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The relationship among frailty, delirium and attentional tests to detect delirium: a cohort study

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ABSTRACT

Background: Few studies explored if frailty predisposes to delirium in hospitalized older patients. The aims of this study were to evaluate if frailty: 1) is independently associated with delirium, and 2) affects the patient's performance in three tests of attention used to detect delirium.
Methods: Data are from a prospective cohort study of patients admitted to an Acute Geriatric Unit (AGU). Frailty was operationalized using the health deficit accumulation model (38-item Frailty Index). Delirium was screened using the 4AT, and the diagnosis confirmed with the DSM-5th criteria. During the first 7 days from the hospital admission, patients also underwent a double-blind assessment of attention using three *ad hoc* tests (i.e., Months of the year backwards, MOTYB; Days of the week backwards, DOWB; and Count backwards from 20 to 1, CB).
Results: Eighty-nine patients were included (mean age 83.1 years, standard deviation 6.0). Forty-two (47.19%) patients were frail, and 37 (41.7%) had delirium. The likelihood of delirium was significantly higher in frail compared to the non-frail patients; it was also inversely associated with the three attention tests. Using the MOTYB test, the ability to discriminate delirium was similar in patients with (Area Under the Receiving Operator Characteristic [AUROC] 0.88, 95% Confidence Interval [CI] 0.82-0.92) and without frailty (AUROC 0.93, 95%CI 0.90-0.95) whilst was markedly different between the same groups using either DOWB and CB.
Conclusions: Frailty is associated with delirium in hospitalized older patients and can influence the patient's performances at attentional tests that are commonly used to screen delirium.

Introduction

Frailty and delirium are two medical conditions of older people that have been described as geriatric giants (1). Frailty is characterized by a decrease of functional reserves due to a multisystemic physiological dysregulation. It results in an increased level of vulnerability to endogenous and exogenous stressors (2), and in an increased risk of negative health-related events.

Delirium is an acute and fluctuating neuropsychiatric disorder characterized by impaired attention, reduced awareness of the environment, disorientation, disturbance in visuospatial ability and perception. It develops in association with another underlying medical condition (3).

Frailty and delirium are both common (4, 5) and multidimensional (6, 7). They are also strongly associated with adverse clinical events, including increased risk of functional loss, institutionalization, and mortality (8-10).

The relationship between frailty and delirium is not yet completely understood. Recently, a systematic review and meta-analysis summarized existing knowledge about the interplay potentially existing between these two conditions (11). From more than 1600 articles selected after an initial literature search, the authors found only twenty studies candidates for the systematic review and eight eligible for meta-analysis. It was reported a significant association between frailty and

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subsequent delirium, although a substantial heterogeneity was documented across the methodologies of the studies. Furthermore, the meta-analysis exclusively included studies conducted in surgical settings, none from medical wards.

It also remains largely undetermined the combined effect that delirium and frailty may exert on the patient's outcomes. In this context, it is noteworthy a recent study showing a relatively stronger association of delirium with mortality in fit versus frail patients (12).

There are also important unresolved questions regarding the relationship between the two conditions and the methods to assess delirium in frail patients. First, it is important to understand whether frailty may predispose to delirium in acute medical wards. Second, it should be explored whether frailty may also affect the patients' performance in tests of attention that are commonly supporting the detection of delirium (13). In fact, the inability to sustain attention is a key element of delirium (3, 13). Consequently, if frailty affects delirium, it may also influence the ability to sustain attention in commonly used tests. As a result, different approaches to screening for delirium may be warranted in older patients with frailty.

The first aim of this study was to evaluate whether frailty is independently associated with the presence of delirium in a cohort of older patients admitted to an acute geriatric ward. We also sought to assess whether frailty may affect the patient's performance in three tests of attention that are commonly used in clinical practice. To this aim, we selected three tests of attention that have also been described as markers of concentration, working memory, executive function, cognitive flexibility, and central processing speed (13, 14).

Methods

Study design and participants

This prospective, observational, cohort study was conducted in older adults admitted to the Acute Geriatric Unit (AGU) of the San Gerardo University Hospital between March 24th, 2015 and June 1st, 2015. All individuals consecutively admitted from the emergency department to the AGU were assessed for eligibility. Inclusion criteria were age older than or equal to 65 years, and willingness to participate in the study. Exclusion criteria were patient's deafness and/or blindness, incapacity at participating in the study interviews (for example, due to language barrier, aphasia, or coma on admission), and a length of hospital stay shorter than 7 days. We also excluded patients with incomplete information on medical records at the end of the study.

The Ethical Committee of the Milano-Bicocca University approved the study protocol. We obtained informed consent from all participants or their next of kin (when the participant was not capable of providing it because of severe cognitive impairment, i.e. delirium or dementia).

Comprehensive geriatric assessment

Information on demographic characteristics and clinical, functional, and nutritional data was collected for all patients by one of the authors (MB). The functional status referring to the month prior the hospital admission and acute illness was assessed using the Katz' Activity of Daily Living (ADL) index (15) and the New Mobility Score (NMS) (16). The Katz's index assigns a score of 1 for complete independence and 0 for dependence in six basic ADLs (i.e., bathing, dressing, transfer from bed to chair, toileting, continence, feeding). The NMS is a composite score measuring the individual's ability to walk indoors, walk outdoors, and shop before an acute (i.e., hip fracture) event. Each component is scored between 0 and 3; the total score thus ranges from 0 (lowest functional level) to 9 (highest functional level). Dementia was defined by a documented diagnosis in the medical records and/or use of acetylcholinesterase inhibitors (AChE-I) or memantine prior to admission. Furthermore, we assessed the nutritional status using the Mini Nutritional Assessment Short-Form (MNA-SF) (17). Information on patient's diseases was obtained by reviewing medical records on admission and assessing the number of the drugs taken at home by each patient (see Supplementary Table).

Other variables characterizing the health status at the hospital admission were also collected, including the presence of infections, use of urinary catheter, serum concentrations of albumin and creatinine, and the Sequential Organ Failure Assessment (SOFA) score (18), that is a recently validated tool to predict short-term mortality in older patients admitted to AGUs.

Assessment of frailty

In this study, frailty was defined according to the model proposed by Rockwood (19). The FI is based on the theoretical concept that frailty derives from the age-related accumulation of deficits. It takes into account clinical signs, symptoms, diseases, disabilities, psychosocial risk factors, and geriatric syndromes, resulting in a score that has shown to be strongly associated with negative health-related outcomes (including hospitalizations, institutionalization, and mortality) (8). For the aims of this study, we generated a FI from variables assessed during the Comprehensive Geriatric Assessment, referring to the pre-admission health status. Each deficit included in the FI was coded as 0, 0.5, or 1 to indicate its absence, partial presence, or presence, respectively. Overall, 38 variables were included in the computation of the FI, which made our variable relatively robust (20, 21). Each participant's FI was calculated as the ratio between the presented deficits divided by the number of evaluated items (i.e., 38). Participants with a FI score 0.25 were considered frail, whereas those with lower values were considered non-frail (22).

Assessment of delirium and attentional disorders

Delirium was daily screened in all eligible patients using the 4AT from hospital admission to their discharge. The assessment was conducted by the attending physicians, who were not part of the study team (23). The 4AT evaluates 4 items: item 1 assesses alertness, item 2 assesses orientation using the Abbreviated Mental Test – 4 (AMT4) (24), item 3 assesses attention with the MOTYB test (25), and item 4 assesses the acute change or fluctuation in mental status. When the 4AT scored 4/12 or above, one geriatrician with experience in delirium (GB) confirmed the presence of delirium in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria (3). On Sundays and on holidays, when the geriatrician was not on duty at the AGU, we examined medical and nursing notes to identify the presence of 10 keywords associated with delirium (26). Fluctuation of arousal within the last 24 hours was assessed by two investigators (GB and PM) according to the results of the modified Richmond Agitation and Sedation Scale (m-RASS) (27), a validated test which is routinely applied by AGU physicians and nurses. This information was used to support or reject the diagnosis of delirium.

From admission to discharge (including Sundays and holidays), patients also underwent a daily double-blind assessment of attention by a trained researcher (MB). The assessment of these tests was undertaken 15-30 minutes after the assessment of delirium carried out by the geriatrician. First, the patient was asked to list the months of the year backwards, from December to January (Months of the year backwards, MOTYB test), then to list the days of the week backwards (DOWB), and finally to count backwards from 20 to 1 (CB). The level reached by the patient for each test was recorded.

For the purpose of the study, we analyzed only the data referring to the independent assessments of delirium and attention obtained during the first seven days of hospital admission.

Statistical analysis

Continuous variables were expressed as means ± standard

deviations (SD), or median and interquartile range (for variables that were not normally distributed), and categorical data as frequencies and proportions. To estimate the association between frailty status and the presence of delirium, we applied the Generalized Estimating Equations (GEE) approach (28). In this study, we used a compound symmetry working correlation matrix that assumes a constant correlation among repeated measurements on the same patient. One model for each attentional test was fitted including a time-dependent (e.g., the number of correct responses at the attentional tests) and some fixed covariates (e.g., age, gender, SOFA score, concentrations of albumin and creatinine, and the presence of infections). Moreover, other potential covariates were the time of each measurement and the interaction between frailty and time.

To evaluate the power of each test of attention to predict delirium according to the presence of frailty, we calculated the area under the receiver operating characteristic (AUROC) curve. Furthermore, to test the AUROC difference between frailty and groups (i.e., frail and non-frail participants), we applied a Z-test with the bootstrap percentile method to estimate the standard deviation of each AUROC. Finally, to identify the optimal cut-point of each attentional test according to the presence of frailty, we calculated the Youden's Index.

Results

The study sample consisted of 120 participants (80.5% of the total population approached, N = 149). Of these, fifteen patients were excluded because they were comatose or data were incomplete. Among the remaining 105 patients, the mean baseline FI was 24.54% (SD ± 11.67%; range 3.00%-54.00%). The FI was related both to age (ρ 0.20; p = 0.038) and Charlson's Comorbidity Index (CCI; ρ = 0.40; p < 0.001).

The subsequent analyses were conducted on 89 patients with complete data and a length of hospital stay of at least 7 days (Figure 1). Their mean age was 83.15 (SD ± 6.05) years with a slight predominance of women (51.69%).

The distribution of the frailty levels among participants is reported in the Supplementary Figure. Overall, 47 (52.81%) of them were classified as not being frail (FI < 25%) and 42 (47.19%) as presenting frailty (FI 25%). Thirty-seven patients (41.5%) had delirium; in 25 (67.5%) cases, had it delirium at the hospital admission and in 12 (32.5%) during the 7 days of the study observation.

Table 1 shows the clinical characteristics of the enrolled patients in the two FI groups. In comparison to non-frail participants, the frail ones were more functionally impaired and more malnourished before admission; they also presented a higher prevalence of common clinical conditions. Moreover, frail patients were prescribed more drugs and were more likely to have urinary incontinence. Frail patients were also more commonly affected by delirium than others. No significant differences were noted between groups concerning the SOFA score, the albumin and creatinine serum concentrations, infections, and length of stay.

Table 2 shows the likelihood of presenting delirium during the study period in the unadjusted and adjusted models. In comparison to their counterparts, frail patients showed a five-fold higher likelihood in the unadjusted model. The risk remain substantially high even after adjustment for potential confounders (i.e., age, sex, SOFA score, albumin, creatinine, and infections).

Figure 2 shows the patient's likelihood of experiencing delirium according to the number of correct responses at each attention test. As expected, in both patients' groups, the lower number of correct responses corresponded with a higher probability of delirium. However, frail patients showed a more pronounced curve of association between delirium likelihood and the number of correct responses at each attention test compared to non-frail ones.

Table 3 shows the performance at each cognitive test (MOTYB, DOWB and CB) to detect delirium according to the presence of frailty. The ability to correctly identify delirium using MOTYB was similar in patients with (AUROC 0.88, 95%CI 0.82-0.92) and without frailty (AUROC 0.93, 95%CI 0.89-0.95). On the contrary, DOWB and CB showed different performance in the discrimination of delirium in participants with frailty (AUROC 0.93, 95%CI 0.90-0.96 for DOWB; AUROC 0.92, 95%CI 0.89-0.95 for CB, respectively) and in those without (AUROC 0.75, 95%CI 0.67 to 0.84 for DOWB; AUROC 0.81, 95%CI 0.73-0.88 for CB, respectively). Finally, we calculated the

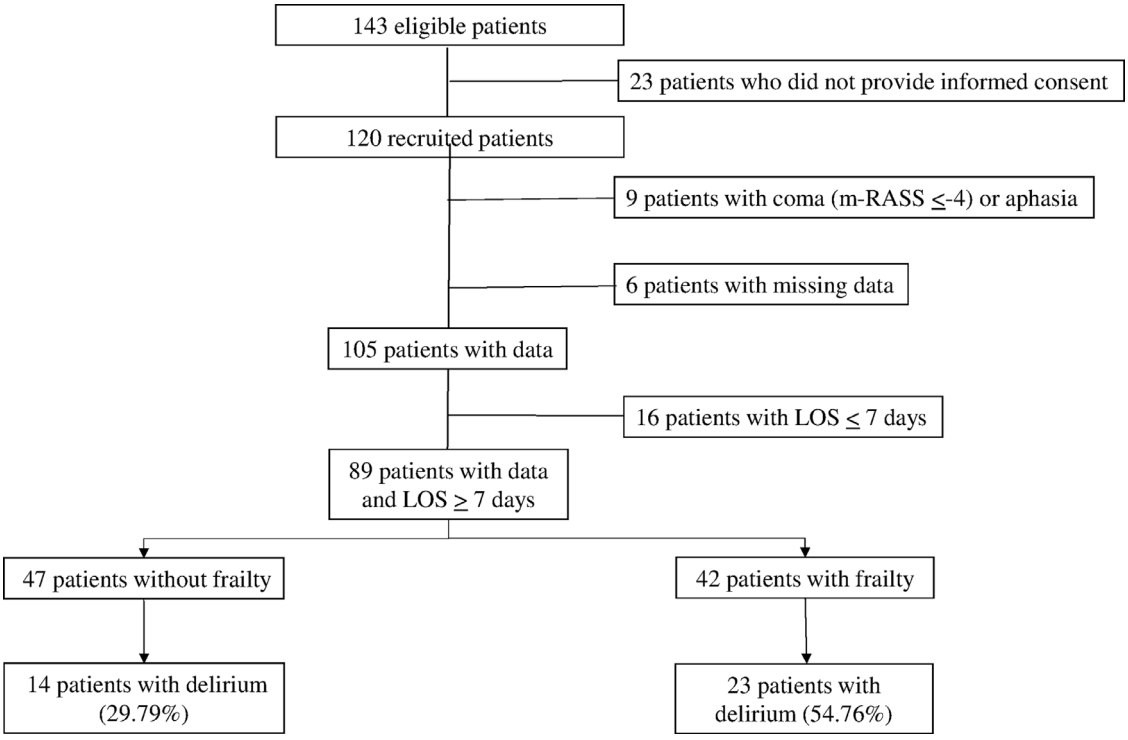

Figure 1. Disposition of the patients in the study.

Table 1
Clinical features of 89 patients recruited for the study according to frailty status

	No frailty N = 47	Frailty	
N = 42	p-value		
Age (years), mean (SD)	82.1 + 5.9	84.3 + 6.0	0.080
Gender female, n (%)	23.0 (48.9)	23.0 (54.8)	0.5830
Variables included in the Frailty Index			
Pre-admission ADL score, median (IQR) §	6.0 (5.0 – 6.0)	1.0 (1.0 – 3.0)	< 0.0001
New Mobility Score, median (IQR) §	11.0 (10.0 – 12.0)	8.0 (7.0 – 10.0)	< 0.0001
Mini Nutritional Assessment, median (IQR) §	6.0 (5.0 – 9.0)	2.0 (0.0 – 3.0)	< 0.0001
Hearing impairment, n (%)	7 (14.9)	8 (19.1)	0.6012
Visual impairment, n (%)	5 (10.6)	9 (21.4)	0.1628
Hypertension, n (%)	36 (76.6)	28 (66.7)	0.2981
Atrial fibrillation, n (%)	14 (29.8)	18 (42.9)	0.1996
Heart failure, n (%)	8 (17.0)	16 (38.1)	0.0253
Coronary heart disease, n (%)	5 (10.6)	10 (23.8)	0.0975
Stroke, n (%)	1 (2.1)	3 (7.1)	0.3399
Cerebrovascular disease, n (%)	9 (19.2)	17 (40.5)	0.0272
Diabetes, n (%)	7 (14.9)	17 (40.5)	0.0066
Pre-existing dementia, n (%)	7 (14.9)	22 (52.4)	0.0002
Chronic respiratory disease, n (%)	11 (23.4)	18 (42.9)	0.0506
Chronic kidney disease, n (%)	8 (17.0)	7 (16.7)	0.9644
Chronic liver disease, n (%)*	3 (6.4)	3 (7.1)	1.0000
Parkinson disease, n (%)*	1 (2.1)	2 (4.8)	0.6002
Connective tissue disease, n (%)*	3 (6.4)	2 (4.8)	1.0000
Gastrointestinal ulcer, n (%)*	2 (4.3)	0 (0.0)	0.4959
Leukemia, n (%)*	1 (2.1)	1 (2.4)	1.0000
Neoplasm, n (%)	5 (10.6)	6 (14.3)	0.6017
Metastasis, n (%)*	1 (2.1)	1 (2.4)	1.0000
Lymphoma, n (%)*	1 (2.1)	0 (0.0)	1.0000
Depression, n (%)	8 (17.0)	6 (14.3)	0.7235
Osteoarthritis, n (%)	11 (23.4)	8 (19.1)	0.6166
Osteoporosis, n (%)	5 (10.6)	6 (14.3)	0.6017
Thyroid disease, n (%)	6 (12.8)	6 (14.3)	0.8340
Peripheral vascular diseases, n (%) *	3 (6.3)	4 (9.5)	0.7028
Skin lesions, n (%)*	0 (0.0)	5 (11.9)	0.0205
Drugs, n (%)	14 (29.8)	29 (69.1)	0.0002
Incontinence, n (%)	4 (8.5)	30 (71.4)	< 0.0001
Variables assessed on admission but not included in the Frailty Index			
SOFA score, median (IQR) §	1.0 (0.0 – 2.0)	1.5 (1.0 – 3.0)	0.0858
Albumin serum levels, median (IQR) §	3.6 (3.3 – 3.9)	3.4 (3.1 – 3.7)	0.0554
Creatinine serum levels, median (IQR) §	1.1 (0.8 – 1.6)	1.2 (0.9 – 1.5)	0.6209
Infections, n (%)	15 (31.9)	13 (31.0)	0.9222
Urinary catheter, n (%)	8 (17.0)	13 (30.9)	0.1223
Length of stay, median (IQR)	12.0 (9.0 – 15.0)	12.0 (9.0 – 16.0)	0.7800
Outcome variable assessed during the first 7 days of hospital stay			
Delirium, n (%)	14 (29.79)	23 (54.76)	0.0170

No frailty indicates a total Frailty Index (FI) score < 0.25; Frailty indicates a total FI score > 0.25.
*Fisher exact test; §Wilcoxon test; IQR = interquartile range;SOFA score, albumin, creatinine serum levels and presence of infections on admission were not computed in the FI calculation since they may have been modified by the clinical reasons that led to hospital's admission and thus they do not necessarily reflect the patients' pre-hospital frailty status.

optimal threshold to detect delirium for each cognitive test. In patients with frailty, the cut-point for the number of uncorrected answers required to identify delirium was higher for both the MOTYB and CB tests, in comparison to those without frailty, while was identical in patients with and without frailty for the DOWB test.

Discussion

In a cohort of older patients admitted to an acute geriatric ward, the presence of frailty increased the likelihood of having delirium. The study also shows an inverse association between the patient's performance in tests of attention and the probability of having delirium. In particular, the probability of having delirium during the study period was linearly associated with the worsening of the performance at each attentional test both in frail and non-frail patients. However, this pattern was especially pronounced in frail patients. Importantly, the three tests used to evaluate attention (i.e., MOTYB, DOWB, and CB) had a similar predictive capacity to detect delirium in frail patients. In contrast, only the MOTYB appeared to be accurate in non-frail patients. Furthermore, we found different cut-points for each attentional test for frail and non-frail patients, suggesting that one predetermined threshold may not represent an optimal choice for both frail and non-frail patients.

Table 2
Effect of frailty status on delirium prevalence ratio in unadjusted and adjusted models.

Variables	Unadjusted model	
PR (95% CI)	Adjusted model	
PR (95% CI)		
Frailty (yes/no)	5.69 (2.55 – 12.70)	4.90 (2.01 – 11.94)
Age, years	-	0.98 (0.91 – 1.06)
Gender (male/female)	-	1.76 (0.69 – 4.53)
SOFA score	-	1.45 (1.03 – 2.04)
Albumin serum levels	-	0.41 (0.15 – 1.16)
Creatinine serum levels	-	0.96 (0.45 – 2.03)
Infection (yes/no)	-	0.84 (0.31 – 2.30)

PR: Prevalence ratio, CI = Confidence Intervals, SOFA = Sequential Organ Failure Assessment

Although it is commonly accepted that frailty predisposes to delirium (29, 30), evidence to support this notion is still inconclusive. Recently, Persico et al. identified only 20 studies on frailty and delirium which were candidates for a systematic review, and only 8 of them (all conducted in surgical wards) eligible for a meta-analysis (11). Most of these were flawed by several limitations, in particular for what concerns the methods for assessing delirium. For example, in some studies delirium was only assessed at the hospital admission (31, 32) or on alternate days between admission and discharge (33), limiting the ability to detect the fluctuations of cognitive performance (a key characteristic of the condition of interest). Additionally, in one study, delirium was assessed using a non-validated method (34) and in another the assessment methods were not specified at all (35). There is also inconclusive evidence regarding the combined effect of frailty and delirium on patient's negative outcomes, as it has been found that delirium contributes to increase mortality in a different manner according to patient's frailty status (12).

In the present study, we tried to shed some lights regarding the association between frailty and delirium. We were also interested at exploring whether frailty can influence the results of attentional tests that are commonly used to detect delirium. Delirium was assessed every day since the hospital admission, using a two-step approach that included a formal screening and then a diagnosis using the DSM-5. The fluctuation of symptoms was assessed using a validated tool, informed by the daily reading of medical and nurse records in the AGU. In addition, frailty was assessed using a FI based on the Rockwood's deficit accumulation model (36). Our 38-item index was created in agreement with a validated standardization procedure (21).

An important finding of our study is that a different, though good performance of each attention tests exists among frailty groups. This is in line with previous studies (37, 38) showing that cognitive processing speed, sustained attention and executive functions are associated with pre-frailty and frailty in older patients, and may represent a potential marker of frailty progression.

Importantly, in our study the tests of attention differed in their usefulness between frail and non-frail patients, with the DOWB test

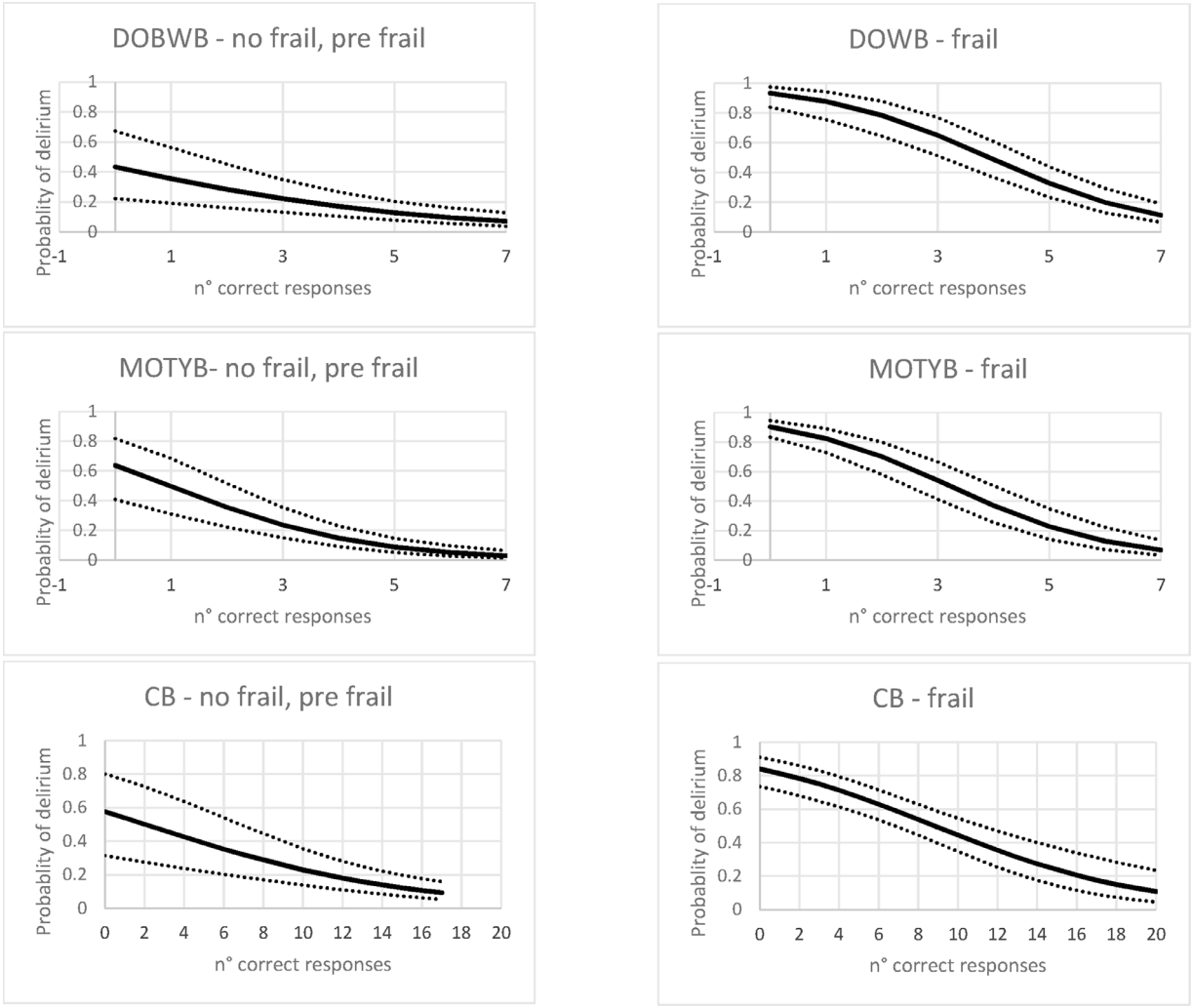

Figure 2. Likelihood of being diagnosed with delirium according to the number of correct responses at each attentional test. The full line represents the value of the model-based likelihood while the dotted lines represent the 95% confidence limits.

Table 3
Performance of the three attention measurements according to frailty status and optimal threshold.

		No frailty	Frailty	p-value
DOWB	AUROC	0.7551 (95% CI 0.6701 to 0.8402)	0.9347 (95% CI 0.9063 to 0.9632)	< .0001
	Cut-point	1/7	1/7	
MOTYB	AUROC	0.8762 (95% CI 0.8260 to 0.9263)	0.9278 (95% CI 0.8983 to 0.9573)	0.1203
	Cut-point	2/12	3/12	
Count 20-1	AUROC	0.8088 (95% CI 0.7309 to 0.8867)	0.9237 (95% CI 0.8918 to 0.9556)	0.0297
	Cut-point	2/20	10/20	

DOWB = Days Of the Week Backwards; MOTYB = Month Of The Year Backwards; Count 20-1: serial counting from 20 to 1. AUROC = Area Under the Receiving Operator Characteristic; 95% CI = 95% Confidence Intervals Cut-point = minimum number of uncorrected answers to detect delirium at each attentional test

appearing quite weak at detecting delirium among non-frail patients. A practical implication of these findings is that, once admitted to an acute hospital, older patients should undergo a formal assessment of their baseline level of frailty. This will help understanding the risk of developing delirium, but also indicate which is the most suitable test for assessing attention (potentially avoiding an overestimation of delirium prevalence).

These findings raise the issue of identifying the mechanisms by which frailty can modulate performance on tests of attention. Attention is a basic component of cognitive functions and, in particular, of the executive functions of the prefrontal cortex to execute purposeful behavior (such as problem solving, planning, and decision making) (39). Importantly, the component processes in attention (i.e., working memory, competitive selection, top-down sensitivity control and salience filters) depend upon the integrity of the underlying neural patterns (40). It could therefore be hypothesized that as frailty worsens, attentional processes perform less efficiently, perhaps because brain interconnectedness becomes less redundant and the amount of energy available to neurons progressively declines (41).

A strength of this study was that the assessors of delirium and attention tests were blind each other, thus limiting the potential influence in the rating of clinical diagnosis of delirium by the objective tests and vice versa. Other strengths were the accuracy in the diagnosis of delirium (which was based on a two-step approach), the careful evaluation of fluctuating symptoms, and a robust validated method to calculate the FI. Importantly, the variables used to construct the FI were all concerning the pre-hospital patient's health status.

Our study presents limitations worth to be noted. It was conducted at a single center and the sample size was relatively small. It is also

possible that third factors not considered in our models may differently explain our findings. For example, we cannot exclude that the onset of delirium during the hospital stay could be due to changing clinical conditions. Furthermore, the 4AT is a screening and not a diagnostic tool, which implies that some patients who were 4AT negative, may have had delirium. However, it should be noted that, in its first validation study, the 4AT showed optimal sensitivity (89.7%) and specificity (84.1%) to detect delirium in comparison to DSM-IV diagnostic criteria (23). Therefore, it is likely that only a minority of cases may have been misclassified in our study.

Despite these limitations, we believe the findings of this study provide new information on the relationship between delirium and frailty and have implications for the assessment of delirium in frail and non-frail patients.

In summary, this study suggests that frailty is associated with delirium also in patients admitted to an AGU and that the presence of frailty may influence the patient's performances at the attentional tests. Further studies in diverse populations with administration by a variety of healthcare team members are needed to determine whether our findings are reproducible and thus generalizable to other patients.

Authorship

All authors had access to the data and played a role in writing the manuscript.

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Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2019.09.008.

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