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

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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.

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-
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-of-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

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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 VDAS 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, hypopactive 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].

| 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) | |
| Married/unmarried | 257 (55.7) | 59 (46.8) | 198 (59.1) | 0.0979 |
| 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) | |
| Education, mean (±SD), years | 9.9 (4.1) | 8.9 (4.1) | 10.3 (4.1) | 0.0012 |
| 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 |
| ≤3 days, n (%) | 50 (10.9) | 28 (22.2) | 22 (6.6) | |
| >3 days, n (%) | 411 (89.1) | 98 (77.8) | 313 (93.4) | <0.0001 |
| 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.
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 $\chi^2$ 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 (4AT $\geq 4$), 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

### 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 ($N = 48$) | $p$ | with delirium ($N = 98$) | without delirium ($N = 287$) | $p$ |
| 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, n (%)               |         |           |     |                   |             |       |
| 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, n (%)    |         |           |     |                   |             |       |
| Never married            | 2 (7.1)  | 6 (12.5)  |         | 6 (6.1)       | 17 (5.9)    |         |
| Married/unmarried        | 13 (46.4)| 20 (41.7) | 0.9290 | 46 (46.9)      | 178 (62.0)  | 0.0753 |
| 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)  | 0.0901 |
| KPS, n (%)               |         |           |     |                   |             |       |
| $\leq 40$                | 26 (96.3)| 44 (91.7) | 0.4404 | 87 (89.7)      | 173 (60.5)  | <0.0001 |
| $\geq 50$                | 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, n (%)      | 11 (39.3)| 9 (18.7)  | 0.0499 | 17 (17.3)     | 13 (4.5)    | <0.0001 |
| More than 4 days, n (%)  | 17 (60.7)| 39 (81.3) |         | 81 (82.7)     | 274 (95.5)  |         |
| Primary diagnosis, n (%) |         |           |     |                   |             |       |
| Cancer                   | 23 (82.1)| 45 (93.8) | 0.1117 | 69 (70.4)     | 266 (92.7)  | <0.0001 |
| Noncancer                | 5 (17.9)| 3 (6.2)   | 0.2836 | 30 (1.2)      | 2.8 (1.2)   | 0.1875 |
| Charlson index (mean±SD) | 3 (1.7)  | 2.6 (1.1) |         | 12 (12.2)     | 3 (1.0)     | <0.0001 |
| Dementia, n (%)          | 3 (10.7) | –         | 0.0220 | –             | –           |         |

KPS, Karnofsky Performance Status; SD, standard deviation.
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.

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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.

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