

Frailty, age, and post-dialysis recovery time in a population new to hemodialysis

Jessica Fitzpatrick,¹ Stephen M. Sozio,^{2,3} Bernard G. Jaar,^{2,3,4,5} Michelle M. Estrella,⁶ Dorry L. Segev,^{3,4,7} Tariq Shafi,^{8,9} Jose M. Monroy-Trujillo,² Rulan S. Parekh,^{1,2,4,10} Mara A. McAdams-DeMarco^{3,4,7}

1 Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada.

2 Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

3 Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD, USA.

4 Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.

5 Nephrology Center of Maryland, Baltimore, MD, USA.

6 Kidney Health Research Collaborative, Department of Medicine, University of California, San Francisco and Department of Medicine, San Francisco VA Medical Center, San Francisco, CA, USA.

7 Department of Surgery, Johns Hopkins University, Baltimore, MD, USA.

8 Division of Nephrology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

9 Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

10 Division of Nephrology, Department of Pediatrics and Medicine, The Hospital for Sick Children, University Health Network and University of Toronto, Ontario, Canada.

Correspondence: Dr. Mara McAdams-DeMarco, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, 615 N. Wolfe Street, W6033, Baltimore, MD 21205. Email: mara@jhu.edu

KEY POINTS

- Nearly three quarters of participants recovered within an hour, 20% required between 1 and 6 hours, and 5% reported recovery times greater than 12 hours
- Frailty and younger age were associated with prolonged recovery time
- Younger frail participants were more likely to report longer recovery times

ABSTRACT

Background: Frailty, a phenotype characterized by decreased physiologic reserve and the inability to recover following confrontation with a stressor like hemodialysis, may help identify which incident hemodialysis patients will experience longer post-dialysis recovery times. Recovery time is associated with downstream outcomes including quality of life and mortality. We characterized post-dialysis recovery times among patients new to hemodialysis and quantified the association between frailty and hemodialysis recovery time.

Methods: Among 285 hemodialysis patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study, frailty was measured using the Fried phenotype. Self-reported recovery time was obtained by telephone interview. We estimated the association of frailty (intermediately frail and frail vs. non-frail) and post-dialysis recovery time using adjusted negative binomial regression.

Results: Median time between dialysis initiation and study enrollment was 3.4 months (IQR: 2.7, 4.9) and that between initiation and recovery time assessment was 11 months (IQR: 9.3, 15). Mean age was 55 years, 24% were >65 years, and 73% were African American. 72% of individuals recovered in ≤ 1 hour, 20% in (1-6] hours, 5% required (6-12] hours, and fewer than 5% required >12 hours to recover. Those with intermediate frailty, frailty, and age ≤ 65 years had a 2.56-fold (95%CI: 1.45-4.52), 1.72-fold (95%CI: 1.03-2.89), and 2.35-fold (95%CI: 1.44-3.85) risk of longer recovery time independent of demographic characteristics, comorbidity, and dialysis-related factors.

Conclusions: In adults new to hemodialysis, frailty was independently associated with prolonged post-dialysis recovery. Future studies should assess the impact of frailty-targeted interventions on recovery time to improve clinical outcomes.

INTRODUCTION

Patient-centered outcomes are increasingly important in hemodialysis patients;(1-3) one important outcome is the length of time required to recover from a dialysis session.(4) Prolonged recovery time is associated with poor health-related quality of life (HRQoL), and increased risk of both hospitalizations and mortality.(5) The question “How long does it take you to recover from a dialysis session?” is a validated patient-centered tool that captures important information about patient health status as well as resilience to hemodialysis.(4) Recovery time, however, has only been studied in prevalent hemodialysis patients with significantly longer recovery times.(5) These results are likely not generalizable to those new to hemodialysis because physical and cognitive declines while on dialysis and mortality rate are high in the first year of dialysis.(6)

In community-dwelling older adults, frailty is a phenotype characterized by decreased physiologic reserve and the inability to recover following confrontation with a stressor.(7) Among patients with end-stage kidney disease (ESKD), hemodialysis represents a major physiologic stressor. Furthermore, frailty is highly prevalent among patients of all ages who are undergoing hemodialysis with prevalence as high as 73%.(8) Frailty prevalence increases with age, and is associated with increased mortality risk, hospitalizations, falls, and reduced HRQoL.(9-13) Non-frail individuals, regardless of age, may have a resiliency when confronted with the stressor of hemodialysis. Whether this resiliency in non-frail individuals extends to shorter recovery time after dialysis is unknown. Additionally, identifying this association could help plan interventions to improve the experience of dialysis patients.

The objectives of this study were to identify the distribution of post-dialysis recovery times among patients new to hemodialysis and quantify the association between frailty and hemodialysis recovery time among both older and younger hemodialysis patients.

MATERIALS AND METHODS

Study design and population

Frailty was measured in 378 patients who had received dialysis for < 6 months and were enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study.⁽¹⁴⁾ Briefly, participants were recruited from 27 dialysis units in Baltimore, MD, from November 2008 to August 2012. Inclusion criteria were: 1) ≥ 18 years of age and 2) ability to speak English. Exclusion criteria were: 1) institutionalized persons; 2) persons with a cancer diagnosis other than nonmelanoma skin cancer; 3) persons with a pacemaker or an automatic implantable cardioverter defibrillator; and 4) pregnant or nursing women. All participants received thrice weekly hemodialysis. The present study additionally excluded participants if they could not be contacted for the telephone interview (N=74) or did not report post-dialysis recovery time (N=19) to afford the final study population (N=285). The study protocol was approved by the Johns Hopkins University Institutional Review Board, MedStar Health Systems, and the medical director of each dialysis unit. Participants provided written informed consent.

Frailty

Frailty, measured at study enrollment on a non-dialysis day, was operationalized using the Fried phenotype, which has been previously validated in both ESKD populations^(9, 10, 13) and older adults,^(7, 15, 16) and previously described in PACE.⁽¹²⁾ The Fried phenotype is the most commonly used measure of frailty in geriatric and renal research.⁽¹⁷⁾ The frailty phenotype is characterized by five components: shrinkage (unintentional weight loss greater than 10 lb dry weight in the previous year), low physical activity (Kcal/week

below an established cut-off), exhaustion (self-report), weakness (grip strength below an established cut-off), and slowed gait speed (time to walk 15 feet below an established cut-off).(7) An overall frailty score was calculated by summing the component scores (range 0-5). The non-frail participants were those with a score of 0 or 1, the intermediately frail were those with a score of 2, and the frail were those with a score of 3 or higher. In secondary analyses, frailty was defined as a score of ≥ 2 as previously done,(9) because the vulnerability to patient-centered outcomes manifests with both intermediately frail and frail status.

Other participant characteristics

At study enrollment, socio-demographic characteristics (age, sex, and race), smoking status, alcohol use, and medical history were collected through standardized questionnaires. Older age was defined as age >65 years.

Body mass index was calculated as the ratio of self-reported dry weight (kg) to height (m) squared.

Comorbidities were assessed by medical chart review, adjudicated by the PACE Endpoint Committee, and classified using the Charlson Comorbidity Index adapted for patients with ESKD.(18) Systolic and diastolic blood pressures were obtained by averaging 3 consecutive measurements with participants in a seated position on a non-dialysis day. Ultrafiltration rate (mL/h/kg) was calculated as interdialytic weight gain/length of dialysis treatment/post-dialysis weight and was analysed as a 90-day average from dialysis initiation. Relative fluid removal was calculated as (pre-dialysis weight – post-dialysis weight)/post-dialysis weight and was examined as a 90-day average from dialysis initiation. Intradialytic systolic and diastolic blood pressure difference was examined as a 90-day average of pre- to post-dialysis blood pressure difference. Measures of dialysate composition, serum albumin, serum creatinine, serum calcium corrected for albumin, serum phosphate, single pool Kt/V, and hemoglobin were examined as 90-day averages from dialysis initiation. Medication use was assessed at baseline by medical record review from electronic dialysis patient records and by participant self-report.

Post-hemodialysis recovery time

Post-dialysis recovery time was assessed by telephoned interview. Participants were asked, “How long does it take you to recover from a dialysis session?” Responses were converted to minutes as follows: answers given in minutes were recorded directly, answers given in hours were multiplied by 60, answers such as “half a day” or the “next day,” were given a value of 720 min, answers of “one day” were given a value of 1440 min.(4) Frailty was measured prior to this patient-centered outcome and participants had time to stabilize following hemodialysis initiation.

Statistical analyses

Participant characteristics were summarized using means and standard deviations for normally distributed data, medians and interquartile ranges for skewed data, and frequencies and proportions for categorical data. Characteristics were compared between those above and below median post-dialysis recovery time (20 minutes) using Student’s t-test, the Mann-Whitney U test, or the χ^2 test.

Association of frailty with post-dialysis recovery time was estimated using negative binomial regression. Negative binomial regression allows for modeling of outcomes that are counts (e.g. number of minutes required to recover from a dialysis session) and accounts for overdispersion of the outcome data. A forward model building approach was employed in which initial variable selection was conducted based on known risk factors for frailty and hemodialysis recovery time, p-values from univariate analyses, and changes in effect size. We also examined the associations of the individual frailty components (shrinkage, low physical activity, exhaustion, weakness, and slowed gait speed) with post-dialysis recovery time.

Heterogeneity of effect was assessed by including separate multiplicative interaction terms between frailty and age, sex, and race in adjusted models. Stratified analyses were performed to estimate the association of age with

post-dialysis recovery time by frailty category (frail [score ≥ 2] vs. non-frail [score 1 or 0]). All statistical analyses were performed in Stata version 14.0.

RESULTS

Study population

Two hundred and eighty-five adults receiving hemodialysis were included in this study (Table 1 and S1). At study enrollment, the mean age was 55 years, 24% were >65 years, 43% were female, and 73% were African American; 51% of participants were frail, 29% were intermediately frail, and 20% were non-frail at the time of study enrollment. Median time between dialysis initiation and study enrollment was 3.4 months (IQR: 2.7, 4.9), median time between study enrollment and assessment of post-dialysis recovery time was 6.8 months (IQR: 5.8-9.5), and median time between dialysis initiation and recovery time assessment was 11 months (IQR: 9.3, 15). Among participants (N=198) for whom frailty was assessed at study initiation and after 1 year, frailty status was stable (P=0.2). In aggregate, 57% of these participants were frail at baseline and 62% were frail after 1 year.

Hemodialysis recovery time

Median hemodialysis recovery time reported in our study population with a median dialysis duration of 11 months, was 20 minutes (IQR: 10, 120). Seven percent of individuals reported requiring no time to recover from hemodialysis, 65% reported recovering in (0-1] hour, 20% in (1-6] hours, 5% required (6-12] hours, and fewer than 5% required >12 hours to recover (Figure 1). Among younger adults, 6% reported needing no time to recover, 63% required (0-1] hours, 21% required (1-6] hours, 5% required (6-12] hours, and 5% required more than 12 hours. In older adults, the distribution was weighed more heavily towards shorter recovery times, with 11% reported needing no time to recover, 71% required (0-1] hours, 14% required (1-6] hours, 4%

required (6-12] hours, and none required more than 12 hours. The distribution of reported recovery times was similar between younger and older adults. Individuals who reported a hemodialysis recovery time ≥ 20 minutes had similar demographic, clinical, and dialysis-related characteristics to those who reported < 20 -minute recovery times (Table 1).

Risk factors for longer hemodialysis recovery time

Within the first year of hemodialysis, the median recovery time reported by younger individuals was 20 minutes (IQR: 10, 120) and that reported by older individuals was 15 minutes (IQR: 10, 60). Younger age was associated with 2.36-fold longer post-dialysis recovery time (95% CI: 1.44-3.85; Table 2), independent of demographic, clinical, and dialysis factors. Individuals with obesity reported a median recovery time of 30 minutes (IQR: 10, 120), as compared to 20 minutes (IQR: 10, 67.5) for the non-obese, and had a recovery time that was 1.76-times longer (95% CI: 1.16-2.63). Those with prevalent cerebrovascular disease at study enrollment reported a median recovery time of 30 minutes (IQR: 13.8, 210), as compared to 20 minutes (IQR: 10, 90) for those without, and had a recovery time that was 2.03-times longer (95% CI: 1.21-3.43).

Frailty and hemodialysis recovery time

The median recovery time among non-frail, intermediately frail, and frail individuals was 25 minutes (IQR: 10, 60), 20 minutes (IQR: 10, 150), and 20 minutes (IQR: 10, 105), respectively. As compared to non-frail individuals, those who were intermediately frail had a longer post-dialysis recovery time (IRR: 2.56, 95% CI: 1.45-4.52), as did those who were frail (IRR: 1.72, 95% CI: 1.03-2.89; $P_{\text{trend}} = 0.2$), independent of demographic, clinical, and dialysis factors. The association of intermediate frailty and frailty with recovery time did not differ by sex or race (all $P_{\text{interaction}} > 0.05$). None of the individual frailty components were associated with dialysis recovery time (Table S2).

Frailty, age, and hemodialysis recovery time

Among participants in this study, 15% were frail (score ≥ 2) and >65 years. The distribution of dialysis recovery time across frailty and age categories is shown in Figure 2. Among frail individuals, younger (≤ 65 years) age remained associated with a longer post-dialysis recovery time (IRR: 2.55, 95% CI: 1.46-4.43; Table 2). There was no evidence of association between age and recovery time among the non-frail (IRR: 1.18, 95% CI: 0.41-3.39). The association of age and length of post-dialysis recovery time, however, was not statistically different between frail and non-frail individuals ($P_{\text{interaction}}=0.8$).

Sensitivity analyses

The association of frailty and dialysis recovery time were similar when separately adjusted for baseline serum albumin, ultrafiltration rate, length of hemodialysis treatment, dialysate composition, relative fluid removal, hemoglobin, antihypertensive medication use, and intradialytic systolic and diastolic blood pressure difference. Additionally, there was no evidence of post-dialysis recovery time differences between centers ($P=0.1$).

DISCUSSION

In this prospective cohort of adults of all ages within the first year of dialysis, nearly three-quarters of participants recovered within an hour, one-fifth required between 1 and 6 hours, and 5% reported recovery times greater than 12 hours. Longer recovery times were associated with frailty and younger age. Individuals that were either intermediately frail or frail had post-dialysis recovery times that were about 2 times longer than those of non-frail individuals. No single frailty component was associated with post-dialysis recovery time. Individuals ≤ 65 years of age had recovery times 2.36-fold longer than older individuals. Among frail individuals, younger age was associated with 2.55-fold longer recovery time. However, among the non-frail, age was not associated with recovery time.

The pathophysiology of dialysis recovery is complex and likely changes over years while on dialysis. We hypothesized that the capacity of an individual to withstand the stress of hemodialysis may be reflected in their recovery time. (5) Self-reported post-dialysis recovery time is validated measure with high test-retest correlation and is sensitive to change over time.(4) Moreover, this metric is simple to obtain and easy for patients to understand. This patient-centered outcome is associated with HRQoL and increased risk of hospitalization and mortality.(4, 5) Our understanding of the physiological mechanisms underlying the post-dialysis fatigue that manifests as perceived recovery time remains incomplete. Hemodialysis instigates osmotic imbalances, and these shifts from homeostasis may be greater following more stressful dialysis sessions. Although exhaustion was not associated with recovery time, the stress imposed on the patient may result in longer recovery times in individuals less equipped to withstand stressors.

The distribution of recovery times in our study of adults having received dialysis for median of 11 months was weighted more heavily towards shorter times than those from studies involving participants with longer dialysis vintage. Notably, prevalent and incident hemodialysis patients comprise very distinct populations that differ significantly due to the high mortality rate in the first year of dialysis, the physical and cognitive decline associated with chronic dialysis, and transplantation following dialysis initiation.(6) For example, whereas 72% of the participants in our study recovered within 1 hour, only 24% of 701 individuals having received dialysis for a median of > 2 years recovered within this time period.(19) Twenty-three percent of these prevalent hemodialysis recipients required over 12 hours to recover, compared to 5% in our study. Nonetheless, 28% of participants in our study reported recovery times greater than 1 h. The disposition of prevalent hemodialysis recovery times to longer periods is found in three other studies as well. In two large cohorts of participants on hemodialysis for a median of 3.3 years, 32-55% reported recovery time of less than 2 hours and 10-20% reported recovery times of greater than 12 h.(5),(20) In a study with median dialysis vintage of 2.4 years, 52%

of the 364 participants reported recovery times less than 2 hours and 27% reported recovery times greater than 7 hours.(21)

A risk factor for prolonged recovery time investigated in a small number of studies of prevalent dialysis patients includes age. As older age is associated with decreased HRQoL,(22) an association with post-dialysis recovery time is likely but remains ambiguous. Among 6,040 prevalent hemodialysis participants, older adults were more likely to report longer recovery times (adjusted OR, 1.03 per 5 years; 95% CI: 1.01-1.06), nonetheless the effect was modest.(5) Age was not associated with post-dialysis recovery time, however, in two smaller studies.(19, 23). Our study extends these findings by demonstrating that, in a cohort of adults new to hemodialysis, age \leq 65 years was associated with longer recovery time. This association runs contrary to the expectation that older individuals might be less equipped to recover from the stress of a dialysis session but, as discussed below, may reflect lower expectations and greater satisfaction despite poorer clinical profiles in older patients.

Frailty, a phenotype characterized by increased susceptibility to stressors, was first described in community-dwelling older adults.(7) In hemodialysis populations, frailty is prevalent in adults of all ages and has been associated with falls,(13) hospitalization,(10) and cognitive dysfunction.(24) We hypothesized that susceptibility to stressors would result in frail individuals requiring longer to recover from the stress of a dialysis session. Indeed, we find that frail and intermediately frail hemodialysis participants in our study report longer dialysis recovery times than their non-frail counterparts. This result was robust to length of hemodialysis treatment and ultrafiltration rate. Importantly, none of the individual frailty components were associated with post-dialysis recovery time, supporting the characterization of frailty as a phenotype in which the combination of components is more important than any individual component.

Although the prevalence of frailty increases with age in the general population, it is highly prevalent among hemodialysis patients of all ages.(10, 11) Possibly because of the common association of frailty with older age, frailty is often overlooked in younger adults undergoing hemodialysis.(25) This oversight may be of clinical significance as our results suggest that younger frail adults may be more susceptible to the stressors of hemodialysis, manifested as longer perceived post-dialysis recovery time. Among non-frail individuals, age was not associated with recovery time suggesting that there are resilient hemodialysis patients across the age spectrum. That is, among those with the most physiologic reserve, patients recover at similar rates regardless of age.

The use of self-reported recovery time can be complicated by the complex subjective nature of this metric, which is influenced by not only the patient's physical state of well-being, but also their perception of their well-being. Shorter recovery times reported by older patients may reflect lowered expectations and greater satisfaction despite poorer clinical profiles. Conversely, younger patients with more active lifestyles may perceive the limitations imposed by dialysis recovery as greater. Interestingly, a study of 714 adults undergoing chronic hemodialysis found that individuals under 75 years of age attained lower levels of emotional health, as measured by the Kidney Disease Quality of Life-Short Form, than their older counterparts despite reporting better physical function.(26) In a study of incident hemodialysis patients, those under 65 years had better physical function KDQOL scores than older participants, but worse scores on pain, kidney disease symptoms, and quality of social interactions.(27) These results were echoed in two further studies conducted in prevalent hemodialysis populations. The first showed that younger patients had better physical well-being but worse effects of kidney disease and poorer sleep quality than patients over 70 years.(28) The second reported that, despite better clinical profiles, patients under 65 years demonstrated worse KDQOL effects of kidney disease and patient satisfaction, and worse overall quality of life than older patients.(29) The extent to which these HRQoL-associated factors may play a role in explaining the prolonged post-dialysis recovery time of younger

frail hemodialysis patients remains unclear, but our observations suggest that this subgroup may comprise an overlooked population who may be vulnerable to the stressors of hemodialysis.

Strengths of the study include the prospective nature of this large cohort of patients new to hemodialysis, the inclusion of adults of all ages, and the use of a validated patient-centered outcome. We also measured frailty status prior to the assessment of recovery time to establish temporality. Additional strengths include the use of a validated and objective instrument to measure frailty, a well characterized cohort, and adjudication of comorbidities. The results of this study may not, however, be generalizable to the entire U.S. hemodialysis population because of possible selection bias that can occur when generally healthier participants are recruited for a prospective study. There was also risk of survival bias because outcome ascertainment was a median of 11 months after dialysis initiation, and 43% of participants for whom we do not have an outcome died within the first year of dialysis. Although 74 participants could not be contacted for telephone interview, these participants did not differ from those included in the study by frailty status or any other clinical factors (Table S3). We are also limited by our lack of information on how frailty status might have changed between frailty assessment and recovery time assessment. We assessed effects of baseline potential confounders and could not account for confounding characteristics that may have changed over study time period. We also lack information on residual kidney function and urine output at dialysis initiation or dialysate temperature, which may impact post-dialysis recovery time. Finally, although this study was sufficiently powered to detect independent associations between frailty and recovery time and age and recovery time, we may not have had sufficient power to detect interactions in the analyses of effect modification.

In summary, we observed that participants within the first year of hemodialysis reported post-dialysis recovery times shorter than those typically reported by prevalent hemodialysis patients in other studies, with almost two-thirds of participants reporting recovery times of less than 1 hour and only 5% greater than 12 hours. Frailty and

younger age were associated with prolonged recovery time among these hemodialysis patients independently of demographic, clinical, and dialysis factors, including length of hemodialysis treatment and ultrafiltration rate. In particular, younger frail participants were more likely to report longer recovery times. Among non-frail hemodialysis patients, however, age was not associated with recovery time. Our results suggest that frail, and particularly younger frail, individuals should be targeted for interventions to improve recovery times. Future studies are needed, however, to confirm these results and to assess the efficacy of such interventions.

Disclosures: M. Estrella reports the following: Consultancy Agreements: Eiland & Bonnin, PC; Research Funding: Booz Allen Hamilton, Bayer Inc.; Honoraria: American Kidney Fund, National Kidney Foundation, Aztra Zeneca, Boehringer Ingelheim; Scientific Advisor or Membership: CJASN Editorial Board member. B. Jaar reports the following: Honoraria: American Board of Internal Medicine – Nephrology; Scientific Advisor or Membership: Clinical Journal of the American Society of Nephrology, American Board of Internal Medicine, National Kidney Foundation, BMC Nephrology, BMC Medicine; Other Interests/Relationships: UpToDate royalties as an author. M. McAdams-DeMarco reports the following: Honoraria: UptoDate. R. Parekh reports the following: Ownership Interest: Synaptive- Stock, Coramed- Stock; Research Funding: NIH, Canadian Institute of Health Research (CIHR), Kidney Foundation of Canada; Scientific Advisor or Membership: CJASN- Associate Editor, ISN Council; Other Interests/Relationships: Bishop Strachan School- Board of Directors. D. Segev reports the following: Consultancy Agreements: Genzyme/Sanofi, Novartis, CSL Behring; Honoraria: Genzyme/Sanofi, Novartis, CSL Behring; Scientific Advisor or Membership: Editor in chief, Current Transplant Reports; Speakers Bureau: Genzyme/Sanofi, Novartis, CSL Behring. T. Shafi reports the following: Consultancy Agreements: Siemens; Research Funding: Baxter (clinical trial); Honoraria: National Institute of Health, Siemens, Cara Therapeutics; Scientific Advisor or Membership: Clinical Journal of the American Society of Nephrology (CJASN), American Journal of Kidney Diseases (AJKD). The remaining authors have nothing to disclose.

Funding: This study was supported by the National Institutes of Health (R01AG042504; K24DK101828; PI: D.S; R01AG055781; PI: M.M.-D.). M.M.-D. was also supported by Johns Hopkins University Claude D. Pepper Older Americans Independence Center (P30AG021334). The PACE Study was supported by National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK072367 (PI: R.P.). This research was undertaken, in part, thanks to funding from the Canada Research Chairs program. R.P. is the recipient of a Canada Research Chair in CKD epidemiology.

Acknowledgments: We thank the participants, nephrologists and the staff of the DaVita and MedStar dialysis units in the Baltimore area who contributed to the PACE study. We also thank Lucy Meoni for her longstanding contributions to the PACE study.

We thank the PACE Study Endpoint Committee: Bernard G. Jaar, MD, MPH (Chair); Michelle M. Estrella, MD, MHS; Stephen M. Sozio, MD, MHS, MEHP; Rulan S. Parekh, MD, MS; N'Dama Bamba, MD; Wei Tsai, MD, MS, MPH; Geetha Duvuru, MD; Julia Scialla, MD, MHS; Teresa K. Chen, MD, MHS; Jose Manuel Monroy Trujillo, MD; Frances-LLena Capili, MD; Ijaz Anwar, MD; Lili Zhang, MD; Manisha Ghimire, MD; Raghotham Narayanaswamy, MD; Ramya Ravindran, MD; Svetlana Chembrovich, MD; and Stefan Hemmings, MD.

Author Contributions: J Fitzpatrick: Formalanalysis; Writing - original draft; Writing - review and editing
S Sozio: Conceptualization; Data curation; Methodology; Writing - review and editing
B Jaar: Conceptualization; Data curation; Methodology; Writing - review and editing
M Estrella: Conceptualization; Data curation; Methodology; Writing - review and editing
D Segev: Conceptualization; Methodology; Writing - review and editing
T Shafi: Conceptualization; Methodology; Writing - review and editing
J Monroy-Trujillo: Conceptualization; Methodology; Writing - review and editing
R Parekh: Conceptualization; Data curation; Methodology; Supervision; Writing - review and editing
M McAdams-DeMarco: Conceptualization; Methodology; Supervision; Writing - review and editing
Each author contributed important intellectual content during manuscript drafting or revision.

Supplemental Material:

Table S1. Extended PACE participant characteristics

Table S2. Associations of baseline age and frailty components with post-dialysis recovery time among adults new to hemodialysis

Table S3. Baseline PACE participant characteristics among those with and without outcome ascertainment

REFERENCES

1. Tong A, Winkelmayer WC, Wheeler DC, van Biesen W, Tugwell P, Manns B, Hemmelgarn B, Harris T, Crowe S, Ju Angela, O'Lone E, Evangelidis N, Craig JC. Nephrologists' Perspectives on Defining and Applying Patient-Centered Outcomes in Hemodialysis. *Clin J Am Soc Nephrol*. 2017;12(3):454-66.
2. Mehrotra R, Agarwal A, Bargman JM, Himmelfarb J, Johansen KL, Watnick S, Work J, McBrude K, Flessner M, Kimmel PL. Dialysis therapies: a National Dialogue. *Clin J Am Soc Nephrol*. 2014;9(4):812-4.
3. Qazi HA, Chen H, Zhu M. Factors influencing dialysis withdrawal: a scoping review. *BMC Nephrol*. 2018;19(1):96.
4. Lindsay RM, Heidenheim PA, Nesrallah G, Garg AX, Suri R, Daily Hemodialysis Study Group London Health Sciences C. Minutes to recovery after a hemodialysis session: a simple health-related quality of life question that is reliable, valid, and sensitive to change. *Clin J Am Soc Nephrol*. 2006;1(5):952-9.
5. Rayner HC, Zepel L, Fuller DS, Morgenstern H, Karaboyas A, Culleton BF, Mapes DL, Lopes AA, Gillespie BW, Hasegawa T, Saran R, Tentori Francesca, Hecking M, Pisoni RL, Robinson BM. Recovery time, quality of life, and mortality in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2014;64(1):86-94.
6. United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016.
7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56.
8. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med*. 2012;172(14):1071-7.
9. McAdams-DeMarco MA, Ying H, Olorundare I, King EA, Desai N, Dagher N, Lonze B, Montgomery R, Walston J, Segev DL. Frailty and Health-Related Quality of Life in End Stage Renal Disease Patients of All Ages. *J Frailty Aging*. 2016;5(3):174-9.
10. McAdams-DeMarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, Walston JD, Segev DL. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc*. 2013;61(6):896-901.
11. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. *J Am Soc Nephrol*. 2007;18(11):2960-7.
12. Fitzpatrick J, Sozio SM, Jaar BG, Estrella MM, Segev DL, Parekh RS, McAdams-DeMarco MA. Frailty, body composition and the risk of mortality in incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study. *Nephrol Dial Transplant*. 2018.
13. McAdams-DeMarco MA, Suresh S, Law A, Salter ML, Gimenez LF, Jaar BG, Walsont JD, Segev DL. Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. *BMC Nephrol*. 2013;14:224.

14. Parekh RS, Meoni LA, Jaar BG, Sozio SM, Shafi T, Tomaselli GF, Lima JA, Tereshchenko LG, Estrella MM, Kao WHL. Rationale and design for the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study. *BMC Nephrology*. 2015;16:63.
15. Bandeen-Roche K, Xue Q-L, Ferrucci L, Walston J, Guralnik JM, Chaves P, Zeger SL, Fried LP. Phenotype of frailty: characterization in the women's health and aging studies. *J Gerontol A Biol Sci Med Sci*. 2006;61(3):262-6.
16. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med*. 2007;167(7):635-41.
17. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, Bandeen-Roche K, Varadhan R. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev*. 2016;26:53-61.
18. Hemmelgarn BR, Manns BJ, Quan H, Ghali WA. Adapting the Charlson Comorbidity Index for use in patients with ESRD. *Am J Kidney Dis*. 2003;42(1):125-32.
19. Davenport A, Guirguis A, Almond M, Day C, Chilcot J, Da Silva Gane M, Fineberg N, Friedl K, Spencer B, Wellsted D, Farrington K. Postdialysis recovery time is extended in patients with greater self-reported depression screening questionnaire scores. *Hemodial Int*. 2018.
20. Hussein WF, Arramreddy R, Sun SJ, Reiterman M, Schiller B. Higher Ultrafiltration Rate Is Associated with Longer Dialysis Recovery Time in Patients Undergoing Conventional Hemodialysis. *Am J Nephrol*. 2017;46(1):3-10.
21. Harford A, Gul A, Cumber S, Paine S, Schrader R, Trujillo N, Zager P. Low dialysate potassium concentration is associated with prolonged recovery time. *Hemodial Int*. 2017;21 Suppl 2:S27-S32.
22. Laudanski K, Nowak Z, Niemczyk S. Age-related differences in the quality of life in end-stage renal disease in patients enrolled in hemodialysis or continuous peritoneal dialysis. *Med Sci Monit*. 2013;19:378-85.
23. Jayanti A, Foden P, Morris J, Brenchley P, Mitra S, group B-Hs. Time to recovery from haemodialysis : location, intensity and beyond. *Nephrology (Carlton)*. 2016;21(12):1017-26.
24. McAdams-DeMarco MA, Tan J, Salter ML, Gross A, Meoni LA, Jaar BG, Kao WHL, Parekh RS, Segev DL, Sozio SM. Frailty and Cognitive Function in Incident Hemodialysis Patients. *Clin J Am Soc Nephrol*. 2015;10(12):2181-9.
25. Salter ML, Gupta N, Massie AB, McAdams-DeMarco MA, Law AH, Jacob RL, Gimenez LF, Jaar BG, Walston JD, Segev DL. Perceived frailty and measured frailty among adults undergoing hemodialysis: a cross-sectional analysis. *BMC Geriatr*. 2015;15:52.
26. van Loon IN, Bots ML, Boereboom FTJ, Grooteman MPC, Blankestijn PJ, van den Dorpel MA, Nube MJ, Ter Wee PM, Verhaar MC, Hamaker ME. Quality of life as indicator of poor outcome in hemodialysis: relation with mortality in different age groups. *BMC Nephrol*. 2017;18(1):217.
27. Walters BA, Hays RD, Spritzer KL, Fridman M, Carter WB. Health-related quality of life, depressive symptoms, anemia, and malnutrition at hemodialysis initiation. *Am J Kidney Dis*. 2002;40(6):1185-94.
28. Unruh ML, Newman AB, Larive B, Dew MA, Miskulin DC, Greene T, Beddhu S, Rocco MV, Kusek JW, Meyer KB. The influence of age on changes in health-related quality of life over three years in a cohort undergoing hemodialysis. *J Am Geriatr Soc*. 2008;56(9):1608-17.

29. Griva K, Yu Z, Chan S, Krisnasamy T, Yamin RB, Zakaria FB, Wu SY, Oei E, Foo M. Age is not a contraindication to home-based dialysis - Quality-of-Life outcomes favour older patients on peritoneal dialysis regimes relative to younger patients. *J Adv Nurs*. 2014;70(8):1902-14.

TABLES

Table 1. PACE participant characteristics

Variables	N	Overall	Post-dialysis	Post-dialysis
			recovery time < 20 min (N=147)	recovery time ≥ 20 min (N=138)
Mean (±SD), median (IQR), frequency (%)				
Demographic and clinical factors				
Age, years	285	55 ± 13	56 ± 12	54 ± 14
Female sex	285	123 (43)	63 (43)	60 (43)
African American	285	207 (73)	109 (74)	98 (71)
Body mass index (kg/m ²)	283	29.5 ± 7.9	28.9 ± 7.4	30.1 ± 8.3
Ever smoker	285	164 (58)	89 (61)	75 (54)
Diabetes	285	161 (56)	85 (58)	76 (55)
History of coronary artery disease	285	98 (34)	47 (32)	51 (37)
History of congestive heart failure	285	114 (40)	61 (41)	53 (38)
History of cerebrovascular disease	285	60 (21)	25 (17)	35 (25)
Systolic blood pressure, mmHg ^a	284	136.9 ± 25.6	136.1 ± 25.0	137.5 ± 26.3
Diastolic blood pressure, mmHg ^a	284	74.3 ± 14.4	73.4 ± 13.8	75.3 ± 15.0
Dialysis factors				
Vascular access type	285			
Arteriovenous fistula		92 (32)	41 (28)	51 (37)
Arteriovenous graft		7 (2)	2 (1)	5 (4)
Venous catheter		186 (65)	104 (71)	82 (59)
Relative fluid removal, %	246	3.1 ± 1.3	3.0 ± 1.0	3.1 ± 1.4
Inter dialytic weight gain, kg	271	2.16 ± 0.84	2.20 ± 0.81	2.13 ± 0.88
Length of dialysis treatment, min	261	215 ± 20	215 ± 20	216 ± 19
Intra dialytic systolic blood pressure change, mmHg	284	-9.6 ± 11.6	-9.8 ± 11.1	-9.4 ± 12.2
Intra dialytic diastolic blood pressure change, mmHg	284	-4.9 ± 6.2	-4.8 ± 5.8	-5.1 ± 6.6
Calcium dialysate concentration, mEq/L	269	2.29 ± 0.24	2.29 ± 0.23	2.29 ± 0.24
Potassium dialysate concentration, mEq/L	269	2.15 ± 0.34	2.14 ± 0.33	2.17 ± 0.34
Bicarbonate dialysate concentration, mEq/L	245	37 ± 2	37 ± 2	37 ± 2
Ultrafiltration rate, mg/Kg/hour	261	7.4 ± 2.9	7.6 ± 3.0	7.1 ± 2.7
Medication use				
Total number of antihypertensive medications	273	3 (2, 4)	3 (2, 3)	3 (2, 4)
Alpha blockers	261	26 (9)	12 (9)	14 (10)
Beta blockers	261	180 (69)	90 (67)	90 (71)
Angiotensin-converting-enzyme inhibitors	261	85 (33)	37 (27)	48 (38)
Angiotensin II receptor blockers	261	34 (13)	21 (16)	13 (10)
Centrally acting agents	261	39 (14)	21 (16)	18 (14)
Diuretics	261	62 (24)	29 (21)	33 (26)
Vasodilators	261	87 (33)	43 (32)	44 (35)
Calcium channel blockers	261	167 (64)	89 (66)	78 (62)

Erythropoietin stimulating agents 277 270 (97) 138 (98) 132 (97)

^a Blood pressures were obtained by averaging 3 consecutive measurements with participants in a seated position on a non-dialysis day

Table 2. Associations of baseline age and frailty with post-dialysis recovery time among adults new to hemodialysis

Model	Unadjusted Associations		Adjusted Associations	
	IRR (95% CI)	P-value	IRR (95% CI)	P-value
<i>Demographic factors and frailty^{a, b}</i>				
Age ≤ 65, vs > 65 years	2.18 (1.36, 3.47)	0.001	2.36 (1.44, 3.85)	0.001
Obese vs. non-obese	1.35 (0.79, 2.29)	0.3	1.76 (1.16, 2.68)	0.008
Prevalent cerebrovascular disease	1.79 (0.99, 3.23)	0.05	2.03 (1.21, 3.43)	0.007
Frailty status				
Non-frail	ref		ref	
Intermediately frail	1.46 (0.85, 2.51)	0.2	2.56 (1.45, 4.52)	0.001
Frail	1.06 (0.65, 1.72)	0.8	1.72 (1.03, 2.89)	0.04
<i>Age stratified by frailty (score ≥ 2)^{c, d}</i>				
<i>Among non-frail (N=58)</i>				
Age ≤ 65, vs > 65 years	2.74 (0.96, 7.89)	0.06	1.18 (0.41, 3.39)	0.8
<i>Among frail (N=227)</i>				
Age ≤ 65, vs > 65 years	2.07 (1.23, 3.49)	0.006	2.55 (1.46, 4.43)	0.001

^a Model also adjusted for sex, race, smoking status, diabetes mellitus, coronary artery disease, congestive heart failure, and mean inter dialytic weight gain

^b Non-frail defined as a score of 0 or 1, intermediately frail a score of 2, and frailty a score of 3 or higher

^c Frailty defined as a score of ≥2, which includes intermediately frail and frail.

^d Models adjusted for sex, race, obesity, cerebrovascular disease

FIGURES

Figure 1. Distribution of post-dialysis recovery time among adults new to hemodialysis

Figure 2. Distribution of post-dialysis recovery time by frailty status and age among adults new to hemodialysis. Frailty defined as a score of ≥ 2 , which includes intermediately frail and frail.

Figure 1

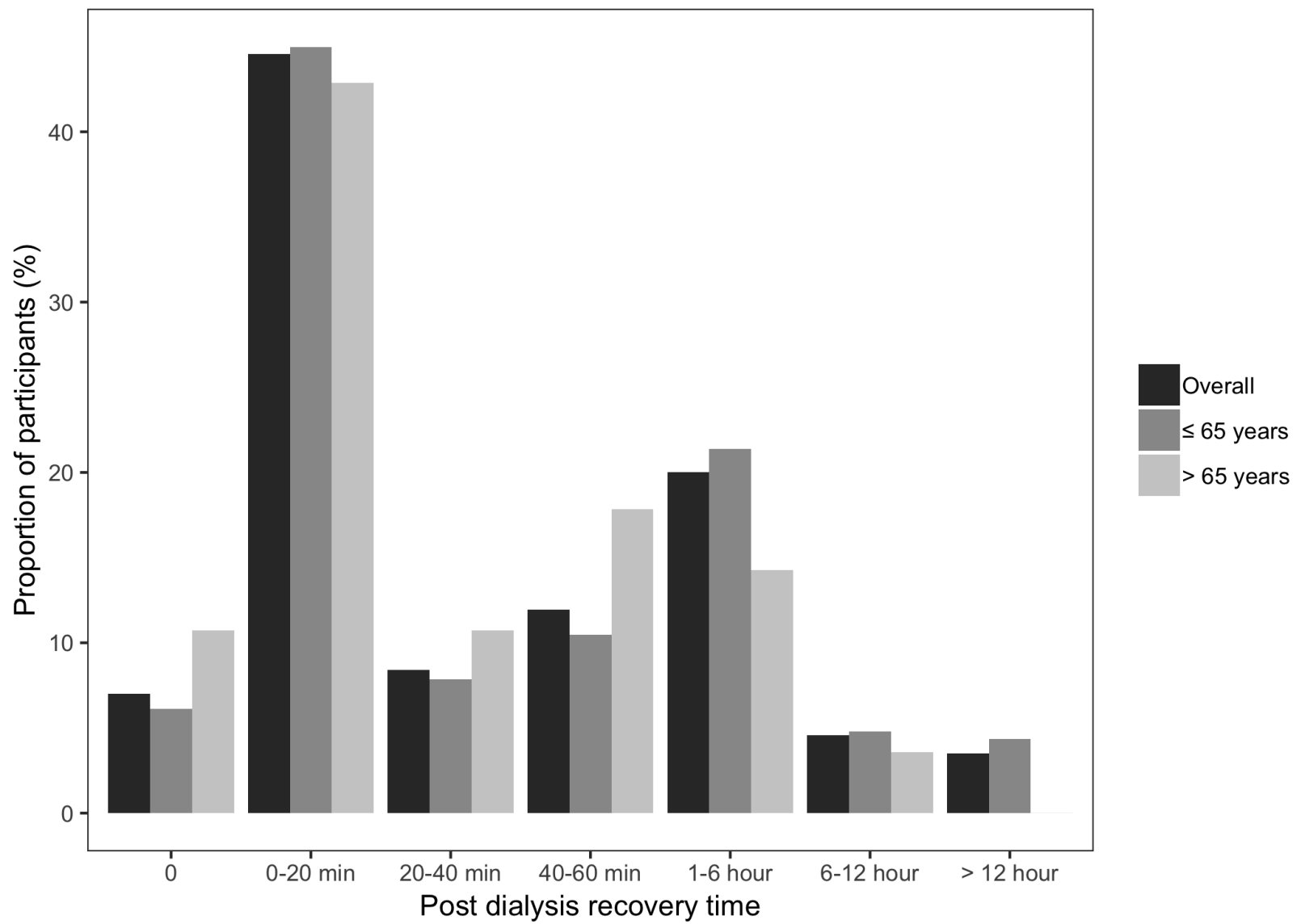
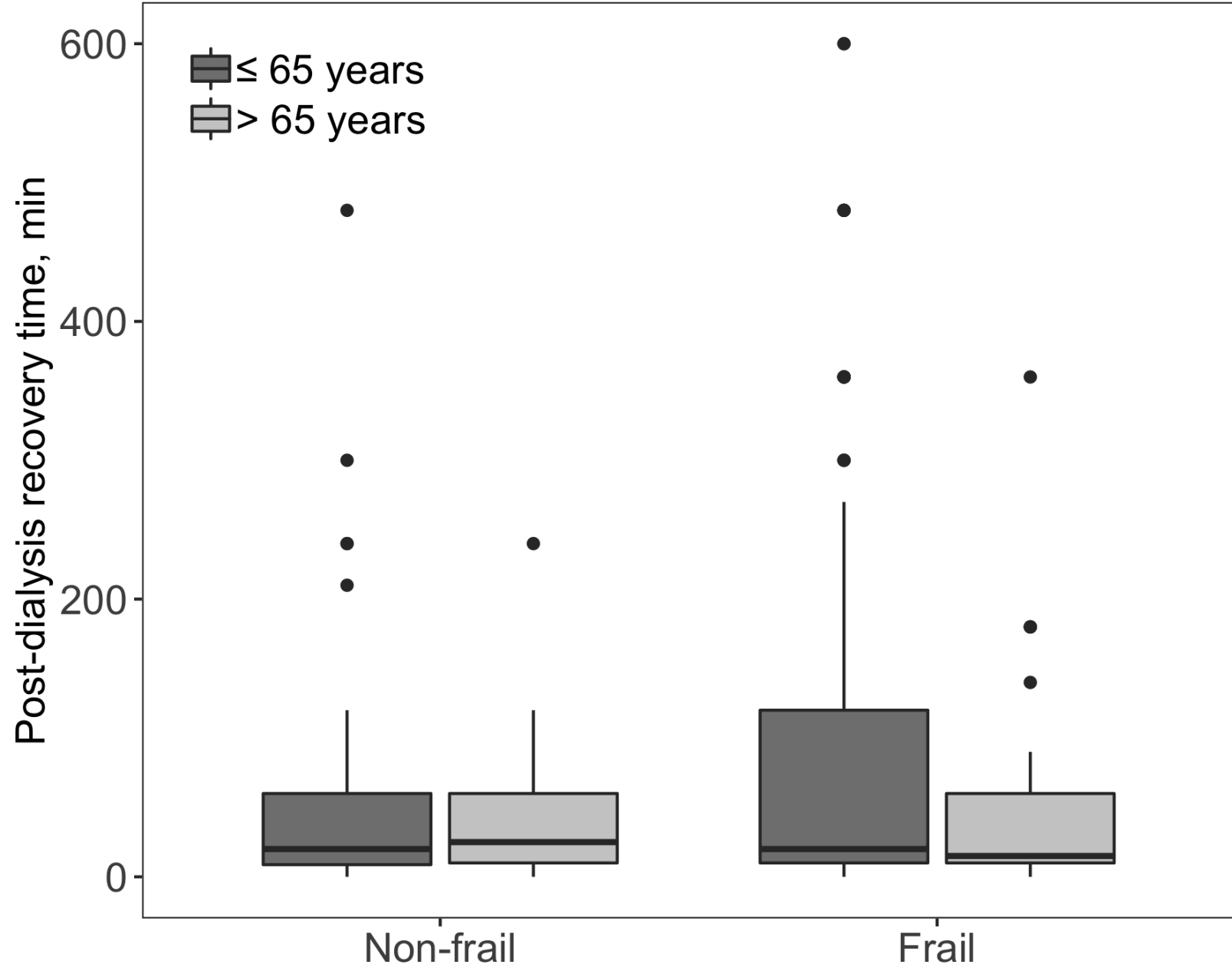


Figure 2



Frailty, age, and post-dialysis recovery time in an incident hemodialysis population

SUPPLEMENTAL MATERIAL

	Page
Table S1. Extended PACE participant characteristics	2
Table S2. Associations of baseline age and frailty components with post-dialysis recovery time among adults initiating hemodialysis	3
Table S3. Baseline PACE participant characteristics among those with and without outcome ascertainment	4

Table S1. Extended PACE participant characteristics

Variables	N	Overall	Post-dialysis	Post-dialysis
			recovery time < 20 min (N=147)	recovery time ≥ 20 min (N=138)
Mean (±SD), median (IQR), frequency (%)				
Frailty				
Non frail	285	58 (20)	29 (20)	29 (21)
Intermediately frail		83 (29)	43 (29)	40 (29)
Frail		144 (51)	75 (51)	69 (50)
Frailty components				
Shrinkage	271	143 (53)	71 (51)	72 (54)
Exhaustion	282	102 (36)	49 (34)	53 (39)
Weakness	278	134 (48)	70 (49)	64 (47)
Low physical activity	285	156 (55)	80 (54)	76 (55)
Slowed gait speed	273	179 (66)	92 (65)	87 (66)
Laboratory measurements				
Serum Albumin, g/dL	282	3.6 ± 0.4	3.7 ± 0.4	3.6 ± 0.5
Hemoglobin, g/dL	282	10.8 ± 1.2	10.8 ± 1.3	10.9 ± 1.2
Serum creatinine, mg/dL	265	7.2 ± 2.5	7.1 ± 2.3	7.2 ± 2.6
Single pool Kt/V	260	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3

^a Blood pressures were obtained by averaging 3 consecutive measurements with participants in a seated position on a non-dialysis day

Table S2. Associations of baseline age and frailty components with post-dialysis recovery time among adults initiating hemodialysis

Model	Unadjusted Associations		Adjusted Associations	
	IRR (95% CI)	P-value	IRR (95% CI)	P-value
<i>Frailty components^a</i>				
Shrinkage, yes vs. no	0.90 (0.61, 1.31)	0.6	1.25 (0.84, 1.87)	0.3
Exhaustion, yes vs. no	1.09 (0.73, 1.62)	0.7	1.09 (0.71, 1.69)	0.7
Weakness, yes vs. no	0.69 (0.47, 1.01)	0.06	0.85 (0.53, 1.36)	0.5
Low physical activity, yes vs. no	1.28 (0.87, 1.86)	0.2	1.12 (0.74, 1.68)	0.6
Slowed gait speed, yes vs. no	0.75 (0.50, 1.12)	0.2	0.82 (0.54, 1.24)	0.3

^a Associations of frailty components and recovery time were evaluated separately in models adjusted for sex, race, smoking status, diabetes mellitus, coronary artery disease, congestive heart failure, and mean inter dialytic weight gain

Table S3. Baseline PACE participant characteristics among those with and without outcome ascertainment

Variables	Complete Data	No Outcome	P-value
	(N=285)	Data (N=74)	
	Mean (\pm SD), median (IQR), frequency (%)		
Demographic and clinical factors			
Age, years	55.0 \pm 13.2	54.8 \pm 12.7	0.9
Female sex	123 (43)	28 (38)	0.5
African American	207 (73)	53 (72)	0.9
Body mass index (kg/m ²)	29.5 \pm 7.9	29.3 \pm 8.0	0.9
Ever smoker	164 (56)	52 (70)	0.06
Diabetes	161 (57)	44 (60)	0.7
History of coronary artery disease	98 (34)	32 (43)	0.2
History of congestive heart failure	114 (40)	34 (46)	0.4
History of cerebrovascular disease	60 (21)	17 (23)	0.8
Systolic blood pressure, mmHg ^a	136 \pm 26	138 \pm 24	0.7
Diastolic blood pressure, mmHg ^a	74 \pm 14	76 \pm 15	0.5
Frail	144 (51)	43 (58)	0.3

^a Blood pressures were obtained by averaging 3 consecutive measurements with participants in a seated position on a non-dialysis day

Frailty, age, and post-dialysis recovery time in an incident hemodialysis population

SUPPLEMENTAL MATERIAL

	Page
Table S1. Extended PACE participant characteristics	2
Table S2. Associations of baseline age and frailty components with post-dialysis recovery time among adults initiating hemodialysis	3
Table S3. Baseline PACE participant characteristics among those with and without outcome ascertainment	4

Table S1. Extended PACE participant characteristics

Variables	N	Overall	Post-dialysis	Post-dialysis
			recovery time < 20 min (N=147)	recovery time ≥ 20 min (N=138)
Mean (±SD), median (IQR), frequency (%)				
Frailty				
Non frail	285	58 (20)	29 (20)	29 (21)
Intermediately frail		83 (29)	43 (29)	40 (29)
Frail		144 (51)	75 (51)	69 (50)
Frailty components				
Shrinkage	271	143 (53)	71 (51)	72 (54)
Exhaustion	282	102 (36)	49 (34)	53 (39)
Weakness	278	134 (48)	70 (49)	64 (47)
Low physical activity	285	156 (55)	80 (54)	76 (55)
Slowed gait speed	273	179 (66)	92 (65)	87 (66)
Laboratory measurements				
Serum Albumin, g/dL	282	3.6 ± 0.4	3.7 ± 0.4	3.6 ± 0.5
Hemoglobin, g/dL	282	10.8 ± 1.2	10.8 ± 1.3	10.9 ± 1.2
Serum creatinine, mg/dL	265	7.2 ± 2.5	7.1 ± 2.3	7.2 ± 2.6
Single pool Kt/V	260	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3

^a Blood pressures were obtained by averaging 3 consecutive measurements with participants in a seated position on a non-dialysis day

Table S2. Associations of baseline age and frailty components with post-dialysis recovery time among adults initiating hemodialysis

Model	Unadjusted Associations		Adjusted Associations	
	IRR (95% CI)	P-value	IRR (95% CI)	P-value
<i>Frailty components^a</i>				
Shrinkage, yes vs. no	0.90 (0.61, 1.31)	0.6	1.25 (0.84, 1.87)	0.3
Exhaustion, yes vs. no	1.09 (0.73, 1.62)	0.7	1.09 (0.71, 1.69)	0.7
Weakness, yes vs. no	0.69 (0.47, 1.01)	0.06	0.85 (0.53, 1.36)	0.5
Low physical activity, yes vs. no	1.28 (0.87, 1.86)	0.2	1.12 (0.74, 1.68)	0.6
Slowed gait speed, yes vs. no	0.75 (0.50, 1.12)	0.2	0.82 (0.54, 1.24)	0.3

^a Associations of frailty components and recovery time were evaluated separately in models adjusted for sex, race, smoking status, diabetes mellitus, coronary artery disease, congestive heart failure, and mean inter dialytic weight gain

Table S3. Baseline PACE participant characteristics among those with and without outcome ascertainment

Variables	Complete Data	No Outcome	P-value
	(N=285)	Data (N=74)	
	Mean (\pm SD), median (IQR), frequency (%)		
Demographic and clinical factors			
Age, years	55.0 \pm 13.2	54.8 \pm 12.7	0.9
Female sex	123 (43)	28 (38)	0.5
African American	207 (73)	53 (72)	0.9
Body mass index (kg/m ²)	29.5 \pm 7.9	29.3 \pm 8.0	0.9
Ever smoker	164 (56)	52 (70)	0.06
Diabetes	161 (57)	44 (60)	0.7
History of coronary artery disease	98 (34)	32 (43)	0.2
History of congestive heart failure	114 (40)	34 (46)	0.4
History of cerebrovascular disease	60 (21)	17 (23)	0.8
Systolic blood pressure, mmHg ^a	136 \pm 26	138 \pm 24	0.7
Diastolic blood pressure, mmHg ^a	74 \pm 14	76 \pm 15	0.5
Frail	144 (51)	43 (58)	0.3

^a Blood pressures were obtained by averaging 3 consecutive measurements with participants in a seated position on a non-dialysis day