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Brief Report

The Number of Medications Is Associated with Fractures in a Population of Dialyzed Older Patients with Frailty

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Abstract

Older persons with chronic kidney disease (CKD) undergoing hemodialysis represent a growing portion of patients characterized by high vulnerability but still marginally studied. This study aimed at exploring the relationship between the number of prescriptions and fractures in older patients with CKD undergoing hemodialysis. A 24-item Frailty Index (FI) based on sociodemographic, clinical and biological data was computed. Unadjusted and adjusted logistic regression models were performed to test the association of prescribed medications with history of fractures. A total of 107 older patients undergoing hemodialysis (38 [35.5%] women, mean age 79.1 standard deviation, SD=7.7) were included in the study. Mean number of prescribed medications was 9.9 (SD=3.9) and was significantly associated with fractures (OR 1.18, 95% CI 1.06-1.32, p=0.003), even after adjustment for potential confounders (OR 1.16, 95% CI 1.03-1.30, p=0.016). If these results will be confirmed, interventions based on deprescribing will become essential in older persons undergoing hemodialysis.

Key words: Chronic kidney disease, falls, older people, aging, polypharmacy.

Introduction

A large and growing segment of the older population is characterized by the presence of multiple morbidities and mutually interactive syndromes. As a consequence, the use of multiple medications is quite common in older people and is associated with several adverse outcomes including falls, functional impairment, adverse drug reactions, increased length of hospital stay, hospital readmissions, and mortality (1). In particular, the term 'polypharmacy' refers to the simultaneous use of multiple medications (i.e., five or more) (2). With aging, a physiological decline in both renal and hepatic function is seen (3). Such a decline, which can be further exacerbated by comorbid conditions, make older patients at an even greater risk of adverse effects (4).

Chronic kidney disease (CKD) is increasingly prevalent in the older population, with also a growing portion of older people undergoing hemodialysis (5). Despite being a life-saving replacement therapy, hemodialysis is also associated with several adverse outcomes (i.e., cardiovascular disease, renal osteodystrophy, insulin resistance, bleeding, malnutrition) (6) exposing older people to the frailty disabling cascade. End-stage renal disease (ESRD) patients usually present some other (chronic) morbidities requiring the long-term use of multiple medications (7). Of note, polypharmacy has been indicated as an important contributing factor for falls and fractures (8). Additionally, it has been reported that patients undergoing hemodialysis present a higher risk of any type of fracture compared to the general population (9). Fractures represent an important public health issue increasing the risk of morbidity and mortality and subsequently healthcare costs, especially in older people (10).

The present study aimed to investigate the association between the number of prescribed medications and fractures in a population of older people undergoing hemodialysis.

Methods

Study design and population

We conducted a retrospective longitudinal study on data retrieved from the clinical charts of 107 older patients (i.e., aged 65 and older) with CKD receiving hemodialysis at the Nephrology Unit of a tertiary hospital in Milan (Italy). The main exclusion criterion consisted in a short-term hemodialysis treatment (i.e., less than three months) for avoiding the inclusion of individuals with a terminal illness. Information about clinical status, nutrition, and physical function were recorded.

The study was approved by the Ethical Committee of the Fondazione IRCCS Ca' Granda – Policlinic Hospital of Milan (approval number: 383_2020) and adhered to the principles of the Declaration of Helsinki. Since all the procedures being performed were part of the routine care, no written informed consent was required according to local regulations (AIFA Resolution of 20 March 2008).

Number of medications

The number of medications was defined as the count of all prescribed medications and was used as a continuous variable.

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Outcome measure

The outcome of interest for the present study was defined as any type of fracture event. Participants were regularly followed over time by the study center as referent for their hemodialyitic procedures. Fractures events were retrieved from medical charts, patient's proxies, and administrative data.

Other measurements

Sociodemographic data (i.e., age, sex, education) and the presence of comorbidities (i.e., diabetes, hypertension, depression, psychiatric disorders, dementia, cancer) were collected. However, the item defining fractures (dependent variable of the present study) was excluded from the computation of the total score used in the analyses.

A 24-item Frailty Index (FI), standardized according to the criteria described by Searle and colleagues (11) was then computed from the results of a comprehensive geriatric assessment. In particular, each item constituting the FI (Table S1) was categorized as 0 (if the deficit was absent) or 1 (if the deficit was present). The resulting FI was calculated as the ratio between the number of deficits presented by each patient divided by the total number of considered health deficits (i.e., 24). The prognostic value of the FI in this patient's population (i.e., CKD older patients on hemodialysis) has been recently reported (12). The FI is a multidimensional and comprehensive instrument for capturing the clinical complexity of older persons. In the present analyses, its adoption as a potential confounder allows to potentially take into account some residual confounding without substantially affecting the statistical power of the model.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD), while categorical variables as absolute numbers and percentages. The number of medications was used as a continuous variable in the analyses. Unadjusted and adjusted (Model 1: for age and sex; Model 2: for Model 1 and FI) logistic regression models were performed to test the association of the number of medications (independent variable of interest) with fractures (dependent variable of interest). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported. Statistical significance was set at p value <0.05. All analyses were performed with the software JAMOVI version 1.6.

Results

The main characteristics of the study sample are presented in Table 1. A total of 107 CKD older patients undergoing hemodialysis (mean age 79.1, SD 7.7 years; women n= 38, 35.5%) were included in the analyses. Median follow-up was 24 (interquartile range [IQR]=11-33) months. The mean number of prescribed medications was 9.9 (SD 3.9). Fracture events were found in 29 (27.1%) patients. The median FI was 0.25 (IQR=0.17-0.29), with 31 (29%) patients who died during the follow-up period.

Table 1. Participant characteristics

Variable	N (%), or mean (SD) n=107
Age, y	79.1 (7.7)
Women	38 (35.5)
Diabetes	40 (37.4)
Depression	28 (26.2)
Psychiatric disorders	8 (7.5)
Hypertension	85 (79.4)
Cognitive impairment	23 (21.5)
Cancer	17 (15.9)
COPD	25 (23.4)
Medications	9.9 (3.9)
CPR	1.20 (2.08)
Fractures	29 (27.1)
Albumin, g/dL	3.72 (0.5)
Death	31 (29)
Frailty index	0.25 (0.10)

COPD= Chronic obstructive pulmonary disease; CPR= C-reactive Protein; SD= Standard Deviation

Results of the logistic regression analyses are reported in Table 2. At univariate analysis, the number of medications was positively associated with fractures (OR 1.18, 95% CI 1.06-1.32, P=0.003). This association was confirmed both in Model 1 adjusted for age and sex (OR 1.17, 95% CI 1.05-1.31, P=0.005) and in Model 2, after the additional inclusion of the FI (OR 1.16, 95% CI 1.03-1.30, P=0.016).

Discussion

Our study demonstrated a significant association between the number of medications and fractures in a population of CKD dialyzed older patients, independently of potential confounders.

Both polypharmacy and fractures are frequently observed in patients undergoing hemodialysis. Patients on hemodialysis are prescribed an average of 10-12 medications (13). Unfortunately, hemodialysis patients are rarely represented in clinical trials (14) and very few studies have been focused on older people.

A recent article (15) reported that dialysis-dependent CKD patients with hyperpolypharmacy (i.e., ≥10 medications) had about a five-fold higher risk of fracture, with a continuous exponential rise as the number of medications increased. However, it should be noted that this study included also adult patients. Cook et al. (16) reported a positive association between dependency in the activities of daily living and the total number of medications taken in older people on hemodialysis. Other studies have been focused on older patients but not undergoing hemodialysis (8). Most medications are largely eliminated through the kidney. Therefore, medication-related adverse events may be exacerbated in this patient's

Table 2. Relationship of number of medications with fractures in dialyzed older patients

	Unadjusted OR (95% CI)	P	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P
N of drugs	1.18 (1.06-1.32)	0.003	1.17 (1.05-1.31)	0.005	1.16 (1.03-1.30)	0.016

N= number; OR= odds ratio; CI= confidence interval; Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex and frailty index

population. One mechanism linking polypharmacy to fractures may be falls. In fact, hemodialysis patients, especially those older people, are at greater risk of falls. There are multiple factors (i.e., long-term predisposing and short-term precipitating factors) contributing to falls including comorbidities and the number of medications. It is thus evident that patients experiencing a fall are more susceptible to serious injuries such as fractures.

An alternative lecture of our analysis can be also considered. In fact, the retrospective nature of our analysis does not allow to exclude that fracture events and/or more broadly frailty status may have determined an increased medications use, suggesting a bidirectional relationship.

Our study may present some limitations such as the small sample size. However, it should be also considered that the exclusion of those patients not surviving the first three months after dialysis initiation, allowed us the opportunity to optimally focus on a population of older people in chronic need of hemodialysis. In other words, we have been able to well define the clinical relevance of the variables of interest without the acute/terminal phase of the renal disease. A further limitation may be represented by the single-site experience, limiting the generalizability of our findings, which may be explained by specific peculiarities of our setting. It should not be overlooked that some medications incorporated in the concept of polypharmacy may also include those drugs with a beneficial effect in the treatment of osteoporosis and/or potentially decreasing the risk of falls and fractures, like Vitamin D. In other words, when considering the total number of medications it is not possible to discriminate the beneficial or side effect of a single medication on a certain condition. We hypothesized not to specifically explore the contribution of treatment with these drugs, since at our center they are usually prescribed as needed (in terms of posology and duration of treatment) to maintain Parathormone (PTH) levels between 2 and 8 folds of the upper normal limit of our lab, and vitamin D between 30 and 40 ng/ml. Therefore, in order to correct for the frequent variations of therapy that occurred during observation, we decided to consider only PTH values beyond the lower and upper limit of the desired range as proxies of uncontrolled disease in terms of adynamic bone disease or uncontrolled tertiary hyperparathyroidism. Finally, the retrospective nature of our study may have limited causal relationship.

In conclusion, our study showed a significant association between the number of prescribed medications and fractures in older patients undergoing hemodialysis. Dialysis patients receive a significant number of medications compared to other patient's population. Therefore, given the burden it poses in terms of adverse outcomes including fractures, it is important to quantify the number of medications that each patient receives and identify those medications potentially inappropriate in order to implement interventions aimed at deprescribing.

Conflict of interest: The authors declare no conflict of interest.

Author contributions: DA and MC contributed to conceptualizing and writing the manuscript. SV, MMP and AS edited and revised manuscript. DA, SV, MMP, AS, and MC approved the final version of manuscript.

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References

1. Maher RL, Hanlon JT, Hajjar ER. Clinical Consequences of Polypharmacy in Elderly. Expert Opin Drug Saf. 2014 Jan;13(1):https://doi.org/10.1517/14740338.2013.827660.
2. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017 Oct 10;17:230; https://doi.org/10.1186/s12877-017-0621-2.
3. Musso CG, Oreopoulos DG. Aging and Physiological Changes of the Kidneys Including Changes in Glomerular Filtration Rate. Nephron Physiol. 2011;119(Suppl. 1):p1–5; https://doi.org/10.1159/000328010.
4. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: Misleading, but manageable. Clin Interv Aging. 2008 Jun;3(2):383–9; https://doi.org/10.2147/CIA.S2468.
5. Rodrigues J, Cuppari L, Campbell KL, Avesani CM. Nutritional assessment of elderly patients on dialysis: pitfalls and potentials for practice. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2017 Nov 1;32(11):1780–9; https://doi.org/10.1093/ndt/gfw471.
6. Checheriţă IA, Turcu F, Dragomirescu RF, Ciocâlteu A. Chronic complications in hemodialysis: correlations with primary renal disease. Romanian J Morphol Embryol Rev Roum Morphol Embryol. 2010;51(1):21–6.
7. Fink JC, Chertow GM. Medication errors in chronic kidney disease: one piece in the patient safety puzzle. Kidney Int. 2009 Dec 1;76(11):1123–5; https://doi.org/10.1038/ki.2009.315.
8. Lai SW, Liao KF, Liao CC, Muo CH, Liu CS, Sung FC. Polypharmacy Correlates With Increased Risk for Hip Fracture in the Elderly: A Population-Based Study. Medicine (Baltimore). 2010 Sep;89(5):295–9; https://doi.org/10.1097/MD.0b013e3181f15efc.
9. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. J Am Soc Nephrol JASN. 2013 Sep;24(9):1461–9; https://doi.org/10.1681/ASN.2012090916.
10. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. J Am Geriatr Soc. 2003 Mar;51(3):364–70; https://doi.org/10.1046/j.1532-5415.2003.51110.x.
11. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008 Sep 30;8(1):24; https://doi.org/10.1186/1471-2318-8-24.
12. Soldati A, Poggi MM, Azzolino D, Vettoretti S, Cesari M. Frailty index and adverse outcomes in older patients in haemodialysis. Arch Gerontol Geriatr. 2022 Jul 1;101:104673; https://doi.org/10.1016/j.archger.2022.104673.
13. Kimura H, Kalantar-Zadeh K, Rhee CM, Streja E, Sy J. Polypharmacy and Frailty among Hemodialysis Patients. Nephron. 2021;145(6):624–32; https://doi.org/10.1159/000516532.
14. Battistella M, Ng P. Addressing Polypharmacy in Outpatient Dialysis Units. Clin J Am Soc Nephrol. 2021 Jan 7;16(1):144–6; https://doi.org/10.2215/CJN.05270420.
15. Wakasugi M, Yokoseki A, Wada M, Momotsu T, Sato K, Kawashima H, et al. Polypharmacy, chronic kidney disease, and incident fragility fracture: a prospective cohort study. J Bone Miner Metab [Internet]. 2021 Nov 3 [cited 2022 Jan 14]; Available from: https://doi.org/10.1007/s00774-021-01272-9
16. Cook WL, Jassal SV. Functional dependencies among the elderly on hemodialysis. Kidney Int. 2008 Jun 1;73(11):1289–95; https://doi.org/10.1038/ki.2008.62.

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