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Authors
Kimura, Hiroshi
Kalantar-Zadeh, Kamyar
Rhee, Connie M
et al.

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Polypharmacy and Frailty among Hemodialysis Patients

Hiroshi Kimura[a] Kamyar Kalantar-Zadeh[a] Connie M. Rhee[a] Elani Streja[a]
John Sy[a, b]

[a]Division of Nephrology and Hypertension, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, School of Medicine, Orange, CA, USA; [b]Division of Nephrology, Veterans Affairs Long Beach Healthcare System, Long Beach, CA, USA

Keywords
Polypharmacy · Frailty · Dialysis

Abstract
Background: Both polypharmacy and frailty are highly prevalent among the patients on hemodialysis and associated with adverse outcomes; however, little is known about the association between them. ***Methods:*** We examined 337 patients enrolled in the ACTIVE/ADIPOSE dialysis cohort study between 2009 and 2011. The number of prescribed medications and frailty were assessed at baseline, 12, and 24 months. Frailty was defined based upon the Fried's frailty phenotype. We used logistic regression with generalized estimating equations to model the association of the number of medications and frailty at baseline and over time. A competing-risk regression analysis was also used to assess the association between the number of medications and incidence of frailty. ***Results:*** The mean number of medications was 10 ± 5, and 94 patients (28%) were frail at baseline. Patients taking >11 medications showed higher odds for frailty than the patients taking fewer than 8 medications (OR 1.54, 95% CI 1.05–2.26). During the 2-year of follow-up, 87 patients developed frailty among those who were nonfrail at baseline. Compared with the patients taking fewer than 8 medications, the incidence of frailty was approximately 2-fold in those taking >11 medications (sub-distribution hazard ratio 2.15, 95% CI 1.32–3.48). ***Conclusions:*** Using a higher number of medications was associated with frailty and the incidence of frailty among hemodialysis patients. Minimizing polypharmacy may reduce the incidence and prevalence of frailty among dialysis patients.

Introduction

Many patients undergoing maintenance dialysis have multiple medical comorbidities, including hypertension, diabetes, cardiovascular disease, and mineral and bone disorders, most of which require long-term medication management and can inevitably lead to polypharmacy. Several surveys in the USA have reported that dialysis patients take an average of 10–12 prescribed and over-the-counter medications, and an average of 19 pills per day [1, 2].

Elani Streja and John Sy contributed equally.

karger@karger.com
www.karger.com/nef

Correspondence to:
John Sy, john.sy@va.gov

Medication burden results in considerable societal and personal costs. According to the 2016 US Renal Data System (USRDS) Annual Data Report, per-patient per-year Medicare Part D spending on prescriptions for end-stage renal disease (ESRD) patients with stand-alone Part D plans was 4.1 times higher than the general Medicare population [3]. Medication costs in the USA are projected to continue increasing. Furthermore, polypharmacy increases the risk of medication-related problems (MRPs), defined as experiences associated with drug therapy that interferes with or have the potential to interfere with desired outcomes [4]. Indeed, a high prevalence rate of MRPs has been found among dialysis patients [5–7]. Minimizing unnecessary medication can potentially lead to both a reduction in health-care costs as well as a decrease in MRPs among dialysis patients.

Studies have demonstrated that exposure to polypharmacy in community-dwelling individuals is associated with both a greater incidence and prevalence of frailty [8]. Frailty, which is also highly prevalent among dialysis patients [9], is a phenotype of multisystem dysregulation leading to a loss of resilience and diminished capacity to respond to health stressors [10]. Frailty has been associated with poor outcomes such as higher mortality, hospitalizations, falls, cognitive impairment, vascular access failure, and poor quality of life [11–15]. With higher frailty and comorbidity rates among dialysis patients, it remains unclear if polypharmacy is still associated with the incidence of frailty among dialysis patients. In this study, we aimed to examine the independent association between polypharmacy and frailty among hemodialysis patients.

Materials and Methods

Patients, Demographic, and Laboratory Measures

We retrospectively examined the data from the A Cohort to Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD (ACTIVE/ADIPOSE) cohort study, a USRDS special study conducted by the Nutrition and Rehabilitation/Quality of Life Special Studies Centers that enrolled 771 dialysis patients from the Atlanta and San Francisco Bay areas between June 2009 and August 2011 [16]. Patients of at least 18 years of age, who spoke either English or Spanish, were on hemodialysis for at least 3 months, and capable of providing informed consent, were enrolled at 14 dialysis centers. The patients were excluded if they were scheduled for living donor kidney transplantation or planned to change another dialysis center or peritoneal dialysis within the next 6 months. The patients were followed for 3 years with frailty and laboratory measurements assessed at baseline, 12, and 24 months. The procedure for obtaining demographic and comorbid conditions and a description of lab processing have been described in a previous study [17, 18].

Medications and Frailty

Only patients in the ACTIVE/ADIPOSE study who were enrolled in Medicare Parts A, B, or D with Medicare serving as the primary payer (MPP) were used to obtain the comprehensive claims data as we did not have access to records from other payers (Fig. 1). Once patients with MPP and Medicare Part D claims were identified, the dataset was then linked with Part D claims information to ascertain the prescription medication information. Annual time periods after the date of enrollment were created corresponding to frailty measurements (baseline to the 12-month follow-up visit, 12-month to 24-month follow-up visit, 24-month to 36-month end of follow-up, or the last date of frailty evaluation to the date of death, transplantation, or loss to follow-up) and claims by date of service were delegated to the appropriate time period. All medication claims within the baseline to the 12-month follow-up visit period were considered being taken at baseline. The total number of medications in each assessment period represented our exposure variable of the number of prescribed medications during the period associated with the latest frailty measurement and do not include over-the-counter medications. We categorized the patients into 3 approximately equal groups according to the number of medications as follows: low medication group with fewer than 8 medications, intermediate medication group with 8 to 11 medications, and high medication group with more than 11 medications. Some medications have been associated frailty [19, 20], and we assessed the prevalence of frailty-related drugs in each medication group defined as medications within the following categories: anticholinergics, H2-receptor antagonists, benzodiazepines, nonbenzodiazepines, and benzodiazepine receptor agonist hypnotics (online suppl. Table; for all online suppl. material, see www.karger.com/doi/10.1159/000516532).

We identified frail individuals according to the Fried's frailty phenotype at each assessment [10]. Frailty was defined as the presence of 3 or more of the following 5 criteria: weight loss, exhaustion, low physical activity, slow gait speed, and weakness [15].

Statistical Analyses

Baseline characteristics of each medication group were ascertained with data presented as mean ± standard deviations, median with interquartile range, or as frequency (proportions), where appropriate. Differences in baseline characteristics among groups were evaluated by nonparametric trend tests (Cuzick's test).

We assessed the relationship between the medication groups (low, intermediate, and high) and frailty at baseline using the logistic regression. We then also used a logistic regression analysis to ascertain whether there was any association between the medication groups and each frailty criterion (weight loss, exhaustion, low physical activity, slow gait speed, and weakness).

Given our longitudinal data, we proceeded to examine the association of the medication group over time with frailty and each frailty criteria over time using generalized estimating equations (GEEs) with an exchangeable correlation matrix [21]. Frailty, number of medications, and laboratory data were time-updated in our model. In the event of death or loss to follow-up, patients contributed to time at risk after the last annual frailty measurement until date of death or loss to follow-up.

We then wanted to assess the potential relationship between high medication use and incident frailty. The incident frailty was defined as meeting frailty criteria at either the 12- or 24-month assessment among those who were not frail at baseline. On account

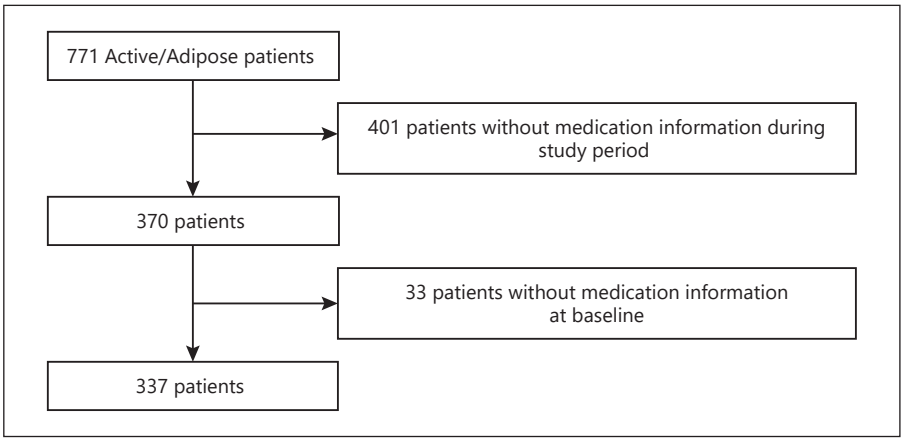

Fig. 1. Study flow diagram.

Table 1. Baseline characteristics according to the number of medications

Variables	Overall (N = 337)	Low medication (1–7) (N = 114)	Intermediate medication (8–11) (N = 108)	High medication (≥12) (N = 115)	p_{trend}
Age, years	56±13	57±13	55±14	56±13	0.60
Men, %	55	60	56	50	0.13
Race, %					
White	14	13	17	12	0.83
Black	78	77	77	80	0.61
Other	8	10	*	*	0.61
Comorbidities, %					
Diabetes	45	34	44	55	0.002
Coronary artery disease	8	*	*	10	0.24
Congestive heart failure	16	16	13	18	0.61
BMI, kg/m^2	27.9 (23.6–33.5)	27.8 (23.8–33.3)	28.5 (24.2–34.2)	26.9 (23.2–32.9)	0.51
Albumin, g/dL	3.98±0.38	4.05±0.34	3.96±0.42	3.92±0.37	0.001
Prealbumin, mg/dL	29.0±7.4	30.0±7.4	28.6±7.0	28.5±7.8	0.06
CRP, mg/dL	4.1 (1.6–10.9)	3.7 (1.4–8.1)	4.5 (1.9–10.9)	4.6 (1.2–13.0)	0.22
Medication number	9 (6–13)	5 (3–6)	9 (8–10)	15 (13–18)	<0.001
Frailty-related drug use, %	44	20	40	71	<0.001
Frailty, %	28	30	24	30	0.97
Individual frailty criteria, %					
Weight loss	32	32	32	30	0.74
Exhaustion	34	34	31	38	0.52
Low physical activity	38	32	36	46	0.02
Slow gait speed	28	25	23	36	0.06
Weakness	50	46	56	50	0.64

Values are expressed as mean ± SD, medians (interquartile range), or percentage as appropriate. CRP, C-reactive protein; BMI, body mass index; SD, standard deviation. At baseline, 2 patients were missing BMI, and 1 patient was missing a CRP, level. * Represents patient counts fewer than 11.

of high mortality rates in dialysis patients, we used a competing-risk regression model (the Fine-Gray model) based on a cumulative incidence function when assessing this relationship [22, 23]. Mortality information was ascertained by linkage to USRDS standard analysis files. As a sensitivity analysis, a similar analysis was run using the number of medications as a continuous variable, and their relationship was estimated using restricted cubic spline functions with 4 knots at the 5th, 35th, 65th, and 95th percentiles of each index. We also performed an interaction test to see if the presence of frailty-related drugs may have affected our association.

For each analysis, we used hierarchical adjustment with 3 models as follows: (1) an unadjusted model, (2) a case mix-adjusted

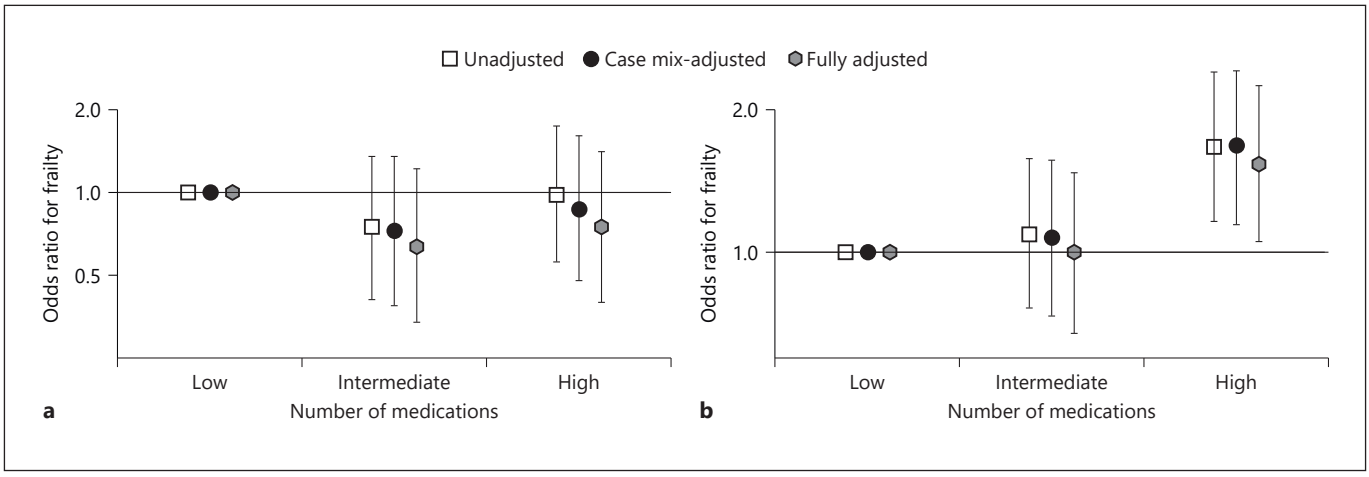

Fig. 2. a ORs for the association between number of medications at baseline and frailty. **b** ORs for the association between the number of medications and frailty using the longitudinal data analysis among 337 maintenance HD patients with 3 levels of adjustment Medication groups: low (1–7 medications), intermediate (8–11 medications), and high (≥12 medications), case mix-adjusted model: adjusted for age, sex, race, and comorbidities (diabetes, coronary artery disease, and congestive heart failure), the fully adjusted model: adjusted for case-mix model + BMI, serum albumin, CRP (log-transformed). OR, odds ratio; BMI, body mass index; CRP, C-reactive protein.

model that included age, sex, and race (white, black, and other), and comorbidities (diabetes, coronary artery disease, and congestive heart failure), and (3) a fully adjusted model that include all of the covariates in the case-mix model plus body mass index (BMI), serum albumin, and log-transformed C-reactive protein (CRP). We defined the fully adjusted model (Model 3) as the primary model of interest.

At baseline, no included patients had missing data on frailty or comorbidities, but 2 patients were missing BMI and 1 patient was missing a CRP level. Missing variables over time were frailty (9.9%), number of medications (9.2%), BMI (10.0%), serum albumin (11.7%), and log-transformed CRP (13.6%). To account for missing variables, we used a multiple imputation method with 10 datasets in our baseline analyses and competing-risk regression analysis. As for logistic regression with GEE, we used a multiple imputation then deletion procedure that included our outcome variable [24, 25]. A complete case analysis was performed as a sensitivity analysis. All analyses were conducted using STATA MP, version 13.1 (Stata Corp, College Station, TX, USA).

Results

Patient Characteristics

Among 771 patients enrolled in the ACTIVE/ADIPOSE study, 337 patients with Medicate Part D coverage at baseline were included in our analysis (Fig. 1). The mean age of the patients was 56 ± 13 years, of whom 55% were men, 14% were white, 78% were black, and 45% had diabetes. The mean number of medications was 10 ± 5, and 94 (28%) patients were frail at baseline.

Patients with a higher number of medications were more likely to have diabetes and lower albumin (p_{trend} = 0.002 and 0.001, respectively). We also noted an increasing percentage of frailty-related drugs with a higher number of medications (p_{trend} < 0.001). While there was no difference in the prevalence of frailty at baseline between the 3 medication groups, low physical activity was more prevalent in the high medication group than the lower medication groups (p_{trend} = 0.02) (Table 1).

Number of Medications and Frailty at Baseline

When assessing the relationship between the number of medications and frailty at baseline using a logistic regression analysis, we found that the number of medications at baseline was not associated with frailty at baseline after adjustment (Fig. 2a). We also did not find any statistically significant association between baseline number of medications and each frailty criterion (Table 2a).

In our assessment using our longitudinal data with a GEE model, we found a significant trend toward higher odds of frailty over time with a higher number of medications. Compared to the patients who were taking fewer than 8 medications, those who were taking >11 medications showed significantly higher odds of being frail in unadjusted (OR 1.67, 95% CI 1.16–2.42), case mix-adjusted (OR 1.67, 95% CI 1.14–2.43), and fully adjusted models (OR 1.54, 95% CI 1.05–2.26) (Fig. 2b). We also found that the patients taking the highest number of med-

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Table 2. OR (95% CI) for the association between number of medications (a) at baseline and (b) overtime utilizing longitudinal data analysis and frailty as well as the individual components of frailty overtime

Outcome	Adjusted OR (95% CI)					
	(a) Baseline associations			(b) Longitudinal associations		
	medications, *n*			medications, *n*		
	low (1–7)	intermediate (8–11)	high (≥12)	low (1–7)	intermediate (8–11)	high (≥12)
Overall frailty (*n* = 337)	Referent	0.64 (0.34–1.22)	0.75 (0.40–1.40)	Referent	1.00 (0.67–1.47)	1.54 (1.05–2.26)
Individual frailty criteria						
Weight loss		0.92 (0.51–1.65)	0.72 (0.39–1.30)		1.44 (0.95–2.17)	1.42 (0.95–2.12)
Exhaustion		0.80 (0.45–1.43)	1.08 (0.61–1.90)		1.16 (0.81–1.66)	1.62 (1.11–2.35)
Low physical activity		1.14 (0.64–2.03)	1.68 (0.95–2.98)		1.07 (0.77–1.48)	1.52 (1.09–2.12)
Slow gait speed		0.69 (0.34–1.41)	1.21 (0.62–2.37)		0.79 (0.55–1.14)	1.22 (0.82–1.82)
Weakness		1.37 (0.76–2.44)	1.10 (0.62–1.97)		1.18 (0.90–1.53)	1.16 (0.87–1.56)

ORs adjusted for age, sex, race, comorbidities (diabetes, coronary artery disease, congestive heart failure), BMI, serum albumin, CRP (log-transformed). BMI, body mass index; CRP, C-reactive protein; OR, odds ratio.

Table 3. Frequency and incidence of frailty among 243 hemodialysis patients who were not frail at baseline

Medication group	Nonfrail in group, *n*	Developed frailty, *n*	Person-years	Incidence (events per pt-yr) (95% CI)	SHR (95% CI)	Adjusted SHR (95% CI)
Low (1–7)	80	19	189.1	0.10 (0.06–0.16)	Referent	
Intermediate (8–11)	82	27	194.8	0.14 (0.10–0.20)	1.36 (0.80–2.31)	1.28 (0.76–2.17)
High (≥12)	81	41	166.1	0.25 (0.18–0.34)	2.34 (1.44–3.79)	2.15 (1.32–3.48)

SHR, adjusted for age, sex, race, and comorbidities (diabetes, coronary artery disease, and congestive heart failure), BMI, serum albumin, and CRP (log-transformed). BMI, body mass index; CRP, C-reactive protein; SHR, sub-distribution hazard ratio.

ications showed significantly higher odds of having exhaustion and low physical activity over time than the patients taking fewer than 8 medications (OR 1.62, 95% CI 1.11–2.35 and OR 1.52, 95% CI 1.09–2.02, respectively) (Table 2b).

Number of Medications and Incident Frailty

During the 2-year follow-up, 87 patients (36%) of the 243 patients who were not frail at baseline developed frailty (Table 3). Using our competing-risk regression model, we found that patients taking >11 medications showed a higher risk of frailty incidence than the patients taking fewer than 8 medications (sub-distribution hazard ratio 2.15, 95% CI 1.32–3.48) (Fig. 3a). However, the patients who were taking 8 to 11 medications did not appear to have a significantly higher risk of developing frailty than the low medication group (sub-distribution hazard ratio 1.28, 95% CI 0.76–2.17). In our sensitivity analysis using a restricted cubic spline function, we continued to see a dose-dependent association between the number of medications and risk of incident frailty (Fig. 3b). We also did not find any significant interaction between frailty-related medications and the association between the number of medications and frailty ($p_{interaction}$ = 0.94). In our complete case-sensitivity analysis excluding the patients with the missing data, we did not find any significant differences in our findings.

Discussion

In this observational study of hemodialysis patients who had available medication and frailty data in the USA, we found a significant relationship between higher medi-

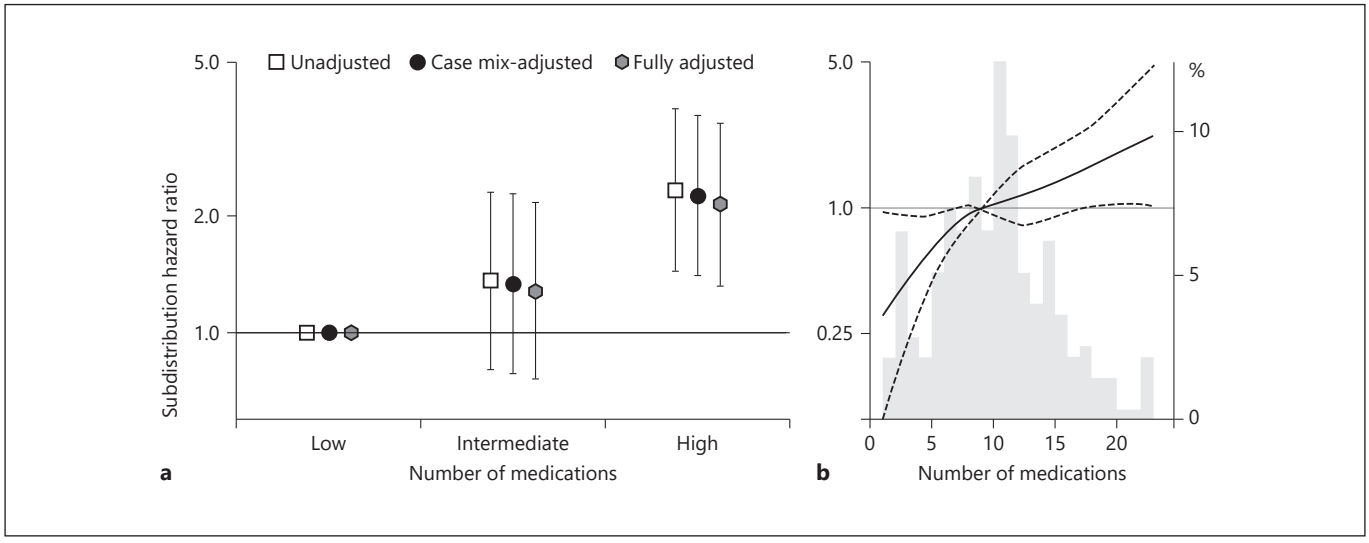

Fig. 3. a SHR for the association between with number of medications and incidence of frailty among 243 nonfrail patients at baseline with 3 levels of adjustment Medication groups: low (1–7 medications), intermediate (8–11 medications), and high (≥12 medications). **b** Distribution of the number of medications and fully adjusted restricted cubic splines comparing the relationship of the number of medications with the SHR for incident frailty. Case mix-adjusted model: adjusted for age, sex, race, and comorbidities (diabetes, coronary artery disease, and congestive heart failure), the fully adjusted model: adjusted for case-mix model + BMI, serum albumin, CRP (log-transformed). SHR, sub-distribution hazard ratio.

cation usage and frailty when assessing our longitudinal data. We also found that using a higher number of prescribed medications was associated with a greater risk of frailty incidence over our 2-year follow-up. The association between the number of medications and frailty over time may be driven by the development of exhaustion and low physical activity.

Polypharmacy is common in older adults, and several observational studies have reported that a higher number of medications were associated with incident frailty and greater risk of mortality [8, 26, 27]. Most studies in this field have focused on community-dwelling older adults and our study suggests that this association between medications and frailty persists among dialysis patients. In this study, we showed a similar association between a high number of medications and the higher prevalence and incidence of frailty among a cohort of hemodialysis patients. While there was no statistically significant association between moderate medication use and incident frailty, there was a trend toward higher risk of frailty and our spline analysis suggests a possible graded response (Fig. 3a, b). Interestingly, we did not find any association between baseline number of medications and frailty. While this may be due to our small sample size, the cross-sectional association may also have been more difficult to elucidate due to confounding by indication in this analysis. Any small reduction in the number of medications can still result in polypharmacy among dialysis patients and may not be associated with a significant reduction in risk of poor outcomes [28].

When investigating potential pathophysiological pathways through which polypharmacy results in frailty, we found that a higher number of medications were associated with a greater risk of exhaustion and low physical activity. Potentially higher number of medications may cause an increase in MRPs among dialysis patients resulting in an increase in exhaustion and low physical activity, but the underlying pathophysiology linking higher medication consumption and frailty remains unclear and larger studies are likely needed to confirm our findings.

While we observed that a higher number of medications are associated with frailty over time and the incidence of frailty, it remains unclear whether altering the number of medications could have a role in decreasing the risk developing frailty. Our findings suggest that aiming to achieve a lower medication burden for our patients can potentially reduce the risk of frailty among hemodialysis patients, which in turn can lead to a risk reduction in poor outcomes. Indeed, several reviews suggested that good medication reconciliation and medication management services could decrease MRPs and improve outcomes for ESRD patients [6, 28].

According to the American Geriatrics Society Beers Criteria, many medications cause mental/cognitive and/or physical deterioration [29]. For example, anticholinergic drugs are associated with frailty through increased functional decline, falls, and a greater incidence of dementia and delirium [19, 20]. Our study found that frailty-related drugs use increased with the number of medications (though the *p* value for interaction was not statistically significant). Unfortunately, we were unable to assess the influence of over-the-counter medications and other medications that are not covered under Medicare Part D (e.g., intravenous medications provided at the dialysis unit). We also acknowledge that an updated cohort, especially with the advent of newer medications such as iron-based phosphorous binders that assist with targeted reduction of polypharmacy among dialysis patients, may assist with further clarifying the association between polypharmacy and frailty.

One of the strengths of our study is a longitudinal measurement of frailty and the number of medications, which allow us to determine potential risk factors leading to the development of frailty. Several limitations of this study should be acknowledged. First, we utilized a relatively small cohort of patients primarily due to our strict inclusion criteria that required both physical frailty measurements as well as inclusion in Medicare Part D in order to obtain medication data. Second, we noted that potential selection bias may also exist due to the exclusion of more than half of the original ACTIVE/ADIPOSE population either not having Medicare Part D prescription coverage or missing medication data. Third, the study population's racial, ethnic, and age distribution may limit external generalizability and may not adequately represent that of the USA dialysis population. Our cohort included a higher proportion of black patients and was younger than the average dialysis patient, likely due to the demographics of the areas from which the ACTIVE/ADIPOSE study was performed. We have attempted to adjust for demographic factors in our analysis and noted that a previous study did not find any association between race and frailty [30]. Fourth, even though we adjusted for serum albumin and log-transformed CRP in multivariate analysis, residual confounding may still be present. Fifth, use of the Fried's frailty phenotype to define frailty is both a strength and limitation [14, 31]. While the phenotype is the most widely accepted definition of frailty, there are potential limitations when ascertaining individual frailty criteria. The weight loss criterion relies on self-report and does not consider the composition of the body weight, which might be less informative than objectively measuring the muscle mass loss. Also, when defining exhaustion, there are limited studies assessing the reliability and validity of using the 2 CES-D questions that define the exhaustion criterion [10]. While we included benzodiazepines, non-benzodiazepines, and benzodiazepine receptor agonist hypnotics in our analysis, we acknowledged that these medications were not covered under Medicare Part D until January 1, 2013. There may have been some patients who obtained these medications outside of Medicare, but we attempted to restrict our cohort to only patients with MPP. In addition, few dialysis patients use benzodiazepines and most providers refrain from prescribing benzodiazepines to frail patients, given the association with higher rates of overdoses and falls [32], suggesting that this limitation would likely have a very limited impact on the study findings but may have resulted in misclassification of the exposure and skew of the results toward the null.

Our analyses provide longitudinal evidence of an association between a higher number of medications and frailty as well as the incidence of frailty in dialysis patients. While further studies are needed on the association of polypharmacy and adverse outcomes among the dialysis patients, judicious use of medications and any achievable reduction in polypharmacy may have a positive impact on the quality of life of the patients and lead to a reduction in health-care costs.

Acknowledgements

The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

Statement of Ethics

The ACTIVE/ADIPOSE study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards at the University of California, San Francisco, and Emory University. This study was reviewed and approved by the University of California, Irvine Institutional Review Board. Participants provided written informed consent upon enrollment and were followed for 3 years with the study visits and assessments at baseline, 12, and 24 months.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

H.K. contributed to the conception and design of the study, conducted all statistical analyses, interpreted results, and wrote the manuscript. J.S. contributed to the data collection and study measurements, conducted statistical analyses, interpreted the results, and wrote the manuscript. E.S. contributed to the data collection and study measurements, conducted statistical analyses, interpreted the results, and wrote the manuscript. C.M.R. contributed to the data collection and study measurements, conducted statistical analyses, and interpreted the results. K.K.-Z. contributed to the data collection and study measurements, conducted statistical analyses, and interpreted the results. All the authors read and approved the final manuscript.

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