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Original Article

Differential diagnosis of unexplained falls in dementia: Results of "Syncope & Dementia" registry

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ABSTRACT

Background: Dementia patients have an increased risk of fall, and some of them might suffer from undiagnosed syncope. The present analysis aimed at identifying predictors of differential diagnosis between syncopal and non-syncopal fall in patients with dementia included in the "Syncope & Dementia" registry.

Methods: We enrolled patients aged 65 + with a diagnosis of dementia and a history of syncope and/or unexplained fall. All subjects underwent a comprehensive geriatric assessment, including the syncope protocol of the European Society of Cardiology. Subjects whose syncope diagnosis was confirmed were labeled as "Confirmed Syncope" (CS). Patients with unexplained fall were labeled as "Syncopal Fall" (SF), if a final diagnosis of syncope was performed, or as "Non-Syncopal Fall" (NSF), if syncope was excluded.

Results: We included 372 subjects (mean age 84, 61% females). Mini Mental State Examination score was higher among SF (18.5 ± 4.9) compared to NSF patients (15.6 ± 5.8, $p = 0.02$). In a multinomial logistic regression model with NSF as the reference group, CS patients less often suffered injuries and more often reported history of syncope, while patients with SF had a better cognitive status and were more often exposed to precipitating factors, including postural changes and neck movements. The absence of prodromes and the intake of benzodiazepines and insulin was highest in NSF patients. A simple score including main clinical predictors showed an 82% sensitivity with a 56% specificity in discriminating SF from NSF patients.

Conclusion: Simple clinical markers can aid in the differential diagnosis of unexplained falls in dementia, separating syncopal from non-syncopal falls.

1. Introduction

Falling is a well-recognized multi-factorial geriatric syndrome [1]. Older subjects with dementia have an increased risk of fall [2] and fall-related hospitalizations [3]. Moreover, the occurrence of a fall is associated with an increased mortality and risk of nursing home admission in patients with dementia [4]. In clinical practice some falls are clearly due to a medical or an accidental condition, while for others, that are defined "unexplained", no cause can be readily identified [5].

Patients with dementia often experience syncope, which is one of the most frequent causes of Emergency Department admission in Alzheimer's disease [3]. Moreover, it has been recently reported that the occurrence of a syncope is independently associated with a worse cognitive performance in the general population [6]. Finally, it is

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increasingly recognized that several unexplained falls among older adults are actually due to a non-clinically apparent syncope [7], which has been recently defined as "syncopal fall" [8]. The identification of syncopal falls among unexplained ones might be difficult or even impossible, as the event is often unwitnessed and characterized by very short prodromes and/or retrograde amnesia [8]. This is even more striking among persons with dementia, who are traditionally considered as a separate group of fallers [5], typically with multiple risk factors, thus suggesting that the identification of specific causes is not feasible in this group of patients. Although we acknowledge the multifactorial origin of falls in older subjects with dementia [1], we feel that the concept of syncopal fall might be useful to identify subjects with dementia suffering from an unexplained fall that might be at least partially explained by a syncopal/hypotensive episode. In fact, the lack of recognition as syncope as a potential cause of falling might represent a preventable risk for these patients, who are often treated with drugs that are recognized risk factors for syncope [9].

The "Syncope & Dementia" (SYD) registry has evaluated subjects with dementia suffering transient loss of consciousness, including syncope or unexplained fall, revealing that unexplained fall may mask a diagnosis of syncope in almost the 50% of the cases [10]. Therefore, given the lack of published data on this issue, the aim of the present research is to identify predictors of syncopal versus non-syncopal fall in the SYD registry population, focusing on the characteristics of patients with unexplained falls.

2. Methods

The SYD registry include patients recruited from acute care settings or outpatient clinics of 11 geriatric wards. Methods and baseline data have been published elsewhere [10]. Briefly, the SYD registry has enrolled patients aged 65 + years, with a diagnosis of dementia (following the criteria of the Diagnostic and Statistical Manual of Mental Disorders - 4th edition, text revision - DSM-IV-TR) [11] and one or more suspected transient loss of consciousness and/or unexplained falls, during the previous 3 months. The only exclusion criterion was unwillingness/inability to provide informed consent by either the patient or his/her legal representative.

The anamnestic assessment of index event was conducted with the support of proxy information and included: history of previous syncope, precipitating factors (postural changes, neck movements, pain, fear), predisposing conditions (event occurred in crowded or warm environments, prolonged standing, fever, dehydration, prolonged confinement to bed), situational causes of syncope (post-voiding, post-defecation, post-prandial, post-effort), neurovegetative prodromes (pallor, sweating, nausea, epigastric discomfort), and consequent injury. The assessment also included: a complete physical examination, including the presence of any gait and balance disorder; the assessment of functional disability one month before the event, measured with Activities of Daily Living (ADL, range 0–6 with 6 indicating complete disability: bathing/showering, dressing/undressing, using WC, in-home mobility, bowel and bladder control, feeding) [12] and Instrumental Activities of Daily Living (IADL, range 0–8, with 8 indicating complete disability: using telephone, shopping, cooking, house-keeping, washing clothes, transportation, management of money and medications) [13]; cognitive assessment with Mini Mental State Examination (MMSE) [14]. Patients with a MMSE score > 16 have been evaluated for the presence of depressive symptoms through the 15-items Geriatric Depression Scale (GDS) [15]. Comorbidity has been assessed with the Cumulative Illness Rating Scale (CIRS-comorbidity), objective quantitative measure of physical illness burden in which a cumulative score is obtained from ratings of impairment severity of single organ systems [16]. Pharmacological treatment before the index event was also recorded.

All participants underwent the initial evaluation protocol proposed by the European Society of Cardiology (ESC) guidelines on syncope [17], including blood pressure measurement in the supine and standing position, 12-leads electrocardiogram (ECG) and carotid sinus massage, when not contraindicated, in the supine position under ECG monitoring [17]. A second level neuro-autonomic (Tilt Test and upright CSM), neurologic or cardiologic evaluation, when needed according to the ESC guidelines [17], was undertaken in those patients in whom a reliable diagnosis could not be achieved after the initial evaluation.

After the application of the protocol, each subject was assigned to three mutually exclusive group according to index event (syncope or fall) and final diagnosis:

- "Confirmed Syncope" (CS) if the initial suspicion of syncope was confirmed (index event syncope, final diagnosis syncope);
- "Syncopal Fall" (SF) if the index event was a fall but a final diagnosis of syncope was performed (index event fall, final diagnosis syncope);
- "Non-Syncopal Fall" (NSF) if a diagnosis of syncope was excluded at the end of the diagnostic work-up (index event fall, final diagnosis fall).

Among subjects in whom diagnosis of syncope was performed, this was defined according to the current pathophysiological classification [17] as "cardiac syncope", if an arrhythmic of structural heart disease could be identified as the cause of the index event; "syncope due to orthostatic hypotension", if a blood pressure drop upon standing was deemed to be the main cause of the event; and "neurally mediated syncope" if a reflex mechanism (a vasovagal reflex, a situational cause, or a carotid sinus syndrome) was identified as a significant contributor to the index event.

By June 2012 to November 2015, 431 patients have been enrolled: 225 with syncope, 196 with unexplained falls and 10 with both syncope and unexplained falls as index event. The latter group was excluded from the present analysis, which was specifically focused on unexplained falls. Among the remaining 421, 49 subjects with a diagnosis different from syncope or fall at the end of diagnostic work-up were excluded (including stroke, epilepsy, metabolic disorder, drop attack, psychogenic attack and unexplained transient loss of consciousness). The remaining 372 subjects were included in the present analysis (see Fig. 1).

2.1. Ethics

The study was approved by the Research Ethics Committee at the University of Naples School of Medicine, and subsequently by the institutional review boards of all participating centers. A written consent was obtained from all participants.

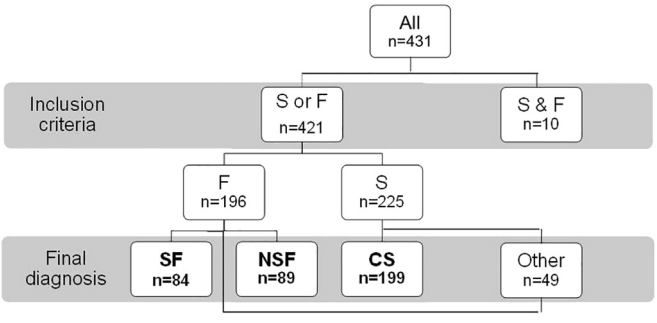


Fig. 1. Flow chart of selection of patients groups according to index event (syncope or unexplained fall) and final diagnosis.
Legend: F = unexplained fall, S = suspected syncope, S & F = coexistence of syncope and fall; SF = Syncopal Fall; NSF = Non-Syncopal Fall; CS = Confirmed Syncope; Other = stroke, epilepsy, metabolic disorder, drop attack, psychogenic attack and unexplained transient loss of consciousness.

Table 1
Characteristics of the population and main features of the index event by final diagnosis.

	CS (n = 199)	SF (n = 84)	NSF (n = 89)	p
Age (mean ± SD)	83.5 ± 6.5	83.3 ± 6.6	84.2 ± 5.9	0.620
Female (n, %)	120 (60.3)	54 (64.3)	52 (58.4)	0.415
CIRS comorbidity (mean ± SD)	3.2 ± 1.8	3.3 ± 2.0	3.3 ± 1.6	0.877
Cause of dementia				0.513
Alzheimer's disease (n, %)	93 (46.7)	37 (44.0)	41 (46.1)	
Vascular dementia (n, %)	85 (42.7)	41 (48.8)	35 (39.3)	
Other causes (n, %)	48 (24.1)	16 (19.0)	22 (24.7)	
Outpatients (n, %)	91 (45.7)	17 (20.2)	17 (19.1)	< 0.001
MMSE (mean ± SD)	16.5 ± 5.5	18.5 ± 4.9	15.6 ± 5.8	0.002[a,b]
ADL (mean n impaired ± SD)	3.0 ± 2.1	2.6 ± 2.0	3.3 ± 1.8	0.070
IADL (mean n impaired ± SD)	6.3 ± 2.4	5.7 ± 2.6	6.3 ± 2.3	0.128
GDS (mean ± SD)	6.0 ± 3.6	5.2 ± 3.1	5.7 ± 3.1	0.317
Gait and balance disorders (n, %)[c]	105 (52.8)	43 (51.2)	48 (53.9)	0.936
History of syncope (n, %)	114 (57.3)	17 (20.2)	11 (12.4)	< 0.001
History of fall (n, %)	29 (14.6)	44 (52.4)	48 (53.9)	< 0.001
Predisposing factors[d] (n, %)	79 (39.7)	30 (35.7)	24 (27.0)	0.114
Precipitating factors[e] (n, %)	66 (33.2)	42 (50.0)	30 (33.7)	0.021
Neurovegetative prodroms[f] (n, %)	78 (39.2)	18 (21.4)	3 (3.4)	< 0.001
Injuries (n, %)	64 (32.2)	51 (60.7)	60 (67.4)	< 0.001

CIRS = cumulative Illness Rating Scale; MMSE = Mini Mental State Examination; ADL = Activity of Daily Living; IADL = Instrumental Activity of Daily Living; GDS = Geriatric Depression Scale.

[a] Confirmed syncope vs syncopal fall $p < 0.05$.

[b] Syncopal fall vs not syncopal fall $p < 0.05$.

[c] Gait and balance disorders: slow, broad-based, shuffling and cautious walking pattern, ataxia, focal motor or sensory deficits, rigidity and postural instability.

[d] Predisposing factors: crowded or warm places, prolonged standing, fever, dehydration, prolonged confinement to bed.

[e] Precipitating factors: postural changes, neck movements, pain, fear.

[f] Neurovegetative prodroms: pallor, sweating, nausea, epigastric discomfort.

Table 2
Pharmacotherapy of subjects by final diagnosis.

	CS (n = 199)	SF (n = 84)	NSF (n = 89)	p
Mean number of drugs (mean ± SD)	6.3 ± 2.8	6.0 ± 3.0	6.1 ± 3.1	0.761
ACE-inhibitors (n, %)	71 (35.7)	21 (25.0)	28 (31.5)	0.211
Sartans (n, %)	44 (22.1)	15 (17.9)	10 (11.2)	0.089
Diuretics (n, %)	72 (36.2)	40 (47.6)	32 (36.0)	0.163
Beta blockers (n, %)	59 (29.6)	23 (27.4)	23 (25.8)	0.787
Statins (n, %)	65 (32.7)	20 (23.8)	20 (22.5)	0.123
Ca-channel blockers (n, %)	34 (17.1)	15 (17.9)	14 (15.7)	0.930
Antiarrhythmics (n, %)	17 (8.5)	5 (6.0)	8 (9.0)	0.716
Digital (n, %)	9 (39.1)	7 (8.3)	7 (7.9)	0.359
Antiplatelets (n, %)	114 (57.3)	52 (61.9)	50 (56.2)	0.709
Anticoagulants (n, %)	21 (10.6)	15 (17.9)	14 (15.7)	0.198
Nitrates (n, %)	28 (14.1)	10 (11.9)	10 (11.2)	0.765
Alpha blockers (n, %)	17 (8.5)	18 (21.4)	10 (11.4)	0.010
Antidiabetic oral medication (n, %)	27 (13.6)	11 (13.1)	15 (16.9)	0.718
Insulin (n, %)	6 (3.0)	4 (4.8)	13 (14.6)	0.001
Antidepressives (n, %)	71 (35.7)	27 (32.1)	29 (32.6)	0.797
Antipsychotics (n, %)	55 (27.6)	12 (14.3)	18 (20.2)	0.040
Benzodiazepines (n, %)	30 (15.1)	15 (17.9)	30 (33.7)	0.001
Cholinesterase-inhibitors (n, %)	38 (19.1)	8 (9.5)	7 (7.9)	0.016
Antiparkinsonians (n, %)	17 (8.5)	5 (6.0)	10 (11.2)	0.464
Memantine (n, %)	26 (13.1)	7 (8.3)	6 (6.7)	0.206
Anticonvulsants (n, %)	12 (6.0)	7 (8.3)	6 (6.7)	0.779
Levo-thyroxine (n, %)	12 (6.0)	3 (3.6)	8 (9.0)	0.332

ACE-inhibitors = Angiotensine Converting Enzyme inhibitors.

2.2. Statistical analysis

Continuous and categorical variables are presented as mean ± standard deviations (SD) and as percentages, respectively. ANOVA test with Bonferroni's post-hoc correction was performed to compare continuous variables across groups and Pearson's chi-square test was used for categorical variables. Factors that differed significantly among the three groups in univariate analysis were entered into a multinomial regression model with backward deletion with NSF as reference group, adjusted for age, gender and care setting (outpatient vs. acute care). Variables independently associated with SF diagnosis were rescaled dividing each regression coefficient by the lowest one and rounding the score obtained. A summary score was then computed for the questionnaire by addition of the weighted subscores to obtain a Syncopal Fall Score in Dementia (SFS-D). Sensitivity, specificity and receiver operating characteristic (ROC) area under the curve (AUC) of SFS-D in discriminating SF vs. NSF were calculated, excluding subjects with CS, to identify the possible cut-off. A p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS 24.0 (IBM Corp, Armonk, NY).

Table 3
Results of the multinomial logistic regression analysis, adjusted for age, gender and clinical setting of enrollment.

	CS vs. NSF OR [95% CI]	SF vs. NSF OR [95% CI]
Outpatient setting	2.14 [0.99, 4.63]	0.62 (0.26–1.49)
History of syncope	3.66 [1.51, 8.90]	1.22 [0.42, 3.57]
History of fall	0.38 [0.18, 0.82]	1.36 [0.62, 2.98]
Neurovegetative prodromes	12.99 [2.92, 57.84]	10.53 [2.24, 49.37]
Precipitating factors	1.33 [0.67, 2.64]	2.15 [1.06, 4.34]
MMSE > 16	0.89 [0.46, 1.72]	2.23 [1.09, 4.55]
Injuries	0.27 [0.14, 0.52]	0.66 [0.32, 1.39]
BDZ	0.41 [0.18, 0.90]	0.36 [0.15, 0.85]
Insulin	0.29 [0.07, 1.15]	0.20 [0.05, 0.83]
Alpha-blockers	0.93 [0.30, 2.86]	2.63 [0.93, 7.40]

CS = Confirmed Syncope; SF = Sincopal Fall; NSF = Non-Sincopal Fall; MMSE = Mini Mental State Examination; BDZ = Benzodiazepines.
Variables excluded from the model: antipsychotics, cholinesterase inhibitors, ADL, situational cause of syncope.

Table 4
Weights of factors differentiating SF from NSF: development of Syncopal Fall Score in Dementia (SFS-D).

	b	Weight	Score
Neurovegetative prodromes	2.354	3.085190039	3
Precipitating factors	0.763	1	1
No benzodiazepines	1.021	1.338138925	1
No insulin	1.631	2.137614679	2
Alpha blockers	0.966	1.266055046	1
Mini mental state examination > 16/30	0.8	1.048492792	1
Total			0–9

b represents the regression coefficient in multinomial regression model. Weight of each variable is calculated as b/minimum b (0.763). Total score is the sum of single items, if present.

3. Results

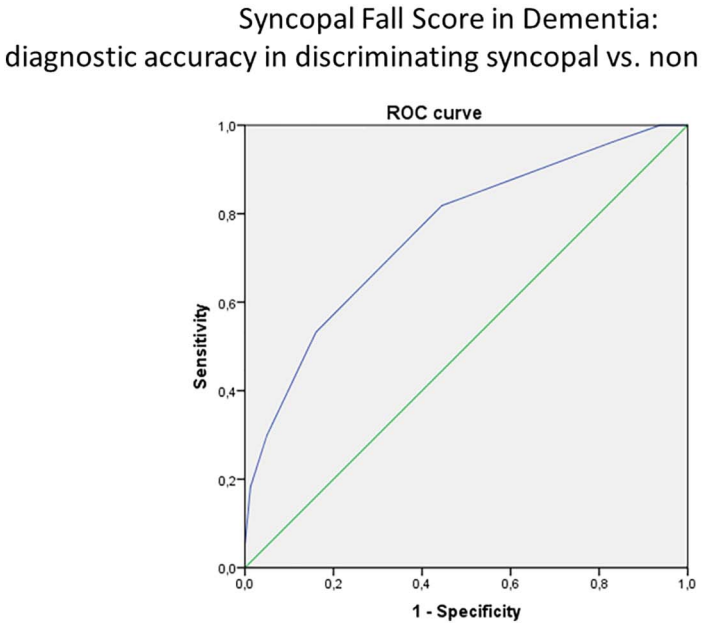
The present sample had a mean age of 84 ± 6 and included 61% females with two third of subjects from acute care and the remaining from outpatient clinics. Final diagnosis was CS in 199. Among 196 subjects enrolled for unexplained fall, 84 (43%) received a final diagnosis of SF and the remaining 89 of NSF. CS and SF were mainly due to orthostatic hypotension (50%; 47% in CS vs. 55% in SF group, $p = 0.247$), followed by neurally-mediated syncope (26%; 31% in CS vs. 17% in SF group, $p = 0.015$) and cardiac syncope (13%; 11% in CS vs. 17% in SF group, $p = 0.196$), while 11% of cases remained unexplained.

There were no significant differences in age, gender, comorbidity and functional status among CS, SF and NSF group. CS was less frequent in acute compared with outpatient care, while no difference in setting was observed between SF and NSF. MMSE score was significantly higher among patients with SF (18.5 ± 4.9) compared to CS (16.5 ± 5.5, $p = 0.016$) and NSF (15.6 ± 5.8, $p = 0.02$). Patients from the CS group reported more frequently situational causes of syncope and neuro-vegetative prodromes and had lower rate of injuries. Conversely, in patients from the SF group precipitating factors were reported more often (Table 1). With regard to drug treatment, patients from the CS group were more frequently on antipsychotics and cholinesterase inhibitors, those from the SF group on alpha blockers, and those from the NSF on insulin and benzodiazepines (Table 2).

In the multivariate model, with NSF as the reference group, CS diagnosis remained negatively associated with the occurrence of injury and history of falls, and positively associated with history of syncope. Conversely, a diagnosis of SF was independently associated with precipitating factors and a better cognitive function and showed a trend association with alpha-blockers treatment. Absence of neurovegetative prodromes and treatment with benzodiazepines and insulin were independently associated with NSF in the comparison with the other two groups (with borderline significant difference for insulin in the comparison between NSF and CS) (Table 3). After weighting each factor that was significantly different between SF and NSF subgroup, a Syncopal Fall Score in Dementia (SFS-D) was calculated, with total score being represented by the sumscore of single items (Table 4). ROC curve analysis of SFS-D showed an AUC of 0.759 in discriminating SF from NSF (Supplementary Fig. 1). Best cut-off score was 4, with values 4 + showing a sensitivity of 0.82 [95% CI 0.71, 0.89] and a specificity of 0.56 [95% CI 0.44, 0.66] in identifying cases with a final diagnosis of SF.

4. Discussion

In the present sample of older adults with dementia, we have included a substantial number of subjects with unexplained fall, who received a final diagnosis of syncope in the 43% of the cases. According



Supplementary Fig. 1. Syncopal Fall Score in Dementia: ROC curve assessing diagnostic accuracy in discriminating syncopal vs. non syncopal falls.

to Alboni et al., [8] we have defined this condition "syncopal fall" (SF). We have identified the presence of precipitant factors in the clinical history (mainly including postural changes and neck movements) and a better cognitive function as independent predictors of SF versus non-syncopal fall (NSF). Conversely subjects with NSF were more often treated with insulin and benzodiazepines and less often reported prodromes (especially neuro-vegetative symptoms) compared with SF and confirmed syncope (CS). We were able to develop a score that showed good sensitivity in identifying SF among subjects with unexplained fall.

While it has been suggested that the identification of SF might not be feasible, we suggest that patients with SF might possess specific clinical features, which may aid their targeting in comparison with NSF. Of notice, this was observed in subjects with dementia, who by definition have retrograde amnesia for the event and whose falls are often considered not amenable to specific diagnostic processes. Present data suggest that information regarding the onset of the episode, including prodromes and precipitating factors, may aid in differential diagnosis between syncope and falls. Due to the cognitive impairment observed in the present sample, this imply the crucial role of an accurate interview of witnesses, if available, including also minimal prodromal symptoms and dynamics of the falls.

Moreover, we have observed that the likelihood of SF diagnosis was significantly higher among subjects with better cognitive status. Therefore, we pose that clinicians should carry a higher suspicion for syncope in subjects with mild-to-moderate dementia and unexplained fall. The risk score we have developed seems to be able to identify about 4 out of 5 patients with SF, although, not unexpectedly, possess only limited specificity. Therefore we feel it should be further tested, as it may represent a simple instrument to screen for subjects that deserve to undergo the further assessment protocol proposed by syncope guidelines [17], including at least orthostatic hypotension test, ECG and carotid sinus massage.

Only few studies have addressed the causes of unexplained falls. This issue is not negligible, as among older subjects with carotid sinus syndrome (mean age 76 years, mean MMSE score 27) the occurrence of a fall without syncope is not rare and is typically associated with retrograde amnesia for the event, regardless the cognitive status [18]. It has been previously shown that 61% of older subjects (mean age 75 years) with unexplained fall could be diagnosed with neurally-mediated syncope [7]. In the present sample, including older subjects with major neurocognitive impairment, a similar diagnostic protocol was applicable too, with orthostatic hypotension being a more frequent diagnosis compared to previous studies.

The observed association of insulin and benzodiazepines with NSF is consistent with the well known drug-associated fall risk in older subjects [19–22] and may aid in the differential diagnosis between NSF and SF also in older subjects with dementia, in whom the presence of this objective information may compensate for the frequent vagueness of the anamnestic data. Specifically, our data are consistent with those associating insulin therapy with fall risk in the elderly [19], as hypoglycemia might go unrecognized in cognitively impaired older subjects, who are less likely to report symptoms and less able to self-check blood sugar. Therefore insulin treatment should be suspected as a cause of fall also without an objective evidence of hypoglycemia, and be managed with special caution in this frail population. Similarly, we have confirmed that benzodiazepines are a risk factor for fall [20] and therefore should be avoided as much as possible in older subjects with dementia [21].

Consistently with previous literature [23], we observed an association between cholinesterase inhibitor treatment and CS. Yet this association was excluded from the multivariate model, as it was probably explained by the higher rate of prescription observed in outpatients vs. inpatients and in subjects with previous history of syncope (data not shown).

Differently from a previous study [24], we did not observe an association between gait disorders and NSF. Inconsistent findings between the two studies can be explained by the different case-mix (only 22% of subjects in the cited study had a MMSE < 26), the different setting (the cited study was carried out in an outpatient fall clinic, while only 34% of subjects included in the present study were outpatients), and the lack of a quantitative gait assessment in the present study.

A first study limitation is represented by the case-mix including patients referred to geriatric clinics, as results might have been different in patients recruited from Emergency Department and primary care. Moreover, as we have specifically focused on subjects with dementia, we cannot exclude that some diagnosis of SF might be have been missed, especially among subjects with more severe cognitive decline, due to greater issues in clinical history collection. Yet the diagnostic protocol was based on internationally approved guidelines, which represent the most reliable tool for the diagnostic definition of syncope. Finally, regarding SFS-D, the limited sample size prevented us from testing its diagnostic accuracy in a validation sample. Therefore the assessment if its validity should be replicated before possibly adopting it in clinical practice.

5. Conclusion

A differential diagnosis between syncopal and non-syncopal falls is feasible in older subjects with dementia. This seems clinically relevant, in light of the lack of strong evidence regarding fall prevention in this high-risk population [25,26]. Hopefully, the identification of syncopal falls may aid in targeting a subgroup of fallers with dementia which might undergo specific preventive approaches. Intervention studies are needed to confirm this hypothesis.

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