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CLINICAL RESEARCH

Physical Resilience Phenotype Trajectories in Incident Hemodialysis: Characterization and Mortality Risk Assessment

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Introduction: Although life-saving, the physiologic stress of hemodialysis initiation contributes to physical impairment in some patients. Mortality risk assessment following hemodialysis initiation is underdeveloped and does not account for change over time. Measures of physical resilience, the ability of a physiologic state to overcome physiologic stressors, may help identify patients at higher mortality risk and inform clinical management.

Methods: We created 3 resilience categories (improving, stable, and declining) for trajectories of 4 phenotypes (physical function [PF], mental health [MH], vitality [VT], and general health [GH]) using SF-36 data collected the first year after hemodialysis initiation in the Choices for Healthy Outcomes in Caring for ESKD (CHOICE) study on 394 adults aged more than 55 years. Using mixed effects and Cox proportional hazard modeling, we assessed mortality following the first year on dialysis by resilience categories for each phenotype, adjusting for baseline phenotype and other confounders defined *a priori* over 4 years average follow-up.

Results: Based on global Wald tests, statistically significant associations of PF ($P = 0.03$) and VT ($P = 0.0004$) resilience categories with mortality were found independent of covariates. Declining PF trajectory was associated with higher mortality risk (hazard ratio [HR] = 1.32; 95% confidence interval [CI], 1.05–1.66), whereas improving VT trajectory was associated with lower mortality risk (HR= 0.73; 95% CI, 0.53 to 1.00), each as compared to stable trajectory.

Conclusion: Decreased resilience in PF and VT was independently associated with mortality. Phenotypic trajectories provide added value to baseline markers and patient characteristics when evaluating mortality. Hence, resilience measures hold promise for targeting population health interventions to the highest risk patients.

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Dialysis is a life-extending treatment for those with kidney failure. Dialysis can also, however, potentiate complications.[1,2] Available mortality risk assessment models postdialysis initiation for older adults evaluate mortality risk over short time periods, have not been externally validated, and do not take into account change over time.[3,4] Risk assessment models also rarely account for patient reported information.[5,6] Improved methods for identifying older adults at highest risk of death following dialysis initiation must be further explored to improve clinical decision-making and health outcomes.

One potential way to improve mortality risk assessment is through physical resilience measurement.[7,8]

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Physical resilience is defined as "the ability of a physiologic system to retain its function and identity following a powerful stressor."[9,10] It is hypothesized to arise from the fitness of one's stress-response physiology, considered as a dynamical system.[11] Because physical resilience is inherently dynamical, its measurement occurs over time, as trajectories rather than static measures. Resilience phenotype are health and functional markers thought to respond to experiencing specific stressors. Resilience trajectories of those phenotypes track such markers longitudinally, ideally beginning before the stressor onset and continuing through the stressor initiation and recovery phases, and are a crucial way to operationalize the resilience paradigm.[12] They allow for a dynamic understanding of the resilience phenomenon and have promise both to differentiate adverse outcome risk (e.g., postdialysis mortality) and to anchor discovery of prestressor factors that lead to a resilient response (or not).[11]

There is growing literature conceptualizing the study of physical resilience, but few studies have evaluated the clinical utility of the physical resilience concept in those undergoing hemodialysis. The initiation of dialysis requires a great deal of physiologic reserve to withstand the hemodynamic changes with each dialysis treatment, which is partially why those with physical frailty experience higher mortality and morbidity following dialysis initiation.[13] In this case, physical frailty is the underlying biologic vulnerability to stressors due to decreased physiologic reserve. High physical resilience may well reflect healthy reserve in physiologic mechanisms overlapping with those underlying frailty. The concept of physical resilience, however, is distinguished from frailty by addressing response to a specific stressor, as opposed to a global vulnerability. Therefore, distinct physiological mechanisms may be involved.[10] As such, physical resilience and frailty may involve different physiologic mechanisms.[14] Exploring the role of physical resilience trajectories in an incident dialysis among an older adult population may add greater understanding to the physical resilience concept and greater insight into accurate mortality risk prediction. Currently, we are undertaking an observational study to evaluate underlying mechanisms of resilience in a small cohort of older adults with impending end-stage renal disease. This present work aimed to inform that study by characterizing resilience trajectories and their implications for long-term survival in a large observational cohort with end-stage renal disease.

METHODS

Study Population and Design

The CHOICE study was a prospective cohort of 1067 incident dialysis patients enrolled between 1995 and 1998; 73% ($n = 783$) initiated hemodialysis and 27% ($n = 284$) initiated peritoneal dialysis.[15]. Eligible participants were within 3 months following initial onset of dialysis treatment at study enrollment, aged 18 years and older, and English or Spanish speaking.[15,16] Patients receiving hospice care were excluded. Following enrollment and baseline questionnaires, participants completed study visits at 3, 6, 9, and 12 months, followed by 6-monthly questionnaires for a mean time of 4 years.[15] The CHOICE cohort was followed for mortality through 2004.[17]

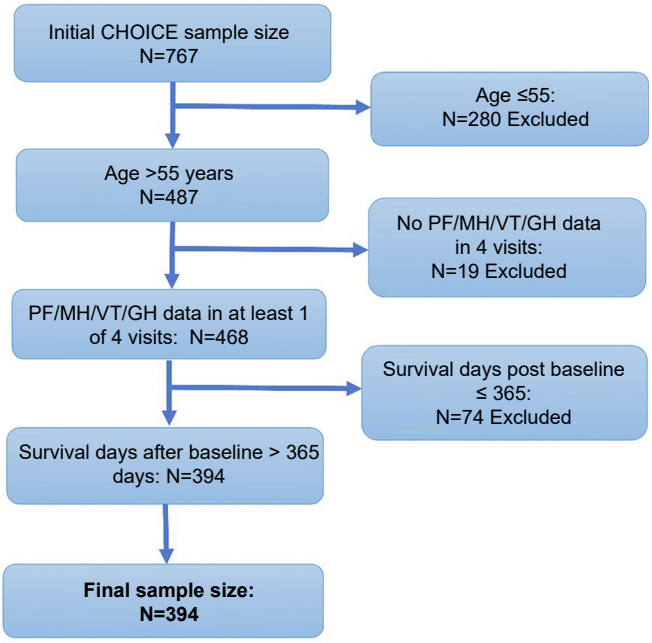

Figure 1. Flow Chart for Sample Size
GH, general health; MH, mental health; PF, physical function; VT, vitality.

For the purposes of our study, participants were included if they initiated hemodialysis and were older than 55 years ($n = 485$); this is the eligibility criterion for our observational study. We chose 55 years or older (as opposed to 65 years or older) as our cut-off age because of the age accelerating nature of end-stage renal disease.[18] Time point 0 was first study visit following dialysis initiation. Because we aimed to evaluate the potential for first year resilience trajectories to forecast subsequent survival, participants were excluded if they died within 365 days postdialysis initiation ($n = 74$). Descriptive statistics were examined to explore key baseline contributors to first-year mortality risk. Figure 1 shows the inclusion flow chart.

Measures to Characterize Resilience

The resilience trajectory measures in this study were derived from the PF, emotional well-being (henceforth "mental health"; MH); energy or fatigue (henceforth

"vitality"; VT), and GH subscales of the 36-item Short-Form Health survey (SF-36), considered as our resilience phenotypes.[19,20] These 4 measures were chosen because of their clinical relevance within both hemodialysis[21] and general populations.[22] They were also the closest surrogates available to our physical resilience theoretical framework, wherein we hypothesize phenotypes such as PF, VT, GH and MH to be resilient manifestations of the complex biological dynamics resulting from the stressor of hemodialysis initiation.[10] Our 4 resilience phenotypes included the following: (i) the 10-item PF subscale, which contained items such as "Does your health now limit you in climbing several flights of stairs?" using a 3-item response scale of "yes, limited a lot," "yes, limited a little" or "no, not limited at all"; (ii) the 5-item MH subscale, which includes items such as "In the past 4 weeks, how much of the time have you felt downhearted and blue?" using 6-point response options ranging from "all of the time" to "none of the time"; (iii) the 4-item VT subscale, which included items such as "In the last 4 weeks, how much of the time have you felt full of pep?" with the same answer option range as MH; and (iv) the 5-item GH subscale, which includes items such as "My health is excellent" using 5-point response options ranging from "definitely true" to "definitely false." Each subscale was scored from 100 (highest possible score indicating best health) to 0 (lowest possible score).

Socio-demographics

A standard baseline questionnaire assessed characteristics including the following: age (in years); sex (male or female); race or ethnicity (White, African American, or Other) because of the established racial differences in survival on dialysis;[23,24] education (less than high school, high school or some college, or college or higher); and insurance status (dichotomized as any inclusion of Medicaid insurance or no insurance vs. private insurance and/or Medicare without Medicaid).

Covariates

Covariates were included based on associations with mortality in previous dialysis research. Body mass index (in kg/m^2) was based on height and weight reported on the Health Care Financing Administration Medical Evidence Report (HCFA Form 2728).[17] Kidney disease specific markers selected included the following: (i) type of vascular access, by category: arteriovenous fistula or graft, or central venous catheter or unknown;[25] (ii) predialysis initiation nephrology consult timing (early [>12 months], intermediate [4–12 months], late [<4 months], unclassified, or missing)[26]; (iii) laboratory values for serum albumin (g/dl) obtained from HCFA Form 2728;[27] and (iv) estimated glomerular filtration rate, calculated using the 4-variable Modification of Diet in Renal Disease Study equation.[28] We modeled comorbidities using the Index of Coexistent Disease (ICED), a validated index of presence and severity of comorbid conditions used extensively in mortality risk prediction in patients with kidney failure. ICED scores included 0 and 1 (mild), 2 (moderate), and 3 (severe).[27,29,30]

Statistical Analysis

Our first aim was to characterize resilience trajectories based on SF-36 subscales over the baseline and follow-up assessments at 3, 6, and 12 months, with 1 per each resilient phenotype (PF, MH, VT, and GH). We conceptualized key features in terms of trends over time as well as the potential nonlinearity or variability relative to a straight-line trend. As a first step, repeated measures from each resilient phenotype were characterized using linear mixed effects models with random intercept and slope terms. We then estimated each participant's intercept and slope, thus a straight-line approximation to their trajectory, using best linear unbiased predictor values.[31] Next, we categorized trajectories into a few subgroups with similar characteristics based on the slope of their straight-line approximation as increasing or decreasing as well as the closeness of fit of a straight-line approximation to their actual trajectory values (details are provided in the Supplemental Material). This process identified 3 mutually exclusive groups who exhibited generally improving, declining, or stable (flat) trajectories (henceforth, "resilience categories"), which were utilized for further analysis.

Participant characteristics were compared for those with survival of less than 12 months versus those surviving more than 1 year. We next characterized post-12-month survival by resilience categories using Kaplan-Meier curves and Cox proportional hazards models adjusted for potential confounders. One set of analyses, each, was conducted per resilience phenotype (PF, VT, MH, and GH). In Cox modeling, models adjusted for random intercept estimates from the initial phenotype-specific trajectory modeling, so that we could address the value added by trajectory information beyond measures of baseline resilience phenotype values. A robust variance correction was applied to address CHOICE data clustering by dialysis clinics. Multiple imputation using sequential imputation with chained equations was performed to address missingness in serum albumin, type of vascular access, nephrology referral time, body mass index, estimated glomerular filtration rate, urine albumin-creatinine ratio and ICED score.[32,33] We hypothesized lower

Table 1. Sociodemographic and medical characteristics comparing those Surviving more than 1 year[a] versus 1 year or less

Baseline Sample Characteristics	Overall ($N = 468$)	Survival >1 year[a] ($n = 394$)	Survival ≤ 1 year ($n = 74$)
Age[b]	68.89 (7.83)	68.35 (7.67)	70.56 (8.52)
Female, *n* (%)	227 (49)	193 (49)	34 (46)
BMI	26.84 (6.34)	26.97 (6.17)	26.12 (7.19)
Education, *n* (%)			
< high school	177 (38)	147 (37)	30 (41)
High school and some college	233 (50)	198 (50)	35 (47)
College or higher	58 (12)	49 (13)	9 (12)
Race, *n* (%)[b]			
African American or Other	152 (32)	140 (35)	12 (16)
White	316 (68)	254 (65)	62 (84)
ICED, *n* (%)[c]			
1	127 (27)	119 (30)	8 (11)
2	199 (43)	167 (43)	32 (43)
3	140 (30)	106 (27)	34 (46)
Insurance, *n* (%)			
Medicaid	103 (23)	87 (23)	16 (23)
Private insurance/Medicare	352 (77)	298 (77)	54 (77)
Access type, *n* (%)[b]			
Graft/Fistula	186 (46)	169 (49)	17 (27)
Catheter	222 (54)	177 (51)	45 (73)
Nephrology consult, *n* (%)			
Early	163 (43)	141 (44)	22 (39)
Intermediate	87 (23)	76 (24)	11 (20)
Late	126 (34)	103 (32)	23 (41)
eGFR	8.00 (3.27)	7.83 (2.94)	8.88 (4.56)
Serum creatinine (mg/dl)[d]	8.42 (6.75)	8.21 (4.73)	9.46 (12.81)
Serum albumin (g/dl)	3.30 (0.56)	3.31 (0.55)	3.21 (0.57)
Baseline resilient phenotype scores[e]			
Physical function[b]	39.41 (26.71)	41.20 (27.14)	30.06 (22.29)
Mental health[b]	69.50 (20.43)	70. 64 (20.20)	63.40 (20.74)
Vitality[b]	40.75 (21.55)	42.09 (21.97)	33.58 (17.68)
General health[b]	41.46 (18.82)	42.47 (18.68)	36.19 (18.84)

BMI, body mass index; eGFR, estimated glomerular filtration rate; ICED, index of coexistent diseases
[a]Survival > 1 year ($n = 394$) is sample used in resilience trajectory analyses.
[b]*P*-value < 0.05.
[c]*P*-value < 0.001.
[d]Serum Creatinine reported here but not used in statistical modeling. eGFR used in its place.
[e]Range options for each subscale was 0–100 with higher scores equaling better function.
Measures are displayed as mean (SD), except where indicated. Sample sizes may differ across covariates. For continuous variables, Kruskal-Wallis test was used; for categorical variables, Chi-squared test was used.

mortality across improving (lowest), stable and declining trajectories for each resilience phenotype.

To explore adequacy of our primary analysis, several sensitivity analyses were implemented. To ensure that findings were not unduly influenced by individuals having only 1 measurement occasion and no trajectory information in the first year, an analysis excluding these individuals was performed. To further explore dependence of trajectory on persons' baseline phenotypic values, analyses adding interactions between the random intercept estimate and resilience category, and replacing random intercept estimates with persons' measured baseline values were performed. To ensure that there was not undue information loss in categorizing resilience trajectories, an analysis replacing resilience categories with random slope estimates for first year functional change was performed. To further evaluate whether phenotypic variability, and not only mean trend, may have survival implications, analyses were performed adding the logarithm of the residual variance of individuals' phenotype values about their estimated trend to the analysis described in the previous sentence. All analyses that employed continuously scaled covariates were checked for linearity and undue influence using Martingale residual plots. Proportionality of hazards was evaluated using Schoenfeld residual plots.

RESULTS

Our study sample had average age of 68.4 years with nearly equal gender distribution, diversely distributed education levels, and 23% on Medicaid (Table 1). Body mass index, ICED category, and

clinical characteristics relating to nephrology care and dialysis type were heterogeneously distributed. Mean resilience phenotype scores at baseline were low compared to a community dwelling sample of older adults[34] at 41.2 for PF, 42.5 for GH, and 42.1 for VT (all out of 100). The average baseline MH score was 70.6.

Individual characteristics were similarly distributed, in many respects, by survival status of less than or equal to 1 year versus greater than 1 year (Table 1). Characteristics exhibiting statistically significant differences (survival $\leq$ 1 year vs. >1 year), included race (84% vs. 65% White), ICED category (46% vs. 27% category 3), and access type (73% vs. 51% catheter). Mean resilience phenotypes at baseline were 6 to 8 points lower among those dying earlier versus those surviving longer for all subscales except PF, where the deficit exceeded 11 points.

For each resilience phenotype, substantial heterogeneity in baseline to 12 month trajectories was observed, encompassing both baseline function level and patterns of change over 1 year. Figure 2 displays, for each phenotype, trajectories according to the improving, stable and declining "resilience categories" defined earlier. In each case, despite heterogeneity, our categorization distinguished trajectories that were improving, stable and declining overall. In addition (data not shown), individuals' trajectories tended to be positively associated across domains. Analytical sample characteristics are tabulated by resilience categories, and multiple regression analyses of resilience categories by personal characteristics are presented in the Supplementary Materials and Supplementary Table S1 to S4.

Post-12-month survival was followed on average for over 4 years. In fully adjusted Cox models to evaluate determinants of this outcome (Table 2), both PF (P = 0.03) and VT (P = 0.0004) resilience categories were associated with mortality risk (adjudicated by global Wald tests). For the PF phenotype, mortality risk for the declining versus the stable trajectory category was higher by 32% (HR = 1.32, 95% CI = 1.05–1.66) after adjustments for socio-demographics, body mass index, comorbidities, and nephrology specific gold standard measures. Likewise, the risk of mortality was lower by 27% among those in the improving VT resilience category compared with those in the stable VT resilience category after adjustments for the same covariates (HR = 0.73, 95% CI = 0.53–1.00). Importantly, these associations were present after adjusting for many well-established variables that predict mortality, including the baseline phenotype (random intercept) itself. Kaplan-Meier plots characterizing crude mortality associations with resilience categories were consonant with Cox model findings for each resilience phenotype for the first 5 to 6 years of follow-up, after which some crossover of survival curves was observed (Supplementary Figure S1). These plots lend insight into the counterintuitive, albeit not statistically significant, HR in the direction of a slight mortality deficit for those with increasing versus stable PF trajectory category (HR = 1.15, 95% CI = 0.90–1.48). Kaplan-Meier curves mirrored this trend in the first 6 years of follow-up, but a survival benefit for those with improving trajectory category was observed thereafter. Interestingly, baseline phenotypic status estimated by random intercepts was not associated with mortality after adjustments for any of the 4 resilience phenotypes.

Analytical sample characteristics overall and by PF resilience categories are presented in Table 3. Many characteristics were similarly distributed across resilience categories. Nevertheless, the percentage of African American or Other participants among those with improving resilience category (46%) was significantly higher than in stable (30% African American or Other) and declining (35% African American or Other) categories (chi-squared P = 0.021). Analogous data on other phenotypes are presented in Supplementary Table S1 to S3. Higher education was significantly associated with improving MH and declining GH resilience categories. For MH, differentiation by race was observed with African American or Other participants making up a larger percentage of the MH stable and improving resilience categories compared to White participants (32% stable, 47% improving, chi-squared P = 0.049). For VT, there was an association with serum albumin at dialysis initiation, which was lower among those with improving or declining VT categories versus the stable VT category (Kruskal-Wallis P = 0.004). In mutually adjusted multinomial logistic regression models to characterize trajectory category by covariates (Supplementary Table S4), only education consistently sustained statistical significance. The most striking pattern was that those with college education were less likely to have the declining trajectory category for both MH and VT, but also less likely to have improving GH category.

Sensitivity Analysis

Sensitivity analyses both supported and added nuance to our primary analysis. Findings were slightly strengthened in analyses excluding individuals with only 1 phenotypic measurement over time. In addition in these analyses, the declining (vs. stable) resilience category for GH was significantly associated with a 49% increased risk of mortality (95% CI = 5.6% to 110%, P = 0.023; n = 364).

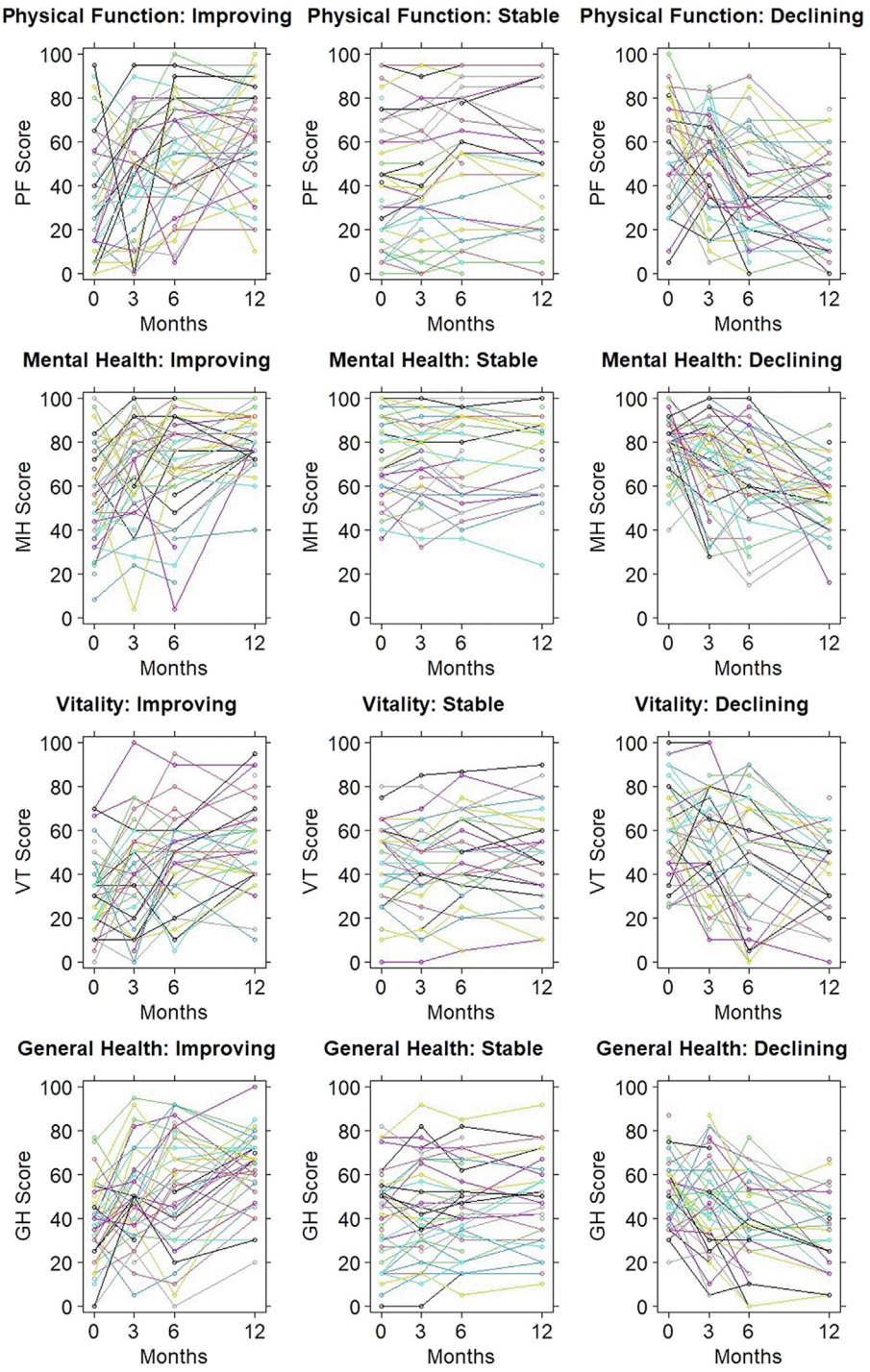

Figure 2. First 150 Resilience Trajectories for each Resilient Phenotype
GH, general health; MH, mental health; PF, physical function; VT, vitality.

Analyses evaluating interactions between baseline resilience phenotype (random intercept) and resilience phenotype trajectories did not identify significant moderation for either the VT or GH phenotypes (VT: $P = 0.650$, GH: $P = 0.401$). For the PF phenotype, a slight synergistic survival benefit of improving PF trajectory together with higher baseline PF was observed (global P-value for interaction $= 0.039$ with 15.1% reduction in the relative hazard for mortality for improving vs. stable trajectory per 1 SD higher baseline score, 95% CI = 0.5%–27.4%). For the MH phenotype, where no main effect was shown, the mortality association with a declining MH trajectory was considerably increased among persons with low MH to start (global P-value for interaction < 0.0001 with 30.9% increase in the relative hazard for declining vs. stable trajectory per 1 SD lower baseline score, 95% CI = 22.9%–38.0%).

Table 2. Adjusted risk of mortality by resilience phenotype and resilience category

	Outcome domains ($N = 394$) HR (95% CI)			
	Physical function	Mental health	Vitality	General health
Resilience category				
Stable	ref	ref	ref	
Improving	1.15 [0.90, 1.48]	1.07 [0.86, 1.33]	0.73[a] [0.53, 1.00]	0.93 [0.71, 1.23]
Declining	1.32[a] [1.05, 1.66]	0.94 [0.63, 1.43]	1.18 [0.91, 1.53]	1.38 [0.99, 1.93]

CI, confidence interval; HR, hazard ratio; ref, reference.
[a]*P*-value ≤ 0.05
Adjusted GEE model results with imputed data (Adjustment included: age, sex, race, body mass index, education, random intercept, Index of Coexistent Diseases, estimated glomerular filtration rate, serum albumin, access type, nephrology consult timing, and insurance type).

Fully adjusted analysis representing resilience trajectories as subject specific random slopes for first year phenotypic change, rather than categorizing, amplified findings from our primary analysis as follows: improving trajectory was significantly associated with decreased mortality for PF (HR = 0.758, 95% CI 0.616–0.932) and VT (HR = 0.628, 95% CI 0.461–0.856) as well as GH (HR = 0.749, 95% CI 0.623–0.902) phenotypes. Adding one's residual variance in phenotype scores to these models did little to alter these estimates, and these variability measures were not associated with mortality in their own right. Lastly, in each of our final models, there were no meaningful changes to our results after replacing random intercepts with actual baseline values for each resilience phenotype.

DISCUSSION

This study of 394 patients surviving more than 12 months following hemodialysis initiation found mortality to be substantially differentiated across both PF and VT resilience categories. Notably, these associations were independent of gold standard indicators thought to contribute to mortality risk as well as baseline phenotype measures. Therefore, resilience trajectories stand to assess post-12-month mortality risk more accurately

Table 3. Sociodemographic and medical characteristics by physical function resilience phenotype

Characteristic	Total ($N = 394$)	Declining ($n = 102$)	Stable ($n = 193$)	Improving ($n = 99$)
Age	68.35 (7.67)	68.72 (8.15)	68.27 (7.71)	68.12 (7.12)
Female, *n* (%)	193 (49)	48 (47)	95 (49)	50 (51)
BMI	26.97 (6.17)	26.72 (6.16)	27.13 (6.36)	26.92 (5.85)
Education, *n* (%)				
Less than high school	147 (37)	49 (48)	59 (31)	39 (39)
High school and some college	198 (50)	43 (42)	107 (55)	48 (49)
College or higher	49 (13)	10 (10)	27 (14)	12 (12)
Race, n (%)[a]				
African American or Other	140 (35)	36 (35)	58 (30)	46 (46)
White	254 (65)	66 (65)	135 (70)	53 (54)
ICED, *n* (%)				
1	119 (30)	27 (27)	60 (31)	32 (32)
2	167 (43)	47 (46)	80 (42)	40 (41)
3	106 (27)	28 (27)	51 (27)	27 (27)
Insurance, *n* (%)				
Medicaid	87 (23)	25 (25)	35 (19)	27 (28)
Private insurance/Medicare	298 (77)	76 (75)	154 (81)	68 (72)
Access type, *n* (%)				
Graft/Fistula	169 (49)	40 (49)	87 (50)	42 (47)
Catheter	177 (51)	42 (51)	88 (50)	47 (53)
Nephrology consult, *n* (%)				
Early	141 (44)	39 (48)	67 (43)	35 (42)
Intermediate	76 (24)	19 (24)	37 (24)	20 (24)
Late	103 (32)	23 (28)	52 (33)	28 (34)
Serum albumin (g/dl)	3.31 (0.55)	3.25 (0.54)	3.35 (0.57)	3.31 (0.52)
eGFR	7.83 (2.94)	7.98 (2.95)	7.97 (3.03)	7.40 (2.75)
Serum creatinine (mg/dl)[b]	8.42 (6.75)	8.05 (3.06)	8.21 (5.94)	8.39 (3.17)

BMI, body mass index; eGFR, estimated glomerular filtration rate; ICED, index of coexistent diseases
[a]*P*-value < 0.05
[b]Serum Creatinine reported here but not used in statistical modeling. eGFR used in its place.
Measures are displayed as mean (SD), except where indicated. Sample sizes may differ across covariates, for continuous variables, Kruskal-Wallis test is used; for categorical variables, Chi-squared test is used.

than patients' baseline information alone, and may be intervenable if proactively monitored, particularly in the categories of VT and PF. Sensitivity analyses strengthened findings and suggested protective effect modification of higher MH and PF status at baseline.

There have been few studies exploring the role of physical resilience trajectories in renal failure. In other populations, Gijzel *et al.*[35] showed that dynamic resilience indicators collected during hospitalization of older adults improved recovery assessment at 3 months postdischarge. Parker *et al.*[36] and Colón-Emeric *et al.*[12] created resilience trajectories for a cohort undergoing hip replacement ($n = 541$) and explored a set of function-related biomarkers that explained 27% of variance in physical resilience trajectories. Laskow *et al.*[37] identified factors predictive of nonresilient physical phenotypes following total knee replacement. Our study adds to this literature as follows: (i) by considering a different stressor (hemodialysis initiation), (ii) by categorizing physical resilience trajectories with distinct methodology, and (iii) by evaluating associations of resilience trajectories with mortality independently of baseline phenotypic status and other personal characteristics.

We consider this study as proof of concept that physical resilience trajectory measurement can improve risk prediction modeling. Developing and evaluating predictive algorithms is an important next goal. Steps needed to achieve this include formal assessment of predictive accuracy, comparison of candidate methods for summarizing the resilience trajectory,and including easier to assess methods in clinical practice (e.g., fewer serial measurements, simpler algorithm). In addition to mortality risk assessment, we believe that resilience trajectories can aid clinicians in evaluating improvements or declines in symptoms or function, allowing for intervention on concerning trends with dialysis patients. Utilizing declining trajectory data, for example, clinical interventions could include a physical therapy or nutrition consult or could trigger a more in-depth nephrology or cardiology evaluation.

We only performed a descriptive analysis of first-year mortality, focusing primarily on the analysis of post-12-month mortality. This was because of the following reasons: (i) data limitations, in which 74 deaths spread out evenly over the first year made it infeasible to assess a relationship to the evolving first-year resilience trajectory and (ii) our primary focus on the implications of first year phenotypic trajectories for subsequent mortality. As documented in Table 1, the cohort surviving beyond a year is considerably strongly selected for younger age, African American or Other race, and better PF, MH, VT and GH status at baseline. Work to study the first-year resilience and outcome experience in a larger cohort is warranted.

The current analysis has other limitations as well. To fully capture a resilience trajectory, relevant data must be gathered before, during and after stressor onset. In the CHOICE study, prestressor measures were not collected. We performed an empirical categorization into trajectory categories rather than a more formal growth mixture trajectory analysis; we considered our dataset size not adequately large to perform the latter reliably. Nevertheless, our categorization exhibited strong face and predictive validity, thereby providing compelling proof of principle for the resilience trajectory approach in the hemodialysis setting. A third limitation is that data on covariates were frequently incomplete such that 47% of participants had complete data on all covariates. Nevertheless, in more than 75% of incomplete covariate profiles missingness was confined to the 3 variables of access type, nephrology consult timing, and albumin concentration. Therefore, we deem the overall covariate adjustment strong and highlight that, despite the use of multiple imputations, the precise adjustment for the variables in question was not possible given their frequent omission.

The study also possessed compelling strengths. Not only were we able to construct our resilience trajectories using 4 time points, but mortality follow-up took place for an average of 4 years. The large number of sociodemographic and disease specific covariates in our models that are specifically predictive of post-12 month mortality allows us to report our resilience phenotype trajectory findings with confidence that they are additive to current knowledge.

This research strengthens previous studies that recognized the importance of quality of life assessments, such as those used to create our resilient phenotypes,[3,20] by emphasizing the potential implications of SF-36–based resilience trajectories for longer-term survival posthemodialysis initiation. Patient reported outcomes such as ours have garnered a great degree of interest in hemodialysis research because of initiatives such as the Standardized Outcomes in Nephrology, which aims to use a shared priorities platform among researchers, clinicians and patients to direct core outcomes for hemodialysis research trials.[38,39] In addition, this work has potential to more generally influence clinical care. SF-36 data are regularly collected in dialysis centers and can direct proactive intervention when trajectories appear declining or suboptimal. Therefore, the physical resilience paradigm promises multiple benefits in the hemodialysis setting.

DISCLOSURE

The authors declare no conflicting interests.

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AUTHOR CONTRIBUTIONS

KBR, RV, TS, JDW, DCC, MDH designed the study. JZ and KBR analyzed the data. MDH, BB, and KBR drafted the manuscript. All authors (MDH, JZ, DCC, MMD, BB, RV, TS, JDW, and KBR) contributed to interpretation of results, and revisions of the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Statistical Analysis: Supplemental Details.

Figure S1. Post 12-month Kaplan-Meier survival curves by resilience trajectories for each resilient phenotype.

Table S1. Sociodemographic and medical characteristics by mental health resilience phenotype.

Table S2. Sociodemographic and medical characteristics by vitality resilience phenotype.

Table S3. Sociodemographic and medical characteristics by general health resilience phenotype.

Table S4. Adjusted multinomial logistic regression models to characterize trajectory type by covariates.

STROBE Statement.

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