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Essays on quality of therapy and impact of comorbidities in older hospitalized subjects.

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To my children

Marta and Gabriele

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1. Introduction

With the progressive population aging, health-care systems have to face the overwhelming challenges of older subjects, who nowadays represent the great majority of those acutely admitted to hospital wards. These patients typically present with some clinical and social peculiarities that differentiate them from younger in-patients, and that interact together and predispose to particularly ominous clinical outcomes during and also after hospital stay.[1]

First of all, they are typically characterized by the coexistence of multiple diseases whose impact on health status is well-known to be higher than the sum of the expected impact of each single pathology on its own.[2] In other words, the cumulative effect is multiplicative and synergistic, rather than additive.[3] Moreover, the clinical course and phenotypical expression is much different and heterogeneous in the context of multimorbidity. This clearly lead to a more complex clinical management, because older patients are often treated by many different specialists with poor integration between them and related proliferation of prescribed drugs (polypharmacy).[1]

Polypharmacy and multimorbidity are strictly related problems.[4] Selected medications are prescribed based on clinical trial including populations of middle aged individuals free from significant comorbidities, and their effectiveness and safety may not be confirmed in older subjects with multiple diseases.[5] Moreover, drugs prescribed for a selected disease can interact with others prescribed for other diseases (drug-drug interactions), or negatively influence the clinical course of another concomitant disease (drug-disease interaction).[6] These interactions are both pharmaco-kinetic and dynamic in nature, and they altogether often lead to clinically significant adverse drug reaction which are cause of relevant health and socio-economic problems.[7]

All these aspects are particularly impactful in older patients in presence of frailty which reduces the homeostatic response to external stressor, and expose them to high rates of physical function decline, rehospitalization and, ultimately, mortality (in-

hospital or post-discharge).[8] Increasing awareness should be promoted on these issues in order to better design tailored strategies of care able to improve health outcomes of older in-patients. Similarly, dedicated tools should be derived or improved and validated to wisely optimize drug therapy reducing its adverse events in older subjects.

With these aims, three topics were identified as deserving further investigation given the current state-of-the-art in scientific literature.

1. DRUG-DRUG INTERACTION (DDI). Alterations in the pharmacokinetic process (drug absorption, distribution, metabolism or excretion) can result in changed serum drug concentration and possible different clinical response. The most frequent pharmacokinetic DDIs involve several isoenzymes of the hepatic cytochrome P450 (CYP) and drug transporters such as P-glycoprotein (P-gp).[9, 10] CYP3A4 is one of the most important as it is involved in the metabolism of a wide range of commonly used drugs, such as statins, antibiotics, and antiarrhythmic agents. Since there are no systematic data about the prevalence and pathways of interactions associated with CYP3A4 and P-gp in real-life hospitalized older people, this topic is aimed at assessing which are the most prevalent interactions involving CYP3A4 or P-gp pathways observed at admission, during hospitalization and at discharge in older patients.

2. TOOLS FOR OPTIMIZING DRUG THERAPY. Many tools have been developed to improve the quality of therapy by reducing the prescription of potentially inappropriate medications (PIMs) and potential DDIs. Explicit different lists of PIMs (as provided for example by Beers' and STOPP criteria) have been suggested to be best avoided by older adults in most circumstances or in presence of specific diseases.[11, 12] Specific scales have been designed to grade the total anticholinergic burden of a therapy and allow its pre-emptive modulation in order to reduce related possible adverse health events.[13] Electronic prescription software have been made available to favour an easy and fast medication review with respect to severe DDIs. Since no consistent data is currently available, the present topic is aimed at evaluating the association of a large panel of therapy quality indicators, including explicit lists of PIMs, DDI and anticholinergic burden scale, with re-hospitalization, physical function decline and mortality within 3 months from hospital discharge in hospitalized older patients.

3. IMPACT OF COMORBIDITIES. In the context of multimorbidity, congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are among the most prevalent diseases in older in-patients, and a bulk of literature is already available on their impact in this scenario.[14– 16] While less frequent, liver cirrhosis is expected to confer an at least comparable impact on health status.[17] Since data are scares, this topic is aimed at specifically investigating the prevalence, main clinical characteristics, prognostic impact, and phenotypic profiles of patients with liver cirrhosis among older in-patients

These three topics were investigated exploiting data from the REPOSI registry.

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2. Drug-drug interactions involving CYP3A4 and P-glycoprotein in hospitalized elderly patients.


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Original article

Drug–drug interactions involving CYP3A4 and p-glycoprotein in hospitalized elderly patients

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Abstract

Polypharmacy is very common in older patients and may be associated with drug-drug interactions. Hepatic cytochrome P450 (notably 3A4 subtype, CYP3A4) is a key enzyme which metabolizes most drugs; P-glycoprotein (P-gp) is a transporter which significantly influences distribution and bioavailability of many drugs. In this study, we assess the prevalence and patterns of potential interactions observed in an hospitalized older cohort (Registro Politerapia Società Italiana di Medicina Interna-REPOSI) exposed to at least two interacting drugs involving CYP3A4 and P-gp at admission, during hospitalization and at discharge. Individuals aged 65 and older (N= 4039; mean age 79.2; male 48.1%), hospitalized between 2010 and 2016, were selected. The most common combinations of interacting drugs (relative frequency of more than 5%) and socio-demographic and clinical factors associated with the interactions were reported. The prevalence of interactions for CYP3A4 was 7.9% on admission, 10.3% during the stay and 10.7% at discharge; the corresponding figures for P-gp interactions were 2.2%, 3.8% and 3.8%. The most frequent interactions were amiodarone-statin for CYP3A4 and atorvastatin-verapamil-diltiazem for P-gp. The

prevalence of some interactions, mainly those involving cardiovascular drugs, decreased at discharge, whereas that of others, e.g. those involving neuropsychiatric drugs, increased. The strongest factor associated with interactions was polypharmacy (OR 6.7, 95% CI 5.0-9.2). In conclusion, hospital admission is associated with an increased prevalence, but also a changing pattern of interactions concerning CYP3A4 and P-gp in elderly. Educational strategies and appropriate use of dedicated software seem desirable to limit drug interactions and the inherent risk of adverse events in older patients.

Introduction

Polypharmacy is very common in older population and is a major risk factor for inappropriate prescriptions, inadequate compliance, adverse drug events and worse clinical outcomes [1]. Adverse drug reactions (ADRs) are an important cause of morbidity and mortality, responsible for up to 6-7% of hospital admissions with a significant impact on healthcare costs [2-3]. The risk of serious ADRs increases linearly with age and is estimated at around 40% and more in patients aged 85 or older [4]. Among ADRs, those derived from drug-drug interactions (DDIs) can be prevented with appropriate prescribing [5].

In Italy the highest prevalence of drug consumption is ascribable to the population aged 65 years or more [4]. Therefore, this population is at highest risk of potential DDI and ADRs. Beside polypharmacy, this risk is also increased in older patients because of age-related changes in hepatic/renal metabolism and overall pharmacokinetic and pharmacodynamic processes [6], comorbidities and multiple prescribers [7-8].

The prevalence of DDIs in older hospitalized people has been reported to be as high as 45% [7] and has been associated with the length of hospital stay [9]. However, an extensive picture of this phenomenon is lacking because published studies are very heterogeneous in terms of population, settings, DDIs considered and databases used [9, 10-11].

DDIs can be pharmacokinetic or pharmacodynamic in nature [12]. Alterations in the pharmacokinetic process involve the influence of one drug on the absorption, distribution, metabolism or excretion of another drug, resulting in changed serum drug concentration and possible different clinical response. The most frequent

pharmacokinetic DDIs involve several isoenzymes of the hepatic cytochrome P450 (CYP) and drug transporters such as P-glycoprotein (P-gp) [13-14]. CYPs are the major enzymes involved in drug metabolism, accounting for about 75% of the total processes [15] and are a major source of adverse drug reactions. P-gp is extensively distributed and expressed in the body and is a well-characterized ATP-binding cassette-transporter [16] which influences the efficacy of drugs regulating their distribution and bioavailability.

Of the several different CYP enzymes, CYP3A4 is one of the most important as it is involved in the metabolism of a wide range of commonly used drugs, such as statins, antibiotics, and antiarrhythmic agents. Additionally, some studies described a significant reduction in activity of this enzyme with ageing [17] and chronic kidney disease, a common condition in older people, seems to affect its activity through direct inhibition by circulating toxins and through epigenetic modulation [18].

The effect of ageing on P-gp function is not completely understood. There is evidence both in vitro and in vivo that expression and function of P-gp in lymphocytes increases over time [16-19]. A study of duodenal P-gp activity in older and younger patients suggested no appreciable difference in P-gp activity [20] while another report involving a P-gp substrate (verapamil) showed decreased P-gp activity in the blood-brain barriers of older subjects [21], which could indicate that the aging brain is at higher risk of drug exposure. The risk of toxicity related to alterations in P-gp expression in other tissues is as yet unknown. Therefore, a changed expression of this protein with advancing age may be responsible of unexpected clinical effects in the elderly. Finally, it is worth considering that P-gp and CYP3A4 share several substrates and inhibitors [14].

Since there are no systematic data about the prevalence and pathways of interactions associated with CYP3A4 and P-gp in real-life hospitalized older people, we purposed to assess which are the most prevalent interactions involving CYP3A4 or P-gp pathways observed at admission, during hospitalization and at discharge in older patients enrolled in the REPOSI study.

Methods

We extracted data from a database employed by internal and geriatric medical wards participating in the "Registro Politerapia SIMI (Società Italiana di Medicina Interna) (REPOSI)", which is a register including hospitalized patients aged 65 years or more and organized by the Italian Society of Internal medicine (SIMI), by the Istituto di Ricovero e Cura a Carattere Scientifico - IRCCS Istituto di Ricerche Farmacologiche "Mario Negri" and IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, both in Milan. The collection of data occurred every 2 years between 2008 and 2014, since 2015 data collection has become annual. The study design is described in details elsewhere [22].

Enrollment lasted for one week each quarter, for a total of 4 weeks/year, and was repeated from 2010 to 2016. All patients admitted to the 107 Italian wards participating to the study during the enrollment periods were consecutively recruited. All the data were revised by a central monitor at the IRCCS-Mario Negri Institute. The study was approved by the Ethical Committee of the IRCCS Cà Granda Maggiore, Policlinico Hospital Foundations in Milan, as well as by the local Ethical Committees of the participating centers.

From the full database of 4713 patients, 443 were excluded because they were transferred to another ward or discharged in critical conditions, 196 because they died during hospitalization, 167 and 104 because of lack of information on discharge and admission therapy, respectively. The final sample size was 3803. All drugs taken at hospital admission, during hospital stay and prescribed at discharge were recorded in a standardized web-based database by the attending physicians and were encoded according to the Anatomical Therapeutic Chemical classification system (ATC) [23]. All drug interactions involving CYP3A4 isoenzymes and P-gp (Supplementary Material) were identified in accordance with the classification proposed by the FDA and by other sources mostly focused on statins [24-26] and analytically reported at admission, during hospital stay and at discharge. Other clinical and demographic characteristics were retrieved. Comorbidities were reported according to the Cumulative Illness Rating Scale (CIRS) [27]. Disability was defined as a Barthel Index scale ≤ 90 [28], cognitive impairment as a Short Blessed Test ≥ 10 [29] and depression

as a Geriatric Depression Scale (≥ 2) according to the short version by Hickie and Snowdon [30].

We reported general characteristics of the study population as means and standard deviations (SD) or percentages, as appropriate. The number of patients with CYP3A4 and P-gp interactions was calculated at hospital admission, during hospital stay and at discharge, as absolute numbers and percentages. The most common combinations of interacting drugs were extracted as those having a relative frequency of more than 5%. The relative change from admission to discharge of each interacting medication was also presented. A sub-analysis in patients who died during hospitalization (n 196) was conducted, as well.

Finally, the prevalence of simultaneous administration of more than 1 substrate of CYP3A4 or more than one substrate of P-gp was calculated and factors associated with the presence of interaction at admission and discharge was evaluated computing odds ratios (OR) with 95% confidence intervals (CI) for the principal socio-demographic and clinical features. Continuous variables were dichotomized to present the risk of interactions in categories of patients potentially at higher risk (e.g., older, disabled, etc.), because this information may be more useful for the practicing clinician. Multivariable models were fitted including potential confounders. All analyses were performed using R 3.3.3 software for Mac (R Foundation for Statistical Computing, Vienna, Austria).

Results

Main characteristics of the study population

The general characteristics of the study population are reported in Table 1 (panel A). Mean age was 79.3 (SD: 7.5) and men were 48.1%. The median CIRS Severity Index and Comorbidity Index were 1.7 (SD: 0.3) and 3.1 (SD: 1.9), respectively. At admission 47% of patients showed disability while 42.5% presented cognitive impairment. Depressive symptoms were observed in 40.9% of patients. The average length of hospital stay was 10.4 (SD: 5.8) days.

Table 1. General characteristics of study population (panel A) and CYP3A4 or P-gp interactions and drugs involved (panel B).

PANEL A						
Variable						
N	3803					
Age (years), mean (SD)	79.3 (7.5)					
Sex (male), n (%)	1831 (48.1%)					
BMI (Kg/m^2)	26.2 (5.3)					
Disability at admission (Barthel Index<= 90), n (%)	1771 (47.1%)					
Cognitive impairment (Short Blessed Test >= 10), n (%)	1502 (42.9%)					
Depressive symptoms (Geriatric depression scale >= 2), n (%)	1346 (41.3%)					
CIRS Severity Index	1.7 (0.3)					
CIRS Comorbidity Index	3.1 (1.9)					
Length of hospital stay (days)	10.4 (5.8)					
PANEL B						
	Admission		**Inhospital**		**Discharge**	
	n	**%**	**n**	**%**	**n**	**%**
Total subjects	3803		3533		3803	
Subjects with CYP3A4 interactions	299	7.9	363	10.3	408	10.7
Subjects with P-gp interactions	82	2.2	135	3.8	144	3.8
Mean number (SD) of drugs per subject	5.8 (2.9)		8.3 (5.1)		8.5 (4.3)	
Subjects with 2 or more CYP interactions	69	1.8	121	3.4	113	3.0
Subjects with 2 or more P-gp interactions	17	0.4	32	0.9	32	0.8

CYP450 3A4 or P-gp interactions and drugs involved

As reported in Table 1 (panel B), 299 (7.9%) and 82 (2.2%) patients had at least a CYP3A4 or P-gp interaction at admission, respectively. Of these, 69 (23.1%) and 17 (20.7%) presented 2 or more CYP3A4 or P-gp interactions. During hospitalization, we observed an increasing mean number of medications per patient (5.8, 8.3 and 8.5 at admission, in-hospital and at discharge) along with an increased prevalence of

interactions (10.3% and 10.7% for CYP3A4 and 3.8% and 3.8% for P-gp in-hospital and at discharge, respectively).

The drugs most frequently involved in interactions at admission (Figure 1) were proton pump inhibitors and cardiovascular drugs (statins, amiodarone, verapamil, diltiazem and amlodipine for CYP3A4 and verapamil, diltiazem, omeprazole, amiodarone, atorvastatin and carvedilol for P-gp), followed by antidepressants/antipsychotics (paroxetine and sertraline, venlafaxine, haloperidol for CYP3A4 and venlafaxine and haloperidol for P-gp). The most commonly observed interactions (Table 2) were amiodarone-statin for CYP3A4 (15.5%) and atorvastatin-verapamil-diltiazem for P-gp (22.9%). To note, most of these drugs were at the same time involved in CYP3A4 and P-gp pathways.

A qualitative difference in drugs involved at discharge vs. admission was found (Figure 2) with a decreased prescription of statins, calcium channel blockers (verapamil, diltiazem), amiodarone and cyclosporine, and an increased prescription of other medications such as dexamethasone, fentanyl, haloperidol, omeprazole.

Similar results were observed in patients died during hospitalization (Supplementary Materials) in which a slight increased prevalence of interactions was consistent with an increased number of prescriptions for patient.

Factors associated with the presence of interactions at admission were higher BMI (OR 1.3, 95% CI 1.0-1.7), disability (OR 1.4, 95% CI 1.1-1.7), depressive symptoms (OR 1.3, 95% CI 1.0-1.6) and burden of comorbidity (OR 2.3, 95% CI 1.8-2.9 and OR 2.2, 95% CI 1.8-2.8 for CIRS-SI and -CI, respectively) (Table 3). Accordingly, depressive symptoms (OR 1.3, 95% CI 1.1-1.6) and burden of comorbidities (OR 1.8, 95% CI 1.5-2.2 and OR 1.7, 95% CI 1.4-2.1 for CIRS-SI and -CI, respectively), together with the length of hospital stay (OR 1.6, 95% CI 1.3-2.0), were associated with the presence of interactions at discharge. However, the strongest associated factor was the number of prescribed medications (OR 6.7, 95% CI 5.0-9.2 at admission and OR 4.1, 95% CI 3.3-5.1 at discharge), that remained associated also in adjusted model (aOR 5.01, 95% CI 3.39-7.59 at admission and aOR 2.65, 95% CI 2.02-3.49 at discharge), together with the length of hospital stay (aOR 1.33, 95% CI 1.05-1.69).

Table 1. CYP450 3A4 or P-gp most common (> 5%) interactions and drugs involved.

	At admission	n	%	In-hospital	n	%	At discharge	n	%
CYP450									
1	**Amiodarone** - Statin	49	16.3	**Amiodarone** - Statin	45	12.4	**Amiodarone** - Statin	58	14.2
2	**Verapamil/Diltiazem** – Statin	34	11.3	**Verapamil/Diltiazem** – Statin	28	7.7	**Verapamil/Diltiazem** – Statin	29	7.1
3	**Sertraline** – Statin	17	5.6	**Sertraline** – Statin	20	5.5	**Sertraline** – Statin	22	5.4
4	Paroxetine - Statin	16	5.3						
5									
P-gp									
1	Atorvastatin – **Verapamil/Diltiazem**	20	24.4	Atorvastatin – **Verapamil/Diltiazem**	16	11.8	Atorvastatin – **Verapamil/Diltiazem**	19	13.2
2	Omeprazole – **Verapamil/Diltiazem**	14	17.1	Omeprazole – **Verapamil/Diltiazem**	13	9.6	Omeprazole – **Verapamil/Diltiazem**	16	11.1
3	**Haloperidol** - Omeprazole	6	7.3	**Haloperidol** - Omeprazole	11	8.1	**Haloperidol** - Omeprazole	11	7.6
4				**Dexametason** - Omeprazole	11	8.1	**Dexametason** - Omeprazole	11	7.6
5				Amiodarone – **Verapamil/Diltiazem**	10	7.4			

In bold *Combined CYP3A4 and P-gp substrates, inhibitors and inducers.*

Table 2. Prevalence of and risk factors for CYP450 3A4 and P-gp interactions at admission and at discharge.

	Patients with interactions at admission (%)				Patients with interactions at discharge (%)			
Variable	*No*	*Yes*	*OR (95%CI)*	*aOR (95%CI)*	*No*	*Yes*	*OR (95%CI)*	*aOR (95%CI)*
Age > 79.2	8.5	9	*1.07 (0.86-1.34)*	1.03 (0.77-1.37)	11.5	13	*1.16 (0.95-1.40)*	*1.11 (0.87-1.42)*
Sex (male)	8.5	9.1	*1.08 (0.87-1.35)*	1.13 (0.86-1.50)	12.7	11.7	*0.91 (0.75-1.10)*	*0.88 (0.69-1.12)*
BMI >26.1	7.5	9.6	*1.30 (1.03-1.66)*	1.10 (0.83-1.45)	12.3	11.8	*0.96 (0.78-1.18)*	*0.82 (0.64-1.04)*
Disability at admission (Barthel Index<= 90)	7.5	10.2	*1.39*	1.03	11.4	13.2	*1.18*	*0.97*

			(1.12-1.74)	(0.76-1.39)			*(0.98-1.44)*	*(0.75-1.26)*
Cognitive impairment (Short Blessed Test >= 10)	8.3	8.7	*1.05 (0.83-1-33)*	0.92 (0.68-1.23)	11.4	12.9	*1.15 (0.94-1.40)*	*1.12 (0.87-1.44)*
Depressive symptoms (Geriatric depression scale >= 2)	8	10.1	*1.30 (1.02-1.64)*	0.99 (0.74-1.32)	11.3	14.1	*1.28 (1.05-1.58)*	*1.04 (0.81-1.33)*
CIRS Severity Index >1.7	5.7	12.1	*2.26 (1.80-2.87)*	1.25 (0.92-1.71)	9.3	15.5	*1.79 (1.47-2.18)*	*1.06 (0.82-1.38)*
CIRS Comorbidity Index >3	6.3	12.9	*2.20 (1.75-2.75)*	-	9.9	16.1	*1.74 (1.44-2.13)*	-
Days of hospital stay >10	7.5	10.8	*1.48 (1.18-1.86)*	1.15 (0.87-1.53)	10	15.2	*1.61 (1.32-1.96)*	*1.33 (1.05-1.69)*
N drugs at admission >6	2.6	15.1	*6.70 (4.98-9.18)*	5.01 (3.39-7.59)	7.3	17.7	*2.73 (2.22-3.38)*	*1.65 (1.25-2.20)*
N drugs at discharge >8	4.9	13.9	*3.12 (2.46-3.98)*	1.56 (1.14-2.13)	6	20.8	*4.11 (3.34-5.09)*	*2.65 (2.02-3.49)*

Continuous variables have been dichotomized below or above their mean value.
aOR adjusted for all the variables in the table, except for CIRS Comorbidity Index (removed for collinearity with CIRS Severity Index).

Figure 1. Drugs involved in CYP450 3A4 (upper panel) and P-gp (lower panel) interaction at admission, in-hospital or discharge.

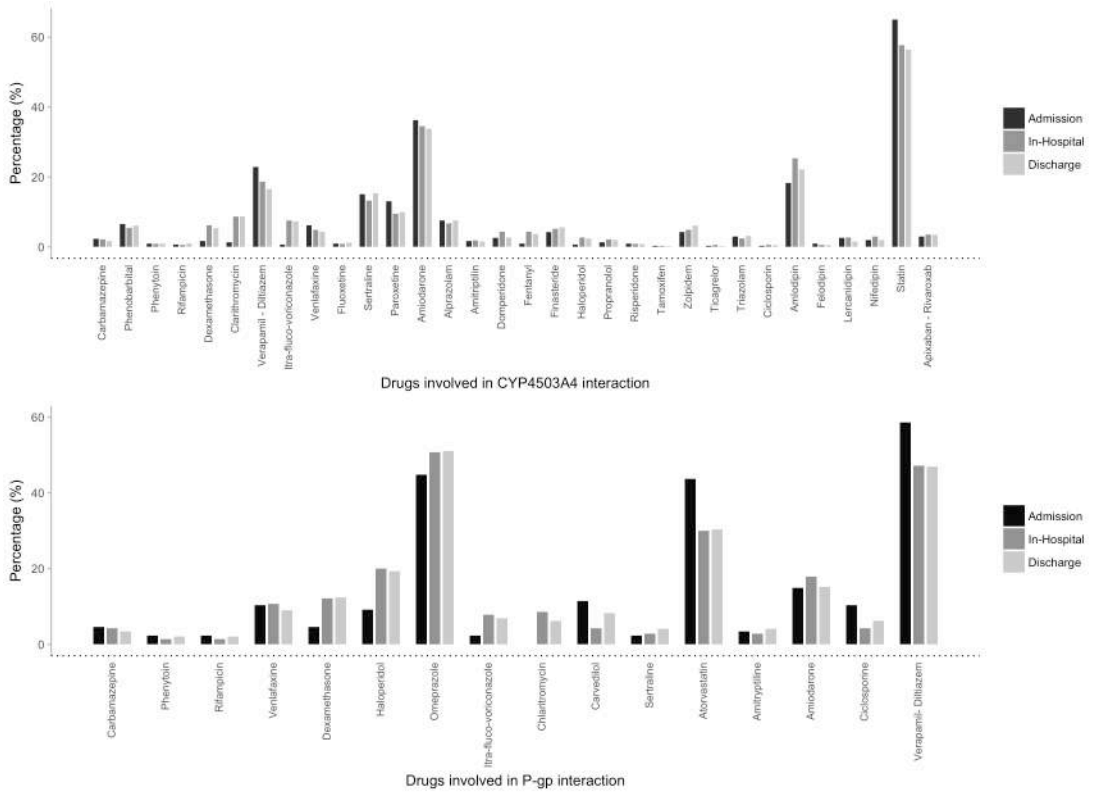
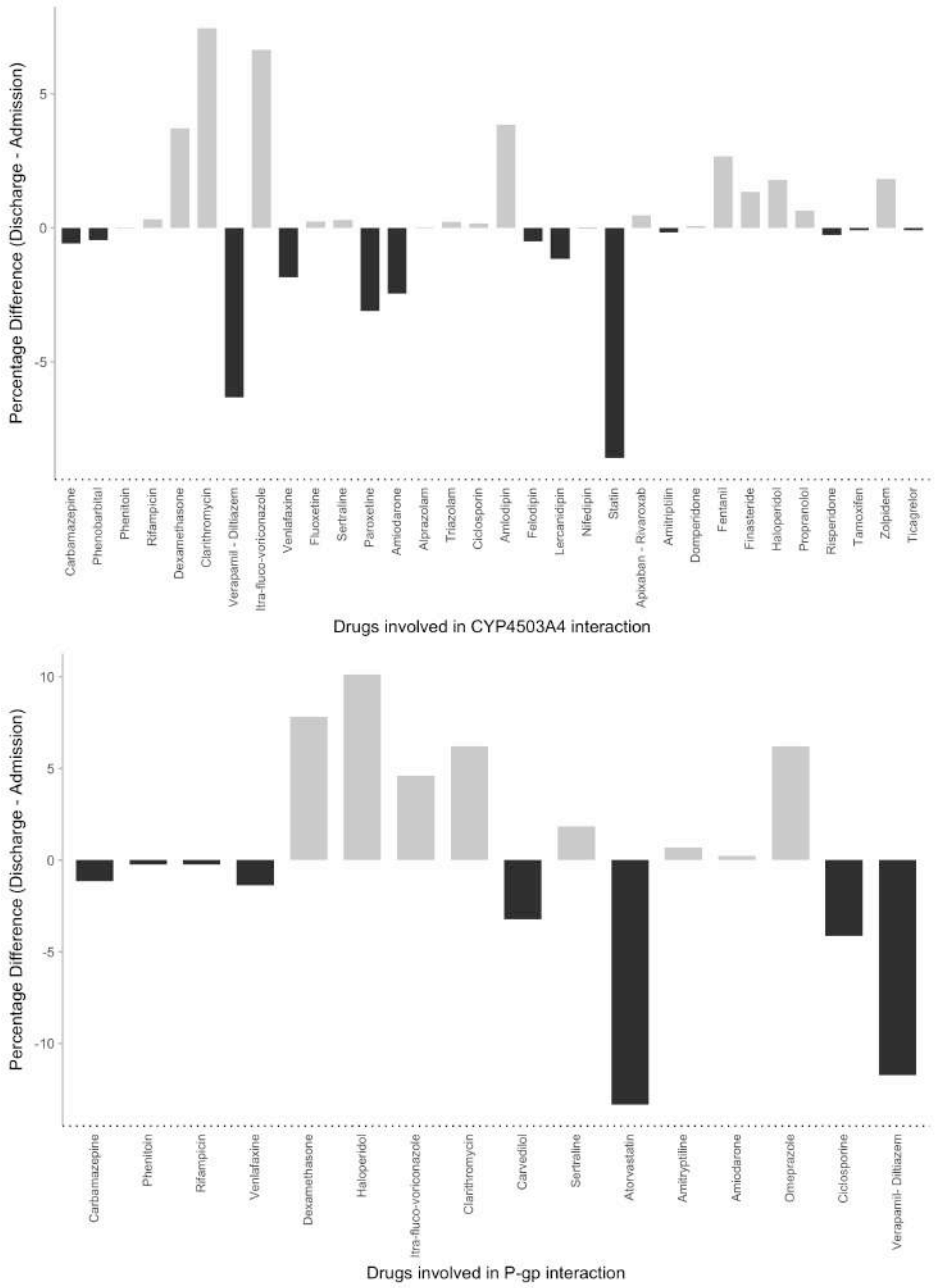


Figure 2. Percentage difference between discharge vs admission, in drugs involved in CYP450 3A4 (upper panel) and P-gp (lower panel) interaction.



Discussion

In this study, the prevalence of interactions involving CYP3A4 and P-gp increases during hospitalization and at discharge, rising from 7.9% at admission to 10.3% at

discharge for CYP3A4 and from 2.2% to 3.8% for P-gp. Consistently with previous studies [31-32], the strongest factor associated with interactions was polypharmacy.

As expected, drugs most frequently responsible for interactions are those widely used in primary care and in older people such as cardiovascular, antidepressant and antipsychotic ones. Moreover, omeprazole surprises for the frequency of interactions involving P-gp. As it is one of the PPI more inappropriately prescribed in older population [33], this information is of a great concern for clinicians who should be more aware of the high risk of drug-interactions associated to long-term and often inappropriate use of these drugs [34].

Although a greater number of interactions is observed throughout hospitalization and at discharge compared to admission, also a qualitative difference in drugs involved was found. While selected potential interactions, e. g. for cardiovascular drugs, decreased during hospital stay, others involving other drugs, such as neuropsychiatric ones, increased during hospital stay and discharge (for example, haloperidol). This finding seems to be important because REPOSI is focused on older patients who are at higher risk of clinically relevant adverse events associated to these interactions. This information is in keeping with what was reported in another study where critical potential DDIs involving CYP3A4 and psychotropic agents were found to be up to 11 % in an older population admitted to psychiatric wards [35]. Compared to interactions at admission, interactions at discharge more commonly involved drugs that are taken only for a definite period (such as antibiotics, etc.); thus, the prevalence of DDIs for these drugs is expected to decrease to some extent over time.

Anyhow, it should be noted that although reduced at discharge, the frequency of DDIs involving cardiovascular drugs remains sizeable. For example, DDIs more frequently observed were amiodarone-statin for CYP3A4 and atorvastatin-verapamil/diltiazem for P-gp, both at admission and discharge. These combinations may result in an increase of side effects or toxicity of statins (myalgia, myopathy, hepatotoxicity) [36] and nondihydropyridine calcium channel blockers (hypotension, bradycardia, constipation). To point out the clinical relevance of these interactions, for example, we have to consider that the risk for rhabdomyolysis in patients treated with a statin without DDI has been estimated to be in the range of 1:10000 patients/year [37]. This risk increases approximately by a factor of ten (to 1:1000 patients/year)

when a CYP3A4-inhibitor is co-administered [38]. Therefore, for instance, in the case of macrolide antibiotics or azole fungicides, which are usually used for a finite period, it seems logical to stop statins or other drugs metabolized by CYP3A4 during treatment. Finally, it has to be noted that most of these drugs are at the same time involved in CYP3A4 and P-gp pathways, making the final result even more unpredictable. For instance, azoles are strong CYP3A4 and P-gp inhibitors, clarithromycin is a strong CYP3A4 inhibitor, but a weak P-gp inhibitor, while verapamil is a weak CYP3A4 inhibitor, but a strong P-gp inhibitor.

Many studies have shown the association between hospitalization and drug interactions in different and heterogeneous settings [1,9,31,39], using a clinical classification of DDIs and, at variance with our study, extensively exploring all major pharmacological pathways of interactions, not only CYP3A4 and P-gp. The mean reported prevalence of at least one DDIs in the older population was up to 46% [40] and Bjerrum et al showed a risk linearly increased with age, raising from 24% in individuals aged 60-79 years to 36% in those over 80 [41]. Other studies reported data on CYP-mediated DDIs and described a prevalence of potential interactions from 68% to 80% [35, 42-43], significantly higher than that reported in our study, but authors included all CYPs in the analysis and a multidrug software were used to detect interactions. Conversely, our data are partially comparable to those reported in studies conducted selectively on CYP3A4, analyzing co-prescription of statins with CYP3A4 inhibitors. These studies showed that approximately 6-9% of patients exposed to a statins metabolized from CYP3A4 had a concomitant inhibitor [44] while a study conducted in UK primary care population showed an inappropriate co-prescription in 11% of patients [45]. These data, however, were extracted from the general population and not applicable to hospitalized older people. Conversely, our data shed light more broadly on all drugs involved in interactions with the above-mentioned pathways in the hospitalized patients, confirming the general trend observed in other studies with statins but also showing the evolution of prescriptive pattern during hospitalization.

We could not compare our data regarding P-gp associated interactions in the older with other series because there is a distinct lack of information on this topic in older people. Indeed, the only evidence pertains to preclinical studies which showed a

changed expression of this protein with advancing age, possibly responsible of a different exposure to drugs in the different tissues [46].

Many guidelines and indicators have been developed to guide and evaluate the quality of prescriptions in the older population. Explicit criteria developed to address inappropriate polypharmacy and widely used, for instance, are Beers' Criteria, STOPP/START criteria (the Screening Tool of Older Persons potentially inappropriate Prescriptions and the Screening Tool to Alert doctors to the Right Treatment) and FORTA (Fit fOR The Aged) criteria. Moreover, to reduce DDIs and associated adverse events, many drug interaction software programs have been developed, ranging from computerized prescription support systems such as INTER-check [47-48] to some cytochrome-specific multidrug analysis software [42-43]. These programs could decrease the frequency of hazardous DDIs up to 67.5% [49]. The prevalence of inappropriate prescriptions at discharge was significantly reduced also by reviewing medications with INTERcheck [48]. However, up to 33% of relevant DDI were not recognized by computer softwares [50], and numerous alerts of insignificant DDIs might lead the clinicians to ignore the instrument. Thus, these software have many limitations and careful clinical judgement is mandatory to prevent or detect DDIs.

The strength of our study is the real-life setting and the representative sample of older in-patients in medical wards in Italy. Furthermore, our study could assess the changing prevalence of DDI starting from clinical practice throughout the stay in the acute care ward up to discharge. On the other hand, limitations include our lack of information about adverse clinical events and outcomes for patients with DDIs that make difficult to estimate the clinical relevance of potentially interacting drug combination at discharge and the relationship between drug interaction and adverse drug reactions. Even if this was not among the aims of the study, a sub-analysis was conducted in the 196 patients who died during hospitalization and, as such, were excluded from the main analysis. A prevalence of 9.1% and 2.5% of patients with CYP3A4 and Pgp interactions was found, that, to note, was not significantly different from that observed in patients discharged at home (7.9% for CYP3A4 and 9.1% for P-gp), testifying to the absence of any association between the presence of CYP3A4 and Pgp interactions and in-hospital mortality. Unfortunately, ADRs secondary to

pharmacokinetic DDIs are less easily recognizable than, for instance, the ADRs following a hypoglycemic drug. It may be easy to identify ADRs to a statin or haloperidol, but whether and to which extent they reflect a DDI remains uncertain and rarely investigated. Thus, only "straightforward" ADRs are commonly reported among the admission diagnoses. Finally, another associated limitation of our study is the lack of information about the dosage and the duration of therapy that, undoubtedly, influence the clinical relevance of interaction. This study shows that hospital admission is associated with an increased prevalence of interactions involving CYP3A4 and P-gp in older patients. Moreover, during hospital stay and at discharge, an increased prevalence of interactions involving selected drug categories, such as neuropsychiatric ones, was observed. This finding is disturbing because decreased homeostatic reserve, comorbidity and polypharmacy make the older at special risk of ADRs from DDIs. Thus, the judicious clinician has to make all efforts to prevent or limit potential interactions. Educational strategies are desirable to increase awareness and vigilance about DDIs and related risks.

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3. Potentially inappropriate medications, drug-drug interactions and anticholinergic burden in elderly hospitalized patients: does an association exist with post-discharge health outcomes?

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SHORT COMMUNICATION

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Potentially Inappropriate Medications, Drug–Drug Interactions, and Anticholinergic Burden in Elderly Hospitalized Patients: Does an Association Exist with Post-Discharge Health Outcomes?

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Abstract

Introduction. Polypharmacy is very common in elderly patients and it is associated with detrimental outcomes.

Objective. To evaluate the association of a large panel of therapy quality indicators, including explicit lists of potentially inappropriate medications (PIMs; Beers' and STOPP criteria), the Anticholinergic Cognitive Burden (ACB) score and the number

of drug-drug interactions, with respect of mortality, re-hospitalization and physical function decline within 3 months from hospital discharge in a cohort of hospitalized elderly patients.

Methods. We studied 2631 individuals aged≥65 (median age 79.6; male 48.6%) enrolled in the REPOSI registry. The relationships with mortality and rehospitalization were evaluated through Cox regressions, while those with functional status change (as percentage variation of Barthel Index -BI-) through mixed linear model.

Results. None of the studied indicators was found associated with mortality and rehospitalization. Conversely, only ACB was associated with physical function decline, even after correction for confounders (adjusted(a-) mean BI variation of -7.55%, 95%CI -12.37 - -2.47). The number of medications at discharge and, even more, polypharmacy (>5 drugs daily) were the only therapy-related factors associated with mortality (a-hazard ratio-HR- 1.05, 95%CI 1.01-1.10 and 1.70, 95%CI 1.12-2.58, respectively) and rehospitalization (a-HR 1.05, 95%CI 1.01-1.08 and 1.31, 95%CI 1.01-1.71, respectively).

Conclusion. Polypharmacy, a very simple measure, outperformed sophisticated PIM and DDI indicators of quality of the therapy as a correlate of primary clinical outcomes, while ACB associated with physical function decline. Thus, innovative approaches to the definition and research of PIM and DDI are eagerly awaited in the perspective of averaging the quantitative burden and qualitative interaction of drugs.

Introduction

Polypharmacy, a very common condition in older hospitalized people, is associated with an increased risk of adverse drug reactions and with several negative outcomes, including longer length of stay, hospital readmission, and mortality.[1–3]

Additionally, the risk of adverse events is increased in presence of potentially inappropriate medications (PIMs) or drug-drug interactions (DDIs). PIMs can be defined as drugs potentially harming more than benefiting elderly subjects due to their pharmacological effect or related adverse events[4]. A class of PIMs of particular importance in older people are anticholinergic drugs, because older patients are generally more susceptible to acetylcholine blockage[5] and may experience higher rates of falls and of cognitive or physical function decline.[6,7]. Moreover elderly

population is at the highest risk of DDIs.[8,9] Beside polypharmacy, this risk is increased because of age-related physiological changes affecting the pharmacokinetics and pharmacodynamics processes.[10]

Many tools have been developed to improve the quality of therapy by reducing the prescription of PIMs and potential DDIs . Explicit different lists of PIMs (as provided for example by Beers' and STOPP criteria) have been suggested to be best avoided by older adults in most circumstances or in presence of specific diseases.[11,12] With respect to anticholinergic drugs, specific scales have been designed to grade the total "anticholinergic burden" of a therapy and allow its pre-emptive modulation in order to reduce related possible adverse health events. The Anticholinergic Cognitive Burden (ACB) score is one of the most currently used and is based on the sum of the anticholinergic effect of each medication, scored as 1, 2 or 3 according to the evidence for their effective antagonist activity at muscarinic receptor.[13]

A similar approach is unfeasible for DDI, and electronic prescription software have been made available to favour an easy and fast medication review with respect to severe DDIs.

Whereas many efforts have been done to identify strategies for reducing polypharmacy and driving deprescribing in clinical practice, the prevalence of DDIs or PIMs and the related risk of adverse clinical outcomes vary significantly across available studies. Beers were found associated with many clinical events,[14–16] but not with disability, mortality and rehospitalization.[17–22] Similarly, no association was evidenced between STOPP and hospitalization and death in community-dwelling and hospitalized elderly individuals,[20,21,23,24] but selected studies reported STOPP to be related to avoidable hospitalizations.[23,25,26] While consistently linked to loss of physical independence,[6,7,27–29] more controversial is the relation of ACB with mortality.[30–35] Finally, the clinical impact of DDI in real life setting has been scantly explored and needs to be more adequately disclosed.[9,36] All in all, these apparently conflicting findings testifies to the great heterogeneity of analysed cohorts, clinical scenarios (community dwelling, in-hospital or post-discharge), considered outcomes and information source used. Indeed, in-hospital adverse events are more likely related to the severity of the pathologic condition leading to hospitalization than to PIM or DDI, which in critical conditions only to some extent are avoidable.

Conversely, inappropriate prescribing may more probably impact post-discharge health outcomes, determining premature rehospitalizations, loss of independence and, ultimately, death. Therefore, the present study is aimed at evaluating the association of a large panel of therapy quality indicators, including explicit lists of PIMs, DDI and anticholinergic burden scale, with re-hospitalization, physical function decline and mortality within 3 months from hospital discharge in a cohort of hospitalized elderly patients.

Patients and methods

Data source

We used data from "Registro Politerapia Società Italiana di Medicina Interna" (REPOSI), including patients aged 65 years or more hospitalized in 107 Italian medical wards and organized by the Italian Society of Internal Medicine (SIMI) together with the Istituto di Ricerche Farmacologiche "Mario Negri" and the Fondazione Ca' Granda Ospedale Maggiore Policlinico, both in Milan. The study design is described in details elsewhere.[37] Enrollment lasted for one week each quarter, for a total of 4 weeks/year, and was repeated from 2010 to 2016. The study was approved by the Ethical Committee of the organizing centres, as well as by the local Ethical Committees of the participating hospitals. From the full database of 4713 patients aged 65 years or more, subjects discharged at home were selected (N 3788). Of these, 1157 were lost at 3-month follow-up. The final sample size was 2631. All drugs prescribed at discharge were recorded in a standardized web-based database by the attending physicians and were encoded according to the Anatomical Therapeutic Chemical classification system (ATC).[38] Similarly, other clinical and demographic characteristics were registered and accessible. Comorbidities were reported according to the Cumulative Illness Rating Scale (CIRS).[39] Barthel Index (BI) was measured in all patients once a clinically stable condition was reached during hospitalization. Disability was defined as a BI scale ≤ 90,[40] cognitive impairment as a Short Blessed Test ≥ 10 [41] and depression as a Geriatric Depression Scale (≥ 2) according to the short version by Hickie and Snowdon.[42] After hospital discharge, participants were followed up after 3 months by a phone call. Vital status, occurrence of rehospitalization were verified and BI was repeated.

Exposure to potentially inappropriate medications (PIMs), drug-drug interactions (DDIs) and polypharmacy

The exposure to PIMs or DDIs was verified using discharge medical documentation and medication list. PIMs were evaluated according to diagnosis-independent 2019 Beers' criteria,[11] STOPP criteria,[12] and with respect to the anticholinergic load with the ACB score.[13] STOPP criteria evaluating appropriateness according to evidence-based principles (A1), time of exposure to specific drugs (A2, C8-9, D5, F2, H3-4-6), prescription as first line therapy (A5-6-10, D2-12) and dosage (C1, E1, F4) were not analyzed because of lack of the required information. Therefore, 63 out of 80 STOPP criteria were analyzed. When referring to anticholinergic drugs (generic, without specifying the intended pharmaceutical products), STOPP criteria were approached considering only anticholinergic agents for Parkinson disease (ATC codes N04A including N04AA, N04AB, N04AC). Notably, other medications with known anticholinergic effect (neuroleptics and tricyclic antidepressant) are already addressed by other STOPP violations. DDIs were identified according to two different methodology. The first takes into account all possible DDIs potentially leading to severe clinical consequences, based on pharmaco-kinetic or dynamic principles, by means of a computerized system (INTERcheck®)[43] using the Italian interaction database, an electronic version of an Italian textbook of clinical pharmacology.[44] DDIs were defined as "potentially severe" if the specific drug combination should usually be avoided as it may lead to serious clinical consequences, such as severe adverse effects or lack of clinical effects, and close monitoring is required.[43] The second method is principally aimed at detecting pharmacokinetic DDIs on CYP3A4 and P-gp enzymes (henceforth defined pk-DDIs), following the same method applied in our previous study.[45] The number of prescribed medication at discharge was computed and polypharmacy was defined as taking more than 5 medications.

Outcomes

Information on survival, occurrence of rehospitalization and functional status decline at 3 months from discharge was obtained. In particular, functional status variation was estimated with the difference of BI measured during hospitalization and at 3-months' follow-up, only in a subset of 2255 subjects (86% of the total sample).

Accordingly, 192 (7.3%) were not included because died before 3 months follow-up, whereas other 184 (7%) did not repeat BI after 3 months.

Analytical approach

General characteristics of the study population were presented as means and standard deviations (SD) or as medians and interquartile range (IQR), as appropriate, if continuous variables, or as absolute numbers and percentages, if categorical variables. Comparison between groups were carried out with Kruskal-Wallis test or chi-squared test. Additional comparisons were performed with subjects excluded from the analysis because lacking of follow-up data or only of BI at 3 months (presented as Supplementary tables). The occurrence of death or rehospitalization was analyzed through Kaplan-Meier curves according to increasing Beers, STOPP, ACB, DDIs and pkDDI, and compared by means of log-rank test. Then, the association with mortality and rehospitalization within 3 months from hospital discharge was evaluated through Cox proportional hazard regression models and expressed as hazard ratios (HR) with 95% confidence intervals (CI). To evaluate the longitudinal association with functional status change, we used a mixed linear model with random intercept to account for repeated measures of the BI (during hospitalization and at 3-months' follow-up). In these models the number of PIMs, ACB or DDIs was modeled as a continuous variable truncated at 2 to allow a sufficient number of observations at the highest value. In addition, possible threshold effects were evaluated modelling PIMs, ACB or DDIs as binary variables dichotomized considering only subjects having at least 1 or at least 2 violations of PIM or DDI indicators. Concerning physical function variation, mixed models were calculated using the log of BI as the dependent variable. The coefficients of such models allow to estimate the expected subject-specific mean percentage difference in BI (at 3 months' follow-up minus at hospitalization -baseline-), using the following formula: $(e^{Beta} - 1) \times 100$. Finally, the associations of the number of medications and polypharmacy at discharge with the study outcomes were computed with the same methods and comparatively analyzed with those observed for PIM and DDI indicators. Models for Beers, STOPP, ACB, DDI and pkDDIs were adjusted for age, sex, CIRS comorbidity index, length of hospital stay and number of medications at hospital discharge, whereas those for number of medications and polypharmacy at discharge were corrected for age, sex, CIRS comorbidity index,

Beers, STOPP, ACB, DDI and pkDDIs. Possible collinearity between variables entered in adjusted models was evaluated by the inspection of the variance inflation factor (VIF) and was excluded if VIF<3. Analyses were performed using R 3.3.3 software for Mac (R Foundation for Statistical Computing, Vienna, Austria).

Results

The general characteristics of study population are reported in Table 1, according to the presence of at least 1 indicator of PIMs or DDIs. Out of 2631 patients, 817 (31.1%) and 676 (25.6%) presented at least 1 PIM according to Beers' and STOPP criteria, and 1411 (53.6%) had an ACB of 1 or more. In this line, 710 (26.4%) and 341 (13%) patients were discharged with a prescription of at least 1 DDI or 1 pk-DDI, respectively.

Median age was 79 (IQR: 12) years and 48.6% were male. The median CIRS Severity Index and Comorbidity Index were 1.6 (IQR: 0.4) and 3 (IQR: 2), respectively; 42.3% of the patients presented cognitive impairment and 45.6% were disable with a median BI of 93 (IQR: 27). The median length of hospital stay was 9 (IQR: 8) days. Within 3 months from hospital discharge, 412 (15.7%) and 192 (7.3%) patients were re-hospitalized or died, respectively, and the median BI was 92 (IQR: 33). Subjects with at least 1 PIM or DDI indicator were more likely to be older, depressed and disabled. Cognitive impairment was more common in subjects with higher ACB. Lastly, patients with PIM/DDI violations had a higher number of comorbidities with a longer duration of hospital stay and more medications at discharge.

Figure 1 shows the Kaplan-Meier estimator of the risk of mortality and rehospitalization according to the studied therapy quality indicators. Overall, subjects with increasing number of PIM, DDI and higher ACB did not have worse curve of occurrence of any outcomes. In univariate models, ACB and DDI showed significant associations with mortality (HR 1.23, 95%CI 1.00-1.52 and 1.24, 95%CI 1.01-1.54, respectively), that were not confirmed after correction for potential confounders. No associations were found for Beers, STOPP and pk-DDI with mortality. Similarly, none of the indicators was associated with rehospitalization within 3 months' from hospital discharge (Table 2).

Concerning physical function decline, Beers' criteria were associated with a mean BI variation of -4.8% (95%CI -9.2 - -0.2), that was not consistent in adjusted models (Table 2). Conversely, BI significantly reduced with increasing ACB (mean variation of -11.6%, 95%CI -15.5 - -6.8), even after correction for confounders (adjusted mean variation of -7.55%, 95%CI -12.37 - -2.47 – Table 2). Replicating these analyses, after dichotomizing PIM, ACB and DDI variable considering subjects having at least 1 or at least 2 violations, did not unravel significant relations with study outcomes (data not shown).

The number of medication at discharge and, even more, polypharmacy were strongly associated with mortality (adjusted (a-)HR 1.05, 95%CI 1.01-1.10 and 1.70, 95%CI 1.12-2.58, respectively) and rehospitalization (a-HR 1.05, 95%CI 1.01-1.08 and 1.31, 95%CI 1.01-1.71, respectively), independently of potential confounders, including PIM and DDI indicators. Conversely, the observed association with physical function change (mean variation of -1.4%, 95%CI -2.29 – -0.51 and of -9.46%, 95%CI -16.24 – -2.14) was not confirmed in adjusted models (adjusted mean variation of 0.58%, 95%CI -0.51 – 1.67 and of 3.53%, 95%CI -4.71 – 12.48). Supplementary table 1 compares the study population to subjects excluded from the analysis because lacking of follow-up data, evidencing no significant differences for the main demographic and clinical characteristics. Similarly, subjects not included in the analysis of physical function decline were compared (Supplementary table 2). Those surviving at 3 month's follow-up but lacking of BI were, in general, more disabled and experienced a lower incidence of rehospitalization after hospital discharge.

Table 1. **General characteristics of the study population and according to the presence of at least 1 PIM or DDI indicator.**

	Population	Beers		STOPP		ACB		DDI		pkDDI	
		0	>=1	0	>=1	0	>=1	0	>=1	0	>=1
N	2631	1814	817 (31.1%)	1955	676 (25.6%)	1220	1411 (53.6%)	1921	710 (26.4%)	2290	341(13%)
Age (years), median (IQR)	79 (12)	79 (11)	80 (11)*	79 (11)	79 (12)*	78 (12)	80 (11)*	79 (11)	80 (11)*	79 (12)	80 (10)*
Sex (male), n(%)	1278 (48.6%)	933 (51.4%)	345 (42.2%)*	978 (50%)	300 (44.4%)*	639 (52.4%)	639 (45.3%)*	935 (48.7%)	343 (48.3%)	1123 (49%)	155 (45.5%)
BMI (Kg/m^2), median (IQR)	25.4 (6.1)	25.5 (5.9)	25.2 (6.4)*	25.4 (6.1)	25.3 (6.2)*	24.9 (5.5)	26 (6.5)*	25.4 (6)	25.4 (6.7)*	25.4 (6)	25.1 (6.7)*
Barthel index at baseline, median (IQR)	93 (27)	93 (25.2)	92 (31.2)*	93 (26)	92 (31)*	97 (20)	90 (35)*	94 (25)	90 (35)*	93 (27)	90 (31)*
Barthel index at 3 months, median (IQR)	92 (33)	92 (31)	89 (39)*	92 (31)	89 (39.2)*	95 (25)	88 (41)*	92 (30)	86.5 (42)*	92 (32)	85.5 (37.8)*
Disability (Barthel Index<= 90), n(%)	1189 (45.6%)	798 (44.4%)	391 (48.2%)	869 (44.9%)	320 (47.5%)	460 (38.1%)	729 (52.1%)*	834 (43.8%)	355 (50.4%)*	1015 (44.7%)	174 (51.3%)*
Cognitive impairment (SBT>= 10), n(%)	1037 (42.3%)	699 (41.5%)	338 (44%)	761 (42%)	276 (43.1%)	432 (38.4%)	605 (45.6%)*	767 (42.7%)	270 (41.2%)	891 (41.7%)	146 (46.3%)
Depressive symptoms (GDS >= 2), n(%)	941 (41%)	609 (38.8%)	332 (45.7%)*	672 (39.8%)	269 (44.1%)	396 (37%)	545 (44.4%)*	682 (40.5%)	259 (42.3%)	801 (40.2%)	140 (45.8%)
CIRS Severity Index, median (IQR)	1.6 (0.4)	1.6 (0.5)	1.7 (0.5)*	1.6 (0.4)	1.6 (0.5)*	1.5 (0.4)	1.7 (0.5)*	1.6 (0.5)	1.7 (0.4)*	1.6 (0.5)	1.7 (0.5)*
CIRS Comorbidity Index, median (IQR)	3 (2)	3 (2)	3 (2)*	3 (2)	3 (2)*	3 (3)	3 (3)*	3 (2)	3 (3)*	3 (2)	3 (3)*
Length of hospital stay (days), median (IQR)	9 (8)	9 (7)	11 (9)*	9 (8)	10 (9)*	8 (7)	10 (8)*	9 (7)	10.5 (9)*	9 (8)	11 (9)*
Number of medication at discharge, median (IQR)	8 (6)	7 (5)	9 (5)*	7 (5)	9 (6)*	6 (4)	9 (5)*	7 (5)	10 (6)*	7 (5)	11 (6)*
Mortality (within 3 months), n(%)	192 (7.3%)	132 (7.3%)	60 (7.3%)	136 (7%)	56 (8.3%)	77 (6.3%)	115 (8.2%)	129 (6.7%)	63 (8.9%)	162 (7.1%)	30 (8.8%)
Rehospitalization (within 3 months), n(%)	412 (15.7%)	285 (15.7%)	127 (15.5%)	303 (15.5%)	109 (16.1%)	173 (14.2%)	239 (16.9%)	299 (15.6%)	113 (15.9%)	356 (15.5%)	56 (16.4%)

Data reported as median (IQR) and frequency (%). Cognitive impairment: Short Blessed Test (SBT)≥10; Depressive symptoms: 4-item GDS≥2; Disability: Barthel index≤90.
BMI, body mass index. * p<0.05 using Wicoxon test or chi-squared test.

Figure 1. ***Kaplan-Meier curves for mortality and rehospitalization after hospital discharge, according to increasing number of PIM, DDI and higher ACB***

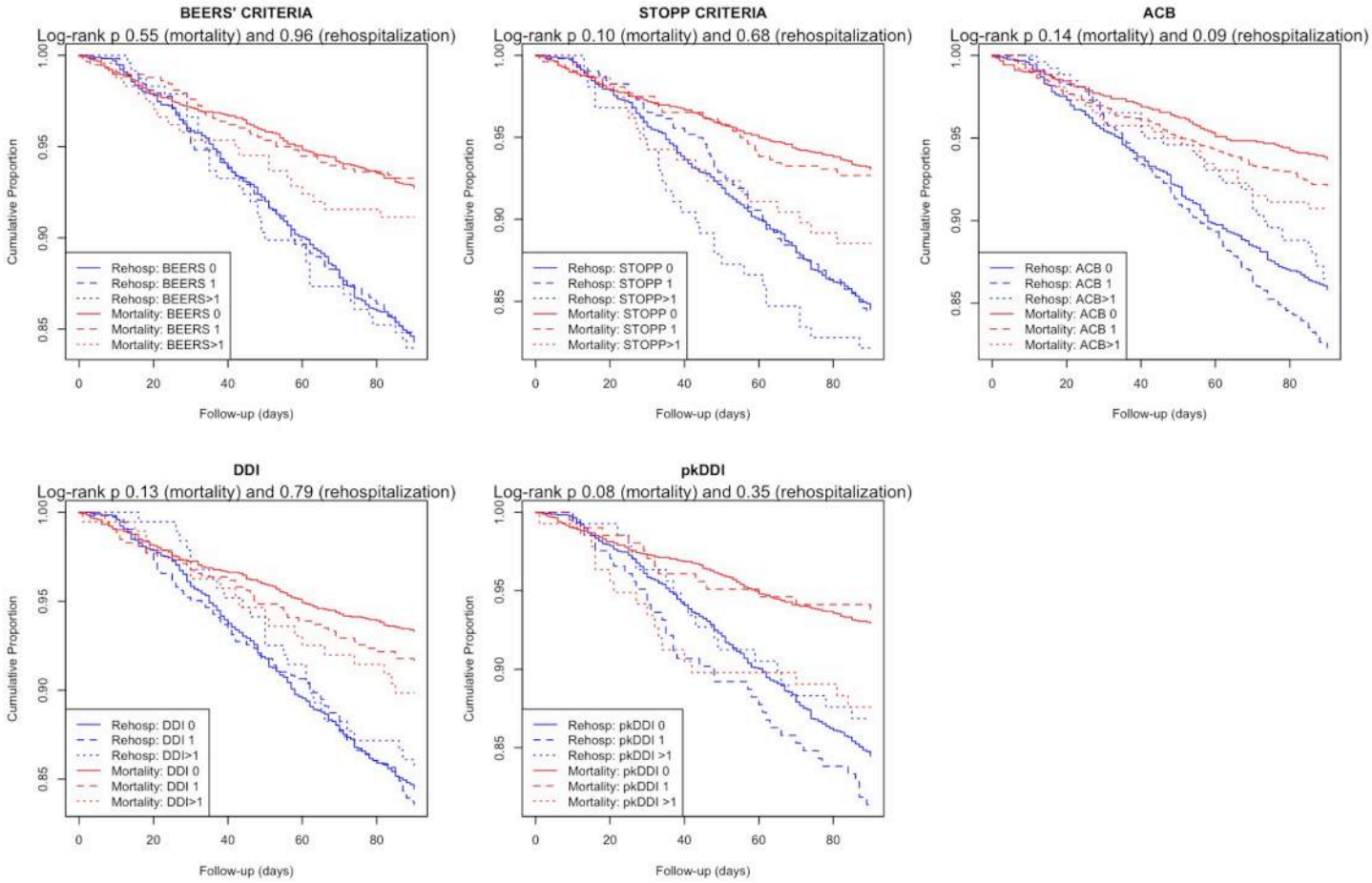

Table 2. ***Associations of PIM or DDI indicators with mortality, rehospitalization and physical function variation at 3 months' follow-up.***

Mortality				
	HR (95%CI)	P value	**aHR (95%CI)**	P value
Beers	1.06 (0.85 - 1.31)	0.616	0.97 (0.78 - 1.21)	0.776
STOPP	1.22 (0.97 - 1.52)	0.086	1.12 (0.89 - 1.41)	0.331
ACB	1.23 (1 - 1.52)	0.05	1.09 (0.87 - 1.37)	0.448
DDI	1.24 (1.01 - 1.54)	0.043	1.05 (0.83 - 1.32)	0.701
pkDDI	1.26 (0.99 - 1.61)	0.063	1.11 (0.86 - 1.44)	0.424
N medications	*1.08 (1.04 - 1.12)*	*< 0.001*	*1.05 (1.01 - 1.10)*	*0.023*
Polypharmacy	*2.01 (1.37 - 2.95)*	*< 0.001*	*1.7 (1.12 - 2.58)*	*0.013*
Rehospitalization				
Beers	1 (0.86 - 1.16)	0.982	0.95 (0.81 - 1.11)	0.529
STOPP	1.05 (0.9 - 1.24)	0.522	1 (0.84 - 1.18)	0.965
ACB	1.07 (0.92 - 1.23)	0.376	0.99 (0.85 - 1.16)	0.893
DDI	0.99 (0.85 - 1.16)	0.932	0.9 (0.76 - 1.07)	0.222
pkDDI	1 (0.82 - 1.21)	0.963	0.9 (0.74 - 1.1)	0.309
N medications	*1.04 (1.02 - 1.07)*	*< 0.001*	*1.05 (1.01 - 1.08)*	*0.006*
Polypharmacy	*1.4 (1.11 - 1.78)*	*0.005*	*1.31 (1.01 - 1.71)*	*0.04*
Physical function				
	Mean % variation (95%CI)	P value	**Adjusted mean % variation (95%CI)**	P value
Beers	-4.8 (-9.18 - -0.21)	0.04	-2 (-7.03 - 3.31)	0.454
STOPP	-2.55 (-8.15 - 3.38)	0.391	-1 (-6.59 - 4.92)	0.734
ACB	-11.58 (-15.46 - -7.52)	< 0.001	-7.55 (-12.37 - -2.47)	0.004
DDI	-4.64 (-9.9 - 0.93)	0.101	-1.55 (-7.13 - 4.37)	0.6
pkDDI	-2.45 (-8.9 - 4.44)	0.476	2.64 (-4.18 - 9.94)	0.458
N medications	*-1.4 (-2.29 - -0.51)*	*0.002*	*0.58 (-0.51 - 1.67)*	*0.298*
Polypharmacy	*-9.46 (-16.24 - -2.14)*	*0.012*	*3.53 (-4.71 - 12.48)*	*0.412*

Adjusted models have been corrected for age, sex, CIRS comorbidity, length of hospital stay and number of medications at hospital discharge. Models for n. medications at discharge and polypharmacy (>5 medications) have been additionally corrected for Beers, STOPP, ACB, DDI and pkDDI. Physical function decline expressed as mean predicted Barthel Index variation at 3 months' follow-up. For physical function, the expected mean percentage variation of Barthel Index at 3 months' follow-up was computed for linear mixed models with the formula: (e^Beta-1)×100 (see Methods section).

Discussion

In the present study, none of the studied therapy quality indicators was found consistently associated with the explored health outcomes, and only subjects with

higher ACB were shown to be at significantly higher risk of physical function decline. Polypharmacy was the only therapy-related predictor of rehospitalization and death in older subjects discharged from acute care hospitals.

Hitherto, explicit lists of PIMs have been developed to optimize drug selection and reduce the risk of death or hospitalization. However, the few studies testing their actual association with these outcomes lead to inconclusive results. Indeed, Beers' criteria were found associated with delirium, gastrointestinal bleeding, falls and fractures,[14–16] but not with in-hospital or post-discharge outcomes, such as disability, mortality and rehospitalization.[17–22] Unlike Beers, available evidence for STOPP is more contrasting. While some studies highlighted STOPP to be significantly associated with avoidable hospitalization related to ADR,[25,26,23] other investigations did not confirm this relation with respect to hospitalization and death either in community dwelling[24] or in hospitalized elderly persons.[20,21,23] However, all but one study [17] were carried out in relatively small cohorts and usually did not compare different therapy quality indicators.[14–16,18–26] Finally, available studies frequently differ in the type and assessment of studied outcomes.

Our study adds to the available literature by providing data on the prognostic meaning of both the currently most used PIM indicators, i.e. Beers and STOPP, along with the ACB and the presence of DDI, obtained from the so far largest analyzed cohort of hospitalized elderly patients. Moreover, it's the first to assess PIMs according to the 2019 version of Beers' criteria in this setting. The observed inconsistent associations of both Beers and STOPP with all the study outcomes are in line with the majority of the previously mentioned studies. This might reflect the fact that recommendations for potentially inappropriate prescriptions do not always translate in the identification of definitely inappropriate medications.[46] In fact, their correct identification should include the recognition of the situations effectively leading to excessive patient's harms compared to expected benefits, and this is frequently difficult in "real life" clinical practice.[46] In any case, our negative results should not discourage from checking and reducing PIMs, which is known to produce significant benefits on other outcomes and to optimize the use of economic resources.[47]

A related issue concerns the cumulative effect of anticholinergic drugs on health outcomes. Each point increase in ACB scale at discharge was associated with an added 7-8 percent reduction of BI after 3 months. This is in keeping with previous studies in the same setting and testifies to the great importance in terms of quality of life and physical independence of carefully tailoring the prescription of anticholinergic medications in the elderly.[6,7,27–29] Conversely, more controversial is the impact on mortality.[30–35] It's plausible that this association, if any, could be evident only after a medium-long time lapse and could be mediated by specific geriatric syndromes, such as cognitive impairment or occurrence of falls and disability.[6,27,48] Accordingly, the apparent disagreement of our results with other studies could be likely explained by the shorter follow-up period (3 months) after hospital discharge.

DDI are also very frequent in older subjects with complex polypharmacy regimens, and hospitalization leads to an increase of potentially severe DDI, raising concerns of avoidable harm.[8,9] We found around a quarter of elderly subjects are discharged from acute care hospitals with at least one DDI. We also recently highlighted the frequency of pkDDI targeting CYP3A4 and P-gp peaking around 11% and 4%, respectively, at hospital discharge.[45] However, the clinical importance of both general and pk-DDIs in the real life seems lesser than theoretically expected.[9,36]

The present study has some limitations. First, ADR were not systematically collected for all the patients and, then, could not be object of analysis. Second, while well deemed to explore incident rehospitalization and disability, the available follow-up period (3 months) could not optimally assess the outcome mortality. Unfortunately, the high rate of missing information did not allow us to investigate longer time lapses after hospital discharge. However, subjects with missing follow-up information at 3 months did not significantly differ from the population included in the analysis (see Supplementary table 1), accordingly it's unlikely that selection bias may affect our results. Third, patients transferred to other wards/hospitals/nursing homes or discharged in critical conditions for home palliative care were excluded from the analysis. As such, obtained results apply only to patients discharged at home. Lastly, the retrospective evaluation of explicit PIM list could have hampered their tailored identification and, as such, influenced our results. After all, this is a common feature of all available studies. Nevertheless, this study has some strengths, mainly the real-

life setting and the representative sample of older in-patients in medical wards in Italy. To the best of our knowledge, it represents the largest study comparatively investigating in the same population the associations of a large panel of widely used and popular quality therapy indicators with respect of a set of clinically significant outcomes for elderly hospitalized patients. While potentially inadequate to detect very small effects sizes (power <80% for HR<1.2), the study is excellently powered to exclude clinically-significant associations between the explored indicators and health outcomes, such as those in the range of HRs obtained for polypharmacy (power 99%).

In conclusion, results from the present study show that, even if deemed inappropriate for the elderly, PIMs identified by Beers 2019 and STOPP criteria do not seem to be associated with any added risk of post-discharge adverse outcomes, in particular if compared with the global burden of medications. They also suggest that, despite potentially harmful based on a theoretical knowledge, the clinical importance of DDIs is generally poorly relevant at the epidemiological level. Alternatively, this kind of epidemiological study does not confirm or could not adequately assess the risk of DDIs, which is expected on theoretical grounds. Thus, the available instruments cautioning the prescribing practice for the elderly need to be improved in order to be a true help for the practicing physician, and the recently released FORTA[49] should also be tested. On the other hand, a selective index of pharmacological risk such as the ACB, a measure of anticholinergic burden, seems worthy of use as it predicts the decline of personal independence as if it were an index of frailty. Indeed, the anticholinergic burden of many drug is not obvious, and drugs with a given primary pharmacologic effect frequently have also an anticholinergic effect. Being aware of this risk might improve our prescribing practice for the elderly.

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Supplementary material

Table S1. **General characteristics of subjects according to availability of 3 months' follow-up data, thus included or excluded from the analysis.**

	Included	**Excluded – Lost at FU**	**P value°**
N	2631	1157	-
Age (years), median (IQR)	79 (12)	79 (10)	0.35
Sex (male), n(%)	1300 (48.4%)	557 (48.1%)	0.903
BMI (Kg/m^2), median (IQR)	25.4 (6)	25.7 (5.5)	0.824
Barthel index at baseline, median (IQR)	93 (27)	92 (34)	0.19
Disability, n(%)	1217 (45.8%)	541 (47.5%)	0.334
Cognitive impairment, n(%)	1048 (42%)	427 (41.1%)	0.649
Depressive symptoms, n(%)	959 (40.9%)	382 (40.2%)	0.716
CIRS Severity Index, median (IQR)	1.6 (0.4)	1.6 (0.5)	0.12
CIRS Comorbidity Index, median (IQR)	3 (2)	3 (3)	0.09
Length of hospital stay (days), median (IQR)	9 (8)	10 (7)	0.017
N of drugs at discharge, median (IQR)	8 (6)	7 (6)	0.534

4. The multifaceted spectrum of liver cirrhosis in elderly hospitalized patients: analysis of the REPOSI registry.

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RESEARCH PAPER

The multifaceted spectrum of liver cirrhosis in older hospitalised patients: analysis of the REPOSI registry

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Abstract

Background. Knowledge on the main clinical and prognostic characteristics of elderly multimorbid subjects with liver cirrhosis(LC) admitted to acute medical wards is scarce.

Objectives. To estimate the prevalence of LC among elderly patients admitted to acute medical wards and to assess the main clinical characteristics of LC along with its association with major clinical outcomes; to explore the possibility that well distinguished phenotypic profiles of LC have classificatory and prognostic properties.

Methods. A cohort of 6193 elderly subjects hospitalized between 2010 and 2018 and included in the REPOSI registry was analyzed.

Results. LC was diagnosed in 315 patients (5%). LC was associated with rehospitalization (age-sex adjusted hazard ratio[aHR] 1.44, 95%CI 1.10-1.88) and

with mortality after discharge, independently of all confounders (multiple aHR 2.1, 95%CI 1.37-3.22), but not with in-hospital mortality and incident disability. Three main clinical phenotypes of LC patients were recognized: relatively fit subjects (FIT, N 150), subjects characterized by poor social support (PSS, N 89), and, finally, subjects with disability and multimorbidity (D&M, N 76). PSS subjects had an increased incident disability (35% vs 13%, $p<0.05$) compared to FIT. D&M patients had a higher mortality (in-hospital 12% vs 3%/1%,$p<0.01$; post-discharge 41% vs 12%/15%,$p<0.01$) and less rehospitalization (10% vs 32%/34%,$p<0.01$) compared to PSS and FIT.

Conclusions. LC has a relatively low prevalence in elderly hospitalized subjects, but, when present, accounts for worse post-discharge outcomes. Phenotypic analysis unraveled the heterogeneity of LC elderly population and the association of selected phenotypes with different clinical and prognostic features.

Introduction

With the progressive population aging, health-care systems are being challenged by elderly patients, who nowadays represent the great majority of those acutely admitted to hospital wards. These patients typically present with multiple diseases which are often treated by different specialists with poor integration and related proliferation of prescribed drugs.[1–3] Accordingly, the clinical presentation along with the in-hospital and post-discharge impact of diseases may be markedly different from those observed in the younger patient population.[4] Increasing knowledge in this field plays a pivotal role in order to better design tailored strategies of care able to improve health outcomes of elderly in-patients. Clinical characteristics and health outcomes have been widely investigated for many diseases,[5–8] but specific data on elderly patients admitted to hospital with a diagnosis of liver cirrhosis (LC) are sparse.[9–13] LC is a world-wide challenge frequently leading to physical disability, hospitalization and mortality, but the relatively low prevalence of LC in elderly in-patients (from 2 to 10%)[10,11,13,14] has probably prioritized more prevalent and highly impacting diseases such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD).[5,6,15] Notwithstanding, results from previous studies suggest that,

even if relatively less prevalent, LC is prognostically relevant, both in absolute terms and in comparison with other highly impacting diseases.[9–13]

With this background and gaps of knowledge, we sought a) to analyze the prevalence of and main clinical characteristics of LC patients in the frame of a registry of older patients hospitalized in internal medicine or geriatric wards for acute illness, b) to comparatively investigate the association with major clinical outcomes (incident disability, in-hospital-mortality, rehospitalization and mortality up to 12 months from discharge) of LC with other high-impacting conditions such as CHF and COPD, c) to verify whether LC patients cluster in well distinguished phenotypic profiles and whether these phenotypes differently associate with clinical outcomes.

Methods

Data source

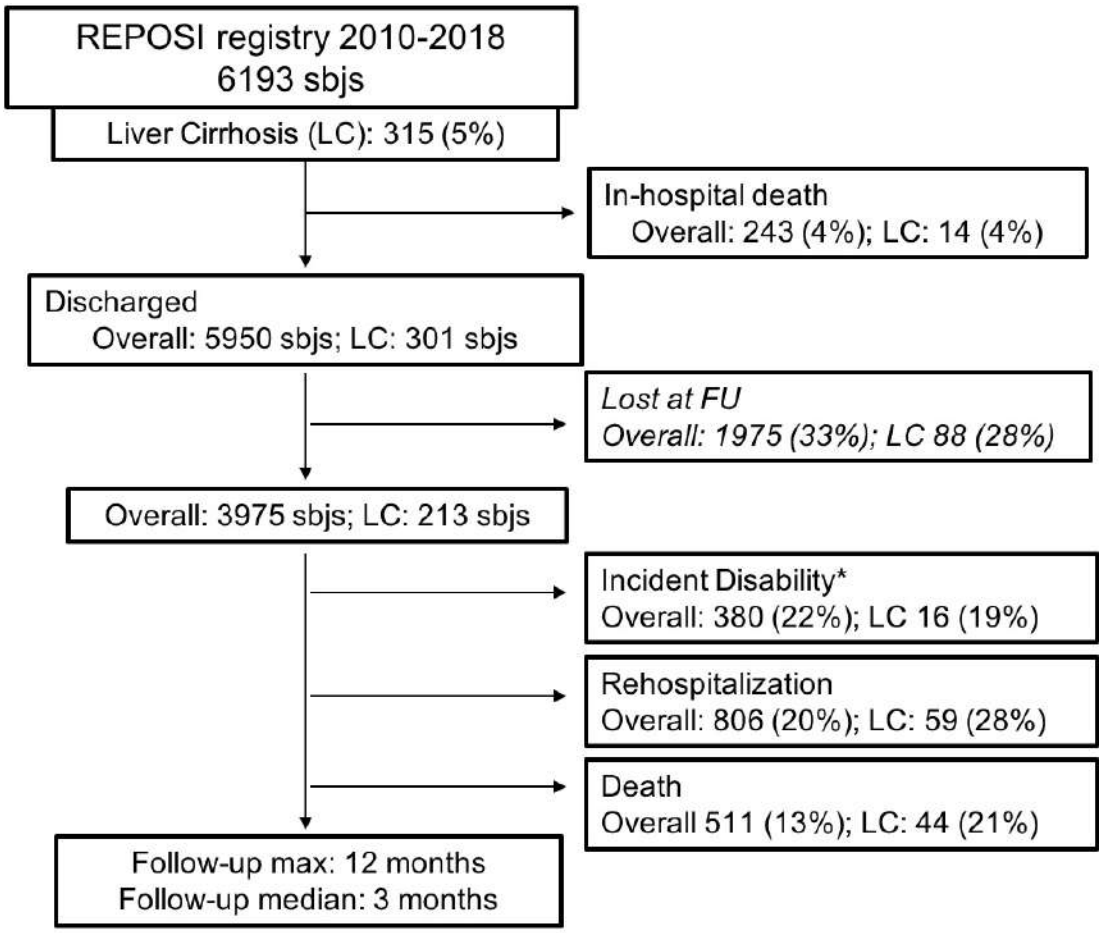
We used data from "Registro Politerapia Società Italiana di Medicina Interna" (REPOSI), enrolling patients aged 65 years or more admitted to more than 100 Italian medical wards and sponsored by the Italian Society of Internal Medicine (SIMI) together with the Istituto di Ricerche Farmacologiche "Mario Negri" and the Fondazione Ca' Granda Ospedale Maggiore Policlinico, both in Milan. The study design is described in details elsewhere.[1]

The full database of 6193 patients was analyzed (Figure 1). The presence of LC and other diseases was ascertained through the appropriate International Classification of Diseases (ICD) 9 codes (Supplementary table S1), whereas the burden of comorbidities was analyzed according to the Cumulative Illness Rating Scale (CIRS).[16] The main socio-demographic and clinical characteristics were also registered and available. The Barthel Index was measured in order to assess the patient status before the acute illness leading to hospitalization.[17] Katz's activities of daily living (ADL) were retrieved through the items of the Barthel Index, with disability defined as loss of independence in at least one of the six ADL (eating, bathing, dressing, toileting, transferring and maintaining continence).[18] Moreover, cognitive impairment was identified by a Short Blessed Test ≥ 10 19 and depression by a

Geriatric Depression Scale (≥ 2) according to the short version by Hickie and Snowdon.[20]

After hospital discharge, participants discharged alive (N 5950) were followed up after 3 and/or 12 months by a phone call (Figure 1), in order to verify the occurrence of death and rehospitalization and any variation of the functional status. Overall, 2537 patients (43%) could be ultimately contacted after 3 months and 1438 (24%) after 12 months, whereas 1975 of them (33%) were lost to follow-up (Figure 1). Incident disability was defined as the loss of one or more ADL during follow-up among patients who were independent before hospitalization in all of 6 ADL.

Figure 1. ***Flow diagram of subjects included in the analyses, for the overall REPOSI population and for the sub-cohort of subjects with liver cirrhosis (LC).*** **Out of 1739 subjects and 84 LC subjects independent in activities of daily living (ADL) at hospital admission and with available FU data. Sbjs, subjects.*



Analytic approach

The general characteristics of the study population were presented by means of descriptive statistics. Data were shown as stratified by the presence of LC diagnosis.

Comparison between groups was carried out with the Kruskal-Wallis test or chi-squared test, with Holm's correction for multiple testing when needed. The association with mortality and rehospitalization after discharge was evaluated through Cox proportional hazard regression models and expressed as hazard ratios (HR) with 95% confidence intervals (CI). The association with incident disability was computed through log-binomial regression models and expressed as risk ratios (RRs) with 95%CI. All models were first corrected for age and sex, then also for low education, living alone, marital status, previous hospitalizations within 3 months, hypertension, diabetes mellitus, body mass index, CHF, COPD, LC, neoplasms, CIRS severity index (CIRS-SI), active smoking, alcohol assumption, glomerular filtration rate, disability, cognitive decline and depression.

Finally, we assessed whether socio-demographic and clinical features aggregated into distinct classes (clinical phenotypes) using the latent class analysis (LCA). We used this method to test our study hypothesis that the REPOSI population of LC patients comprises N sub-populations (classes) characterized by the co-occurrence of similar comorbidities, disabilities or social-economical features. N was fixed at 3, corresponding to the value that maximized the goodness-of-fit (evaluated by Bayesian information factor -BIC-) of models with different class numbers (Suppl Figure 1). Once the classes were obtained, the specific incidence of study outcomes within each clinical phenotype was computed and each other compared. Analyses were performed using R 3.6.1 software for Mac (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study population of 6193 subjects included 315 (5%) with the diagnosis of LC (Table 1). These patients were younger than those without LC (median age 76 vs 80 years, $p<0.001$) and more likely to be male (60% vs 48%, $p<0.001$), married (63% vs 53%, $p<0.001$) and former vs active alcohol users (28%/21% vs 13%/31%, $p<0.001$). No differences were observed for cognitive, functional and mood status at hospital admission, but LC patients were more frequently hospitalized in the preceding 3 months (27% vs 19%, $p=0.002$). Concerning comorbidities, they showed a higher

prevalence of diabetes mellitus and neoplasms (mainly hepatocellular carcinoma - HCC-), but a lower prevalence of all the other major comorbidities that when present, accounted for a more severe clinical picture shown by a higher CIRS (Table 1). Overall, the hospital stay was shorter in LC patients (median stay of 8 vs 10 days, p<0.001), with a comparable incidence of in-hospital mortality (4% vs 4%, p=0.73). After a median follow-up of 90 days, the incidence of disability was similar to that observed in the non-LC population (19% vs 22%, p=0.54; Figure 2). Conversely, LC patients showed an increased risk of rehospitalization (age-sex aHR 1.44, 95%CI 1.10-1.88; Figure 2) and mortality (age-sex aHR 2.08, 95%CI 1.52-2.83; Figure 2), that was consistent also in multiple adjusted models for mortality (multiple aHR 2.1, 95%CI 1.37-3.22; Figure 2). Diagnoses of CHF and COPD were both associated with rehospitalization, even after multiple corrections for CHF, but not with mortality (Figure 2 and Suppl table 2).

Finally, by means of the LCA, 3 clinical phenotypes were identified (Figure 3 and Suppl table S3). The first one (relatively fit patients – FIT – but with a higher prevalence of HCC) included 150 younger patients characterized by a relatively low prevalence of comorbidities and disability, and with a nearly 50% absolute risk of HCC. The hospital admission was secondary to liver-related problems in 68% of the cases, due to ascites (13%), bleeding (17%), encephalopathy (7) or HCC (18%) (Suppl table S4). When the admission diagnosis was HCC (ICD9 code 155), the hospital stay was shorter (median 4 days, IQR 2-9, vs 8 days, IQR 5-12, p<0.01).

The second clinical phenotype (poor social support - PSS) was made up of 89 patients with a higher prevalence of poor socio-economical features - such as low income, low education, living alone, not married - when compared to the previous phenotype. The main causes of hospitalization were liver-related (61%), but with a higher frequency of admissions for infections (12%).

The third phenotype (disability and multimorbidity – D&M) included 76 patients with the highest prevalence of major comorbidities and physical and cognitive disabilities. Compared to the other phenotypes, they were less frequently hospitalized for liver problems (46%), but more for infections, lung or heart related disorders. Figure 3 visually represents the characteristics of the aforementioned phenotypes according to the variables included in the LCA. All in all, PSS subjects had an

increased incident disability (35% vs 13%, p<0.05; Figure 3), and a similar incidence of rehospitalization and death in comparison with FIT. D&M patients had a higher mortality (in-hospital 12% vs 3% and 1% for PSS and FIT with p<0.01 in both comparisons; post-discharge 41% vs 12% and 15% for PSS and FIT with p<0.01 in both comparisons; Figure 3) and less rehospitalization (10% vs 32% and 34% for PSS and FIT with p<0.01 in both comparisons; Figure 3).

Table 1. ***Socio-demographic and clinical features of hospitalized elderly patients with or without a diagnosis of liver cirrhosis.***

	REPOSI population without liver cirrhosis	**REPOSI patients with liver cirrhosis**	**p**
N	5878	315 (5%)	-
Demographic, social and anthropometric features			
Age (yrs), median(IQR)	80 (74-85)	76 (71-81)	< 0.001
Sex (male), n(%)	2837 (48%)	190 (60%)	< 0.001
Smoke (former/active), n(%)	2102 (37%) / 495 (9%)	111 (37%) / 32 (11%)	0.498
Alcohol consumption (former/active), n(%)	712 (13%) / 1738 (31%)	86 (28%) / 64 (21%)	< 0.001
Education level (years), median(IQR)	5 (5-8)	5 (5-8)	0.66
Living alone, n(%)	1330 (24%)	53 (18%)	0.013
Marital status (married), n(%)	3031 (53%)	193 (63%)	< 0.001
Low income, n(%)	3818 (72%)	216 (76%)	0.152
BMI (Kg/m^2), median(IQR)	25.8 (5)	25.6 (4.5)	0.507

Comorbidities			
Diabetes mellitus, n(%)	1647 (28%)	114 (36%)	0.002
Arterial hypertension, n(%)	4566 (78%)	193 (61%)	< 0.001
Hypercholesterolemia, n(%)	355 (6%)	2 (1%)	< 0.001
CHF, n(%)	1377 (23%)	35 (11%)	< 0.001
IHD, n(%)	1294 (22%)	35 (11%)	< 0.001
COPD, n(%)	1368 (23%)	55 (17%)	0.02
Atrial fibrillation, n(%)	1535 (26%)	39 (12%)	< 0.001
Cerebro-vascular disease, n(%)	1398 (24%)	32 (10%)	< 0.001
Neoplasms, n(%)	1144 (19%)	116 (37%)*	< 0.001
CKD, n(%)	1674 (29%)	88 (28%)	0.859
Genito-urinary disorders, n(%)	1441 (25%)	61 (19%)	0.041
Musculo-skeletal disease, n(%)	2031 (35%)	78 (25%)	< 0.001
CNS disorders, n(%)	1467 (25%)	64 (20%)	0.069
Psychiatric disorders, n(%)	1388 (24%)	39 (12%)	< 0.001
CIRS-CI>3 (median), n(%)	2129 (36%)	137 (43%)	0.013
CIRS-SI>1.6 (median), n(%)	2699 (46%)	184 (58%)	< 0.001
Hospital admission parameters			

Disability, n(%)	2957 (51%)	161 (51%)	0.997
Cognitive impairment, n(%)	2178 (42%)	129 (44%)	0.52
Depressive symptoms, n(%)	1995 (42%)	119 (44%)	0.477
Previous hospitalization (within 3 months), n(%)	1131 (19%)	84 (27%)	0.002
Hospital discharge parameters			
Length of hospital stay (days), median(IQR)	10 (7-15)	8 (6-13)	< 0.001
Discharge destination (other ward/home/home in critical conditions), n(%)	500 (9%) / 4972 (86%) / 64 (1%)	18 (6%) / 276 (89%) / 3 (1%)	0.34
In-hospital mortality, n(%)	229 (4%)	14 (4%)	0.734
Follow-up			
Follow-up time (days), median(IQR)	90 (90-365)	90 (90-95)	< 0.001
Lost at follow-up, n(%)	1887 (32%)	88 (28%)	0.138
Incident disability, n(%)	364 (22%)	16 (19%)	0.539
Rehospitalization, n(%)	747 (20%)	59 (28%)	0.007
Deaths, n(%)	467 (12%)	44 (21%)	< 0.001

Comparison carried out with chi-squared or Kruskal-Wallis test, as appropriate. * 102 on 116 (88%) patients with neoplasms had hepato-cellular carcinoma. IQR, interquartile range; SD, standard deviation; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive, pulmonary disease; IHD, ischemic heart disease; CNS, central nervous system; CIRS, cumulative illness rating, scale; -CI, comorbidity index; -SI, severity index; CKD, chronic kidney disease.

Figure 2. ***Association between the diagnoses of liver cirrhosis (LC), congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) and study outcomes.*** *Multiple adjusted models corrected for age, sex, living alone, low education, marital status, previous hospitalization within 3 months, hypertension, diabetes mellitus, body mass index (BMI), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), LC, neoplasms, cumulative illness rating scale severity index (CIRS SI), active smoking, alcohol assumption, glomerular filtration rate (GFR),*

baseline disability, cognitive decline and depression. Disabled subjects at baseline excluded from the analysis.

In-Hospital Mortality	**RR**	**95%CI**
Liver Cirrhosis age-sex adj	1.38	0.76-2.28
Liver Cirrhosis multiple adj	0.55	0.13-1.51
CHF age-sex adj	1.29	0.98-1.7
CHF multiple adj	1.28	0.8-2.01
COPD age-sex adj	1.17	0.87-1.54
COPD multiple adj	1.29	0.8-2.04
Incident Disability	**RR**	**95%CI**
Liver Cirrhosis age-sex adj	0.93	0.54-1.48
Liver Cirrhosis multiple adj	0.73	0.36-1.32
CHF age-sex adj	1.17	0.91-1.48
CHF multiple adj	0.83	0.6-1.13
COPD age-sex adj	1.26	0.99-1.6
COPD multiple adj	1.06	0.78-1.41
Rehospitalization	**HR**	**95%CI**
Liver Cirrhosis age-sex adj	1.44	1.1-1.88
Liver Cirrhosis multiple adj	1.17	0.81-1.68
CHF age-sex adj	1.43	1.22-1.68
CHF multiple adj	1.39	1.14-1.7
COPD age-sex adj	1.32	1.12-1.54
COPD multiple adj	1.15	0.94-1.41
Mortality	**HR**	**95%CI**
Liver Cirrhosis age-sex adj	2.08	1.52-2.83
Liver Cirrhosis multiple adj	2.1	1.37-3.22
CHF age-sex adj	1.12	0.92-1.37
CHF multiple adj	1.17	0.89-1.54
COPD age-sex adj	0.92	0.75-1.13
COPD multiple adj	0.88	0.66-1.17

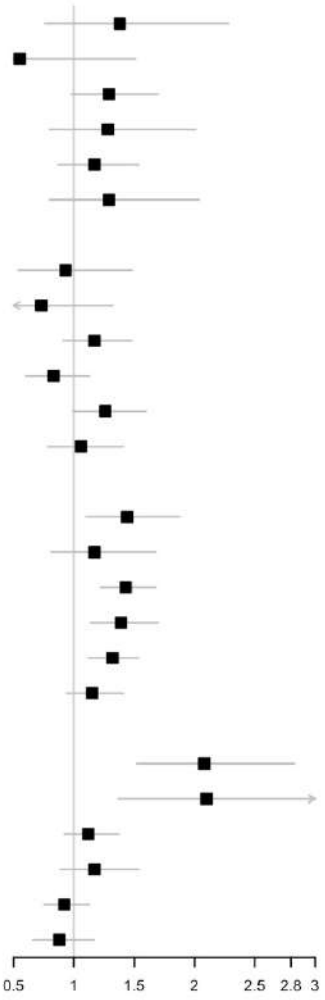
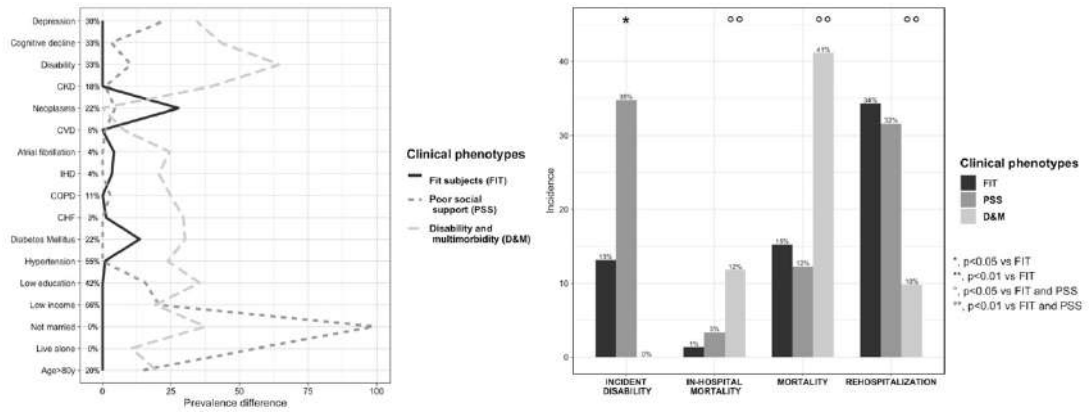


Figure 3. The clinical phenotypes of subjects with liver cirrhosis admitted to medical wards along with the specific incidence of adverse health outcomes. *Left panel) Characterization of the clinical phenotypes according to the prevalence of the different variables included in the Latent Class Analysis (LCA). The lines represent the prevalence difference between each clinical phenotype and that with the lowest observed prevalence (reported as value label beside y-axis). Right panel) Incidence of in-hospital mortality, disability, rehospitalization and death up to 12 months from hospital discharge across different clinical phenotypes. Comparison between groups carried out with chi-squared test with Holm's correction for multiple comparisons. CHF, congestive heart failure;*

COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; CVD, cardiovascular disease; CKD, chronic kidney disease.



Discussion

This study shows that LC has a relatively low prevalence in elderly subjects admitted to medical wards for acute illness, but LC patients have a more severe burden of comorbidities and worse post-discharge outcomes. The diagnosis of LC was associated with rehospitalization as also shown for CHF and COPD, but, at variance with these diseases, LC was also associated with mortality up to 1 year from hospital discharge, independently of other confounders. Finally, LC older in-patients showed 3 different clinical phenotypes. The majority of them were relatively young with a low prevalence of comorbidities and physical or cognitive disability, but a higher likelihood of HCC (FIT). A few others were characterized by poor socio-economic conditions (PSS). Finally, a small but not negligible part of LC patients were older, with a high prevalence of comorbidities and disability (D&M). While D&M patients had increased in-hospital and post-discharge mortality, PSS ones showed comparable mortality and rehospitalization to FIT, but a higher incident disability.

With the steady worldwide increase in the burden of chronic disease among elderly patients seeking hospital admission, much attention has been paid so far to highly impacting and frequent conditions such as CHF and COPD, but LC remained nearly unexplored in this context. Available studies have shown that LC affected 2-10% of

patients acutely hospitalized for any cause, compared to 20-25% for CHF and COPD.[6,13,14] In this study, we found a 5% prevalence of LC in a representative population of elderly hospitalized subjects in Italy. In line with another study,[14] LC was more frequently associated with diabetes mellitus and malignancy, but in approximately a fourth of the cases LC co-occurred with other major comorbidities, thus accounting for a more complex clinical scenario. Overall, we found the diagnosis of LC to be associated with a 44% increased risk of rehospitalization and a more than double risk of dying up to 1 year after hospital discharge. To allow a more accurate interpretation of these findings, we put them in the context of other chronic resource-intensive conditions (i.e. CHF and COPD). Similarly to LC, they were associated with rehospitalization, but none of them showed an increased risk of post-discharge mortality, that in the case of LC was independent from an extensive list of socio-demographic and clinical factors. Interestingly, we found no associations between LC (but also CHF and COPD) and in-hospital mortality and post-discharge incident disability. While the reported effect on disability is novel, the absence of influence on in-hospital mortality is in disagreement with other studies.[5,6,10,13] The different setting and statistical measures used, along with the specific population characteristics may partially explain this difference. Moreover, with the exception of a single study,[6] the younger age of the previously studied populations may explain the major impact of a specific diagnosis over all the other clinical variables, compared to older cohorts in which the global health status may play a more relevant role. Similarly, patient-level factors (such as frailty, sarcopenia, cognitive status, but not morbidities) have been already advocated to influence the occurrence of disability after hospital discharge.

In an attempt to profile hospitalized elderly subjects with LC on the basis of their socio-demographic and clinical features, we identified 3 main phenotypes. FIT patients were mainly those hospitalized for liver-related problems (ascites, encephalopathy, bleeding or HCC). When admitted with a diagnosis of liver malignancy (HCC), some of them showed a significantly shorter hospital stay, so that it is realistic to assume that they included a number of patients admitted with the goal of undergoing locoregional procedures for HCC. Compared to FIT, PSS patients had a higher rate of admissions for infections and a higher incident disability. Finally,

D&M patients were generally admitted for liver-related, but also heart and lung-related problems, due to the increased prevalence of these organ comorbidities. Accordingly, they showed the highest in-hospital and post-discharge mortality, but on the other hand a lower rehospitalization, probably explained by a mortality selection bias. Thus, recognizing these phenotypes might help to foresee health care needs and to plan care at discharge. For instance, PSS patients might be the object of dedicated interventions designed to prevent the onset of disability, while assessing the respective roles of LC and other chronic diseases in conditioning the rehospitalization of D&M patients might find an in depth assessment of their medical status. Thus, these patients seem to be the optimal target of a comprehensive geriatric assessment, a procedure largely shown to benefit many categories of elderly patients, but, as far as we know, insofar untested in LC patients.

This study has some limitations. First, being solely based on ICD-9 codes, some bias related to coding mistakes and inaccurate diagnosis cannot be excluded. Particularly, ICD9 codes allowed to disclose LC etiology in only the 30% of subjects, highlighting alcoholic disease as the most common cause, accounting for the 20.1% of all LC subjects. Even though these data are in line with previous reports[9,12], the present study cannot be intended to provide data on LC etiology in Italian elderly in-patients, because assessing the etiology of selected diseases was out of the scope of REPOSI study. Second, owing to the limited dataset of the register, disease specific clinical stages were unavailable for LC (Child-Pugh class), but also for CHF (New York Heart Association -NYHA- classification) and COPD (Global Initiative for COPD -GOLD- classification), so that we could not correct the analysis for these factors. Third, follow-up data were not available for 33% of the baseline population. However, these subjects did not significantly differ from the population included in the analysis (Suppl table 5), so that it is unlikely that selection bias may have affected our results. Due to the fact that our register was not specifically designed and powered to detect differences in the subgroups considered, some data should be considered with caution, particularly that stemming from small numbers. Finally, being derived from a cohort of hospitalized subjects, these results should not be generalized to the population of LC out-patients.

This study has also some strengths, mainly the real-life setting and the representative sample of older medical in-patients in Italy. Moreover, it represents the largest study comparatively investigating the impact of LC along with CHF and COPD on post-discharge outcomes up to 12 months, and clinical phenotypes of LC older in-patients were described for the first time.

In conclusion, this study adds to our knowledge of LC in the acute care setting by showing that the LC elderly population is heterogeneous and that selected phenotypes associate with different clinical and prognostic features. This should allow to identify health status trajectories not currently evident based on a classical analysis of the LC population.

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Supplementary materials

Table S1. ***List of ICD9 codes for diagnosis of the main study diseases and comorbidities.***

Diagnosis	**ICD9 codes**
Liver Cirrhosis	571, 571.2, 571.5, 571.6, 070.22, 070.23, 070.44
Congestive heart failure	428*
Chronic obstructive pulmonary disease	491*, 492*
Diabetes mellitus	250*
Hypercholesterolemia	272.0
Atrial fibrillation	427.31
Ischemic heart disease	414*
Cerebrovascular disease	from 431* to 438*
Neoplasms	from 140* to 239*
Hepatocellular carcinoma	155*

Table S2. ***General characteristics of patients with liver cirrhosis (LC), congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD).***

	LC	**CHF**	**COPD**
N	315	1412	1423
Age (yrs), median(IQR)	76 (71-81)	82 (77-87)	80 (75-85)
Sex (male), n(%)	190 (60%)	688 (49%)	869 (61%)
Smoke (former/active), n(%)	111 (37%) / 32 (11%)	559 (41%) / 80 (6%)	718 (52%) / 216 (16%)
Alcohol consumpt (former/active), n(%)	86 (28%) / 64 (21%)	190 (14%) / 426 (31%)	220 (16%) / 487 (35%)
Education level (yrs), median(IQR)	5 (5-8)	5 (5-8)	5 (5-8)
Live alone, n(%)	53 (18%)	320 (24%)	322 (24%)
Marital status (married), n(%)	193 (63%)	676 (50%)	742 (54%)
Low income, n(%)	216 (76%)	961 (75%)	941 (72%)
BMI (Kg/m^2), median(IQR)	25.6 (4.5)	26.6 (5.3)	26.3 (5.3)

Comorbidities			
CIRS-CI, median(IQR)	3 (2-5)	3 (2-5)	3 (2-5)
CIRS-CI (>median), n(%)	137 (43%)	681 (48%)	700 (49%)
CIRS-SI, median(IQR)	1.8 (1.5-2)	1.8 (1.5-2)	1.8 (1.5-2)
CIRS-CI (>median), n(%)	184 (58%)	857 (61%)	881 (62%)
Diabetes mellitus, n(%)	114 (36%)	452 (32%)	445 (31%)
Arterial hypertension, n(%)	193 (61%)	1178 (83%)	1127 (79%)
Hypercholesterolemia, n(%)	2 (1%)	79 (6%)	85 (6%)
LC, n(%)	315 (100%)	35 (2%)	55 (4%)
CHF, n(%)	35 (11%)	1412 (100%)	1423 (100%)
IHD, n(%)	35 (11%)	420 (30%)	406 (29%)
COPD, n(%)	55 (17%)	431 (31%)	431 (30%)
Atrial fibrillation, n(%)	39 (12%)	626 (44%)	427 (30%)
Cerebro-vascular disease, n(%)	32 (10%)	306 (22%)	326 (23%)
Neoplasms, n(%)	116 (37%)	225 (16%)	266 (19%)
CKD, n(%)	88 (28%)	603 (43%)	463 (33%)
Genito-urinary disorders, n(%)	61 (19%)	363 (26%)	398 (28%)
Musculo-skeletal disease, n(%)	78 (25%)	483 (34%)	451 (32%)
CNS disorders, n(%)	64 (20%)	343 (24%)	352 (25%)
Psychiatric disorders, n(%)	39 (12%)	306 (22%)	345 (24%)
Hospital admission parameters			
Disability, n(%)	161 (51%)	881 (64%)	810 (57%)
Cognitive impairment, n(%)	129 (44%)	608 (49%)	580 (46%)
Depressive symptoms, n(%)	119 (44%)	551 (48%)	533 (46%)
Hemoglobin (g/dL), median(IQR)	11 (9.8-12.6)	11.7 (10.2-13.1)	12.1 (10.5-13.6)
eGFR (mL/min), median(IQR)	64.4 (42.8-84.2)	48.7 (31.7-69.1)	58.7 (38.6-80.9)
Previous hospitalization (within 3 months), n(%)	84 (27%)	369 (26%)	354 (25%)
Hospital discharge parameters			
Length of hospital stay (days), median(IQR)	8 (6-13)	10 (7-15)	10 (7-15)
Discharge destination (other ward/home/home in critical conditions), n(%)	18 (6%) / 276 (89%) / 3 (1%)	91 (7%) / 1210 (87%) / 16 (1%)	92 (7%) / 1233 (88%) / 16 (1%)
In-hospital mortality, n(%)	14 (4%)	76 (5%)	67 (5%)
Follow-up			
Follow-up time (days), median(IQR)	90 (90-105)	90 (90-365)	90 (90-365)
Lost at FU, n(%)	88 (28%)	423 (30%)	445 (31%)
Incident disability, n(%)	16 (19%)	84 (27%)	92 (26%)
Rehospitalization, n(%)	59 (28%)	220 (25%)	220 (24%)
Deaths, n(%)	44 (21%)	132 (15%)	122 (13%)

Table S3. ***General characteristics of subjects according to the presence of liver cirrhosis and to the availability of follow-up information, thus included or excluded from the analysis of post-discharge outcomes (incident disability, rehospitalization and mortality).***

	Subj with Liver Cirrhosis			**REPOSI population w/o liver cirrhosis**		
	Lost at FU			**Lost at FU**		
	NO	*YES*	*p*	*NO*	*YES*	*p*
N	227	88		3991	1887	
Age (yrs), median(IQR)	76 (71-81)	76 (71-81)	0.996	80 (74-85)	80 (74-85)	0.92
Sex (male), n(%)	133 (59%)	57 (65%)	0.38	1942 (49%)	895 (47%)	0.414
Smoke (former/active), n(%)	80 (37%) / 26 (12%)	31 (37%) / 6 (7%)	0.46	1457 (37%) / 328 (8%)	645 (36%) / 167 (9%)	0.325
Alcohol consumpt (former/active), n(%)	70 (32%) / 39 (18%)	16 (19%) / 25 (29%)	0.021	512 (13%) / 1227 (32%)	200 (11%) / 511 (28%)	< 0.001
Education level (yrs), median(IQR)	5 (5-8)	5 (5-8)	0.896	5 (5-8)	5 (5-8)	0.59
Live alone, n(%)	36 (17%)	17 (20%)	0.594	896 (24%)	434 (25%)	0.307
Marital status (married), n(%)	142 (64%)	51 (61%)	0.66	2093 (54%)	938 (52%)	0.33
Low income, n(%)	155 (75%)	61 (78%)	0.714	2644 (72%)	1174 (72%)	0.748
BMI (Kg/m^2), median(IQR)	25.4 (4.5)	26.2 (4.3)	0.217	25.9 (5)	25.8 (4.9)	0.876
CIRS-CI, median(IQR)	3 (2-5)	3 (2-4)	0.764	3 (2-4)	3 (1-4)	0.003

CIRS-CI (>median), n(%)	98 (43%)	39 (44%)	0.954	1488 (37%)	641 (34%)	0.028
CIRS-SI, median(IQR)	1.8 (1.5-2)	1.8 (1.5-2)	0.753	1.6 (1.5-1.8)	1.6 (1.4-1.8)	< 0.001
CIRS-CI (>median), n(%)	97 (43%)	35 (40%)	0.726	1901 (48%)	798 (43%)	< 0.001
Diabetes mellitus, n(%)	80 (35%)	34 (39%)	0.666	1133 (28%)	514 (27%)	0.376
Arterial hypertension, n(%)	140 (62%)	53 (60%)	0.914	3111 (78%)	1455 (78%)	0.887
Hypercholesterolemia, n(%)	1 (0%)	1 (1%)	1	243 (6%)	112 (6%)	0.864
CHF, n(%)	29 (13%)	6 (7%)	0.19	923 (23%)	454 (24%)	0.45
IHD, n(%)	21 (9%)	14 (16%)	0.137	884 (22%)	410 (22%)	0.741
COPD, n(%)	44 (19%)	11 (12%)	0.201	934 (23%)	434 (23%)	0.758
Atrial fibrillation, n(%)	31 (14%)	8 (9%)	0.361	1057 (26%)	478 (25%)	0.364
Cerebro-vascular disease, n(%)	21 (9%)	11 (12%)	0.517	996 (25%)	402 (21%)	0.002
Neoplasms, n(%)	81 (36%)	35 (40%)	0.586	781 (20%)	363 (19%)	0.791
CKD, n(%)	66 (29%)	22 (25%)	0.56	1143 (29%)	531 (28%)	0.867
Genito-urinary disorders, n(%)	44 (19%)	17 (19%)	1	1006 (25%)	435 (23%)	0.112
Musculo-skeletal disease, n(%)	61 (27%)	17 (19%)	0.212	1440 (36%)	591 (32%)	< 0.001
CNS disorders, n(%)	43 (19%)	21 (24%)	0.413	1012 (25%)	455 (24%)	0.414
Psychiatric disorders, n(%)	30 (13%)	9 (10%)	0.595	999 (25%)	389 (21%)	< 0.001
Disability, n(%)	117 (52%)	44 (51%)	0.95	1988 (51%)	969 (53%)	0.143
Cognitive impairment, n(%)	94 (45%)	35 (42%)	0.735	1527 (43%)	651 (41%)	0.321
Depressive symptoms, n(%)	88 (46%)	31 (41%)	0.54	1386 (42%)	609 (42%)	0.983
eGFR (mL/min), median(IQR)	65.8 (42.5-85.2)	63.9 (43.5-83.3)	0.867	60.1 (40.8-80.1)	60.9 (40.3-81)	0.536
Previous hospitalization (within 3 months), n(%)	60 (26%)	24 (27%)	0.992	801 (20%)	330 (17%)	0.021
Length of hospital stay (days), median(IQR)	9 (5-13)	8 (6-12.8)	0.682	10 (6-15)	10 (7-15)	< 0.001

IQR, interquartile range; SD, standard deviation; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive, pulmonary disease; IHD, ischemic heart disease; CNS, central nervous system; CIRS, cumulative illness rating, scale; -CI, comorbidity index; -SI, severity index; CKD, chronic kidney disease.

Figure S1. ***Scree plot showing variation of Bayesian Information Criterion (BIC) at increasing numbers of latent classes.*** *The optimal number of explicative latent classes was chosen at the elbow of the line (N=3), corresponding to the maximum number of classes with the lowest BIC.*

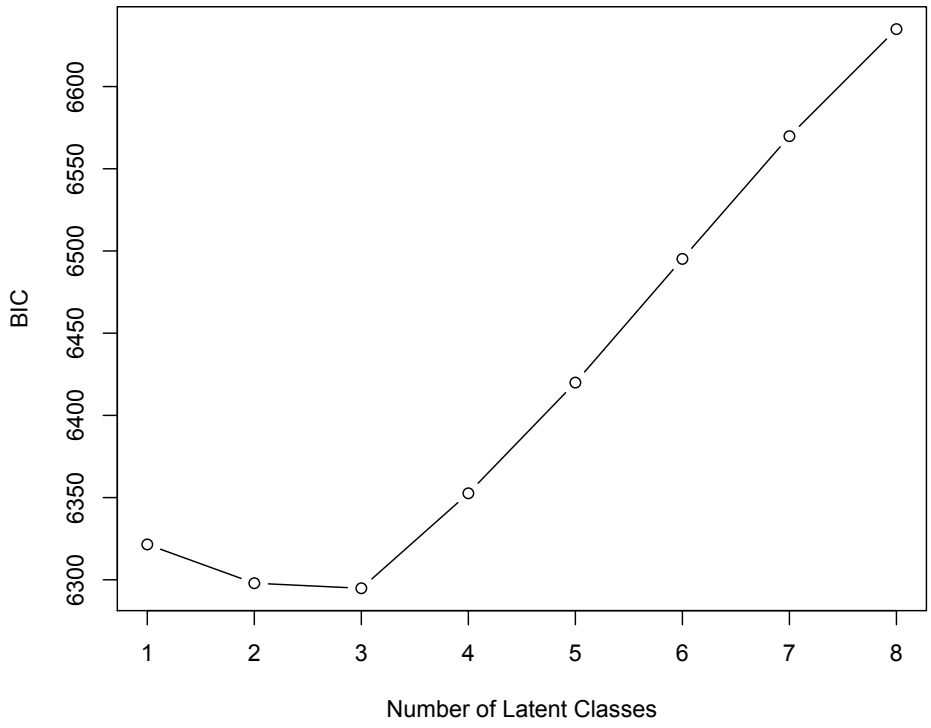

Table S4. ***Association of the different clinical phenotypes of patients with liver cirrhosis, with factors not included in LCA models and main in-hospital and post-discharge health outcomes.***

	Clinical phenotypes			
	FIT	**PSS**	**D&M**	**p**
N	150 (48%)	89 (28%)	76 (24%)	-
Age (years), median(IQR)	75 (70-78.8)	77 (72-83)**	78 (70.8-83)*	0.004
Sex (male), n(%)	111 (74%)	36 (40%)**	43 (57%)	< 0.001
Length of hospital stay (days), median(IQR)	8 (4-11)	9 (7-14)*	10 (7-15)*	0.005
Follow-up time (days), median(IQR)	90 (90-365)	90 (90-95)	90 (74.5-90)*	0.039
Previous hospitalization (within 3 months), n(%)	39 (26%)	20 (22%)	25 (33%)	0.31

Lost at FU, n(%)	43 (29%)	29 (33%)	16 (21%)	0.249
In-hospital mortality, n(%)	2 (1%)	3 (3%)	9 (12%)**$^{++}$	0.001
Incident disability, n(%)	8 (13%)	8 (35%)**	0 (0%)**$^{++}$	0.068
Rehospitalization, n(%)	36 (34%)	18 (32%)	5 (10%)**$^{++}$	0.004
Deaths, n(%)	16 (15%)	7 (12%)	21 (41%)**$^{++}$	< 0.001

FIT, relatively fit subjects with higher likelihood of HCC; PSS, poor social support; D&M, disability and multimorbidity; IQR, interquartile range.
Comparison carried out with chi-squared or Kruskal-Wallis test, as appropriate, along with Holm's correction for multiple testing. * and ** $p < 0.05$ and 0.01 vs FIT. + and ++ $p < 0.05$ and 0.01 vs PSS.

Table S5. ***Most frequent causes of hospital admission in patients with liver cirrhosis according to the different clinical phenotypes.***

	ICD9 3-digit code	**Short descriptor***	**FIT** (150 sbj)	**PSS** (89 sbj)	**D&M** (76 sbj)
Liver-related	789	Ascites	20 (13%)	17 (19%)	7 (9%)
	578, 456, 280, 648, 285	Hematemesis, Esoph varices w bleed, Iron defic anemia, Blood in stool, Anemia, Ac posthemorrhag anemia	26 (17%)	12 (13%)	8 (10%)
	571	Cirrhosis of liver NOS, Alcohol cirrhosis liver, Chronic liver disease and cirrhosis	20 (13%)	14 (16%)	10 (13%)
	348, 572, 349	Encephalopathy, not elsewhere classified, Hepatic encephalopathy, Toxic encephalopathy	11 (7%)	4 (4%)	11 (14%)
	155	Mal neo liver, primary	27 (18%)**	8 (9%)	-
		Total liver-related cause of hospital admission	68%	61%	46%
Heart-related	410, 414, 427, 248, 458	Acute myocardial infarction, Chr ischemic hrt dis NEC, CHF NOS, Cardiac dysrhythmias, Hypotension NOS	-	5 (6%)	13 (17%)
Lung-related	786, 518, 511	Dyspnea and respiratory abnormalities, Acute respiratory failure, Pleural effusion NOS	<1%	2 (2%)	9 (12%)

Infective	482, 780, 009, 995, 038	Bacterial pneumonia NOS, Fever, Malaise and fatigue NEC, Diarrhea of infect orig, Sepsis, Septicemia NOS	<1%	11 (12%)	5 (7%)

*Short descriptor is for the specific full ICD9 code retrieved from the cause of hospital admission.
** Given an overall median hospital stay of 8 days (IQR 4-11) in FIT phenotype, FIT cirrhotic patients admitted to hospital for "Malignant Neoplasm of Liver, primary" (ICD9 155) have shorter hospital stay compared to other subjects belonging to the same clinical phenotype: 4 days (IQR 2-9) vs 8 (IQR 5-12). This is likely to indicate they were hospitalized to undergo loco-regional treatment of hepatocellular carcinoma. No procedure codes were available in the REPOSI to confirm this data.
FIT, fit with HCC; PSS, poor social support; D&M, disability and multimorbidity.

5. Conclusions

Older subjects admitted to acute medical wards represent a global challenge that healthcare systems worldwide are facing with relevant difficulties, and their management still presents many open issues.[1, 2] They are characterized by multiple coexisting pathologies, frailty, disability and polypharmacy, which variably combine and interact each other to determine increased rates of ominous health outcomes, such as physical function decline, rehospitalization and, ultimately, mortality (both in-hospital and also post-discharge).[1, 2] This obviously translates into high socio-economic costs, and no strategies are currently available to forecast the occurrence and modality of presentation of these adverse events. Comorbidities often manifest with heterogeneous clinical pictures, and available clinical trials for their management have been conducted on younger populations, free from relevant comorbidities, and that poorly conform with the peculiar features of older in-patients.[3]

The present research line was focused on further deepening selected sequential topics in this complex scenario. Firstly, we showed that the prevalence of drug-drug interactions involving CYP3A4 and P-gp increases during the hospitalization of older in-patients and at discharge, and the strongest factor for this increase is constituted by polypharmacy. Secondly, we highlighted the associations of a large panel of therapy quality indicators (including Beer's and STOPP explicit list of potentially inappropriate medications, scale of anticholinergic burden and indicators of drug-drug interactions), and evidenced that none of them was consistently associated with relevant post-discharge outcomes. Only individuals with higher anticholinergic burden scale were shown to be at significantly higher risk of physical function decline. Polypharmacy confirmed again as the only therapy-related predictor of rehospitalization and death in older subjects discharged from acute care hospitals. Finally, the last study focused on a poorly explored, but significantly impacting comorbidity in older subjects, *i.e.* liver cirrhosis. Liver cirrhosis was shown to have a relatively low prevalence in older subjects admitted to medical wards for acute illness,

but patients with liver cirrhosis have a more severe burden of comorbidities and worse post-discharge outcomes. The diagnosis of liver cirrhosis was associated with rehospitalization as also shown for congestive heart failure and chronic obstructive pulmonary disease, but, at variance with these diseases, liver cirrhosis was also associated with mortality up to 1 year from hospital discharge, independently of other confounders. Older in-patients with liver cirrhosis showed 3 different clinical phenotypes, which showed differential health trajectories.

Beside study-specific considerations, some general messages stem from the overall interpretation of the obtained data. Multimorbidity and polypharmacy are strictly related aspects of older subjects, which confer high clinical heterogeneity. Comorbidities have synergistic effect, and polypharmacy accounts for increased rates of drug-drug and drug-disease interactions, and is an independent risk factor for adverse events. To note, the negative effect of polypharmacy has been robustly observed across different studies. However, it's worth underlying the modality of its expression at the clinical and prognostic level may be widely influenced by the presence and the degree of frailty, along with the burden of comorbidities.

In any case, in this scenario, medical intervention showed to be associated with increasing polypharmacy and drug-drug interaction, which uncertain accomplishment of patients' needs and priorities. Available tools were also ineffective in helping physicians to optimize drug therapy. All in all, this scenario turns to be somehow unexpected and disappointing since medical intervention is conversely expected to induce an improvement, not worsening, of patients' conditions and risk factors. The actual disease-centered model of care may be responsible for these results.[4] Indeed, the changed spectrum of health conditions, the complex interplay of biological and nonbiological factors, the aging population, and the interindividual variability in health priorities render medical care that is centered primarily on the diagnosis and treatment of individual diseases potentially harmful.[4] Accordingly, a paradigm shift would be welcome to better align medical care with health needs by integrating existing knowledge and effective strategies. Indeed, clinical decision making should be predicated on the attainment of patient goals and on the identification and treatment of modifiable biological and nonbiological factors, rather than on the management of individual diseases. This could be achievable only if an interdisciplinary and integrated

care is provided to address individual patient's needs and priorities, *i.e.* applying the so called patient-centered model of care. In this perspective, many strategies should be implemented to overcome actual structural and cultural barriers. Firstly, the transition to this new model requires a major reorganization of health care system from education to delivery system methods. Medical education should move from the classical pathophysiologic mechanisms or organ systems, toward a more integrated curriculum. Similarly, research should leave organ- and specialty-based configuration, and help in providing alternative ways for disentangling the whole complexity of older subjects. To this purpose, phenotyping studies applying clustering methods (such as K-means or latent class analysis) are absolutely needed and pertinent, because they are able to detect alternative explicative profiles based on *N* patients' characteristics and needs, beyond the classificatory aid conveyed by the concept of disease. Finally, the organization of clinical services is called to evolve to address this alternative paradigm of care, along with reimbursement criteria, that should switch from disease-specific endpoints and be based on evidence of effectiveness and on transparent societal and personal priorities.

Specific research should continue in this field in order to improve the capacity to identify older in-patients with worse in-hospital and post-discharge trajectories by disentangling the complex relations between frailty, multimorbidity and polypharmacy, and translating and adapting it at the patients' perspectives and priorities. New marker and indicator should be identified to this purpose, and an effective operational definition of frailty is eagerly awaited. Among possible experimental techniques, the application of modern technologies based on sensor arrays on different human fluids (e.g. electronic nose for the exhaled breath or electronic tongue for liquids) is worth to be pursued.

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