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ORIGINAL RESEARCH ARTICLE

Potential Drug–Drug Interactions Among Hospitalised Elderly Patients in Northern Sri Lanka, A Lower Middle-Income Country: A Retrospective Analysis

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Abstract

Background and Objectives Elderly individuals are more vulnerable to potential drug–drug interactions (pDDIs) as age-related physiological changes, polypharmacy and hospitalisations are known to increase the risk of pDDIs. The aims of this study were to assess the impact of hospitalisation and other associated factors on pDDIs in elderly patients, in a resource-limited setting.

Methods This is a retrospective analysis of data of elderly patients (aged ≥ 65 years) admitted to the medical units of Jaffna Teaching Hospital. Preadmission and post-admission data were collected from clinic and hospital records, respectively. The British National Formulary was used to identify and categorise pDDIs. Point prevalence of pDDIs in elderly patients and the total number of pDDIs before and after hospitalisation were estimated. Factors contributing to pDDIs were determined by univariate and multivariable logistic regression.

Results Two hundred and eighty-eight hospitalised elderly patients with a median age of 71 years (interquartile range 67–76 years) showed a significant increase in the prevalence of pDDIs post-admission compared with the preadmission values (77.1% vs 61.5%; $p < 0.001$) associated with an increase in total pDDIs (377 vs 488; $p < 0.001$) where the majority (> 75%) were potential pharmacodynamic interactions. An unadjusted analysis showed a significant association between pDDI and polypharmacy [taking five or more medications] (odds ratio [OR] = 14.17; 95% confidence interval [CI] 7.41–27.10), the presence of more than three underlying medical conditions (OR 4.14; 95% CI 1.70–10.06), ischaemic heart disease (OR 3.25; 95% CI 1.78–5.94) and asthma (OR 8.14; 95% CI 2.46–26.88). However, when adjusted for confounders only polypharmacy (OR 14.10; 95% CI 6.50–30.60) and the presence of underlying asthma (OR 11.61; 95% CI 2.82–47.85) were associated with pDDIs.

Conclusions The prevalence of pDDIs among elderly patients was high and increased with hospital admissions. Polypharmacy and relevant comorbidities were contributory factors. Increased awareness of the potential for pDDIs through appropriate training and simple measures including a proper drug history, creating a bespoke pDDI list and frequent medication reviews by healthcare professionals would help to mitigate pDDIs in resource-limited and technology-limited settings.

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Key Points

Hospitalisation significantly increases the potential drug–drug interactions (pDDIs) among elderly patients and more than 70% of the identified pDDIs both before and after admission among hospitalised elderly patients were due to predictable and clinically identifiable pharmacodynamic mechanisms.

The five most common medications that contributed to the pDDIs were those used to treat common cardiovascular diseases. Patients with polypharmacy (taking five or more medications) and asthma were at an increased risk for pDDIs.

Creating a bespoke list of clinically important drug–drug interactions by investigating actual outcomes of the pDDIs in local settings and sharing it with healthcare professionals involved in the clinical care of elderly patients would be a realistic exercise for resource-limited countries where digital drug–drug interaction alert systems are not readily available.

1 Introduction

A drug–drug interaction (DDI) is the alteration of the effect of a medication by another medication when taken simultaneously, thereby modifying the action or effectiveness of medications by altering the pharmacodynamic and/or pharmacokinetic processes [1, 2]. It has been reported that DDIs are significant contributors to clinically relevant adverse drug reactions [1, 3, 4]. A systematic review reported that patients with adverse drug reactions had a much higher prevalence of DDIs (22.2%) compared with the prevalence of DDIs for all hospital admissions (1.1%) [5]. Studies also reported that the occurrence of drug interactions adversely influences the length of hospital stay [3, 6]. Though many DDIs are potentially harmful, they are often preventable [7, 8]. Although actual DDIs are identified from the occurrence of adverse outcomes in patients, potential DDIs (pDDIs) are assessed through the analysis of the pharmacodynamic and pharmacokinetic properties of each medicine prescribed for a particular patient, thereby predicting the possibility of adverse outcomes in the individual patient through DDIs [1]. Identification and management of pDDIs therefore have significant preventable public health benefits, especially in resource-limited settings, where digital alert systems are not easily accessible.

Risks for the exposure to pDDIs are multifactorial. Old age, polypharmacy and comorbidities increase the risk of exposure to pDDIs [9]. Multiple comorbidities leading to polypharmacy as well as age-related physiological changes, particularly in the drug-handling organs (kidney and liver), make elderly patients more vulnerable to DDIs [10–12]. Although hospitalisations increase the likelihood of DDIs [1, 12–14], DDIs are also known to be contributory causes for hospitalisations [3, 4, 15], thus further confounding the effect on DDIs and leading to adverse outcomes in a vulnerable elderly population. Despite this effect, studies comparing the DDIs before and after hospitalisation are limited [14].

Sri Lanka is a lower middle-income country exhibiting demographic features comparable to many developing countries. The elderly (aged ≥ 65 years) population is on the rise in Sri Lanka and is currently around 8% of the overall population [16] with the population ageing rate being the fastest in South Asia [17]. Non-communicable diseases have also been on the rise, thereby further increasing the disease burden in the elderly population [18]. Studies that reported the information on medication use among the elderly population in Sri Lanka are limited. There was one study reporting the mean number of medications (4.46) prescribed to the residents of an elders' home in Sri Lanka [19]. There is, therefore, a growing need to address the health-related issues of elderly individuals, including the potential for DDIs. This is the first study conducted in Sri Lanka to specifically investigate the DDIs among hospitalised elderly patients.

The aims of this paper are to compare the pDDIs before and after hospitalisation and to determine the factors associated with pDDIs among elderly patients admitted to the medical units of Jaffna Teaching Hospital, which is the largest tertiary healthcare setting in Northern Sri Lanka. Although the hospital provides tertiary care facilities, as is the case with many low-income and middle-income countries, it also services the primary and secondary care needs of the local population, thereby stretching already limited human and technological resources.

2 Methods

2.1 Study Design, Setting and Study Population

We conducted a retrospective analysis of data collected from elderly patients (aged 65 years and above) admitted to the medical units of Jaffna Teaching Hospital, over a period of 3 months (March–June 2011). The monthly admissions (13 years and above) to medical wards were around 1200. As there were no studies conducted to determine the prevalence of pDDIs before and after hospitalisation in low-income or middle-income countries to date, prevalence of pDDIs (36.9%) reported from a

population-based study among older adults in Brazil [20] and prevalence of pDDIs (62.2%) among hospitalised elderly patients from an Ethiopian study [21] were used to determine the adequacy of the sample size to show statistically significant differences between before and after hospitalisation data [22]. Patients who died during the hospital stay or had been transferred to other units or institutes were excluded. The following information was collected using a data extraction sheet: age and sex of the participants, medications the patient was taking at the time of admission and medications prescribed on discharge, and the number and types of medical conditions at the time of discharge. Pre-admission data were collected from patients' clinic follow-up records. When clinic records were not available, information was obtained directly from the patients. Post-admission data were obtained from the bed-head tickets. Informed consent was obtained from each participant or a legally acceptable guardian before data collection. Ethics approval (Reference number: J/ERC/10/14/NDR/0012) from the Ethics Review Committee of the Faculty of Medicine, University of Jaffna and administrative approvals from relevant authorities were obtained before commencing the data collection.

2.2 Definitions

Potential drug–drug interactions were defined as the encounters where two medications known to interact are concurrently prescribed irrespective of the occurrence of adverse event [10]. Pharmacodynamic interactions (PDIs) are defined as those altering the pharmacological activity of the interacting medicines by interfering with receptor or biological/physiological functions or additive/opposing effects and pharmacokinetic interactions (PKIs) are defined as those altering with the effects of medications by affecting the absorption, distribution, metabolism or excretion of the medicines [2].

Medication that is subjected to modification in its therapeutic effect by the DDI is called an "object medicine", whereas medication that affects the pharmacological action or pharmacokinetic properties of other medications is called a "precipitant medicine" [9]. Because it is difficult to differentiate the object and precipitant medicines in many PDIs, object and precipitant medicines are described only for PKIs in this paper.

In this study, "pDDIs before hospitalisation" was defined as those identified among the medications the patient was already taking at the time of admission and the pDDIs identified among the medications prescribed on discharge were defined as "pDDIs after hospitalisation". Polypharmacy is defined as taking five or more medications [23].

2.3 Data Analysis

The British National Formulary (version 80) was used as the pharmaceutical reference to identify and categorise the pDDI [24]. The pDDIs were categorised as PDIs or PKIs. Pharmacokinetic interactions were further classified as mild, moderate and severe, which were defined as follows: mild, unlikely to cause concern or incapacitate the majority of patients; moderate, could cause considerable distress or partially incapacitate but, unlikely to cause a life-threatening event or result in long-term effects; and severe, may cause a life-threatening event or have a permanent detrimental effect. Potential PDIs were identified using the tables at the beginning of Appendix 1 in the paper version of the British National Formulary (version 80) [24]. Descriptive statistics such as frequency, percentage, median and interquartile range (IQR) are used to present the results. Point prevalence of all pDDIs irrespective of the severity was used to describe the presence of pDDIs before and after hospitalisation. Percent difference was used to compare data before and after hospitalization, which was calculated as follows:

$$\frac{\text{Value after hospitalisation} - \text{Value before hospitalisation}}{\text{Value before hospitalisation}} \times 100.$$

The Chi-square test was used to determine significance in the difference in the proportion of patients with pDDIs before and after hospitalisation. The Mann–Whitney U test was used to compare total pDDIs, PDIs and PKIs before and after hospitalisation. Univariate and multivariable logistic regression with a 95% confidence interval (CI) were performed to investigate the association between the presence of pDDIs after hospitalisation and the following factors measured at discharge: age, sex, polypharmacy, number of underlying medical conditions and the ten most prevalent medical conditions. Results were presented as unadjusted and adjusted odd ratios (ORs). Median values were used to categorise the age and number of medical conditions. All the tests were two-tailed and statistical significance was predetermined at a p value < 0.05.

3 Results

Data from 288 hospitalised elderly patients were analysed. The median age of the participants was 71 years (IQR, 67–76 years). The male-to-female ratio was 1.15 ($n = 154$; 53.5% vs $n = 134$; 46.5%). The median number of medications per patient before and after admission was 5 (IQR, 0–7) and 6 (IQR, 4–7), respectively. The proportions of elderly patients exposed to polypharmacy before and after hospitalisation were 51.7% ($n = 149$) and 72.2% ($n = 208$), respectively.

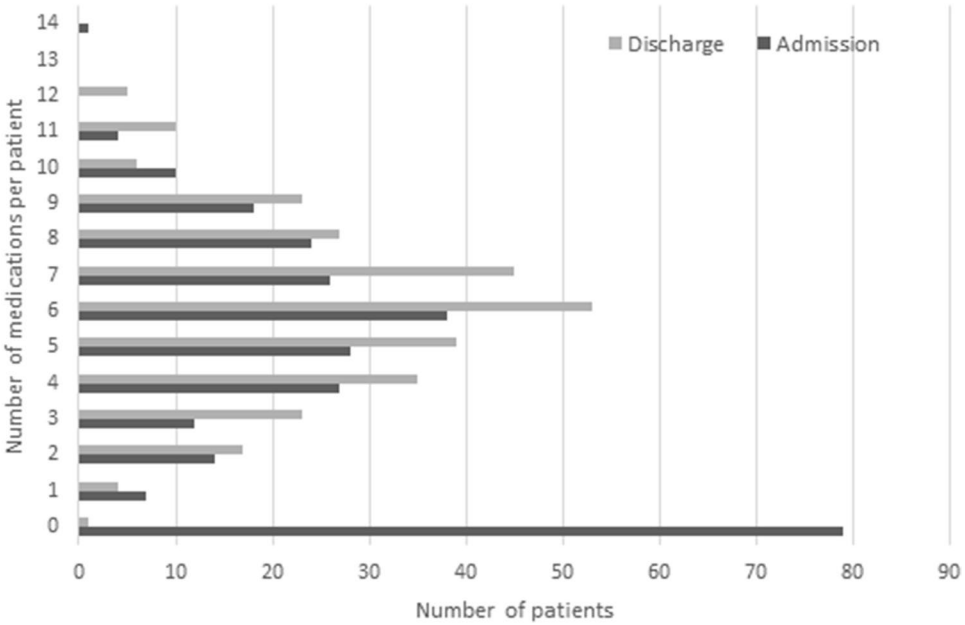

Fig. 1 Medications per patient at the time of admission and discharge

Figure 1 shows the distribution of the number of medications per patient at the time of admission and discharge.

The median number of underlying diseases at discharge was 3 (IQR, 2–3) as is expected of an elderly cohort. Table 1 compares the pre-hospitalisation and post-hospitalisation measurements of the ten most prevalent medical conditions and the ten most prescribed medications at the time of discharge. After hospitalization, almost all the medications increased by 50% or more, whereas among the medical conditions more than a 50% increase was observed only for cerebrovascular disease.

3.1 Description and Comparison of pDDIs Before and After Admission

A total of 377 pDDIs in 177 patients were identified at the time of admission. Of them, 297 (78.8%) were potential PDIs and 80 (21.2%) were potential PKIs. On discharge, a total of 488 pDDIs were observed in 222 patients and potential PDIs and PKIs were 380 (77.9%) and 108 (22.1%), respectively. Point prevalence of all pDDIs before hospitalisation was 61.5% and after hospitalisation was 77.1% ($p < 0.001$).

Figure 2 illustrates the distribution of number of pDDIs per patient at the time of admission and discharge. The median number of pDDIs before as well as after hospitalisation was 1 with an IQR of 0–2 and 1–3, respectively. More than half ($n = 93$) had no change in the number of pDDIs whilst 44 patients showed an increased potential (1.70 pDDIs per patient vs 2.39 pDDIs per patient) and the remaining 40 patients showing a decreased potential (2.53 pDDIs per patient vs 1.59 per patient). However, over half of the 111 patients ($n = 58$) who were not exposed to a pDDI on admission were newly exposed to a pDDI during hospitalisation. Among these 58, patients exposed to

Table 1 Ten most prevalent conditions and ten most prescribed medications among hospitalised elderly patients

	Admission *n* (%)	Discharge *n* (%)	Percent difference
Medical conditions			
Hypertension	141 (49.0)	153 (53.1)	8.5
Ischaemic heart disease	126 (43.8)	140 (48.6%)	11.1
Diabetes mellitus	113 (39.2)	120 (41.7)	6.2
Asthma	63 (21.9)	65 (22.6)	3.2
Cerebrovascular disease	18 (6.3)	37 (12.8)	105.6
Anaemia	29 (10.1)	34 (11.8)	17.2
Heart failure	29 (10.1)	33 (11.5)	13.8
Dyslipidaemia	20 (6.9)	26 (9.0)	30.0
Chronic kidney disease	25 (8.7)	25 (8.7)	0.0
Peptic ulcer disease	25 (8.7)	25 (8.7)	0.0
Medications			
Atorvastatin	132 (45.8)	233 (80.9)	76.5
Aspirin	97 (33.7)	163 (56.6)	68.0
Clopidogrel	68 (23.6)	109 (37.8)	60.3
Furosemide	54 (18.8)	81 (28.1)	50.0
Losartan	50 (17.4)	79 (27.4)	58.0
Inhaled β_2 agonist	48 (16.7)	76 (26.4)	58.3
Metformin	55 (19.1)	69 (24.0)	25.5
Inhaled corticosteroid	46 (16.0)	62 (21.5)	34.8
Enalapril	36 (12.5)	54 (18.8)	50.0
Omeprazole	29 (10.1)	54 (18.8)	86.2

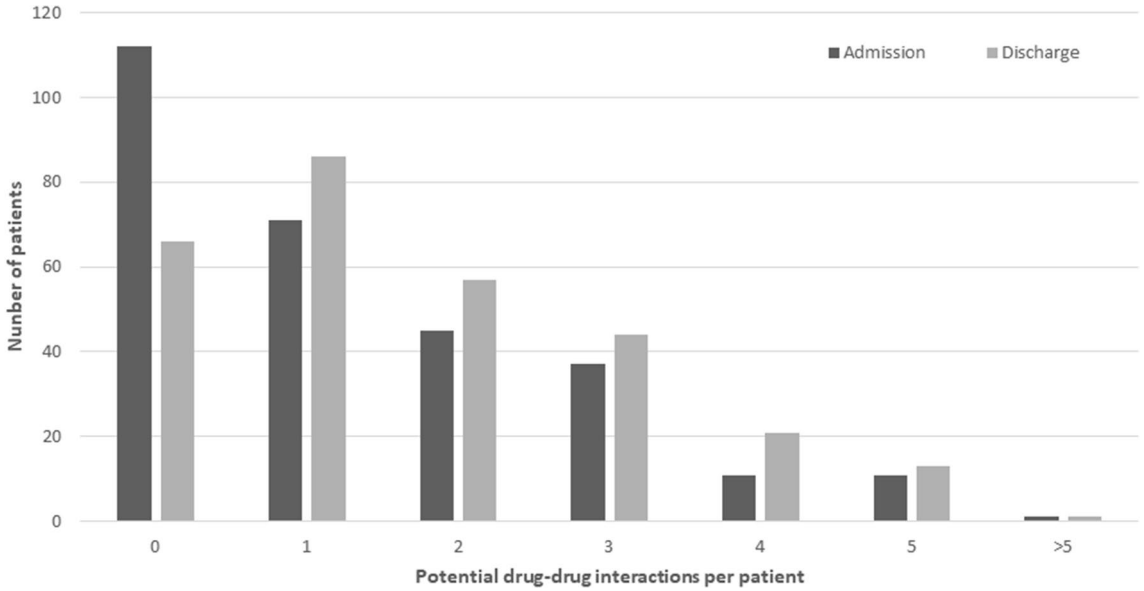

Fig. 2 Potential drug–drug interactions per patient at the time of admission and discharge

polypharmacy increased from 2 to 44 after hospitalisation and 90% ($n = 52$) had one or more cardiovascular condition.

Potential PDIs are summarised in Table 2. Among the potential PDIs, hypotension, hypokalaemia, enhanced antiplatelet effect, hypoglycaemia and hyperkalaemia contributed to 70% of the pDDIs before as well as after admission.

The potential PKIs before and after admission are summarised in Table 3. The number of drug pairs for pPKIs on admission was 21 rising to 28 on discharge. The identified pPKIs were all of clinical relevance, being moderate or severe in nature. It is important to note the preponderance of pPKIs related to atorvastatin, clopidogrel and digoxin as object medicines with diltiazem, carbamazepine and spironolactone as relevant precipitant medicines.

The top five medications contributing to the potential drug–drug interactions at the time of discharge were spironolactone ($n = 88$), furosemide ($n = 78$), clopidogrel ($n = 61$), atorvastatin ($n = 52$) and losartan ($n = 52$)

Table 4 summarises the overall prevalence of pDDIs both at the time of admission and at discharge. Hospitalisation resulted in an increase in the number of patients with pDDIs, in the number of total pDDIs, potential PDIs and potential PKIs, although the potential PKIs did not reach statistical significance

3.2 Factors Associated with pDDIs

Results of unadjusted and adjusted analyses for factors associated with pDDIs were given in Table 5. In the unadjusted analysis, polypharmacy (OR 14.17; 95% CI 7.41–27.10), the presence of more than three underlying medical conditions (OR 4.14; 95% CI 1.70–10.06), ischaemic heart disease (OR 3.25; 95% CI 1.78–5.94) and asthma (OR 8.14; 95% CI 2.46–26.88) were significantly associated with pDDIs. However, when adjusted for confounders, a statistically significant association was observed only for polypharmacy (OR 14.10; 95% CI 6.50–30.60) and the presence of underlying asthma (OR 11.61; 95% CI 2.82–47.85).

4 Discussion

Our study confirmed the extremely high prevalence of pDDIs in elderly patients and that hospitalisations enhanced the potential for DDIs. The number of patients with a potential for DDIs and the overall total of pDDIs were adversely impacted by hospitalisation. The OPERAM trial also reported a similar significant increase in the prevalence of DDIs between admission and discharge from hospital [14]. Our pre-admission and post-admission rates (61.5% increasing to 77.1%) are comparable to other studies that reported a similar high prevalence of DDIs/pDDIs from 58% to 77.8% among hospitalised elderly patients [12–14, 21]. A substantial increase in the medications prescribed compared with the medical conditions after hospitalisation (Table 1) in this study suggests inadequate control of the diseases leading to hospitalisation. It was also observed that the number of medications post-discharge was higher at almost every level of medications per patient (Fig. 1), demonstrating an increase in prescriptions during hospitalisation. These observations could explain the significant increase in the pDDI after hospitalisation. The additive impact of both increasing age and hospitalisation on pDDIs is apparent when compared with the considerably lower prevalence of DDI or pDDIs reported

Table 2 Potential pharmacodynamic interactions[a] among hospitalised elderly patients

Pharmacodynamic interaction	Medications contributed	Admission (n = 288)	Discharge (n = 288)
Hypotension	ACEI[2] or ARB[3] + β blocker	10	15
	ACEI or ARB + calcium channel blocker	13	15
	ACEI or ARB + diuretic	24	30
	ACEI or ARB + nitrate	5	8
	ACEI or ARB + other[2]	2	4
	ACEI or ARB + α blocker + diuretic	3	3
	ACEI or ARB + α blocker + nitrate	0	1
	ACEI or ARB + α blocker + calcium channel blocker + diuretic + nitrate	1	0
	ACEI or ARB + β blocker + α blocker	1	1
	ACEI or ARB + β blocker + calcium channel blocker	0	1
	ACEI or ARB + β blocker + diuretic	4	4
	ACEI or ARB + β blocker + nitrate	5	4
	ACEI or ARB + β blocker + calcium channel blocker + diuretic	0	1
	ACEI or ARB + β blocker + diuretic + nitrate	1	4
	ACEI or ARB + calcium channel blocker + diuretic	5	10
	ACEI or ARB + calcium channel blocker + nitrate	6	8
	ACEI or ARB + calcium channel blocker + diuretic + nitrate	2	6
	ACEI or ARB + diuretic + nitrate	8	6
	β blocker + diuretic	2	3
	β blocker + nitrate	1	3
	Calcium channel blocker + diuretic	9	10
	Calcium channel blocker + nitrate	1	2
	Calcium channel blocker + other	2	6
	Calcium channel blocker + α blocker + diuretic	1	1
	Calcium channel blocker + α blocker + nitrate	1	1
	Calcium channel blocker + α blocker + diuretic + nitrate	2	2
	Calcium channel blocker + diuretic + nitrate	1	0
	Calcium channel blocker + diuretic + other	0	1
	Diuretics (two)	5	3
	Diuretic + α blocker	0	1
	Diuretic + α blocker + nitrate	0	1
	Diuretic + nitrate	5	6
	Diuretic + other	2	0
Hypokalaemia	β_2 agonist + corticosteroid	33	38
	β_2 agonist + K^+-depleting diuretic	1	1
	β_2 agonist + K^+ methylxanthine	0	1
	β_2 agonist + corticosteroid + K^+-depleting diuretic	3	6
	β_2 agonist + corticosteroid + methylxanthine	10	12
	β_2 agonist + corticosteroid + K^+-depleting diuretic + methylxanthine	2	2
	Corticosteroid + K^+-depleting diuretic	0	2
	Corticosteroid + methylxanthine	1	2
	K^+-depleting diuretic (two)	1	2
Enhanced antiplatelet effect	Aspirin + clopidogrel	30	40
	Aspirin + dipyridamole	4	7
	Aspirin + clopidogrel + dipyridamole	1	2
	Clopidogrel + diclofenac	2	2
	Clopidogrel + dipyridamole	0	1

Table 2 (continued)

Pharmacodynamic interaction	Medications contributed	Admission (n = 288)	Discharge (n = 288)
Hypoglycaemia	Metformin + insulin	2	2
	Metformin + sulphonylurea	20	23
	Metformin + thiazolidinedione	1	1
	Metformin + sulphonylurea + thiazolidinedione	1	0
	Sulphonylurea + insulin	3	1
	Sulphonylurea + thiazolidinedione	2	1
	Sulphonylurea + insulin + thiazolidinedione	0	1
Hyperkalaemia	ACEI + K^+-sparing diuretic	11	22
	ACEI + KCl	1	0
	ACEI + K^+-sparing diuretic + KCl	2	0
	ARB + K^+-sparing diuretic	11	12
	ARB + KCl	1	1
Hyponatraemia	Loop diuretic + K^+-sparing diuretic	15	21
	Loop diuretic + thiazide	1	2
Hepatotoxicity	Atorvastatin + carbamazepine	12	9
	Atorvastatin + valproate	2	1
Bradycardia	Atenolol + carvedilol	1	1
	Digoxin + verapamil	0	2
CNS depression	Chlorpromazine + clonazepam	1	0
	Chlorpromazine + haloperidol	0	1
Total		297	380

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CNS* central nervous system

[a]Potential pharmacodynamic interactions were identified using the tables at the beginning of Appendix 1 of the paper version of the British National Formulary (version 80) and presented as either a drug class or an individual drug in Table 2

[b]Other, amitriptyline or dipyridamole or sildenafil

among elderly patients in primary healthcare (25–36%), community-dwelling older adults (22.65%) and hospitalised adult patients (33%) [7, 25, 26].

Though there was a significant increase in the prevalence of pDDIs and the total number of pDDIs after admission, the median number of pDDIs per patient before and after hospitalisation remained unchanged (one with the IQR 0–2 and IQR 1–3, respectively). A similar observation was reported in a study conducted among hospitalised adult patients [27]. This is perhaps indicative of the insensitivity and hence the inappropriateness of using averages of pDDIs per patient to assess the impact of hospitalisation on pDDIs in elderly patients who are prone to polypharmacy and multiple comorbidities. Our data have shown the variability (no change, increase and decrease in equal measure) of the additional exposure to pDDIs during hospitalisation in this cohort of patients. It is, therefore, important to acknowledge this variability in response and note the fact that a substantial number of the total patients in our study (35.4%) had either a new or an increased exposure to pDDIs during hospitalization, thus highlighting the grave but variable nature of the problem, which necessitates an individualised and targeted monitoring of the attendant risk of pDDIs in every elderly patient.

In our study, more than three-fourths of pDDIs were potential PDIs, although hospitalisation had very little effect on the pattern of distribution of PDIs. These findings are consistent with the results of other studies among hospitalised elderly patients as well as non-elderly adults, where PDIs at baseline and at discharge were in the 70–80% range [12, 14, 27]. Although DDIs are generally considered to be harmful, they are often used intentionally by the prescribing physicians to obtain additive therapeutic benefits [10, 11] as is often the case in the control of hypertension and type 2 diabetes mellitus and with dual antiplatelet therapy. For example, many patients will require more than one medication for the control of blood pressure [28] and blood sugar [29], thereby increasing the risk of hypotension and hypoglycaemia, both potentially lethal events particularly in elderly patients with concomitant heart failure and ischaemic heart disease. Dual therapy is also the recommended treatment with antiplatelet drugs (aspirin and clopidogrel) for thromboembolic events [30] and for the use of inhaled

Table 3 Potential pharmacokinetic interactions among hospitalised elderly patients

Object medicine	Precipitant medicine	Severity	Admission (n = 288)	Discharge (n = 288)
Alendronate	Oral calcium salt	Moderate	2	3
Amlodipine	Phenytoin	Moderate	1	1
Atorvastatin	Carbamazepine	Moderate	12	9
	Diltiazem	Severe	18	31
	Gemfibrozil	Severe	0	1
	Rifampicin	Moderate	1	1
Clopidogrel	Omeprazole	Moderate	15	16
Digoxin	Spironolactone	Moderate	8	10
	Thyroxine	Moderate	1	1
	Verapamil	Severe	0	2
Dipyridamole	Omeprazole	Moderate	2	1
Ethambutol	Isoniazid	Severe	1	1
Folic acid	Phenytoin	Severe	1	1
Gliclazide	Gemfibrozil	Moderate	0	1
Lithium	Hydrochlorothiazide	Severe	1	0
Methyldopa	Oral iron	Moderate	1	2
Nifedipine	Carbamazepine	Moderate	0	1
Norfloxacin[a]	Oral iron	Moderate	0	1
Oral calcium salt	Hydrochlorothiazide	Severe	3	3
Oral iron	Oral calcium salt	Moderate	4	8
Paracetamol	Carbamazepine	Moderate	0	1
Phenobarbital	Carbamazepine	Moderate	1	1
Sildenafil	Verapamil	Moderate	0	1
Simvastatin	Diltiazem	Severe	1	0
Thyroxine	Oral calcium salt	Moderate	2	4
	Oral iron	Moderate	3	3
Tolbutamide	Gemfibrozil	Moderate	1	1
Valproate	Phenytoin	Severe	1	1
Warfarin	Paracetamol	Moderate	0	1
	Prednisolone	Moderate	0	1
Total			80	108

[a]Oral iron reduces the exposure of quinolones

Table 4 Summary of pDDIs at the time of admission and discharge

Variable	Admission (n= 288)	Discharge (n = 288)	Percent difference	p value
Number of patients with pDDIs	177	222	25.4	< 0.001*
Total number of interactions	377	488	29.4	< 0.001*
Pharmacodynamic interactions	297	380	27.9	0.001*
Pharmacokinetic interaction	80	108	35.0	0. 156
Mild	0	0	–	–
Moderate	54	68	25.9	0.535
Severe	26	40	53.8	0.313

pDDIs potential drug–drug interactions

*Statistically significant ($p < 0.05$) difference between admission and discharge

Table 5 Factors associated with potential drug–drug interactions among elderly patients

Factors	*N* (%)	Unadjusted odd ratio (95% confidence interval)	Adjusted odd ratio (95% confidence interval)
Age, years			
≤ 71	150 (52.1)	Referent	Referent
> 71	138 (47.9)	1.05 (0.61–1.82)	0.80 (0.39–1.64)
Sex			
Female	134 (46.5)	Referent	Referent
Male	154 (53.5)	1.11 (0.64–1.92)	1.09 (0.51–2.31)
Polypharmacy, number of medications			
< 5	80 (27.8)	Referent	Referent
≥ 5	208 (72.2)	14.17 (7.41–27.10)*	14.10 (6.50–30.60)*
Number of medical conditions			
≤ 3	217 (75.3)	Referent	Referent
> 3	71 (24.7)	4.14 (1.70–10.06)*	2.05 (0.56–7.51)
Hypertension	153 (53.1)	1.05 (0.61–1.83)	0.77 (0.34–1.74)
Ischaemic heart disease	140 (48.6)	3.25 (1.78–5.94)*	1.79 (0.80–3.98)
Diabetes mellitus	120 (41.7)	0.96 (0.55–1.68)	0.96 (0.43–2.11)
Asthma	65 (22.6)	8.14 (2.46–26.88)*	11.61 (2.82–47.85)*
Cerebrovascular disease	37 (12.8)	0.78 (0.35–1.70)	1.38 (0.50–3.86)
Anaemia	34 (11.8)	1.17 (0.48–2.82)	0.81 (0.25–2.62)
Heart failure	33 (11.5)	2.33 (0.79–6.89)	1.13 (0.29–4.36)
Dyslipidaemia	26 (9.0)	0.64 (0.27–1.55)	0.97 (0.27–3.50)
Chronic kidney disease	25 (8.7)	1.21 (0.44–3.35)	0.59 (0.17–2.09)
Peptic ulcer disease	25 (8.7)	1.62 (0.54–4.90)	1.49 (0.34–6.53)

*$p < 0.05$

corticosteroids and beta2 agonists for bronchial asthma [31] with a potential for hypokalemia, another potentially lethal outcome in the elderly. Additionally, potential DDIs between the medications recommended for different comorbidities are also common [7]. Although rational therapeutic strategies could explain the preponderance of potential PDIs among pDDIs, this does not deviate from the need for careful monitoring of pDDIs to prevent any exacerbated effects leading to adverse clinical outcomes. These "overshoot effects" of intentional therapeutic strategies such as hypotension, hypoglycaemia or haemorrhagic states could have life-threatening outcomes in elderly patients.

It is also important to recognise that the risk of harm related to DDIs depends on patient-related factors as well as to the prescribed medications. For example, patients with diabetes and renal impairment are more susceptible to develop hyperkalaemia with the combination of an angiotensin-converting enzyme inhibitor and a potassium-sparing diuretic [32]. In our study, nearly all the interactions with an increased risk of hyperkalaemia were due to the concurrent use of potassium-sparing diuretics with angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists. Among them more than 50% ($n = 20$) had diabetes ($n = 15$), chronic kidney disease ($n = 3$) or both ($n = 2$).

Similarly, certain medications are more likely to cause drug interactions. In this study, all ten of the most prescribed medications on discharge contributed to pDDIs (PDIs, PKIs or both), demonstrating the close relationships between prescription patterns and pDDIs in elderly patients. The five most frequently involved medications in pDDIs were spironolactone, furosemide, clopidogrel, atorvastatin and losartan, all medications often used to treat cardiovascular disorders. A high prevalence of cardiovascular comorbidities in the study population could explain the preponderance of cardiovascular medications in contributing to pDDIs, which was further supported by the observation that 90% of the patients who were newly exposed to pDDIs after hospitalisation had one or more cardiovascular disease. A previous study conducted among out-of-hospital patients had also reported that cardiovascular drugs contributed to the five most frequently involved drug pairs [8]. Of the medications causing pDDIs, atorvastatin, clopidogrel and furosemide contributed to both PDIs and PKIs, demonstrating the need to monitor these medications closely during medication reviews. Aspirin, enalapril, inhaled beta2 agonists and inhaled corticosteroids, losartan and metformin contributed solely to PDIs whilst omeprazole only to PKIs. As reported previously [14, 26, 33], the highest number of interactions

was seen with diuretics and drugs acting on the renin angiotensin system, a finding of significance in elderly patients with a potential for compromises in renal function. However, unlike observations reported by the studies conducted in developed countries [12, 14, 26], medications acting on the central nervous system did not contribute significantly to pDDIs in our study. The OPERAM trial reported that PDIs due to the prescription of three or more centrally acting medications and a combination of non-steroidal anti-inflammatory agents and selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors were among the five most prevalent DDIs [14]. Findings of a Norwegian study show that centrally acting medications contributed to most some of the frequent types of risks (excessive sedation and a lack of attention) associated with DDIs [12]. Escitalopram was among the most involved medications in potentially severe DDIs reported by Hughes et al. [26]. In our study, centrally acting medications contributed to less than 5% of the pDDIs. According to the 2019 health statistics of Sri Lanka, hospitalisation due to cardiovascular disorders was more than two and a half times higher than that of the diseases affecting the central nervous system. Furthermore, the majority of hospitalisation due to hypertension (78.5%), ischaemic heart disease (81.4%) and cerebrovascular accident (87.5%) occurred in the age group 50 years and above while hospitalization due to diseases of the nervous system and mental and behavioural disorders among those aged 50 years and above were 41.1% and 33.4%, respectively [34], which was also reflected in our study. It has been reported that mental health needs of elderly patients has been a neglected area in many developing countries especially in Asia owing to cultural, financial and social barriers [35], leading to a paucity in the use of pharmacological interventions. This could also explain the low prevalence of pDDIs associated with centrally acting medications in our study. Further, in contrast to other studies, [12, 14, 21, 26] in this study, the impact of oral anticoagulants in pDDIs was also negligible. A tendency to under-prescribe anticoagulants because of the fear of bleeding complications [36] and/or lower reported rates of venous thromboembolism in Asia [37] could be the reason for this observation.

The ultimate clinical objective of avoiding adverse health outcomes from DDIs could be a difficult proposition. The evidence for the occurrence of clinical consequences of DDIs is limited and varies widely [32, 38] and therefore remains under the radar for many clinicians and for the bulk of the more junior healthcare professionals. This is of relevance in most resource-limited healthcare systems because of the enhanced workload of junior medical and allied healthcare staff who bear the bulk of the clinical workload. Furthermore, as most elderly patients have multiple comorbidities, including cardiovascular diseases, many potential PDIs are inevitable as a combination of medications is needed as part of the treatment plan. In our study, a majority (>70%) of pDDIs were due to the above-mentioned combinations, confirming the clinical relevance of our findings and the need to increase awareness and institute medication reviews and close monitoring.

Many studies have reported that the polypharmacy was associated with DDIs [14, 18, 21, 25, 26, 33, 39]. In our study, the median number of medications prescribed before and after hospitalisation was 5 and 6, respectively, indicating the high prevalence of polypharmacy (taking five or more medications). On par with the previous studies, this study also confirmed a significant link of polypharmacy to the risk of pDDIs.

Results of this study showed that the presence of pDDI was not associated with age or sex. Variable findings have been reported on the association of increasing age with pDDIs within the cohort of elderly patients, some showing a positive association [26, 39] and others a lack of association [21, 33]. Inconsistence findings were also observed for the association between DDI/pDDI and the presence of comorbidities [21, 26]. In our study, only asthma and ischaemic heart disease showed a statistically significant association with pDDI, although association trends were observed for a number of other comorbidities. Medical conditions associated with DDIs in the literature included atrial fibrillation, coronary heart disease, cardiac failure and depression [14, 26]. Interestingly, the most prevalent and third most prevalent of the medical conditions in our study, namely hypertension and diabetes, respectively, had negative relationships with pDDIs. Higher target blood pressure [40] and blood sugar [29] for elderly patients could have led to a reduced use of combination therapy for hypertension and diabetes, which might have contributed to these observations. However, the wide CIs may reflect the small sample size for the analysis of the association with the presence of pDDI and studies with a larger number of elderly patients are needed to confirm these findings.

Findings of the present study and other studies indicate that clinically relevant pDDIs have a high prevalence in elderly patients and careful attention is needed to reduce harm arising from these interactions. Providing clinically relevant information on DDIs to clinicians and implementing a clinical decision support system or DDI alert system will improve the safety of medications. However, developing and maintaining a DDI alert system is a challenging task even for resource-rich countries [39, 40]. Mitigation of harm related to pDDIs is even more difficult in developing countries such as Sri Lanka where medical records are not fully digitalised. Several simple measures such as improving the awareness of common pDDIs including associated major object and precipitant medicines, deploying a structured approach to targeted drug history, close monitoring of patients at risk for PDIs, and frequent medication reviews with dose and

timing adjustments [3, 11, 14, 26] could be more realistic interventions to mitigate pDDIs within resource-limited countries. Further, active and wider involvement of pharmacists in medication reviews of DDIs will also help to reduce medication-related harm among elderly patients. Instilling audits such as ours in every healthcare institution will provide local data to facilitate the mitigation strategies including programmes to improve the prescribing habits.

Our study has some limitations that need to be acknowledged. An important limitation of this study was that actual health outcomes of the identified pDDIs were not assessed over time in individual patients. We are therefore unable to comment on the actual clinical significance of the identified pDDIs. Further, we conducted the study at a single point in time and did not consider the medical conditions at an individual level, which also could have influenced the outcome of the pDDI. Prospective assessment of actual outcomes of the pDDIs considering the medical conditions and clinical status at individual level over a longer period of time will help to understand the effect of both adherence to medications and control of disease on DDIs and to distinguish the more clinically relevant DDIs from those that are less relevant. However, our findings clearly indicate that hospitalisation increases the risk of exposure to DDIs among elderly patients and the need for carefully distinguishing pDDIs with low and high clinical significance. Another limitation is that we did not collect data on the concomitant use of over-the-counter medicines and herbal medicines that are frequently used in different cultural settings and are therefore unable to comment on any significant pDDIs between prescription medicines and these alternative therapies. Furthermore, a small sample size and residual confounding could influence the results of factors associated with pDDIs. Investigation of the actual health outcomes in a larger population is needed to determine the risk factors for DDIs in elderly patients. As this study was conducted in a lower middle-income country, results may not be generalisable to developed countries because of the differences in sociodemographic characteristics, healthcare infrastructure and disease profiles.

5 Conclusions

The prevalence of pDDIs among elderly patients was high and increased with hospitalisation. Most of the pDDIs were PDIs and can therefore be predicted, easily identified and managed clinically. Although all pDDIs can never be avoided, as many of them are related to medications commonly used for comorbidities in elderly patients, an increased awareness of the high level of prevalence and the factors impacting on the potential for DDIs will result in the control and reduction of DDIs in elderly patients. We have recommended bespoke measures, especially for resource-poor settings, where digital DDI alert systems are not readily available. These could include an increased focus on a detailed drug history, the creation of locally relevant pDDI lists based on assessments of comorbidities and commonly prescribed object and precipitant medicines, and the closer monitoring of patients at a greater risk of pDDIs through medication reviews. A greater emphasis on the potential for DDIs in elderly patients should remain a focus in undergraduate and postgraduate training programmes of not only doctors but all healthcare professionals.

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Declarations

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Ethical approval Ethics approval (Reference number: J/ERC/10/14/NDR/0012) was obtained from Ethics Review Committee of Faculty of Medicine, University of Jaffna.

Consent to participate Informed consent was obtained from each participant or legally acceptable guardian before collecting information.

Consent for publication As a part of the informed consent, participants were also informed that results of the study would be published without revealing personal information.

Availability of Data and Material The datasets of the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

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