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Disability in Patients with End-Stage Liver Disease: Results from the Functional Assessment in Liver Transplantation (FrAILT) Study

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Abstract

Cirrhosis leads to sarcopenia and functional decline that can severely impact one's ability to function at home and in society. Self-reported disability scales to quantify disability – Activities of Daily Living (ADL) and Instrumental ADL (IADL) – are validated to predict mortality in older adults. To evaluate disability in liver transplant (LT) candidates and quantify its impact on outcomes, consecutive outpatients ≥18y listed for LT with laboratory Model for End-stage Liver Disease (MELD) score ≥12 at a single high-volume U.S. LT center were assessed for ADLs and IADLs during clinic visits. Multivariable competing risk models explored the effect of disabilities on waitlist mortality (death or delisting for illness). Of 458 patients: 36% were women, median (IQR) age was 60y (54–64), initial MELD-Na was 16 (13–20). At first visit, 31% had lost ≥1 ADL, 40% ≥1 IADL. The most prevalent ADLs lost were continence (22%), dressing (12%), and transferring (11%); the most prevalent IADLs lost were shopping (28%), food preparation (23%) and medication management (22%). After adjustment for age, MELD-Na, and encephalopathy, dressing (SHR 1.7, 95%CI 1.0–2.8, p=0.04), toileting (SHR 1.9, 95%CI 1.1–3.5, p=0.03), transferring (SHR 1.9, 95%CI 1.1–3.0, p=0.009), housekeeping (SHR 1.8, 95%CI 1.2–3.0, p=0.009), and laundry (SHR 2.2, 95%CI 1.3–3.5, p=0.002), remained independent predictors of waitlist mortality.

Conclusion—ADL/IADL deficits are common in LT candidates. LT candidates would benefit from chronic disease management programs developed to address the impact of cirrhosis on their daily lives.

Keywords

frailty; activities of daily living; instrumental activities of daily living; mortality; cirrhosis

Patients with cirrhosis experience premature and accelerated physiologic aging (1,2). Although end-stage liver disease frequently develops well before the age of 65 years in individuals with underlying chronic liver disease, cirrhotics often suffer from common geriatric conditions such as functional decline, polypharmacy, and cognitive impairment, all of which contribute to a high risk of physical disability(3)(4).

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The Activities of Daily Living (ADLs) represent the domains of function that a person must be able to manage in order to live independently. Disability in ADLs and IADLs often develops in older age, but patients with chronic illness are often disabled earlier. In cirrhosis, just as in older age, the need for help with these activities suggests a severity of cirrhosis that threatens independent living. In other long-term conditions such as heart failure, chronic disease management programs engaging in patient education and medication management have been effective at reducing the burden of disabling symptoms of chronic disease(5,6). Disease management programs for liver failure also have emerged as promising tools for improving quality of life(7). However, little is known of specific domains in which patients with end-stage liver disease experience disability. Understanding *how* a patient with cirrhosis is disabled would enable us to better develop interventions to improve their quality of life.

As has been demonstrated in older adults and select surgical and inpatient populations – including cirrhotics hospitalized for hepatic decompensation – disability is also a well-established predictor of mortality(8)(9)(10)(11). This is even more critical for a patient awaiting liver transplantation, for whom it is particularly important to determine whether the disability is expected to reverse after transplantation.

Therefore, in this study, we aimed to fully characterize disability in cirrhotics on the liver transplant waitlist, to isolate predictors of subsequent disability, and to identify individual disabilities associated with poor outcomes.

METHODS

The Functional Assessment in Liver Transplantation (FrAILT) Study, initiated in July 2012, is an ongoing prospective, longitudinal cohort of adults (≥18 years) with cirrhosis listed for liver transplant with Model for End-stage Liver Disease (MELD) score ≥12 at a single high-volume liver transplant center. Patients were included if they had at least two visits in the study. Excluded were patients with severe hepatic encephalopathy (>120 sec on the Numbers Connection Test) due to potential difficulty in following study procedures.

At enrollment and at every subsequent clinic visit, we assessed disability in every study participant using two validated scales. For Activities of Daily Living (ADL) (12), study staff asked “Do you have difficulty with ___?”; for Instrumental Activities of Daily Living (IADL) (13), study staff asked “Are you able to ___?”, with follow-up questions to determine degree of disability if indicated. Individuals were considered to have lost an ADL/IADL ability if unable to perform the minimum activity criteria detailed in Table 1. Disabilities were analyzed as individual categorical variables.

Laboratory tests were collected from the patient’s electronic health record at the time of each visit. Hepatic encephalopathy was classified based on performance on the Numbers Connection Test Score, as none/mild (≤60 sec) and moderate/severe (>60 sec). Race was dichotomized as white/non-white for statistical modeling. Frailty was assessed at each visit using a previously described three-level score combining objective weight loss, grip

strength, walk speed, and self-reported activity level and exhaustion measures(14). Lactulose use was collected from the medication list at the initial study visit.

Statistical analysis

Differences in baseline characteristics by presence of disability at first visit were compared using chi-square test for categorical variables, and paired t-test for continuous variables. Initial disability on the waitlist was described in the subset of patients with no disabilities at first visit.

Competing risks regression(15) evaluated the effect of time-varying ADL and IADL disabilities on wait-list mortality, defined as death or de-listing for being too sick for transplant, with transplant as competing risk. Patients were censored when de-listed for other reasons. Multivariable models initially included age, presence of HCC, and indicators of liver disease status: MELD-Na, albumin, ascites, and encephalopathy. To improve precision, backwards stepwise selection was used to trim models to predictors with $p < 0.1$. A more conservative cutoff of $p<0.1$ was used to reduce the possibility of residual confounding with a relatively small number of outcomes. Final multivariable models were adjusted for age, MELD-Na, and hepatic encephalopathy. A similar analysis evaluated the contribution of the total number of disabilities.

Competing risks regression also evaluated the predictors of new or subsequent disability, with transplant and waitlist mortality as competing risks. Backwards stepwise selection was used to select predictors with $p < 0.1$.

The UCSF institutional review board approved this study. All statistical analyses were performed using STATA (v13, College Station, TX).

Results

Baseline patient characteristics

458 patients were included in this study, whose baseline characteristics are shown in Table 2. Median age was 60 years (interquartile range, IQR 54–64), 54% had chronic hepatitis C virus; 31% had hepatocellular carcinoma (HCC). Median MELD-Na was 17. Median (IQR) follow-up time was 8.5 (4.3–16.8) months.

Physical disability in the cohort

At their first visit, 31% reported difficulty with ≥1 ADL; 40% need for help with ≥1 IADL. Patients reporting difficulty with at least one ADL or IADL (n=224) were more likely to be men, more likely to have a higher BMI, higher MELD-Na, more ascites, more likely to be encephalopathic, and less likely to have HCC.

The most prevalent ADL disabilities at the initial visit were continence (20%), dressing(9%), and transferring (9%); the most prevalent IADL disabilities were shopping (24%), food preparation(20%), and management of medications (17%). At their first study visit, 55% of patients were on lactulose. Patients on lactulose were more likely to be incontinent (26% vs. 14%, p=0.001).

Over time, 125 (27%) of those who did not report any disabilities at baseline developed difficulty with at least one ADL; 127 (28%) reported difficulty with at least one IADL. The most frequent first ADL disabilities were transferring and continence; the most frequent first IADL disabilities lost were shopping and food preparation (Figure 1).

Baseline disability, male gender, higher MELD-Na, ascites, and frailty were predictive of new or increasing IADL disability. Men had 1.6 (95%CI 1.2–2.2, p=0.004) times the hazard of subsequent disability compared to women. Baseline disability and higher BMI were independently predictive of subsequent ADL disability. Each additional ADL disability at baseline was associated with 1.8 (95%CI 1.4–2.4, p<0.001) times the hazard of new ADL disabilities (Table 3). Neither gender, MELDNa, nor frailty was predictive of subsequent ADL disability.

Physical disability and waitlist outcome

By the end of follow-up, 33% of patients received a transplant, 18% died or were de-listed due to illness, and 39% were still waiting.

On univariable competing risks regression, almost all ADL/IADL disabilities were significantly associated with waitlist mortality. After adjustment for age, MELD-Na, frailty, and hepatic encephalopathy, difficulty dressing (subdistribution hazard ratio [SHR] 1.7, 95%CI 1.0–2.8, p=0.04), difficulty toileting (SHR 1.9, 95%CI 1.1–3.5, p=0.03), transferring (SHR 1.9, 95%CI 1.1–3.0, p=0.009), needing help with housekeeping (SHR 1.8, 95%CI 1.2–3.0, p=0.009), and laundry (SHR 2.2, 95%CI 1.3–3.5, p=0.002), remained independent predictors of waitlist mortality (Table 4). After adjusting for MELD-Na, hepatic encephalopathy, age, frailty, and lactulose use, incontinence was associated with an increased hazard of waitlist mortality (SHR 1.9 95%CI 1.1–3.2 p=0.02).

DISCUSSION

Much of the management of liver disease focuses on helping patients manage the physiologic derangements caused by cirrhosis. The measurement of self-reported ADL and IADL disability has not traditionally been a part of the clinical assessment of cirrhosis, but conveys crucial information beyond that found in laboratory values and performance-based frailty metrics. For a patient with decompensated cirrhosis, disability reflects the accumulation of deficits from not only portal hypertension and sarcopenia, but also malnutrition, coronary artery disease, and depression (among many other conditions). While related to frailty – i.e., a frail individual is more likely to experience disability – disability tells us *how* an individual's frailty impacts his or her day-to-day activities. By describing the specific ways in which a patient cannot complete his daily activities, the ADL/IADL scales are, in a way, the most patient-oriented outcomes that we can measure in our clinical practice. How better and more directly can we address our patients' daily unmet needs than by asking the ways in which they cannot function at home and within their communities?

In this outpatient cohort of cirrhotics awaiting liver transplant, more than half are not able to do at least one basic activity necessary for function within the home or in society. Despite 75% being under 65 years of age, cirrhotics suffer more functional disability than adults 80

years of age and older(16). Prevalent disability was the strongest risk factor for subsequent disability, and over half of our cohort experienced new or increasing ADL and IADL disability during their time on the wait-list. This rate far outstrips age-related loss of ability, which at this age range is expected increase by less than 10% *per decade*.(17)

We particularly emphasize the high prevalence of incontinence in our cohort. At 26% among lactulose users, it is as common in our cirrhotics as is fecal incontitence in patients who have suffered a stroke(18). Fecal incontinence can lead to embarrassment, social isolation, loss of self-esteem, and loss of employment. (19–21) Despite the impact of incontinence on daily life, most patients do not volunteer this information unless the provider explicitly inquires (22–24). We suggest that providers *should* inquire about what is essentially an iatrogenic disability.

With this information, we can begin to develop mechanisms of addressing our patients' daily disabilities. Incontinence is a problem familiar to the gastroenterologist, with an armamentarium of conservative management tools (25). Simple interventions such as barrier creams, absorptive products, and bowel training can reduce the impact of incontinence on quality of life with minimal provider time investment (26,27). Intensive education regarding titration of the dosage and timing of lactulose – and use of adjunctive therapies (e.g., rifaximin, probiotics, zinc) to enhance control of hepatic encephalopathy – could offer significant benefits through reduction of incontinence and increased adherence to therapy. Finding that 17% of our cohort are dependent in medication management reminds the clinician to involve caregivers and clinic pharmacists in this discussion.

In congestive heart failure, comprehensive disease management programs have become a class 1 recommendation in practice guidelines.(28) Similar programs for end-stage liver disease may have their greatest impact in standardizing implementation of practice guidelines (29) and increasing patient understanding of complex plans of care(30), and have already been successful in reducing pre-procedure and peri-admission mortality (31,32). They may also have the potential to greatly improve our patients' quality of life. Perhaps even more importantly, screening for disability can help us identify those who are at greatest risk for subsequent disability, and therefore, in greatest need of such chronic disease management programs.

We acknowledge several limitations to this study. This study did not account for intervening hospitalizations, which likely contributed to subsequent disability (as has been previously demonstrated in older adults without chronic liver disease(33)), and should be evaluated in future studies as both a predictor and a result of disability. Inclusion of only outpatients with MELD scores ≥12 limits this study's generalizability to the liver transplant population as a whole, but we suspect that patients with MELD scores <12 have much lower rates of disability and would have contributed relatively few waitlist events to our analyses. Finally, despite enrolling most of the liver transplant waiting list at one of the largest transplant centers in the nation over a period of six years, we do not presently have enough post-transplant outcomes to evaluate disability as a modifiable risk factor for post-transplant outcomes. We anticipate addressing this question in the future.

Despite these limitations, this study demonstrates the high overall prevalence of disability on the liver transplant waitlist and identifies the specific areas in which liver transplant candidates are disabled. These data underscore the importance of developing chronic disease management programs to help address the many ways in which cirrhosis impacts individuals' lives – beyond ascites and varices. We advocate for the routine assessment of disability using these simple, low-cost disability scales to identify those in greatest need of integrated disease management programs and simple interventions. These data are a crucial step towards future work addressing post-transplant outcomes, including disability resolution.

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List of Abbreviations

ADL	Activities of Daily Living
CI	confidence interval
HCC	hepatocellular carcinoma
IADL	Instrumental Activities of Daily Living
IQR	interquartile range
LT	Liver transplant
MELD-Na	Model for End-stage Liver Disease- Sodium
SHR	subdistribution hazard ratio

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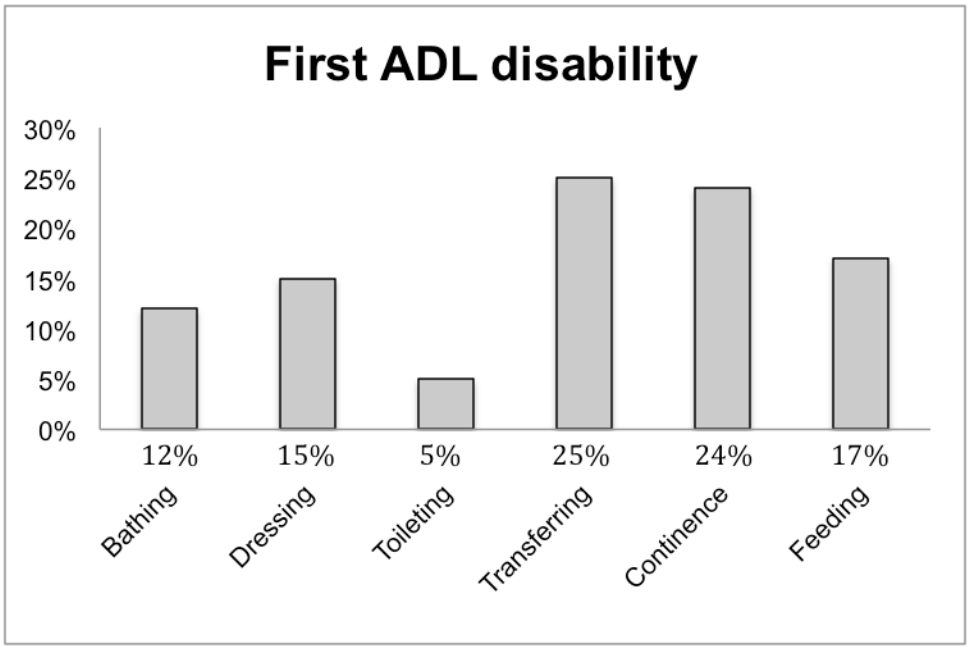

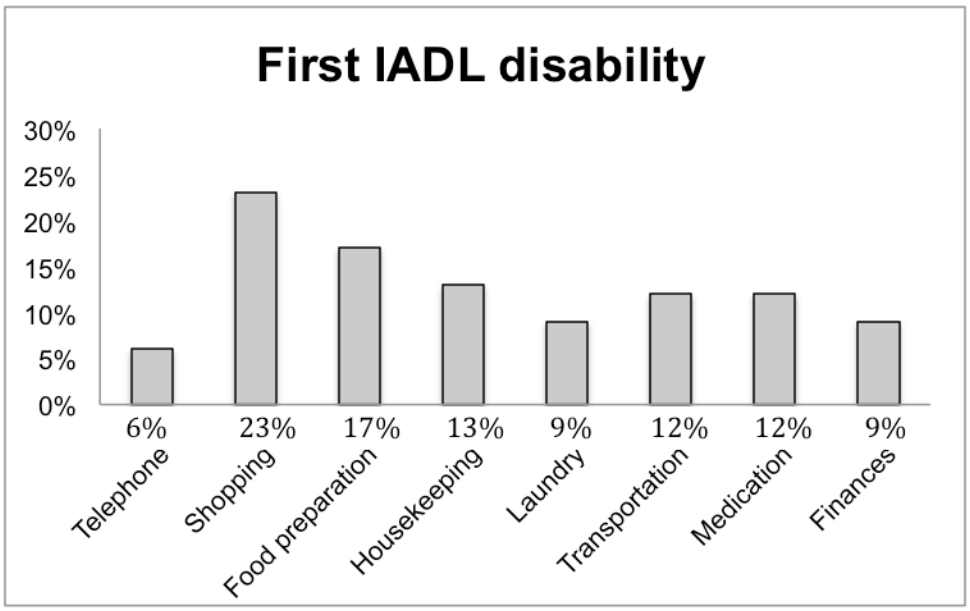

Figure 1.
First ADL and IADL disabilities among the previously able.

Table 1

Patient questions and minimum criteria for being considered able for each Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL).

Activities of Daily Living
1. Bathing – “Do you have difficulty bathing in the last two weeks?” (receives no assistance in bathing, except for at most one part of body.)
2. Dressing – “Do you have difficulty dressing in the last two weeks?” (gets clothes or dresses without assistance, except for tying shoes.)
3. Toileting – “Do you have difficulty using the toilet in the last two weeks?” (goes to toilet room, uses toilet, arranges clothes, and returns without assistance. May use cane/walker, and bedpan/urinal at night.)
4. Transferring – “Do you had difficulty transferring in the last two weeks?” (moves in and out of bed and chair without assistance, may use cane/walker.)
5. Continence – “Have you had any accidents before you’ve reached the restroom in the last two weeks?” (controls bowel and bladder completely by self.)
6. Feeding – “Have you had difficulty feeding yourself in the last two weeks?” (feeds self without assistance (except for help with cutting meat or buttering bread.)
Instrumental Activities of Daily Living
1. Telephone – “Are you able to answer the telephone?” (answers telephone.)
2. Shopping – “Are you able to shop independently?” (takes care of all shopping needs independently.)
3. Food preparation – “Are you able to prepare your own food?” (plans, prepares, and serves adequate meals independently.)
4. Housekeeping – “Are you able to do housekeeping?” (participates in some housekeeping tasks.)
5. Laundry – “Are you able to do your own laundry?” (launders at least small items.)
6. Transportation – “Are you able to arrange your own transportation?” (arranges own travel by car/taxi, may be accompanied by another on public transit.)
7. Medication management – “Are you able to manage your own medications?” (is responsible for taking correct dosage of medication at correct times.)
8. Finances – “Are you able to manage your finances?” (manages day-to-day purchases, may receive assistance with banking.)

Table 2

Baseline characteristics of 458 liver transplant candidates, for the entire cohorts, and categorized by presence of disability at first study visit.

Patient characteristic	n=458	No disability at first visit n=224	>= 1 ADL/IADL disability at first visit n=234	p-value
Male gender	170 (36%)	69 (29%)	97 (43%)	0.002
Age, years, median(IQR)	60 (54–64)	61 (55–64)	59 (53–64)	0.1
Race/ethnicity				
White	263 (56%)	135 (58%)	120 (54%)	0.2
Black	18 (4%)	11 (5%)	7 (3%)	
Hispanic	130 (28%)	54 (23%)	73 (33%)	
Asian	36 (8%)	20 (9%)	16 (7%)	
Other	22 (5%)	14 (6%)	8 (4%)	
Etiology				
HCV	254 (54%)	131 (56%)	117 (52%)	0.4
HBV	17 (4%)	10 (4%)	7 (3%)	
EtOH	79 (17%)	43 (18%)	34 (15%)	
NASH	47 (10%)	18 (8%)	27 (12%)	
Autoimmune hepatitis, PBC, PSC	51 (11%)	24 (10%)	26 (12%)	
Other	21 (4%)	8 (3%)	13 (6%)	
HCC	145 (31%)	82 (35%)	57 (25%)	0.03
BMI, median(IQR)	28 (25–33)	28 (25–31)	29 (25–34)	0.003
Laboratory tests				
MELD-Na	17 (14–20)	16 (12–19)	18 (14–22)	<0.001
Total bilirubin, mg/dL	2.1 (1.3–3.2)	2.1 (1.2–3.2)	2.4 (1.6–3.4)	0.2
INR	1.4 (1.2–1.6)	1.3 (1.2–1.5)	1.4 (1.2–1.6)	0.003
Sodium, mEq/L	137 (134–139)	137 (135–139)	136 (134–139)	0.003
Albumin, g/dL	3.1 (2.7–3.5)	3.2 (2.8–3.7)	3 (2.6–3.4)	<0.001
Creatinine	0.91 (0.76–1.2)	0.9 (0.8–1.2)	0.9 (0.8–1.2)	0.2
Ascites				
Absent	345 (74%)	186 (79%)	150 (68%)	0.01

Patient characteristic	n=458	No disability at first visit n=224	>= 1 ADL/IADL disability at first visit n=234	p-value
Mild-moderate	103 (22%)	43 (18%)	58 (26%)	
Severe	18 (4%)	5 (2%)	13 (6%)	
Moderate hepatic encephalopathy	80 (17%)	23 (10%)	55 (25%)	<0.001

Table 3

Independent predictors of new or increasing ADL/IADL disability, results of multivariable competing risks regression.

Predictors	**Univariable Subsequent ADL disability**		**Multivariable Subsequent ADL disability**	
	SHR (95% CI)	**p-value**	**SHR (95% CI)**	**p-value**
ADL disability at first visit	1.8 (1.3–2.4)	<0.001	1.8 (1.4–2.4)	<0.001
White race	0.6 (0.4–0.97)	0.04	0.7 (0.4–1.02)	0.07
BMI	1.1 (1.02–1.1)	0.002	1.05 (1.0–1.1)	0.01
Ascites	1.6 (0.98–2.7)	0.06	1.6 (0.97–2.7)	0.06
Predictors	**Univariable Subsequent IADL disability**		**Multivariable Subsequent IADL disability**	
	SHR (95% CI)	p-value	SHR (95% CI)	p-value
IADL disability at first visit	1.5 (1.4–1.6)	<0.001	1.3 (1.2–1.5)	<0.001
Male gender	1.9 (1.4–2.5)	<0.001	1.6 (1.2–2.2)	0.004
MELD-Na	1.1 (1.0–1.1)	<0.001	1.03 (1.0–1.1)	0.04
Ascites	1.6 (1.4–2.8)	<0.001	1.6 (1.1–2.3)	0.02
Fried Frailty Index				
robust	1 (reference)		1 (reference)	
pre-frail	2.7 (1.8–4.2)	<0.001	2.2 (1.5–3.4)	<0.001
frail	7.2 (4.4–11.5)	<0.001	3.0 (1.7–5.2)	<0.001

Table 4

Individual disability predictors of waitlist mortality: multivariable competing risks regression adjusted for age, MELD-Na, and hepatic encephalopathy.

Individual ADL disabilities	**Univariable**		**Multivariable**	
	SHR (95% CI)	**p-value**	**SHR(95% CI)**	**p-value**
Bathing	1.8 (1.0–3.1)	0.05	1.5 (0.9–2.5)	0.2
Dressing	2.2 (1.3–3.7)	0.002	1.7 (1.0–2.8)	0.04
Toileting	2.7 (1.5–5.0)	0.002	1.9 (1.1–3.5)	0.03
Transferring	2.1 (1.3–3.4)	0.002	1.9 (1.2–3.0)	0.009
Continence	1.8 (1.1–2.8)	0.02	1.6 (1.0–2.5)	0.06
Feeding	1.1 (0.5–2.1)	0.9	0.8 (0.4–1.7)	0.6
Any ADL disability	2.1 (1.3–3.3)	0.002	1.6 (1.0–2.6)	0.04
Individual IADL disabilities	Univariable		Multivariable	
	SHR (95% CI)	p-value	SHR (95% CI)	p-value
Telephone	1.3 (0.6–2.5)	0.5	1.1 (0.6–2.3)	0.7
Shopping	2.1 (1.4–3.4)	0.001	1.5 (1.0–2.4)	0.07
Food preparation	1.6 (1.0–2.6)	0.06	1.2 (0.7–1.9)	0.6
Housekeeping	2.3 (1.4–3.7)	0.001	1.8 (1.2–3.0)	0.009
Laundry	2.5 (1.5–4.0)	<0.001	2.2 (1.3–3.5)	0.002
Transportation	1.5 (0.8–2.6)	0.2	1.0 (0.6–1.8)	0.9
Medication management	2.0 (1.3–3.2)	0.003	1.4 (0.9–2.3)	0.2
Finances	2.0 (1.1–3.4)	0.02	1.4 (0.8–2.5)	0.2
Any IADL disability	1.9 (1.2–3.0)	0.006	1.4 (0.8–2.2)	0.2