International Journal of Gerontology 18 (2024) 91–95
https://doi.org/10.6890/IJGE.202404_18(2).0006

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Polypharmacy is Associated with the Risk of Chronic Kidney Disease in the Elderly: A Nationwide Ten-Year Propensity Analysis in Taiwan

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ARTICLE INFO

Accepted 28 October 2023

Keywords:
polypharmacy,
chronic kidney diseases,
elderly

SUMMARY

Background: The relationship between the use of multiple medications and the risk of chronic kidney disease (CKD) warrants investigation. The aim of this study was to examine the association between polypharmacy and CKD.

Methods: A population-based case-control study was conducted using data from the Taiwanese National Health Insurance Research Database. Medication use was assessed from 2002 to 2003, and newly diagnosed CKD using the International Classification of Disease, 9th revision, Clinical Modification (ICD-9 CM) from 2004 to 2011 was analyzed. Propensity score analysis was used to recruit 3,249 cases and 3,249 controls through random selection. The risk of CKD was compared among individuals who used less than five medicines per day and those who used more than five medicines per day.

Results: A dose-response relationship was observed between the number of medications used and the risk of CKD. Propensity score analysis showed an increased risk of CKD among patients who used five to nine medicines per day (odds ratio (OR), 1.90; 95% CI, 1.69–2.14) and those who used more than ten medicines per day (OR, 3.06; 95% CI, 3.61–2.60). Nevertheless, the use of ICD codes to identify CKD may result in misclassification bias. The severity of renal impairment was not assessed. Non-adherence and over-the-counter drugs were not accounted for.

Conclusion: In a nationwide study, polypharmacy was found to be associated with CKD in the older population, and this trend persisted after propensity score matching. There was a positive correlation between the number of medications used and the incidence of CKD.

1. Introduction

Chronic kidney disease (CKD) is a prevalent and serious public health issue with a growing global burden, affecting more than 10% of the population worldwide.[1] In Taiwan, the prevalence of CKD is high, with a rate of up to 11.9%.[2] Moreover, Taiwan has the highest incidence and prevalence of end-stage renal disease in the world.[3] Despite this, awareness of CKD in Taiwan remains low.[4]

CKD is a chronic and progressive disease that typically emerges with age, and its development can be accelerated by cardiometabolic factors.[5] CKD can be considered a "geriatric giant," with a prevalence among older adults ranging from 20% to 60%.[6] The higher prevalence of CKD in older adults is largely due to their increased risk of developing comorbidities such as hypertension, diabetes mellitus (DM), and cardiovascular disease (CVD).[7]

Managing the chronic diseases and risk factors associated with CKD in older adults is critical to impeding the development and progression of CKD.[8] However, managing these conditions typically involves multiple drug combination therapies,[9] with the use of more than five medications for treatment being common. As a result, CKD patients have a high medication burden due to their kidney disease and comorbidities.[10] They are also at high risk of polypharmacy and the use of potentially inappropriate medications (PIMs).[11] One study found that older CKD patients took an average of eleven medications and visited multiple physicians' clinics due to various comorbidities.[12] Polypharmacy in older CKD patients is directly linked to the number of chronic diseases they have and is associated with an increased risk of adverse drug reactions (ADRs), drug-drug interactions (DDIs), and PIMs, as some specific drug clearance and metabolism are related to kidney function.[13] Severe complications of polypharmacy also lead to increased health-care expenditure, as they often result in more frequent emergency department visits and hospitalizations.[14]

Managing elderly individuals with CKD is medically complex and carries a higher risk of ADRs, particularly in the context of polypharmacy. Therefore, we aimed to investigate the association between polypharmacy and CKD in older adults in Taiwan.

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2. Materials and methods

This is a case-control study. This study was approved by the Institutional Review Board of Taipei City Hospital (TCHIRB No: 101 0518-E).

2.1. Data source

This study utilizes data from the Taiwan National Health Insurance Research Database (NHIRD) spanning the period between 2002 and 2011, as provided by the Taiwan National Health Research Institutes (NHRI). The NHIRD is a comprehensive nationwide reimbursement database covering over 99% of the population, and it contains a wealth of medical information.[15] To construct a representative sample of 1,000,000 individuals, the NHI Administration authorized the NHRI to generate a random sample. The NHIRD includes original claims data from the NHI program, including registries of contracted medical facilities and board-certified physicians, as well as complete encounter data on outpatient visits and inpatient care. In addition, patients' demographic characteristics, diagnoses, prescriptions, and encrypted identification are available. We merged the encounter data with outpatient pharmacy data using unique encrypted patient identifiers, and all diagnosis codes were included according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM).

2.2. Study population

We enrolled participants aged ≥ 65 years old between 2004 and 2011. The inclusion criteria for cases were patients who had been newly diagnosed with CKD (ICD-9-CM Codes: 250.4*, 274.1*, 283.11, 403.1*, 404.2*, 404.3*, 440.1, 442.1, 447.3, 572.4, 580–588, 642.1*, and 646.2*; * can be 0–9). Cases were included regardless of the stage of CKD and whether they were receiving dialysis or not. The index date was defined as the first date of CKD diagnosis. Controls were randomly selected from non-CKD individuals and matched with their corresponding CKD cases based on index date. Participants were stratified into three age groups: 65–74, 75–84, and ≥ 85.

2.3. Measurements

The study investigated the association between medication use and chronic kidney disease (CKD) in older adults aged ≥ 65 years. The exposure of interest was medication use in the two years (730 days) prior to the index date, with the number of average daily prescribed medications calculated as the total amount of prescribed medications divided by 730 days. Medications were coded using the Anatomical Therapeutic Chemical Classification (ATC) System and included both oral and injectable forms. Participants were categorized by the number of medications used per day (< 5, 5–9, and ≥ 10), with polypharmacy and extreme polypharmacy defined as the average daily use of five and ten or more medications, respectively.[16,17]

DM was diagnosed using ICD-9-CM codes 250.XX, while hypertension was diagnosed using codes 401.X, 402.X, 403.X, 404.X, and 405.X, both of which are prevalent conditions in Taiwan and major causes of CKD that often require multiple medications to be treated on target.

2.4. Statistical analysis

We conducted statistical analyses using SAS software version 9.4 (SAS Institute Inc., Carey, North Carolina, USA). A p value < 0.05 was considered statistically significant. We used logistic regression to calculate the odds ratios (ORs) and examine the association between the number of medications used per day in the previous two years and CKD. We adjusted for age, gender, hypertension, and DM in our multivariate model.

To further reduce selection bias, we carried out a propensity score analysis. The binary dependent variable was the conditional probability for participants to be prescribed multiple medications, and age and gender were included in a multivariable logistic regression model. We used the predicted probability from the logistic regression analysis as the propensity score for each participant, regardless of outcome. We then individually matched cases and non-CKD controls at a 1:1 ratio.

3. Results

3.1. Baseline characteristics of the study population

We enrolled a total of 3,249 cases and 3,249 controls. The baseline characteristics of the study population are presented in Table 1. Cases were slightly older than controls (mean age: cases vs. controls: 75.2 ± 7.5 vs. 76.4 ± 7.3 years old). Men were more prevalent in the case group (cases vs. controls: 55.2% vs. 50.5%). A higher proportion of cases had hypertension (86.5% vs. 70.5%) and DM (54.6% vs. 31.4%). The number of daily medications was significantly higher among cases than controls (mean: 7.2 ± 6.8 vs. 3.4 ± 4.2 pills per day).

3.2. Gender-specific and age-specific risk of CKD

Compared to participants taking less than five medications per day, the risk of CKD increased in both genders with the number of medications used per day, indicating a dose-response relationship

Table 1
Baseline characteristics of the participants (n = 6498).

	Case (n = 3249)		Control (n = 3249)		Total (n = 6498)	
	n	%	n	%	n	%
Age (mean ± SD)	76.36 ± 7.34		75.21 ± 7.52		75.78 ± 7.45	
65–74	1448	44.6	1702	52.4	3150	48.5
75–84	1313	40.4	1133	34.9	2446	37.6
≥ 85	488	15.0	414	12.7	902	13.9
Gender (men)	1792	55.2	1640	50.5	3432	52.8
Hypertension	2809	86.5	2290	70.5	5099	78.5
Diabetes mellitus		54.6	1775	31.4	2794	43.0
Number of medications (mean ± SD)	7.17 ± 6.81		3.40 ± 4.16		5.29 ± 5.94	
< 5	1357	41.8	2406	74.1	3763	57.9
5–9	1208	37.2	646	19.9	1854	28.5
≥ 10	684	21.1	197	6.1	881	13.6

(Table 2a). Women who consumed more than ten medicines per day had the highest OR (3.75; 95% CI, 2.90–4.84). Furthermore, a strong positive correlation was observed between age and the number of medications used per day (Table 2b). For individuals aged ≥ 85 who used more than ten medicines per day, the OR for CKD rose to 6.30 (95% CI, 4.15–9.56), compared to those aged 65–74 who consumed less than five medications per day.

3.3. Risk factors for CKD

Multivariate logistic regression analysis revealed that women had a lower likelihood of developing CKD (OR, 0.73; 95% CI, 0.65–0.81), while hypertension (OR, 1.69; 95% CI, 1.48–1.94), diabetes mellitus (OR, 1.92; 95% CI, 1.72–2.15), older age, and polypharmacy were associated with higher odds of CKD (Table 2c). Compared to individuals aged 65–74 years, those aged 75–84 years had an OR of CKD of 1.17 (95% CI, 1.04–1.31), and those aged ≥ 85 years had an OR of 1.42 (95% CI, 1.21–1.67). Patients who used 5–9 medicines per day had a 2.60-fold greater odds of CKD than those who used less than 5 medicines per day (95% CI, 2.30–2.93).

Table 2a
Gender-specific odds ratio of chronic kidney disease after controlling for age, hypertension and diabetes mellitus.

Number of medications	Men OR (95% CI)	Women OR (95% CI)
< 5	1.00 (reference)	0.71 (0.62–0.82)
5–9	2.70 (2.28–3.19)	1.79 (1.51–2.12)
≥ 10	3.70 (2.90–4.71)	3.75 (2.90–4.84)

Table 2b
Age-specific odds ratio of chronic kidney disease.

Number of medications	Age (years)		
	65–74 OR (95% CI)	75–84 OR (95% CI)	≥ 85 OR (95% CI)
< 5	1.00 (reference)	1.25 (1.07–1.45)	1.18 (0.96–1.46)
5–9	2.58 (2.16–3.07)	2.73 (2.28–3.27)	5.23 (3.89–7.03)
≥ 10	4.90 (3.66–6.57)	4.73 (3.69–6.06)	6.30 (4.15–9.56)

Table 2c
Univariate and multivariate regression models for the factors associated with chronic kidney disease.

	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
Gender		
Men	1.00 (reference)	1.00 (reference)
Women	0.83 (0.75–0.91)	0.73 (0.65–0.81)
Age		
65–74	1.00 (reference)	1.00 (reference)
75–84	1.36 (1.23–1.51)	1.17 (1.04–1.31)
≥ 85	1.39 (1.19–1.61)	1.42 (1.21–1.67)
Hypertension	2.67 (2.36–3.03)	1.69 (1.48–1.94)
Diabetes mellitus	2.64 (2.38–2.92)	1.92 (1.72–2.15)
Number of medications		
< 5	1.00 (reference)	1.00 (reference)
5–9	3.32 (2.95–3.73)	2.60 (2.30–2.93)
≥ 10	6.16 (5.18–7.31)	4.39 (3.67–5.25)

3.4. Propensity score analysis

In the propensity-matched analysis, we selected 3,249 matched pairs, as shown in Table 3. Our results indicated that participants with polypharmacy had consistently higher odds for CKD, and a dose-response relationship was observed, especially in the oldest-old group (Table 4a, 4b).

Table 4c presents the multivariate regression analysis results in the propensity score-matched cohort. Polypharmacy (OR, 1.90; 95%

Table 4a
Gender-specific odds ratio of chronic kidney disease after propensity score matching.

Number of medications	Men OR (95% CI)	Women OR (95% CI)
< 5	1.00 (reference)	0.92 (0.80–1.06)
5–9	2.14 (1.83–2.51)	1.54 (1.31–1.82)
≥ 10	2.67 (2.16–3.30)	3.31 (2.62–4.18)

Table 4b
Age-specific odds ratio of chronic kidney disease after controlling for gender, hypertension and diabetes mellitus.

Number of medications	Age		
	65–74 OR (95% CI)	75–84 OR (95% CI)	≥ 85 OR (95% CI)
< 5	1.00 (reference)	0.99 (0.85–1.15)	0.78 (0.63–0.95)
5–9	2.05 (1.72–2.45)	1.41 (1.19–1.67)	2.80 (2.15–3.64)
≥ 10	2.49 (1.93–3.20)	2.71 (2.18–3.39)	6.28 (4.00–9.89)

Table 4c
Univariate and multivariate regression models for the factors associated with chronic kidney disease after propensity score matching.

	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
Hypertension	2.32 (2.04–2.63)	1.54 (1.35–1.77)
Diabetes mellitus	2.05 (1.86–2.27)	1.52 (1.37–1.70)
Number of medications		
< 5	1.00 (reference)	1.00 (reference)
5–9	2.33 (2.08–2.60)	1.90 (1.69–2.14)
≥ 10	3.83 (3.29–4.48)	3.06 (2.61–3.60)

Table 3
Baseline characteristics of the propensity score-matched sample (n = 6498).

	Case (n = 3249)		Control (n = 3249)		Total (n = 6498)		p value
	n	%	n	%	n	%	
Age (mean ± SD)			76.36 ± 7.34				1
65–74	1448	44.6	1448	44.6	2896	44.6	1
75–84	1313	40.4	1313	40.4	2626	40.4	
≥ 85	488	15	488	15	976	15	
Gender (men)	1792	55.2	1792	55.2	3584	55.2	1
Hypertension	2809	86.5	2383	73.3	5192	79.9	< 0.0001
Diabetes mellitus	1775	54.6	1201	37	2976	45.8	< 0.0001
Number of medications (mean ± SD)	7.18 ± 6.81		4.01 ± 4.71		5.59 ± 6.07		< 0.0001
< 5	1357	41.8	2146	66.1	3503	53.9	< 0.0001
5–9	1208	37.2	821	25.3	2029	31.2	
≥ 10	684	21.1	282	8.7	966	14.9	

CI, 1.69–2.14), particularly severe polypharmacy (OR, 3.06; 95% CI, 2.61–3.60), remained significant factors associated with CKD, in addition to hypertension (OR, 1.54; 95% CI, 1.35–1.77) and diabetes mellitus (OR, 1.52; 95% CI, 1.37–1.70).

4. Discussion

In this case-control study, we observed that polypharmacy was significantly associated with a higher risk of CKD, particularly in men. We also observed a dose-response relationship between the number of medications used per day and the risk for CKD. Along with medication use, older age, hypertension, and diabetes mellitus were also associated with CKD.

Patients with renal impairment often require multiple medications, which can complicate their treatment and increase their risk of adverse outcomes. To address this issue in this study, we used propensity score matching to compare medication use between CKD patients and controls. We found that CKD patients used a mean of 7.17 medicines per day, compared to 3.40 medicines per day in controls. Polypharmacy was also more prevalent in CKD patients, with 58.3% having polypharmacy, which was more than double that of controls (26.0%). Prevalence of polypharmacy and extreme polypharmacy among Japanese were 43% and 9% for non-CKD, 62% and 23% for non-dialysis-dependent CKD, and 85% and 34% for dialysis-dependent CKD, respectively.[18] However, in a large-scale multicenter study in Korea, 55.6% of renal hazard in increased medication counts was mediated by the kidney function in medication analysis. The direct renal hazard of multiple medications was not identified, and most of the potential renal hazard was derived from disease burden.[19]

In the European Quality study, it was found that 91% of older people with advanced CKD experienced polypharmacy, while 43% experienced extreme polypharmacy. The most commonly prescribed medications were for cardiovascular conditions.[11] Additionally, in a study utilizing Dutch health claims data, older age, DM, and vascular disease were identified as risk factors for polypharmacy in CKD patients.[10] However, there are international differences in prescribing practices, which may indicate a lack of consensus regarding appropriate prescribing for this high-risk population where pharmacological treatment has the potential for both benefit and harm.[11]

Early intervention with medications aimed at slowing the rate of deterioration of comorbidities is crucial for reducing the risk of CKD, managing symptoms, and improving the quality of life for patients. However, prescribing for this vulnerable population can be challenging due to multiple factors, including the potential for medications to impair renal function. Previous studies have demonstrated a positive correlation between polypharmacy due to multiple comorbidities and the incidence of CKD in older patients.[12,20] Although the exact mechanisms linking polypharmacy to CKD are unclear, several studies have shown that it increases the risk of potentially inappropriate medication (PIM) prescription and use, drug-drug interactions (DDIs), and adverse drug reactions (ADRs), all of which could contribute to the deterioration of kidney function.[21] These situations can lead to a "prescribing cascade," resulting in severe complications, more frequent emergency department visits, and hospitalizations.[14] Major polypharmacy has consistently been associated with increased mortality and severe CKD.[22,23] Polypharmacy in elderly populations is a public health issue that requires identification, coordination, and prevention.

This case-control study utilized the NHIRD as a comprehensive and representative cohort of older citizens in Taiwan, covering up to 99% of the national population. Our results demonstrate a clear overall dose-response relationship between the use of multiple medications and CKD. In Taiwan, more than half of the elderly CKD patients take more than five medicines per day, and 21.1% of them take even more than ten medicines per day. It is noteworthy that a patient taking 5–9 medicines per day had a 50% probability of DDI, and the risk increased to 100% when taking 20 or more medicines per day.[24] Although some studies have shown no significant relationship between polypharmacy and CKD,[25,26] the significant positive association observed in our study remained after propensity score analysis. These results emphasize the urgent need for an interdisciplinary, structured, and patient-centered approach to medication review among elderly CKD patients.[27]

In Taiwan, the NHI system does not have a formal referral system that requires patients to be referred before visiting specialists' clinics in hospitals. Additionally, the NHI system does not set a limit on the number of doctor visits an individual can make per day.[28] As a result, the large population of older CKD patients in Taiwan may be more susceptible to polypharmacy due to their tendency to seek medical care from multiple specialties to manage their various co-morbidities.

This study has several notable characteristics. The high coverage rate of the nationwide population ensures the representativeness of the study, and the use of population-based data minimizes the risk of selection bias. The longitudinal design of the study allowed us to track patients for up to ten years and follow up for eight years to assess the effect of polypharmacy on CKD development. Additionally, we were able to obtain a complete list of prescription medications from the claims data, which is more accurate than relying on patient recall. This is one of the few claims datasets that contains prescription medication information in the world which provides a unique opportunity for analysis. Confounding by indication is a valid concern in observational studies, and we controlled for it using propensity score analysis. Furthermore, the amount of missing data was less than 1% which ensured the reliability of our findings.

This study has some limitation. Firstly, the use of ICD codes to identify CKD patients may be prone to inaccuracies and may result in misclassification bias.[29] We might potentially underestimate or overestimate the true incidence of CKD, and under-diagnosis might be the most probable direction. In this case, some CKD patients might be misclassified as controls. Secondly, data including blood or urine test results as well as other major co-morbidities was not available. These factors are crucial for evaluating the severity of renal function impairment and controlling for potential confounding variables. Therefore, ascertaining the severity of renal function impairment was not feasible. The effects of angiotensin receptor blockers (ARB) were not analyzed. Given the importance of ARBs in managing CKD, their potential impact on the association between polypharmacy and CKD should be addressed in future studies. The number of medications reported may not be the exact number taken due to non-adherence and the use of over-the-counter (OTC) drugs. We might potentially overestimate the true number of NHI medications taken by the older people and overlooked other OTC medicines with renal toxicity. The drug effect was investigated in the same race, and generalizability to other ethnicities may be limited. Additionally, due to the observational nature, we can only speculate about a positive association between polypharmacy and the incidence of CKD without definitive causal inference.

5. Conclusion

This study provides strong evidence of a dose-response relationship between the use of multiple medications and the incidence of CKD in the elderly population, with more than half of CKD patients

taking over five medicines per day. Comorbidities such as hypertension and DM can exacerbate the risk of CKD development in patients taking multiple medications. Using multiple medications is also an expected condition in CKD patients due to multi-morbidity. Future research using causal mediation analysis could help identify potential mediators of this relationship, and randomized controlled trials to establish a causal relationship between polypharmacy and CKD is needed.

Given the modifiability of medication exposure, it is crucial to adopt an interdisciplinary, structured, and patient-centered approach to prescribing for elderly CKD patients, such as the setting up of geriatric comprehensive clinics. This study highlights the urgent need for authorities to implement a more prudent prescribing system and should serve as a springboard for further research in this area.

Acknowledgements

We thank assistant Mr. Hua Chung for his help in data analysis. We thank assistant Mr. Guo-Shou Wang for his managerial help.

Declaration of any potential financial and non-financial conflicts of interest

None.

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