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Original Article

Predictors and patterns of polypharmacy in chronic diseases in a middle-income country

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Abstract: Low and middle-income countries (LMIC) are increasingly affected by non-communicable diseases (NCDs), which overburden the health system. With the rising prevalence of multimorbidity, polypharmacy is inevitable. Sri Lanka too faces the burden of polypharmacy and multimorbidity, and it is a strain on the economy as Sri Lankan health care is free-of-charge to all citizens. Therefore, steps to reduce inappropriate polypharmacy are a necessity. The aim of the study was to assess the prevalence and patterns of polypharmacy and its associated factors. In the medical clinics of a tertiary care hospital and a University primary care department, a descriptive cross-sectional study was carried out. Data were extracted from the clinical records of patients over the age of 20 years with a minimum of one NCD diagnosed by either a consultant physician or a consultant family physician. The sample size was 1600. Multimorbidity was present among 63.5% of patients. Polypharmacy (five or more than five drugs) was seen in 36.8% of the patients. Diabetes, hypertension, and coronary heart disease were the commonest of all diseases. Those on more than 11 drugs were found to have diabetes mellitus, hypertension, coronary heart disease, chronic kidney disease, and cardiac failure. 15% of the patients in the primary care setting and 59% of the patients in tertiary care experienced polypharmacy. Multiple regression analysis confirmed that polypharmacy increased with male gender, advancing age, and the degree of multimorbidity. Horizontal and vertical integration of multidisciplinary teams in all disciplines to manage patients is needed to combat inappropriate polypharmacy. This will help in optimizing the management of patients with NCDs.

Keywords: Multimorbidity, non-communicable disease, primary health care, polypharmacy

Introduction

Polypharmacy is the concomitant use of several drugs by an individual. Polypharmacy results from multimorbidity. There is no universally accepted definition of polypharmacy. There are several definitions of polypharmacy. Commonly used definitions include “the concomitant use of five or more drugs”, “potentially inappropriate medication combination” or “use of more medications than are medically necessary [1]”. There are two varieties of polypharmacy: appropriate and inappropriate. It is inappropriate polypharmacy that leads to problems [2]. Despite the above definition, the most conventional definition used in clinical literature is the numerical definition of five or more drugs [2]. Polypharmacy can be any combination of prescription drugs, over-the-counter medications, and dietary or herbal supplements.

Polypharmacy is now a global problem with the increasing burden of non-communicable diseases (NCDs) worldwide. Polypharmacy is increasing worldwide [3]. Polypharmacy at times is inevitable. The use of polypharmacy can be clinically appropriate if they result in a higher quality-of-life [4, 5]. Polypharmacy can lead to serious adverse events [6]. The reason for adverse effects is various. With polypharmacy, there is an increased probability of drug-drug interaction. There is also an increased possibility of drug-disease interactions. Drug-drug interactions are said to occur when two or more

drugs interact in a way that the efficacy or toxicity of one or more of the drugs is altered. The occurrence of drug-drug interactions is proportionate to the number of drugs prescribed [7]. Apart from drug-drug interactions, polypharmacy results in higher healthcare costs, increased risk of adverse drug events, drug-drug interactions, and medication nonadherence [7, 8]. Polypharmacy is associated with a higher risk of hospitalization and mortality [9].

Increasing NCD's result in multimorbidity [10]. Multimorbidity results in polypharmacy. Sri Lanka is a country in South Asia, with an increasing burden of NCDs. One-third of the world's total population lives in South Asia, and the region is affected both by infectious disease and NCDs [11]. The prevalence of multimorbidity in South Asia ranges widely from around 5% to 83%. The prevalence of multimorbidity in Sri Lanka is 64.1% of patients [12]. This was the result of a study carried out in Colombo. Nearly 44.44% of the patients aged 20-35 years have a minimum of two disorders, and by the time they reach 50 years and nearly 64% of the patients have two or more non-communicable diseases. Nearly 7% of those aged over 65 years were diagnosed with four or more disorders.

Evidence is scarce from Sri Lanka on polypharmacy. This study aimed at the identification of the patterns of prescribing drugs for patients diagnosed with NCD's in a state-sector primary and tertiary healthcare setting while delineating specific predictors influencing the prescribing practice.

Ethics approval: Ethical approval was received from the Ethics Review Committee of Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (ERC No: 35/19).

Materials and methods

A descriptive retrospective cross-sectional study was carried out basing one primary care and one tertiary care general medical clinic. The methodology of the study has been described and published previously [12].

This study was carried out in the medical clinics of a tertiary care teaching hospital in Sri Lanka and a University primary care department (Family Practice Centre). These two study settings were selected as the patients in the suburbs of the University are cared in a coordinated manner between these two institutions through a referral and back-referral system, where a secondary level hospital rarely has any involvement. The tertiary level teaching hospital is managed by the central Ministry of Health, whereas the University managed the primary care department. Both these University-operated institutions are located in the southern part of Colombo, the commercial capital of Sri Lanka.

Data extraction was limited to the clinical records of adult patients (18 years or older) with a minimum of one non-communicable disease (NCD) diagnosed by either a consultant physician or a consultant family physician, and the most recent encounter occurred during the year 2019. Clinic records lacking any one of the following information; i.e. the age, the sex, area, drugs administered were excluded.

The study population was divided into four age groups; 18-35 years, 36-50 years, 51-65 years, 66 and more years. Since many NCDs were considered for multimorbidity, a prevalence (p) of 50% was used to obtain the largest sample size at 95% confidence level with 5% margin of error (e) using the equation $n = Z^2\ p\ q/e^2$. A sample size of 384 was obtained for one age group of adults in order to extract data from a finite number of records while also yielding a sufficient statistical power. Therefore, a sample size of 1600 was obtained from both settings, 800 records from each setting with including all four age groups.

All clinic records from the 1st of January 2019 were scrutinized until the sample size was achieved. Investigators collected data from the clinical records of the two settings. Personally Identifiable Information (PII) pertaining to the patient, such as name or address was not extracted, and the anonymized records of each patient were assigned an alphanumeric identifier and kept in the safe custody of the investigators. A data extraction form was used to extract the data from clinic records.

The outcome indicator was the number of drugs the patient was on. This was extracted from the prescriptions of the patients, which was provided to the patient by the treating physician. All such drugs were extracted and then catego-

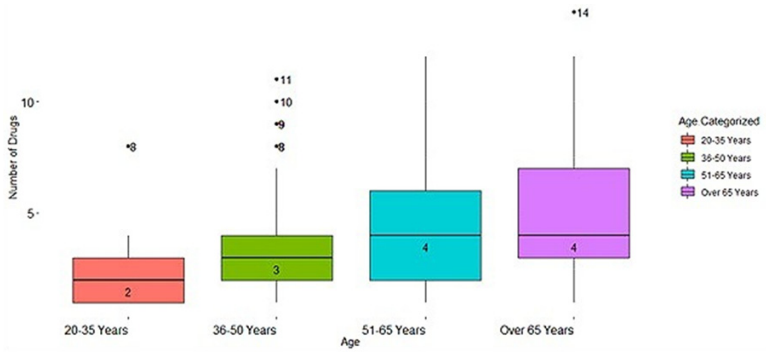

Figure 1. Number of drugs with respect to age.

rized during data analysis. The Type of non-communicable disease was obtained from the diagnosis card of the patient. A diagnosis card is provided by the treating physician who is usually a consultant physician.

The protocol was approved by the Ethics Review Committee of Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (ERC No: 35/19), which bases the guidance and management procedures on the International Guidelines on Biomedical Research prescribed by the World Health Organization (WHO) and the Council for the International Organizations of Medical Sciences (CIOMS).

Statistical analysis

In order to achieve the objective several statistical methods such as frequencies, percentages with 95% confidence intervals, cross-tabulations were used along with a thorough graphical analysis. Software tools like MS Excel, R, and SPSS were helpful in conducting the univariate and graphical analyses. A multiple linear regression model was fitted with the main objective of assessing the significance of the variables in the data set towards predicting the number of drugs which will thus be important in understanding the big picture through this study regarding multimorbidity based on polypharmacy. 'R Studio' software tool was used in conducting the advanced analysis, which included model fitting and obtaining the estimated coefficients, their significances, and the other summary statistics.

Results

Of the 1600 patient records assessed, 54.06% were females. The proportional contribution from primary and tertiary care settings to the records was exactly equal. Most of the patients (43.88%) belonged to the age group of 51-65 years, while individuals over 65 years of age accounted for 38.44%.

Over 50% (63.48%) of the patients in the sample were diagnosed with multimorbidity, and this study focused on seventeen common non-communicable diseases [12]. Diabetes Mellitus (51.5% = 824/1600), Hypertension (46.1% = 737/1600) and Coronary Heart Disease (27.3% = 436/1600) were the most prevalent conditions among the subjects. Among those with multimorbidity, the greatest proportion (45.35%) was over 65 years of age, 43.66% were between 51 and 65 years old while the least affected (1.09%) were those between 20-35 years old. However, by the age of 50 years, nearly 11% of the subjects were diagnosed in excess of two disorders.

Figure 1 illustrates the relationship between polypharmacy and the age of the patients in the study. The median number of drugs is likely to increase with advancing age. However, the median number of drugs is found to be 4 for the patients over 50 years of age, whereas the mode was found to be 3.

The number of drugs the individuals were on was categorized as shown in the table below (**Table 1**) in order to provide a simple, yet meaningful interpretation. The majority of the patients 63.2% (1011/1600) were not on polypharmacy, and 35.75% (572/1600) were on 3-4 drugs closely followed by the category of 1-2 drugs 27.18% (435/1600). Polypharmacy with more than nine drugs was determined to be significantly more prevalent among those over 40 years of age (8.24%) as compared to the younger individuals (3.37%) as shown in **Table 1**.

In an evaluation of the number of drugs with the care settings, it was determined that nearly 85% of the patients in the primary care setting were on four or lesser number of drugs whereas this figure for tertiary care was 41% (**Figure 2**). **Figure 3** shows the number of drugs with regards to the presence of multimorbidity. However, a contradictory finding was the signifi-

Table 1. Number of drugs with respect to a different age categorization

	Number of Drugs						
	Not experiencing polypharmacy (1007 = 63.2%)		Experiencing polypharmacy (586 = 36.8%)				Grand Total
	1 to 2	3 to 4	5 to 6	7 to 8	9 to 10	11 or more	
Below 40 Years	29.21%	34.83%	17.98%	14.61%	2.25%	1.12%	100.00%
Over 40 Years	27.19%	35.97%	16.36%	12.23%	6.12%	2.13%	100.00%
Grand Total	435	572	262	197	94	33	100.00%
[Percentage prevalence]	[27.18%]	[35.75%]	[16.38%]	[12.75%]	[5.88%]	[2.06%]	
(95% CI)	(25%, 29%)	(33.4%, 38.1%)	(14.6%, 18.2%)	(10.7%, 13.9%)	(4.7%, 7%)	(1.4%, 2.8%)	

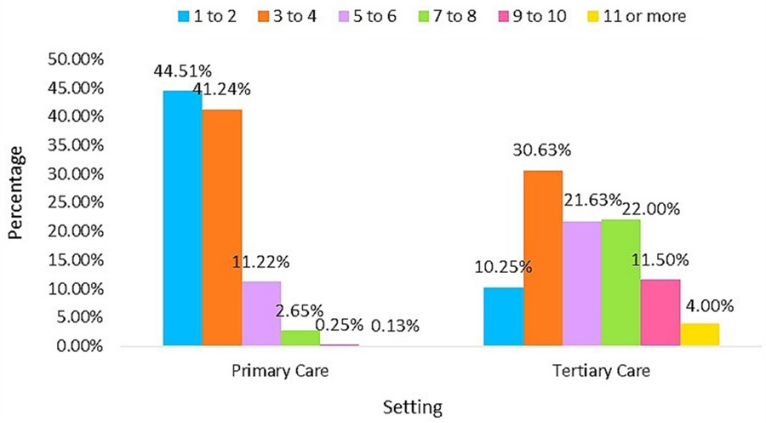

Figure 2. Number of drugs with respect to each care setting.

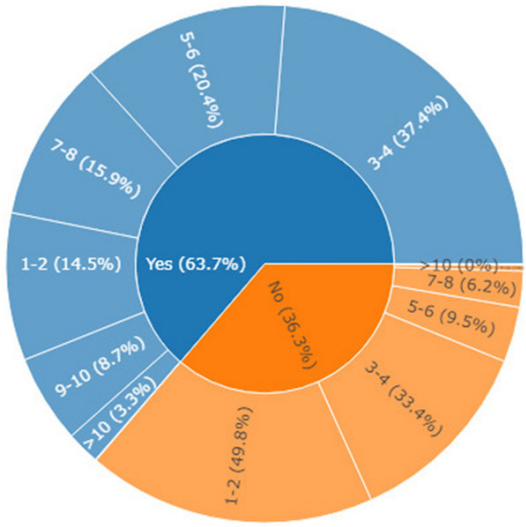

Figure 3. Number of drugs with respect to the presence of multimorbidity.

cantly higher prevalence of multimorbidity (P<0.05) among the patients of the primary care setting (53.19%) as compared to those in tertiary care (46.81%).

Figure 3 gives a sunburst diagram that illustrates the number of drugs in relation to the presence of multimorbidity. Nearly half (48.22% = 489/1014) of the subjects suffering from more than two non-communicable diseases were managed by the clinicians on more than five drugs which resulted in polypharmacy, whereas 83.2% (481/578) of the patients who were not experiencing multimorbidity were managed on 1 to 4 drugs.

The patients who were on more than 11 drugs were found to be having specific conditions that include, diabetes mellitus, hypertension, coronary heart disease, chronic kidney disease, and cardiac failure. In consideration of the three most prominent diseases (diabetes mellitus, hypertension, and coronary heart disease), it was observed that the majority of the individuals with a diagnosis of either diabetes mellitus or hypertension were placed on 3 to 4 drugs. Strikingly, seven or more drugs were co-prescribed for 80% of the patients with heart failure and 60% with coronary heart disease (**Figure 4**).

To be able to envisage the influence of variables such as gender, age, mental disorders, and the degree of multimorbidity on polypharmacy (the number of drugs), a multiple linear regression model was fitted. The model resulted from the estimated coefficients along with the standardized coefficients of the predictors and their respective significances in the model as shown in **Table 2**. A significant regression equation was adapted with F (5, 1587) = 135.4 and *P*-value = $2.2*10^{-16}$<0.05 at 95% significance level.

According to the coefficients and the significances of the predictor variables, it is clear that

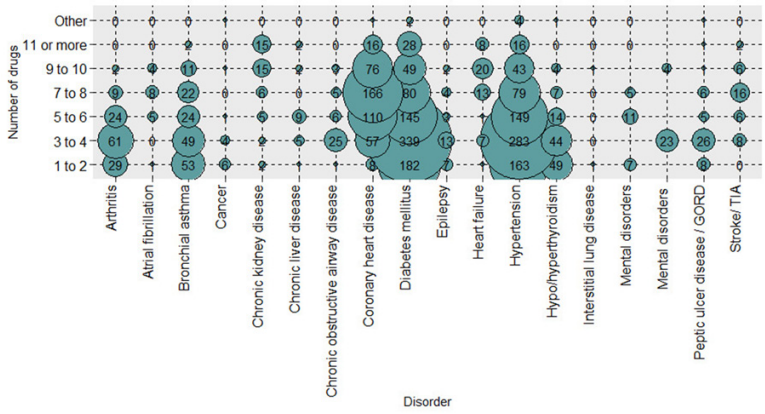

Figure 4. Number of drugs with respect to each non-communicable disease.

at a 95% confidence level, all the predictor variables are significant (P<0.05), and only the presence of mental disorders seems to have a negative influence on the number of drugs.

The model equation for the predicted number of drugs could be stated as, Number of Drugs = 0.0253* Age + 0.8462* Gender (Male) -1.0079* Mental Disorders (Yes) + 1.423* Number of Disorders.

Discussion

This is the first study of its kind conducted in Sri Lanka assessing polypharmacy at once in both primary and tertiary care settings. This study was done as a secondary study of the study assessing multimorbidity in Sri Lanka [12]. Polypharmacy was defined as the use of five or more drugs in the present study. This has been the definition used by many studies previously. In the current study, 36.8% of all the patients experienced polypharmacy. In a small-scale study done at tertiary clinics in Sri Lanka previously, polypharmacy was present in 235 (67.1%) patients. In studies done in other countries in South Asia, a systematic review and meta analysis done in India shows the pooled prevalence of polypharmacy was 49% [13]. The prevalence of polypharmacy in the present study is lower than the pooled prevalence of polypharmacy in South Asia. This could be due to a number of reasons. Firstly, the study included a family practice centre, which is less crowded and allows doctors to scrutinize the prescriptions which could have reduced polypharmacy. Secondly, the other centre that was included is a university medical unit armed with post graduate trainee doctors and a number of consultants as opposed to a medical clinic manned by a single consultant. This could have resulted in reduced polypharmacy.

Despite been lower compared to the region's prevalence there is still a substantial amount of polypharmacy. There is no coordinated standard referral pathway in Sri Lanka as patients are not mandatorily registered with one practitioner. These patients may be seeking treatment from multiple physicians for the same illness, which could result in polypharmacy. With the lack of existence of an integrated electronic medical record system, most prescribers in Sri Lanka be it primary or tertiary care, are unfamiliar with a patient's medication history and are dependent upon the patient's ability to give a description of the drugs they are on. Another reason for polypharmacy is the expectations of the patient. Sri Lankans culturally expect to receive specific medications when they visit a physician, due to the influence of Ayurveda medicine where prescribing substances is quite common [14].

Tertiary care experienced more polypharmacy in our study; a tendency that was also evident from studies carried out in many other countries. In a study conducted in Norway, polypharmacy was present among 47% of patients admitted to rheumatology and internal medicine wards. Polypharmacy was present among 66.2% [15] of the resident tertiary care patients in India and the respective figure for Saudi Arabia was 89% [16]. The primary reason for increased polypharmacy in tertiary care may be attributable to its patients with complex diseases, some of whom are being referred from primary and secondary care to this referral centre. Another reason could be the free health care system in Sri Lanka provided at tertiary health care centres. Previous studies conducted in countries with free health care have also reported high levels of polypharmacy in tertiary care [16]. However, the degree of multimorbidity in the current study was higher in the primary care setting. This discrepancy may denote the emphasis placed by primary care physicians on

Table 2. Results from the multiple linear regression model

	Regression Coefficients	Standard Error	Beta Coefficients	95% CI	*P*-Value
(Intercept)	-0.0758	0.2791	0.0000	(-1.086, 1.378)	0.78605
Age	0.0253	0.004606	0.0686	(-0.006, 0.036)	<0.001
Gender (Male)	0.8462	0.1076	0.1776	(0.448, 1.409)	<0.001
Mental Disorders (Yes)	-1.0079	0.313	-0.1100	(-4.2425, -0.378)	<0.001
Number of Disorders	1.423	0.0661	0.5437	(1.314, 1.887)	<0.001

appropriate deprescribing, as coordinators of specialist and generalist care [17-19]. However, this dilemma warrants further investigation.

Males experienced polypharmacy more than females in the present study as was observed in many other studies [20, 21]. Males may be experiencing higher polypharmacy rates owing to the higher comorbidities among them [22].

Polypharmacy is known to increase with age [11]. In the present study, the patients over 40 years experienced more polypharmacy than those under 40 years. Increasing polypharmacy with age is clinically detrimental. With increasing age, an individual's physiological capacities and reserves deteriorate in terms of body weight, liver and renal excretion, and cardiac output. These changes make them prone to adverse drug interactions and drug-disease interactions. Sri Lanka is a country undergoing demographic transition. The population of elders in Sri Lanka is expected to rise in the coming years. The elders are at increased risk of medical problems which warrant treatment. A proper health care plan for them is vital as they need to be cared for as an individual and not as a person with multiple diseases. This holistic geriatric care has to be in built in the health system of the country in order to reduce inappropriate polypharmacy.

A feature that is found in many studies on polypharmacy is that the number of diseases an individual is diagnosed with invariably necessitates polypharmacy. Polypharmacy was more common in patients with three or more clinical conditions compared to those with at least one clinical condition (7.1%). In our study, more than two non-communicable diseases were managed by the clinicians with more than five drugs which resulted in polypharmacy, whereas the patients who were not experiencing multimorbidity were managed with one to four drugs.

The risk of adverse effects escalates with increasing numbers of medications in clinical practice [2]. A study by Nolan and O'Malley showed that patients who were on ten or more medications had over a 90% probability of having significant drug-drug interactions [7]. In our study, there were about 4.3% of patients who were on 11 drugs. We also found the cluster of morbidities; dyslipidaemia, hypertension, and diabetes mellitus to be associated with polypharmacy [16]. Polypharmacy in cardiovascular medicine is quite prevalent. In the present study, seven or more drugs were co-prescribed for 80% of the patients with heart failure and 60% with coronary heart disease. Patients with HF with reduced ejection fraction (HFrEF) were most frequently prescribed a combination of diuretic, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta-blockers (BB), aldosterone receptor antagonist (ARA), and digoxin. This practice is endorsed by many international guidelines [23]. Besides the prescription medications, most patients with heart failure use a variety of other drugs for comorbidities and various symptoms [23]. Heart failure and cardiovascular diseases are a field in medicine where polypharmacy may be justified as under treatment may have adverse sequalae [23]. One method to combat or reduce polypharmacy in cardiovascular medicine would be to encourage lifestyle modifications. Clinicians could actively encourage patients to adopt healthy lifestyles.

One of the problems associated with polypharmacy in LMICs is the expense associated with it [14]. Sri Lankan health care system is free-of-charge to all in the state sector. Despite being free, there are many instances where their drugs are unavailable, and patients are bound to purchase from the private sector. The out-of-pocket expenditure associated with polypharmacy is perceived as a burden in all LMICs. If polypharmacy can be curtailed, there would be

economic benefits and improvement of quality life.

Conclusion

Evaluation of polypharmacy is vital with the rising prevalence of multimorbidity. The purpose of this large study carried out in both primary and tertiary health care was not only to study polypharmacy in Sri Lanka but also to build momentum toward taking effective steps to combat polypharmacy. Polypharmacy is present in Sri Lanka, further studies are needed to study the reasons for polypharmacy. This will help rational prescribing and minimizing polypharmacy which will reduce morbidity associated with NCDs while plummeting the economic and healthcare burden in an LMIC like Sri Lanka.

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Disclosure of conflict of interest

None.

Abbreviations

LMIC, Low and middle-income countries; NCD, Non communicable diseases; WHO, World Health Organization; CIOMS, Council for the International Organizations of Medical Sciences; HFrEF, HF with reduced ejection fraction; ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB, Beta-blockers; ARA, Aldosterone receptor antagonist.

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