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Association of the overlap of cognitive impairment and depression with 6-month mortality in hospitalized older adults: results from the Re.Po.SI register

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Abstract

Background When admitted to hospital for unplanned medical needs, the complexity of multiple conditions, including cognitive and mental health, might put older people at greater risk, affecting their survival. This study aimed to investigate the prevalence of cognitive impairment versus cognitive impairment with depression and their association with six-month mortality in older people after an unplanned hospital admission in Italy.

Methods In Re.Po.SI. a multi-centre study performed in Italy, standardized web-based case report forms were used to collect data on socio-demographic factors, clinical parameters, diagnoses, treatment history and at discharge, clinical events during hospitalization, and outcome data was collected. A comprehensive geriatric assessment was conducted using Cumulative Illness Rating Scale (CIRS), Geriatric Depression Scale (GDS-4), Barthel Index, and Short Blessed Test (SBT). To explore the interrelationship between depression and cognitive impairment, a variable categorized the study population into four mutually exclusive groups. This variable assessed the association between its categories and six-month mortality in a Cox multivariate analysis.

Results One thousand nine hundred fifty six participants were included, with a median age of 80 years (IQR: 73–85). Those who died within six months were likely to be older (82 vs. 79 years), male (56.2% vs. 47.2%), had moderately reduced ability to perform daily activities (82.0 vs. 93.0), exhibited greater illness severity (CIRS-IS: 1.8 vs. 1.6), had more chronically prescribed medications (6.0 vs. 5.0), and had a worse SBT score (10.0 vs. 7.0). When stratified based on cognitive impairment and depression, one-third had neither condition (33.2%), 21.9% had depression, 20.7% had a cognitive impairment, and 24.3% had both conditions. Six-month mortality was higher among people with cognitive impairment only (33.2%) followed by those with both conditions (28.8%), and depression only (22.7%). The unadjusted semi-parametric survival analysis revealed that the hazard ratio (HR) for people with cognitive impairment only was 2.08, for those with both conditions HR was 1.75, and for people with depression only HR was 1.30.

Conclusion While depression alone may contribute to mortality risk, cognitive impairment appears to play a more substantial role in increasing the risk of dying within 6 month from an acute hospitalization. Further research is needed to confirm these finding.

Keywords Older people, Depression, Cognitive impairment, Mortality

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Background

The Italian population is aging and living longer. Along with this trend, clinicians will meet more, older people with complex and multiple chronic diseases. Older people admitted to hospital for unplanned medical needs will often need longer hospital stays and are at higher risk of mortality [1]. Depression is commonly found in older physically ill patients in general hospitals, but risk estimates vary widely (5–58%), and has been found to unfavourably affect the outcome of numerous medical conditions, reduces treatment compliance, impairs rehabilitation, and decrease survival [2]. Similarly, cognitive impairment is highly prevalent in acute care environments and commonly indicates a poorer prognosis in hospitalized older people [3], since memory loss, slower thinking skills, decreased concentration and ability to make decisions affect capabilities in everyday life [4]. However, a gap remains in the research and literature if the interplay between the two affects mortality in older people after an unplanned hospital admission.

The aim of this study was to investigate the prevalence of cognitive impairment versus cognitive impairment with depression and their association with mortality after 6 months in older people admitted to hospital for unplanned medical needs.

Material and methods

Study design

The Re.Po.SI [5] is a collaborative effort between the Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute of Pharmacological Research (Milan). The Re.Po.SI registry was designed to function as a network of internal medicine and geriatric wards evaluating patients affected by multiple diseases and prescribed with polypharmacy. Participation in the network was on a voluntary basis, but choosing to be a participating centre, has increased the attention given to their homogeneous composition in terms of geographic distribution, size, and unselected admissions from the territory or the emergency department. All the patients admitted to the wards participating in the study were recruited consecutively if they were 65 years old or older. Participation in the study was voluntary and all the patients signed an informed consent. The first wave of the Re.Po.SI register was held between January and December 2008 [6]. A standardized web-based case report form was filled in by the attending physicians, which included the patient's socio-demographic factors, clinical parameters, diagnoses and treatments at both hospital admission and discharge, clinical events during hospitalization, and outcome. The Ethical Committees of all the participating institutions approved the study. The study was conducted according to the guidelines of the Declaration of Helsinki, and since this study is an observational study, a Clinical Trial Number is not applicable. For more protocol information see The RE.PO.SI study [6].

In this study, the following information were used:

1. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) was employed to categorize diseases [7] and the *Anatomical Therapeutic Chemical Classification System* (ATC) was employed to categorize drugs [8].
2. The severity of chronic conditions affecting the participant was rated using the *Cumulative Illness Rating Scale* (CIRS) [9], which includes 14 organs and systems that can be affected by diseases and records the severity of the diseases. CIRS is scored ranging from 0 ("no problem affecting the system) to 4 ("Extremely severe problem and/or immediate treatment required and/or organ failure and/ or severe functional impairment"). In addition, the clinicians were allowed to specify directly the diseases affecting each system using free text. The *Cumulative Illness Rating Scale – Severity Index* (CIRS-SI) result is from the average of the scores in the first 13 categories (excluding the psychiatric/behavioural pathology category). The *Cumulative Illness Rating Scale – Comorbidity Index* (CIRS-CI), represents the number of categories in which a score greater than or equal to 3 was obtained, these scores were used to summarise the burden of chronic conditions affecting the participant.
3. The *Barthel Index* (BI) [10] was used to evaluate disability and physical function in activities of daily living (ADL).
4. Demographics, information on smoking habit and alcohol consumption, as well as civil status, living situation, and education were also collected by the attending physician by interviewing the participant or her/his proxies.

We defined our exposure as follows:

Cognitive impairment was defined as the presence of at least one among the following criteria:

1) A Short Blessed Test (SBT) score of 10 or higher. The SBT was administered during hospitalization when the attending physician deemed the patient stable from the acute condition. The SBT has demonstrated excellent reliability and the ability to accurately discriminate between different levels of cognitive impairment. A score of 10 or higher is consistent with a diagnosis of dementia [11–13]

2) A diagnosis of dementia recorded on the discharge form using ICD-9CM codes (290.0,290.1,290.2,290.3 ,290.4,291.2,294.1,294.2)
3) A diagnosis of depression noted in the written specifications of the Cumulative Illness Rating Scale (CIRS) by identifying the term "depress*"
4) The chronic prescription of drugs with ATC code"N06D*"
5) An inability to complete the Geriatric Depression Scale-4 (GDS-4) [14] due to cognitive impairment, as registered by the attending physician

Depression was defined as the presence of at least one among the following criteria:

1) *The Geriatric Depression Scale-4* (GDS-4) [14] a score of 2 or higher indicated depression. GDS-4 has been proposed for the screening of depression in older adults and it can be used in hospital and community settings [15] with a sensitivity of 0.77 and a specificity of 0.75 [14].
2) A diagnosis of dementia recorded on the discharge form using ICD-9CM codes (290.0,290.1,290.2,290.3 ,290.4,291.2,294.1,294.2)
3) A diagnosis of depression noted in the written specifications of the Cumulative Illness Rating Scale (CIRS) by identifying the term "depress*"
4) The chronic prescription of drugs with ATC code"N06A*"

The study population was further stratified in four mutually exclusive categories: 1) No cognitive impairment/ no depression; 2) Depression alone; 3) Cognitive impairment alone; 4) Cognitive impairment and depression.

Mortality data was collected through phone interviews conducted at predefined follow-up intervals (3 and 12 months), during which information about the date of death was obtained from a proxy of the patient. For this study, we focused on 6-month mortality data. Patients who were still alive at the 3-month follow-up but did not complete the 12-month follow-up were excluded from the study.

Statistical analysis

The characteristics of the study population were described using counts and proportions, means and standard deviations, or medians and interquartile ranges (IQR), as appropriate. Differences between groups were assessed using Chi-squared tests, Fisher's exact test, or Mann–Whitney U-test, as appropriate. Additionally, the Shapiro–Wilk test was employed to assess the normality of continuous variables to determine the suitability of parametric or non-parametric tests for further analysis. The association between the presence of cognitive impairment and/or depression and 6-month mortality was investigated using Cox proportional hazards models. The proportionality of hazards was evaluated through graphical inspection of Schoenfeld residuals. All analyses were conducted using R version 4.3.0 (R Foundation for Statistical Computing, Vienna).

Results

An initial sample of 8417 participants was included in the Re.PO.SI register. Participant with missing information on age or the SBT were excluded ($N=3624$). Further, 11 participants were excluded because of errors in the date of death. Participants who were not dead within 12 months from hospital admission and missing the 12-month follow-up were excluded ($N=2826$). The final analytical sample was 1956 participants, depicted in Fig. 1.

As shown in Supplementary Table S1, those included in the study were rather similar to those excluded, although the former were older and prescribed, on average, more medications than the latter. In this secondary analysis, the interviews and data taken from the Re.Po.SI study [6], yielded a sample of 1956 participants had a median age of 80.0 years (IQR: 73.0—85.0) and half of the population was male (49.4%; $N=967$), as shown in Table 1. The median number of years of education was 5 (IQR: 5–8) and nearly half of the participants were married (52.7%, $N=1001$). The median score on the BI was 91.0 (IQR: 68.0—100.0). The median number of prescribed medications was 6.0 (IQR: 4.0—8.0) while the median CIRS-CI was 3.0 (IQR: 2.0—4.0). In total, 44.9% and 46.2% of the study population meet the criteria for cognitive impairment or depression, respectively. When the study population was stratified in four mutually exclusive categories, a third of the population was found to be free from both conditions, 24.3% were affected by both conditions simultaneously, 20.7% were affected by cognitive impairment only and 21.9% were affected by depression only. The 6-month mortality was nearly 25% ($N=484$) and the median follow-up was 71.5 days.

Those who died within 6 months were more likely to be older (82.0 years vs. 79.0 years), male (56.2% vs. 47.2%), had a reduction in the ability to perform ADL, were moderately dependent on others (BI 82.0 vs. 93.0), and were prescribed with higher number of medications (6.0 vs. 5.0). A diagnosis of cognitive impairment was more likely among those dying within 6 months from the hospitalization (56.0% vs 41.3%, $p<0.001$), although the proportion of persons with depression was similar within the groups (48.3% vs 45.4%, $p=0.290$).

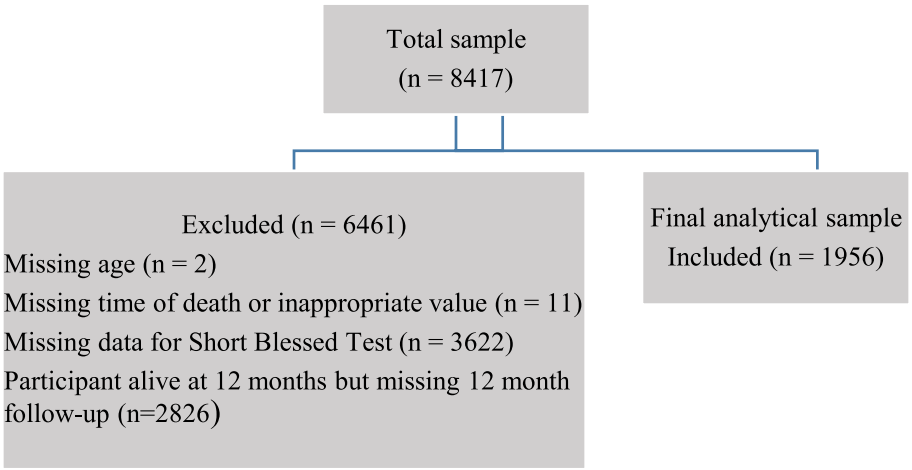

Fig. 1 Flow chart for the inclusion of participants in the study

Table 2 shows the characteristics of the study population stratified according to the presence of cognitive impairment and/or depression. The median age was higher among those with both conditions (83.0 years old) and was lower among those diagnosed with depression only (77.0 years old). The proportion of males was higher among those with neither condition (61.6%) and was lower among those with both (38.3). The median BI score ranged between 100 (independent in ADL, with neither condition present) and 74.0 (moderately dependent in ADL with both cognitive impairment and depression present). Mortality at six months for the population was nearly one in four participants (24.7), and the group with the highest odds of mortality had cognitive impairment only, effecting one in three participants (33.2).

As shown in Table 3, the group with the highest incidence rate of death (IR, per 100 person-years) was cognitive impairment alone (IR 81.1, CI 57.9–115.0), followed by cognitive impairment with depression (IR 68.9, CI 49.2–97.3).

In Table 4, the groups with cognitive impairment and/or depression were compared to those with neither condition. People with cognitive impairment only exhibited the highest increase in the relative hazard of 6-month mortality (Hazard Ratio [HR]: 2.1; 95% CI: 1.6–2.7), followed by those with both conditions (HR: 1.7; 95% CI: 1.4–2.2), and finally those affected by depression only (HR: 1.3; 95% CI: 1.0–1.81.7). These results were confirmed in the adjusted analysis, though slightly attenuated.

We also conducted a sensitivity analysis including cognitive decline, depression, and their multiplicative interaction term, shown in Supplementary Table S2, confirming the strong association between cognitive decline and mortality, the association between depression and mortality and the presence of a negative interaction between cognitive decline and depression.

Lastly, we conducted a sensitivity analysis including all study participants and censoring them at the date of the last available follow-up. The results were similar to those shown in the main analyses, for both direction and magnitude shown in Supplementary Table S3.

Discussion

In this secondary analysis of the RE.PO.SI data, we identified that both cognitive impairment and depression are prevalent in a population of older persons acutely admitted to the hospital, since nearly a quarter (24%) of our study population was affected by both conditions. The cumulative mortality at six month was almost 25% and, although those with both cognitive impairment and depression were older, exhibited greater dependence in their ADLs, had a higher burden of chronic illnesses, they exhibited a risk of dying similar to those with cognitive impairment only. Lastly, in the depression only group there was a lower risk of dying at six months, compared to both groups with cognitive impairment and cognitive impairment with depression.

In this study, roughly 22% of the study participants had depression only. These findings are similar to other studies, confirming that depression is common in older physically ill patients in general hospitals with a mean prevalence of 29% [16]. Similarly, we identified that nearly 21% of the study participants had a cognitive impairment which concurred with a recent cohort study of more than 21,000 hospitalised older adults, of which 27% had a cognitive impairment [17]. Furthermore, our study results correspond with

Table 1 Demographics and characteristics of participants stratified by 6-month mortality

	Final analytical sample	Death at 6 months = NO	Death at 6 months = YES	*p*
Number of participants, n (%)	**1956 (100)**	1472 (75.3)	484 (24.7)	
Age, median [IQR]	**80.0 [73.0, 85.0]**	79.0 [73.0, 84.0]	82.0 [76.0, 87.0]	< 0.001[c]
Sex = Male (%)	**967 (49.4)**	695 (47.2)	272 (56.2)	0.001[a]
Education years, median [IQR]	**5.0 [5.0, 8.0]**	5.0 [5.0, 8.0]	5.0 [5.0, 8.0]	0.958[c]
Civil status, n (%)				0.642[a]
married	**1001 (52.7)**	757 (52.8)	244 (52.5)	
widowed	**720 (37.9)**	549 (38.3)	171 (36.8)	
separated	**29 (1.5)**	21 (1.5)	8 (1.7)	
divorced	**32 (1.7)**	25 (1.7)	7 (1.5)	
single	**116 (6.1)**	81 (5.7)	35 (7.5)	
Living with = others (%)	**1394 (75.1)**	1050 (74.5)	344 (76.8)	0.367[a]
Alcohol consumption (%)				0.055[a]
Never	**1013 (53.1)**	755 (52.5)	258 (55.1)	
ex-drinker	**103 (5.4)**	69 (4.8)	34 (7.3)	
drinker	**318 (16.7)**	253 (17.6)	65 (13.9)	
Social drinker	**472 (24.8)**	361 (25.1)	111 (23.7)	
Collar[1] = White (%)	**549 (38.2)**	407 (37.6)	142 (40.1)	0.431[a]
P-ADL[2] median [IQR]	**91.0 [68.0, 100.0]**	93.0 [74.0, 100.0]	82.0 [44.2, 96.0]	< 0.001[c]
Specific P-ADL[2]: Personal hygiene (%)				< 0.001[a]
0	**135 (7.0)**	80 (5.5)	55 (11.5)	
1	**102 (5.3)**	51 (3.5)	51 (10.6)	
3	**229 (11.8)**	155 (10.6)	74 (15.4)	
4	**277 (14.3)**	203 (13.9)	74 (15.4)	
5	**1192 (61.6)**	967 (66.4)	225 (47.0)	
Specific P-ADL[2]: Bathing (%)				< 0.001[a]
0	**211 (10.9)**	131 (9.0)	80 (16.7)	
1	**128 (6.6)**	76 (5.2)	52 (10.9)	
3	**288 (14.9)**	206 (14.1)	82 (17.1)	
4	**318 (16.4)**	221 (15.2)	97 (20.3)	
5	**990 (51.2)**	822 (56.5)	168 (35.1)	
Specific P-ADL[2]: Feeding (%)				< 0.001[a]
0	**65 (3.4)**	41 (2.8)	24 (5.0)	
2	**58 (3.0)**	34 (2.3)	24 (5.0)	
5	**169 (8.7)**	107 (7.3)	62 (12.9)	
8	**211 (10.9)**	144 (9.9)	67 (14.0)	
10	**1432 (74.0)**	1130 (77.6)	302 (63.0)	
Specific P-ADL[2]: Toileting (%)				< 0.001[a]
0	**147 (7.6)**	85 (5.8)	62 (12.9)	
2	**111 (5.7)**	60 (4.1)	51 (10.6)	
5	**160 (8.3)**	117 (8.0)	43 (9.0)	
8	**251 (13.0)**	183 (12.6)	68 (14.2)	
10	**1266 (65.4)**	1011 (69.4)	255 (53.2)	
Specific P-ADL[2]: Stair Climbing (%)				< 0.001[a]
0	**328 (17.0)**	195 (13.4)	133 (27.8)	
2	**150 (7.8)**	106 (7.3)	44 (9.2)	
5	**317 (16.4)**	234 (16.1)	83 (17.3)	
8	**351 (18.1)**	262 (18.0)	89 (18.6)	
10	**789 (40.8)**	659 (45.3)	130 (27.1)	
Specific P-ADL[2]: Dressing (%)				< 0.001[a]

Table 1 (continued)

	Final analytical sample	Death at 6 months = NO	Death at 6 months = YES	*p*
0	**141 (7.3)**	77 (5.3)	64 (13.4)	
2	**123 (6.4)**	70 (4.8)	53 (11.1)	
5	**231 (11.9)**	169 (11.6)	62 (12.9)	
8	**287 (14.8)**	211 (14.5)	76 (15.9)	
10	**1153 (59.6)**	929 (63.8)	224 (46.8)	
Specific P-ADL[2]: Bladder control (%)				< 0.001[a]
0	**152 (7.9)**	98 (6.7)	54 (11.3)	
2	**87 (4.5)**	45 (3.1)	42 (8.8)	
5	**174 (9.0)**	124 (8.5)	50 (10.5)	
8	**285 (14.7)**	205 (14.1)	80 (16.7)	
10	**1236 (63.9)**	984 (67.6)	252 (52.7)	
Specific P-ADL[2]: Bowel control (%)				< 0.001
0	**112 (5.8)**	66 (4.5)	46 (9.6)	
2	**73 (3.8)**	40 (2.7)	33 (6.9)	
5	**133 (6.9)**	87 (6.0)	46 (9.6)	
8	**187 (9.7)**	128 (8.8)	59 (12.3)	
10	**1430 (73.9)**	1135 (78.0)	295 (61.6)	
Specific P-ADL[2]: Ambulation (%)				< 0.001[a]
0	**146 (7.7)**	80 (5.6)	66 (14.2)	
3	**135 (7.1)**	79 (5.5)	56 (12.0)	
8	**285 (15.1)**	211 (14.8)	74 (15.9)	
12	**452 (23.9)**	337 (23.6)	115 (24.7)	
15	**874 (46.2)**	719 (50.4)	155 (33.3)	
Specific P-ADL[2]: Wheelchair (%)				0.019[a]
0	**80 (44.2)**	57 (42.5)	23 (48.9)	
1	**21 (11.6)**	12 (9.0)	9 (19.1)	
3	**20 (11.0)**	16 (11.9)	4 (8.5)	
4	**7 (3.9)**	3 (2.2)	4 (8.5)	
5	**53 (29.3)**	46 (34.3)	7 (14.9)	
Specific P-ADL[2]: Bed to chair transfer (%)				< 0.001[a]
0	**143 (7.4)**	85 (5.8)	58 (12.1)	
3	**152 (7.9)**	96 (6.6)	56 (11.7)	
8	**238 (12.3)**	163 (11.2)	75 (15.7)	
12	**358 (18.5)**	265 (18.2)	93 (19.4)	
15	**1043 (53.9)**	846 (58.1)	197 (41.1)	
CIRS[3] Illness Severity Index, median [IQR]	**1.7 [1.5, 1.9]**	1.6 [1.4, 1.8]	1.8 [1.5, 2.0]	< 0.001[c]
CIRS[3] Co-morbidity Index, [median] [IQR]	**3.0 [2.0, 4.0]**	3.0 [2.0, 4.0]	3.0 [2.0, 5.0]	< 0.001[c]
Prescribed pharmaceuticals median [IQR]	**6.0 [4.0, 8.0]**	5.0 [4.0, 8.0]	6.0 [4.0, 8.0]	0.043[c]
GDS[4], median [IQR]	**1.0 [0.0, 2.0]**	1.0 [0.0, 2.0]	1.0 [1.0, 3.0]	< 0.001[c]
SBT[5], median [IQR]	**8.0 [3.8, 14.0]**	7.0 [2.0, 13.0]	10.0 [4.0, 19.0]	< 0.001[c]
Cognitive impairment (CI) = yes (%)	**879 (44.9)**	608 (41.3)	271 (56.0)	< 0.001[a]
CIRS ICD for CD[6,7], (%)	**165 (8.4)**	94 (6.4)	71 (14.7)	< 0.001[a]
CIRS text, (%)	**162 (8.3)**	92 (6.2)	70 (14.5)	< 0.001[a]
Pharmaceuticals ATC code for CD[8], (%)	**20 (1.0)**	17 (1.2)	3 (0.6)	0.452[b]
SBT ≥ 10, (%)	**860 (44.0)**	593 (40.3)	267 (55.2)	< 0.001[a]
Depression diagnosis = yes (%)	**903 (46.2)**	669 (45.4)	234 (48.3)	0.290[a]
CIRS ICD for depression[9], (%)	**77 (3.9)**	60 (4.1)	17 (3.5)	0.676[a]
CIRS text for depression, (%)	**205 (10.5)**	153 (10.4)	52 (10.7)	0.895[a]
Pharmaceuticals ATC code for depression[10], (%)	**331 (16.9)**	255 (17.3)	76 (15.7)	0.457[a]

Table 1 (continued)

	Final analytical sample	Death at 6 months = NO	Death at 6 months = YES	*p*
GDS ≥ 2, (%)	**706 (42.0)**	516 (39.8)	190 (49.5)	0.001[a]
Presence of CI and/or depression (%)				< 0.001[a]
none	**649 (33.2)**	533 (36.2)	116 (24.0)	
depression only	**428 (21.9)**	331 (22.5)	97 (20.0)	
CI only	**404 (20.7)**	270 (18.3)	134 (27.7)	
both	**475 (24.3)**	338 (23.0)	137 (28.3)	
Presence of FU[11] at 12 months = 1 (%)	**1480 (75.7)**	1422 (96.6)	58 (12.0)	< 0.001[a]
Days of follow-up median [IQR]	**180.0 [180.0, 180.0]**	180.0 [180.0, 180.0]	54 [25.0, 94.0]	< 0.001[c]

[1] White-collar workers generally perform job duties in an office or other administrative settings

[2] Personal Activities of Daily Living score with Barthel Scale

[3] Cumulative Illness Rating Scale

[4] Geriatric Depression Scale (4-point scale

[5] Short Blessed Test

[6] Cognitive decline

[7] Presence of ICD (The International Classification of Diseases, Ninth Revision, Clinical Modification) codes for dementia in CIRS (290.0, 290.1, 290.2, 290.3, 290.4, 290.8, 290.8, 290.9, 291.2, 294.1)

[8] Presence of medications coded as "N06D" (Anti-dementia drugs) under the Anatomical Therapeutic Chemical (ATC) Classification System

[9] Presence of ICD (The International Classification of Diseases, Ninth Revision, Clinical Modification) codes for depression in CIRS (296.1, 296.3, 296.4, 298.0, 300.4)

[10] Presence of medications coded as "N06A" (Antidepressants) under the Anatomical Therapeutic Chemical (ATC) Classification System

[11] Follow up

MISSING

Civil status, n (%) = 58 (3.0)

Living with, n (%) = 99 (5.1)

Alcohol consumption, n (%) = 50 (2.6)

Collar, n (%) = 519 (26.5)

Specific P-ADL[2]: Personal hygiene, n (%) = 21(1.1)

Specific P-ADL[2]: Bathing, n (%) = 21(1.1)

Specific P-ADL[2]: Feeding, n (%) = 21(1.1)

Specific P-ADL[2]: Toileting, n (%) = 21(1.1)

Specific P-ADL[2]: Stair Climbing, n (%) = 21(1.1)

Specific P-ADL[2]: Dressing, n (%) = 21(1.1)

Specific P-ADL[2]: Bladder control, n (%) = 22(1.1)

Specific P-ADL[2]: Bowel control, n (%) = 21(1.1)

Specific P-ADL[2]: Ambulation, n (%) = 64(3.3)

Specific P-ADL[2]: Wheelchair, n (%) = 1775 (90)

Specific P-ADL[2]: Bed to chair transfer, n (%) = 22(1.1)

Pharmaceuticals ATC code for CD[8], n (%) = 2(0.1)

Pharmaceuticals ATC code for depression[10] n (%) = 2(0.1)

GDS ≥ 2, n (%) = 274 (14.0)

STATISTICAL TEST USED

Chi-squared test[a]

Fisher's exact test[b]

Mann–Whitney U-test[c]

earlier findings that cognitive impairment is independently associated with mortality [17]. In our analysis, individuals with depression only showed a lower six-month mortality risk compared to those with cognitive impairment, with or without depression, in both the unadjusted and adjusted models. However, in the adjusted Cox proportional hazards model, there was no statistically significant difference (adjusted HR 1.33, 95% CI: 0.99–1.79). This suggests a possible trend of higher mortality in groups with cognitive impairment, regardless of the presence of depression. This trend is evident in Table 3, where the age-adjusted incidence rate is lowest in the group without cognitive impairment or depression and highest in the

Table 2 Demographics and characteristics of participants stratified by presence of cognitive impairment and/or depression

	Final analytical sample	None	Depression only	Cognitive Impairment (CI)[6] only	Both	*P* value
Number of participants, n (%)	**1956 (100)**	649 (33.2)	428 (21.9)	404 (20.7)	475 (24.3)	
Age, median [IQR]	**80.0 [73.0, 85.0]**	78.0 [72.0, 83.0]	77.0 [71.0, 83.0]	82.0 [76.0, 87.0]	83.0 [77.0, 87.0]	< 0.001[c]
Sex = Male (%)	**967 (49.4)**	400 (61.6)	192 (44.9)	193 (47.8)	182 (38.3)	< 0.001[a]
Education years, median [IQR]	**5.0 [5.0, 8.0]**	8.0 [5.0, 12.0]	8.0 [5.0, 10.0]	5.0 [5.0, 8.0]	5.0 [5.0, 8.0]	< 0.001[c]
Civil status, n (%)						< 0.001[a]
married	**1001 (52.7)**	372 (59.4)	233 (55.2)	187 (48.1)	209 (45.3)	
widowed	**720 (37.9)**	197 (31.5)	139 (32.9)	165 (42.4)	219 (47.5)	
separated	**29 (1.5)**	11 (1.8)	9 (2.1)	6 (1.5)	3 (0.7)	
divorced	**32 (1.7)**	12 (1.9)	9 (2.1)	6 (1.5)	5 (1.1)	
single	**116 (6.1)**	34 (5.4)	32 (7.6)	25 (6.4)	25 (5.4)	
Living with = others (%)	**1394 (75.1)**	453 (73.3)	301 (74.3)	286 (74.1)	354 (79.0)	0.166[a]
Alcohol consumption (%)						0.013[a]
Never	**1013 (53.1)**	322 (51.1)	216 (51.3)	195 (49.5)	280 (60.7)	
ex-drinker	**103 (5.4)**	28 (4.4)	25 (5.9)	30 (7.6)	20 (4.3)	
drinker	**318 (16.7)**	117 (18.6)	67 (15.9)	73 (18.5)	61 (13.2)	
Social drinker	**472 (24.8)**	163 (25.9)	113 (26.8)	96 (24.4)	100 (21.7)	
Collar[1] = White (%)	**549 (38.2)**	215 (45.6)	134 (43.5)	96 (32.7)	104 (28.7)	< 0.001[a]
P-ADL[2] median [IQR]	**91.0 [68.0, 100.0]**	100.0 [89.0, 100.0]	92.0 [77.2, 100.0]	82.0 [53.0, 97.0]	74.0 [39.5, 92.0]	< 0.001[c]
Specific P-ADL[2]: Personal hygiene (%)						< 0.001[a]
0	**135 (7.0)**	18 (2.8)	16 (3.8)	39 (9.8)	62 (13.1)	
1	**102 (5.3)**	13 (2.0)	14 (3.3)	26 (6.5)	49 (10.4)	
3	**229 (11.8)**	34 (5.3)	28 (6.6)	77 (19.2)	90 (19.1)	
4	**277 (14.3)**	53 (8.3)	72 (17.1)	67 (16.8)	85 (18.0)	
5	**1192 (61.6)**	523 (81.6)	292 (69.2)	191 (47.8)	186 (39.4)	
Specific P-ADL[2]: Bathing (%)						< 0.001[a]
0	**211 (10.9)**	29 (4.5)	36 (8.5)	56 (14.0)	90 (19.1)	
1	**128 (6.6)**	18 (2.8)	15 (3.6)	32 (8.0)	63 (13.3)	
3	**288 (14.9)**	45 (7.0)	51 (12.1)	88 (22.0)	104 (22.0)	
4	**318 (16.4)**	71 (11.1)	92 (21.8)	76 (19.0)	79 (16.7)	
5	**990 (51.2)**	478 (74.6)	228 (54.0)	148 (37.0)	136 (28.8)	
Specific P-ADL[2]: Feeding (%)						< 0.001[a]
0	**65 (3.4)**	17 (2.7)	7 (1.7)	20 (5.0)	21 (4.4)	
2	**58 (3.0)**	6 (0.9)	3 (0.7)	16 (4.0)	33 (7.0)	
5	**169 (8.7)**	19 (3.0)	22 (5.2)	49 (12.2)	79 (16.7)	
8	**211 (10.9)**	34 (5.3)	39 (9.2)	61 (15.2)	77 (16.3)	
10	**1432 (74.0)**	565 (88.1)	351 (83.2)	254 (63.5)	262 (55.5)	
Specific P-ADL[2]: Toileting (%)						< 0.001[a]
0	**147 (7.6)**	18 (2.8)	18 (4.3)	42 (10.5)	69 (14.6)	
2	**111 (5.7)**	20 (3.1)	15 (3.6)	32 (8.0)	44 (9.3)	
5	**160 (8.3)**	16 (2.5)	30 (7.1)	45 (11.2)	69 (14.6)	
8	**251 (13.0)**	59 (9.2)	54 (12.8)	60 (15.0)	78 (16.5)	
10	**1266 (65.4)**	528 (82.4)	305 (72.3)	221 (55.2)	212 (44.9)	
Specific P-ADL[2]: Stair Climbing (%)						< 0.001[a]
0	**328 (17.0)**	40 (6.2)	60 (14.2)	94 (23.5)	134 (28.4)	
2	**150 (7.8)**	26 (4.1)	28 (6.6)	35 (8.8)	61 (12.9)	
5	**317 (16.4)**	63 (9.8)	70 (16.6)	79 (19.8)	105 (22.2)	
8	**351 (18.1)**	122 (19.0)	83 (19.7)	70 (17.5)	76 (16.1)	
10	**789 (40.8)**	390 (60.8)	181 (42.9)	122 (30.5)	96 (20.3)	

Table 2 (continued)

	Final analytical sample	None	Depression only	Cognitive Impairment (CI)[6] only	Both	*P* value
Specific P-ADL[2]: Dressing (%)						< 0.001[a]
0	**141 (7.3)**	20 (3.1)	15 (3.6)	41 (10.2)	65 (13.8)	
2	**123 (6.4)**	14 (2.2)	19 (4.5)	34 (8.5)	56 (11.9)	
5	**231 (11.9)**	33 (5.1)	44 (10.4)	60 (15.0)	94 (19.9)	
8	**287 (14.8)**	61 (9.5)	62 (14.7)	77 (19.2)	87 (18.4)	
10	**1153 (59.6)**	513 (80.0)	282 (66.8)	188 (47.0)	170 (36.0)	
Specific P-ADL[2]: Bladder control (%)						< 0.001[a]
0	**152 (7.9)**	30 (4.7)	15 (3.6)	43 (10.8)	64 (13.6)	
2	**87 (4.5)**	10 (1.6)	11 (2.6)	25 (6.2)	41 (8.7)	
5	**174 (9.0)**	18 (2.8)	32 (7.6)	54 (13.5)	70 (14.9)	
8	**285 (14.7)**	52 (8.1)	61 (14.5)	77 (19.2)	95 (20.2)	
10	**1236 (63.9)**	531 (82.8)	303 (71.8)	201 (50.2)	201 (42.7)	
Specific P-ADL[2]: Bowel control (%)						< 0.001[a]
0	**112 (5.8)**	19 (3.0)	9 (2.1)	34 (8.5)	50 (10.6)	
2	**73 (3.8)**	11 (1.7)	10 (2.4)	20 (5.0)	32 (6.8)	
5	**133 (6.9)**	17 (2.7)	25 (5.9)	39 (9.8)	52 (11.0)	
8	**187 (9.7)**	26 (4.1)	36 (8.5)	58 (14.5)	67 (14.2)	
10	**1430 (73.9)**	568 (88.6)	342 (81.0)	249 (62.3)	271 (57.4)	
Specific P-ADL[2]: Ambulation (%)						< 0.001[a]
0	**146 (7.7)**	21 (3.3)	21 (5.1)	43 (10.9)	61 (13.5)	
3	**135 (7.1)**	21 (3.3)	23 (5.6)	30 (7.6)	61 (13.5)	
8	**285 (15.1)**	45 (7.1)	62 (15.0)	80 (20.4)	98 (21.7)	
12	**452 (23.9)**	125 (19.7)	96 (23.2)	114 (29.0)	117 (25.9)	
15	**874 (46.2)**	421 (66.5)	212 (51.2)	126 (32.1)	115 (25.4)	
Specific P-ADL[2]: Wheelchair (%)						< 0.001[a]
0	**80 (44.2)**	20 (40.8)	20 (51.3)	17 (47.2)	23 (40.4)	
1	**21 (11.6)**	2 (4.1)	4 (10.3)	4 (11.1)	11 (19.3)	
3	**20 (11.0)**	1 (2.0)	1 (2.6)	8 (22.2)	10 (17.5)	
4	**7 (3.9)**	1 (2.0)	2 (5.1)	3 (8.3)	1 (1.8)	
5	**53 (29.3)**	25 (51.0)	12 (30.8)	4 (11.1)	12 (21.1)	
Specific P-ADL[2]: Bed to chair transfer (%)						< 0.001[a]
0	**143 (7.4)**	19 (3.0)	16 (3.8)	36 (9.0)	72 (15.3)	
3	**152 (7.9)**	28 (4.4)	27 (6.4)	38 (9.5)	59 (12.5)	
8	**238 (12.3)**	33 (5.1)	46 (10.9)	72 (18.0)	87 (18.4)	
12	**358 (18.5)**	90 (14.0)	84 (19.9)	89 (22.3)	95 (20.1)	
15	**1043 (53.9)**	471 (73.5)	249 (59.0)	164 (41.1)	159 (33.7)	
CIRS[3] Illness Severity Index, median [IQR]	**1.7 [1.5, 1.9]**	1.6 [1.4, 1.8]	1.7 [1.5, 1.9]	1.7 [1.5, 1.9]	1.7 [1.5, 2.0]	< 0.001[c]
CIRS[3] Co-morbidity Index, median [IQR]	**3.0 [2.0, 4.0]**	3.0 [1.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 5.0]	< 0.001[c]
Prescribed pharmaceuticals median [IQR]	**6.0 [4.0, 8.0]**	5.0 [3.0, 7.0]	6.0 [4.0, 8.0]	5.0 [3.0, 8.0]	6.0 [4.0, 8.0]	< 0.001[c]
GDS[4], median [IQR]	**1.0 [0.0, 2.0]**	0.0 [0.0, 1.0]	2.0 [2.0, 3.0]	1.0 [0.0, 1.0]	2.0 [2.0, 3.0]	< 0.001[c]
SBT[5], median [IQR]	**8.0 [3.8, 14.0]**	4.0 [0.0, 6.0]	4.0 [2.0, 6.0]	15.0 [12.0, 21.0]	16.0 [12.0, 22.0]	< 0.001[c]
Cognitive impairment diagnosis = yes (%)	**879 (44.9)**	0 (0.0)	0 (0.0)	404 (100.0)	475 (100.0)	< 0.001[a]
CIRS ICD for CI[6,7], (%)	**165 (8.4)**	0 (0.0)	0 (0.0)	68 (16.8)	97 (20.4)	< 0.001[a]

Table 2 (continued)

	Final analytical sample	None	Depression only	Cognitive Impairment (CI)[6] only	Both	*P* value
CIRS text, (%)	**162 (8.3)**	0 (0.0)	0 (0.0)	66 (16.3)	96 (20.2)	< 0.001[a]
Pharmaceuticals ATC code for CI[8], (%)	**20 (1.0)**	0 (0.0)	0 (0.0)	4 (1.0)	16 (3.4)	< 0.001[b]
SBT ≥ 10, (%)	**860 (44.0)**	0 (0.0)	0 (0.0)	397 (98.3)	463 (97.5)	< 0.001[a]
Depression diagnosis = yes (%)	**903 (46.2)**	0 (0.0)	428 (100.0)	0 (0.0)	475 (100.0)	< 0.001[a]
CIRS ICD for depression[9], (%)	**77 (3.9)**	0 (0.0)	38 (8.9)	0 (0.0)	39 (8.2)	< 0.001[a]
CIRS text for depression, (%)	**205 (10.5)**	0 (0.0)	104 (24.3)	0 (0.0)	101 (21.3)	< 0.001[a]
Pharmaceuticals ATC code for depression[10], (%)	**331 (16.9)**	0 (0.0)	147 (34.4)	0 (0.0)	184 (38.8)	< 0.001[a]
GDS ≥ 2, (%)	**706 (42.0)**	0 (0.0)	340 (83.5)	0 (0.0)	366 (85.9)	< 0.001[a]
Death at 6 months = yes (%)	**484 (24.7)**	116 (17.9)	97 (22.7)	134 (33.2)	137 (28.8)	< 0.001[a]
Days of follow up median [IQR]	**180.0 [180.0, 180.0]**	180.0 [180.0, 180.0]	180.0 [180.0, 180.0]	180.0 [91.0, 180.0]	180.0 [115.0, 180.0]	0.061

[1] White-collar workers generally perform job duties in an office or other administrative settings

[2] Personal Activities of Daily Living score with Barthel Scale

[3] Cumulative Illness Rating Scale

[4] Geriatric Depression Scale (4-point scale)

[5] Short Blessed Test

[6] Cognitive impairment

[7] Presence of ICD (The International Classification of Diseases, Ninth Revision, Clinical Modification) codes for dementia in CIRS (290.0, 290.1, 290.2, 290.3, 290.4, 290.8, 290.8, 290.9, 291.2, 294.1)

[8] Presence of medications coded as "N06D" (Anti-dementia drugs) under the Anatomical Therapeutic Chemical (ATC) Classification System

[9] Presence of ICD (The International Classification of Diseases, Ninth Revision, Clinical Modification) codes for depression in CIRS (296.1, 296.3, 296.4, 298.0, 300.4)

[10] Presence of medications coded as "N06A" (Antidepressants) under the Anatomical Therapeutic Chemical (ATC) Classification System

[11] Follow up

MISSING

Civil status, n (%) = 58 (3.0)

Living with, n (%) = 99 (5.1)

Alcohol consumption, n (%) = 50 (2.6)

Collar, n (%) = 519 (26.5)

Specific P-ADL[2]: Personal hygiene, n (%) = 21(1.1)

Specific P-ADL[2]: Bathing, n (%) = 21(1.1)

Specific P-ADL[2]: Feeding, n (%) = 21(1.1)

Specific P-ADL[2]: Toileting, n (%) = 21(1.1)

Specific P-ADL[2]: Stair Climbing, n (%) = 21(1.1)

Specific P-ADL[2]: Dressing, n (%) = 21(1.1)

Specific P-ADL[2]: Bladder control, n (%) = 22(1.1)

Specific P-ADL[2]: Bowel control, n (%) = 21(1.1)

Specific P-ADL[2]: Ambulation, n (%) = 64(3.3)

Specific P-ADL[2]: Wheelchair, n (%) = 1775 (90)

Specific P-ADL[2]: Bed to chair transfer, n (%) = 22(1.1)

Pharmaceuticals ATC code for CD[8], n (%) = 2(0.1)

Pharmaceuticals ATC code for depression[10] n (%) = 2(0.1)

GDS ≥ 2, n (%) = 274 (14.0)

STATISTICAL TEST USED

Chi-squared test[a]

Fisher's exact test[b]

Mann–Whitney U-test[c]

group with cognitive impairment only; with intermediate values in the other two groups. Nonetheless, the overlap of the 95% confidence intervals indicates that these results should be interpreted with caution, highlighting the need for further studies to validate these observations.

Table 3 Incidence rates (IR) of death (per 100 people/year) for variable with mutually exclusive classes between cognitive impairment and depression

	Unweighted IR (95% CI)	Weighted IR (95% CI)
No cognitive impairment, no depression	**43.4 (29.9–62.7)**	41.1 (28.6 – 59.2)
No cognitive impairment, depression	**55.9 (37.1 – 84.6)**	54.0 (36.5 – 80.3)
Cognitive impairment, no depression	**81.1 (57.9 – 115.0)**	89.0 (65.0 – 123.0)
Cognitive impairment, depression	**68.9 (49.2 – 97.3)**	73.9 (53.8 – 102.0)

The weighted incidence rates (IR) and their confidence intervals (CI) was calculated by dividing the age variable into quintiles. This approach ensures that the age distribution was evenly represented across different groups, providing a more accurate comparison of IR

Table 4 Hazard ratio (HR) for association between 6-month mortality and a variable with 4 mutually exclusive classes between cognitive impairment and depression

	HR (95% CI) unadjusted	HR (95% CI) adjusted[a]
No cognitive impairment, no depression	**REF**	REF
No cognitive impairment, depression	**1.30 (1.00 – 1.71)**	1.37(1.03 – 1.84)
Cognitive impairment, no depression	**2.08 (1.63 – 2.67)**	1.94 (1.47 – 2.56)
Cognitive impairment, depression	**1.75 (1.36 – 2.24)**	1.74 (1.33 – 2.29)

[a] Adjusted for age, sex, years of education, prescribed pharmaceuticals and civil status

This finding contradicts previous research from a meta-study reported that depression is associated with an increased risk of all-cause mortality [18]. It also contradicts several earlier studies that concluded that when depression is added to cognitive impairment, mortality increases [19, 20], as we found no increase of mortality in our study. While our study refutes multiple earlier findings, it concurs with a recent study published exploring cognitive impairment and depression, in older people hospitalized for hip fractures, as their study too identified that people with depression only had a lower risk of mortality after discharge [21]. Nonetheless, the overlap of the 95% confidence intervals indicates that these results should be interpreted with caution, highlighting the need for further studies to validate these observations.

While the participants in the RE.PO.SI study received a through medication reviews in an effort to optimize treatment [5], this effort may have fallen short related to the use of anti-depressants in our cohort, since the older people in our study population were under prescribed depression medications despite having a depression diagnosis. Previously reported findings in the literature have identified that very few older adults admitted to acute hospitals are diagnosed with depression during their inpatient stays, and that opportunities for improving the mental health as well as physical health appear to be often missed in this population [22].

Merely 17% of our participants were prescribed antidepressant medications, despite nearly 46% identified as having some level of depression (dependent on which depression scale or instrument was used). Despite this large gap, our study had similar antidepressant prescription rates similar to a comprehensive geriatric assessment study of older inpatient people in Sweden, where roughly 60% of the population had some level of depression, but only 30% were prescribed anti-depressants [23]. Prescribing patterns of anti-depressants may vary, and it is possible that some clinicians despite identifying depression, may decline to prescribe anti-depressants to their older patients [24]. This could be due to some uncertainty related to questions of efficacy, or possible concerns related to other comorbidities and medications. Furthermore, there is no way to know if some of the older adults with a depression diagnosis in our study may have been reluctant to seek care or treatment. Furthermore, previously reported findings in the literature have identified that very few older adults admitted to acute hospitals are diagnosed with depression during their inpatient stays, and that opportunities for improving the mental health as well as physical health appear to be often missed [22].

Older people experiencing disorders such as depression and cognitive impairment are at a higher risk of experiencing poor quality of life, disability, increased risk for somatic disorders, and increased mortality [25]. Despite these facts, our study suggests that depression did not increase the risk for mortality. One possible interpretation is the protective impact of antidepressant therapy on mortality previously reported in the literature [26], however it should be noted that the exclusion of participants on antidepressant therapy from our analysis did not change the outcome. It is also possible that doctors

were more likely to prescribe antidepressant medication to those people who were identified as at lower risk of short-term mortality, regardless of cognitive impairment, promoting a "reverse causality". The difficult differential diagnosis between depression and cognitive impairment could further complicate the interpretation of the results. Our results highlight the complexity of the relationship between mortality, depression and cognitive impairment, suggesting the need to standardize the diagnostic methodologies for the classification of these pathologies and emphasizing the need for a holistic management of patients with these conditions.

Future studies are warranted to further explore and untangle the association of depression, cognitive impairment and mortality in older people. Such a study designed should include previous mental health history, including levels of depression and cognitive impairment, medications, therapies and ADL status, prior to, during and after hospital care to better comprehend this phenomenon.

Our study has both strengths and weaknesses. On the positive side, this study's focus was on older people requiring unplanned hospital admissions, which is an under-researched group, especially when it comes to exploring their mental health. Using the Re.Po.SI data gave us a large sample size and diverse populations, since it represents all territories of Italy. Lastly, we used multiple sources to identify both depression and cognitive impairments, which allowed more diversity in the data. Some weaknesses are our study lacks data on the participant's mental health history and duration of current depressive symptoms; it was not possible to determine whether depression was a reaction to the stress associated with acute illness and hospital admission. Additionally, we analysed antidepressants as a single class rather than as individual drugs: this approach may have masked specific effects associated with different types of antidepressants. Lastly, the sample methodology may have had falsely inflated the mortality rate. However, the sensitivity analysis conducted showed results similar to those obtained from the main analyses.

The stress of getting sick and being hospitalized can be considered an adverse condition for older people and this increases the risk of depression [27]. Due to the design of this study, we had no way of knowing what attitudes people had about their mental health conditions, and if they had negative views about receiving anti-depression treatment.

Another methodological weakness to the study is the use of different depression scales and instruments, which did not always show a statistically significant relationship to a diagnosis of depression. For example, CIRS has good validity and interrater reliability [28], and maybe useful in developing differential illness profiles associated with mortality, hospitalization, and disability. However, the data used is from self- and physician-report surveys, with archival data drawn from medical charts and facility records [29], could be subjective. Similarly while the GDS-4 [14] is one of many scales that can be used for screening depression in older adults, this scale's strength is that it is considered easier to use in people with cognitive impairment because of the simple responses (yes–no), and it can be used in hospital and community settings [15]. However, the GDS-4's clinical value is limited in assessing the severity of a person's depressive episode [14], and nearly a third of our participants had missing data for this screen. It is prudent to be mindful that depression-screening tools are only tools. Clinicians need to use person-centered care [30] approaches with personal interviews to truly understand the person behind the patient with cognitive impairment with depression, so the best clinical analysis and diagnosis can be made.

Conclusion

The risk of dying within 6 month from an acute hospitalization was similar for both older people with cognitive impairment and for those with cognitive impairment and depression. While depression alone may contribute to mortality risk, cognitive impairment appears to play a more substantial role in increasing this risk, even though older adults with depression were generally under-prescribed antidepressants. Further research is needed to confirm these findings and explore potential underlying mechanisms.

Appendix

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Abbreviations

Re.Po.SI	Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute of Pharmacological Research (Milan)
CIRS	Cumulative Illness Rating Scale (CIRS)
GDS-4	Geriatric Depression Scale (GDS-4)
BI	Barthel Index
SBT	Short Blessed Test
IQR	Interquartile ranges
vs	Versus
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ATC	Anatomical Therapeutic Chemical Classification System
ADL	Activities of daily living
N	Number
P	Probability
IR	Incidence rate
CI	Confidence intervals

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
TW and AM designed the study. TW was the primary author of the manuscript. AN and MT managed the collected the data. GB, AN, MT, AM, and AZ did the statistical analyses. TW, AM and AZ contributed to the writing and review of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and analysed during the current study using data and materials from Re.Po.SI are available from the corresponding authors on reasonable request. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made.

Declarations

Ethics approval and consent to participate
Re.Po.SI is a network of Italian internal medicine hospital wards, which, voluntarily and without any financial support, agreed to participate in data collection. Participation in the study was voluntary and all the patients signed an informed consent. The Re.Po.SI is overseen by the *Steering Committee and Institutions*:Pier Mannuccio Mannucci (Chair) (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano), Alessandro Nobili (co-chair) (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano), Giorgio Sesti (Presidente SIMI), Antonello Pietrangelo (Direttore CRIS – SIMI), Nicola Montano (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano), Antonio De Vincentis (Policlinico Universitario Campus Bio-Medico, Roma), Alessandra Marengoni (Spedali Civili di Brescia, Brescia), Mauro Tettamanti, Luca Pasina, Carlotta Franchi (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano).

Consent for publication
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The authors declare no competing interests.

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