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[1]Department of Family and Community Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

[2]College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

[3]Department of Psychiatry, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Corresponding author: Shahad Alsheikh, MBBS, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, 34224, Saudi Arabia, phone: 00966536158642. E-mail: sheloolshe@hotmail.com , ORCID ID: https://orcid.org/0000-0002-2408-8014.

Association Between Multi-Morbidities and Polypharmacy Among Older Adults at an Academic Medical Center in Saudi Arabia

Assim AlAbdulKader[1], Shahad Alsheikh[2], Rizam Alghamdi[2], Khalid AlHarkan[1], Nouf AlShamlan[1], Hatem Alqahtani[1], Feras Al Awad[3], Raed Alotaibi[1]

ABSTRACT

Background: Polypharmacy, or the routine use of five or more medications, can result in impacting patients' quality of life. **Objective:** to examine the association between multi-morbidities and polypharmacy, and to examine prescription practices in the elderly. **Methods:** This is a retrospective cross-sectional study. Data were gathered from electronic medical records (EMR) at King Fahad University Hospital (KFHU) and the Family & Community Medicine Center (FCMC) of Imam Abdulrahman bin Faisal University (IAU), between January 1, 2019, and December 31, 2020. We included individuals aged 60 and above with at least one dispensed prescription in 2019 and 2020. Of the 76,216 patient records reviewed, 5,060 met the inclusion criteria. Polypharmacy was defined as a monthly average of five or more prescribed medications. The prevalence of polypharmacy was calculated by year, sex, and age group, and findings were summarized using mean medication numbers and standard deviations for each stratum. An app using R programming language was developed to help visualize patients' medication histories through interactive plots. **Results:** Polypharmacy prevalence was 46% in 2019 and 44.6% in 2020. The mean and standard deviation of medications per person was 5.17 (3.42) in 2019 and 5.04 (3.37) in 2020. Females had a higher average number of medications than males, 5.17 (3.47) vs 5.04 (3.32). The age group of 80-85 had the highest number of medications at 5.6 (3.6), while those aged 90 and above had the lowest number at 4.48 (2.64). The presence of comorbidities was positively associated with the mean monthly medication count (P value < 0.01). **Conclusion:** Our study revealed a high prevalence of polypharmacy among elderly patients at KFHU/FCMC, and a positive association with multi-morbidities. Consequently, measures must be taken to mitigate this globally emerging issue's impact and rapid progression.

Keywords: polypharmacy, prevalence, geriatrics, older adults, multimorbidity.

1. BACKGROUND

The advances in medical practice had many improvements in the patient's quality of life and years, collectively leading to a growing population. The older population is expected to increase from 1:9 to 1:5 by 2050, accounting for almost half the world's population growth. With increasing age, comorbidities, and associated medications, the issue of polypharmacy has been escalating (1). The definition of polypharmacy in the clinical literature is of great debate and generally refers to using five or more medications. Studies have shown that an average elderly patient takes two to nine medications daily. However, taking more than ten medications is considered excessive polypharmacy or hyper-polypharmacy (1,2,3). Polypharmacy can be attributed to various factors, including multiple comorbidities, inadequate patient knowledge about their medications, insufficient counseling about instructions and precautions, and inefficient prescribing methods (4, 5).

Polypharmacy has significant adverse impacts, including an increased risk of adverse drug reactions (ADR) and non-adherence, which can further complicate management plans and put the patient at tremendous risk. ADR may lead to prescribing cascade when more medications are further prescribed to manage signs and symptoms caused by ADR and were misconceived as a new

disease. The risk of ADRs increases with the number of medications taken, estimated to be 15% in patients using two medications, 58% in five, and as high as 82% in seven medications. Non-adherence rates have been observed to be approximately 50% in older patients and can increase with polypharmacy (1,4). This study aims to describe the pattern of drug prescription to older patients served at King Fahad University Hospital and Imam Abdulrahman bin Faisal University Family Medicine Center Outpatient Clinics (IAU-KFHU and FCMC), measure the prevalence of polypharmacy among older patients, and describe the pattern of polypharmacy and its associated factors. By better understanding polypharmacy's causes and adverse impacts, we can develop more effective medication management plans and promote safer medication use in the older population.

2. OBJECTIVE

The aim of this study was to examine the association between multi-morbidities and polypharmacy, and to examine prescription practices in the elderly.

3. MATERIAL AND METHODS

Study design

This retrospective cross-sectional study was conducted in outpatient clinics of KFUH and FCMC of IAU in Dammam and Khobar, Saudi Arabia. Based on the study's inclusion criteria, we included male and female patients aged 60 years or older who had received regular healthcare (i.e., at least three outpatient visits) and had at least one dispensed prescription in 2019 and 2020.

Data collection tools and techniques

Data, including demographic information, prescription details, and relevant lab results, were collected by reviewing eligible patients' electronic medical records (EMR) charts. The collected data were de-identified, stored in a secure platform, and entered into a structured MS Excel sheet to maintain the confidentiality and privacy of the patients.

Polypharmacy definition

Polypharmacy was defined as taking an average of 5 or more medications per month, per year. To calculate polypharmacy, we first created a time interval for each prescribed medication (i.e., from the start of the prescription until the end of the prescription duration). Overlapping intervals of the same medication were counted as one to prevent double counting. Next, we calculated the total number of medications within each month. Then, we calculated the average value for all the months per year. Individuals with an annual average of 5 or more monthly medications were considered a prevalent polypharmacy case.

Statistical analysis

The prevalence of polypharmacy was estimated for the study period and stratified by sex and age group. The mean and standard deviation of the monthly aver-

age total medication count across the strata were also reported. A paired t-test was conducted to test for differences in average monthly medications between 2019 and 2020, and a multivariate analysis using a multiple linear regression model was conducted to control for a year, age group, and sex. A p-value ≤0.05 was considered significant. The analysis was conducted using R (version 4.2.1) (6).

Multiple linear regression analysis was used to investigate the relationship between mean monthly medications and various factors. We estimated coefficients and their corresponding 95% confidence intervals for each independent variable. We calculated the R-squared (R2) and adjusted R-squared values to assess the proportion of variance in the dependent variable explained by the independent variables. The overall significance of the model was evaluated using the F statistic.

Ethical Consideration/Approval

This study was conducted with ethical approval from the Institutional Review Board Committee of Imam Abdulrahman bin Faisal University (IRB number: IRB-2021-01-212). Patient data were kept confidential and private; no consent was required as all patient data were anonymized, and no identifiable information was used.

4. RESULTS

Out of the 76,216 patient records assessed, only 5,060 were found to meet the inclusion criteria, and these records included more than 230,000 medications.

Table 1 shows the prevalence of polypharmacy in 2019 and 2020, categorized by gender, age group, and the number of medications. The data suggests that the

	2019		2020		Total
	≥5 meds	<5 meds	≥5 meds	<5 meds	
All	2327 (46.0%)	2733 (54.0%)	2259 (44.6%)	2801 (55.4%)	(N=5060)
Female	1260 (46.8%)	1433 (53.2%)	1181 (43.9%)	1512 (56.1%)	(N=2693)
Male	1067 (45.1%)	1300 (54.9%)	1078 (45.5%)	1289 (54.5%)	(N=2367)
60-<65	886 (42.4%)	1204 (57.6%)	850 (40.7%)	1240 (59.3%)	(N=2090)
65-<70	569 (48.1%)	614 (51.9%)	545 (46.1%)	638 (53.9%)	(N=1183)
70-<75	349 (48.0%)	378 (52.0%)	357 (49.1%)	370 (50.9%)	(N=727)
75-<80	270 (48.8%)	283 (51.2%)	258 (46.7%)	295 (53.3%)	(N=553)
80-<85	164 (53.9%)	140 (46.1%)	158 (52.0%)	146 (48.0%)	(N=304)
85-<90	64 (45.4%)	77 (54.6%)	68 (48.2%)	73 (51.8%)	(N=141)
≥90	25 (40.3%)	37 (59.7%)	23 (37.1%)	39 (62.9%)	(N=62)

Table.1: Prevalence of Polypharmacy by year, sex, and age group

	2019	2020
All	5.18 (3.42)	5.04 (3.37)
Female	5.28 (3.52)	5.07 (3.41)
Male	5.06 (3.31)	5.02 (3.33)
60-<65	4.89 (3.31)	4.76 (3.24)
65-<70	5.32 (3.45)	5.15 (3.42)
70-<75	5.47 (3.63)	5.39 (3.62)
75-<80	5.36 (3.43)	5.17 (3.3)
80-<85	5.65 (3.6)	5.54 (3.58)
85-<90	5.2 (3.48)	5.29 (3.39)
>=90	4.63 (2.55)	4.33 (2.74)

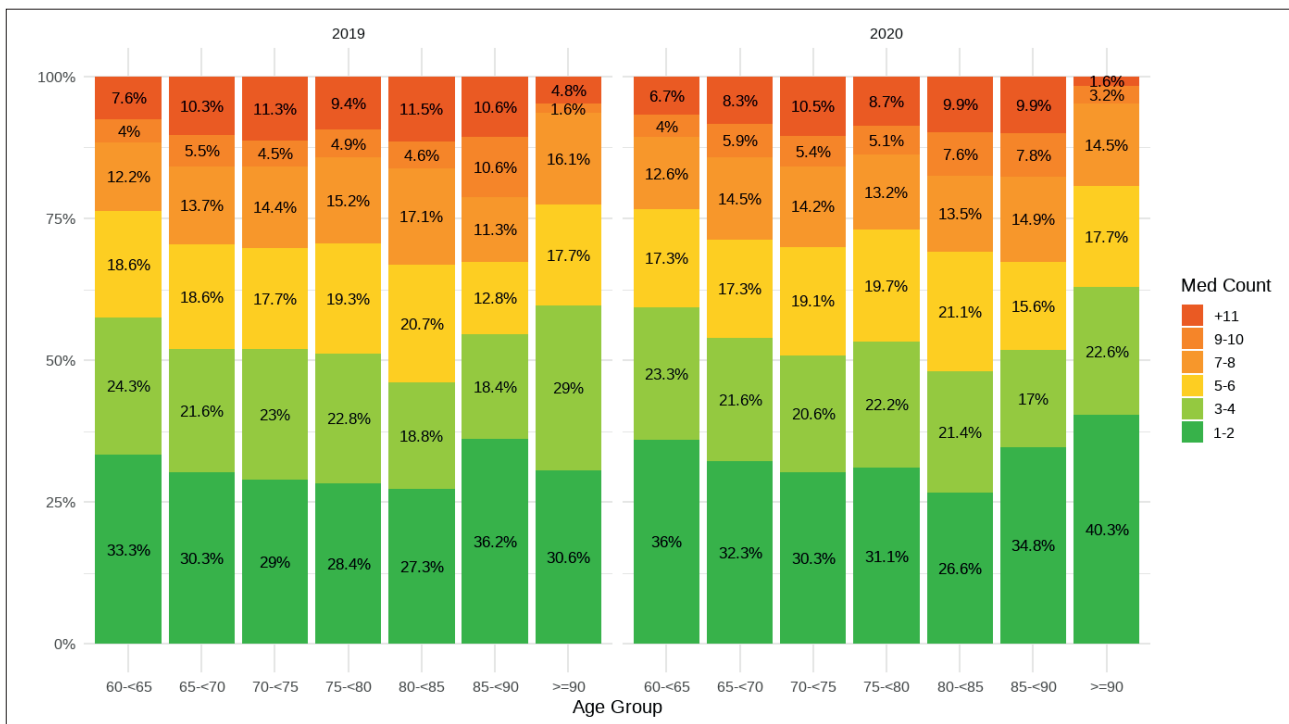**Table 2: Mean and Standard Deviation of Monthly Medications**

Figure.1: Medication count distribution for each age group. The model was statistically significant (F statistic = 555.04, p < 0.01) and explained approximately 38% of the variance in mean monthly medications (R2 = 0.38, adjusted R2 = 0.38

percentage of individuals taking five or more medications decreased from 46.0% in 2019 to 44.6% in 2020. The results indicate that females had a higher prevalence of polypharmacy than males (p < 0.01). In addition, individuals aged 80 to <85 had the highest prevalence of polypharmacy across all age groups (p < 0.01) (figure 1).

Table 2 shows the monthly medications' mean and standard deviation (SD) for 2019 and 2020. The mean medication count decreased slightly from 5.18 in 2019 to 5.04 in 2020. Females had a higher mean medication count than males in both years. The highest mean medication counts were observed in the 80 to <85 age group in both years. The lowest mean medication count was observed in the >=90 age group in both years.

The paired t-test result shows a statistically significant difference between the mean monthly medication count in 2019 and 2020 (p<0.05). The mean difference is -0.13, with a 95% confidence interval ranging from -0.18 to -0.09, indicating that the mean monthly medication count was lower in 2020 compared to 2019.

The multilinear regression analysis (Table 3) found that the mean number of medications was significantly associated with year, sex, and age. Specifically, being in the year 2020 (compared to 2019), being male, and being in the age group of 65 to <70 years old were all associated with lower mean medication counts. On the other hand, being in the age groups of 70 to <75, 75 to <80, 80 to <85, and 85 to <90 years old were all associated with higher mean medication counts. The R2 value of 0.01 indicates that the model explains only a tiny portion of the variance in the mean medication count.

Our multiple linear regression analysis revealed significant associations between the independent variables and the mean monthly medications. The model was statistically significant (F statistic = 555.04, p < 0.01) and

explained approximately 38% of the variance in mean monthly medications (R2 = 0.38, adjusted R2 = 0.38).

In 2020, the mean monthly medications decreased by 0.13 units compared to 2019 (95% CI: -0.24, -0.03, p < 0.05). Males had, on average, 0.36 fewer monthly medications than females (95% CI: -0.46, -0.25, p < 0.01). Regarding age groups, we observed significant increases in mean monthly medications for all age groups between 65 and 90 years compared to the reference age group (<65 years). However, for the ≥90 age group, there was no significant difference in mean monthly medications compared to the reference group (coefficient = -0.14, 95% CI: -0.62, 0.34, p > 0.05).

The presence of comorbidities was positively associated with the mean monthly medication count. Patients with one comorbidity had 0.94 additional mean monthly medications (95% CI: 0.76, 1.12, p < 0.01), those with two comorbidities had 2.81 additional mean monthly medications (95% CI: 2.65, 2.97, p < 0.01), and patients with all three comorbidities had 5.21 additional mean monthly medications (95% CI: 5.06, 5.35, p < 0.01).

5. DISCUSSION

Polypharmacy is an emerging global dilemma. The prevalence of polypharmacy was hypothesized and observed in the literature to increase over time. A cross-sectional study conducted in the Netherlands showed an increase in polypharmacy prevalence during the study period between 2012 – 2016 (7). Similarly, Another cross-sectional study conducted in Ireland, and studied the period between 1997 – 2012, showed a significant increase from 17.8% to 60.4% (8).In contrast, the prevalence of polypharmacy in our study decreased from 46% (2019) to 44.6% (2020). These findings were similar to a cross-sectional study conducted in Japan that

	Dependent variable:
	Mean Monthly Medications
	ordinary least squares (OLS)
Intercept	2.20** (2.05, 2.36)
Year 2020	-0.13* (-0.24, -0.03)
Sex-Male	-0.36** (-0.46, -0.25)
Age group 65 to <70	0.20** (0.07, 0.34)
Age group 70 to <75	0.42** (0.26, 0.58)
Age group 75 to <80	0.28** (0.10, 0.46)
Age group 80 to <85	0.44** (0.21, 0.67)
Age group 85 to <90	0.36* (0.03, 0.68)
age group ≥90	-0.14 (-0.62, 0.34)
Comorbidity (+1) +	0.94** (0.76, 1.12)
Comorbidity (+2)	2.81** (2.65, 2.97)
Comorbidity (+3)	5.21** (5.06, 5.35)
Observations	10,120
R2	0.38
Adjusted R2	0.38
Residual Std. Error	2.69 (df = 10108)
F Statistic	555.04** (df = 11; 10108)

Note:+ Comorbidity (the presence of DM, HTN, and Dyslipidemia; categorized as +1 for any one condition, +2 for any two conditions, and +3 for all three conditions).*P-value <0.05 **P-value <0.01

Table.3: Multilinear Regression - dependent variable is the mean number of medications.

showed a decrease in the prevalence of polypharmacy from 50.1% in 2014 to 48.2% in 2019 (9). In the lateral study, these unexpected findings were attributed to the emerging laws of deprescribing. However, since these findings were observed in recent studies, we hypothesize that this decrease in prevalence may be attributed to COVID-19 lockdown or a change in drug formulary or available medications. More studies to investigate these findings are required.

Our study showed a higher prevalence of polypharmacy in females than in males, which is in line with previous studies that can be traced back to 1998 (10-14). A recent study in Sweden has discussed the possible causes for the increase in polypharmacy in females, as their findings showed that polypharmacy increased in females and lower education levels (14). The study elaborated on the possible causes behind this association, including higher life expectancy in females, hence, a more extended period with chronic diseases and their complications. Also, females' behavior towards their health condition where they are more likely to report signs or symptoms that lead to further treatment (15). Lastly, fe-

males are more likely to receive primary and secondary preventive care. (16).

In our study, patients at age ≥90 years had the lowest medication count with a mean of 4.48 (2.64), whereas patients in the age range of 80 to 85 had the highest mean number of medications of 5.6 (3.6). It is crucial to highlight a gap in the literature regarding the difference in geriatrics age groups' medication numbers. There is no evidence to explain this difference. However, it can be attributed to other phenomena like survival bias, where those who survived to the extreme age are likely to be healthier with less need for treatment (17). On the other hand, the older generation could have lower physiological reservoirs and loss of body functions (e.g., liver, kidney, heart). Therefore, fewer medication benefits and more can increase the risk of harm, eventually reducing medications prescription by their treating physicians. Another possible etiology is under-prescription for older patients, a medical problem. Some potentially appropriate medications can be under-prescribed in older patients as some physicians fear harmful drug side effects. Some patient-associated factors with under-prescription are frailty, multimorbidity, dementia, polypharmacy, risk of adverse drug events, and economic factors (18). Unfortunately, our study could not assess the above hypothesis due to incomplete information (e.g., comorbidities, physician notes, and medication data from earlier years). Thus, this highlights the possible role of further literature to undercover if patients at the age of ≥90 years are healthier or undertreated.

The current study evaluated the factors associated with polypharmacy among a sample of older people in a healthcare institution in Saudi Arabia. Several factors (year of visit, sex, age, and comorbidities) were significantly associated with polypharmacy. In the present study, the mean monthly medications were significantly increased for all age groups between 65 and 90 years compared to the younger age group (<65 years). This finding is consistent with previous studies results, which demonstrated that older patients are more susceptible to polypharmacy (19-23). The reason is that multiple chronic diseases increase with age (19). This finding is alarming in Saudi Arabia since the proportion of older adults in the country is increasing.

On the other hand, we reported that for the≥90 age group, there was no significant difference in mean monthly medications compared to the reference group (<65 years). In agreement with this finding, Lizhen Ye et al. study in five European countries (the United Kingdom, Spain, Croatia, Greece, and the Netherlands) among a sample of older community-dwelling adults, with a mean age of 80 revealed no association between polypharmacy and age. This could be explained by the fact that utilization and prescription of medication are usually treated with extreme caution in very old patients (24).

Interestingly, this study showed that the mean monthly medications for patients visited during 2020 were significantly lower compared to 2019. This could be an impact of the COVID-19 pandemic. A lockdown during

the pandemic and individuals' efforts to avoid unnecessary visits to healthcare services and keep them from becoming overwhelmed could affect the accessibility of non-urgent conditions to healthcare institutions. Moreover, the geriatric population and patients with comorbidities received special attention during the pandemic. They were considered a high-risk population, making them more likely to comply with preventive measures and maintain home isolation. An additional risk among these populations is polypharmacy, which increases their likelihood of having a severe COVID-19 infection with its associated morbidity and mortality, and drug interactions with the medications used to manage the COVID-19 infection, which makes healthcare providers more cautious in prescribing medications to these patients. All these reasons could explain the decrease in monthly mean medications in the current study during 2020. This agrees with the results of a study among a large sample of the Spanish population (25).

The present study showed that males had significantly fewer mean monthly medications than females. This aligns with previous findings that females had an increased risk of polypharmacy. (19, 23, 25) The association between polypharmacy and gender was an area of discussion. A possible explanation is that females are usually more cautious about their health conditions, seek medical assistance for their illnesses, and communicate with healthcare providers more often. Moreover, chronic diseases were reported more frequently among females than males. (19) This emphasizes the role of family physicians, geriatricians, and women's health specialists in dealing with this issue, especially among females. However, our finding did not align with results from other studies, which reported that females had a lower risk of polypharmacy than males(21, 24).

In agreement with previous studies, the current study found a significant positive association between mean monthly medication and the number of comorbidities (19, 24, 25). The possible reason behind this finding is that patients with multiple comorbidities were treated by different medical specialists who may not know what medications their patients are utilizing, which may cause inappropriate prescriptions (24). Therefore, patients' education on their medical conditions and medications is crucial to the clinical encounter, especially for older patients more prone to medication side effects. Moreover, communication between healthcare providers caring for older patients, especially those with multimorbidities, is essential. Additionally, the utilization of standardized tools in reviewing and prescribing medications for geriatric patients, such as the STOPP criteria (Screening Tool for Older Person's potentially inappropriate Prescriptions), the Beers' criteria, and the START criteria (Screening Tool to Alert doctors to the Right Treatment) is also vital(26-28). Another recommended solution to reduce polypharmacy is maintaining regular access to the primary care physician for medication reconciliation and deprescribing (20).

STUDY STRENGTHS AND LIMITATIONS

Our study tackles a very critical and emerging issue. Moreover, It is one of the few studies conducted in Saudi Arabia utilizing a significant study period and analyzing medication prescription patterns. The findings of our study shed light on many hypotheses that would form the base of future projects. However, the limitations of our study are gathering information on whether all these medications were dispensed after prescription and their consumption. For example, we cannot calculate over-the-counter medications, other healthcare institutions' prescriptions, or if there have been any changes in the available medications over the years. Moreover, the COVID-19 crisis and lockdown significantly impacted many healthcare aspects. The pandemic's effect on polypharmacy has yet to be wholly understood, and further studies are required to establish the impact.

6. CONCLUSION

Data science methods were employed to analyze over 230,000 prescriptions, revealing a high prevalence of polypharmacy among elderly patients at KFHU/FCMC, and a positive association with multi-morbidities. Consequently, measures must be taken to mitigate this globally emerging issue's impact and rapid progression. Our findings highlighted the possible role of further literature to undercover if patients at the age of ≥90 years are healthier or undertreated and the underlying cause of the difference in mean monthly medications in different age groups.

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