was a significant difference in KPS between outpatients with and without delirium (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000521994).

The prevalence of delirium varied according to the setting. According to the 4AT score, 33.8% (23) cancer inpatients were with delirium, and 20.6% (69) outpatients were with delirium. In addition, 55.0% (11) were actively dying inpatients, within 3 days, 56.7% (17) outpatients had delirium, while among those with life expectancy longer than 4 days, 30.4% (17) inpatients and 22.8% (81) outpatient had delirium.

Discussion

We found that delirium is a common condition in end-of-life patients; about 27% of the end-of-life patients had delirium. This accounts for 36.8% of inpatients and outpatients 25.5% for outpatients, thus suggesting the need for accurate diagnosis and prevention. The higher prevalence of delirium on admission in hospice might be related to the more complex condition of patients. In fact,

inpatients have a higher clinical instability, as indicated by the higher percentage of KPS ≤ 40 which indicates the inability of patients to care for themselves and requires the equivalent of institutional or hospital care; in addition, the disease may be progressing rapidly.

Our results are consistent with the literature on inpatients [20], but this study add new information on the prevalence of delirium in outpatients, suggesting that the 4AT test, a very simple tool to assess delirium, is useful to assess delirium in the everyday practice. Delirium in palliative care can be easily and quickly assessed with 4AT, which does not require training and the ability to assess patients with a fluctuating level of consciousness, hypoactive delirium, and cognitive impairment.

In a systematic review [11], the prevalence of delirium in adult cancer palliative care inpatients ranges from 13.3% to 42.3% at admission, from 26% to 62% during admission and from 58.8% to 88% 1 week or hours before death. In the subsequent update of the systematic review [14], the prevalence ranged from 4–12% in the community, from 9–57% in hospital palliative care services, and from 6 to 74% in inpatient palliative care units. This wide range of delirium prevalence in palliative care may reflect heterogeneity in patient populations, settings, delirium assessment methods [19], design study and sample size [11], and in the disease trajectory. The majority of studies were in advanced cancer patients, and only a few have addressed delirium in other life-limiting diseases. In the literature, some prevalence studies have mixed patient populations or subtypes [19], as well as carry over point prevalence and period prevalence [27]. Comparison with most end-of-life studies is difficult because of their heterogeneity; the settings of patients in our study are hospice and home care, which are different from those admitted to acute palliative care or hospital palliative care units. Furthermore, point and period prevalence are two different models to provide estimates, respectively, at a specific time (on a particular date) and in a specific period (any time during the interval) [28].

A previous Italian study by Mercadante et al. [20] in advanced cancer patients assessed the prevalence of delirium in palliative home care and in hospice on admission and after 1 week; the prevalence was significantly lower in home care than in hospice patients. This is similar to our results which show that the prevalence at admission for palliative care cancer outpatients is lower than for hospice cancer inpatients. However, the study by Mercadante et al. [25] excluded patients who were close to death, while we included dying patients, because the 4AT can assess delirium in patients with fluctuating levels of consciousness

and in those who cannot undergo cognitive testing or interviews due to severe drowsiness or agitation. Nevertheless, even excluding the dying cancer patients (1–3 days) from our sample, the frequency of delirium was lower in home care than in the hospice. In summary, the prevalence of delirium in cancer patients in palliative home care and hospice settings on admission is comparable to the previous study [20], providing support for our findings.

Our sample also included noncancer life-limiting diseases and represents the whole palliative care and end-of-life population in general adult palliative care services in Italy. According to the latest consensus-based definition of palliative care, “Palliative Care is the active holistic care of individuals of all ages with serious health-related suffering because of severe illness and especially of those near the end of life” [29]. Palliative care therefore regards patients suffering severe illness and not only cancer. Moreover, this new definition shifts from a disease-centered concept to a person-centered model of palliative care, so proper attention to symptom burden and suffering should be the basis for individually tailored treatments. The prevalence of delirium research [11, 14] should therefore be personalized for delirium screening and management [19] because palliative care patients have very different and very personal characteristics.

A strength of this study is the large number of unselected palliative care patients, all consecutively admitted and who died in the hospice or at home. Another strength is the use of a very simple tool to assess delirium, the 4AT test [30]. To our knowledge, this is the first palliative care study that evaluated end-of-life patients for delirium with the 4AT test. The novelty of this study is the assessment of the prevalence of delirium using a new screening tool for delirium diagnosis, the 4AT test, and by leveraging its advantages and strengths over other existing tools. This study has several limitations. First, the sample comprised of only a small group of noncancer patients admitted to the hospice. Unfortunately, estimating the frequency of delirium for inpatients hampers the generalizability of results, and these frequency estimates should be considered preliminary pending confirmation in a larger study. Even with these limitations, this is the first study to record delirium in noncancer home care patients. Future studies on delirium in end-of-life palliative care patients may benefit from including noncancer disease in the sample population. Another limitation is that study was conducted in a single center. Assessment of delirium, which fluctuates by its nature, requires serial measurements as part of a mandatory repeated patient evaluation, providing information of paramount importance for decision-making when

delirium does not change after multifactorial interventions and is likely to be associated with imminent death.

Our study confirms that delirium is a common syndrome in cancer and noncancer palliative care patients. Its prevalence at admission in end-of-life home patients is lower than in hospice inpatients. There are very few studies on the prevalence of delirium in noncancer patients in palliative care, and more studies have focused on subtype populations, but there are only a handful of studies on the prevalence of delirium in home palliative care patients. According to Lawlor et al. [31], further studies on delirium in palliative care settings should consider three main groups of research questions: the first is epidemiologic, the second covers management questions, and the third relates to the development of predictive models for delirium outcome. Delirium is one of the more common irreversible symptoms requiring palliative sedation. In the presence of irreversible or terminal delirium with distressing agitated symptoms, judicious proportional palliative sedation should be considered [9].

Conclusions

While confirming that delirium is common in cancer and noncancer palliative care patients, our study also suggests that the use of a quick, simple, and easy tests to assess delirium that do not require any special training is feasible in palliative care in routine clinical practice. The total human experience of delirium at the end of life is a common devastating complication. Despite the significant implications of end-of-life delirium for the relational experience of all those in the palliative care setting, research in this area is challenging, and the literature data are owing to patients’ vulnerability close to the end of life, with difficulty in patient accrual and high attrition rates. Further research on delirium in end-of-life palliative care patients should consider the complexity of palliative care of this population as well as of the setting’s characteristics.

Acknowledgments

The authors are grateful to the “Associazione VIDAS” for the possibility of conducting the study and J.D. Baggott for language editing.

Statement of Ethics

The study was approved by Comitato Etico Milano Area 2 Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico Milano.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources to declare.

Author Contributions

All the authors participated in drafting the manuscript and critical revision of the manuscript for important intellectual content and gave approval for the final version submitted. Individual contributions are as follows: A.R. and L.P. designed the study, interpreted data, and wrote the manuscript; A.F. interpreted the data and wrote the manuscript; A.R. did the statistical analyses; and A.N. and B.R. made final critical revisions. All the authors approved the final version of the paper.

References

- 1 Arlington VA. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
- 2 Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLulich AMJ, et al. Delirium. *Nat Rev Dis Primers*. 2020 Nov 12; 6(1):90.
- 3 Hosie A, Amgarth-Duff I, Agar M. Delirium. In: MacLeod R, Van den Block L, editors. *Textbook of palliative care*. Cham: Springer; 2019.
- 4 Pasina L, Rizzi B, Nobili A, Recchia A. Anticholinergic load and delirium in end-of-life patients. *Eur J Clin Pharmacol*. 2021;77(9): 1419–4.
- 5 Davis DH, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG, et al. Association of delirium with cognitive decline in late life: a Neuropathologic Study of 3 Population-Based Cohort Studies. *JAMA Psychiatry*. 2017;74:244–51.
- 6 Irwin SA, Pirrello RD, Hirst JM, Buckholz GT, Ferris FD. Clarifying delirium management: practical, evidenced-based, expert recommendations for clinical practice. *J Palliat Med*. 2013;16:423–35.
- 7 Hui D, Nooruddin Z, Didwaniya N, Dev R, De La Cruz M, Kim SH, et al. Concepts and definitions for “actively dying,” “end of life,” “terminally ill,” “terminal care,” and “transition of care”: a systematic review. *J Pain Symptom Manage*. 2014;47:77–89.
- 8 Agar MR. Delirium at the end of life. *Age Ageing*. 2020;49:337–40.
- 9 Bush SH, Leonard MM, Agar M, Spiller JA, Hosie A, Wright DK, et al. End-of-life delirium: issues regarding recognition, optimal management, and the role of sedation in the dying phase. *J Pain Symptom Manage*. 2014; 48:215–30.
- 10 Breitbart W, Strout D. Delirium in the terminally ill. *Clin Geriatr Med*. 2000;16:357–72.
- 11 Hosie A, Davidson PM, Agar M, Sanderson CR, Phillips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med*. 2013;27:486–98.
- 12 Hosie A, Agar M, Lobb E, Davidson PM, Phillips J. Improving delirium recognition and assessment for people receiving inpatient palliative care: a mixed methods meta-synthesis. *Int J Nurs Stud*. 2017;75:123–9.
- 13 MacLulich AM, Shenkin SD, Goodacre S, Godfrey M, Hanley J, Stiobhairt A, et al. The 4 “A”s test for detecting delirium in acute medical patients: a diagnostic accuracy study. *Health Technol Assess*. 2019;23:1–194.
- 14 Watt CL, Momoli F, Ansari MT, Sikora L, Bush SH, Hosie A, et al. The incidence and prevalence of delirium across palliative care settings: a systematic review. *Palliat Med*. 2019;33:865–77.
- 15 Leonard MM, Nikolaichuk C, Meagher DJ, Barnes C, Gaudreau JD, Watanabe S, et al. Practical assessment of delirium in palliative care. *J Pain Symptom Manage*. 2014;48:176–90.
- 16 Baird L, Spiller JA. A quality improvement approach to cognitive assessment on hospice admission: could we use the 4AT or short CAM? *BMJ Open Qual*. 2017;6:e000153.
- 17 Gibb K, Krywonos A, Shah R, Jha A, Davis D. What prompts patients to present with delirium? *Eur Geriatr Med*. 2021;12(3):643–51.
- 18 Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a Prospective Study. *Arch Intern Med*. 2000;160:786–94.
- 19 Hui D. Delirium in the palliative care setting: “sorting” out the confusion. *Palliat Med*. 2019;33:863–4.
- 20 Mercadante S, Masedu F, Balzani I, De Giovanni D, Montanari L, Pittureri C, et al. Prevalence of delirium in advanced cancer patients in home care and hospice and outcomes after 1 week of palliative care. *Support Care Cancer*. 2018;26:913–9.
- 21 Hamano J, Mori M, Ozawa T, Sasaki J, Kawahara M, Nakamura A, et al. Comparison of the prevalence and associated factors of hyperactive delirium in advanced cancer patients between inpatient palliative care and palliative home care. *Cancer Med*. 2021 Feb;10(3): 1166–79.
- 22 Pasina L, Recchia A, Agosti P, Nobili A, Rizzi B. Prevalence of preventive and symptomatic drug treatments in hospice care: an Italian Observational Study. *Am J Hosp Palliat Care*. 2019;36:216–21.
- 23 Pasina L, Recchia A, Nobili A, Rizzi B. Inappropriate medications among end-of-life patients living at home: an Italian Observational Study. *Eur Geriatr Med*. 2020;11:505–10.
- 24 ATS della Città Metropolitana di Milano Cure Palliative 2019. Available from: <https://www.ats-milano.it/portale/Epidemiologia/Valutazione-della-rete-dei-servizi/Id/9302> Accessed 2021 Jun 18
- 25 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.
- 26 Regione Lombardia. Regole 2019- Deliberazione No1046 del 17/12/2018 “Determinazioni in ordine alla gestione del servizio sociosanitario per l’esercizio 2019”. 2018. Available from: <https://www.regione.lombardia.it/wps/portal/istituzionale/HP/DettaglioServizio/servizi-e-informazioni/Enti-e-Operatori/sistema-welfare/attuazione-della-riforma-sociosanitaria-lombarda/ser-programmazione-gestione-sistema-sanitario-sal/programmazione-gestione-sistema-sanitario> Accessed 2021 Jun 18
- 27 Koirala B, Hansen BR, Hosie A, Budhathoki C, Seal S, Beaman A, et al. Delirium point prevalence studies in inpatient settings: A systematic review and meta-analysis. *J Clin Nurs*. 2020;29:2083–92.
- 28 Spronk I, Korevaar JC, Poos R, Davids R, Hilderink H, Schellevis FG, et al. Calculating incidence rates and prevalence proportions: not as simple as it seems. *BMC Public Health*. 2019;19:512.
- 29 Radbruch L, De Lima L, Knäul F, Wenk R, Ali Z, Bhatnagar S, et al. Redefining Palliative Care-A New Consensus-Based Definition. *J Pain Symptom Manage*. 2020;60(4):754–764.
- 30 Hendry K, Quinn TJ, Evans J, Scortichini V, Miller H, Burns J, et al. Evaluation of delirium screening tools in geriatric medical inpatients: a Diagnostic Test Accuracy Study. *Age Ageing*. 2016;45:832–7.
- 31 Lawlor PG, Davis DHJ, Ansari M, Hosie A, Kanji S, Momoli F, et al. An analytical framework for delirium research in palliative care settings: integrated epidemiologic, clinician-researcher, and knowledge user perspectives. *J Pain Symptom Manage*. 2014;48:159–75.