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Syncope is associated with multidimensional frailty in older adults

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Abstract

Background Multidimensional frailty and syncope are common in older adults, yet their relationship remains unclear.

Methods This retrospective multicenter study, involving outpatients who underwent Comprehensive Geriatric Assessment, aims to evaluate the relationship between frailty and syncope. Patients were classified as fit/light frail, moderate frail or severe frail based on their fr-AGILE score. Patients reporting one or more episodes of syncope were referred to “Syncope and Fall Unit” and evaluated according to the recommendations of the European Society of Cardiology. Syncope episodes were classified in cardiac, reflex, orthostatic and of unknown origin. Multiple logistic regression analysis was employed to determine the association between the frailty score and syncope, independent of age, sex, comorbidity, and polypharmacy.

Results Among 560 patients (mean age 77.7 ± 6.9 years, 54.5% female), 107 reported experiencing syncopal episodes. Patients with history of syncope had a higher prevalence of orthostatic hypotension (41.1% vs. 18.8%, $p = 0.001$) and a higher fr-AGILE score (6.5 ± 2.0 vs. 5.4 ± 1.9 , $p = 0.001$). Multivariate logistic regression analysis, adjusted for age, sex, comorbidity, and number of medications, showed that frailty, estimated by the fr-AGILE score, was associated with an increased risk of syncope (OR for each unit increase in fr-AGILE: 1.468, 95% CI: 1.276–1.690, $p = 0.001$). Frailty was associated with syncope, particularly cases of undetermined origin, but not with cardiac syncope.

Conclusions The fr-AGILE score identifies patients at high risk of syncope. Frailty is strongly associated with non-cardiac syncope and with cases where a pathophysiological cause of the syncopal event could not be determined.

Keywords Multidimensional frailty, Syncope, Comprehensive Geriatric Assessment

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Background

Multidimensional frailty is a complex clinical condition that affects individuals experiencing loss in one or more domains of human functioning (physical, nutritional, psychological, and social). It is caused by various influencing factors and increases the risk of adverse outcomes [1]. It is estimated that approximately one-quarter of individuals over the age of 85 is frail [2]. Furthermore, with the aging population, the prevalence of frailty is dramatically increasing, underscoring the urgent need to identify and implement strategies for its management and prevention to minimize its substantial socio-economic impact [3].

Syncope is a transient loss of consciousness (TLOC) resulting from global cerebral hypoperfusion and followed by spontaneous and complete recovery [4]. With a lifetime incidence of over 50%, syncopal episodes are particularly frequent in the later decades of life, significantly impacting quality of life and individual autonomy [5]. The incidence of syncope sharply increases from 5.4 events per 1000 person-year in individuals aged 60 to 69 years to 11.1 events per 1000 person-year in those aged 70 to 79 years and reaches 19.5 events per 1000 person-year in those aged 80 years or older [6]. The prevalence of syncope is even higher among institutionalized older patients, reaching 23% [7]. In older adults, syncope often presents atypically, and they may have difficulty recalling events. Therefore, the true incidence of syncope is likely higher than estimated in some previous studies [8].

Despite extensive literature on syncope as a “geriatric syndrome”, there is limited knowledge regarding the role of multidimensional frailty in the incidence of this disorder. This study aims to address this gap by analyzing the relationship between syncope and multidimensional frailty.

Methods

Study population

A multicenter retrospective observational study was conducted on 575 older adults (≥ 65 years) who attended the general geriatric outpatient clinics of the Teaching Hospitals “Federico II” (Naples, Italy), “San Giovanni di Dio e Ruggi D’Aragona” (Salerno, Italy), and “Antonio Cardarelli” (Naples, Italy) between 2018 and 2022. All patients underwent a Comprehensive Geriatric Assessment (CGA) as part of the clinical evaluation for common geriatric conditions, including disability status, cognitive impairment, mobility disorders, falls, and syncope.

Comprehensive geriatric assessment and multidimensional frailty evaluation

The enrolled subjects underwent a CGA, performed by a geriatrician, that investigated the following aspects: cognitive function with the Mini Mental State Examination (MMSE) [9]; depressive symptoms with the Geriatric

Depression Scale (GDS) [10]; comorbidity severity with the Cumulative Illness Rating Scale (CIRS) [11]; total number of drugs taken; disability with Basic and Instrumental Activities of Daily Living (BADL and IADL) [12, 13], nutritional status with the Mini Nutritional Assessment (MNA) [14]; gait, balance and risk of falls with the Tinetti Scale [15] and the Short Physical Performance Battery (SPPB) [16], and social support with the Social Support Score (SSS) [17]. In addition, all the enrolled subjects were evaluated for orthostatic hypotension (OH). Blood pressure and heart rate were measured using an automatic oscillometric device (OMRON 6) after a 10-min rest in the supine position, followed by measurements in the standing position at 0, 1, and 3 min. A decrease in systolic blood pressure of 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing was considered diagnostic for OH, regardless of the presence or absence of related symptoms [18].

The frailty status of patients was assessed using the fr-AGILE scale. fr-AGILE is a quick frailty screening tool developed from the “Italian Frailty Index” [19] by selecting the 10 most predictive items for mortality out of its 40 items, aiming to uniformly represent the four domains of “multidimensional” frailty: physical, mental, nutritional, and socio-economic. The fr-AGILE scores were then divided into tertiles: light frailty (1–3), moderate frailty (4–7), and severe frailty (8–10). A full description of the fr-AGILE can be found in the original study [20].

Syncope evaluation

Patients who reported one or more suspected syncopal TLOC episodes in the previous year were referred to the “Syncope and Fall Unit” for further evaluation. The assessment in the Syncope Unit was conducted by geriatricians with documented expertise in managing syncope and involved collaboration with cardiologists and neurologists as dictated by the clinical case. Patients with a history of fall suspected to be syncope-related (i.e., falls preceded by syncopal prodromes or occurring in conjunction with predisposing factors for syncopal events such as postural changes) were admitted and categorized as suspected TLOC cases. Additionally, unexplained falls—not related to accidental factors or secondary to other clinical disorders—were also categorized as suspected TLOC cases. However, patients presenting exclusively with pre-syncopal symptoms or dizziness, as well as those with recurrent falls clearly not of syncopal nature, were not subjected to the syncope work-up. Patients were evaluated according to the European Society of Cardiology (ESC) guidelines [4]. Specifically, a detailed event history was obtained for each participant with the information provided by witnesses, and a physical examination was conducted. Furthermore, patients underwent an assessment of OH and an electrocardiogram (ECG).

Syncope was considered to be caused by OH if symptoms of spontaneous episodes were reproduced, or when asymptomatic OH occurred in patients with clinical features suggestive in their history (e.g., postural changes, prolonged standing), and no other evident cause of syncope was present. Carotid sinus massage (CSM) was also performed with the participant in supine position under ECG and beat-to-beat blood pressure monitoring. Contraindications to CSM included stroke within the previous 6 months and carotid stenosis greater than 75%. If the initial evaluation did not permit the definition of an etiological cause, patients were referred to a second-level evaluation. In case of suspected cardiac syncope, participants underwent a cardiology evaluation that included echocardiography, 24-h ECG and blood pressure monitoring. The second-level neuro-autonomic evaluation involved CSM with the subject in upright position and head-up tilt testing (HUTT). The latter was performed according to the Italian protocol during continuous ECG and beat-to-beat blood pressure monitoring.

Statistical analysis

Statistical analysis was performed using SPSS version 29. Continuous and categorical variables were presented as mean $\pm$ standard deviation (SD) or as percentages, respectively. The ANOVA test with Bonferroni's post hoc correction and t-test were used to compare continuous variables across groups, while Chi-square test was used to compare categorical variables. Logistic regression analyses were performed to assess the association between multidimensional frailty and overall syncope and its subtypes (model a), as well as the association between each of the four frailty domains and overall syncope (model b) [21]. Both models were adjusted for age, sex, comorbidities—assessed using the CIRS—and number of medications. Covariates were selected based on evidence from the existing literature [22]. Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

Results

Characteristics of the study sample

Among 575 outpatients aged 65 years and older who underwent a CGA, 8 (1.3%) had a fr-AGILE score of 0 and were excluded from the sample. Additionally, 7 patients referred to the “Syncope and Fall Unit” for suspected syncope did not complete the diagnostic workup and were also excluded. The final study population comprised 560 patients, of whom 107 received a confirmed diagnosis of syncope, while 453 did not, including 9 with alternative diagnoses such as epilepsy, metabolic disorders, or non-syncope falls (Fig. 1).

The average age of the study cohort was 77.7 ± 6.9 years, with females comprising 54.5% of the participants. Those with a history of syncope exhibited significantly higher

fr-AGILE scores (6.5 ± 2.0 vs. 5.4 ± 1.9 , $p = 0.001$), indicating increased frailty. Additionally, this group demonstrated poorer outcomes across all key CGA indices, including the number of medications used (6.9 ± 3.6 vs. 6.0 ± 3.2 , $p = 0.001$). As expected, clinical conditions such as OH, aortic stenosis, coronary artery disease, and heart failure were more prevalent among patients with a history of syncope. The usage of pharmacological treatments like alpha-blockers, beta-blockers, nitrates, and diuretics was also higher in the syncope group, reflecting the complexities of their clinical management. For more details on the clinical characteristics and CGA scores, please refer to Additional File 1.

Table 1 describes the clinical and multidimensional characteristics of the study sample, stratified by degrees of frailty and history of syncope. The analysis revealed that functional differences in the multidimensional assessment between patients with and without syncope were statistically significant only among those with severe frailty. Conversely, no significant differences were observed among patients with mild or moderate frailty. Specifically, except for the MMSE, the following metrics showed significant deterioration in severely frail patients with syncope compared to those without: disability, assessed by BADL and IADL; depression status, evaluated by the GDS; malnutrition, assessed by the MNA; physical performance, measured by the SPPB; risk of falls, evaluated by the Tinetti score; and socio-economic support, assessed by the SSS. Similarly, higher prevalences of comorbidities and medications commonly associated with syncope were observed only in patients with moderate to severe frailty. Only OH showed significant associations with syncope across all levels of frailty.

Analysis of syncope events

The origin of loss of consciousness remained unexplained in 23 out of 107 participants (21.5%). A pathogenic diagnosis was identified in 78.5% of cases, with reflex syncope being the most prevalent cause (37.4%), followed by OH (24.3%) and cardiac causes (16.8%).

As the degree of frailty increased, we observed a higher percentage of patients who had experienced one or more syncopal episodes in the past year. Specifically, 10.9% of individuals with light frailty ($n = 10$), 13.6% with moderate frailty ($n = 34$), and 28.9% with severe frailty ($n = 63$) experienced syncopal events (Fig. 2A). Regarding the etiology of syncope, among patients with light frailty, 30% of episodes were cardiac in origin, 40% reflex, 20% due to OH, and 10% of unknown origin. In the moderate frailty group, the distribution was 20.6% cardiogenic, 41.2% reflex, 20.6% due to OH, and 17.6% unknown. For those with severe frailty, 12.7% of episodes were cardiac, 34.9% reflex, 27% attributable to OH, and 25.4% remained of unknown origin.

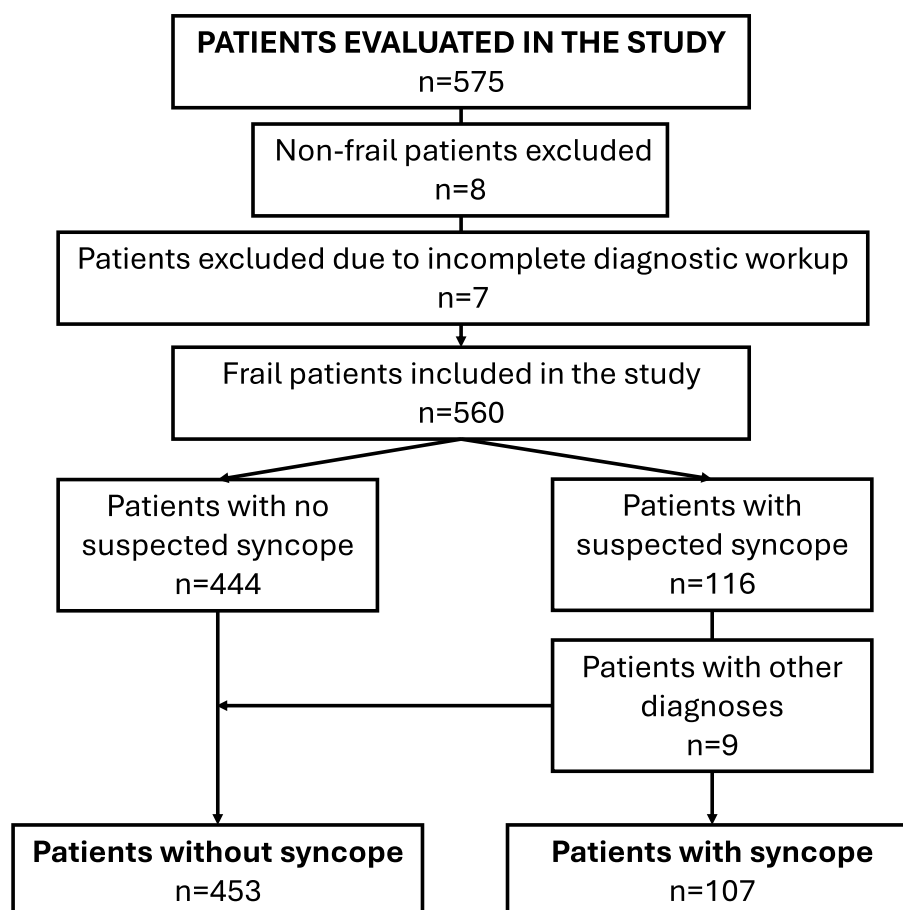


Fig. 1 Flowchart of patient selection process

Further analysis revealed that the average number of syncopal episodes also increased with the degree of frailty. Patients with light frailty reported an average of 1.1 ± 0.3 episodes, which increased to 1.9 ± 0.8 episodes among those with severe frailty (Fig. 2B).

Turning our focus to the prevalence of diagnoses of syncope types in the sample, as illustrated in Fig. 3, it is notable that while the prevalence of cardiogenic syncope remained relatively stable across all degrees of frailty—3.3% ($n=3$) in light, 2.8% ($n=7$) in moderate, and 3.7% ($n=8$) in severe frailty—the prevalence of other types increased with the degree of frailty. The prevalence of reflex syncope increased from 4.3% ($n=4$) in patients with light frailty to 5.6% ($n=14$) in those with moderate frailty, and further to 10.1% ($n=22$) in severe frailty. Similarly, the prevalence of syncope due to OH rose from 2.2% ($n=2$) in light frailty to 2.8% ($n=7$) in moderate and to 7.8% ($n=17$) in severe. The prevalence of syncope of unknown origin escalated from 1.1% ($n=1$) in light frailty to 2.4% ($n=6$) in moderate frailty, and to 7.3% ($n=16$) in severe frailty.

Relationship between syncope and frailty

Multivariate logistic regression analysis, adjusted for age, sex, comorbidities, and the number of medications taken, showed that frailty as estimated by fr-AGILE is strongly associated with the incidence of syncope (OR for each unit increase in fr-AGILE: 1.468, 95% CI: 1.276–1.690, $p=0.001$). In particular, frailty significantly impacted OH syncope (OR: 1.283, 95% CI: 1.001–1.644, $p=0.049$), reflex syncope (OR: 1.463, 95% CI: 1.190–1.797, $p=0.001$), and undetermined cause syncope (OR: 1.844, 95% CI: 1.331–2.558, $p=0.001$). Conversely, frailty was not associated with cardiogenic syncope (Table 2). It is noteworthy that all domains of multidimensional frailty—physical, mental, nutritional, and social—have been shown to be associated with the incidence of syncopal events (Table 2).

Discussion

Multidimensional frailty is strongly associated with syncope in older adults. Our findings reveal that differences between patients who experienced one or more episodes of syncope and those who never had a syncopal episode are primarily notable among subjects with a high degree

Table 1 Characteristics of the study sample stratified by multidimensional frailty degree and syncope history

VARIABLE (%)	Light Frailty (n. 92, 16.4%)			Moderate Frailty (n. 250, 44.6%)			Severe Frailty (n. 218, 38.9%)		
	NO Syncope (n. 82)	Syncope (n. 10)	p	NO Syncope (n. 216)	Syncope (n. 34)	p	NO Syncope (n.155)	Syncope (n.63)	p
Age (years $\pm$ SD)	75.1 $\pm$ 6.1	75.4 $\pm$ 3.1	0.873	77.2 $\pm$ 6.7	75.7 $\pm$ 6.0	0.189	79.3 $\pm$ 7.1	80.2 $\pm$ 7.1	0.383
Sex (% female)	31.7	40.0	0.597	53.2	61.8	0.354	62.6	66.7	0.569
BMI (μ $\pm$ SD)	26.8 $\pm$ 5.6	31.0 $\pm$ 8.2	0.035	28.1 $\pm$ 5.9	28.2 $\pm$ 3.9	0.953	27.0 $\pm$ 5.8	28.5 $\pm$ 4.3	0.080
SBP (mmHg) (μ $\pm$ SD)	135.8 $\pm$ 21.5	129.9 $\pm$ 14.5	0.401	140.3 $\pm$ 21.7	134.6 $\pm$ 17.9	0.144	139.2 $\pm$ 22.1	143.1 $\pm$ 22.1	0.236
DBP (mmHg) (μ $\pm$ SD)	77.3 $\pm$ 9.3	77.2 $\pm$ 10.0	0.970	78.7 $\pm$ 11.2	78.4 $\pm$ 11.7	0.876	79.4 $\pm$ 10.5	80.6 $\pm$ 11.8	0.443
HR (bpm) (μ $\pm$ SD)	70.5 $\pm$ 10.8	62.6 $\pm$ 9.4	0.031	72.0 $\pm$ 12.1	73.2 $\pm$ 10.1	0.557	71.9 $\pm$ 10.8	73.5 $\pm$ 10.6	0.426
OH (%)	14.6	40.0	0.046	17.6	41.2	0.002	22.6	41.3	0.005
CIRS (μ $\pm$ SD)	1.7 $\pm$ 0.4	1.6 $\pm$ 0.4	0.742	1.9 $\pm$ 0.5	2.0 $\pm$ 0.4	0.286	2.0 $\pm$ 0.6	2.0 $\pm$ 0.5	0.398
Drugs n. (μ $\pm$ SD)	4.7 $\pm$ 3.3	4.4 $\pm$ 4.2	0.821	6.2 $\pm$ 3.3	6.9 $\pm$ 3.6	0.255	6.6 $\pm$ 2.9	7.4 $\pm$ 3.3	0.098
BADL lost (μ $\pm$ SD)	0.6 $\pm$ 1.0	0.6 $\pm$ 0.7	0.881	1.8 $\pm$ 1.7	2.0 $\pm$ 1.6	0.596	3.2 $\pm$ 1.6	4.3 $\pm$ 1.0	0.001
IADL lost (μ $\pm$ SD)	1.6 $\pm$ 2.1	1.4 $\pm$ 1.8	0.728	3.9 $\pm$ 2.6	4.7 $\pm$ 2.2	0.008	6.1 $\pm$ 2.1	7.0 $\pm$ 1.6	0.002
MMSE (μ $\pm$ SD)	26.2 $\pm$ 3.4	27.2 $\pm$ 0.8	0.361	22.0 $\pm$ 5.7	23.7 $\pm$ 4.2	0.182	17.3 $\pm$ 5.7	15.8 $\pm$ 7.3	0.116
GDS (μ $\pm$ SD)	3.9 $\pm$ 3.1	4.5 $\pm$ 3.9	0.632	8.0 $\pm$ 3.7	7.8 $\pm$ 2.7	0.519	9.8 $\pm$ 3.6	11.4 $\pm$ 3.0	0.002
MNA (μ $\pm$ SD)	25.9 $\pm$ 2.7	27.3 $\pm$ 2.0	0.133	21.9 $\pm$ 3.8	22.4 $\pm$ 2.9	0.423	19.1 $\pm$ 3.5	17.3 $\pm$ 3.5	0.001
Tinetti scale (μ $\pm$ SD)	25.1 $\pm$ 4.0	25.7 $\pm$ 2.7	0.599	18.0 $\pm$ 7.5	17.7 $\pm$ 7.6	0.765	13.2 $\pm$ 6.7	9.3 $\pm$ 5.3	0.001
SPPB (μ $\pm$ SD)	9.9 $\pm$ 1.9	10.7 $\pm$ 0.9	0.193	7.4 $\pm$ 2.9	7.4 $\pm$ 3.0	0.946	5.6 $\pm$ 2.8	3.4 $\pm$ 2.5	0.001
SSS (μ $\pm$ SD)	6.2 $\pm$ 3.4	7.0 $\pm$ 3.2	0.532	8.6 $\pm$ 2.7	8.7 $\pm$ 2.6	0.820	9.3 $\pm$ 2.3	10.1 $\pm$ 2.4	0.020
fr-AGILE (μ $\pm$ SD)	2.4 $\pm$ 0.8	2.3 $\pm$ 0.9	0.799	5.1 $\pm$ 0.8	5.2 $\pm$ 0.7	0.694	7.5 $\pm$ 0.7	8.0 $\pm$ 0.9	0.001
Hypertension (%)	64.6	70.0	0.737	78.7	79.4	0.925	85.2	77.8	0.188
Heart Failure (%)	24.4	40.0	0.289	34.3	47.1	0.148	33.5	41.3	0.287
CAD (%)	20.7	50.0	0.041	29.2	35.3	0.469	16.8	30.2	0.027
Aortic Stenosis (%)	1.2	10.0	0.072	2.8	5.9	0.339	3.2	7.9	0.132
Diabetes (%)	18.3	10.0	0.514	25.5	32.4	0.397	27.7	36.5	0.202
Parkinson's Disease	1.2	10.0	0.072	2.3	8.8	0.045	1.9	12.7	0.001
RAASi (%)	48.8	30.0	0.261	58.3	67.6	0.304	54.2	58.7	0.541
β -blockers (%)	19.5	20.0	0.971	31.0	44.1	0.130	27.1	36.5	0.169
α -blockers (%)	20.7	20.0	0.957	15.7	35.3	0.006	11.6	28.6	0.002
CCB (%)	26.8	30.0	0.831	31.9	35.3	0.698	36.1	38.1	0.785
Nitrates (%)	6.1	20.0	0.117	2.8	17.6	0.001	3.2	15.9	0.001
Diuretics (%)	15.9	40.0	0.063	26.4	52.9	0.002	44.5	57.1	0.091
AChEIs (%)	6.1	0.0	0.422	10.2	8.8	0.806	25.8	25.4	0.950
Memantine (%)	0.0	0.0	–	5.6	0.00	0.159	10.3	15.9	0.252
Antidepressant (%)	6.1	0.0	0.422	21.8	23.5	0.817	20.6	25.4	0.443
Antipsychotics (%)	4.9	10.0	0.500	14.8	5.9	0.158	28.4	31.7	0.622

Bold emphasis inside table indicate the statistical significance

Legend: SD standard deviation, μ mean, BMI Body Mass Index, SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure, HR Heart Rate, OH Orthostatic Hypotension, CIRS Cumulative Illness Rating Scale, BADL Basic Activity of Daily Living, IADL Instrumental Activity Daily Living, MMSE Mini Mental State Examination, GDS Geriatric Depression Scale, MNA Mini Nutritional Assessment, SPPB Short Physical Performance Battery, SSS Social Support Scale, CAD Coronary Artery Disease, RAASi Renin–Angiotensin–Aldosterone System inhibitors, CCB Calcium Channel Blockers, AChEIs Acetylcholinesterase Inhibitors

of multidimensional frailty. Specifically, in patients with a history of syncope, dependence in ADLs, cognitive decline, polypharmacy, and low physical performance status are more pronounced.

Syncope is highly prevalent in older adults [7]. Age-related changes in blood pressure control increase the susceptibility to syncope in older adults. Baroreflex sensitivity is blunted by aging, resulting in a reduced heart rate and vasoconstriction response to hypotensive stimuli [23]. Furthermore, older patients are prone to dehydration and reduced blood volume due to a decreased thirst

sensation, a reduction in renin–aldosterone activity, and a decreased capacity of the kidney to preserve salt and water [24]. Co-morbidities and concomitant medication can further impair the adaptive response to hypotensive stress. Prolonged bed rest is common in older and frail patients, often leading to syncope when they sit up [25]. The burden of age-related neuro-autonomic changes, comorbidities, and polypharmacy can be identified through multidimensional frailty evaluation, which should be considered a valuable tool in managing older adult patients with syncope.

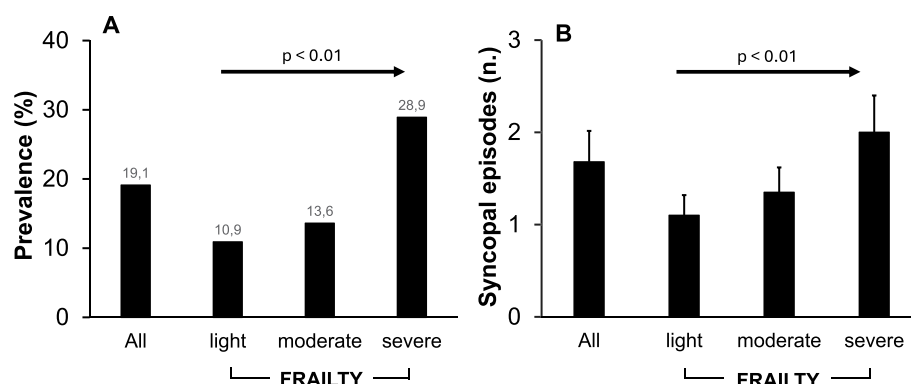


Fig. 2 **A** Percentage of the study population experiencing at least one syncopal episode over a 1-year period, stratified by degree of frailty. **B** Mean number of syncopal episodes over a one-year period, stratified by degree of frailty, in people who experienced syncope. * p for trend < 0.05

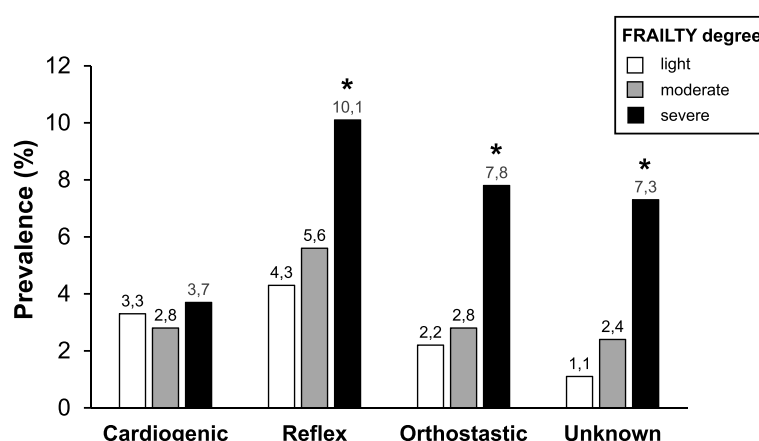


Fig. 3 Prevalence of syncope types in the study population stratified by frailty degree

Table 2 Logistic regression analysis assessing the association of frailty and frailty domains with syncope and its subtypes

FRAILITY	SYNCOPE	OR	95% CI	p
fr-AGILE^a	Overall	1.468	1.276–1.690	0.001
	Cardiogenic	1.034	0.786–1.358	0.813
	Reflex	1.463	1.190–1.797	0.001
	Orthostatic	1.283	1.001–1.644	0.049
	Unknown	1.844	1.331–2.558	0.001
Frailty domains^b	Overall	OR	95% CI	p
	Physical	1.802	1.322–2.456	0.001
	Mental	1.576	1.181–2.102	0.002
	Nutritional	2.178	1.566–3.028	0.001
	Social	1.569	1.012–2.431	0.044

Bold emphasis inside table indicate the statistical significance

OR Odds Ratio, CI Confidence Interval

Legend: ^amultivariate analysis, adjusted for age, sex, comorbidities, and number of medications, showing the association between fr-AGILE score and the incidence of overall and distinct types of syncope

^bmultivariate analysis, adjusted for age, sex, comorbidities, and number of medications, assessing the association between each domain of multidimensional frailty and syncope

Despite the extensive literature on syncope in older adults, there are limited data regarding the role of frailty in syncope. In a small case–control study, Bandhu et al. analyzed the association of recurrent cardiovascular syncope with various geriatric syndromes, demonstrating that syncope was significantly associated with cognitive impairment, hearing impairment, frailty, and the presence of four or more comorbidities. However, in multivariate analysis, significant associations of syncope were only observed with cognitive impairment, hearing impairment, and the presence of four or more comorbidities. This study primarily included patients with recurrent syncope of cardiac origin, which represents only a fraction of older patients with syncope [26].

Although the prevalence of cardiac disease rises dramatically with age, the relative prevalence of cardiac syncope does not show increase with age, remaining around 15%, probably due to the survival bias associated with the high mortality of cardiac syncope [27]. Of particular interest is the observation that in previous studies evaluating the characteristics of syncope type in relation to age, there is a relative reduction in cases of reflex syncope and an increase in those due to OH in older patients [28].

In the GIS study, when comparing patients younger than 75 years to those older than 75, reflex syncope (including vasovagal syncope, situational syncope, and carotid sinus syndrome) was more common in younger patients (60% vs. 35%), whereas OH syncope was more frequent in older ones (35% vs. 10%) [29]. In older patients with dementia from the SYD study, OH was the main form of syncope, accounting for about 50% of cases [30].

Our study results are consistent with these findings. Specifically, as the degree of frailty increases, the relative percentage of reflex syncope events decreases (light and moderate frail: ~40% vs. severe frail: ~35%), while the relative percentage of OH syncope increases (light and moderate frail: ~20% vs. severe frail: ~27%). Taken together, these data suggest that frailty, a condition closely associated with aging, may be a major determinant in the changing etiology of syncope with advancing age. Our research group has also previously established that frailty is a significant marker of OH, which is the primary pathophysiological mechanism underlying syncope in older patients [31].

However, in our study, multidimensional frailty is associated with an increased incidence of all forms of syncope except cardiac syncope. This result underscores the close link between frailty and non-cardiac syncope, potentially highlighting the importance of frailty as a marker of the “vasodepressive phenotype” of syncope [32]. Analysis of tilt-table tests across different age groups shows that the prevalence of vasodepressive responses increases with age, while cardioinhibitory responses decrease, suggesting an age-related decline in the cardioinhibitory component of reflex syncope [33]. This shift likely results from diminished cardiovascular autonomic control, including reduced baroreceptor sensitivity, decreased cardiac response to beta-adrenergic stimulation, and lower vagal drive to the heart [34]. Thus, older adults seem to be more prone to develop neuro-cardiovascular instability and vasodepressive reflex syncope. Additionally, hypotensive medications and comorbidities may further contribute to vasodepressive status in older patients [35].

A significant finding in our results is the close association between the percentage of syncope of “unknown origin” and the degree of multidimensional frailty. This finding is crucial as it underscores the diagnostic challenges in evaluating syncope in older population. Previous studies have demonstrated that adopting a structured and validated diagnostic protocol reduces the percentage of unexplained syncope in older adults even in a challenging population such as older patients with dementia [30]. Our study highlights that the critical factor is the degree of frailty, rather than age or cognitive decline, leading to an inconclusive diagnostic pathway in one out of four syncope cases (10% in light frailty vs. 24.5% in severe frailty). Many factors may be involved in this matter, such

as the difficulty in performing neuro-autonomic assessment tests or in reporting anamnestic elements that can be crucial in the correct framing of the episode [36].

Moreover, our analysis indicates that all domains of multidimensional frailty significantly impact the likelihood of syncopal events. Social isolation can result in a lack of support systems, thereby reducing the likelihood of individuals receiving assistance during pre-syncopal or syncopal events, which may increase the severity of the outcomes [37]. Limited access to healthcare, social services, and community support further exacerbates the underlying factors contributing to frailty and syncope [38]. Furthermore, nutritional risk, associated with dehydration, labile blood pressure values, and OH, constitutes an additional significant risk factor for syncopal events [39].

To our knowledge, this is the first study specifically focused on the relationship between syncope and multidimensional frailty in older adults. One of the major strengths of our research lies in the rigorous and methodologically robust assessment of frailty and syncope. Frailty was evaluated by ensuring a comprehensive and multidimensional approach. Syncope assessment adhered strictly to the European Society of Cardiology guidelines, with detailed diagnostic workups conducted in specialized Syncope and Falls Units. This methodological rigor significantly enhances the reliability of our findings.

However, it is important to acknowledge certain limitations. The retrospective design of our study may introduce potential biases. Notably, as many patients were referred to outpatient centers equipped with dedicated Syncope and Falls Units, the observed incidence of syncope could be elevated compared to the general population of older adults. Additionally, the recruitment of participants exclusively from a single Italian region may limit the generalizability of our results. Future studies should consider incorporating a prospective design and expanding the sample to include more diverse demographic groups. Moreover, exploring interventions aimed at reducing frailty could provide valuable insights into mitigating syncope risks in this population. Such approaches would not only validate our findings but also deepen our understanding of the interactions between frailty and syncope, potentially guiding more effective clinical strategies.

Conclusions

Our findings suggest that multidimensional frailty is strongly associated with the incidence of syncope among older adults. It affects the likelihood of syncopal events across various domains, underscoring the need for CGA and multidimensional frailty evaluation in managing and preventing syncope in this vulnerable population. Notably, frailty appears to be particularly associated with the

prevalence of unexplained syncope, representing a significant limitation in the diagnostic approach to syncope in older adults.

Abbreviations

TLOC	Transient Loss Of Consciousness
CGA	Comprehensive Geriatric Assessment
MMSE	Mini Mental State Examination
GDS	Geriatric Depression Scale
CIRS	Cumulative Illness Rating Scale
BADL	Basic Activities of Daily Living
IADL	Instrumental Activities of Daily Living
MNA	Mini Nutritional Assessment
SPPB	Short Physical Performance Battery
SSS	Social Support Score
OH	Orthostatic Hypotension
ESC	European Society of Cardiology
ECG	Electrocardiogram
CSM	Carotid Sinus Massage
HUTT	Head-Up Tilt Test

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12877-025-06280-2>.

Supplementary Material 1.

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Authors' contributions

All authors have read and approved of the submission of this manuscript. All authors contributed to the acquisition, analysis, and interpretation of data. All authors contributed to critical revisions of the manuscript for important intellectual content. PA was involved in study concept and design and preparation of manuscript. FCu was principal investigator and supervisor and involved in study concept and design and preparation of manuscript. FCa was responsible for statistical analysis provided study supervision. The corresponding author declares that he had listed everyone who contributed significantly was reported to the work.

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Data availability

The data supporting this article can be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional ethics committee (University of Naples Federico II—Comitato Etico per le attività Biomediche “Carlo Romano” prot. n.211/2013) and conducted according to the ethical principles of the Declaration of Helsinki for medical research involving human subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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