Correction for potentially inappropriate prescribing can increase specificity when using drug prescriptions as an adjunct to diagnostic codes to assess comorbidities in older patients

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ABSTRACT

Background: Comorbidities are a growing problem in older patients in many clinical settings, but electronic records may give an unsatisfactory picture of this complexity. Analysis of drug prescriptions can add further diagnostic information to that gathered from billing diagnostic codes, but the risk exhists that potentially inappropriate prescriptions may lead to over-estimating comorbidities.
Methods: We analysed the administrative records and drug prescriptions of the 304 patients discharged during 2016 from a neurological rehabilitation unit. International Classification of Diseases – 9th revision diagnostic codes were matched with prescriptions at discharge, coded according to the Anatomical Therapeutic Chemical classification. The codes of the prescriptions not explained by the diagnostic codes were recorded, grouped, corrected for potential inappropriate prescribing, and analysed.
Results: Of the 304 patients, 295 had at least one prescribed drug not inferable from their diagnostic codes. The mean number of these prescriptions was 3.5 ± 1.9 per patient, and that of prescriptions remaining after correction for potentially inappropriate prescribing was 2.0 ± 1.5. The more frequent groups of potentially inappropriate medications were anti-acids, psychotropic drugs, laxatives, potassium supplements, cardiovascular drugs and lipid modifying agents.
Administrative databases underestimate the complexity of older patients in neurological rehabilitation wards. More reliable data can be obtained by adding the analysis of drug prescriptions, but correction for potentially inappropriate prescription seems necessary to avoid an over-estimation of comorbidities.

Key words: Inappropriate prescribing, Anatomical Therapeutic Chemical (ATC) classification of drugs, International Classification of Diseases- 9th revision (ICD-9), Comorbidities.

INTRODUCTION

International Classification of Diseases – 9th revision (ICD-9) codes have been used to measure the comorbidity burden since the end of last century [1,2,3]. This trend has continued to grow, though some concerns have risen over time.

First, methods of measuring comorbidity have long been debated [4] and comorbidity itself can be defined in different ways, though the definition contained in NICE guidelines [5] appears now to be suitably appropriate.

Second, the definitions used to identify diseases vary greatly in the literature, as is the case, for example with cerebrovascular accidents [6]; moreover, the phenotypes in databases are not uniformly identified and harmonization is needed [7].

Finally, errors could be due to the coding system itself as it happens for example when the same code can describe two different clinical entities, as it happens for the ICD code 410.9, comprising both myocardial infarction with and without ST segment elevation[8]. This can be a problem also when coding neurological diseases: for example, while ischemic stroke can be distinguished from hemorragic stroke on the basis of the ICD code (433.x for the first, 431 and 432.x for the second), this distinction is lost if, as it often happens in rehabilitative settings, only the consequent hemiplegia is coded. This is due to the fact that the ICD system differentiates between hemiplegia due to a damage of the dominant (code 438.21) or non dominant (code 438.22) hemisphere but does not consider if the cause of the damage is a thrombosis or a bleeding.

It is now well established that to deal with the problems related to the use of electronic health records, integration with further information and implementation of algorithms is necessary[9,10,11], especially for chronic conditions as diabetes [12].

One possible way of getting this information is the analysis of drugs prescriptions. These are steadily increasing [13], and polypharmacy is frequent, especially in elderly people with chronic conditions like heart failure [14]. Moreover it is associated with a number of adverse outcomes [15,16]. Therefore it appears that taking into account medications can yield relevant information on diseases especially in older people. Analysis and grouping of prescribed drugs can be conveniently performed using the criteria of the Anatomical Therapeutic Chemical (ATC) classification [17], giving a unique alphanumeric code for each active principle, which can be used appropriately in clinical studies [18]. For example, it has been used to measure prescriptions in frail patients [19], to assess the concordance of therapy with self-reported diseases [20], and, by ourselves, to have an insight into the health status of populations for whom no other epidemiological data are available [21,22], though caution should be used in older patients in consideration of the potential presence of inappropriate prescriptions [23] that can represent an important confounding factor.

Having a more detailed knowledge of the degree of complexity of older patients discharged from rehabilitative units after a major acute neurological event is fundamental for a better prognostic evaluation. For example, stroke survivors experience long-term limitations in participation, defined as "the person's involvement in a life situation"[24], and these limitations depend on several factors, including increasing age and comorbidities [25,26]. Defining disability in itself without evaluating its complexity is not sufficient to have a clear picture of elderly patients after a neurological event and for this reason using only the data available in administrative databases could be misleading.

In this study, we have evaluated the presence of unreported comorbidities by matching the ICD-9 codes with the drugs prescribed at discharge. We also investigated whether and to what extent potentially inappropriate drugs prescriptions can alter the outcome of this analysis.

METHODS

This retrospective study was carried out evaluating data of all the 313 patients with a major neurologic event discharged during 2016 from a 46-bed ward of a rehabilitative hospital in Lombardy, Italy (Gruppo San Donato, Carate Brianza). To be eligible, patients had to complete the projected rehabilitation program. Patients deceased (n=3) and those transferred in emergency to an acute care hospital (n=6) were excluded (see Figure 1).

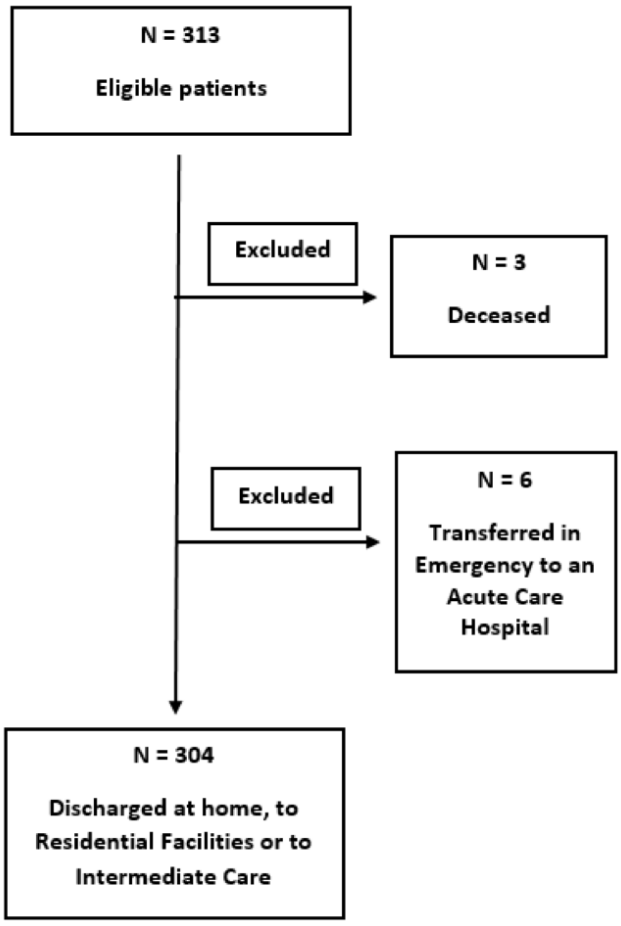
This left 304 patients discharged home, to residential facilities or intermediate care; the primary diagnoses with the associated ICD-9 codes are shown in Table 1.

To assess if the analysis of drug prescriptions at discharge could add further information on patients' comorbidities, we analyzed two databases: the administrative database containing the ICD-9 diagnostic codes (variable of interest: administrative diagnostic codes) and that containing all the discharge letters with drug prescriptions and follow-up suggestions (variable of interest: ATC classes of drugs prescribed at discharge).

For each patient, all ICD-9 codes were extracted from the first database and matched with the prescriptions obtained from the second database.

All drugs at discharge were identified according to the ATC classification [17], as previously described [21]. Briefly, the World Health Organisation (WHO) ATC/DDD 2017 index was used, which includes five levels of classification for each active principle: anatomical subgroup, therapeutic subgroup, pharmacological subgroup, chemical subgroup and chemical substance; we stopped at the fourth level in order to group molecules used to treat the same conditions (e.g.: A02B comprises omeprazole, pantoprazole, esomeprazole, etc). We then associated for each patient, the ICD and the ATC codes and if none of the ICD codes described a condition for which a medication could be prescribed, this medication

FIGURE 1. Flow-chart explaining patient selection.



(i.e. its ATC code) was considered outside the coded diagnosis and thus possibly related to a condition not recorded in the final discharge form. All these ATC codes which did not match with an ICD-9 diagnostic code were then recorded as e-ATC (excess-ATC). We then searched which ATC codes contained potentially inappropriate medications according to Beers criteria [24]. Briefly, these criteria give a directory of drugs which should not be prescribed in elderly patients, since their harmful adverse effects could overwhelm their usefulness. These criteria are applicable to all older adults with the exclusion of those in palliative and hospice care. They are regularly maintained by the American Geriatric Society and therefore sufficiently up-to-date. We used the list of medications labeled as "Potentially Inappropriate in Older Adults" in reference 27. All the medications of the list were recoded using the ATC codes and these were compared with the ATC codes of our patients; all the matching ATC codes were labeled as potentially inappropriate. We then subtracted all the codes of potentially inappropriate prescriptions from the list of e-ATC codes of our patients, obtaining in this way ce-ATC (corrected excess-ATC).

The final database thus contained both ICD-9 and ATC codes for each patient at discharge, plus demographic data.

Finally, to get a more concise indication of the disease indicated at discharge by prescriptions we grouped the ATC codes as suggested by others[19]; we thus obtained 20 groups, shown in table 2.

Statistical analysis was performed using SDA-WINKS and SPSS statistical software. Unless otherwise specified, data is expressed as mean + SD. Simple and multiple linear regression and correlation analysis were used to evaluate the associations of interest; t test and X^2 test were used as appropriate to compare groups; for example t test was used to evaluate the difference in the mean number of prescribed ATC codes between groups, after testing for normality, and X^2 was performed to evaluate the presence or absence of e-ATC in different age groups.

Both e-ATC and ce-ATC were analysed.

The design of the study was communicated to the local ethics committee (ATS Monza e Brianza) and, as the Italian procedure requires, after six weeks without receiving objections, data collection began. All the forms in the data-base contained an informed consent to the use of data for administrative and research purposes signed at the moment of admission by each patient or by his/her next of keen in case neurologic conditions did not allow the patient to understand or to sign.

RESULTS

The mean age of our 304 patients was 76.1 ±12.7 years (median 79.0 years) with females (n=177) being significantly older than males (n=127): 78.6 ± 11.7 vs. 72.8 ± 13.3 years (P = 0.001; t = 4.02, 95% CI: 2.91 – 8.68). Despite this, the number of ICD-9 codes and of medicines prescribed at discharge did not differ in the two groups.

The mean number of e-ATC was 3.5 ± 1.9/patient, with no difference between males and females (3.5 +1.8 vs. 3.6 ± 2.0; P = 0.6). After correcting for potentially inappropriate prescriptions, a significant number of medications remained (mean 2.0 ± 1.5).

In a linear correlation model, age was slightly correlated both with the number of ICD-9 codes (r = 0.22; P <0.001) and with the number of drugs at discharge (r = 0.2; P < 0.001) and, as a consequence, they showed significant correlation (r = 0.39; P <0.001).

In a multiple linear regression model the number of e-ATC showed an association with age, number of ICD-9 codes and number of medicines at discharge (R-square 0.44, Cohen's f-square 0.79; analysis of variance to test regression relation: mean square 257.97, F 78.49, P <0.001). The correlation between number of e-ATC and age was significant (r = 0.18; P = 0.001) as it was that between e-ATC and the number of drugs at discharge (r=

TABLE 1. Primary ICD-9 codes of the study group

ICD-9 CODE	DESCRIPTION	NUMBER OF PATIENTS
331.4	Obstructive hydrocephalus	3
332.0	Paralysis agitans	2
332.1	Secondary parkinsonism	1
333.0	Other degenerative diseases of the basal ganglia	2
342.11	Spastic hemiplegia and hemiparesis affecting dominant side	1
341.2	Myelitis	2
343.2	Quadriplegia	2
344.04	Quadriplegia,C5-C7, incomplete	1
344.1	Paraplegia	4
357.0	Polyneuritis	2
357.81	Chronic inflammatory demyelinating polyneuritis	1
357.89	Other inflammatory and toxic neuropathy	1
357.9	Unspecified inflammatory and toxic neuropathy	6
438.21	Hemiplegia and hemiparesis affecting the dominant side	98
438.22	Hemiplegia and hemiparesis affecting the non-dominant side	70
438.84	Ataxia	34
453.3	Vertebrobasilar artery syndrome	2
722.83	Post-laminectomy syndrome	1
728.3	Muscle atrophy	8
781.2	Abnormality of gait	47
907.0	Late effect of intracranial injury without skull fracture	16

0.64; P < 0.001); no significant correlation was seen between the number of e-ATC and that of ICD-9 codes.

After correcting for potentially inappropriate prescribing, some e-ATC groups disappeared and the correlation of age with the number of e-ATC at discharge remained, but became weaker (r = 0.13; P = 0.02). On the contrary, the importance of age in determining the probability of finding e-ATC at discharge was demonstrated by dividing the entire population into two groups according to age (<65 years and ≥ 65 years): the older group had significantly more subjects with e-ATC (249/250 vs 46/54; P <0.001 at Chi square). The same was true for ce-ATC (221/250 vs 37/54; P <0.001).

After correcting for potentially inappropriate prescribing, a good correlation remained with the number of prescriptions at discharge (r = 0.52; P <0.001).

Figure 2 shows the pattern of e-ATC and ce-ATC in the whole population divided according to age decades.

We also evaluated if a given main diagnosis was responsible for a different number of e-ATC, by comparing their number for the three more frequent ICD-9 codes: 438.21 (hemiplegia affecting dominant side), 438.22 (hemiplegia affecting non-dominant side), 438.84 (ataxia), but the means of e-ATC were not significantly different in the three groups (3.4±1.9, 3.7±1.9 and 3.2±1.8 respectively; Anova P values for group comparisons: 0.4, 0.8, 1.0).

The total number of e-ATC for the 304 patients of the study was 1065, among which the various ATC classes were represented with conspicuous differences. The A02B class, comprising drugs for acid related disorders was the most represented (n=217), followed by laxatives (n=75) potassium supplements (n=71), lipid modifying agents (n=60), psychoanaleptics (n=53) and psycholeptics (n=51); together, these six groups accounted for almost half of the total e-ATC (49.5%).

Given the major part played by drugs in the A02B group, we evaluated how many patients had a record at discharge of an ICD-9 comprised between 520.xx and 579.xx (diseases of the digestive system) and found none.

Correcting for potentially inappropriate prescriptions lead to the elimination of the following ATC groups: A02B (drugs for acid related disorders), A03F (propulsives), C01A (cardiac glycosides), C02A (antiadrenergic agents), C01B (antiarrhythmic drugs), C02C (clonidine and alpha blocking agents), M01A (nonsteroidal anti-inflammatory drugs), N03A (antiepileptic drugs), N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics and sedatives, N06A (psychoanaleptics). This left a total of 620 ce-ATC.

TABLE 2. ATC class composition of the 20 disease groups. BPH: Benign prostatic hyperplasia

GASTRIC PROTECTANTS	A02B											
OTHER GASTROENTERIC	A03F	A05A	A07A	A07F								
ANTI-DIABETICS	A10A	A10B										
BONE METABOLISM	A11C	A12A	M05B									
LAXATIVES	A06A											
POTASSIUM	A12B											
ANTI-THROMBOTICS	B01A											
ANTIANEMICS	B03A	B03B	B03X									
CARDIOVASCULAR	C01A	C01B	C01D	C01E	C02A	C02C	C07B	C08C	C08D	C09A	C09B	C09C
DIURETICS	C03C	C03D	C03A									
STATINS	C10A											
DRUGS FOR BPH	G04C											
THYROID	H03A	H03B										
CYTOTOXICS	H02A	L02B										
PAIN KILLERS	N02A	N02B										
NERVOUS SYSTEM	N03A	N04B	N06D									
PSYCHOTROPIC	N05B	N05C	N05A	N06A								
EYE-DROPS	S01E	S01X										
BRONCHODILATORS	R03A	R03B										
ANTI-HISTAMINES (Cetirizine)	R06A											

To estimate which diseases escape detection more frequently when analyzing administrative databases reporting only ICD-9 codes, we then used the drug groups previously described and counted the number of patients and their percentage in each group. This gives an overall picture, though important details can be missed: e.g. in the group for thyroid disease both thyroid hormone substitutes and anti-thyroid drugs are comprised, but the latter are exceedingly fewer (3 vs 24), so hypothyroidism is missed much more frequently than hyperthyroidism. This cumulative data is shown both for e-ATC and for ce-ATC in Figure 3.

DISCUSSION

In older patients, life expectancy and quality of life after an acute event depend not only on the event itself, but also on several factors related to their general conditions such as frailty [28], capability [29], drug burden [30] and comorbidities [5]. The latter have a well-known role in the outcome of patients with an acute neurological event [24,25,26]. Therefore, identifying comorbidities is of paramount importance both for epidemiological and prognostic purposes. When using administrative databases this may not be easy, and it may be even more complicated in rehabilitative settings since the rehabilitation diagnostic codes have a financial value for reimbursement, while this is only seldom true for the codes of comorbidities. In spite of their billing nature, administrative databases are used to evaluate comorbidities since more than thirty years ago [1,3], sometimes together with further information from other sources as medical notes. The evaluation of patient's medications using the ATC classification method could be a useful tool and indeed it has already been used in several situations by other researchers [19,20,31]. In this study we have used it to evaluate if patients discharged from rehabilitation after a major neurological event are prescribed drugs which cannot be matched with their diagnoses. Moreover we considered if potentially inappropriate medications can be a relevant confounding factor when analyzing drug prescriptions at discharge. To deal with potentially inappropriate prescriptions we used Beers criteria [27]. Though it has been recently suggested that using STOPP/START criteria could me more appropriate [32] we chose Beers criteria because a more recent revision (2015) is available and they are now regularly updated by the American Geriatrics Society. We found that some prescriptions at discharge were not explained by the

FIGURE 2. Number of patients with one or more e-ATC and one or more ce-ATC prescriptions grouped by age decades.

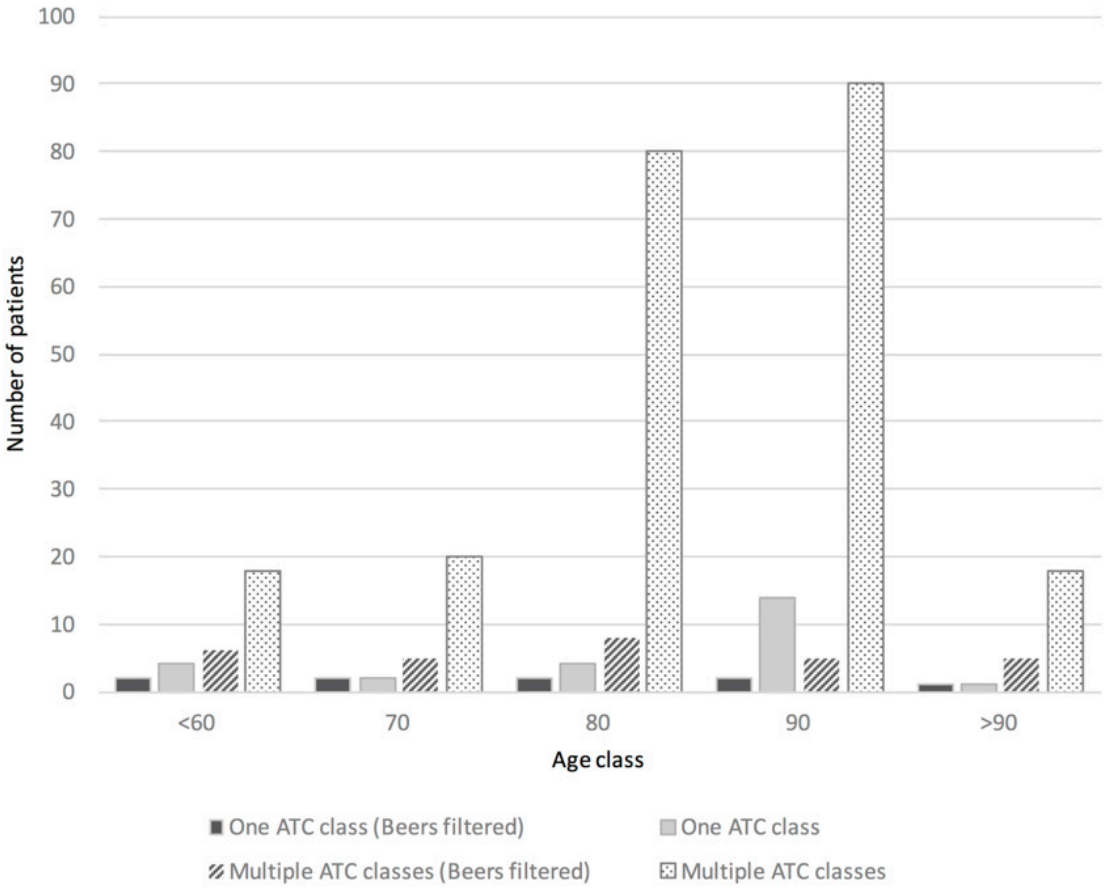
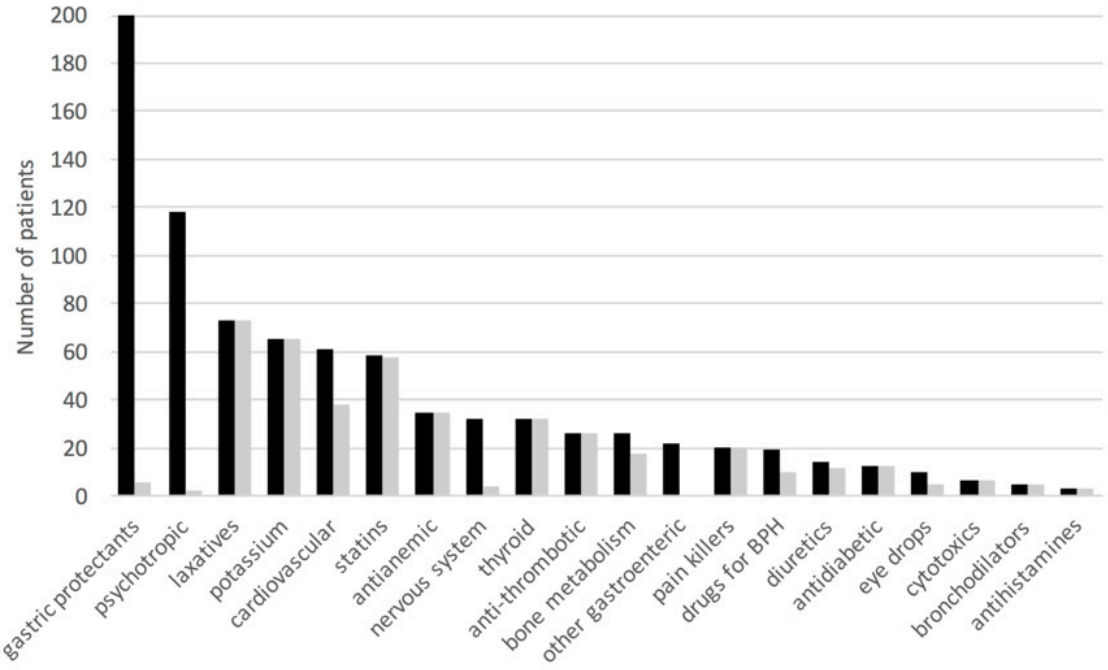


FIGURE 3. Number of patients in each "disease group" before (dark bars) and after (light bars) correction for potentially inappropriate prescribing.



diagnoses found in the administrative databases and that their number was higher in patients with a higher number of prescriptions, possibly due to the presence of more comorbidities. This remained after correcting for potentially inappropriate drugs. The effect of age is not clearly defined by our study. On one hand it is only weakly correlated with the number of e-ATC and ce-ATC; on the other, the probability of finding patients with both e-ATC and ce-ATC is significantly higher among those over 65.

The method we used, cancelling all drugs considered inappropriate by the Beers criteria can result in the potential loss of some diagnoses, but it increases the specificity and gives a more reliable idea of existing co-pathologies. As an example, the A02B ATC code (containing proton pump inhibitors) disappeared after correcting for inappropriate prescription; however, this correction does not seem to cause a diagnostic loss, since in our patients gastric protectants, especially proton pump inhibitors, are mainly used to prevent gastric damage by long-term use of acetylsalicylic acid. Therefore, no diagnosis of gastric disease is underestimated; moreover, their use for this type of prevention can be questioned in older patients [33].

Different considerations have to be made for psychotropic drugs, also significantly reduced with the application of Beers criteria. First, though anxiety seems to be a frequent problem after stroke, affecting almost 25% of patients, many doubts still exist on the benefits and risks of its treatment and, more generally anxiolytics and antidepressants risk to be inappropriately prescribed in the elderly [27]. So, the reduction in psychotropic drugs caused by the correction for inappropriate prescribing does in effect cause a loss in diagnoses, but it should be considered that the majority of such prescriptions appear to be inappropriate and thus should not have been present in the discharge letter. In this case an alternative method should be evaluated to pick up these diagnoses when not present in administrative records.

The group of anticoagulant/antithrombotic medications and that of lipid lowering agents should be considered cautiously since both these classes of drugs are frequently used in secondary prevention after ischemic stroke; moreover, the ATC class B01A comprises also drugs used to prevent thromboembolism in bedridden patients, a condition that can be present in elderly people suffering the consequences of major neurological event. Therefore, these categories could more likely reflect the presence of consequences of the acute event rather than that of comorbidities.

For laxatives (ATC class A06A), their use could be due to constipation induced by concomitant treatment with opioids, frequently used in elderly people to treat non-cancer pain and responsible for such a debilitating side effect. However, this does not seem to be the case with our patients since very few of them were on opioids (ATC classes N01A and N02A).

Finally, for anti-epileptics, it should be noted that they are lost after correcting for potentially inappropriate prescribing; this is due to the fact that they belong to the same ATC class (N03A) as many benzodiazepines and barbiturates, which the Beers criteria strongly recommend to avoid [27]. On the other hand, seizures are frequently a consequence of stroke or major central nervous system surgery. Therefore, also in this case, what we miss is a condition due to the event that lead to patient's admission more than a separate comorbidity.

The remaining groups can be considered as comorbidities. It is interesting to notice that important comorbidities such as cardiovascular diseases could be missed using only data available in administrative databases. On the contrary analysis of medications prescribed at discharge helps in detecting comorbidities, and this remains true also after correcting for potentially inappropriate prescriptions.

Significance for Public Health

The fact that our patients had a mean of two possible comorbidities unrevealed by administrative records can entail several important consequences. First, it does not yield a reliable picture of patients discharged after neurological rehabilitation and this is important when planning the follow-up of these patients and evaluating their need for further assistance. Second, it warns on the crude utilization of administrative data for epidemiological studies, which could be relevant when planning public health interventions.

A consideration has to be made on the elimination of potentially inappropriate drugs from those prescribed at discharge, according to Beers criteria: this allows to obtain a more reliable picture of the real comorbidities in these older patients. Therefore we think this is a useful method when performing this type of analysis.

We are aware of the limitations of this preliminary research and believe that further studies in this field would help to better characterize comordities in this population.

Conflict of interest

The authors report no conflicts of interest.

Ethics approval

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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