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Anderson, Benjamin M; Qasim, Muhammad; Correa, Gonzalo; Evison, Felicity; Gallier, Suzy; Ferro, Charles J; Jackson, Thomas A; Sharif, Adnan

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Kidney Medicine

Cognitive Impairment, Frailty, and Adverse Outcomes Among Prevalent Hemodialysis Recipients: Results From a Large Prospective Cohort Study in the United Kingdom

Benjamin M. Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J. Ferro, Thomas A. Jackson, and Adnan Sharif

Rationale & Objective: Frailty and cognitive impairment are common in hemodialysis recipients and have been associated with high mortality. There is considerable heterogeneity in frailty reporting, with little comparison between commonly used frailty tools and little exploration of the interplay between cognition and frailty. The aims were to explore the relationship between frailty scores and cognition and their associations with hospitalization and mortality.

Study Design: Prospective cohort study

Setting & Population: Prevalent hemodialysis recipients linked to national datasets for hospitalization and mortality.

Predictors: Montreal Cognitive Assessment (MoCA), Frailty Phenotype, Frailty Index (FI), Edmonton Frailty Scale, and Clinical Frailty Scale (CFS) were performed at baseline. Cognitive impairment was defined as MoCA scores of <26, or <21 in dexterity impairment, <18 in visual impairment.

Outcomes: Mortality, hospitalization.

Analytical Approach: Cox proportional hazards model for mortality, censored for end of follow-up. Negative binomial regression for admission rates, censored for death/end of follow-up.

Results: In total, 448 participants were recruited with valid MoCAs and followed up for a median of 685 days. There were 103 (23%) deaths and 1,120 admissions of at least one night. Cognitive impairment was identified in 346 (77.2%) participants. Increasing frailty by all definitions was associated with poorer cognition. Cognition was not associated with mortality (HR, 0.99; 95% CI, 0.95-1.03; $P = 0.41$) or hospitalization (IRR, 1.01; 95% CI, 0.99-1.04; $P = 0.39$) on multivariable analyses. There were interactions between MoCA scores and increasing frailty by FI ($P = 0.002$) and Clinical Frailty Scale ($P = 0.005$); admissions were highest when both MoCA and frailty scores were high, and when both scores were low.

Limitations: As frailty is a dynamic state, a single cross-sectional assessment may not accurately reflect its year-to-year variability. In addition, these findings are in maintenance dialysis and may not be transferable to incident hemodialysis. There were small variations in application of frailty tool criteria from other studies, which may have influenced the results.

Conclusions: Cognitive impairment is highly prevalent in this hemodialysis cohort. The interaction between cognition and frailty on rates of admission suggests the MoCA offers value in identifying higher risk hemodialysis populations with both high and low degrees of frailty.

Visual Abstract included

Complete author and article information provided before references.

Correspondence to A. Sharif (adnan.sharif@uhb.nhs.uk)

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Cognitive impairment is common in hemodialysis recipients[1-3] and worsens in both incident and prevalent hemodialysis recipients.[1,4,5] Cognitive impairment among hemodialysis patients is associated with mortality,[6-10] but little is known about its association with hospitalization. Many factors contribute to development of cognitive impairment, which are common in both general and hemodialysis cohorts.[5,11,12] However, one common factor that is far more prevalent among hemodialysis patients is frailty.

Frailty is a syndrome of increased vulnerability to poor resolution of homeostasis after a stressor event,[13] associated with negative outcomes including mortality, hospitalization, and disability.[14] Frailty prevalence estimates in hemodialysis range from 26% to 63%.[15-21] Several screening tools are available, including the Frailty Phenotype (FP)[22], Frailty Index (FI)[23], Edmonton Frail Scale (EFS)[24], and Clinical Frailty Scale[25]. All have been studied in hemodialysis populations.[15,18-20] Previous work within the FITNESS (Frailty Intervention Trial in End-Stage patientS on haemodialysiS) cohort found agreement upon frailty status between these tools is poor,[21] but all are associated with greater mortality.[26]

A systematic review and meta-analysis identified a relationship between incident cognitive impairment and frailty in the general population,[27] but relatively little is known about the interplay between frailty and cognition in the setting of hemodialysis. FP frailty was associated with cognitive impairment in incident hemodialysis recipients[28] and was associated with cognitive impairment by Montreal Cognitive Assessment (MoCA)[29] in prevalent hemodialysis recipients over 75 years.[30]

There is an unmet need to explore the relationship between other definitions of frailty and cognitive impairment, and how they associate with adverse outcomes. Therefore, the aims of this study are to (1) explore and compare the relationship between cognitive impairment and frailty by FP, FI, EFS, and CFS; (2) ascertain the association of cognitive impairment with mortality and hospitalization in hemodialysis recipients; and (3) explore

PLAIN-LANGUAGE SUMMARY

Frailty and cognitive impairment are both common in people treated by hemodialysis, and both have previously been linked to death and hospitalization. However, little is known about the relationship between frailty and cognitive impairment in hemodialysis recipients. Here, we show in a large, detailed hemodialysis patient cohort that frailty is associated with poorer cognitive test results. Worsening frailty scores, but not worsening cognition, are associated with mortality and hospitalization. However, there is a complex interaction between frailty and cognitive scores in this group. It appears that admissions to the hospital are highest for patients who are severely frail but not cognitively impaired or vice versa. There is a complicated relationship between frailty and cognitive performance that warrants further detailed study.

the interplay between frailty and cognition with respect to mortality and hospitalization in hemodialysis.

METHODS

Study Design

FITNESS is a two-stage study that follows a cohort multiple randomized controlled trial design.[31] The study protocol was approved by the South Birmingham Research Ethics Committee (Ref: 17/WM/0381) and institutional review board assessment of University Hospitals Birmingham NHS Foundation Trust (RRK6082). The first stage is a cross-sectional assessment and long-term follow-up of study participants on maintenance hemodialysis with comprehensive frailty and bioclinical phenotyping at recruitment. The full protocol for the FITNESS study has been described in detail elsewhere.[32] The study is reported in accordance with STROBE guidelines.[33]

Study Setting

Patients were recruited from a single nephrology center located in Birmingham, England that cares for 1 in-center and 10 private provider hemodialysis units across the West Midlands in a mixture of rural and urban settings with a diverse range of ethnic and socioeconomic groups. Eligible patients were identified by electronic patient records and from discussion with clinicians at each dialysis unit. Eligible patients were given written and verbal information before consenting to join the cohort study.

Eligibility Criteria

Inclusion criteria included adults aged 18 and over, anyone receiving regular hemodialysis for at least 3 months, and the ability to give informed consent. The only exclusion criterion was inpatient care within 4 weeks of recruitment unless for vascular access purposes (access dysfunction, excluding access site infection), to avoid confounding with frailty secondary to recent hospitalization.

Baseline Assessment

Baseline assessments of all study participants took place at their relevant dialysis units before and during one of their usual dialysis sessions. To negate the potential effect of the long break from dialysis upon frailty measurements, we avoided assessing participants on Mondays or Tuesdays. Where participants dialyzed twice weekly, the dialysis session after the shortest interval was chosen for baseline assessment.

Study participants completed a number of investigations, which are detailed in our methodology paper.[32] Briefly, before connection to dialysis, participants underwent a timed 4-m walk from standing and bilateral hand-grip strength via dynamometer (Takei Grip D, Takei Scientific Instruments Co Ltd). Once dialysis started, patients were clinically interviewed, including a series of questionnaires including assessments of activities of daily living disability, demography, social history, and frailty-specific questionnaires. Electronic patient records were interrogated for comorbid conditions, drug history, alongside dialysis vintage and adequacy, previous transplantation, and biochemical data. Determination of socioeconomic deprivation was based upon the Index of Multiple Deprivation, a multiple deprivation model calculated according to local area, with 1 representing the most deprived and 5 the least deprived area, respectively.

The FP was determined as a score between 0 and 5, with participants receiving 1 point for each of the following: slow walking speed, weak grip strength, exhaustion, weight loss, and low physical activity (determined by asking 'How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?' with responses of '1-3 times per month' or 'hardly ever or never' indicating low physical activity).[20]

The FI consisted of 32 variables across measuring deficits across multiple body systems, based upon hemodialysis-specific FI from van Munster and colleagues.[20] Each variable was scored out of one by predetermined cutoffs, and the FI comprised a mean average of these scores, giving a continuous variable between 0 and 1. Cognitive impairment comprised one of these deficits, so this was omitted from FI for analyses of association with MoCA scores, giving a composite score of 31 deficits for this particular analysis.

The EFS was determined according to the original study,[34] but to reduce test burden on participants, a 4-m walk was substituted for the timed up and go test. To satisfy EFS scoring criteria, the resulting times were split into tertiles, with the fastest tertile assigned 0 points, the middle tertile 1 point, and the slowest tertile (or unable to walk) 2 points.[21,32] For association with MoCA scores, an amended EFS was used omitting the clock drawing element as this also formed part of the MoCA.

Figure 1. PRISMA flowchart of study participation.

The CFS was determined by the investigator after clinical interview, based upon activities of daily living responses, and given a score between 1-9.[25,35] No participants scored 9 (terminal illness without frailty). All frailty scores were treated as continuous variables for this analysis; further details on frailty scoring are found in the supplementary methods (Item S1) and Tables S1-S3.

MoCA

Study participants completed a MoCA before dialysis connection.[29] Scores on the MoCA range from 0 to 30, with a score of <26 indicating cognitive impairment. The MoCA has been validated in abridged form for the visually impaired by omitting the executive function and naming sections.[36] This protocol was used for participants with visual impairment. A further protocol was devised to perform the MoCA without executive function only for participants with difficulties with manual dexterity. MoCA scores were treated both as raw scores and as a binary measure of cognitive impairment, defined as <26 for participants completing the full MoCA protocol, <21 for participants lacking dexterity, and <18 for visually impaired. Moderate cognitive impairment was defined as MoCA ≤21 for full completion, or ≤18 for participants lacking dexterity, and ≤15 for visually impaired.[37]

Outcomes

Mortality data were obtained by electronic record linkage of all FITNESS study recruits to Office of National Statistics, a UK-wide repository of death certificate data. This ensures robust coverage of mortality data capture and comprehensive description of causality. Electronic patient records, Hospital Episode Statistics were interrogated for hospitalization. Admissions were defined as any hospital episode lasting ≥1 night.

Recruitment

A power calculation was originally performed based upon US data,[38] assuming an adjusted risk ratio of 2.24 for 1-year mortality and 1.56 for 1-year mortality and/or hospitalization for frail versus non-frail patients receiving hemodialysis. A non-frail risk of 5% for 1-year mortality and a 40% risk of 1-year mortality/hospitalization was assumed, powered to 0.8, and with a confidence interval of 0.95. A sample size of 602 was therefore considered to be robustly powered to demonstrate a difference in 1-year mortality or 150 patients to be powered for 1-year mortality/hospitalization. However, in agreement with the sponsor, recruitment of 602 participants was not felt to be feasible in this single center, and a revised target of 500 participants to be recruited was set with follow-up beyond 1 year.

Statistics

Statistical analysis was performed using STATA 17 (Stata Statistical Software, Release 17, StataCorp LLC). Categorical data were presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges. t tests for between age group MoCA comparisons were performed on square-transformed data to satisfy normal distribution and subsequently back-transformed for reporting.

Table 1. Baseline Demographics of FITNESS Study Participants

	No Cognitive Impairment (N = 102)		Cognitive Impairment (N = 346)	
	n/median	%/IQR	n/median	%/IQR
Frailty Phenotype	1	1-3	2	1-3
Frailty Index	0.20	0.11-0.34	0.31	0.20-0.48
Edmonton Frail Scale	6	4-9	8	6-10
Clinical Frailty Scale	4	3-5	5	4-6
Age (y)	58	51-66	65	54-76
Albumin (g/L)	38	35-42	39	35-42
BMI (kg/m^2)	26	23-32	27	23-32
Charlson Index[a,]	4	2-5	5	3-6
HD vintage (mo)	26	10-57	40	19-81
Kt/V	1.58	1.34-1.85	1.61	1.42-1.86
Self-reported change in health				
Better	19	18.6	65	18.8
The same	37	36.3	124	35.8
Worse	46	45.1	157	45.4
IMD Quintile				
1	33	32.4	154	44.5
2	20	19.6	63	18.2
3	23	22.6	60	17.3
4	10	9.8	27	7.8
5	10	9.8	22	6.4
Unknown	6	5.9	20	5.8
Ethnicity				
White	74	72.6	205	59.3
South Asian	14	13.7	70	20.2
Black	11	10.8	63	18.2
Other	3	2.9	8	2.3
Male	63	61.8	194	56.1
Past medical history				
Diabetes mellitus	19	18.6	114	33.0
Myocardial infarction	14	13.7	73	21.1
Congestive cardiac failure	9	8.8	40	11.6
Peripheral vascular disease	10	9.8	35	10.1
Stroke/TIA	4	3.9	51	14.7
Cancer	14	13.7	41	11.9
Smoking status				
Current	16	15.7	51	14.8
Ex	30	29.4	98	28.4
Never	56	54.9	196	56.8
Dialysis via line	32	31.4	75	21.7
Active on transplant list	15	14.7	36	10.4
Employment status				
Employed	33	32.4	33	9.6
Unemployed	28	27.5	107	31.0
Retired	41	40.2	205	59.4
Education level				
High school	41	40.2	269	78.0
College/6th form	34	33.3	54	15.7
University	27	26.5	22	6.4
Residence				
House	75	73.5	248	72.3
Flat	16	15.7	58	16.9
Bungalow	8	7.8	20	5.8

(Continued)

Table 1 (Cont'd). Baseline Demographics of FITNESS Study Participants

	No Cognitive Impairment (N = 102)		Cognitive Impairment (N = 346)	
	n/median	%/IQR	n/median	%/IQR
Warden-controlled flat	2	2.0	10	2.9
Residential home	1	1.0	4	1.2
Nursing home	0	0.0	3	0.9

Note: All values shown n and % or median and IQR.
Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation; IQR, interquartile range; TIA, transient ischemic attack.
[a]Chronic kidney disease omitted from Charlson Score.

Associations between continuous MoCA scores as the dependent variable and continuous frailty scores as an independent variable were explored via linear regression. The linear assumption was satisfied via visual comparison of observed versus Lowess fit lines on scatter plot and augmented component plus residual plots. Robust standard errors were specified to account for heteroscedasticity. Multicollinearity was excluded on all analyses by variance inflation factor <10.

Odds ratios for cognitive impairment were obtained by logistic regression. Linear and logistic regressions were performed on study variables and adjusted for covariables selected a priori for known or suspected relationships with cognitive impairment: known dementia, parathyroid hormone level, hemodialysis vintage, education level, diabetes status, hemoglobin, albumin, smoking status, Patient Health Questionnaire-9 score, and previous cerebrovascular accident.[39]

Survival analyses were performed with the Cox proportional hazards model. The proportional hazard assumption was checked and satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as hazard ratios with 95% confidence intervals).

Incidence rate ratios were obtained for admission count by negative binomial regression, death-censored, and offset by length of follow-up. Negative binomial distribution was confirmed by over-dispersed means and variances and visual interpretation of expected versus observed distribution plots.

Cox and negative binomial regressions were performed treating both frailty and MoCA as continuous independent variables for the main analyses. They included unadjusted analyses with the MoCA as sole independent variable and separate analyses adjusted for each frailty tool as a second independent variable. Further analyses were performed adjusted for an a priori list of covariables, based on a known or suspected relationship with dialysis-related mortality/admission (age, sex, ethnicity [grouped into White, South Asian, Black, and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [chronic kidney disease omitted], number of hospitalization episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, and kidney transplant wait-listing in addition to frailty status).

All interaction analyses were performed on models adjusted for the aforementioned covariables. Contour plots of predicted outcome and marginal effect of MoCA upon

Table 2. Linear Regression of MoCA Scores by Frailty

	β	Lower 95% CI	Upper 95% CI	*P*
Univariable				
Frailty Phenotype	-0.893	-1.21	-0.573	<0.001
Frailty Index[a]	-0.629	-0.852	-0.406	<0.001
Edmonton Frailty Scale[b]	-0.380	-0.553	-0.206	<0.001
Clinical Frailty Scale	-0.959	-1.26	-0.653	<0.001
Multivariable				
Frailty Phenotype	-0.792	-1.12	-0.458	<0.001
Frailty Index[a]	-0.781	-1.05	-0.512	<0.001
Edmonton Frailty Scale[b]	-0.476	-0.669	-0.283	<0.001
Clinical Frailty Scale	-0.904	-1.24	-0.566	<0.001

Note: Negative coefficients indicate that increases in frailty score associate with lower MoCA scores (ie, more severe frailty associates with more severe cognitive impairment). Visually or dexterity impaired participants excluded. Multivariable analysis adjusted for known dementia, PTH, HD vintage, education level, diabetes, hemoglobin, albumin, smoking status, PHQ-9 score, previous CVA.
Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; EFS, Edmonton Frailty Scale; FI, Frailty Index; HD, hemodialysis; MoCA, Montreal Cognitive Assessment; PTH, parathyroid hormone; PHQ-9, Patient Health Questionnaire-9.
[a]Cognitive impairment excluded from FI for this analysis; FI scaled so coefficient corresponds to 0.1 point increase in FI.
[b]Clock-drawing excluded from EFS.

Table 3. Logistic Regression of Cognitive Impairment by Frailty

	OR	Lower 95% CI	Upper 95% CI	*P*
Univariable				
Frailty Phenotype	1.34[a]	1.13[a]	1.58[a]	0.001[a]
Frailty Index[b]	1.19[a]	1.06[a]	1.34[a]	0.004[a]
Edmonton Frailty Scale[c]	1.09[a]	1.00[a]	1.19[a]	0.04[a]
Clinical Frailty Scale	1.33[a]	1.13[a]	1.56[a]	0.001[a]
Multivariable				
Frailty Phenotype	1.19	0.96	1.48	0.11
Frailty Index[b]	1.16	0.97	1.37	0.10
Edmonton Frailty Scale[c]	1.07	0.96	1.21	0.23
Clinical Frailty Scale	1.21	0.99	1.48	0.06

Note: Multivariable analysis adjusted for known dementia, PTH, HD vintage, education level, diabetes, hemoglobin, albumin, smoking status, PHQ-9 score, previous CVA.
Abbreviations: CI, confidence interval; EFS, Edmonton Frailty Scale; FI, Frailty Index; HD, hemodialysis; OR, odds ratio for cognitive impairment; PTH, parathyroid hormone; PHQ-9, Patient Health Questionnaire-9.
[a]Significance at $P < 0.05$ level.
[b]Cognitive impairment excluded from FI for this analysis; FI scaled so coefficient corresponds to 0.1 point increase in FI.
[c]Clock-drawing excluded from EFS.

predicted outcome were generated to explore interactions where these were statistically significant.

To avoid confounding from differing maximum scores, all analyses using MoCA scores as a continuous variable were performed only for participants who completed the full MoCA protocol. Missing Index of Multiple Deprivation Quintile data were handled via a dummy variable. Other missing data were assumed missing at random and handled via listwise deletion as all other covariables had <1% data missing. P values < 0.05 were considered statistically significant.

RESULTS

Study Cohort Demographics

Figure 1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 448 prevalent hemodialysis patients with baseline frailty and MoCA assessments and data linkage. Median follow-up was 685 days (interquartile range: 543-812 days); all participants had a minimum potential follow-up of 365 days from recruitment. Baseline demographics of the FITNESS cohort are described in detail elsewhere.[21] Table 1 shows key demographics stratified by different frailty instruments at study recruitment.

Table 4. Logistic Regression of Moderate Cognitive Impairment by Frailty

	OR	Lower 95% CI	Upper 95% CI	*P*
Univariable				
Frailty Phenotype	1.51	1.31	1.75	<0.001
Frailty Index[a]	1.33	1.20	1.47	<0.001
Edmonton Frailty Scale[b]	1.22	1.13	1.31	<0.001
Clinical Frailty Scale	1.50	1.30	1.73	<0.001
Multivariable				
Frailty Phenotype	1.47	1.23	1.76	<0.001
Frailty Index[a]	1.40	1.22	1.61	<0.001
Edmonton Frailty Scale[b]	1.28	1.16	1.42	<0.001
Clinical Frailty Scale	1.46	1.23	1.74	<0.001

Note: Multivariable analysis adjusted for known dementia, PTH, HD vintage, education level, diabetes, hemoglobin, albumin, smoking status, PHQ-9 score, previous CVA.
Abbreviations: CI, confidence interval; EFS, Edmonton Frailty Scale; FI, Frailty Index; HD, hemodialysis; OR, odds ratio for cognitive impairment; PTH, parathyroid hormone; PHQ-9, Patient Health Questionnaire-9.
[a]Cognitive impairment excluded from FI for this analysis; FI scaled so coefficient corresponds to 0.1 point increase in FI.
[b]Clock-drawing excluded from EFS.

Cognitive Impairment and Frailty

In total, 30 participants completed the visual impairment MoCA protocol, with a further 17 completing the poor dexterity protocol. The median MoCA score was 22 (interquartile range, 19-25). Mean MoCA scores were significantly lower in those over 65 years (21.1; 95% confidence interval, 20.5-21.7) versus those under 65-years (23.2; 95% confidence interval, 22.7-23.8; $P < 0.001$). Overall, 346 (77.2%) participants had some evidence of cognitive impairment.

Table 2 shows simple and multiple linear regression modeling of continuous MoCA scores; greater frailty by each tool was associated with lower MoCA scores. Table 3 shows that each frailty score was associated with higher odds of cognitive impairment on univariable logistic regression, but these associations lost significance upon multivariable analyses. However, Table 4 shows that greater frailty did associate with higher odds of moderate cognitive impairment on multivariable analyses. All fully adjusted linear and logistic regression models are shown in Tables S4-S11.

Mortality and Hospitalization

Total participant follow-up was 799.3 patient-years, during which there were 103 (23.0%) deaths and 1,120 admissions of at least one night. Three hundred twenty-six (72.8%) participants had at least one hospital admission during follow-up; median admissions were 2 (interquartile range, 0-4).

Table 5. Unadjusted and Adjusted Cox Regression Models of Mortality Associated With Continuous Frailty and MoCA Scores

Frailty Tool in Model	Variable	HR	Lower 95% CI	Upper 95% CI	*P*
Unadjusted					
-	MoCA only	0.99	0.95	1.03	0.66
Frailty Phenotype	MoCA	1.02	0.97	1.06	0.52
	FP	1.43[a]	1.22[a]	1.66[a]	<0.001[a]
Frailty Index	MoCA	1.02	0.97	1.07	0.42
	FI[b]	1.25[a]	1.12[a]	1.38[a]	<0.001[a]
Edmonton Frailty Scale	MoCA	1.02	0.98	1.07	0.36
	EFS	1.17[a]	1.08[a]	1.26[a]	<0.001[a]
Clinical Frailty Scale	MoCA	1.02	0.97	1.06	0.51
	CFS	1.41[a]	1.19[a]	1.67[a]	<0.001[a]
Adjusted					
-	MoCA only	1.00	0.95	1.05	0.88
Frailty Phenotype	MoCA	1.01	0.96	1.07	0.76
	FP	1.22[a]	1.00[a]	1.48[a]	0.05[a]
Frailty Index	MoCA	1.01	0.96	1.07	0.62
	FI[b]	1.21[a]	1.05[a]	1.39[a]	0.007[a]
Edmonton Frailty Scale	MoCA	1.01	0.96	1.07	0.72
	EFS	1.08	0.98	1.20	0.13
Clinical Frailty Scale	MoCA	1.01	0.95	1.06	0.79
	CFS	1.32[a]	1.07[a]	1.64[a]	0.01[a]

Note: Obtained by Cox proportional hazards analysis. Multivariable analysis adjusted for age, sex, ethnicity (grouped into White, South Asian, Black, and other ethnicities), body mass index, index of multiple deprivation, Charlson comorbidity index (chronic kidney disease omitted), number of hospitalization episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, and kidney transplant wait-listing in addition to frailty status.
Abbreviations: CI, confidence interval; CFS, Clinical Frailty Scale; EFS, Edmonton Frailty Scale; FI, Frailty Index; FP, Frailty Phenotype; HR, hazard ratio; MoCA, Montreal Cognitive Assessment.
[a]Significance at the $P < 0.05$ level.
[b]FI scaled so HRs correspond to 0.1 point increase in FI.

Mortality and Cognition

Table 5 shows that MoCA scores were not associated with mortality on univariable or multivariable analyses. Full models are shown in Tables S12-S16. Higher frailty scores were associated with mortality on univariable analyses and upon multivariable analyses for the FP, FI and CFS. No significant interactions between frailty and cognition were identified upon mortality.

Hospitalization and Cognition

Table 6 demonstrates no association between MoCA score and rates of admission on univariable or multivariable analyses. Higher frailty scores were associated with higher rates of admission on univariable analyses, but only the CFS retained this association upon multivariable analysis.

There was a significant interaction between MoCA and frailty scores upon rates of admissions for the FI ($P = 0.002$ for interaction) and CFS ($P = 0.005$). There were no significant interactions between MoCA and FP or EFS scores. Figure 2 is a composite contour plot to visualize the effect of changes in both FI and CFS frailty and MoCA scores upon association with predicted admission rates. Predicted admissions were highest when there was greatest discordance between severity of frailty and cognitive impairment. The marginal effects of both frailty and MoCA upon predicted admissions were highest at the extremes of cognition and frailty; each increase in either frailty or MoCA score reduced predicted admissions in less frail individuals, particularly at low MoCA scores. Conversely each increase in frailty or MoCA score increased predicted admissions in more frail participants, particularly at high MoCA scores. Fully adjusted final models are shown in Tables S17-S21.

DISCUSSION

Cognitive impairment is common in hemodialysis recipients[1,2] and has been associated with mortality.[6-8] However, the interplay between frailty, cognitive impairment and outcomes among hemodialysis patients has not been fully explored, and our analysis offers novel insights that have not been previously described. In this study, we report cognitive impairment is highly prevalent in a large single-center hemodialysis cohort of adults greater than 18 years old. Regardless of definition, increasing frailty is associated with lower MoCA scores and moderate cognitive impairment in prevalent hemodialysis recipients. Lower MoCA scores are not associated with either mortality or hospitalization, although some frailty tools interact with MoCA upon rates of admission. Predicted admissions are highest where there was discordance between frailty and cognition, severe frailty with no cognitive impairment, or vice versa. Predicted admissions were fewest in the absence of frailty or cognitive impairment,

Table 6. Incidence Rate Ratios of Hospital Admissions by MoCA and Frailty Scores

Frailty Tool in Model	Variable	IRR	Lower 95% CI	Upper 95% CI	*P*
Unadjusted					
-	MoCA only	1.00	0.98	1.03	0.92
Frailty Phenotype	MoCA	1.02	0.99	1.04	0.24
	FP	1.21[a]	1.11[a]	1.32[a]	<0.001[a]
Frailty Index	MoCA	1.02	0.99	1.04	0.18
	FI[b]	1.17[a]	1.10[a]	1.25[a]	<0.001[a]
Edmonton Frailty Scale	MoCA	1.03	1.00	1.06	0.05
	EFS	1.12[a]	1.08[a]	1.17[a]	<0.001[a]
Clinical Frailty Scale	MoCA	1.02	0.99	1.04	0.24
	CFS	1.26[a]	1.16[a]	1.38[a]	<0.001[a]
Adjusted					
-	MoCA only	1.01	0.99	1.04	0.39
Frailty Phenotype	MoCA	1.01	0.99	1.04	0.34
	FP	1.04	0.94	1.14	0.46
Frailty Index	MoCA	1.06	0.98	1.14	0.13
	FI[b]	1.02	0.99	1.04	0.25
Edmonton Frailty Scale	MoCA	1.02	0.99	1.04	0.25
	EFS	1.03	0.98	1.08	0.31
Clinical Frailty Scale	MoCA	1.02	0.99	1.04	0.21
	CFS	1.15[a]	1.04[a]	1.26[a]	0.006[a]

Note: Obtained by negative binomial regression. Bold text indicates significance at $P < 0.05$ level. Multivariable analysis adjusted for age, sex, ethnicity (grouped into White, South Asian, Black, and other ethnicities), body mass index, index of multiple deprivation, Charlson comorbidity index (chronic kidney disease omitted), number of hospitalization episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, and kidney transplant wait-listing in addition to frailty status.

Abbreviations: CI, confidence interval; CFS, Clinical Frailty Scale; EFS, Edmonton Frailty Scale; FI, Frailty Index; FP, Frailty Phenotype; IRR, incidence rate ratio; MoCA, Montreal Cognitive Assessment.

[a]Significance at $P < 0.05$ level.

[b]FI scaled so IRRs correspond to 0.1 point increase in FI.

and perhaps surprisingly in the setting of severe frailty with severe cognitive impairment. The marginal effect of MoCA scores upon predicted admissions was greater where the discordance between frailty and cognitive impairment was highest. Finally, increases in frailty or MoCA scores augmented predicted admissions in severely frail participants without cognitive impairment but decreased predicted admissions in the not frail but severely cognitively impaired. To our knowledge, these are the first reported data to suggest such an interaction between cognition and frailty, which should stimulate further exploration and validation in other cohorts. Studies to assess frailty interventions should include cognition as an outcome of interest.

In contrast with other hemodialysis cohorts, we did not identify an association between cognitive impairment and mortality. This may be partly explained by different definitions of cognitive impairment. Kurella and colleagues[10] found that known or suspected dementia on clinical noting review was associated with increased mortality risk. This large study is nevertheless limited by reliance upon an indirect measure of cognitive impairment in an exclusively elderly cohort. In our analyses that were adjusted for age, we did not identify any interaction between age and MoCA on mortality or hospitalization episodes. Therefore, age does not appear to satisfactorily explain the differential results. van Zwieten and colleagues[8] have reported increased mortality in cognitive impairment on neurocognitive assessment. Drew and colleagues[7] also report that poorer executive function was associated with all-cause mortality. Interestingly, Mini Mental State Examination scores were not associated with mortality,[7] which we may consider to be a similar cognitive screening tool to the MoCA. These latter 2 studies have the benefit of more detailed cognitive assessment and were performed on hemodialysis recipients of all adult ages. It can be speculated that this greater degree of granular data increases the sensitivity for mortality.

In our study, we describe for the first time that frailty is associated with poorer cognition in a prevalent hemodialysis recipient of all adults aged greater than 18 years. Furthermore, we have demonstrated that—while cognition was not associated with mortality or hospitalization in its own right—there is a statistically significant interaction between cognition and frailty in association with hospitalization. It is interesting that both the predicted admissions, and the marginal effect of MoCA scores upon those predicted admissions, were greater where the greatest discordance was observed between severity of cognitive impairment and of frailty. Figure 2 helps visualize this interaction; it is striking that the marginal effect of an increase in MoCA score (ie, better cognition) is strongly positive upon predicted admissions in those with higher frailty scores (ie, more severe frailty). Potential explanations for these phenomena range from the simple to the more speculative. It is

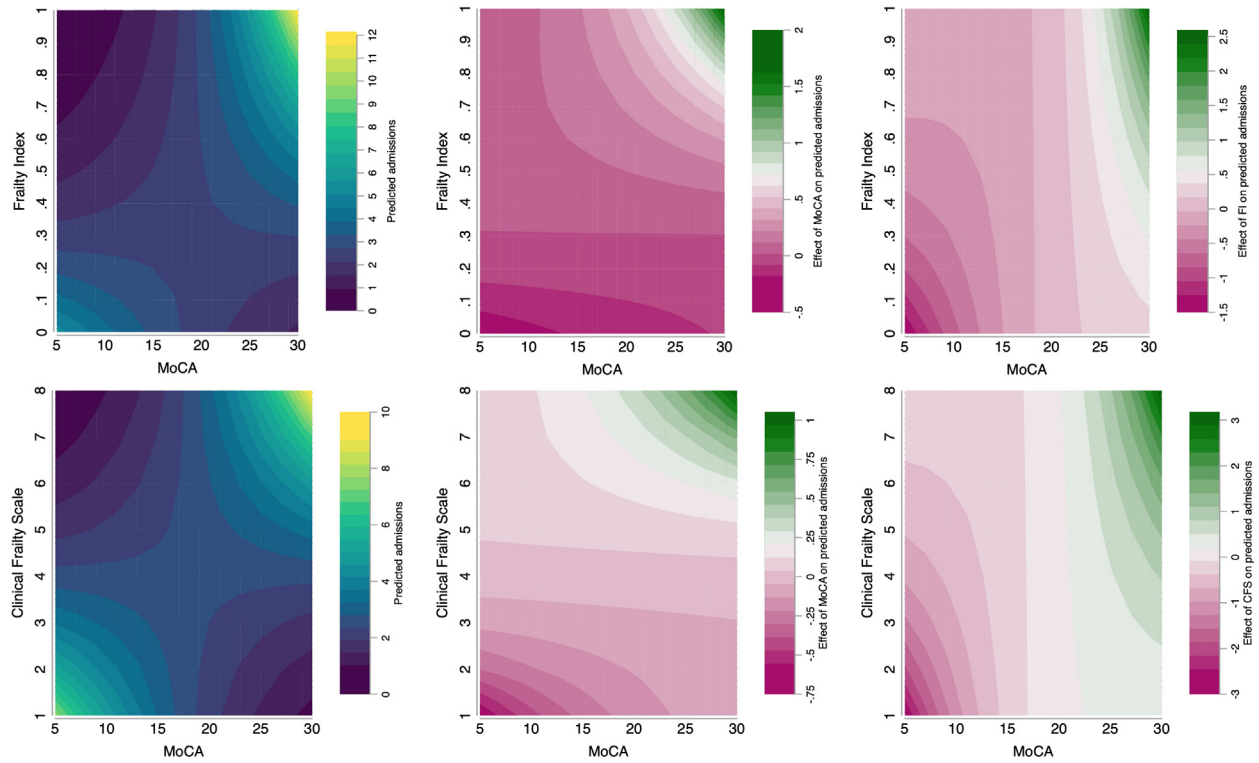

Figure 2. Interaction contour plot of predicted admissions, and marginal effects of MoCA and frailty scores upon predicted admissions, after negative binomial regression. Interactions between MoCA scores with FI (top row) and CFS (bottom row) shown. The leftmost contour plots display predicted number of admissions during follow-up at combinations of the MoCA (x-axes) and frailty scores (y-axes). Yellow coloring indicates greatest predicted admissions, and dark blue fewest predicted admissions. The center graphs demonstrate the effect of each one-point increase in MoCA score upon predicted number of admissions. The rightmost graphs demonstrate the effect of each one-point increase in CFS score or 0.1-point increase in FI upon predicted number of admissions. For each of these, dark green indicates a more positive effect upon predicted admissions for each increase in the independent variable, whereas dark purple indicates a more negative effect of each increase in the independent variable of interest. Abbreviations: FI, Frailty Index; MoCA, Montreal Cognitive Assessment.

intuitive that those who are neither frail nor cognitively impaired are likely to require relatively few admissions. However, we may speculate that those experiencing both severe frailty and severe cognitive impairment may be subject to considerable admission avoidance efforts by caregivers and medical providers. We may also posit that those with severe frailty but with good cognition may be more likely to seek medical attention for the sequelae of their frailty. Furthermore, severe cognitive impairment in the absence of functional impairment may present significant challenges to caregivers, resulting in greater hospital admissions; increases in MoCA score are associated with fewer predicted admissions in those who were less frail.

FITNESS is, to our knowledge, the largest prospective cohort study to compare frequently used frailty tools in hemodialysis, the first to compare their associations with both mortality and hospitalization, and the first to suggest that cognitive impairment may modulate the associations of frailty with admissions. Further strengths include diversity of demographics, comorbid conditions, and socioeconomic backgrounds representative of the local population.[40] However our data should be interpreted with caution in non-English populations, and validation of our findings elsewhere is required. A limitation of FITNESS is the single cross-sectional assessment, as frailty is a dynamic state, with year-by-year variability observed.[41] As a prevalent cohort—albeit with adjustment for dialysis vintage in analyses—our findings are not directly translatable to incident hemodialysis. There were small variations in application of frailty tool criteria from other studies. The CFS was derived after clinical interview but omitted the multidisciplinary discussion as in the original validation cohort.[25] However, our CFS closely represents real-world application of the tool in clinical practice.[35] Our FP included questionnaire responses regarding energy expenditure, rather than a Minnesota Leisure Time Questionnaire, in keeping with work in another hemodialysis cohort.[20] Our EFS included a 4-m walk in lieu of a timed up and go test; we would argue it also tests muscle function but may still have influenced results. Our definition of cognitive impairment included participants who were either visually impaired or unable to write, with proportionate reductions in thresholds for cognitive

impairment in each case. Omitting executive function for those with impaired dexterity lacks validation but is in keeping with previous work on MoCA adjustment for visual impairment. However, such a strategy may influence results, particularly because executive function is a major contributor to cognitive impairment in hemodialysis recipients.[37,42] In another limitation, some 95% confidence intervals crossed the point of no effect by small margins, raising the possibility of type II error. Finally, although these data describe associations, caution should be exercised when considering the applicability of these findings to the individual hemodialysis recipient in clinical practice.

To conclude, in a large prevalent hemodialysis cohort, increasing frailty scores—however defined—were associated with lower MoCA scores, but not with increased odds of cognitive impairment. There is an interaction between MoCA scores and frailty upon the association with hospitalization, but MoCA is not independently associated with hospitalization or mortality. The MoCA may therefore offer added discriminative value in identifying higher risk hemodialysis populations with both high and low degrees of frailty. These results should stimulate further exploration of the interplay between frailty and cognitive impairment, particularly with regards to adverse outcomes.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Supplementary methods; description of how frailty, vulnerability and robustness defined

Table S1: Frailty Phenotype

Table S2: Frailty Index

Table S3: Edmonton Frailty Scale

Table S4: Multiple Linear Regression of MoCA Score by Frailty Phenotype

Table S5: Multiple Linear Regression of MoCA Score by Frailty Index

Table S6: Multiple Linear Regression of MoCA Score by Edmonton Frailty Scale

Table S7: Multiple Linear Regression of MoCA Score by Clinical Frailty Scale

Table S8: Multivariable Logistic Regression of Cognitive Impairment by Frailty Phenotype

Table S9: Multivariable Logistic Regression of Cognitive Impairment by Frailty Index

Table S10: Multivariable Logistic Regression of Cognitive Impairment by Edmonton Frailty Scale

Table S11: Multivariable Logistic Regression of Cognitive Impairment by Clinical Frailty Scale

Table S12: Fully Adjusted Cox Proportional Hazards Model of MoCA Scores Associated With Mortality Hazard

Table S13: Fully Adjusted Cox Proportional Hazards Model of Mortality by MoCA and FP Scores

Table S14: Fully Adjusted Cox Proportional Hazards Model of Mortality by MoCA and FI Scores

Table S15: Fully Adjusted Cox Proportional Hazards Model of Mortality by MoCA and EFS Scores

Table S16: Fully Adjusted Cox Proportional Hazards Model of Mortality by MoCA and CFS Scores.

Table S17: Fully Adjusted Model of Rates of Admission Associated With MoCA Scores

Table S18: Fully Adjusted Model of Rates of Admission Associated With MoCA Scores. FP Included in Model

Table S19: Fully Adjusted Model of Rates of Admission Associated With MoCA Scores. FI Included in Model

Table S20: Fully Adjusted Model of Rates of Admission Associated With MoCA Scores. EFS Included in Model

Table S21: Fully Adjusted Model of Rates of Admission Associated With MoCA Scores. CFS Included in Model

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Benjamin M. Anderson, MB, ChB, Muhammad Qasim, MBBS, Gonzalo Correa, MD, Felicity Evison, MSc, Suzy Gallier, MSc, Charles J. Ferro, MD, Thomas A. Jackson, PhD, and Adnan Sharif, MD

Authors' Affiliations: Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Birmingham, UK (BMA, MQ, CJF, AS); Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK (BMA, TAJ); Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK (MQ, AS); Department of Nephrology, Hospital del Salvador, Santiago, Chile (GC); Department of Health Informatics, Queen Elizabeth Hospital, Birmingham, UK (FE, SG); PIONEER: HDR-UK hub in Acute Care, Edgbaston, Birmingham, UK (SG); Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK (CJF); and Department of Healthcare for Older People, Queen Elizabeth Hospital, Birmingham, UK (TAJ)

Address for Correspondence: Dr. Adnan Sharif, Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2WB, United Kingdom. Email: adnan.sharif@uhb.nhs.uk

Authors' Contributions: Research idea and study design: BMA, TAJ, AS; Data acquisition: BMA, MQ, GC, FE, SG, AS; Data analysis/interpretation: BMA, AS; Statistical Analysis: BMA, FE, AS; Supervision and mentorship: CJF, TAJ, AS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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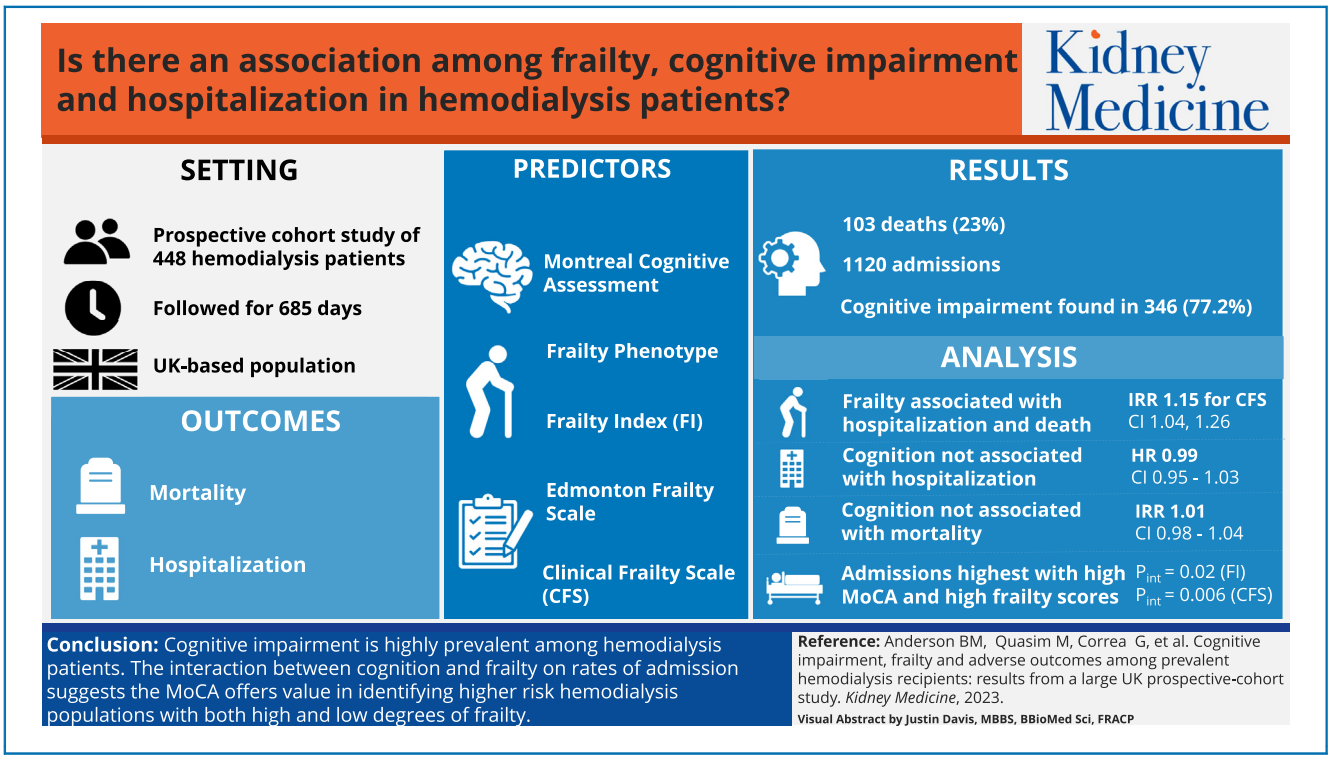
Is there an association among frailty, cognitive impairment and hospitalization in hemodialysis patients?
Kidney Medicine
SETTING
Prospective cohort study of 448 hemodialysis patients
Followed for 685 days
UK-based population
OUTCOMES
Mortality
Hospitalization
PREDICTORS
Montreal Cognitive Assessment
Frailty Phenotype
Frailty Index (FI)
Edmonton Frailty Scale
Clinical Frailty Scale (CFS)
RESULTS
103 deaths (23%)
1120 admissions
Cognitive impairment found in 346 (77.2%)
ANALYSIS
Frailty associated with hospitalization and death
IRR 1.15 for CFS
CI 1.04, 1.26
Cognition not associated with hospitalization
HR 0.99
CI 0.95 - 1.03
Cognition not associated with mortality
IRR 1.01
CI 0.98 - 1.04
Admissions highest with high MoCA and high frailty scores
P_int = 0.02 (FI)
P_int = 0.006 (CFS)
Conclusion: Cognitive impairment is highly prevalent among hemodialysis patients. The interaction between cognition and frailty on rates of admission suggests the MoCA offers value in identifying higher risk hemodialysis populations with both high and low degrees of frailty.
Reference: Anderson BM, Quasim M, Correa G, et al. Cognitive impairment, frailty and adverse outcomes among prevalent hemodialysis recipients: results from a large UK prospective-cohort study. Kidney Medicine, 2023.
Visual Abstract by Justin Davis, MBBS, BBioMed Sci, FRACP