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Depressive symptoms, frailty, and mortality among dialysis patients

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Abstract

Introduction: Frailty and depression are highly prevalent in the dialysis population, but the association between them, the risk factors for their development, and their independent associations with mortality have not been studied.

Methods: We examined 771 patients enrolled in the ACTIVE/ADIPOSE prevalent dialysis cohort study. Fried's frailty phenotype and the Center for Epidemiologic Studies Depression score were used to determine frailty and presence of depressive symptoms, respectively. We assessed the baseline association between frailty and depressive symptoms, whether one entity is a risk factor for development of the other, and associations between frailty and depressive symptoms with mortality.

Findings: At baseline, 13.1% of our population screened positive for depressive symptoms, 21.8% met criteria for frailty, and 10.0% met criteria for both. During follow-up, 26.6% of our population developed frailty and 12.7% developed depressive symptoms. Using multivariable logistic regression, baseline depressive symptoms were associated with 2.14-fold higher odds of being frail at baseline (95% confidence interval [CI] 1.45–3.17) and with a 2.16-fold higher odds of incident frailty during follow-up (95% CI 1.22–3.82). However, baseline frailty was not associated with incident depressive symptoms. Frailty and depressive symptoms were independent predictors of mortality in time-varying survival analysis (meeting frailty criteria: hazard ratio [HR] 1.53, 95% CI 1.05–2.23; depressive symptoms: HR 2.21,95% CI 1.50–3.25).

Discussion: Frailty and depressive symptoms remained highly prevalent over time and were strongly associated with one another and independently associated with mortality among dialysis

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AUTHOR CONTRIBUTIONS

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patients. Future studies should investigate whether interventions for depression could potentially mitigate the appearance of frailty and its associated poor outcomes.

Keywords

Frailty; depression; dialysis; outcomes; United States Renal Data System

INTRODUCTION

Approximately 30% of dialysis patients are frail and 20% are depressed, which is considerably higher than the prevalence of these conditions among community-dwelling elders.[1–6] Frailty and depression are dynamic conditions that are distinct but interrelated in the nondialysis population.[3,7,8] In cross-sectional studies, frail elderly individuals have higher odds of comorbid depression than their nonfrail counterparts (odds ratio [OR] 3.95, 95% confidence interval [CI] 2.36–6.58), and depressed elders have higher odds of being frail (OR 4.07, 95% CI 1.93–8.55).[3] Furthermore, frailty and depression share several risk factors, such as chronic inflammation, oxidative stress, mitochondrial dysfunction, hypothalamic-pituitary axis dysregulation, and vascular disease.[3] However, it is possible that kidney disease may modify the complex relationship between frailty and depression, given that these risk factors are also prevalent among patients with chronic kidney disease.[9–12]

Frailty and depression have been separately associated with higher mortality in dialysis and nondialysis populations.[1,5,13–15] Among nondialysis populations, the simultaneous presence of both conditions is associated with even poorer outcomes than the presence of either condition alone.[3,16] However, the independent contributions of frailty and depression to poor outcomes have not been investigated in the hemodialysis population. Furthermore, given the interrelated nature of frailty and depression, it is unclear if one is a factor in the development of the other or if there are any other risk factors associated with the development of frailty and depression. In this study, we investigated associations between frailty and depressive symptoms among hemodialysis patients, factors related to incident frailty and depressive symptoms, and whether frailty and depressive symptoms are independent predictors of mortality. We hypothesized that depressive symptoms and frailty would be associated with each other and that both would be independently associated with mortality.

METHODS

Study design and participants

We used data from the ACTIVE/ADIPOSE (A Cohort to Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD) study, a United States Renal Data System (USRDS) special study conducted by the Nutrition and Rehabilitation/Quality of Life Special Studies Centers that enrolled 771 prevalent dialysis patients from the Atlanta and San Francisco Bay areas between June 2009 and August 2011.[17] Adult patients (≥18 years of age) who were English or Spanish speaking, on dialysis for at least 3 months, and capable of providing informed consent were enrolled at 14 dialysis centers. Patients were excluded if they were scheduled for living donor renal transplantation or planning to change to another dialysis center or to peritoneal dialysis within the next 6

months. Patients were assessed for frailty and depressive symptoms at baseline and after 12 and 24 months. The study was approved by the institutional review boards at the University of California, San Francisco and Emory University, and all patients provided written informed consent. Participants were actively followed over the course of 2 years with study visits and assessments at baseline, 12 months, and 24 months.

Frailty

Physical frailty was determined using the Fried frailty phenotype, which classifies individuals meeting 3 or more of the following 5 criteria as frail[4]: weight loss, exhaustion, low physical activity, weakness, and slow gait speed. Weight loss was determined by asking individuals if they had greater than 10 pounds of unintentional weight loss over the preceding 12 months. Exhaustion was defined as having a positive response to two questions regarding endurance and energy from the Center for Epidemiologic Studies Depression (CES-D) scale questionnaire [the question is asked “How often in the last week did you feel this way?”, and the following two statements are read: (1) I felt that everything I did was an effort; (2) I could not get going].[4] Low physical activity was obtained using the Modified Minnesota Leisure Time Physical Activity questionnaire. Grip strength was assessed using a handheld dynamometer. Meeting the criterion for low grip strength (i.e., weakness) was established using the average of three measurements of the stronger hand according to norms defined according to sex and body mass index (BMI). Meeting the low gait speed criterion was defined using the faster of two 15-ft walking trials at an individual’s usual pace using standard cut-points based on sex and height.

Depressed state

The depressed state (i.e., depressive symptoms) was determined using the CES-D scale, a 20-item questionnaire with scores ranging from 0 to 60 and higher scores indicating worse symptoms of depression. The CES-D has been validated and used as a depression screening tool among dialysis patients.[14,18,19] We considered a score of greater than 16 to be a positive screen for depressive symptoms in our study.

Mortality

Although ACTIVE/ADIPOSE ended in August 2013, we continued to follow patients through linkage to the USRDS to ascertain mortality outcomes through March 31, 2015.

Covariates

Covariates in cross-sectional and longitudinal analyses included age, race (white, black, and other), sex, body mass index (BMI), comorbid conditions (diabetes, congestive heart failure, and coronary artery disease), and inflammatory markers (serum interleukin-6 [IL-6] and serum C-reactive protein [CRP] concentrations). We selected these variables a priori as potential confounders in the relationship between depressive symptoms and frailty. Given that some of our covariates were not normally distributed and the association between frailty and BMI may not necessarily be linear, we performed a sensitivity analysis in which BMI, IL-6, and CRP were treated as categorical variables (BMI categorized per World Health Organization categories, IL-6 and CRP categorized in quintiles). Age, race, sex, and

comorbidities were extracted from the USRDS Medical Evidence file (CMS form 2728) and through chart review at the baseline study visit. Blood samples were collected before a midweek dialysis session at or around the baseline, 12-month, and 24-month clinical visits, and samples were stored at —196°C until analysis.[7]

Statistical analysis

We summarized participant characteristics at baseline among four groups corresponding to frailty and depressive symptoms (neither met criteria for frailty nor depressive symptoms, screened positive for depressive symptoms only, met criteria for frailty only, met criteria for both) using means and standard deviations for normally distributed variables, medians with interquartile ranges for non-normally distributed variables, and percentages for categorical variables. Differences between groups were tested using ANOVA or Kruskal-Wallis tests, as appropriate.

Associations between frailty and depressive symptoms

We assessed the relationship between depressive symptoms and frailty at baseline using logistic regression. Given the potential overlap in our definitions of frailty and depressive symptoms (i.e., two CES-D questions used to define the exhaustion criterion), we removed these two questions from the CES-D score while maintaining the same cut-off score (i.e., >16) to determine a positive screen.

We then assessed the association between baseline depressive symptoms and incident frailty during the study period using logistic regression. Incident frailty was defined as meeting frailty criteria at the 12 or 24-month visit among those who were not frail at baseline. To account for patients who died, were transplanted, or were lost to follow up prior to the end of the study, we performed a 50-fold single imputation using a logistic regression model for a binary change in frailty status with baseline covariates and death as a predictor. Patients without complete baseline data were excluded in this analysis (n = 23 for frailty and 20 for depressive symptoms). We tested for interactions between age and depressive symptoms. We also performed a sensitivity analysis in which we assumed that all patients who died during the study period became frail prior to death.

To ascertain whether any association between depressive symptoms and incident frailty was linked only through development of exhaustion, we examined the association between baseline depressive symptoms and development of individual components of the frailty construct.

We used a similar multivariable analysis strategy to examine the association between baseline frailty and incident depressive symptoms, defined similarly to incident frailty.

Associations of frailty and depressive symptoms with mortality

We used multivariable Cox models to examine associations between baseline frailty and depressive symptoms with mortality. Patients were censored at the time of transplant or loss to follow up. We then performed a Cox model incorporating time-varying frailty and depressive symptom status to ascertain whether longitudinal assessments were more strongly

associated with mortality compared to using only information obtained at baseline. Longitudinal laboratory data were also included in our models. We also tested for interaction between frailty and depressive symptoms in these models. All statistical analyses were performed using Stata, Version 14.2 (Stata Corp., College Station, TX, USA).

RESULTS

Patient characteristics

Of 746 patients who were enrolled and had data to ascertain both frailty and depressive symptoms at baseline (96.8% of the total cohort of 771 patients), 98 (13.1%) screened positive for depressive symptoms only, 13,663 (21.8%) met frailty criteria only, and 75 (10.0%) screened positive for depressive symptoms and met criteria for frailty at baseline (Table 1). Among patients who met criteria for frailty at baseline, 31.5% also screened positive for depressive symptoms, and among patients who screened positive for depressive symptoms at baseline, 43.4% also met criteria for frailty. Characteristics of the patients according to baseline frailty and depressive symptoms are shown in Table 1. Compared to patients who were not frail and screened negative for depressive symptoms, patients who were frail and had depressive symptoms were older, more likely to be diabetic, had lower education status, and had lower albumin, lower prealbumin, higher IL-6, and higher CRP levels.

Associations between depression and frailty at baseline

In multivariable analysis, depressive symptoms at baseline were associated with 2.14-fold higher odds of being frail at baseline (95% CI 1.45–3.17) (Table 2). Specifically, we found that screening positive for depressive symptoms was associated with meeting the weight loss (OR 2.13, 95% CI 1.48–3.06) and exhaustion (OR 3.87, 95% CI 2.69–5.06) criteria (Table 2). We did not find any statistically significant interaction with age in our analysis. Sensitivity analysis in which BMI, IL-6, and CRP were treated as categorical variables resulted in similar results.

Longitudinal associations between depressive symptoms and frailty

The prevalence of depressive symptoms and frailty remained relatively stable over the 2 years of active follow-up (Figure 1). During this period, 104 patients died and 159 left the study (transplant, transfer to a nonstudy facility, etc.).[7] One hundred thirty-five of the 508 patients (26.6%) who were not frail at baseline developed incident frailty during follow-up. In our primary analysis, screening positive for depressive symptoms at baseline was associated with incident frailty compared to patients who screened negative for depressive symptoms at baseline (OR 2.28, 95% CI 1.27–4.07; P = 0.006). In a sensitivity analysis, we assessed only patients with complete data (357 individuals) and found that screening positive for depressive symptoms at baseline was associated with 2.16-fold higher odds of incident frailty during the follow-up time in multivariable models (95% CI 1.18–3.95; P = 0.01). An additional sensitivity analysis in which we assumed that all patients who died during the study period were frail prior to their death did not substantively change our results (data not shown).

In addition to overall frailty, baseline depressive symptoms were associated with developing the exhaustion (OR 2.40, 95% CI 1.27–4.53; P = 0.007) and low gait speed (OR 1.87, 95% CI 1.07–3.27; P = 0.03) components of frailty (Table 3). This was also confirmed in our sensitivity analysis utilizing only complete data (Table 3).

Association of frailty with incident depressive symptoms

In assessing incident depressive symptoms, 73 of 573 patients (12.7%) who screened negative for depressive symptoms at baseline later developed incident depressive symptoms. Being frail at baseline was associated with a 1.26-fold higher odds of later developing depressive symptoms (95% CI 0.68–2.30; P = 0.46) that was not statistically significant. In our complete case analysis (363 individuals), there was no substantial change in our estimate (OR 1.20, 95% CI 0.66–2.22; P = 0.54).

Associations with mortality

Screening positive for depressive symptoms, frailty, or both at baseline was associated with higher risk of mortality compared to patients who screened negative for both (Figure 2). In a multivariable Cox model incorporating baseline frailty and depressive symptoms, we found that baseline frailty (hazard ratio [HR] 1.40, 95% CI 1.07–1.83; P = 0.01) and baseline depressive symptoms (HR 1.43, 95% CI 1.07–1.92; P = 0.02) were independently associated with a higher risk of mortality. There was no statistically significant interaction between depressive symptoms and frailty status at baseline.

When we incorporated longitudinal data into a time-varying covariate Cox model, frailty and depressive symptoms remained independently predictive of mortality compared to using baseline assessments alone (meeting frailty criteria at any time point: HR 1.53, 95% CI 1.05–2.23; P = 0.03; depressive symptoms at any time point: HR 2.21, 95% CI 1.50–3.25; P < 0.001).

DISCUSSION

In this study, the prevalence of frailty and depressive symptoms was higher among dialysis patients than has been reported among community-dwelling elders,[3] and this high prevalence persisted over 2 years. There was a significant association between depressive symptoms and frailty at baseline, which appears to be similar in magnitude to what has been observed in the nondialysis population (pooled OR 2.64, 95% CI 1.59–4.37 in meta-analysis).[3] We observed an association between baseline depressive symptoms and incident frailty, which appeared to be driven mainly by development of exhaustion and slow gait speed. Interestingly, we did not see evidence of the complementary association between baseline frailty and incident depressive symptoms. Both frailty and depressive symptoms were independently associated with higher mortality compared to patients who were not frail and did not have depressive symptoms. Results of our time-varying Cox analysis further suggested that the presence of depressive symptoms or frailty at time points beyond baseline continued to be predictive of mortality.

To further understand the association between depressive symptoms and frailty, we attempted to assess each as a risk factor for the development of the other. Interestingly, our

findings appear to suggest a unidirectional association, whereby the existence of depressive symptoms is associated with the development of frailty and not vice versa. We hypothesized that depressive symptoms and incident frailty may be causally linked through the development of exhaustion and low physical activity (criteria identified by report rather than measurement). Exhaustion was more likely to develop among patients with depressive symptoms as hypothesized, but slow gait speed was the only other component of frailty to be significantly more likely to develop. However, all frailty criteria were at least slightly more likely to develop among patients who screened positive for depression at baseline.

In nondialysis populations, previous studies suggest a bi-directional relationship between frailty and depression. A meta-analysis involving 6404 community-dwelling older adults showed that baseline depression was associated with 3.72-fold higher risk of incident frailty over an average of 2.9 years (95% CI 1.95–7.08), and a separate pooled analysis of 4852 individuals reported that frailty at baseline was associated with a 90% higher risk of depression over 1–4 years (OR 1.90, 95% CI 1.55–3.32).[3,20] The relatively small number of outcomes in our study precludes definitive evidence that frail dialysis patients are not more likely to develop depressive symptoms, but we hypothesize that individuals who are already frail but do not have depressive symptoms may be able to maintain a good outlook on their health despite physical limitations.[21]

Our time-varying analyses suggest that monitoring symptoms of depression and frailty at regular intervals could continue to identify patients at risk of adverse outcomes. Although it remains unclear whether changes to depressive symptoms and frailty status (e.g., with treatment) can change the risk of mortality, our results show that being neither frail nor having depressive symptoms at any time point was associated with lower risk of mortality. These findings raise the intriguing possibility that treatment of depression could prevent frailty or that intervention to address depression or frailty could improve survival. Although this possibility has not been tested in the ESRD population, studies have suggested that successful treatment of depression may improve physical and social activity levels leading to reductions in frailty among communitydwelling individuals.[3,20] Similarly, exercise interventions may reduce physical frailty and lead to improved mood and decreased depression in dialysis patients.[22–26] Treatment of frailty and depression already appears to improve the quality of life of dialysis patients, a direct benefit even without considering a possible effect on mortality.[27] However, further studies are needed to assess if these interventions can truly affect long-term outcomes such as mortality and hospitalizations.

The strength of our study lies in our novel assessment of longitudinal measures of depressive symptoms and frailty allowing us to determine risk factors leading to their development. Our large population, along with a high prevalence and incidence of both frailty and depressive symptoms, allowed us to obtain estimates for the association between the two. The high mortality and drop-out rates in our population is a potential limitation that we addressed by using single imputation to assess for incident frailty and depressive symptoms for patients who died, were transplanted, or were lost to follow up as censoring for death was likely noninformative. It was reassuring that our sensitivity analysis utilizing only complete cases yielded similar results, suggesting that our assessment was robust. We believe that the use of Fried’s frailty phenotype, allowing for direct comparison with other populations of interest,

was another strength of the study. Although there is no consensus definition of frailty, and multiple operational definitions of frailty have been reported in the literature,[28] Fried's construct has been utilized most often in the geriatric[28] and dialysis[29] populations. However, although the Fried frailty phenotype has been shown to be associated with adverse outcomes in the dialysis population, there are potential limitations of some of the individual components. The weight loss criterion of the Fried frailty phenotype relies on patient self-report and does not consider the composition of the weight loss, which might be less informative than a more objective measure of loss of muscle mass. Measures of grip strength can be affected by arthritis, and although the CES-D scale has been shown to be associated with the stage of exercise reached in graded exercise tests, there are limited studies assessing the reliability and validity of using the two CES-D questions to operationalize exhaustion.[4] Although we did not perform formal diagnostic evaluation for depression, the use of the CES-D screening tool has been validated in the dialysis literature.[19,30] However, use of the CES-D screening tool as a substitute measure for clinical depression may have resulted in misclassification of depression and bias of our results toward the null. Furthermore, polypharmacy and certain medications may be associated with frailty, depressive symptoms, and mortality but were not considered in this study.

In conclusion, frailty and depressive symptoms were common in this cohort of prevalent dialysis patients, were associated with one another, and were independently associated with mortality risk. Furthermore, depressive symptoms were associated with the development of frailty, suggesting that interventions for depression could perhaps mitigate the appearance of frailty and its associated poor outcomes. Lastly, knowledge of an individual's frailty and depression state could identify high risk patients and assist in allocating resources to those with modifiable factors that can potentially alter an otherwise poor prognosis.

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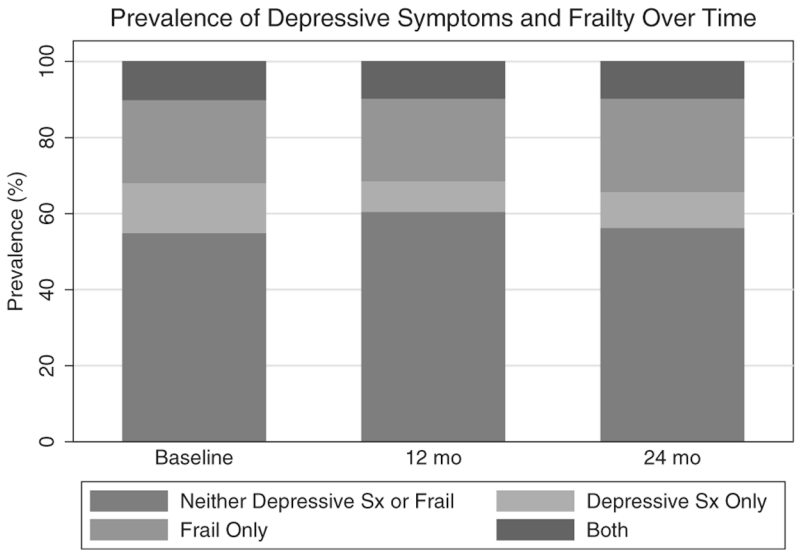

Figure 1.

Prevalence of depressive symptoms and frailty over time. Despite deaths and patients lost to follow up, the prevalence of frailty and depressive symptoms among the cohort remained relatively constant over the course of the study.

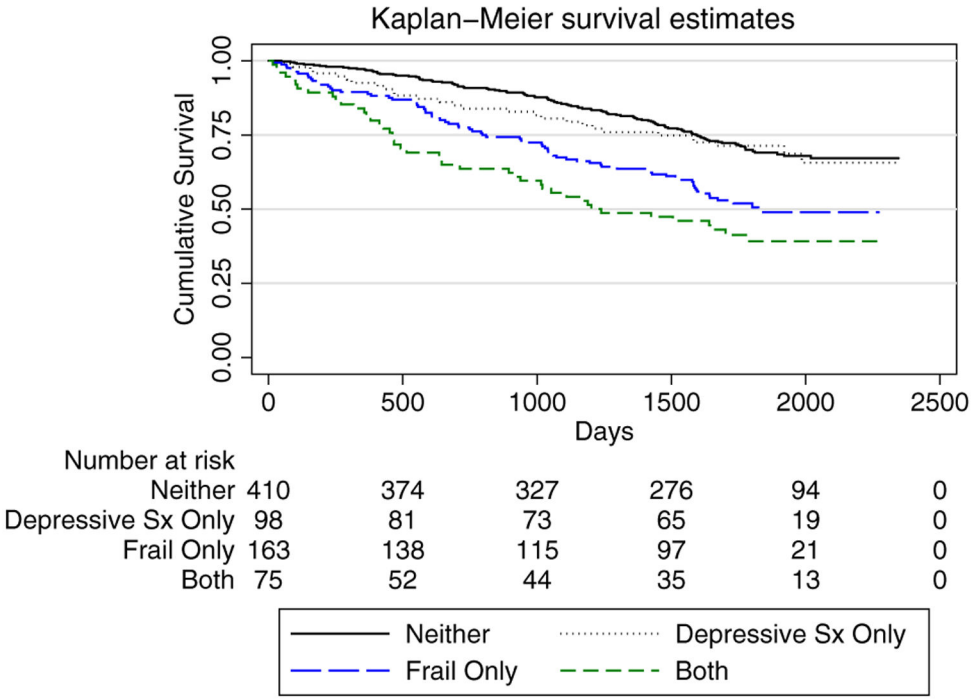

Figure 2.

Kaplan-Meier survival curve according to baseline frailty and depressive symptoms. The table indicates the number of patients at risk at relevant time points. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1

Baseline patient characteristics according to frailty and depressive symptoms

Characteristic	Overall N = 746	Not depressed, not frail N = 410	Depressed, not frail N = 98	Not depressed, frail N = 163	Depressed and frail N = 75	P value[a]
Age (y)	57.2 ± 14.2	55.5 ± 14.0	52.8 ± 12.6	62.6 ± 14.0	60.8 ± 13.7	<0.001
Sex (% female)	40.6	39.8	31.6	47.9	41.3	0.07
Race (%)						0.99
White	23.7	22.2	24.5	26.4	25.3	
Black	61.8	64.6	61.2	55.8	60.0	
Other	14.5	13.2	14.3	17.8	14.7	
Education (%)						<0.001
Below high school	23.7	19.8	31.6	22.7	37.3	
High school	29.1	31.0	28.6	25.8	28.0	
Vocational school	29.5	29.8	30.6	31.3	25.3	
College or above	17.7	19.8	10.2	20.2	9.3	
BMI	28.9 ± 6.9	28.9 ± 6.5	27.6 ± 7.3	29.4 ± 7.3	29.7 ± 7.8	0.14
Albumin (mg/dL)	3.99 ± 0.36	4.03 ± 0.32	4.07 ± 0.34	3.89 ± 0.42	3.84 ± 0.37	<0.001
Prealbumin (mg/dL)	29.7 ± 7.5	30.6 ± 7.2	31.6 ± 7.3	28.0 ± 7.6	26.6 ± 7.9	<0.001
IL-6 (pg/mL)	8.9 (5.6, 16.9)	8.2 (5.3, 14.5)	7.4 (5.4, 13.9)	11.0 (6.7, 26.8)	12.2 (6.1, 22.0)	<0.001
CRP (mg/dL)	3.9 (1.5, 9.8)	3.6 (1.5, 8.9)	3.0 (1.0, 7.0)	5.1 (2.0, 12.8)	5.1 (1.0, 12.1)	0.02
Comorbidities (%)						
Diabetes	46.5	41.0	38.8	59.5	58.7	<0.001
CAD	10.5	8.1	12.2	15.3	10.7	0.07
CHF	20.0	17.6	16.3	26.4	24.0	0.06
CES-D score	9.9 ± 8.9	5.3 ± 4.1	22.3 ± 6.5	7.2 ± 4.5	25.0 ± 6.4	<0.001
Frailty criteria met	1.9 ± 1.2	1.2 ± 0.7	1.5 ± 0.7	3.3 ± 0.6	3.6 ± 0.6	<0.001

[a]P values for ANOVA for normally distributed variables or Kruskal-Wallis tests for non-normally distributed variables.

BMI = body mass index; CAD = coronary artery disease; CES-D = Center for Epidemiological Studies Depression scale; CHF = congestive heart failure; CRP = C-reactive protein; IL-6 = interleukin-6.

Table 2

Association between depressive symptoms and frailty at baseline including individual components of the frailty construct

Outcome	Adjusted odds ratio (95% CI)[a]	P value
Overall frailty	2.14 (1.45–3.17)	<0.001
Individual frailty criteria		
Weight loss	2.13 (1.48–3.06)	<0.001
Exhaustion	3.87 (2.69–5.56)	<0.001
Low physical activity	1.27 (0.88–1.82)	0.20
Slow gait speed	1.50 (0.98–2.31)	0.06
Low grip strength	0.97 (0.66–1.42)	0.86

[a]Odds ratios adjusted for age, sex, race, comorbidities (diabetes, coronary artery disease, congestive heart failure), and inflammatory markers (interleukin-6 and CRP).

Table 3

Association between baseline depressive symptoms and incident frailty at baseline including incident development of individual components of the frailty construct with and without use of single imputation methods to account for death, transplant, and patients lost to follow up

	With imputation		Complete case analysis (sensitivity analysis)	
	Adjusted[a]		Adjusted[a]	
Outcome	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Overall incident frailty	2.28 (1.27–4.07)	0.006	2.16 (1.13–3.95)	0.01
Individual incident frailty components				
Weight loss	1.45 (0.76–2.78)	0.26	1.46 (0.76–2.80)	0.26
Exhaustion	2.40 (1.27–4.53)	0.007	2.28 (1.19–4.38)	0.01
Low physical activity	1.24 (0.67–2.30)	0.49	1.27 (0.70–2.29)	0.43
Slow gait speed	1.87 (1.07–3.27)	0.03	1.88 (1.06–3.32)	0.03
Low grip strength	1.75 (0.90–3.43)	0.10	1.73 (0.86–3.45)	0.12

[a]Adjusted for age, sex, race, comorbidities (diabetes, coronary artery disease, congestive heart failure), and inflammatory markers (interleukin-6 and CRP).