ORIGINAL RESEARCH

Association between frailty and delirium in older adult patients discharged from hospital

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Background: Delirium and frailty – both potentially reversible geriatric syndromes – are seldom studied together, although they often occur jointly in older patients discharged from hospitals. This study aimed to explore the relationship between delirium and frailty in older adults discharged from hospitals.

Methods: Of the 221 patients aged >65 years, who were invited to participate, only 114 gave their consent to participate in this study. Delirium was assessed using the confusion assessment method, in which patients were classified dichotomously as delirious or nondelirious according to its algorithm. Frailty was assessed using the Edmonton Frailty Scale, which classifies patients dichotomously as frail or nonfrail. In addition to the sociodemographic characteristics, covariates such as scores from the Mini-Mental State Examination, Instrumental Activities of Daily Living scale, and Cumulative Illness Rating Scale for Geriatrics and details regarding polymedication were collected. A multidimensional linear regression model was used for analysis.

Results: Almost 20% of participants had delirium (n=22), and 76.3% were classified as frail (n=87); 31.5% of the variance in the delirium score was explained by frailty (R^2=0.315). Age; polymedication; scores of the Confusion Assessment Method (CAM), instrumental activities of daily living, and Cumulative Illness Rating Scale for Geriatrics; and frailty increased the predictability of the variance of delirium by 32% to 64% (R^2=0.64).

Conclusion: Frailty is strongly related to delirium in older patients after discharge from the hospital.

Keywords: Edmonton Frailty Scale, delirium risk factors, cognitive impairment, physical impairment

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Introduction

Delirium is a mental disorder with an acute onset and fluctuating course, characterized by disturbances of consciousness, orientation, memory, thought, perception, and behavior.[1] This syndrome represents a serious problem in acute care hospitals and is associated with decreased functional status, longer periods of time before recovery and discharge, institutionalization, premature mortality, and increased health care costs. The etiology of delirium is considered to be multifactorial, with an occurrence rate as high as 83% in hospitals.[2] Multicomponent delirium prevention strategies have been shown in intervention studies to consistently reduce the occurrence of delirium.[3] Based on this evidence base, the National Institute for Health and Care Excellence has advocated the adoption of multicomponent delirium prevention interventions into the routine care for older inpatients.[4] However, despite successful reductions in incident delirium by about a third, anticipated reductions in mortality or admissions to long-term care have not been conclusively observed.[5] One-third of older patients still have undetected and unresolved symptoms of delirium at hospital discharge.[6]

Frailty is a geriatric condition characterized by diminished strength, endurance, and physiological functions that increase an individual's vulnerability to adverse outcomes such as falls, sarcopenia, institutionalization, worsened disability, and premature death.[7] Frailty was recently defined as a state of increased vulnerability related to a poor level of homeostasis after a stressful event, with a corresponding increased risk of adverse outcomes, including falls, delirium, and disability.[7] Frailty has been linked to the development and progression of many age-related diseases and syndromes.[8]

However, little is known about the relationship of frailty as a precipitating risk factor for specific geriatric syndromes in hospitalized older patients.[9] Frailty associated with hospitalization may occur in one-third of older patients and can be triggered even when the illness causing hospitalization is successfully treated.[7] Frailty has a considerable influence not only on outpatients' independence and quality of life but also on their use of health care services.[10]

Delirium and frailty appear to be distinct clinical geriatric conditions. However, in vulnerable older adults, both syndromes can appear simultaneously in response to a stressor.[9] Besides the elevated rates of delirium during hospitalization, studies have reported about the important consequences of frailty among older adults discharged from hospital, including increased dependence as shown on the Instrumental Activities of Daily Living (IADL) scale, weight loss, and cognitive impairment.[11] These consequences result from the acute syndrome of delirium itself and are also related to the management of patient care during hospitalization. They can lead to a state of severe frailty at discharge, with a high risk of premature death.[12]

Delirium has been associated with increased long-term cognitive impairment and acceleration of existing cognitive decline. Furthermore, it may delay physical and cognitive recovery, ultimately resulting in new or increasing frailty and long-term disability and institutionalization. Both frailty and delirium in older patients can affect independent functioning and the ability to live at home.[9] A study on older patients who had undergone cardiac surgery and then developed postoperative delirium showed that delirium was associated with an approximately twofold increase in the risk of frailty after 1 month.[13] However, few studies have examined the relationship between frailty and delirium among older patients.[14,15]

Therefore, we hypothesized that delirium and frailty were associated in a sample of older adult patients discharged from a hospital.

Methods and materials

Data were sourced from a prospective clinical trial entitled "Effect estimation of an innovative nursing intervention to improve delirium among home-dwelling older adults," which was conducted in 2012 and published elsewhere.[16] The trial protocol was approved by the cantonal medical ethics committee of Valais, Switzerland (CCVEM 030/11). Written informed consent was obtained from all participants or from their closest relatives if they scored <15 points on the Mini-Mental State Examination (MMSE).[17]

Participants

In the original study, a nonprobabilistic sample of 221 eligible participants was contacted within 48 hours of their hospital discharge, in collaboration with a home health care service, in order to request their participation. For different reasons, 107 older adults refused to participate, resulting in a final sample of 114 participants. Patients with a medical prescription for home health care were eligible to participate if they were 1) aged 65 years or older, 2) discharged after hospitalization of at least ≥48 hours, and 3) capable of understanding and answering questions in French. Figure 1 presents the recruitment procedure.

Measurements
Assessment of delirium

Delirium was assessed using the validated French version of the Confusion Assessment Method (CAM).[18] The CAM is an instrument developed to assist clinicians in identifying patients with delirium. It has been considered suitable for bedside use.[19] The psychometric properties of the CAM have been documented as excellent, with 94% sensitivity, 89% specificity, and a Kappa's inter-rater reliability between 0.70 and 1.00.[19] The research nurse or the principal investigator (PI) completed the CAM form based on a structured interview, patient records, and clinical observation of the symptoms/signs described in the CAM. Data were subsequently analyzed categorically by using the CAM algorithm. The inter-rater reliability between the PI and the research nurse (trained in CAM assessment) showed a satisfactory Kappa Cohen's coefficient of 0.79.[20]

Assessment of frailty

The frailty status was assessed using the Edmonton Frailty Score (EFS) developed by Rolfson et al[21] and been evaluated in a systematic review of de Vries et al.[22] This instrument consists of nine domains and eleven items, each scoring 0 points (frailty absent or normal health), 1 point (minor errors or mild/moderate impairment), or 2 points (important errors or severely impaired). The domains include cognitive impairment, autoevaluation of general health status, functional dependency, presence of social support, drug treatments and
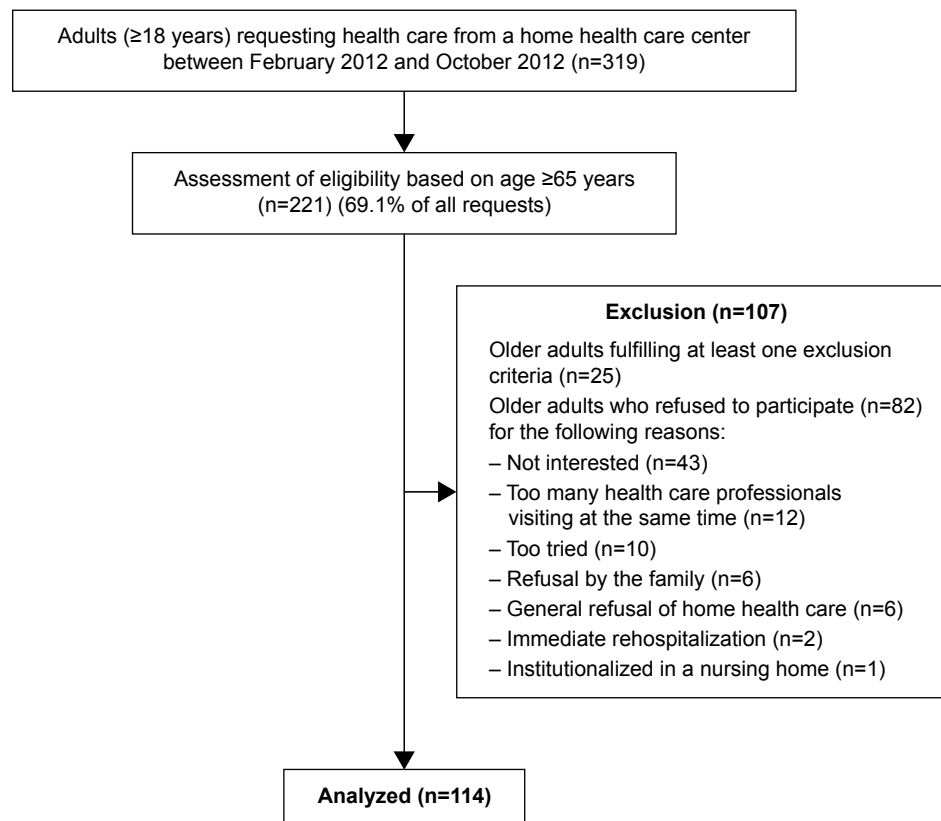
Figure 1 Recruitment of the participants.

adherence, nutrition and mood, presence of incontinence, and the "timed up and go (TUG)" test. The TUG tests the basic mobility skills of frail elderly persons. It consists of a measurement of the time in seconds for a person to rise from sitting from a standard arm chair, walk 3 m, turn, walk back to the chair, and sit down. A cutoff score of ≥ 20 seconds was shown to predict falls in community-dwelling frail elderly people.[23]

The total score from 0 to 3 points indicates no frailty; 4 or 5 points indicate prefrailty; 6 to 8 points indicates frailty; and 9 to 17 points indicates severe frailty. In order to dichotomize between frail and not frail, a score of 6 points or more was considered as frail. The eleven-item EFS has good psychometric properties and showed an acceptable Cronbach's alpha of 0.62 in the present study.[21] The inter-rater reliability between the PI and the research nurse was excellent (Kappa Cohen's coefficient =0.85).

Other variables

Sociodemographic characteristics assessed included age, sex, marital status, and level of education (Table 1).

Cognitive level was assessed using the MMSE by regrouping the seven domains of cognitive functioning.[17,24] The eleven-item instrument measures orientation, memory,

language, and psychomotor skills. The sum of the scores varies from 0 (severe cognitive impairment) to 30 (no cognitive impairment). A score of <24 points was considered as the cutoff point for cognitive impairment. The MMSE was mostly assessed by the PI, and the instrument presents good psychometric proprieties.[25] An excellent inter-rater ratio was obtained between the PI and the research nurse with an intraclass correlation of 0.92.

Table 1 Sociodemographic characteristics of participants (n=114)

Variables	
Age (years)	
Average (SD)	83.2 (7.2)
Sex	
Female (%)	74 (64.9)
Marital status	
Single (%)	7 (6.1)
Married/partner (%)	41 (36.0)
Divorced/separated (%)	6 (5.3)
Widowed (%)	60 (52.6)
Education	
Primary (%)	13 (12.5)
Secondary (%)	38 (36.5)
Vocational (%)	33 (31.7)
University (%)	20 (19.2)

Abbreviation: SD, standard deviation.

Table 2 Health status of participating delirious and nondelirious discharged older adults

Variables	No delirium (n=20)	Delirium (n=94)	P-value
Sex			
Male/female (n=114)	32/62	8/12	0.612[b]
Age			
Average (SD)	83.2 (7.2)	83.5 (7.2)	0.875[c]
Edmonton Frailty Scale (EFS)			
Average (SD)	7.96 (2.6)	10.05 (3.3)	<0.001[c,*]
Range	1–17	1–17	
Frail vs not frail[d]			
Frail (%)	71 (75.5)	18 (90.0)	0.235[e]
Not frail (%)	23 (24.5)	2 (10.0)	
Health status			
Cognitive impairment, MMSE (SD)	24.57 (4.3)	19.20 (5.4)	<0.001[c,*]
Functional status, IADL (SD)	20.59 (5.6)	23.70 (6.0)	0.029[c,*]
Comorbidities, CIRS-G (SD)	13.68 (3.2)	14.25 (2.5)	0.458[c]
Average no daily medications (SD)	6.30 (3.1)	6.30 (2.6)	0.997[c]

Notes: [b]Pearson's chi-squared test. [c]Student's *t*-test. [d]Based on EFS, frail ≥6 points. [e]Fisher's exact test. *Significance $P \leq 0.05$.
Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination; IADL, Instrumental Activities of Daily Living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics.

Functional status was assessed using the Lawton Index of IADL, an assessment considered appropriate for older adults living at home.[26,27] The IADL scale assesses independence versus dependence in more complex areas of daily living, such as using the telephone, shopping, preparing meals, cleaning and laundry, using public transport, management of medication and finances, and maintaining a home.[28] A score of <16 indicates that the patient is independent, as documented elsewhere.[28] Inter-rater reliability was excellent (Kappa Cohen's coefficient =0.85). Finally, comorbidities were assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). The CIRS-G scores diseases in 13 organ systems and grades each organ according to severity using explicit rules for classification. Data for CIRS-G scoring were compiled from comprehensive patient interview and chart records. A CIRS-G index of comorbidity of ≥2 implies the presence of moderate and severe illnesses.[29] Inter-rater scores between the PI and the research nurse were very high (Pearson's correlation =0.81). The number of prescribed medications was recorded during patient interviews and through patient records. Participants' health status and average medication use are presented in Table 2.

Data collection

After the participants had given their consent, data were collected during a single home visit within 48 hours of discharge from the hospital. During the home visits, the data collection procedure was standardized to avoid any bias by using an invariable sequence of questions. Data on delirium, frailty, cognition, health status, comorbidities, and medication

treatment were collected immediately after consent of the patients at their place they live. It is important to mention that during hospitalization and at hospital discharge, no delirium of frailty assessment was done. A detailed description of the data collection procedure has been published elsewhere.[16]

Statistical analyses

Sociodemographic and baseline characteristics of subjects with and without frailty were compared using the Student's *t*-test for continuous variables and a chi-squared distribution for categorical ones. The odds ratio (OR) of delirium/frailty was calculated using a contingency table in a joint frequency distribution. The association between delirium and frailty was assessed using linear regression, and this association was adjusted for age, cognitive state (MMSE), physical state (IADL), chronic conditions reported (CIRS-G), and polymedication. Collinearity was verified using a matrix correlation and tolerance values.[30] All statistical tests were performed using the IBM-Statistical Package for the Social Sciences (IBM-SPSS®), Version 22.[31] Statistical significance was set at $P=0.05$, and all tests were two tailed.

Results
Participant characteristics

No statistically significant differences were found between men and women with regard to being nondelirious or delirious ($P=0.612$) and their ages ($P=0.875$; Table 2). Similarly, there were no statistically significant differences with regard to being frail and nonfrail ($P=0.560$) and their ages ($P=0.742$; Table 3).

Table 3 Health status among frail and nonfrail discharged older adults

Variables	Not frail[a] (n=25)	Frail[a] (n=89)	*P*-value
Sex			
Men/women	10/15	30/59	0.560[b]
Age (SD)			
Average (SD)	82.80 (8.3)	83.34 (6.9)	0.742[c]
Health status			
Cognitive impairment, MMSE (SD)	26.28 (3.5)	22.89 (5.0)	0.002[c,*]
Functional status, IADL (SD)	16.64 (4.7)	22.39 (5.5)	<0.000[c,*]
Comorbidities, CIRS-G (SD)	11.36 (3.6)	14.46 (2.6)	<0.000[c,*]
Average number daily medications (SD)	5.20 (2.4)	6.61 (2.7)	0.019[c,*]

Notes: [a]Based on EFS, frail ≥6 points. [b]Pearson's chi-squared test. [c]Student's *t*-test. *Significance *P*≤0.05.
Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination; IADL, Instrumental Activities of Daily Living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; EFS, Edmonton Frailty Scale.

Prevalence of delirium and frailty

Almost one-fifth of the sample (n=20) presented with delirium as measured by the CAM. Almost two-thirds of the frail older adults presented with three or more symptoms of delirium (Table 2). Three quarters of participants (n=89) presented with frailty, including 90% of the delirious participants (n=18). The mean frailty score for nondelirious participants was significantly lower than that for delirious participants (*P*<0.001; Table 2).

Measurements of IADL at hospital discharge showed statistically significant differences in dependency: nonfrail participants were less dependent than frail ones (*P*<0.001), and nondelirious participants were less dependent than delirious ones (*P*=0.029). Similar statistical differences were observed. With regard to cognitive status, nonfrail participants had a better cognitive status than frail ones (*P*=0.002), and nondelirious participants had a better cognitive status than delirious ones (*P*≤0.001). Most of the participants had comorbidities and were being prescribed more than four medications. A significant difference was observed in the comorbidity rates and the average number of medications of frail and nonfrail participants (*P*=0.019), but the difference was not significant between nondelirious and delirious participants (*P*=0.997; Tables 2 and 3).

The high prevalence of frailty among delirious participants reflects the fact that in four of the eleven EFS items – namely cognitive impairment, medication adherence problems, incontinence, and the "timed up and go" test – the scores significantly increased in delirious participants compared to nondelirious participants (*P*≤0.001, *P*=0.018, *P*=0.004, and *P*=0.041, respectively; Table 4).

Association between frailty and delirium

The OR of delirium/frailty indicated that frailty was 1.19 times more present (statistically significant) among participants with delirium than among participants without delirium, with a 95% confidence interval (95% CI) of 1.00–1.43. Cognitive status (MMSE) seemed to be a stronger risk factor for delirium than frailty, with an OR of 4.31 (95% CI [1.51–12.28]). Neither IADL (OR 1.13; 95% CI [0.91–1.41]), age (OR 1.12; 95% CI [0.43–2.96]), and CIRS-G (OR 1.04; 95% CI (0.58–1.89)) nor polymedication (OR 1.03; 95% CI [0.34–3.14]) were significant risk factors for delirium.

Linear regression indicated that 32% of the variance in delirium was explained by frailty alone (R^2=0.315; *P*<0.001), thus suggesting that frailty could be strongly associated.[32] Being frail explained one-third of the presence of delirium in participants. In a multiple regression model, including age, cognitive and physical state, polymedication, and comorbidities, 64% of the variance in delirium could be explained by these variables (adjusted R^2=0.635; *P*≤0.001; Table 5).

No collinearity was found between frailty scores, CAM scores (T-B Kendall =−0.130; variance inflation factor <10), IADL scores (*r*=0.44; variance inflation factor <10), and MMSE scores (*r*=0.45; variance inflation factor <10).[33]

Discussion

Our results indicate that frailty is strongly associated with delirium in older patients as one-fifth of the participants presented delirium at hospital discharge.[2] Nine of ten delirious participants were frail, whereas only three quarters of the nondelirious participants were frail. These findings are consistent with those of other recent studies indicating an elevated prevalence of frailty among discharged older adults with delirium.[34,35] However, our study results do not allow to explain this association, and it has recently been mentioned by Teale and Young that the underlying interaction between these two geriatric syndromes is poorly understood.[5]

Table 4 Distribution of EFS items in delirious and nondelirious discharged older adults

Variables	Delirium	No delirium	*P*-value
Cognitive impairment			
No errors	3 (15.0%)	19 (20.2%)	
Minor errors	2 (10.0%)	46 (48.9%)	
Major errors	15 (75.0%)	29 (30.9%)	0.001*
General health			
Number of hospitalizations			
0	0 (0.0%)	18 (19.1%)	
1–2	17 (85.0%)	68 (72.3%)	
>3	3 (15.0%)	8 (8.5%)	0.086
Autoevaluation of health			
Excellent to good	3 (15.0%)	20 (21.3%)	
Acceptable	9 (45.0%)	59 (62.8%)	
Bad	8 (40.0%)	15 (16.0%)	0.052
Functional independence			
IADL dependency score			
0–1	1 (5.0%)	9 (9.6%)	
2–4	4 (20.0%)	40 (42.6%)	
5–8	15 (75.0%)	45 (47.9%)	0.087
Social support available			
Always	18 (90.0%)	79 (84.0%)	
Mostly	2 (10.0%)	14 (14.9%)	
No support	0 (0.0%)	1 (1.1%)	0.755
Use of five or more medications			
No	7 (35.0%)	33 (35.1%)	
Yes	13 (65.0%)	61 (64.9%)	0.993
Risks of nonadherence			
No	8 (40.0%)	64 (68.1%)	
Yes	12 (60.0%)	30 (31.9%)	0.018*
Nutrition, weight loss			
No	11 (55.0%)	51 (54.3%)	
Yes	9 (45.0%)	43 (45.7%)	0.952
Mood, sad, or depressed			
No	13 (65.0%)	57 (60.6%)	
Yes	7 (35.0%)	37 (39.4%)	0.716
Incontinence			
No	5 (25.0%)	57 (60.6%)	
Yes	15 (75.0%)	37 (39.4%)	0.004*
Up and go test			
0–10 seconds	7 (35.0%)	47 (50.0%)	
11–20 seconds	2 (10.0%)	22 (23.4%)	
>20 seconds	11 (55.0%)	25 (26.6%)	0.041*

Notes: Pearson's chi-squared test or Fisher's exact test. *Significance *P*≤0.05.
Abbreviations: EFS, Edmonton Frailty Scale; IADL, Instrumental Activities of Daily Living.

Almost all the participants had some functional impairment, and a third of participants presented a significant cognitive impairment at discharge, which corroborates results from other recent studies.[36] This highlighted an urgent need for health care owing to a high number of hospitalized older patients presenting several symptoms of frailty. In addition, as already documented elsewhere, discharged older patients face a risk of delirium due to the presence of multifactorial delirium risk factors.[37] Some studies have observed a strong relationship between delirium and physical decline, as manifested by an elevated number of hospital-related falls. However, the present study was unable to confirm this relationship, as hospital records concerning adverse events during hospitalization, such as falls and other deleterious events, were incomplete.[38] As in other studies, our results showed no association between age and frailty within the cohort.[8]

In the present study, frailty alone is associated with delirium in more than one-third of cases. In a more complex model – including age, physical and cognitive impairment, polymedication, and polymorbidity – the association of delirium increased, having an impact in up to two-thirds of cases. Thus, cognitive screening alone was more strongly related to delirium than frailty, but cognitive and frailty screening together was even better. These findings confirm that comprehensive geriatric assessment (CGA) and screening for frailty increase early detection of delirium and delirium risks in discharged older adults. Above all, hospitalization itself should be considered as an important delirium and frailty risk factor. Interdisciplinary preventive care strategies focusing on limiting physical and cognitive decline during hospitalization may be effective in averting delirium and frailty and other poor posthospitalization outcomes.[39] Health care reforms focusing on building more effective and efficient care models for older inpatients are urgently needed to develop "senior-friendly" hospitals, including specialized geriatric care units.

Although the delirium rate among our participants was consistent with other studies, the prevalence of frailty was less easy to compare.[35] The challenges of detecting delirium in patients after hospital discharge are well described, in contrast to frailty where prevalence is more dependent on the measurement scale.[40] In the present study, delirium detection and frailty assessment were combined within clinical assessment and routinely collected data; they could be determined for all patients, regardless of their cognitive or functional abilities, thus increasing their potential utility in the clinical setting. The presence of both frailty and delirium confer a particularly poor prognosis, such as dependency, institutionalization, or even premature death.[15,41] However, as delirium and frailty are both viewed as modifiable geriatric syndromes and given the current trend for moving health care out of the hospital into the home, this raises important questions about patient care management.[7] Nevertheless, there are links between delirium and frailty.[42,43] Although frailty is a chronic condition and delirium is a more acute condition, the unavoidable question of a common pathophysiological mechanism persists. Frailty and delirium may be different

Table 5 Simultaneous multiple regression analysis summary for age, polymedication, frailty, physical and cognitive impairment, and comorbidity

Variables	B	SE B	Beta	t	*P*-value
Age	−0.036	0.015	−0.143	−2.354	0.020*
Polymedication	−0.029	0.044	−0.042	−0.658	0.512
Cognitive impairment (MMSE)	−0.262	0.027	−0.771	−9.610	<0.001*
Delirium (CAM)	−0.052	0.414	−0.003	−0.903	0.396
Frailty (EFS)	0.193	0.045	0.309	4.324	<0.001*
Physical impairment (IADL)	−0.025	0.022	−0.080	−1.097	0.275
Comorbidity	−0.033	0.040	−0.056	−0.816	0.417
Constant	11.472	1.776	–		

Notes: Adjusted R^2=0.64; $F_{(6, 107)}$ =33.81, $P \leq 0.001$. *Significant association of delirium.
Abbreviations: SE, standard error; MMSE, Mini-Mental State Examination; CAM, Confusion Assessment Method; EFS, Edmonton Frailty Scale; IADL, Instrumental Activities of Daily Living.

clinical expressions of a shared vulnerability to stress in older adults, and future research should determine whether this vulnerability is age related, pathological, genetic, environmental, or most likely, a combination of all of these factors.[44] Besides the fact that both syndromes represent significant sources of morbidity and mortality for older adults, both of them are multifactorial, with risk factors and potentially causative mechanisms (eg, inflammation, atherosclerosis, and poor nutrition) that overlap.[7] Although there are proven measures for preventing delirium, evidence regarding interventions to improve outcomes following delirium remains uncertain.[2,39] Similarly, while complex interventions such as education, optimized nutrition, and exercise have been suggested for delaying or preventing frailty, there is as yet no evidence that such interventions can mitigate these outcomes in frail older inpatients.[45,46] Whether multicomponent, nonpharmacological, interdisciplinary interventions are effective in preventing frailty and delirium in hospitalized older adult patients should be the focus of further inquiry. Further research on a larger group of discharged older adults is also required.

Finally, this study has both strengths and limitations. The first strength was the comprehensive geriatric assessment approach used, involving patient records, clinical and CAM assessment after discharge, and optimized delirium detection and frailty assessment. Another strength was that all the participants were accurately screened for their health status and frailty indicators, and they were discriminated by the presence of delirious or nondelirious symptoms.

In addition to the relatively small sample group, it seems important to mention the limiting factor that data were collected at a single hospital site, and thus generalization of these results needs caution. Furthermore, comprehensive geriatric assessment data from the emergency department was incomplete, and therefore we could not make a precise interpretation of participants' mental status at hospital admission. Another limitation of the study concerns the correctional nature of the data. Using the EFS did impose some methodological limits to the study, as the most widely used screening tool to assess frailty is that proposed by Fried et al.[47] This requires the presence of at least three of the five following criteria: weight loss, exhaustion, weak grip strength, slow walking speed, and low physical activity. However, exhausted older inpatients, once discharged, are often unable to complete these performance-based tests, and thus many of the participants in the present study could not have been assessed using such physical testing.

The syndromes of delirium and frailty are highly associated in discharged older adults. However, currently, detecting their delirium remains problematic for several reasons. On the other hand, assessing frailty, either through systematic CGA or by using specific frailty-detection tools, gives health care professionals the opportunity to improve the effectiveness of primary prevention strategies for delirium, by promptly ascertaining which discharged older adults are at a high risk of presenting with that syndrome.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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