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Letter to the Editor

Undiagnosed cognitive impairment in older adults hospitalized in internal medicine wards: Data from the REPOSI registry

Dear Editor,

A relevant proportion of older adults may have previously undiagnosed cognitive impairment, as reported in several studies enrolling community-dwelling subjects and patients hospitalized in acute settings and nursing homes [1,2]. Cases with undiagnosed cognitive impairment have an increased risk of physical frailty, reduced health status, depression, poor functional recovery after hospitalization and adverse outcomes [1,3,4].

The recognition of cognitive impairment at the earlier stage is an important goal of the geriatric assessment, because this may allow physicians to modify the trajectory of the disease and prevent the resulting functional decline. Moreover, an early diagnosis of cognitive decline allows families to do proper and timely choices on long-care planning, regarding financial and legal affairs and to improve quality of life of patients and caregivers. In this context, a deeper awareness of the related risk factors, predictors and concomitant diseases is very helpful. Considering the high prevalence of multimorbidity, in older adults with undiagnosed cognitive impairment polypharmacy is a relevant issue, because of the related enhanced risk of potentially inappropriate medications (PIMs) and drug-drug interactions (DDIs) [5–7]. Therefore, in these cases a careful evaluation and close revision of each drug appropriateness is warranted [8,9].

To date, data on features, management and clinical impact of undiagnosed cognitive impairment stemming from hospitalized older adults are scarce and heterogeneous. With this background, this study aims to evaluate the prevalence of this condition in a large Italian cohort of older patients hospitalized in internal medicine and geriatrics wards, the use of potentially inappropriate medications among these patients and the related impact on adverse outcomes after hospital discharge.

In this retrospective study, we included 4888 older adults from the Registro Politerapie SIMI (REPOSI) Registry hospitalized between 2010 and 2021 with no previous diagnosis of dementia or cognitive impairment [based on International Classification of Diseases–9th Edition (ICD9)] and not receiving anti-dementia medications at admission [based on the Anatomic Therapeutic Chemical (ATC) Classification System].

Three groups of patients were defined based on the Short Blessed Test (SBT) score performed within 2 days from hospital admission: i) cases with normal cognition or questionable impairment (score 0–9), ii) with moderate undiagnosed cognitive impairment (score 10–19) and iii) severe undiagnosed cognitive impairment (score $\geq$ 20). Patients without SBT evaluation, transferred to other wards or discharged in critical conditions were excluded. Those previously institutionalized were also excluded for the non-home discharge endpoint.

The appropriateness of drug prescription was assessed in terms of prevalence of patients exposed to potentially severe DDIs associated with renal failure, QT interval prolongation or hemorrhage, prevalence of cases receiving the prescription of PIMs (defined according to Beers and STOPP criteria), and drugs related anticholinergic burden as assessed by means of the Anticholinergic Cognitive Burden (ACB) scale.

A standard descriptive statistics was performed. Differences were analyzed with Pearson's chi-squared test (for binomial variables) and F-Test or Kurskal-Wallis test (for numerical variables). Logistic regression models and Cox's regression models (unadjusted and adjusted for age, sex and comorbidity index) were performed to evaluate the impact of undiagnosed cognitive impairment on outcomes.

Further details regarding study design, variables collected in the frame of the REPOSI study, and statistical analysis are reported in the Supplementary material.

In a large cohort of older adults hospitalized in Italian internal medicine and geriatric wards, we found a high prevalence (38%) of previously undiagnosed cognitive impairment, which was severe in 22% of them. Our findings are in line with previous data, reporting a prevalence of cognitive impairment in hospitalized older inpatients varying from 21% to 61% depending on the hospital setting (e.g. medical, surgery), population characteristics (e.g. prevalence of cardiovascular risk factors) and the assessment methods [4]. Consistently with previous studies, cognitive disorders progressively increased with age and cases with undiagnosed cognitive impairment were more frequently women and had a higher prevalence of depression and higher levels of functional impairment [3,4] (Table 1).

Among patients with severe but previously undiagnosed cognitive impairment (n = 412), 20% lived alone, 69% chronically took five or more drugs on average. The prevalence of patients exposed to potentially inappropriate medications was similar among the three groups, except for psychotropic drugs. The proportion of cases chronically treated with at least three psychotropic drugs or at least two antidepressants doubled in patients with undiagnosed severe cognitive impairment compared with the remained two groups. Moreover, concerning was the lack of significant differences regarding the use of hardly manageable drugs compared to the non-cognitively impaired cases. Indeed, 12–16% of patients with and without cognitive impairment chronically used such drugs as warfarin and insulin, 2–5% inappropriate antihypertensive medications and 1–3% sulfonylureas or central alpha antagonists, or dipyridamole, or ticlopidine (Table 1). Based on these observations, the potential risk of low adherence and potentially severe drug-related adverse events is striking in this population. This is not surprising considering that it is well established that the inability to self-administer medications and the reduction of medication adherence are early signs of cognitive decline [10].

As regards DDIs, more than half of patients with severe undiagnosed cognitive impairment took medications causing one or more potentially

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Table 1
Main patient characteristics, outcomes and therapy inappropriateness.

in relation to the Short Blessed Test score.	Normal cognition or questionable impairment (0<SBT<9)	Moderate impairment (10<SBT<19)	Severe impairment (SBT≥20)	*p*
Main patient characteristics				
Patients, n. (%)	3043 (62.3)	1433 (29.3)	412 (8.4)	
Age, mean (SD), years	77.7 (7.3)	80.2 (7.0)	83.1 (7.2)	<0.0001
65–74, n. (%)	1118 (36.7)	318 (22.2)	53 (12.9)	<0.0001
75–84, n. (%)	1330 (43.7)	717 (50.0)	169 (41.0)	
85+, n. (%)	595 (19.6)	398 (27.8)	190 (46.1)	
Women, n. (%)	1433 (47.1)	767 (53.5)	251 (61.1)	<0.0001
Polypharmacy, n. (%)	2145 (70.5)	1074 (75.0)	284 (68.9)	0.0036
Number of comorbidities, mean (SD) [a]	5.7 (2.8)	6.2 (2.8)	6.3 (2.7)	<0.0001
CIRS Comorbidity index, mean (SD) [b]	2.9 (1.9)	3.4 (2.0)	3.5 (2.0)	<0.0001
Living alone, n. (%) [c]	766 (26.1)	320 (23.2)	76 (19.9)	0.0076
Barthel Index cat, n. (%) [d]				<0.0001
minimal	1824 (60.9)	525 (37.4)	46 (11.5)	
mild	558 (18.6)	339 (24.2)	64 (15.9)	
moderate	342 (11.4)	274 (19.5)	66 (16.5)	
severe	156 (5.2)	150 (10.7)	81 (20.2)	
complete	117 (3.9)	115 (8.2)	144 (35.9)	
GDS ≥2, n. (%) [e]	964 (31.7)	637 (44.5)	190 (46.1)	<0.0001
Outcomes				
Length of hospitalization, mean (SD), days [f]	12.1 (11.7)	12.2 (11.3)	12.9 (10.8)	0.4137
Non-home discharged, n. (%) [g]	113 (4.7)	63 (6.1)	14 (5.3)	0.28
Re-hospitalization, n. (%) [h]				
at 3 months	331 (13.3)	169 (14.8)	34 (10.9)	0.19
at 1 year	431 (17.4)	210 (18.4)	42 (13.4)	0.22
Deaths, n. (%) [i]				
at 3 months	128 (5.1)	54 (4.7)	36 (11.4)	<0.0001
at 1 year	211 (8.5)	109 (9.5)	58 (18.4)	<0.0001
PIMs and severe DDIs				
Warfarin, n. (%)	415 (13.6)	222 (15.5)	49 (11.9)	0.1062
Insulin, n. (%)	399 (13.1)	219 (15.3)	56 (13.6)	0.1440
Inappropriate anti-hypertensive drugs, n. (%)*	143 (4.7)	68 (4.7)	10 (2.4)	0.1015
Long acting sulfonylureas, n (%)	51 (1.7)	32 (2.2)	5 (1.2)	0.2744
central alpha antagonists, n (%)	60 (2.0)	21 (1.5)	7 (1.7)	0.4871
Dipyridamole, n. (%)	21 (0.7)	11 (0.8)	2 (0.5)	0.8301
Ticlopidine, n. (%)	90 (2.9)	49 (3.4)	13 (3.2)	0.7073
At least 3 psychotropic drugs, n. (%)	29 (0.9)	15 (1.0)	8 (1.9)	0.1849
At least 2 benzodiazepines, n. (%)	27 (0.9)	6 (0.4)	2 (0.5)	0.1877
At least 2 antidepressants, n. (%)	25 (0.8)	12 (0.8)	8 (1.9)	0.0763
At least 2 antipsychotics, n. (%)	1 (0.03)	8 (0.6)	3 (0.7)	0.0005
At least one potentially severe DDI, n. (%)	1565 (51.4)	773 (53.9)	232 (56.3)	0.0828
DDIs-related GI bleeding, n. (%)	280 (9.2)	156 (10.9)	53 (12.9)	0.0279
DDIs-related Kidney failure, n. (%)	230 (7.6)	135 (9.4)	35 (8.5)	0.1025
DDIs-related QTc elongation, n. (%)	544 (17.9)	298 (20.8)	104 (25.2)	0.0005
ACB score, mean (±SD)	1.0 (1.1)	1.1 (1.2)	1.3 (1.4)	<0.0001
ACB score ≥ 4, n. (%)	112 (3.7)	65 (4.5)	34 (8.2)	<0.0001

Data available for 4888 patients at discharge; 3963 at three months follow-up and 1274 at one year follow-up.
Data available for:.
[a] 4872 patients;.
[b] 4723;.
[c] 4692;.
[d] 4801;.
[e] 4390;.
[f] 4848;.
[g] 3693;.
[h] 3939;.
[i] 3959.
* doxazosin; reserpine; nifedipine, immediate release.
Abbreviations: ACB= Anticholinergic Cognitive Burden, DDIs= drug-drug interactions, CIRS= Cumulative Illness Rating Scale, GDS= Geriatric Depression Scale score, PIMs=potentially inappropriate medications; SBT= Short Blessed Test.

severe DDIs, with a particular higher risk for DDIs-related gastrointestinal bleedings. In these patients there was also a higher prevalence of drug-related anticholinergic burden then in normal and moderately impaired cases, thus enhancing the risk of a faster cognitive decline.

Notwithstanding previous evidence of a positive correlation between cognitive disorders other than delirium during hospitalization and a prolonged length of hospital stay [1,4], our findings did not confirm this (Table S1). The inverse association between SBT and Barthel scores (Pearson's $\rho = -0.43,\ p < 0.0001$) may have affected this association. Moreover, these differences may be partly explained considering the specific characteristics of the internal medicine setting, characterized by the possibility to transfer patients to long-term care facilities or sub-acute hospital wards after resolution of acute phase of the disease. As expected, patients with severe cognitive impairment showed an increased risk of 3-month mortality (HR: 1.86, 95% CI: 1.26–2.73, $p = 0.002$) and 12-month mortality (HR: 2.02, 95% CI: 1.49–2.72, $p<0.001$), also after adjusting for age, sex and comorbidity burden. No association was found with the risk of institutionalization and hospital readmission (Table S1).

This study has some limitations. First, despite the exclusion of

delirium cases but considering the cross-sectional nature of the cognitive assessment, a transient cognitive impairment cannot be ruled out. Second, owing to the lack of a full neuropsychological test battery and to our assessment of the functional status only during the hospitalization, we were unable to differentiate between mild and major neurocognitive disorders, nor to characterize these disorders for probable etiologies. Furthermore, lack of data on adverse drug events limits the possibility of checking the relations between high-risk medications or potentially severe DDIs and adverse reactions. Finally, additional potential confounders might affect the observed associations with the explored outcomes.

In conclusion, this study shows that despite the efforts promoted in the last decades towards prevention of cognitive impairment, a large part of population remains still undiagnosed. Considering that this condition is affected by a high proportion of prescription inappropriateness and a worse prognosis, more effective strategies for cognitive screening of older adults among healthcare professionals and other stakeholders are needed.

Author contributions

P. Agosti designed the study, interpreted the data and wrote the first draft of the manuscript. A. Novella analysed the data, interpreted the data and contributed to write the manuscript. C. Custodero interpreted the data and contributed to write the manuscript. C. Elli interpreted the data and carefully revised the manuscript. L. Pasina designed the study, interpreted the data and contributed to write the manuscript.

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Declarations of Competing Interest

The authors declare they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.07.030.

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