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RESEARCH ARTICLE

The Prevalence of Frailty and Its Association with Adverse Drug Reactions in Hospitalized Older Adults

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Abstract

Background: The complex interplay between altered pharmacokinetics and pharmacodynamics, greater multimorbidity and polypharmacy, are associated with increased risk of adverse drug reactions (ADR) in older adults. There remains a paucity of data on the association between frailty and ADRs. We aimed to determine the association between frailty and the prevalence, presentation and severity of ADRs among hospitalized older adults.

Methods: This was a retrospective, cross-sectional study in an acute care hospital in Singapore. The first 150 older adults admitted from emergency department or outpatient clinic under Geriatric Medicine service in September 2016 were included. We used Clinical Frailty Scale (CFS) to determine frailty status. Probability and severity of ADRs were determined using Naranjo and Hartwig Scale respectively.

Results: The prevalence of frailty was 83.3%; mean age and CFS were 89.7 ± 4.0 years, and 6 ± 1.3 respectively. Majority (70%) experienced at least 1 side effect; more than 40% of these ADRs were of mild to moderate in severity. Constipation was the most common ADR (41.3%) and was associated with calcium supplement. ACE-inhibitors, diuretics and anti-platelets were also frequently associated with ADRs in older adults. Frail older adults significantly experienced lesser cardiovascular ADRs but more central nervous system ADRs compared to the non-frail group ($P < 0.05$).

Conclusions: There is a high prevalence of frailty and ADRs in hospitalized older adults, with ADRs mostly mild to moderate in severity. More robust studies to prospectively explore the relationship between frailty and ADRs are required.

Keywords

Deprescribing, Drug, Elderly, Frailty, Hospital

Abbreviations

ADR: Adverse Drug Reactions; CFS: Clinical Frailty Scale; CNS: Central Nervous System; ACE-inhibitors: Angiotensin II Converting Enzyme-inhibitors; ARBs: Angiotensin II Receptor Blockers; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PASW: Predictive Analytics Software Version

Introduction

Older adults, especially individuals with multimorbidity, have been found to have an increased risk of adverse drug reactions (ADRs). This is believed to be contributed by the presence polypharmacy and complex drug-drug interactions, which are heavily influenced by age-associated alterations in pharmacokinetics and pharmacodynamics [1]. Altered pharmacokinetics, leading to drug accumulation, can result in ADRs and drug toxicities. Studies have demonstrated that older adults often experience heightened response to various medications, especially drugs that act on the central nervous system (CNS). In addition, diminished responses to medications have also been observed in some drugs that act on the cardiovascular system such as beta-blockers [1].

Medication-related ADRs represent a significant cause of societal burden, and are estimated to result

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in 10% to 30% of all hospital admissions involving older adults [2]. These admissions may also result in undesirable health outcomes i.e. nosocomial infections, functional decline, and prolonged length of hospitalization [3]. ADRs in older adults are also associated with increased risk of other adverse health outcomes including institutionalization, falls and impaired mobility, malnutrition, and mortality [4].

Frailty is gaining recognition as a distinct clinical state that is predictive of adverse health outcomes in older adults, including falls, fracture, disability, lower quality of life, hospitalizations, institutionalization, and mortality [5]. It is defined as a clinical state in which there is an increase in an individual's vulner ability for developing increased dependency and/or mortality when exposed to a stressor [6]. In a local study, it was found that frailty was associated with risk factors such as polypharmacy, multimorbidity and functional impairment [7]. There are well recognized concerns regarding ADRs and inappropriate prescribing in this vulnerable group of older adults [8]. However, there remains a paucity of data on the association between frailty and the incidence and severity of ADRs.

Against this backdrop, it is increasingly important to understand and incorporate the concept of frailty into standard geriatric assessments in order to aid in optimizing appropriate prescribing among frail older adults. These individuals may experience more ADRs due to their lowered physiological reserves that can adversely tip the balance between risks and benefits of the pharmacological treatment instituted [9]. Recognizing this, the Asia-Pacific clinical practice guidelines for the management of frailty strongly recommends that polypharmacy be addressed by reducing or de-prescribing any inappropriate medications [10]. Hence, there should be a strong emphasis on personalized medication review among frail older adults.

Our study aimed to identify the prevalence of frailty and ADRs, and to identify risk factors associated with ADRs in acutely ill hospitalized older adults. Our secondary aim was to identify and quantify the severity of ADRs. This added knowledge may aid in the development of future system enhancements or protocols designed to promote medication safety in frail older adults.

Methods

Study design and eligibility criteria

We conducted a retrospective, cross-sectional study on 150 hospitalized older adults in an acute care hospital (Tan Tock Seng Hospital, Singapore). Patients admitted from the emergency department or geriatric outpatient clinic under the geriatric medicine service in September 2016 were included. We excluded patients that passed away at the emergency department before being admitted to the ward, or if no medication was prescribed in the inpatient medication record. Similar studies on frailty and hospitalized older adults studied sample sizes ranging between 179 and 495 subjects [9,11]. Nevertheless, we opted to gather a sample size of 150 for our study.

Demographic, psychosocial, and clinical data were collected by two members of the study team who were geriatric senior resident doctors. Local electronic medical records including discharge summaries, case notes, and inpatient functional assessment records were accessed for data collection. The burden of comorbidities was calculated based on the Charlsons's Comorbidities Index [12]. Three geriatric-trained pharmacists were also involved in gathering medication-related data. Electronic inpatient medication records, pre-admission medication lists, discharge prescriptions, and cluster electronic prescription database were used as sources for medication history. For our study, we defined polypharmacy as the use of ≥ 5 medications and hyper polypharmacy as the use of ≥ 10 medications [13].

Frailty assessment using the clinical frailty scale

The CFS is a well validated frailty measure that aids in scoring an individual's degree of fitness or frailty following a comprehensive geriatric assessment, and is not based solely on physical frailty or the number of deficits accumulated [14]. It consists of clinical descriptors and pictograms, which allows stratification into 9 categories on the continuum of fitness to frailty. The CFS has been validated and studied in hospitalized older adults, and has been shown to predict length of hospitalization, mortality, functional decline, and 30-day outcome (re-admissions and deaths) after discharge with good reliability [15,16]. It can also be used by non-physician healthcare workers, and does not require any special equipment or training to conduct. In our study, the CFS score of each patient was determined retrospectively by 2 senior residents trained in Geriatric Medicine, using information obtained from available medical records.

Assessment of adverse drug reactions

The probability of ADRs was determined using the most widely used and accepted causality assessment scale, the Naranjo ADR Probability Scale [17]. It is a 10-item questionnaire that classifies the probability of a reaction in relation to a drug using concepts such as timing, evidence, plausibility and toxic drug level. These elements of the questionnaire were weighted and the total score was used to categorize events into unlikely, possible, probable, and definite ADR. The Naranjo Scale has been successfully used in previous studies to determine the prevalence of ADRs in hospitalized older adults [9].

Severity of ADRs was categorized using the Hartwig and Siegel Criteria, which categorizes severity into7 groups according to the clinical outcome. It may be

utilized in busy clinical settings and has been widely reported in literature to objectively determine the severity of ADRs in older adults [18].

Statistical analyses

General descriptive statistics were used for prevalence reporting. Chi-square or Fisher's Exact test were used to determine associations between frailty and various outcomes (for categorical data). Spearman's rho correlation test was used to determine the association between CFS scores and various outcomes (for continuous data). An alpha level of 5% was used as cut-off for significance. Data were entered into Microsoft Excel 2010® spread sheets and analysed using Predictive Analytics Software Version 18.0® (PASW Inc., Chicago, USA).

Table 1: Baseline Demographics of Patients.

Baseline Demographics	Non-frail, n = 25	Frail, n = 125	P value
Age, mean (SD†)	88.8 ± 3	89.9 ± 4.2	0.16
Gender, n (%)			1.0
Male	9 (36)	43 (34.4)	
Female	16 (64)	82 (65.6)	
CFS score, median (IQR‡)	4 (3-4)	7 (6-7)	0.01*
Charlson's comorbidity score, median (IQR‡)	6 (3-4)	8 (6-9)	0.01*
Functional status on admission, n (%)			0.01*
Independent	24 (96)	20 (16)	
Assisted	1 (4)	64 (51.2)	
Dependant	0 (0)	41 (32.8)	
Medications on admission, median (IQR‡)	8 (5.5-11.5)	10 (8-13)	0.04*
Medications on discharge, median (IQR‡)	11 (8-15)	11 (8-12)	0.5
Hypertension, n (%)	21 (84)	104 (83.2)	1.0
Baseline systolic blood pressure range			
< 150 mmHg	19 (76)	96 (76.8)	0.20
151-179 mmHg	4 (16)	27 (21.6)	
≥ 180 mmHg	2 (8)	2 (1.6)	
Diabetes, n (%)	9 (36)	58 (46.6)	0.39
Baseline HbA1c, n (%)			
< 6.5%	5 (20)	22 (17.6)	0.58
6.5-7.49%	2 (8)	14 (11.2)	
7.5-8.49%	0 (0)	11 (8.8)	
≥ 8.5%	1 (4)	7 (5.6)	
Hyperlipidaemia, n (%)	18 (72)	83 (66.4)	0.65
Dementia, n (%)	1 (4)	70 (56)	0.01*
Stroke, n (%)	7 (28)	74 (59.2)	0.01*
On medications, n (%)			
Anti-hypertensives	23 (92)	84 (67.2)	0.01*
Hypoglycemia agents	4 (16)	38 (30.4)	0.22
Anti-psychotics	1 (4)	26 (20.8)	0.04*
Anti-depressants	3 (12)	45 (36)	0.03*
Sedatives	0 (0)	11 (8.8)	0.21
Anti-epileptic drugs	5 (20)	18 (14.4)	0.54
Anti-platelets and/or anti-coagulants	18 (72)	105 (84.0)	0.16
Side effects experienced by system, n (%)			
Cardiovascular	12 (48)	30 (24)	0.03*
Central nervous system	0 (0)	23 (18.4)	0.02*
Endocrine	1 (4)	9 (7.2)	0.70
Gastrointestinal	10 (40)	52 (41.6)	1.00
Hematology	4 (16)	16 (12.8)	0.72
Renal	10 (40)	36 (28.8)	0.34

†Standard deviation; ‡Interquartile range; *Chi-square was used for categorical data, and Mann-Whitney U for continuous data, with statistical significance at P < 0.05.

Results

Baseline demographics

A total of 150 patients (mean age 89.7 ± 4.0 years, female 65.3%) were included in our study. Frailty estimated was 83.3% with a mean CFS score of 6 ± 1.3 (Table 1). Frail patients had significantly higher CFS scores, comorbidities, number of medications on admission, prevalence of stroke and dementia when compared with their non-frail counterparts ($p < 0.05$). We note with interest that although the number of medications on admission was significantly lesser in the non-frail group (8 vs. 10, $p = 0.04$), this observation was absent on discharge (11 vs. 11, $p = 0.5$).

Adverse drug reactions

A total of 304 side effects were recorded (Figure 1) with a median number of 2 side effects per patient (Interquartile range (IQR): 0.0-2.0). 70.0% patients experienced at least 1 side effect. Side effects were classified according to frequency, organ systems affected, Naranjo and Hartwig scores (Table 1, Table 2 and Table 3). Gastrointestinal ADRs were the most common when stratified by organ systems, and were largely contributed by the high prevalence of constipation (41.3%). This was followed by acute kidney injury (20.7%), delirium (14.0%), and bradycardia (14.0%). For severity of ADRs, bleeding, deranged liver function, and diarrhoea had the highest Hartwig scores (median score of 4; moderate ADR). Anti-platelets contributed to majority of the bleeding cases (71.4%), while statin was the major drug class that resulted in deranged liver function (44.4%).

Calcium supplement (12.8%), Angiotensin II converting enzyme-inhibitors (ACE-inhibitors)/Angiotensin II receptor blockers (ARBs) (11.2%), diuretics (8.2%), anti-platelets (6.9%) and opioids (6.9%) were most commonly associated with ADRs (Table 4). The

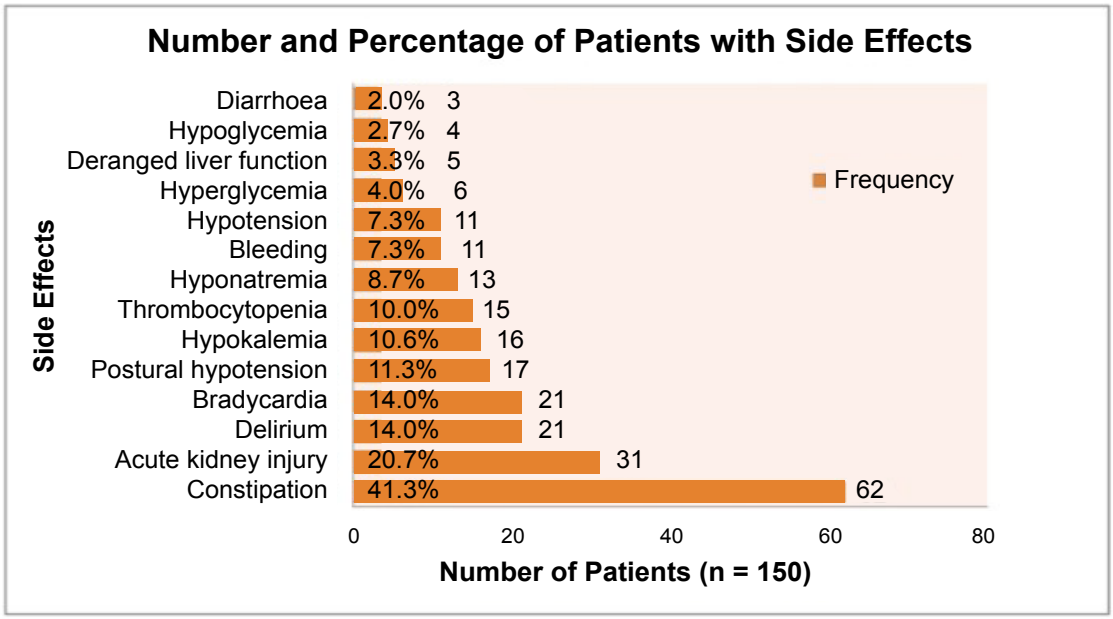

Figure 1: Shows the frequency of side effects experienced in 150 hospitalized older adults. The results were arranged in order of increasing frequency for the types of side effect documented in this study.

Table 2: Frequency and Type of Side Effects Experienced by Patients.

Variables	Number of patients, n = 150
Frequency of side effect, n (%)	
0 side effect	45 (30.0)
1 - 2 side effects	70 (46.7)
3 - 4 side effects	28 (18.7)
≥ 5 side effects	7(4.7)
Types of side effect by system, n (%)	
Cardiovascular	42 (28.0)
Central nervous system	23 (15.3)
Endocrine	10 (6.7)
Gastrointestinal	62 (41.3)
Hematology	20 (13.3)
Renal	46 (30.7)

Table 3: Classification of Side Effects, Stratified by Naranjo and Hartwig scores.

Variables	Values
Top 5 Naranjo scorers for side effects, median (IQR[§])	
Diarrhoea	6 (3 - 6)
Hypoglycemia	5.5 (4.3 - 7.5)
Deranged liver function	5 (1 - 5)
Bradycardia	5 (3.3 - 5)
Hyperglycemia	4.5 (3.3 - 6.3)
Top 5 Hartwig scorers for side effects, median (IQR[§])	
Bleeding	4 (1 - 4)
Deranged liver function	4 (1.5 - 4)
Diarrhoea	4 (2 - 4)
Hypoglycemia	3.5 (2.3 - 4)
Hypotension	3 (2 - 3.3)
[§]Interquartile range	

Table 4: Top 10 Drugs and Related Side Effects.

Drugs	Number of side effects, n = 304	Side effects
Calcium, n (%)	39 (12.8)	Constipation
ACE-inhibitor/ARB[¶], n (%)	34 (11.2)	Hypotension, postural hypotension. Hyponatremia, acute kidney injury
Diuretics, n (%)	25 (8.2)	Hypotension, postural hypotension. Hyponatremia, acute kidney injury
Anti-platelets, n (%)	21 (6.9)	Bleeding, thrombocytopenia
Opioids, n (%)	21 (6.9)	Constipation, delirium
Beta-blocker, n (%)	20 (6.6)	Hypotension, postural hypotension, bradycardia
Iron, n (%)	20 (6.6)	Constipation
Calcium channel blockers, n (%)	15 (4.9)	Hypotension, postural hypotension, constipation
Steroids, n (%)	10 (3.3)	Hyperglycemia, hypokalemia delirium
Anti-histamines, n (%)	7 (2.3)	Constipation, delirium

[¶]angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker.

differences in medication usage and types of ADRs experienced between non-frail and frail older adults were also compared (Table 1). We found that higher proportion of non-frail older adults were on anti-hypertensives (92.0% vs. 67.2%, p = 0.01) and experienced more cardiovascular side effects such as hypotension, postural hypotension, and bradycardia (48.0% vs. 24.0%, p = 0.03) compared to their frail counterparts. Conversely, higher proportion of frail patients were on anti-psychotics (20.8% vs. 4.0%, p = 0.04) and anti-depressants (36.0% vs. 12.0%, p = 0.03), and experienced more CNS side effects such as delirium (18.4% vs. 0.0%, p = 0.02). Both Naranjo and Hartwig scores had weak negative correlation with CFS scores (correlation coefficient -0.19, p = 0.02).

Discussion

To our knowledge, this is the first study exploring the association between frailty and ADRs among hospitalized older adults. The prevalence of frailty in our cohort of hospitalized older adults was 83.3%, which was higher compared to other studies (ranging from 56% to 72%) [19,20]. This may be explained by a higher mean age in our cohort (89 ± 4.02 years) in contrast to other studies, with mean ages ranging from 81 to 85-years-old [19,20]. Perhaps unique to the hospital was the fact that the age criterion for admission under the department of geriatric medicine was 85 years and above. Our result was similar to another study conducted in the same hospital, which reported a frailty prevalence of 81% (mean age of 89 ± 4.6 years) [15]. Hence, our cohort's higher prevalence of frailty may be explained by the higher mean age as increasing age is highly associated with frailty [21].

In our study, the median number of medications on admission for non-frail and frail older adults was 8 and 11 respectively (p = 0.04). It is noteworthy that the majority (69.6%) of the frail older adults have hyper polypharmacy on admission, as compared to their non-frail counterparts (48%). This finding corroborates previous studies, which have similarly found a positive association between polypharmacy and frailty [22,23]. It is also important to be cognisant of the fact that frail older adults were often excluded from clinical trials, and the net benefit of medication may not be apparent compared to healthier cohort. Medication review to mini-

mize polypharmacy should therefore be incorporated as part of routine care of frail older adults.

We observed that gastrointestinal (41.3%), renal (30.7%), and cardiovascular (28.0%) side effects were the most common system-related side effects in our cohort. This is in contrast with other studies, which reported majority of events being haemorrhagic-related ADRs [24,25]. We surmised that the lower rate of bleeding events observed in this study could be due to the lower usage of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-coagulants. Moreover, the concurrent usage of proton pump inhibitors may have prevented upper gastrointestinal bleed from the use of low-dose aspirin in older adults [26].

Consistent with other studies, we found that ACE-inhibitors, ARBs, and diuretics were associated with higher incidences of renal and electrolyte-related ADRs [24,25]. This observation can be explained by age-related changes in the body's ability to conserve fluid and handle electrolyte shift, thus increases the risk of acute kidney injury, dehydration, and electrolyte in older adults who are on these medication. We also found that the majority of our patients (76.7%) had a baseline systolic blood pressure of < 150 mmHg prior to point admission, which may not warrant aggressive blood pressure control in the first place. In a recent landmark trial that compared intensive (< 120 mmHg) versus standard (< 140 mmHg) blood-pressure targets, frail older adults were noted to have a nearly 10-fold higher incidences of severe ADRs including hypotension, acute kidney injuries and electrolyte disturbances compared to non-frail older adults [27]. Results from these studies may suggest that aggressive blood-pressure lowering strategies using ACE-inhibitors, ARB or diuretics, in isolated hypertension might result in deleterious effects, rather than benefits, in frail older adults.

Anti-platelets, opioids, and steroids were also commonly associated with ADRs, similar to previous studies [24,28]. Among all ADRs, bleeding events scored highest on Hartwigscale (median score of 4), with anti-platelets implicated in 71.4% of these cases. This highlighted the importance of concurrent use of proton pump inhibitors in older adults who are at high risk of bleeding (e.g. history of chronic kidney disease, anaemia or concomitant usage of ulcerogenic medications) as they have been shown to prevent upper gastrointestinal bleeds from anti-platelets [26].

The prevalence of ADR in our cohort was higher (70%) in comparison to previous studies on hospitalized older adults, which ranged from 6.7% to 20% [24,25,28]. Our prevalence rate was similar to a study conducted in nursing home residents, which reported an ADR rate of 67.4% [29]. A possible explanation could be the greater proportion of frail patients in our study. This may suggest that frailty is associated with an increased risk of ADRs, possibly due to alterations in homeostatic function as well as reduced physiological reserves.

Perhaps interesting to note was the higher prevalence of cardiovascular side effects observed in non-frail individuals (48.0% vs. 24.0%, p = 0.003) in our study. This could be explained by the higher usage of anti-hypertensives in the non-frail group. It was noted that irrespective of frailty status, the incidence of cardiovascular-related side effects from anti-hypertensives was higher among older adults when compared to younger adults [30]. In patients with moderate to severe frailty, the benefits of secondary prevention may be limited by their shorter life expectancy and poorer functional status. This further illustrated the need to avoid tight blood-pressure control by balancing the risk and benefit of treatment in frail older adults.

Conversely, higher utilization of anti-psychotics and anti-depressants were observed in the frail group, and these individuals experienced more CNS-related side effects compared to their non-frail counterparts. Apart from the iatrogenic effect of medications, the use of anti-psychotics and anti-depressants may suggest that frail patients have higher prevalence of underlying psychological or cognitive conditions that further predispose them to incident delirium. Being frail increases the risk of delirium, as insults from acute conditions or iatrogenic causes can hastily overwhelm the body's ability to cope with stressors [5]. Delirium has also been associated with worsening cognitive function and may retard physical and cognitive recovery after hospital discharge, resulting in worsening frailty and disability [5]. Our study has highlighted the higher incidences of delirium in frail compared to non-frail older adults and prescribing of agents that can potentially induce delirium should be discouraged in these individuals, if possible.

We hypothesized that increasing frailty is associated with higher incidence or severity of ADRs. However, we were unable to find positive association between CFS scores and number of side effects, Naranjo and Hartwig scores. Similarly, there was no literature available that explicitly compared the risk of ADRs in non-frail and frail older adults. The lack of positive results in this study could be related to the small sample size in the non-frail group (n = 25), which prevented meaningful comparison between both groups. Another explanation for this observation was that the patients recruited were from the same admitting discipline (geriatric medicine). Geriatricians specialize in the care of older adults and are well-aware of the complexities and challenges of managing frailty. Hence, their prescribing practices, regardless of whether a patient is frail or not, may be more personalized with careful considerations of the risk-benefit ratio in prescribing or de-prescribing medications. This may in turn ameliorates the reported harm of ADRs in frail older adults.

Our study has a few limitations. Firstly, the retrospective nature of our study may have allowed uncontrolled confounders such as incomplete documentation to impact our findings. Causality relationship between frailty and ADRs may also be reduced with a retrospective design. Secondly, as our study population consisted of acutely ill hospitalized oldest-old, our results may not be generalizable to younger group of patients. In addition, the nature of recruitment, by convenience sampling, may have affected the generalizability of the results. However, convenience sampling can still provide reliable information on correlation, since the focus of the study was not on the proportion of target population, but on the relationship between variables in our cohort. Lastly, the high prevalence of frailty in this study may have resulted in difficulty in discriminating the differences in findings between non-frail and frail individuals. A larger sample size may be needed to provide meaningful comparison between both groups. A larger prospective cohort study that incorporates block randomization to ensure adequate sampling in each group, which can better examine the relationship between frailty and ADRs, is needed.

In conclusion, our study highlighted the high prevalence of frailty and ADRs in hospitalized older adults, with ADRs mostly mild to moderate in severity. Constipation was the most common side effect, whilst ACE-inhibitors, ARBs, diuretics, and anti-platelets were drugs most frequently associated with ADRs in older adults. We propose the need for more robust studies to explore the relationship between frailty and ADRs, with aims to promote safer prescribing practices and to develop preventive measures to minimize harm from medications in frail older adults.

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The authors confirm that they have reviewed and approved the final version of the manuscript and that they have taken due care to ensure its integrity. Each author contributed equally to the design, execution of the study and preparation of the manuscript.

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