



Abraham Ortelius, 1589

Rehabilitation/quality of life
and nutrition special studies

A prospective, multi-center special data collection study coordinated by the USRDS Special Studies Centers, ACTIVE/ADIPOSE is a Cohort Study to Investigate the Value of Exercise in ESRD/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD. More than 750 prevalent patients undergoing hemodialysis have participated. Adults older than 18 were eligible if they spoke English or Spanish, had been on hemodialysis at least three months, and were able to give informed consent. During 2009–2011, approximately 85 percent of eligible patients were enrolled at seven outpatient dialysis clinics in the Atlanta, Georgia metropolitan area and seven outpatient dialysis clinics in the San Francisco Bay area of California.

An overview of ACTIVE/ADIPOSE objectives and methods can be found in Chapter Nine of the 2011 ADR. This year we present cross-sectional data from ACTIVE/ADIPOSE about frailty and two related health outcomes: the need for assistance with activities of daily living and the occurrence of falls and fractures.

The concept of frailty represents reduced physiological capacity in neurologic control, mechanical performance, and energy metabolism, which heighten an individual's vulnerability to adverse outcomes. Frailty is an important clinical focus not only in geriatric populations but also in chronic disease populations that are not exclusively geriatric. Studies of chronic kidney disease (CKD) patients and incident dialysis patients have found an increased risk of frailty in these populations compared with the general population. ACTIVE/ADIPOSE is the first investigation of frailty in a large cohort of prevalent ESRD patients undergoing dialysis.

In baseline assessments completed during 2009–2011, information was obtained from 745 participants for at least three of the five criteria that make up the Fried frailty index (Table 9.b). Participants ranged in age from 20 to 92. Their median time since ESRD treatment start was three years, with a range of three months to 25 years. The study cohort was representative of the overall U.S. prevalent in-center hemodialysis population in gender composition and the proportion with diabetes and/or hypertension as the primary cause of ESRD. The cohort included higher proportions of black/African American patients and patients of other races, as would be expected from the selected study sites (Table 9.a).

It thrilled through him when he first felt the keel answer to his hand on the spokes and slide over the long hollows as the foresail scythed back and forth against the blue sky.

Rudyard Kipling
CAPTAINS COURAGEOUS

Patients were classified as non-frail (i.e. positive for no frailty indicators), frail (i.e. positive for three or more indicators), and pre-frail (i.e., positive for one or two indicators), as shown in Figure 9.1. For the distributions of grip strength, walk time, and physical activity level, the lowest quintiles were defined as indicative of frailty (Fried Frailty Index, Table 9.b).

Patients classified as non-frail were more likely than those classified as frail and pre-frail to meet 4–5 of the following hemodialysis quality-of-care indicators: kt/v > 1.2; no catheter; hemoglobin 10–12 g/dl; serum albumin > 4.0 g/dl; and serum phosphorus 3.5–5.5 mg/dl (Figure 9.2).

Individuals who need assistance with activities of daily living (ADL) are restricted in carrying out routine self-care activities that are essential for living independently. Many studies of community dwelling adults, including research focusing on individuals with non-dialysis-dependent CKD, have shown that ADL difficulty is associated with frailty.

ACTIVE/ADIPOSE participants were asked: “At the present time, do you need help from another person

- to bathe (wash and dry your whole body)?
- to dress (like putting on a shirt or shoes, buttoning, and zipping)?
- to get in and out of a chair?
- to walk around your home or apartment?”

Need for ADL assistance was indicated by a response of “yes, need help” or “unable to do” to one or more items.

Almost 20 percent reported needing ADL assistance. In analyses adjusted for demographic and clinical variables, and compared to patients classified as non-frail, the odds of needing ADL assistance were about 11-fold greater for individuals classified as frail, and approximately twice as high for individuals classified as pre-frail (Figure 9.3).

ADL difficulty and frailty overlapped in ACTIVE/ADIPOSE participants (Figure 9.4). However, the need for ADL assistance and frailty can be considered distinct clinical entities,

vol 2 9.a Characteristics of the ACTIVE/ADIPOSE & hemodialysis populations (percent)		
	ACTIVE/ADIPOSE	Hemodialysis
Count	745	378,293
Age ≥65	28.2	44.7
Male	59.5	55.7
White	23.6	55.1
Black/Af Am	61.9	37.8
Other	14.5	7.1
Hispanic	12.8	17.1
Diabetes	36.2	45.2
Hypertension	34.9	28.8

vol 2 9.b Fried Frailty Index: criteria & indicators	
Frailty criteria	Indicators
Weight loss	Loss of >10 pounds in past 12 months, unintentional.
Exhaustion	Response of “a moderate amount of the time (3–4 days)” or “most of the time” to either of two CES-D scale items: “I felt that everything I did was an effort;” “I could not get going” during the past week.
Weakness	Maximal grip strength in kg using Jamar hand-held dynamometer. Lowest 20%, stratified by gender and BMI quartiles.
Slowness	Time in seconds to walk 15 feet at usual pace. Slowest 20%, stratified by gender and standing height.
Low physical activity level	Weighted score of kilocalories expended per week in physical activities “you have done in the past 2 weeks” reported on short version of Minnesota Leisure Time Activity questionnaire. Lowest 20% for each gender.
Frailty	Presence of 3 or more of the above criteria.

BMI: body mass index. CES-D: Center for Epidemiologic Studies-Depression.

each having its own unique content and challenges for clinical management.

For each ADL task, participants were asked: "If you need help or are unable to do, what is the main symptom or condition that causes you to have difficulty or prevents you from doing the activity?" Open-ended responses to this question were grouped into five categories identified in the Women's Health and Aging Study: pain, balance, endurance, weakness, and other symptoms. Figure 9.5 shows the proportion of participants who named each of the five symptoms/conditions as causes for their ADL difficulty. Weakness, balance, and other symptoms/conditions were named most often. "Other symptoms/conditions" named — e.g., need to protect catheter, graft in chest, foot infection, had surgery, broken hip, broken leg, double amputee, vision not good — included dialysis-related issues, acute conditions such as an infection or fracture, and long-standing conditions such as vision limitations and amputations. Concerns about balance and avoiding falls were more often named by whites than blacks/African Americans, but the proportions of whites and blacks/African Americans who named the remaining categories did not differ significantly.

Although research is limited, dialysis patients have an increased prevalence of falls, which may be complicated by hip or other types of fractures. The syndrome of frailty has been shown to be a strong predictor of falls in the general population, but no prior research has investigated frailty and falls in ESRD patients undergoing hemodialysis.

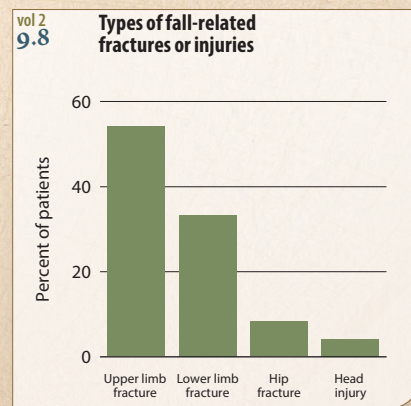
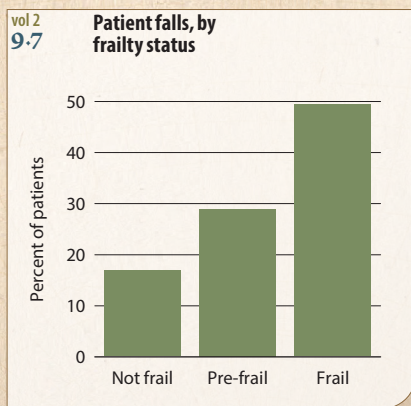
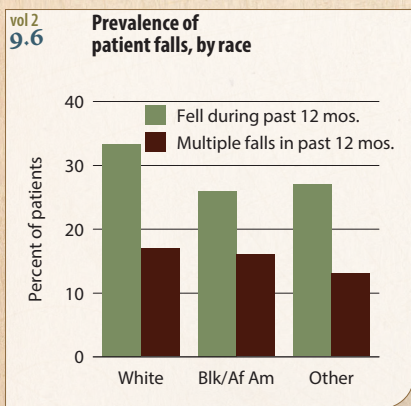
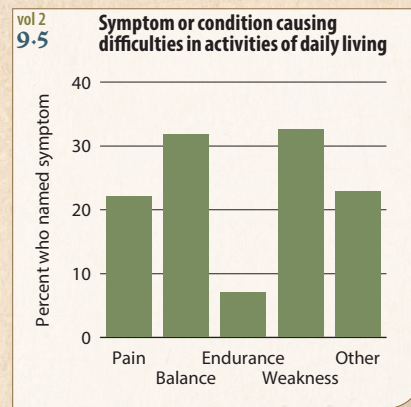
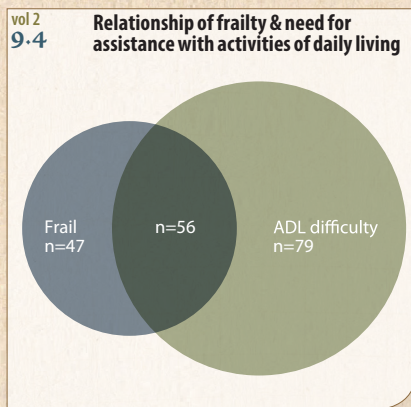
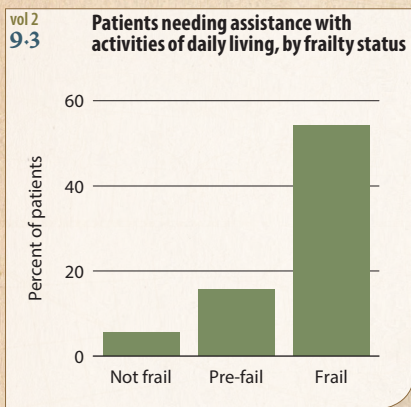
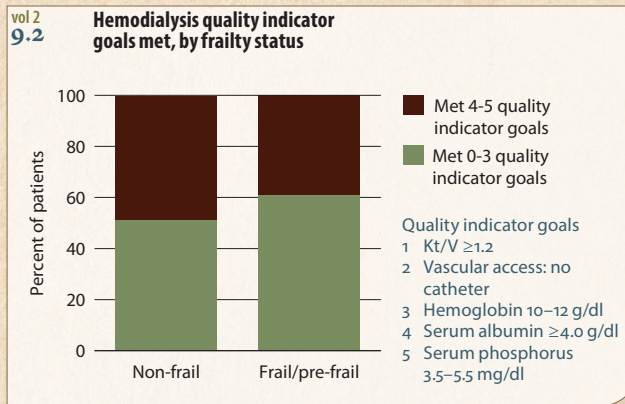
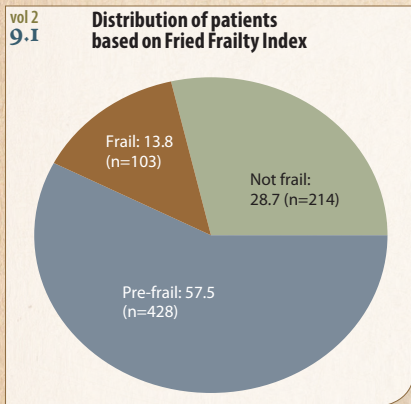
ACTIVE/ADIPOSE participants were asked: "In the past 12 months, have you had a fall (a fall is defined as unintentionally coming to rest on the ground, floor or other lower level)? If YES, number of falls in the past year: ___." A follow-up question asked participants to identify the types of fractures they had sustained.

Overall, 28.4 percent reported having fallen during the previous 12 months. Of the 216 patients who fell, 124 (57 percent) had multiple falls. A total of 671 falls was reported, for a fall incidence rate of 0.88 falls per person year. After excluding two participants who reported an extreme number of falls (i.e. 100, or approximately two falls per week, and 52, or one fall per week), the number of reported falls ranged from 1–24, and the fall incidence rate was 0.68 falls per person year. Fall rates did not differ significantly by participant race (Figure 9.6).

In analyses adjusted for demographic and clinical variables, and compared with patients classified as non-frail, the odds of having fallen were about 3 times greater for individuals classified as frail, and 1.6 times higher for individuals classified as pre-frail (Figure 9.7).

Fall-related fractures were sustained by 11.2 percent of patients reporting a fall. Proportional odds models showed that being classified as frail or pre-frail increased the odds for having a fall complicated by a fracture, compared with having a fall without a fracture or having no fall. A higher number of prescribed medications and prescription of a selective serotonin reuptake inhibitor (SSRI) antidepressant were also associated with increased odds for falls and fractures. Most fractures involved the upper or lower limbs; two hip fractures and one head injury were also reported. Types of fall-related fractures are summarized in Figure 9.8.

Impaired gait and lower limb strength may be improved through exercise interventions, which would address components of the frailty syndrome and could in turn help reduce risks for falls and fractures. ACTIVE/ADIPOSE data are also consistent with data from other falls research in suggesting that risks for falls and fractures may be reduced by more selective prescription of medications, especially SSRI antidepressants.



a major aim of the Nutrition Special Studies Center in conducting ACTIVE/ADIPOSE was to explore associations between physical function and body composition. Muscle wasting, or sarcopenia, is thought to be a major factor underlying the frailty phenotype. However, patients with end-stage renal disease may have disease-related or other comorbidity-related factors that contribute to frailty independently. In ACTIVE/ADIPOSE we therefore sought to determine the extent to which markers of muscle mass and body fat were related to frailty.

Body composition was measured using whole-body bioelectrical impedance spectroscopy immediately before a dialysis session. Total body water (TBW) was estimated using the resistance extrapolated to infinite frequency, and total body fat mass was calculated by subtracting $TBW/0.73$ from body weight. Extracellular water (ECW) was estimated from resistance extrapolated to zero frequency, and intracellular water was calculated as $TBW - ECW$.

We defined frailty by applying the Fried frailty criteria in a manner consistent with international guidelines, our pre-specified analysis plan, and a recent publication that used these criteria in a prevalent dialysis cohort. Patients meeting three or more of the criteria were considered to meet the definition of frailty. Weight loss was ascertained by patient report of unintentional loss of more than 10 pounds within the last year; exhaustion was defined by patient report; and weakness, slow walking and low physical activity were defined based on a standard developed in a community-dwelling elderly cohort (Table 9.c).

Of the 778 participants, 762 had available data on comorbidity and frailty, and 31.4 percent were frail. Figure 9.9 shows the percentage of men and women meeting each of the criteria for frailty and the percentage meeting three or more. Women were more likely to be frail than men, and this was driven entirely by more women meeting the slow walking speed criterion.

Figure 9.10 shows intracellular water (ICW) per kg body mass and percent fat mass among frail and non-frail men and women. Men and women who were frail had significantly lower ICW per kg, a marker of muscle mass. Conversely, frail men and women had higher percent fat mass, suggesting that excess adiposity is more common among frail individuals.

In addition, we explored the extent to which markers of inflammation and nutritional status were associated with frailty. Figure 9.11 shows that frail patients had significantly higher levels of c-reactive protein and lower serum albumin and prealbumin concentrations, indicating greater burden of inflammation and poor nutritional status among frail individuals.

Several factors related to kidney disease, including anemia, bone and mineral disorders, and acidosis, could also lead to or exacerbate frailty. We collected participants' most recent monthly laboratory results and examined

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9.C **Fried Frailty Index: standard criteria for application to chronic disease populations**

Frailty criteria	Indicators
Weight loss	"In the past 12 months, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?"
Weakness	<i>Weakness was defined as adjusted mean grip time in the stronger arm in the lowest 20th percentile of a community-dwelling population of adults age 65 and older.</i> Men: BMI ≤ 24 kg/m ² : ≤ 29 kg BMI 24.1 – 26 kg/m ² : ≤ 30 kg BMI 26.1 – 28 kg/m ² : ≤ 31 kg BMI > 28 kg/m ² : ≤ 32 kg Women: BMI ≤ 23 kg/m ² : ≤ 17 kg BMI 23.1 – 26 kg/m ² : ≤ 17.3 kg BMI 26.1 – 29 kg/m ² : ≤ 18 kg BMI > 29 kg/m ² : ≤ 21 kg
Exhaustion	Two items from the CES-D: (1) I felt that everything I did was an effort. (2) I could not get "going." Patients were asked how often in the last week they felt this way, and those who chose "a moderate amount of the time (3-4 days)" or "most or all of the time (5-7 days)" to either question were considered to meet the exhaustion criterion for frailty.
Low activity	Leisure time physical activities over the 2 weeks before the study assessment were assessed using the short version of the Minnesota Leisure Time Activities Questionnaire. Weekly activities were converted to kilocalories of energy expenditure, and the frailty criterion if individuals were below the 20 th percentile of a community-dwelling elderly population based on gender (men, <383 kcal/week; women, <270 kcal/week).
Slow speed walking	Individuals with a walking speed less than the 20 th percentile of a community-dwelling elderly population, adjusted for gender and height: Men: Height ≤ 173 cm: ≥ 7 s Height > 173 cm: ≥ 6 s Women: Height ≤ 159 cm: ≥ 7 s Height > 159 cm: ≥ 6 s

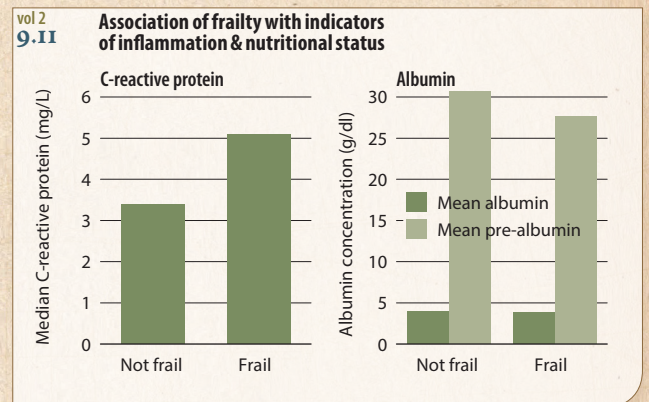
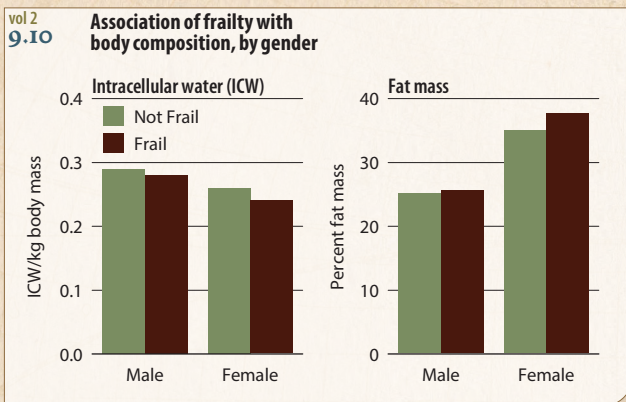
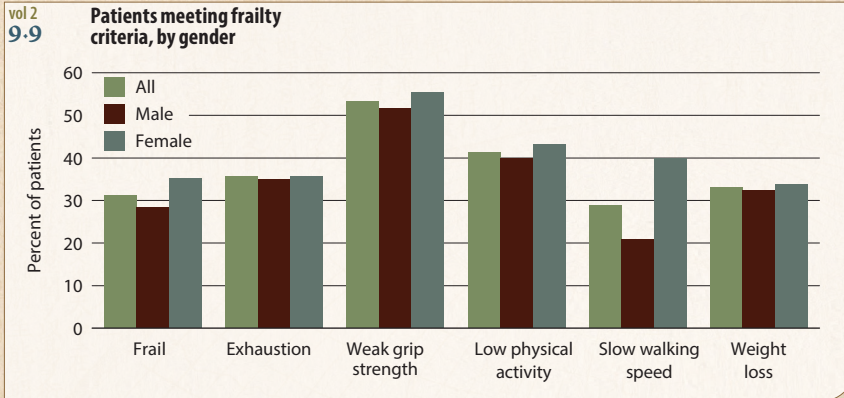
the association between these laboratory parameters and frailty (Table 9.d). Hemoglobin was slightly lower among frail patients, but there was no significant association between frailty and bone and mineral parameters. Frail participants had slightly higher predialysis serum bicarbonate than non-frail individuals, which could indicate lower dietary acid intake related to low protein intake.

In addition to kidney-related factors, frailty may be associated with comorbid conditions often present among patients on hemodialysis. We collected information on comorbidity by chart review and by information recorded on the Medical Evidence form (CMS Form 2728). We examined the percentage of frail and non-frail patients with a history of hypertension, diabetes mellitus, heart failure, cerebrovascular accident or transient ischemic attack, and peripheral vascular disease (Figure 9.12). Frail patients had a higher prevalence of diabetes, heart failure, and CVA/TIA, with a particularly large difference in the prevalence of diabetes. There was no significant difference in the prevalence

of hypertension or peripheral vascular disease among frail and non-frail patients.

The prevalence of frailty by the Fried criteria was substantially higher than the 7 percent observed in a community-dwelling elderly cohort but slightly lower than the 41.8 percent recently reported in a cohort of hemodialysis patients from Baltimore. Frailty by the Fried criteria was more common among women than men, mostly because more women met the slow gait criterion, even though the cutpoint was lower for women.

Although inflammation, malnutrition, age, and comorbidity may contribute to development of frailty among patients with ESRD, the expected associations between frailty and body composition are preserved in this population. There is a need for prospective testing of interventions to address wasting or other components of the frailty syndrome to determine whether frailty can be reversed and whether improvements in frailty are associated with improved survival.



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9.d

Association of frailty with anemia, bone & mineral metabolism, & serum bicarbonate level*

	Frail	Not frail	P-value
Count	239	523	
Hemoglobin, g/dL	11.6 ± 2.8	11.8 ± 2.5	0.03
Phosphorus, mg/dl	5.3 ± 1.6	5.6 ± 1.8	0.18
Calcium, mg/dl	8.7 ± 0.9	8.8 ± 0.9	0.24
Parathyroid hormone, pg/ml	347 (203, 551)	356 (224, 540)	0.5
Bicarbonate, meq/L	23.4 ± 3.3	22.7 ± 3.6	0.008

*Mean ± S.D. or median (25th & 75th percentile)

