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RESEARCH PAPER

The relationship between frailty and delirium: insights from the 2017 Delirium Day study

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Abstract

Background: although frailty and delirium are among the most frequent and burdensome geriatric syndromes, little is known about their association and impact on short-term mortality.
Objective: to examine, in hospitalized older persons, whether frailty is associated with delirium, and whether these two conditions, alone or in combination, affect these patients' 30-day survival.
Design: observational study nested in the Delirium Day project, with 30-day follow-up.
Setting: acute medical wards ($n = 118$) and rehabilitation wards ($n = 46$) in Italy.
Subjects: a total of 2,065 individuals aged 65+ years hospitalized in acute medical (1,484 patients, 71.9%) or rehabilitation (581 patients, 28.1%) wards.
Methods: a 25-item Frailty Index (FI) was created. Delirium was assessed using the 4AT test. Vital status was ascertained at 30 days.
Results: overall, 469 (22.7%) patients experienced delirium on the index day and 82 (4.0%) died during follow-up. After adjustment for potential confounders, each FI score increase of 0.1 significantly increased the odds of delirium (odds ratio, OR: 1.66 [95% CI: 1.45–1.90]), with no difference between the acute (OR: 1.65 [95% CI: 1.41–1.93]) and rehabilitation ward patients (OR: 1.71 [95% CI: 1.27–2.30]). The risk of dying during follow-up also increased significantly for every FI increase of 0.1 in the overall population (OR: 1.65 [95% CI: 1.33–2.05]) and in the acute medical ward patients (OR: 1.61

[95% CI: 1.28–2.04]), but not in the rehabilitation patients. Delirium was not significantly associated with 30-day mortality in either hospital setting.
Conclusions: in hospitalized older patients, frailty is associated with delirium and with an increased risk of short-term mortality.

Keywords: frailty, delirium, Delirium Day, mortality, older people

Key Points

- Although frailty and delirium are among the most frequent and burdensome geriatric syndromes, little is known about either their association or their independent and combined effects on short-term mortality in older persons. This study aimed to address this knowledge gap.
- In 2017, a multicenter study named Delirium Day (DD) was conducted to assess the in-hospital point prevalence of delirium. In total, 118 acute medical wards and 46 rehabilitation facilities in Italy were involved, with a total of 2,065 patients participating in the study.
- A 25-item Frailty Index (FI) was constructed, based on a list of chronic diseases and other health deficits. Delirium was assessed on a single day (index day) using the 4AT test, administered by each ward's attending physicians.
- Higher FI scores were associated with a greater likelihood of delirium on the index day and with an increased risk of 30-day mortality.

Introduction

Delirium is a serious acute-onset neuropsychiatric condition characterized by impaired attention and awareness, a fluctuating course, and global cognitive dysfunction [1]. Particularly common among older and critically ill patients, it has multiple predisposing and precipitating factors and frequently arises as a complication of: acute medical conditions, intoxication with or withdrawal of medication, surgery or electrolyte or metabolic imbalances; it can also arise simply as a result of hospitalization [2].

Despite its high prevalence [3–5], delirium is often under-recognized, misdiagnosed [6] and inadequately managed.

A recent systematic review and meta-analysis explored the existence of an independent relationship between frailty and delirium, two common geriatric syndromes [7]. Among 1,626 articles retrieved, 20 were available for the systematic review and eight for the meta-analysis. Although an association between frailty and delirium was found, there was heterogeneity among the criteria used to select the populations, and also among the methods with which both frailty and delirium were assessed. Furthermore, most data pertained to studies performed in surgical wards [7]. Therefore, there is still a need for research examining in depth the relationship between the two conditions.

In 2017, a study named 'Delirium Day' (DD) was conducted in Italy to evaluate the prevalence and outcomes of delirium among patients admitted to various care settings (i.e. acute hospital wards, rehabilitation facilities and nursing homes). On the basis of the data collected in acute medical and rehabilitation wards, we set out to evaluate whether frailty is associated with delirium, and whether frailty and delirium, alone or in combination, influence short-term mortality.

Methods

Study population and hospitals

The DD study originated as a cross-sectional study, whose primary aim was to assess the point prevalence of delirium, on a single day, across a nationwide sample of hospital units. To this end, hospital physicians associated with 12 scientific medical societies (see Acknowledgments) were invited by email to participate in the study on a voluntary basis and without incentives.

For each center, we recorded the ward types and number of beds. Data were collected on a single day (27 September 2017) and all patients who were admitted to the participating wards from 00.00 to 23.59 on that day were potentially eligible for inclusion.

To be included, patients had to be aged 65 years or older, willing to participate, and able to speak Italian. We excluded those with clinical conditions precluding adequate verbal and visual communication, including aphasia, coma, severe hearing impairment or deafness, and severe visual impairment or blindness. Severe hearing impairment was defined as inability to understand the interviewer at a distance of less than 1 m, and severe visual impairment as the inability to distinguish two fingers at a distance of less than 1 m, as in a previous study [8]. Furthermore, we excluded patients who refused to sign the informed consent document; next of kin provided informed consent on behalf of patients unable to do so because of delirium or dementia.

Frailty assessment

A 25-item Frailty Index (FI) was constructed in accordance with the Rockwood model [9]. The principle of this model is to count the number of functional and health deficits

(e.g. symptoms, signs, diseases and disabilities), assuming that the more deficits someone has, the more likely he/she is to be frail. Since previous studies considered different sets and numbers of deficits, yet nevertheless seemed to obtain similar findings (in terms of the rate of deficit accumulation, the relationship between deficit accumulation and mortality, and limits to deficit accumulation, for example) [9], no distinction was made between types of deficit; therefore, it did not matter if the total count comprised mainly diseases rather than functional, or other, deficits. The variables included in the FI and the method used to construct it are reported in Supplementary Table S1, Supplementary data are available in *Age and Ageing* online.

Other variables

Other variables assessed on the index day included the National Early Warning Score (NEWS) [10], the use of psychotropic drugs (i.e. acetylcholinesterase inhibitors/memantine, benzodiazepines, antidepressants, typical and atypical antipsychotics and antiepileptics), the use of medical devices (i.e. intravenous catheters, urinary catheter, feeding tubes, percutaneous endoscopic gastrostomy) and/or the use of physical restraints.

Outcome measures

The presence/absence of delirium on the index day was assessed on that day by the attending physician, using the 4AT test [11]. In previous studies, the 4AT has shown excellent sensitivity and specificity to diagnose delirium at a threshold score of $\geq$4 [11, 12].

Vital status was ascertained at 30 days from the index day through a phone interview with participants or their caregivers, or from medical records in the case of patients who were still hospitalized.

Data protection

The DD data were collected through a web-based case report form. The database was anonymized and secured with password-protected access systems. Printed information was stored in locked file cabinets in areas with access limited to the leading researchers.

Statistical analysis

The characteristics of the cohort were described by mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate, for continuous variables, and by frequency and percentages for categorical variables. Univariate analyses were conducted using the Chi-square test for categorical variables, and the Mann–Whitney or Student's t tests for continuous variables. After adjusting for potential confounders, selected a priori on the basis of existing knowledge and clinical experience, the association between frailty and delirium was investigated through multivariable logistic regression analysis with a random intercept for hospitals. The functional form of the association between FI and delirium occurrence was explored graphically on a logit scale, and the model assuming a linear effect on the same scale was compared with those modeling it as a restricted cubic spline with 3–5 knots using Akaike's information criterion (AIC). The model assuming a linear effect had the smallest AIC and was therefore selected. To help interpretation, odds ratio (OR) values were calculated for every 0.1 unit increase in frailty. To assess the impact of both delirium and frailty on 30-day mortality, we used a multivariable logistic regression model including potential confounders, again selected on the basis of existing knowledge and clinical experience. All the analyses were performed on the whole sample of patients and also separately for types of ward. The results of the regression models were reported as adjusted ORs and 95% confidence intervals (CIs). All tests were two-sided, with a significance level of 0.05. All analyses were conducted using the R software version 3.6.2 (https://www.r-project.org/).

Ethical standards

The Brianza Ethics Committee approved the study (deliberation n 2,572, 22/06/2017). Each participant was required to sign an informed consent form; proxies were asked to provide consent on behalf of individuals with severe cognitive impairment or delirium.

Results

Figure 1 shows the patient selection process. Overall, 2,065 patients hospitalized in 118 acute medical wards and 46 rehabilitation units participated in the study. The acute medical wards accounted for 1,484 of the patients (71.9%) and the rehabilitation wards for 581 (28.1%). In detail, 1,143 participants (79.6% of the acute medical ward patients) were in geriatrics, general or internal medicine wards, while 163 (11.4%) were in neurology, 30 (2.1%) in orthopedics and 100 (6.0%) in cardiology, hematology or nephrology wards. Overall, 469 (22.7%) participants experienced delirium on the index day and the median FI was 0.20 (IQR: 0.12–0.28). At the 30-day follow-up, 82 (4.0%) patients had died; there was no difference in the mortality rate between patients from the acute medical and rehabilitation settings (n = 61, 4.1% vs. n = 21, 3.6%, respectively).

The characteristics of the patients are reported in Table 1, both overall and by ward type. The mean age of the whole sample was 82.2 (SD = 7.4) years; 845 (40.9%) patients were males; 1,484 (71.9%) were hospitalized in acute medical wards. Dementia was diagnosed in 26.9% of patients, with no difference found between ward types, whereas frailty was more common in acute medical (0.20 [IQR: 0.12–0.28]) than in rehabilitation ward patients (0.16 [IQR: 0.08–0.25]). Similarly, the median NEWS (1.0 [IQR: 0.0–3.0] in acute medical vs. 1.0 [IQR 0.0–2.0] in rehabilitation wards), and the use of peripheral venous catheter (75.3% in acute medical vs. 29.4% in rehabilitation wards), oxygen support (12.7% in acute medical vs. 6.9% in rehabilitation wards) and urinary catheter (33.6% in acute medical vs.

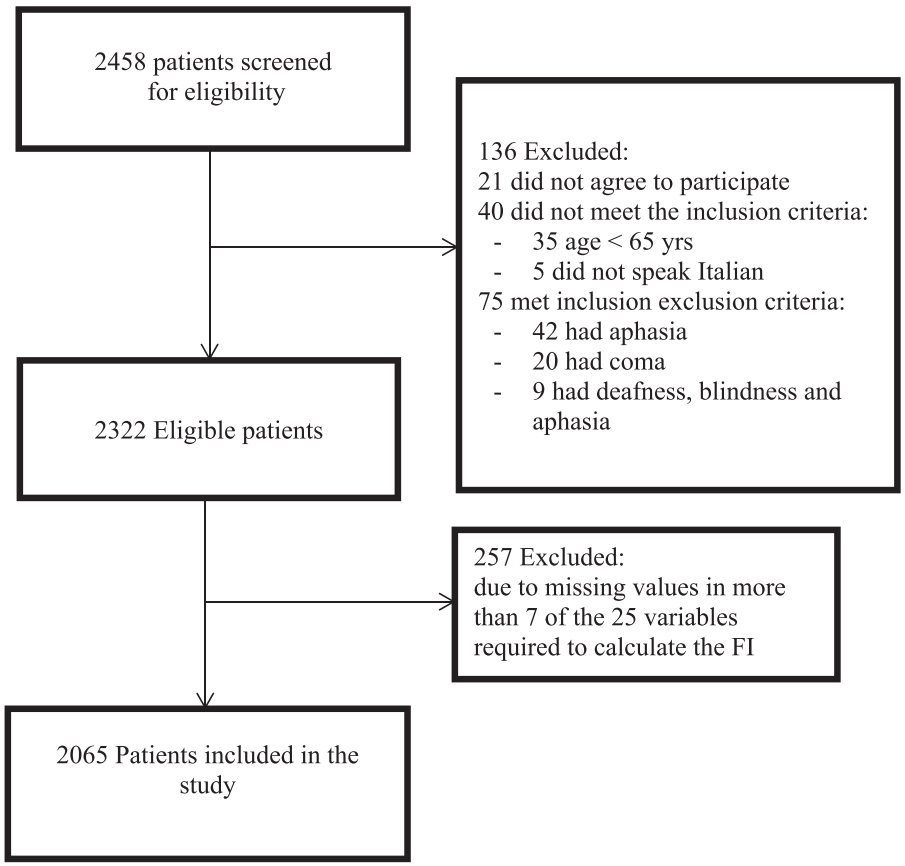

Figure 1. Flowchart showing the patient selection process.

17.7% in rehabilitative wards) were significantly different between the settings. On the contrary, the use of physical restraints and other medical devices was comparable. However, delirium was significantly more common in acute medical (23.9%) than in rehabilitation ward patients (19.8%).

Table 2 shows the results of the multivariable analysis for the presence of delirium on the index day. For every 0.1 unit increase in the FI, the risk of delirium increased significantly (OR: 1.66 [95% CI: 1.45–1.90]), with no difference found between acute (OR: 1.65 [95% CI: 1.41–1.93]) and rehabilitation (OR: 1.71 [95% CI: 1.27–2.30]) ward patients. The use of antipsychotics and physical restraints were also associated with an increased risk of delirium across both settings. Notably, the effect of antipsychotics was greater in acute medical than in rehabilitation patients (OR: 6.44 in acute medical vs. 2.45 in rehabilitation wards), while the inverse was found with regard to physical restraints (OR: 4.63 in acute medical vs. 6.79 in rehabilitation wards). We also observed that antiepileptics, oxygen support and NEWS result were associated with the odds of a patient being delirious, both in the whole population and in the acute medical ward patients, but not in the rehabilitation ward patients.

In a multivariable regression model (Table 3) including delirium, FI, age, sex and NEWS result, neither delirium nor age was associated with the risk of 30-day mortality. Instead, for every 0.1 unit FI increase, the risk of death during the 30-day follow-up increased significantly both in the overall study population (OR: 1.65 [95% CI: 1.33–2.05]) and in the acute medical patients (OR: 1.61 [95% CI: 1.28–2.04]), although not in the rehabilitation ward patients (OR: 1.69 [95% CI: 0.95, 3.01]). On the contrary, males had a 71% higher risk of dying with respect to females (95% CI: 1.05–2.76), both in the overall population and in the rehabilitation ward patients (OR = 4.84, 95% CI: 1.34–17.52), but not in the acute medical ward population. The NEWS value was also associated with increased mortality risk, both in the study population as a whole (OR = 1.24, 95% CI: 1.14–1.34) and in both the hospital settings considered.

The interaction between delirium and frailty was not significant and was not included in the final model ($P = 0.477$).

Discussion

This is the first multicenter study that specifically investigates the association between frailty, delirium and 30-day mortality risk in a large, representative sample of older patients admitted to acute medical and rehabilitation wards. We found that frailty significantly increased the odds of delirium across the entire sample, with no difference found between the acute and rehabilitation ward patients, while it

Table 1. Clinical characteristics of the study population, overall and by ward type

	Overall (n = 2,065)	Acute medical wards (n = 1,484, 71.9%)	Rehabilitation wards (n = 581, 28.1%)	P-value
Age, years, mean ± SD	82.2 ± 7.4	82.3 ± 7.7	81.9 ± 7.1	0.374
Male sex, n (%)	845 (40.9)	643 (43.3)	202 (34.8)	<0.001
FI score, median (IQR)	0.20 (0.12, 0.28)	0.20 (0.12, 0.28)	0.16 (0.08, 0.25)	<0.001
Dementia diagnosis, n (%)	555 (26.9)	388 (26.1)	167 (28.7)	0.253
NEWS, median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)	<0.001
Drugs, median (IQR)	7.0 (5.0, 10.0)	7.0 (5.0, 9.0)	9.0 (6.0, 10.0)	<0.001
Benzodiazepines, n (%)	469 (22.7)	301 (20.3)	168 (28.9)	<0.001
Antipsychotics, n (%)	308 (14.9)	203 (13.7)	105 (18.1)	0.014
Antidepressants, n (%)	342 (16.6)	218 (14.7)	124 (21.3)	<0.001
Antiepileptics, n (%)	133 (6.4)	80 (5.4)	53 (9.1)	0.003
AChE-i/memantine, n (%)	42 (2.0)	21 (1.4)	21 (3.6)	0.003
Peripheral venous catheter, n (%)	1,287 (62.4)	1,116 (75.3)	171 (29.4)	<0.001
Oxygen support (nasal cannula/Ventimask), n (%)	228 (11.0)	188 (12.7)	40 (6.9)	<0.001
Urinary catheter, n (%)	601 (29.1)	498 (33.6)	103 (17.7)	<0.001
Physical restraints (at least one), n (%)	1,065 (51.7)	765 (51.7)	300 (51.7)	1.000
Other devices, n (%)	147 (7.1)	113 (7.6)	34 (5.9)	0.189
Delirium, n (%)	469 (22.7)	354 (23.9)	115 (19.8)	0.054
Length of hospital stay, days, median (IQR)	16.0 (10.0, 27.0)	13.0 (9.0, 19.0)	38.0 (26.0, 61.0)	<0.001
Death, n (%)	82 (4.0)	61 (4.1)	21 (3.6)	0.697

AChE-I, acetylcholinesterase inhibitors.

Table 2. Multivariable regression model investigating the association between delirium and clinical variables

	Overall			Acute medical wards			Rehabilitations wards		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
FI score (for a 0.1-unit increase)	1.66	1.45, 1.90	<0.001	1.65	1.41, 1.93	<0.001	1.71	1.27, 2.30	<0.001
Age (years, scaled)	1.01	0.99, 1.04	0.164	1.01	0.99, 1.04	0.285	1.02	0.98, 1.06	0.438
Sex (Males vs. Females)	0.95	0.73, 1.25	0.731	0.88	0.64, 1.21	0.444	1.09	0.62, 1.93	0.762
Ward type (Rehabilitation vs. Acute) medical wards)	0.81	0.51, 1.29	0.375	–	–	–	–	–	–
Benzodiazepines (Yes vs. No)	0.74	0.53, 1.02	0.068	0.69	0.47, 1.02	0.064	0.90	0.49, 1.67	0.744
Antipsychotics (Yes vs. No)	4.88	3.53, 6.72	<0.001	6.44	4.35, 9.52	<0.001	2.45	1.33, 4.52	0.004
Antidepressants (Yes vs. No)	0.90	0.64, 1.28	0.558	1.15	0.77, 1.73	0.503	0.51	0.26, 1.03	0.061
Antiepileptics (Yes vs. No)	2.16	1.32, 3.52	0.002	2.42	1.31, 4.46	0.005	1.67	0.72, 3.88	0.237
Peripheral venous catheter use (Yes vs. No)	0.85	0.60, 1.19	0.340	0.74	0.49, 1.12	0.152	1.04	0.56, 1.92	0.908
Urinary catheter use (Yes vs. No)	1.15	0.86, 1.54	0.352	1.06	0.76, 1.49	0.717	1.62	0.87, 3.02	0.125
Oxygen support* (Yes vs. No)	0.47	0.30, 0.74	0.001	0.46	0.28, 0.76	0.003	0.51	0.17, 1.59	0.245
Other medical devices (Yes vs. No)	1.33	0.82, 2.14	0.246	1.22	0.70, 2.15	0.484	1.34	0.50, 3.60	0.558
Physical restraints (At least one vs. None)	4.89	3.47, 6.89	<0.001	4.63	3.13, 6.86	<0.001	6.79	3.13, 14.73	<0.001
NEWS	1.12	1.05, 1.20	0.001	1.13	1.05, 1.22	0.002	1.10	0.93, 1.29	0.266

*nasal cannula or Ventimask.

Table 3. Multivariable regression model investigating the association between frailty, delirium and 30-day mortality

	Overall			Acute medical wards			Rehabilitations wards		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Delirium (Present vs. absent)	1.18	0.70, 1.98	0.545	1.05	0.58, 1.90	0.885	1.97	0.58, 6.70	0.278
FI score (for a 0.1 increase)	1.65	1.33, 2.05	<0.001	1.61	1.28, 2.04	<0.001	1.69	0.95, 3.01	0.077
Age (years, scaled)	1.02	0.98, 1.05	0.325	1.01	0.97, 1.05	0.518	1.03	0.95, 1.12	0.491
Sex (Males vs. Females)	1.71	1.05, 2.76	0.030	1.27	0.74, 2.18	0.397	4.84	1.34, 17.52	0.016
NEWS score	1.24	1.14, 1.34	<0.001	1.17	1.06, 1.29	0.001	1.57	1.24, 1.98	<0.001

increased the risk of dying during follow-up in the overall population and in the acute medical ward patients, but not in the rehabilitation group. Delirium was not significantly associated with 30-day mortality in either hospital setting.

The finding that frailty is associated with delirium deserves comment. In fact, even though this association might seem obvious, existing literature supporting it is poor and mainly concerns studies conducted in surgical settings

(7). A recent single-center study explored the relationship between frailty and delirium in patients admitted to an acute geriatric unit [13] and found that frailty was associated with delirium and that it significantly influenced the results of attentional tests commonly used to assess delirium [13]. Our study recruited a large cohort of inpatients from a sizeable number of acute hospital and rehabilitation wards and, therefore, expands previous knowledge of clinicians and researchers regarding the relationship between frailty and delirium.

An important finding of our study is that the association of frailty with delirium remained significant even after adjusting for several covariates that are potentially correlated with delirium. Indeed, antipsychotics, antiepileptics and physical restraints may be considered precipitating factors, whereas frailty is a predisposing factor of delirium; this suggests that the use of certain psychotropic drugs and physical restraints should be avoided in frail individuals. The association of delirium with increased need of oxygen support and with high NEWS values supports the notion that delirium is caused by acute medical conditions [1, 14] and suggests that assessing frailty can shed light on an individual patient's risk of delirium, regardless of his/her illness severity.

A single-center study investigating the effect of frailty and delirium on patients' survival showed that, among those with delirium, frail individuals had a greater long-term mortality risk than fit ones [15]. This observation is consistent with the present results and with the clearly documented general effect of frailty on mortality [16, 17]. Our failure to detect an effect of frailty on mortality among patients in the rehabilitation wards is likely to depend on the small sample size in these settings. Conversely, a novel finding of our study is that delirium alone did not significantly increase 30-day mortality risk. The independent effect of delirium on short-term mortality is still debated. In fact, while it is agreed that delirium is associated with death [14, 18, 19], there is a lack of agreement as to whether delirium is directly harmful to patients or is instead a marker of their intrinsic vulnerability. One recent study supported the first hypothesis (i.e. that delirium may be directly harmful to patients and that noxious insults occurring during hospitalization may be mediators) [14]. However, the study did not control for patients' baseline frailty. The importance of controlling for frailty when studying the association between delirium and mortality has already been suggested [20, 21], given that frailty may act as a confounder, explaining the increased risk both of delirium, associated with vulnerability to stressor events, and of adverse outcomes [21]. Despite the need for prospective studies with longer observation times and more rigorous methods for detecting delirium, the results of the current study somehow support this hypothesis. The effect of NEWS on short-term mortality was to be expected, given that this score reflects acute clinical instability.

This study may have implications for delirium prevention in clinical practice. Several reviews and clinical trials have shown that multicomponent non-pharmacological interventions can prevent delirium, reducing its incidence by more than 40% [22, 23]. These interventions include assessment and correction of precipitating factors of delirium. However, their implementation is often impeded by staffing and time constraints. Our findings, which suggest that these efforts should primarily target frail patients who have an increased risk of superimposed delirium and therefore of short-term mortality, may help to provide some guidance in this regard. This hypothesis deserves to be tested in intervention studies including subjects stratified for frailty status. Frailty itself may be another important prevention target. Indeed, there is evidence that frailty can be delayed and reversed through simple and practical approaches, which should be initiated some years before hospitalization [24, 25]. However, even if such prevention has been tried and failed, frailty assessment could still be particularly helpful in order to identify and target individuals at high risk of delirium and death.

The present study has several strengths. It is the first real-world multicenter study evaluating the association between delirium and frailty, and their relationship with short-term mortality in a large cohort of hospitalized older patients. The study involved a large number of acute medical and rehabilitation wards, spread across Italy. Another strength is that delirium was assessed using a validated tool, and frailty according to a standardized procedure. However, the study has also potential limitations. The main limitation lies in its original cross-sectional design; indeed, some might argue that, in this framework, establishing a causal relationship between frailty and delirium is impossible. Yet, since patient frailty was measured on the basis of health deficits present prior to hospitalization, while delirium can reasonably be assumed to have appeared during hospitalization, reverse causation is not plausible. Second, we did not collect data about the reasons for hospital admission or about the causes of death. Third, our single assessment of delirium with the 4AT might have led to an underestimation of its prevalence due to possible fluctuations of delirium itself. Fourth, the exclusion of patients with missing data and the lack of data quality control may have biased, at least partially, the findings on delirium prevalence. Fifth, we cannot exclude that the lack of association between delirium and mortality could be due to our possibly having missed the most severe cases of delirium among the individuals who were excluded from the study. Indeed, patients with more severe delirium are probably at higher risk of death. Further studies are warranted to evaluate whether the severity of delirium is significantly associated with increased mortality, regardless of the presence of frailty. A final limitation is that we excluded the patients with severe hearing and visual impairments. Therefore, we cannot rule out that the true proportion of hospitalized older people with delirium may be greater than that found in our study. This may also explain the absence of an association between delirium and death.

Conclusions

In conclusion, this study showed that frailty in hospitalized older patients is significantly associated with a high

prevalence of delirium and with an increased risk of short-term death.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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