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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) 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 > 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.

1. 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 [9–11].

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

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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 ageing 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.

2. Materials and 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 through different sources (in accordance with the classification proposed by *Hansten and Horn* in their textbook [24] and by the FDA [25], with an additional reference focused on statins [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 ($\geq$ 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 > 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 > 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).

3. Results

3.1. 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.

3.2. 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 (Fig. 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

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

pathways.

A qualitative difference in drugs involved at discharge vs. admission was found (Fig. 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.

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).

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).

4. 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-

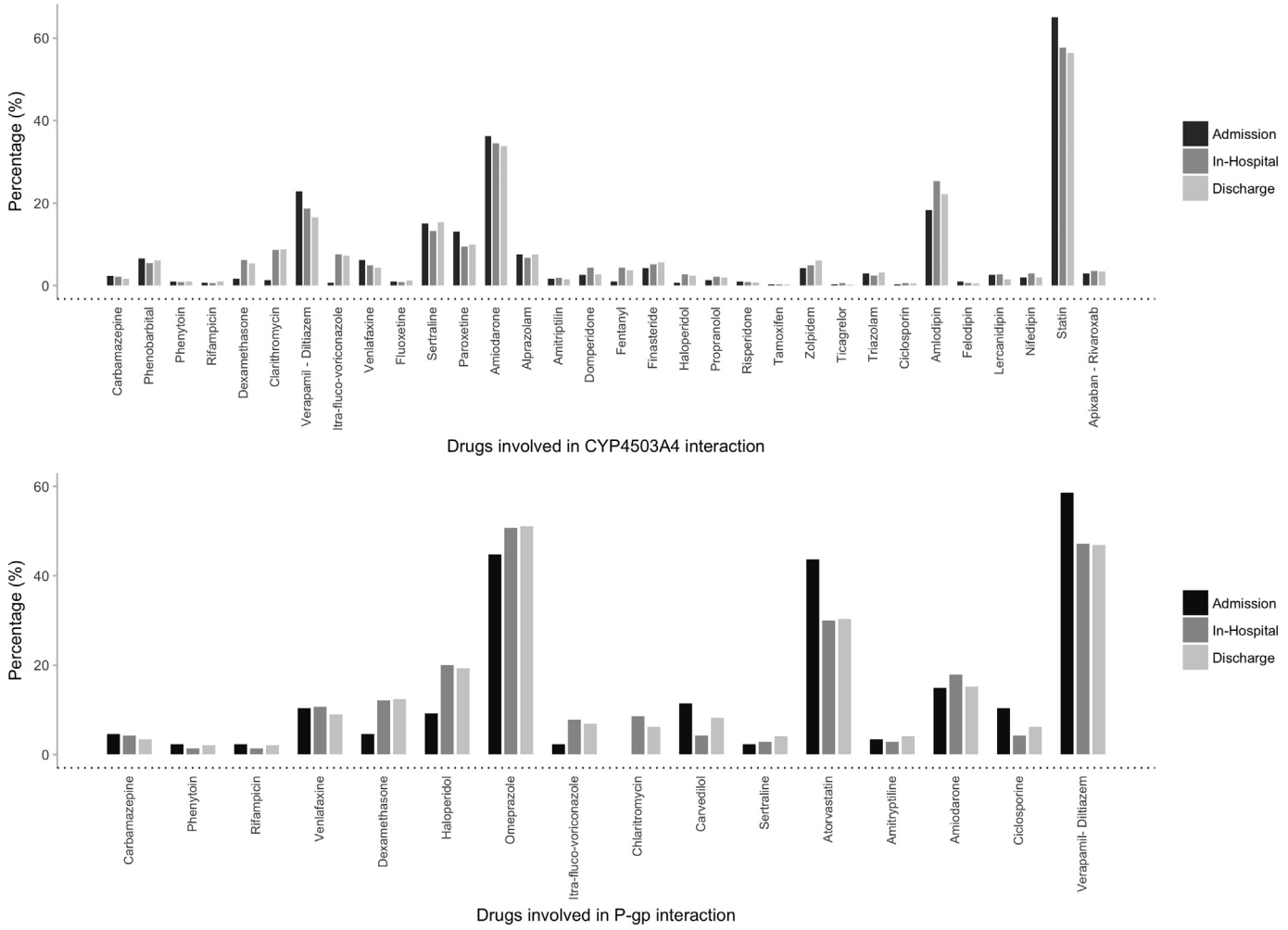

Fig. 1. Drugs involved in CYP450 3A4 (upper panel) and P-gp (lower panel) interaction at admission, in-hospital or discharge.

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.

Lastly, the sub-analysis conducted in patients who died during hospitalization and were excluded from the main analysis, has shown a prevalence of interactions not significantly different from that observed in patients discharged at home, suggesting that DDI are not associated with in-hospital mortality.

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

Table 2
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.

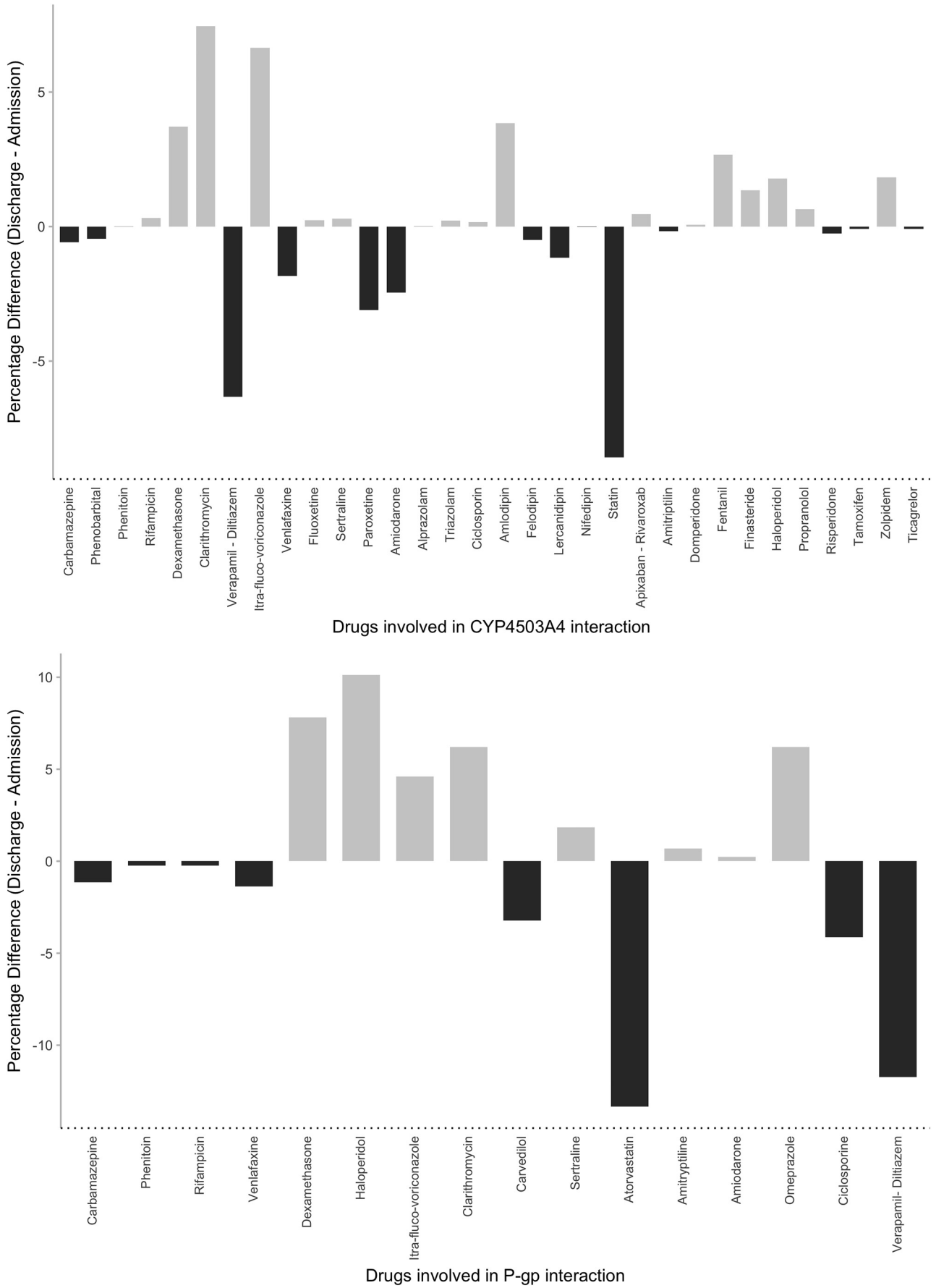

Fig. 2. Percentage difference between discharge vs admission, in drugs involved in CYP450 3A4 (upper panel) and P-gp (lower panel) interaction.

Table 3
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 (1.12–1.74)*	1.03 (0.76–1.39)	11.4	13.2	*1.18 (0.98–1.44)*	*0.97 (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).

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 (Biblio add). 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 report 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. 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.

5. Conclusion

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.

Authors disclosures

The authors declare no conflict of interest and confirm no financial interest in a business or commercial entity that relates to the manuscript.

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The final version of the manuscript has been seen and approved by all the authors. We deny any financial, personal or other relationships with drug manufacturers that could lead to a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.05.002.

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