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Loneliness in adults awaiting liver transplantation at 7 U.S. transplant centers

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Abstract

Introduction: Loneliness, “a subjective feeling of being isolated”, is a strong predictor of adverse health. We characterized loneliness in patients with end-stage liver disease (ESLD) awaiting liver transplantation (LT).

Methods: We surveyed loneliness in ambulatory ESLD adults awaiting LT at 7 U.S. sites using the validated UCLA Three-Item Loneliness Scale, May2020-Jan2021; “lonely”=total ≥5. Liver

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Author contributions

KB participated in funding acquisition, research design, performance of the research, data analysis, writing of the manuscript; DK participated in performance of the research, review of the manuscript drafts; SS participated in performance of the research, review of the manuscript drafts; RW participated in performance of the research, review of the manuscript drafts; YM participated in performance of the research, review of the manuscript drafts; FY participated in performance of the research, review of the manuscript drafts; MND participated in performance of the research, review of the manuscript drafts; SW participated funding acquisition, in review of the manuscript drafts; BB participated in funding acquisition, performance of the research, review of the manuscript drafts; RR participated in performance of the research, review of the manuscript drafts; ADR participated in performance of the research, review of the manuscript drafts; MK participated in performance of the research, review of the manuscript drafts; MV participated in performance of the research, review of the manuscript drafts; DL participated in performance of the research, review of the manuscript drafts; DS participated in funding acquisition, performance of the research, review of the manuscript drafts; MMD participated in performance of the research, review of the manuscript drafts; EV participated in performance of the research, review of the manuscript drafts; DG participated in performance of the research, review of the manuscript drafts; JL participated in funding acquisition, conceptual and research design, drafting and review of the manuscript.

Declaration of interest

None

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Frailty Index (LFI) assessed frailty; “frail”=LFI≥4.4. Logistic regression associated loneliness and co-variables.

Results: Of 454 participants, median MELDNa was 14 (IQR 10-19) and 26% met criteria for “lonely”. Compared to those not lonely, those lonely were younger (57 v. 61y), more likely to be female (48% v. 31%) or frail (21 v. 11%), and less likely to be working (15% v. 26%) or in a committed partnership (52% v. 71%). After multivariable adjustment, frailty (OR=2.24, 95%CI=1.23-4.08), younger age (OR=1.19, 95%CI=1.07-1.34), female sex (OR=1.83, 95%CI=1.14-2.92), not working (OR=2.16, 95%CI=1.16-4.03), and not in a committed partnership (OR=2.07, 95%CI=1.29-3.32) remained significantly associated with higher odds of loneliness.

Conclusion: Loneliness is prevalent in adults awaiting LT, and independently associated with younger age, female sex and physical frailty. These data lay the foundation to investigate the extent to which loneliness impacts health outcomes in LT, as in the general population.

Clinical Trial Registry Website: https://clinicaltrials.gov Trial Number: NCT03228290

Keywords

Frailty; Psychosocial; Social isolation; Quality of life; Cirrhosis; End-stage liver disease; Mental health; Social support

1. Introduction

Loneliness, defined by the National Academy of Medicine as “a subjective feeling of being isolated”, has emerged as a critical determinant of adverse health conditions such as heart disease and dementia, as well as a 26% increased likelihood of death—an effect size that has been likened to smoking 15 cigarettes per day. [1] Concerns of loneliness in the general population have only grown with the Coronavirus (COVID-19) pandemic. Prior to 2020, one-third of Americans met criteria for loneliness; this has risen to as high as 50% during the pandemic. [1,2]

Loneliness represents a possible intervenable target for decreasing the high burden of disability and quality of life experienced by liver transplant (LT) candidates. [1] Yet the prevalence of and factors associated with loneliness in LT candidates have not previously been investigated. This was the aim of the current study.

2. Methods

We surveyed adults with ESLD awaiting LT during May 2020 through January 2021 who were seen in the ambulatory setting at 7 U.S. sites. Loneliness was assessed by trained personnel using the validated UCLA Three-Item Loneliness Scale. [3] Participants were asked if they felt: 1) they lack companionship, 2) left-out, or 3) isolated on a 3-point scale per category (1=hardly ever, 2=some of the time, or 3=often; total score=3-9). [3] Co-variables included: 1) frailty, from the most recent in-person Liver Frailty Index (LFI) score (composite of grip strength, chair stands, balance,https://liverfrailtyindex.ucsf.edu/), [4] 2) demographic data, 3) comorbidities, 4) presence of hepatic encephalopathy and

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ascites, from hepatologists' notes on frailty testing date, and 5) MELDNa scores, from most recent laboratory data. Self-reported co-variables included relationship status, work status, and education level.

Participants with total loneliness score ≥5 were classified as "lonely." Characteristics of lonely vs. non-lonely participants were compared using chi-square, Kruskal-Wallis, or Wilcoxon rank-sum. Logistic regression assessed odds ratios (OR) associated with loneliness. Co-variables for the multivariable model were selected based on *a priori* hypotheses of loneliness.

Statistical analyses were performed using Stata (Version 16, StataCorp, College Station, Texas). Written informed consent was obtained from each study participant. As a study involving human subjects, the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review boards at all participating sites. All co-authors had access to the study data and reviewed and approved the final manuscript.

2.1. Ethical statement

Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of University of California San Francisco (11-07513).

3. Results

Of 454 participants, 36% were female, median age was 60 years (IQR=53-64), median MELDNa was 14 (IQR=10-19), and 14% were frail (Table 1); 118 (26%) met criteria for lonely.

Compared to those who did not meet criteria for being lonely, those who were lonely were younger (57 v. 61y), and more likely to be female (48% v. 31%) or frail (21 v. 12%). Lonely compared to non-lonely participants were less likely to be working (15% v. 26%) or in a committed partnership (52% v. 71%). There were no differences by disease etiology, or MELDNa score (Table 1).

In univariable analysis, frailty, younger age, female sex, not working status, and not being in a committed partnership were associated with increased odds of loneliness. After multivariable adjustment, frailty (OR=2.24, 95%CI=1.23-4.08), younger age (OR=1.19, 95%CI=1.07-1.34), female sex (OR=1.83, 95%CI=1.14-2.92), not working (OR=2.16, 95%CI=1.16-4.03), and not being in a committed partnership (OR=2.07, 95%CI=1.29-3.32) remained significantly associated with higher odds of loneliness. Compared to non-Hispanic White race, Black race (OR=0.17, 95%CI=0.03-0.82) was inversely associated with loneliness (Table 2).

There were no significant associations between loneliness and transplant outcome (p=0.40), though there was a trend toward increased de-listing for reasons other than being too sick in those lonely vs. not lonely. Among the 71 subjects in "De-listed, other" category, there was a

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higher proportion of participants de-listed due to medical non-adherence in those lonely vs. not lonely (39% vs. 16%) (Supplementary Table).

4. Discussion

In our multi-center study, 1 of 4 patients with ESLD awaiting LT met criteria for being lonely. This is similar to rates in the general population during the pandemic (20-50%), [2,3] despite LT candidates being a select subgroup in which social support is a criterion for listing. Younger age, female sex, and frailty were independently associated with higher odds of loneliness, even after adjustment for social factors like relationship and work status, while Black race was independently associated with lower odds of loneliness.

Notably, frailty emerged as a key co-variable with the largest effect size. Our approach did not assess directionality of this association, but is consistent with previous prospective research in other populations showing that loneliness is strongly linked to functional decline. [2] Likewise, it would also be consistent with evidence that functional decline may contribute to loneliness through diminished social contact. [2] While the literature has found mixed effects of age, sex, and race on loneliness, [2] we observed in our cohort that adults awaiting LT were younger, female, and less often black. Given that past work has identified sex-based disparities in frailty among LT candidates (i.e, women were more frail than men), our findings raise the possibility that sex-based differences in loneliness may contribute to differences in frailty, or vice versa. [5]

Our study is one of the first to expand the frailty construct beyond physical function to more global contributors to the frail phenotype in patients with ESLD. [6,7] Our findings suggest that loneliness is one aspect of psychological distress that should be considered within this expanded “global frailty” construct. Given that meta-analysis of prospective studies have demonstrated that baseline loneliness leads to a 26% increased mortality risk, [2] our findings should motivate future work to characterize how loneliness affects outcomes in LT. Finally, we have helped identify those likely to benefit more from support services—such as to enhance community engagement—as a part of future multidisciplinary interventions for tackling frailty and its sequelae.

We acknowledge the following limitations. First, the COVID-19 pandemic likely influenced our results in ways we were unable to measure—perhaps affecting prevalence, risk factors, or both. We also could not assess directionality of the association between frailty and loneliness with our cross-sectional design, but past work suggests evidence of bi-directional causality. [1] Next, because we had few deaths/de-listings in our study, we were not able to draw firm conclusions about associations between loneliness and adverse transplant outcomes. Future work with a larger study population should examine whether loneliness affects risk of waitlist mortality or the type of de-listing experienced by patients. Finally, while we adjusted for several key socio-economic forces associated with loneliness such as age, sex, race, marital status, education level, and employment status, these factors cannot fully encapsulate the complex sum of social and structural support an individual experiences. Additional factors that would be important to consider in future work include living arrangements (i.e. % living alone) and comorbid psychological factors. Though research

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has shown loneliness to be distinct from depression and that the majority of those qualifying as lonely are not depressed, [1,2] our inability to incorporate depression and other comorbid psychiatric conditions into our model remains a limitation.

5. Conclusions

In conclusion, loneliness is prevalent in adults awaiting LT, and independently associated with younger age, female sex and physical frailty after adjusting for psychosocial factors including work status, relationship status and race. These data lay the foundation for future work investigating the extent to which loneliness impacts health outcomes in LT, as it does in the general population.

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Data availability

All raw and analyzed data presented in this manuscript can be made available to those requesting it. Any investigator willing to provide minimal information about their identity and plans for the data will be permitted access.

Abbreviations:

ESLD	End-Stage Liver Disease
LT	liver transplantation
MELDNa	Model for End-Stage Liver Disease-sodium
LFI	Liver Frailty Index
OR	odds ratio
CI	confidence interval
IQR	interquartile range

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Table 1

Characteristics of 454 liver transplant candidates, categorized by loneliness status.

Characteristics	**All*n*=454 *(100%)***		**By Loneliness Status**		**p-value**
			Lonely (score ≥ 5*)*n*=118 *(26%)*	**Not Lonely(score <5)*n=336 (74%)***	
Age, years	60 (53-64)	57 (50-63)	61 (54-65)	<0.001	
Sex	Male	64%	52%	69%	<0.001
	Female	36%	48%	31%	
Race/Ethnicity	Non-Hispanic White	59%	61%	58%	0.31
	Black	5%	2%	6%	
	Hispanic	25%	24%	26%	
	Asian	9%	12%	8%	
	Other	2%	2%	2%	
Work status	Yes, Working	23%	15%	26%	0.08
	No, On disability	30%	36%	27%	
	No, Retired	34%	31%	35%	
	No, Other	13%	18%	12%	
Relationship Status	Committed partnership	66%	52%	71%	<0.001
	Single	19%	21%	18%	
	Separated or Divorced	11%	20%	8%	
	Widowed	4%	7%	3%	
	Unknown	0%	0%	1%	0.87
Highest education level achieved	≤ 8th grade	8%	4%	10%	
	≤12th grade	33%	39%	31%	
	Any college	48%	44%	49%	
	Any post-grad	9%	8%	9%	
	Unknown	3%	4%	2%	
Frail (LFI≥4.4)†	14%	21%	12%	0.01	
Liver Frailty Index (LFI)†	3.7 (3.2-4.1)	3.8 (3.4-4.3)	3.6 (3.1-4.1)	<0.01	
Weight, kg	83.5 (69.9-96.6)	83.5 (65.3-96.2)	83.5 (70.8-96.9)	0.34	
Body mass index, kg/m^2	28.6 (24.8-32.5)	28.1 (24.2-32.8)	28.6 (24.8-32.3)	0.83	

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Characteristics	All *n*=454 *(100%)*		By Loneliness Status		p-value
			Lonely (score ≥ 5*) *n*=118 *(26%)*	Not Lonely(score <5) *n=336 (74%)*	
Etiology of liver disease	EtOH	29%	28%	29%	0.71
	Chronic hepatitis C	25%	24%	25%	
	Non-alcoholic fatty liver disease	20%	21%	20%	
	Autoimmune/cholestatic	11%	11%	11%	
	Other	15%	16%	15%	
Hypertension	48%	47%	48%	0.98	
Diabetes	35%	37%	35%	0.59	
Coronary artery disease	5%	4%	5%	0.72	
MELDNa	14 (10-19)	13 (9-19)	14 (10-19)	0.43	
HCC	33%	32%	34%	0.68	
Dialysis	4%	3%	5%	0.52	
Ascites history	61%	58%	62%	0.45	
Hepatic encephalopathy (HE) history	55%	62%	53%	0.08	

Median (interquartile range) or %

*Using UCLA Three-Item Loneliness Scale, validated for interviewer-administered loneliness assessment

†n=436. 18 subjects (4%) were unable to receive in-person LFI testing due to COVID19-related clinical constraints

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Table 2

Factors associated with loneliness among liver transplant candidates.

Factor		Association with Loneliness (score≥5*)	
		Univariable Analyses	Multivariable Models†
		Odds Ratio (95% CI)p-value	Odds Ratio (95% CI)p-value
Frailty (LFI≥4.4)	2.05 (1.17-3.61) p=0.01	2.24 (1.23-4.08) p<0.01	
Age, per 5-year decrease	1.18 (1.07-1.30) p<0.01	1.19 (1.07-1.34) p<0.01	
Female sex	2.06 (1.40-3.16) p<0.01	1.83 (1.14-2.92) p=0.01	
Race/ethnicity	Non-Hispanic White	Reference	Reference
	Black	0.27 (0.06-1.19) p=0.08	0.17 (0.03-0.82) p=0.03
	Hispanic	0.87 (0.52-1.44) p=0.58	0.72 (0.41-1.2) p=0.24
	Asian	1.35 (0.67-2.70) p=0.40	1.46 (0.68-3.12) p=0.33
	Other	0.77 (0.16-3.79) p=0.75	0.69 (0.13-3.70) p=0.66
Work status	Working	Reference	Reference
	Not Working	1.97 (1.13-3.44) p=0.02	2.16 (1.16-4.03) p<0.01
Relationship status	Committed partnership	Reference	Reference
	No committed partnership	2.26 (1.47-3.48) p<0.0005	2.07 (1.29-3.32) p<0.01
	Unknown	1 (n=2)	1 (n=2)
Highest level of education achieved	≥12th grade	Reference	–
	>12th grade	0.85 (0.55-1.30) p=0.45	–
	Unknown	1.89 (0.57-6.23) p=0.30	–
Etiology	EtOH	0.96 (0.60-1.52) p=0.85	–
	Other	Reference	–
MELDNa	0.99 (0.96-1.03) p=0.60	–	
HCC	0.91 (0.58-1.43) p=0.68	–	
Ascites history	0.88 (0.66-1.17) p=0.38	–	
Hepatic Encephalopathy (HE) history	1.46 (0.95-2.24) p=0.09	–	

*Using UCLA Three-Item Loneliness Scale, a validated metric for loneliness scaled from 3-9, in which higher scores indicates higher degrees of loneliness. Given that various cut points have been reported in the literature[1], we chose ≥5 as the cut-point for loneliness in our primary analysis because it balances sensitivity and specificity. We also performed several sensitivity analyses to test the robustness of our final multi-variable model; and none qualitatively change the results of our primary analysis: 1. alternate loneliness cut-points 2. simple linear regression, with total loneliness scores treat as a continuous interval outcome variable 3. Ordinal regression analyses: ordered logit and ordered probit regressions

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† Sensitivity analysis including all variables assessed in UV analysis—except for height and education due to high collinearity with sex and Hispanic race, respectively—did not qualitatively change the MV model. Likewise, excluding loneliness scale assessment modality in sensitivity analysis did not change the MV model.