Use of potentially inappropriate medications among older outpatients and inpatients in a tertiary care hospital in Malaysia

Syed Shahzad Hasan[1], Ismail Abdul Sattar Burud[2], Chia Siang Kow[3], Muhammad Kamran Rasheed[4], Karmelia Sook Ching Chan[3], Peik Khon Tay[3], Syed Imran Ahmed[3]

[1]Department of Pharmacy, University of Huddersfield, Huddersfield, United Kingdom

[2]School of Medicine, Department of Surgery, International Medical University, Malaysia.

[3]School of Pharmacy, International Medical University, Malaysia

[4]College of Pharmacy, Qassim University, Al-Qassim, Saudi Arabia

Contact Details:

SSH: S.Hasan@hud.ac.uk

IAB: ismail_burud@imu.edu.my

CSK: chiasiang_93@hotmail.com

MKR: mk.rashed@qu.edu.sa

SCC: karmelia0208@gmail.com

PKT: peikkhon_94@hotmail.com

SIA: sia194@yahoo.com

Correspondence

Dr Syed Imran Ahmed, MClinPharm, PhD.

Senior Lecturer

Head, Department of Pharmacy Practice

School of Pharmacy

International Medical University

Kuala Lumpur, 57000, Malaysia

Email: sia194@yahoo.com

Running Head: Medication appropriateness in elderly patients

ABSTRACT

Background: Older individuals are seemingly having more medical conditions, which predispose them to a greater risk of polypharmacy. Potentially inappropriate medications (PIMs), including those having anticholinergic and sedative properties, are common in their prescriptions, often associated with functional decline and negative health outcomes. Thus, this study reports proportions of inappropriate drugs and drug burden exposures and its correlation with patient-reported outcomes (PROs) among cognitively intact older adults admitted to a ward or visiting the outpatient clinic at a tertiary care hospital in Malaysia.

Methods: This cross-sectional study included data from 344 older (173 inpatients, 171 outpatients), aged 60 years and above, through validated questionnaires. Medication appropriateness was assessed via Medication Appropriateness Index (MAI) tool, whereas, Beers and Screening Tool of Older Person's Potentially Inappropriate Prescribing (STOPP) criteria were used to evaluate PIMs & potentially inappropriate prescribing (PIP), respectively. The Drug Burden Index (DBI) and polypharmacy, as well as PROs, included Groningen Frailty Indicator (GFI), Katz Index of Independence in Activities of Daily Living (Katz ADL) and Older People's Quality of Life (OPQOL) were also evaluated.

Results:
Overall, inpatients received significantly higher medications (6.90 ± 2.70 vs. 4.49 ± 3.20) than outpatients. A significantly higher proportion of inpatients received at least one PIM (65% vs 57%) or PIP (57.4% vs. 17.0%) and higher mean MAI score (1.76 ± 1.08 and 1.10 ± 0.34) and DBI score (2.67 ± 1.28 vs. 1.49 ± 1.17) than outpatients. Inpatients had significantly higher total OPQOL (118.53 vs. 79.95) and GFI score (5.44 vs. 3.78) than outpatients. We only found significant correlations between GFI and DBI and total OPQOL and the number of PIMs.

Conclusions: Proportions of PIMs and DBI exposure were significantly higher in an inpatient setting. No significant correlations between exposures to inappropriate medications or drug burden and PROs were observed.

Keywords: Medication appropriateness; medication burden; physical functioning status; outpatients; elderly people

What is already known about this topic?

Older people living in aged care homes are at significant risk of receiving potentially inappropriate medications and carry significant drug burden.

What does this article add?

The present study conducted in a clinical setting (in & out-patient settings) to explore medication appropriateness, drug burden, and patient-reported outcomes.

Introduction

Population ageing has become a virtually global phenomenon.[1] In Malaysia, as of the second quarter of 2019, the population ages 65 and above constituted 6.7% of the total population.[2] While the figure may look insignificant, it is worth noting that the figure is in increasing trend and has more than doubled in 20 years' duration (0.9 million or 3.9% of the total population in 1999).[3] The older population is projected to triple to about 6 million in another 20 years' duration.[3]

Ageing is associated with a decrease in physiological and homeostatic functions of the body, which leads to an increase in the vulnerability to the development of multiple chronic non-communicable diseases such as hypertension, dyslipidaemia, and diabetes mellitus.[4] The existence of multi-morbidity presents a challenge to the therapeutic management in older patients and inevitably leads to the prescription of several medicines in this population.[5] Careful prescribing practices among older patients are needed to ensure medication appropriateness.

Several implicit and explicit criteria have been developed to assess the medication appropriateness in older patients. Among these is the detection of PIMs using explicit criteria, including the Beers and the Older Person's Potentially Inappropriate Prescribing (STOPP) criteria.[6,7] On the other hand, the Medication Appropriateness Index (MAI) is a reliable, valid, and standardized assessment tool with implicit criteria to evaluate medication use in elderly patients.[8] In another approach, a Drug Burden Index (DBI) has been developed to measure an individual's exposure to medications with anticholinergic and sedative effects.[9]

Although the evaluation of medication appropriateness in older patients is of utmost importance, there is a lack of data on potentially inappropriate medication use among this population in the different healthcare settings in Malaysia. To the best of authors' knowledge, there is only a recent study that reported the potentially inappropriate medication use among Malaysian primary care patients (21.3%) while no studies have reported on inappropriate medication use among Malaysian patients receiving secondary or tertiary care.[10] Therefore, having a study at a larger set-up (tertiary care) would be advantageous as it could provide a better sampling of the variety of the diseases and patients, which could be taken as a better representation of the Malaysian population receiving medical care. Moreover, the studies exploring the association between medication inappropriateness and patient reported outcomes are largely conducted in aged care settings and very rarely in outpatient or inpatient hospital settings. This study specifically aimed to examine whether DBI and inappropriate medicines (e.g. Potentially Inappropriate Medication (PIM)) use were

correlated with patient reported outcomes (PROs) (e.g. frailty) among older inpatients and outpatients in Malaysia. We also aimed to report the proportion of patients exposed to inappropriate medications and DBI.

Methods

Study design and population

This was a cross-sectional and descriptive study of elderly people, aged 60 years and above, admitted to a ward or attended outpatient clinics at Hospital Tuanku Jaa'far Seremban (HTJS), a tertiary care hospital under the Ministry of Health (MOH) Malaysia. Patients aged 60 years and above, any gender or ethnicity attending outpatient clinics or admitted to a ward, patients who provided consent, able to articulate, as well as having at least one long term medical condition and/ or receiving one long-term medication, were recruited.

Sample size and sampling procedure

The sample size was estimated using a standard formula. Based on an estimation of the population aged ≥ 60 years (6.7%), 6% margin of error, and 95% confidence interval, the required sample size was 267.[11-13] Consenting patients admitted to a ward or attending outpatient clinics were selected using convenience sampling. Information was provided to patients prior to obtaining their written consent.

An interviewer-administered data collection tool consisted of socio-demographic information, a combination of questionnaires as well as medical conditions, medications use, and biochemical measurements were used to gather cross-sectional data. Such forms were used to gather information from patients' medical records and interviewing patients. Data sources included: scanned paper notes, medication charts, laboratory results, drug usage summary reports, and discharge sheets. The scanned paper notes, medication charts, laboratory results, and discharge sheets were used as the main sources of information for each patient. We also extracted the number of long-term medical conditions for each patient (list of comorbid conditions in supplementary Figures S1 and S2).

All data were recorded on Microsoft Excel. Appropriateness of prescribing was measured against the standard criteria. The validated English version of the data form was translated into Malay and Chinese using a forward–backward translation process, with the aim of obtaining versions conceptually equivalent to the English version. This has been reported in our previous in article.[35,36]

Tools to measure medication appropriateness

MAI was used to measure the appropriateness of each medication based on 10 criteria, which were an indication, effectiveness, dosage, directions, directions practical, drug-drug interaction, drug-disease interaction, duplication, duration, and cost. MAI ranged from 0 (appropriate) - 18 (maximal inappropriateness) for each medication[8]. The total MAI of each participant was obtained by summing up MAI of all medications prescribed. The average MAI of each participant was then calculated.

Beer's Criteria (2015) was used to identify potentially inappropriate medications (PIMs) in participants' drug regimens.[14] Beers Criteria was a list of medications to avoid or use with caution when prescribing for elderly patients.[14] STOPP 2014 criteria were used to identify potentially inappropriate prescribing (PIP) in participants' drug regimens.[7] Average PIPs were calculated using STOPP criteria. Polypharmacy was defined as five or more than five concurrent medications being dispensed at any one time during the study period.

DBI was used to quantify the medication burden attributed to each anticholinergic and sedative medication, using the equation below.[9] The total DBI of each participant was then calculated by summing up DBI of all anticholinergic and sedative medications prescribed.

$$\boldsymbol{DBI} = \frac{\boldsymbol{D}}{\boldsymbol{D} + \boldsymbol{\delta}}$$

where D is the daily dose taken by the individual within 24 hours extracted from dosing instructions available through medical records, and δ is the minimum efficacious dose that was approved and registered. Herbal medicines, health supplements, and medications prescribed on a when required basis were excluded from the DBI calculations

The information about the medicines use was based on patients' medical records obtained from each inpatient and outpatient. The data collected included the name of the drug, dosing regimen, and instructions for all medications used in the three months prior to the start date of the study. Exposure to a PIM, PIP, or DBI medication was defined as exposure to an affected medication during the three-month period.

Tools to measure physical health outcomes

Groningen Frailty Indicator (GFI) was used to measure frailty. It comprised of 15 items for evaluation. The total score ranged from 0 (Capable of performing normal activities without restriction) to 15 (complete disability).[15] For this study, participants with GFI of 4 and above, were considered frail. Katz Activity of Daily Living (ADL) was used to determine an

individual's independence in carrying out daily activities. Six activities were assessed. The total score ranged from 0 (fully dependent) to 6 (fully independent).[16]

Older People's Quality of Life (OPQOL) was used to assess the quality of life. It comprised of eight domains, including life overall, health, social relationships, independence, control over like, freedom, home, and neighbourhood, psychological and emotional well-being, financial circumstances, leisure, and activities. For this study, OPQOL total score and score of each domain were calculated. OPQOL total score ranged from 35 (worst possible QOL) to 175 (best possible QOL).[17,18]

Ethical approval and confidentiality

Ethical approval was obtained from the International Medical University Joint-Committee (IMU-JC). This research was registered under the National Medical Research Register (NMRR) (NMRR-17-776-35607). No personal details of patients and healthcare professionals (HCPs) were recorded other than the consultant in charge of each surgery for the patient. No personal details of patients were recorded as each patient was given a unique identifier to distinguish between them.

Statistical analysis

Statistical analysis was carried out with the use of SPSS® version 25, keeping 0.05 as the level of significance. Descriptive analysis was used to summarise the characteristics of participants. For all of the categorical data to be stated, the frequency of patients per category was analysed and recorded with the associated percentages. For the continuous data, mean and standard deviation with any associated range were analysed and recorded. Where applicable, the p-value was computed for categorical variables using the chi-squared test and continuous variables using the independent-sample t-test to distinguish whether the characteristics are statistically significant or not. Spearman's correlation was performed to examine the correlations between medication appropriateness (e.g. average PIMs, PIPs, MAI), medication burden (total DBI), and physical functioning status (Katz ADL, GFI, OPQOL). We used NVivo® to produce a figure illustrating the participants' medical conditions.

Results

A total sample of 344 older patients (173 inpatients, 171 outpatients) was recruited; which was more than the estimated sample size of 267. Patients' demographic characteristics were summarised in **Table 1**. The mean ages for hospitalised patients and outpatients were 70 years (SD=6.77) and 71 years (SD=8.65), respectively, with no significant differences between inpatients and outpatients (p=0.067). Female patients made up 45.7% and 44.1% of inpatients and outpatients, respectively, with no significant differences between inpatients and outpatients (p=0.773). Hypertension and Diabetes Mellitus were the two most associated medical conditions among the participants (**Figure 1**), however, no significant differences were found between in and outpatients and disease conditions.

Overall, inpatients received significantly higher medications (6.90 ± 2.70 vs. 4.49 ± 3.20, p=0.001) compared to outpatients. About 65% (n=113) of inpatients and 57% (n=98) of outpatients received at least one PIM. Similarly, significantly higher proportion of inpatients (57%, n=101) received at least one PIP than outpatients (17.0%, n=29) (**Table 2**). Inpatients received a significantly higher mean number of PIP compared to outpatients (1.11 ± 1.25 vs. 0.33 ± 0.82, p=0.001) (**Table S1**). Almost all hospitalised patients (99.4%, n=172) had a DBI score of more than 1, while 87.1% (n=149) of outpatients had a DBI score of more than 1. There was also a significant difference between older inpatients and outpatients in terms of DBI score, where inpatients and outpatients had mean DBI scores of 2.67 ± 1.28 and 1.49 ± 1.17, respectively.

More than three-quarter of inpatients (78.6%, n=136) were exposed to polypharmacy, while only less than half of outpatients (38.0%, n=65) was exposed to polypharmacy. Inpatients and outpatients had mean MAI scores of 1.76 ± 1.08 and 1.10 ± 0.34, respectively, with a significant difference between the two patient settings (p=0.001) (**Table 3**).

Inpatients had significantly higher total OPQOL (118.53 vs. 79.95, p=0.001) and GFI score (5.44 vs. 3.78, p=0.001) than outpatients. Overall, weak correlations were observed between medication appropriateness and OPQOL and medication appropriateness and GFI, in both inpatients and outpatients ($r<0.80$). The mean number of PIMs was inversely correlated with the mean OPQOL score in both inpatients (r=-0.085) and outpatients (r=-0.157), but statistical significance was only observed among outpatients (p=0.040). The mean DBI score was positively correlated with the mean OPQOL score among inpatients (r=0.034) but negatively correlated with the mean OPQOL score among outpatients (r=-0.069), with no observed statistical significance in both groups of patients ($p>0.050$). The mean MAI score of both hospitalised patients (r=-0.036) and outpatients (r=-0.092) were inversely correlated with the mean OPQOL score, with no statistical significance observed ($p>0.050$).

The mean number of PIMs was positively correlated with the mean GFI score in both inpatients (r=0.097) and outpatients (r=0.025), with no statistical significance observed (p>0.050). While the mean number of PIPs was inversely correlated with the mean GFI score among inpatients (r=-0.065), the reverse was true among outpatients (r=0.041). However, statistical significance was not observed in both groups of patients (p>0.050). The mean DBI score was inversely correlated with the mean GFI score in both inpatients (r=-0.158) and outpatients (r=-0.096), with observed statistical significance only among inpatients (p=0.038). The mean MAI score was positively correlated with the mean GFI score in both inpatients (r=0.078) and outpatients (r=0.034), with no observed statistical significance in both groups of patients (p>0.050) (**Table 4**).

Discussion

To the best of authors' knowledge, this is the first study in Malaysia which compared various parameters of medication appropriateness between inpatients and outpatients under secondary and/ or tertiary care. In the present study, both explicit criteria of medication appropriateness, which include Beers and STOPP criteria, as well as implicit criteria of medication appropriateness, MAI, were applied simultaneously to two cohorts of patients (inpatients and outpatients). Hospitalised patients received a significantly higher number of PIMs and PIPs compared to their outpatient counterparts. In fact, there were more patients exposed to at least one PIMs or PIPs among hospitalised cohort compared to the outpatient cohort, although only the association between exposure to at least one PIP and type of patient setting achieved statistical significance. While we observe no statistical significance between exposure to PIM and type of patient setting, it was felt to be of clinical significance since the exposure to PIMs could translate into adverse clinical events such as emergency department visits and increased medical cost.[19,20]

The finding that more hospitalised patients received PIMs and PIPs than their ambulatory counterparts has logical validity for several reasons. The utilisation of PIMs and PIPs itself could lead to hospitalisation and increased length of stay.[19,21-23] Besides, patients hospitalised for an acute event may have more comorbid diseases and take more medications than community-dwelling older adults. In addition, new medications are typically prescribed to treat acutely ill patients during hospitalisation. In fact, hospitalised patients received significantly a greater number of medications, with a significantly greater proportion of them experienced polypharmacy, compared to outpatients in the present study. Other than that, certain diagnoses such as acute myocardial infarction may have protocol-driven prescribing, which includes PIMs or PIPs, that may be used only a single time, such as promethazine. Furthermore, a higher DBI, as observed among inpatients in the current study, was also associated with increased hospital days, increased hospitalisation for delirium, and readmission to the hospital within the literature.[24,25] DBI serves to measure the cumulative exposure to anticholinergic and sedative medications, which are considered to be potentially inappropriate in both Beers criteria and STOPP criteria.

The exposure prevalence of PIMs among hospitalised patients found in this study (65.3%) was in accordance with prevalence ranging from 7.0% to 80.5% reported in a 2018 systematic review of related studies using the Beers criteria.[26] Nonetheless, comparison with other studies must be interpreted carefully. Reasons for this include differences in the version of the Beers criteria utilised. Different versions of Beers criteria may have led to variation in PIM prevalence, with later modifications and updates changing the number of

PIMs that may be captured. We used 2015 Beers criteria to screen for PIMs among the hospitalised participants. There were only two studies included in the systematic review which used 2015 Beer's criteria to screen for PIMs, and the prevalence reported (50.0% and 71.0%) were close to the one observed in the present study.[26] Similarly, the exposure prevalence of PIPs (57.4%) among inpatients was in line with prevalence ranging from 20.0% to 88.5% reported in the same systematic review when studies using STOPP criteria were concerned.[26] While there was a trend towards a higher prevalence of inappropriate medications among hospitalised patients between studies when using STOPP over the Beers criteria as reported in the systematic review, the reverse was true in the present study where the exposure prevalence of PIMs was higher than the exposure prevalence of PIPs.[26] This may be explained by the fact that almost all studies included in the systematic review utilised 2012 and older versions of Beers criteria, while the 2015 Beer's criteria, which is more sensitive than its previous versions, was applied in our study. In fact, it was observed that the 2015 Beers criteria detected significantly more PIMs than the 2012 criteria among inpatients.[27] In addition, a recent study which compared between Beers criteria of 2015 and STOPP criteria found a higher prevalence of inappropriate medication detected among inpatients with 2015 Beers criteria.[28]

The exposure prevalence of PIMs among outpatients in the present study (57.3%) was within the range of 11.5% to 62.5% found in a 2011 systematic review of studies utilising Beers criteria among community-dwelling elderly.[29] In addition, a similar study conducted in the neighbouring country Thailand in 2014 reported a prevalence of 49.8% among outpatients with at least 1 PIM.[30] The higher prevalence observed in our study may be because 2015 Beers criteria were being applied instead of older 2012 Beers criteria utilised in the Thai study. The 2015 Beers criteria are more sensitive in which three new medications and two new classes of medications were added compared to the 2012 Beers criteria. The finding where the exposure prevalence of PIMs was higher than the exposure prevalence of PIPs among outpatients in the present study, as opposed to a previous study which reported the reverse was true when the older version of Beers criteria being utilised, could also be partly explained by higher sensitivity of 2015 Beers criteria compared to its previous versions.[31]

We observed only a weak correlation between various parameters of medication appropriateness and quality of life as well as frailty in both inpatients and outpatients. Quality of life is a multi-level and amorphous concept, which encompasses the individual's physical health, psychosocial well-being and functioning, independence, control over life, material circumstances, and the external environment.[32] While medication appropriateness may influence physical and psychological well-being and possibly behavioural and social competence, it may not influence the external, objective, and physical environment as much.

A recent study in Malaysia also reported no significant association between inappropriate medication use and health-related quality of life among hospitalised elderly patients[33]. Similarly, frailty is a multidimensional concept that considers the complex interplay of physical, psychological, social, and environmental factors, in which medication appropriateness may only affect a part of these interplay factors.[34] A study among institutionalised elderly in Malaysia also reported a weak correlation between inappropriate medication use and frailty.[35]

Several limitations should be noted in the present study. The study involved only one tertiary care hospital in Malaysia and thus the results are limited in their generalisability. We believe larger, randomised, multi-centre studies are needed to confirm the findings of the present study. In addition, while we observed an association between medication appropriateness and patient setting, the cross-sectional design of the present study prevents the establishment of a causal relationship between them.

Conclusions

Proportions of PIMs and DBI exposure were significantly higher in inpatients than outpatients. Patients attending outpatients were ambulant, relatively healthy, less frail, and ADL-independent as well as having low incidences of PIPs and polypharmacy. No significant correlations between exposures to inappropriate medications or drug burden and PROs were observed. Striking the balance between the risk of polypharmacy and sub-optimal prescription in elderly patients is a challenge to all prescribers. Integrating prescribing guidance tools into practice is the most tremendous barrier to overcome because the awareness of the existence and updates of these tools are still underwhelming in prescribing practices. Continuous professional development is highly encouraged to improve current practices.

Future directions

Future studies with larger sample sizes, multiple sites, and preferably longitudinal in the design are needed to confirm these findings.

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Competing interests

The authors declare no competing interests.

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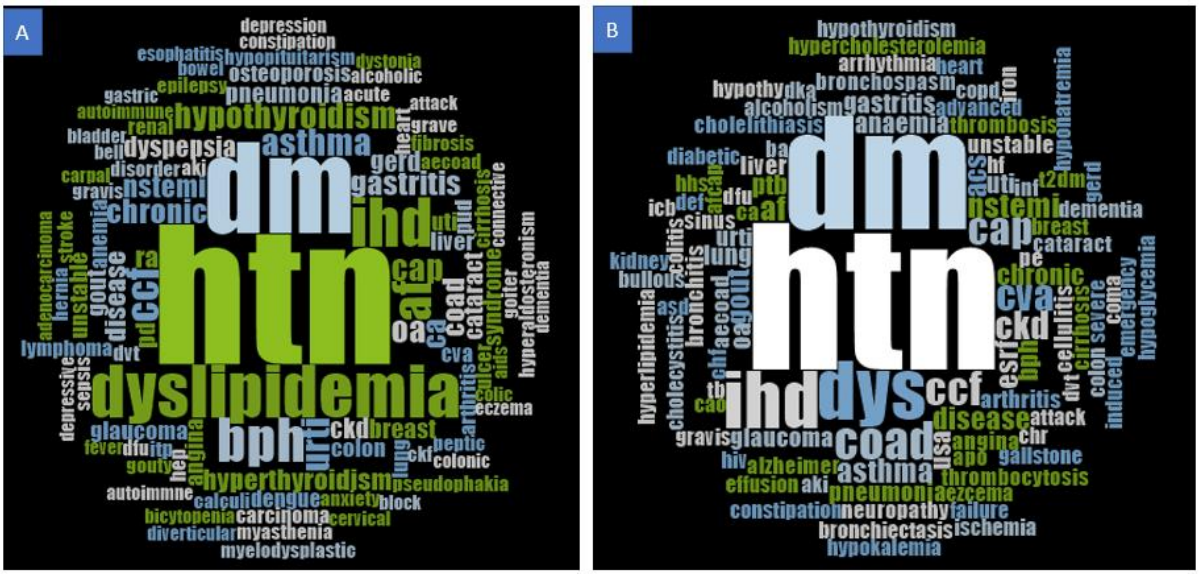

Figure 1: List of medical conditions associated with study participants in (A) inpatient and (B) outpatient.

Table 1: Demographic characteristics of study participants (n = 344)

Variable	Total (n=344) n (%)	Inpatient (n=173) n (%)	Outpatient (n=171) n (%)	p-value
Age (yrs)				
60 - 64	90 (26.16)	45 (26.32)	45 (26.00)	0.037
65 - 70	101 (29.35)	53 (31.00)	48 (27.70)	
71 - 76	74 (21.50)	30 (17.30)	44 (25.70)	
> 76	79 (22.95)	29 (17.00)	50 (28.90)	
Age, mean ± SD	70.71 ± 7.71	69.94 ± 6.77	71.47 ± 8.65	0.067
Gender				
Male	189 (55.10)	94 (54.3)	95 (55.9)	0.773
Female	154 (44.90)	79 (45.7)	75 (44.1)	
Ethnicity				
Malay	121 (35.65)	77 (45.6)	44 (25.7)	0.001
Chinese	133 (39.05)	55 (32.5)	78 (45.6)	
Indian	86 (25.30)	37 (21.9)	49 (28.7)	
No of comorbidities, mean ± SD	3.51 ± 1.38	3.58 ± 1.41	3.44 ± 1.34	0.358

Abbreviation: n, number of participants; SD, standard deviation; p-values obtained from Chi-Sq and t-test

Table 2: Variables of medication appropriateness by patient setting (inpatient and outpatient)

Variable	Total (n=344) n (%)	Inpatient (n=173) n (%)	Outpatient (n=171) n (%)	p-value
PIM				
Without PIM	133 (36.70)	60 (34.7)	73 (38.7)	0.079
Received at least 1 PIM	211 (61.30)	113 (65.3)	98 (57.3)	
PIP				
Without PIP	214 (62.30)	72 (41.6)	142 (83.0)	0.001
Received at least 1 PIP	130 (37.20)	101 (57.4)	29 (17.0)	
DBI				
DBI=0	23 (6.75)	1 (0.6)	22 (12.9)	0.001
DBI>0	321 (93.25)	172 (99.4)	149 (87.1)	
Presence of polypharmacy				
No	143 (41.70)	37 (21.4)	106 (62.0)	0.001
Yes	201 (58.30)	136 (78.6)	65 (38.0)	

Abbreviation: n, number of participants; PIMs, Potentially Inappropriate Medications; PIPs, Potentially Inappropriate Prescribing; DBI, Drug Burden Index

Table 3: Mean differences in study variables by patient setting (inpatient and outpatient)

Item	Setting	n	Mean (SD)	p-value
Total OPQOL score	Inpatient	173	118.53 (11.57)	0.001
	Outpatient	171	79.95 (11.65)	
GFI	Inpatient	173	5.44 (3.71)	0.001
	Outpatient	171	3.78 (2.81)	
No of PIM	Inpatient	173	1.25 (1.19)	0.020
	Outpatient	171	0.96 (1.06)	
No of PIP	Inpatient	173	1.11 (1.25)	0.001
	Outpatient	171	0.33 (0.82)	
MAI score	Inpatient	173	1.76 (1.08)	0.001
	Outpatient	171	1.10 (0.34)	
DBI	Inpatient	173	2.67 (1.28)	0.001
	Outpatient	171	1.49 (1.17)	
No of Medicines	Inpatient	173	6.90 (2.70)	0.001
	Outpatient	171	4.49 (3.20)	

Abbreviation: n, number of participants; SD, standard deviation; PIM, Potentially Inappropriate Medication; PIPs, Potentially Inappropriate Prescribing; MAI, Medication Appropriateness Index; DBI, Drug Burden Index; GFI, Groningen Frailty Indicator; OPQOL, Older People's Quality of Life

OPQOL total score ranged from 35 (worst possible QOL) to 175 (best possible QOL)
Frail = GFI of 4 and above

Table 4: Correlation between variables of medication appropriateness and OPQOL as well as GFI by patient setting (inpatient and outpatient)

Item		Inpatient		Outpatient	
		Total OPQOL Score	**GFI**	**Total OPQOL Score**	**GFI**
No of PIM	Coefficient (r)	-0.085	0.097	-0.157	0.025
	p-value	0.267	0.206	**0.040**	0.745
No of PIP	Coefficient (r)	0.022	-0.065	-0.052	0.041
	p-value	0.774	0.399	0.501	0.595
MAI score	Coefficient (r)	-0.036	0.078	-0.092	0.034
	p-value	0.639	0.308	0.232	0.655
DBI	Coefficient (r)	0.034	-0.158*	-0.069	-0.096
	p-value	0.656	**0.038**	0.369	0.210

Abbreviation: PIMs, Potentially Inappropriate Medications; PIPs, Potentially Inappropriate Prescribing; MAI, Medication Appropriateness Index; DBI, Drug Burden Index; GFI, Groningen Frailty Indicator; OPQOL, Older People's Quality of Life