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Exploring Caregiver Support as a Potential Mediator of Neighborhood Socioeconomic Disadvantage and Reduced Likelihood of Liver Transplant Waitlisting

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Background. Individuals from socioeconomically disadvantaged neighborhoods may be at risk of inequitable access to the liver transplant (LT) waitlisting (WL), but mechanisms mediating this relationship are not well understood. We assessed whether area deprivation index (ADI), a measure of neighborhood socioeconomic deprivation, was associated with LT WL and assessed whether caregiver support, a potentially modifiable factor, mediated this relationship. **Methods.** We performed a single-center retrospective cohort study of adults referred for LT evaluation from January 2015 to December 2021. First, we assessed the association between ADI and LT WL using univariate and multivariable logistic regression analyses. Second, we analyzed caregiver support as a potential mediator through mediation analysis. **Results.** During the study period, 2574 patients were referred for LT, 2057 patients initiated evaluation, and 622 patients were waitlisted. Residence in the highest ADI quartile was associated with lower probability of WL (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.52-0.99) after adjusting for individual medical and sociodemographic factors, and distance from the transplant center. In adjusted mediation analysis, caregiver support did not mediate the relationship between ADI and LT WL (OR, 0.90; 95% CI, 0.80-1.01), and highest ADI quartile also did not have significant direct effects on LT WL (OR, 0.95; 95% CI, 0.72-1.26). **Conclusions.** ADI may be useful as a screening tool to identify candidates who could benefit from early intervention in the LT process when individual social needs information is not available. Caregiver support did not mediate the ADI and LT WL association. Additional work is needed to understand which modifiable factors may mediate this association to inform potential interventions for this population.

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It is widely known that social drivers of health (SDOH), such as education, occupation, transportation, and housing stability, can impact individual morbidity and mortality through mechanisms such as access to healthcare, health literacy, medication adherence, and exposure to stress.[1-4] However, this information is often not readily available in the electronic health record. Composite indices of neighborhood socioeconomic disadvantage have been developed that

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integrate census tract- or block group-level information about education level, employment, housing quality, and income level from the American Community Survey[5] to better capture the multidimensionality of neighborhood disadvantage and with stronger explanatory power than single measures alone.[6] These neighborhood measures have been associated with a range of poor health outcomes.[7-11] This association can be partly attributed to individual SDOH, but studies have also shown that neighborhood disadvantage itself contributes to disparities.[12,13] One of the most widely used composite measures and the only 1 available at the granular neighborhood level of the Census block group is the area deprivation index (ADI).

Both individual and neighborhood socioeconomic disadvantages have been associated with inequities at various stages of the complex liver transplant (LT) process, from referral to posttransplant outcomes. Hasjim et al[14] found that ADI was associated with higher risk of decompensation from cirrhosis and all-cause mortality, as well as a lower likelihood of LT waitlisting. Multiple single-center studies have demonstrated an association between area-level socioeconomic disadvantage and lower odds of LT waitlisting, although none of these studies adjusted for individual socioeconomic variables beyond insurance type.[15-18]

Given that SDOH are challenging to intervene in, we sought to understand whether caregiver support, a key pretransplant requirement at most centers, could be a potentially modifiable factor that mediates the relationship between neighborhood disadvantage and LT waitlisting. In a national survey carried out by Ladin et al,[19] the authors found that a majority of transplant providers were concerned that social support requirements disproportionately impacted patients of low socioeconomic status. We conceptualized caregiver support as potentially modifiable through paid caregivers or policies such as paid family and medical leave that could help alleviate the financial burden of caregiving.[20,21] Although there are other potentially modifiable mediators, including individual health-related social needs (HRSN) such as access to transportation, these factors are not as universally assessed as caregiver support during the LT evaluation process.

Therefore, by collecting individual sociodemographic factors alongside neighborhood disadvantage (measured by ADI), we aimed to (1) robustly evaluate the association between ADI and the likelihood of waitlisting at our transplant center and (2) perform a mediation analysis to assess whether caregiver support is a potentially modifiable mediator in the relationship between ADI and LT waitlisting.

MATERIALS AND METHODS

Study Design and Population

The University of Washington Medical Center (UWMC) is a transplant center in the United Network for Organ Sharing Region 6 and receives LT referrals from Washington state as well as the neighboring states of Oregon, Wyoming, Idaho, Montana, and Alaska. In this retrospective cohort study, we included adults (age 18 y and older) who were referred to UWMC for LT consideration from January 1, 2015, to December 31, 2021, including inpatient referrals. We excluded patients who underwent previous LT, were referred for multiorgan transplant, including the liver, had missing insurance information, or had addresses that could not be geocoded into a corresponding ADI rank. We followed patients for outcomes from the time of referral through November 2022. The study was conducted in accordance with both the Declaration of Helsinki and Declaration of Istanbul and was approved by the University of Washington Institutional Review Board (IRB# STUDY00015831).

Individual-level Data

We obtained data from UWMC transplant database and electronic medical records. We reviewed notes from patients' initial LT clinic evaluation, social work visits, or available records through health systems linked to UWMC. We collected the following clinical variables: cause of liver disease, model for end-stage liver disease score, complications of liver disease, prior abdominal surgery, presence of hepatocellular carcinoma, and presence of relevant comorbidities; sociodemographic factors: patient home address, age, self-identified variables including sex, marital status, race and ethnicity, primary language, employment status, education level, social worker-assessed caregiver support (described in detail below), and distance from the transplant center (straight-line distance based on geocoding). If race and ethnicity was listed in our health system's medical record, then it was self-identified, but race and ethnicity could also be obtained from outside medical records linked to ours, and protocos of other health systems for identifying race and ethnicity were not known.

Transplant social workers assess a patient's plan for caregiver support before transplant via in-person or telehealth visit (including telephone visits); requirements for caregiver support include the availability of caregiver/s to provide continuous caregiver support for the patient for approximately 3 mo posttransplant, including staying near UWMC, providing transportation, and accompanying the patient to/from follow-up appointments during this time. Multiple caregivers are permitted. Caregivers are also required to attend a transplant education class before transplant, but this may not have occurred by the time of initial evaluation, so our determination of caregiver support was based on the transplant social workers' initial assessment of support based on the earlier criteria with the patient. If documentation of caregiver support was not identified in the medical record or caregiver assessment was deferred due to more information or time being needed, "unknown" was entered. The social workers' evaluation of patients does not differ for inpatient versus outpatient LT referrals, aside from the greater urgency of inpatient referrals. Standardized chart review process and training were provided for each chart reviewer to ensure consistency across reviews.

Neighborhood-level Data

The primary exposure of interest was the patient's ADI rank, a composite measure of 17 Census-based measures under the primary domains of income, employment, education, and housing quality and affordability. The ADI for each patient was derived from the home address at the time of referral. The 2019 ADI file (block group files V3.0) was obtained through the University of Wisconsin-Madison School of Medicine and Public Health.[22] The study team geocoded patients' street addresses to obtain 12-digit Federal Information Processing Standards codes, according to the University of Washington Institutional Review Board regulations for electronic transfer of addresses. This 12-digit

Federal Information Processing Standards code was linked to the ADI file and each patient was then assigned a neighborhood ADI. In this study, we used nationally ranked ADI due to our referrals originating from multiple states. An ADI percentile ranking of 1 signifies the least disadvantage nationally, whereas an ADI of 100 signifies the greatest disadvantage. To create more meaningful categories that may inform future interventions, we evaluated the ADI as a categorical variable by dividing observed ADI into 4 quartiles. We also conducted a sensitivity analysis treating ADI as a continuous variable.

Outcome Measures

The primary outcome was, among referred individuals who initiated evaluation, whether they were waitlisted versus not (reasons included denial due to medical or nonmedical ineligibility, clinical improvement, inability to contact patient, patient withdrawal [transfer to/transplanted at another center, patient choice], still being in work-up, or patient death).

Statistical Analysis

For the descriptive statistics, continuous variables were described by the median and interquartile ranges. Categorical variables were described as counts and percentages. The Kruskal-Wallis rank sum test was used to compare the continuous variables, and Pearson's chi-square test was used to compare the categorical variables by ADI quartile. Recognizing that individuals referred to as inpatients may be different from patients referred to as outpatients in terms of disease severity, acuity, and access to expedited transplant evaluation, we analyzed the inpatient versus outpatient evaluation cohorts separately.

To assess the association between ADI quartiles and LT waitlisting, we performed univariate and multivariable logistic regression models with the population who initiated evaluation in the clinic. We first assessed ADI quartiles alone with LT waitlisting (model 1), then introduced medical factors (model 2), added sociodemographic factors without medical factors (model 3), and finally added both medical and sociodemographic variables (model 4). Potential confounders were identified in the conceptual model (Figure 1), and because caregiver support was hypothesized as a potential mediator on the causal pathway, it was not included as a confounder in the regression analysis to avoid potentially attenuating results.

In the regression analysis, we addressed missing data using multiple imputations, implemented with the "mice" package in R. Imputation was only performed on the population that initiated LT evaluation. Multiple imputations create multiple data sets where missing values are imputed using statistical models, allowing for the variability and uncertainty of the imputations. We selected predictive mean matching, a nonparametric method, to impute missing values, ensuring that the replacements were closely matched to observed data. After imputation, we performed our analyses on 5 separate, complete data sets and combined the findings using Rubin's rules.[23] We ensured that 5 imputations were adequate through assessment of the fraction of missing information values, which were all <0.15, indicating a stable and reliable estimate of our parameters.[24]

Statistical significance was defined as a P value of <0.05. Although ADI is generated at the Census block group level, we did not need to account for clustering since individuals in this study resided in different Census block groups.

Mediation Analysis

Descriptive analyses were first performed on individuals with caregiver support stratified by ADI quartile and waitlisting status. Second, we conducted a mediation analysis of natural direct and indirect effects to investigate the role of caregiver support as a potential mediator in the relationship between ADI and waitlisting for LT for individuals who initiated evaluation in the clinic. Direct effects reflect the effect of the exposure (ADI) on the outcome (LT waitlisting) without the mediator (caregiver support). Indirect effects reflect the effect of ADI on LT waitlisting via the possible mediating pathway of caregiver support. Because multinomial logistic regression cannot be implemented for

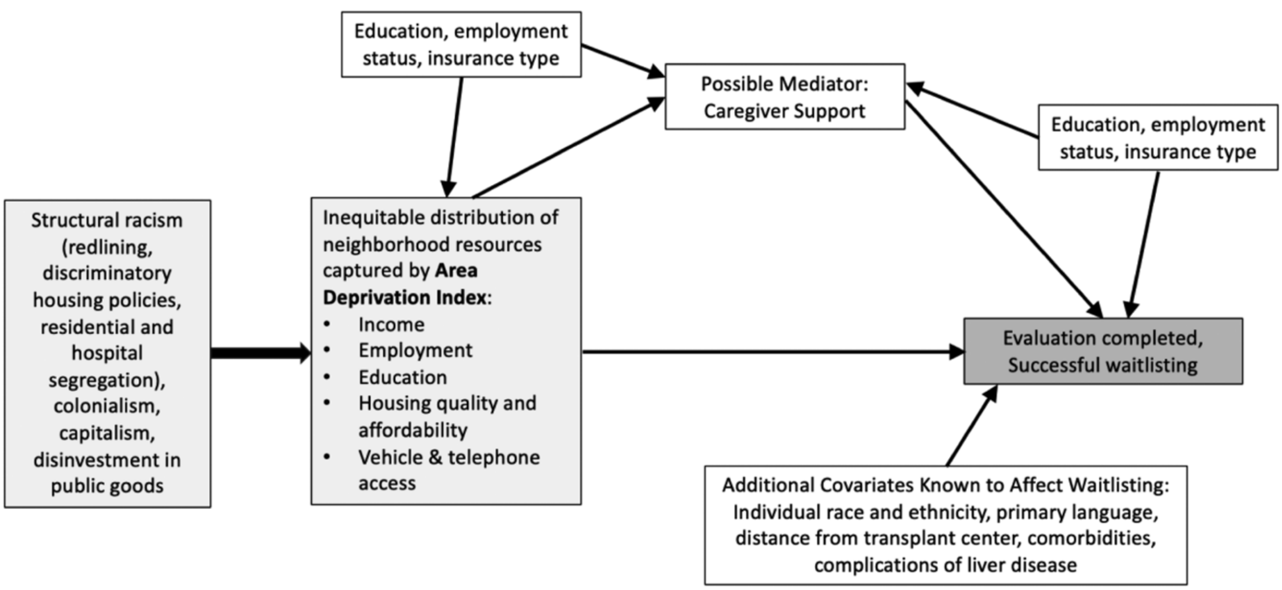

FIGURE 1. Conceptual model.

mediation analysis, we dichotomized caregiver support by treating "unknown" caregiver support as "no" caregiver support. A sensitivity analysis was performed, excluding those with unknown caregiver support (n = 355). In the adjusted mediation analysis, we controlled for factors identified as potential confounders of the exposure-mediator (ADI-caregiver support) and mediator-outcome (caregiver support-waitlisting) relationships, specifically education, employment status, and insurance type (Figure 1). Variables included in the regression models and mediation analysis were also assessed for collinearity, and none were found to be collinear. Finally, we also assessed caregiver support as a moderator by performing an interaction analysis between ADI and caregiver support.

Analyses were conducted in R (version 4.0.0, copyright 2020 The R Foundation for Statistical Computing) and JMP Pro (version 17.0.0 copyright 2022 JMP Statistical Discovery LLC). Mediation analysis was performed using the "medflex" package in R, which is specifically designed for conducting causal mediation analysis and quantifying the natural direct and indirect effects of variables.

RESULTS

Referral Population

A total of 2574 patients were referred to UWMC for LT consideration during the study period. We excluded 11 patients who did not fulfill the inclusion criteria and 13 patients whose addresses could not be geocoded to a corresponding ADI. A total of 2550 patients were included in our final study cohort. Figure 2 illustrates a flow diagram of the patients who were included and excluded from the study from the time of referral (n = 2550), evaluation (inpatient [n = 265] versus clinic [n = 1792]), and waitlisting (n = 698). Our referral population spanned multiple Western states, namely Washington (n = 1970), Wyoming (n = 2), Alaska (n = 179), Montana (n = 158), Oregon (n = 90), and Idaho (n = 128), whereas a small number lived in other outlying states (n = 23). The median age of the referral population was 58 y (interquartile range [IQR], 49–64 y), with 57% (n = 1462) of the referred patients identifying as men and 43% (n = 1088) as women.

Among those referred for LT, median ADI was similar among the different cohorts—clinic versus inpatient versus not evaluated (32 [IQR, 21–46] for patients evaluated in clinic versus 32 [IQR, 21–47] for inpatient evaluations versus 34 [IQR, 23–49] for those not evaluated, $P = 0.2$). The median distance from the transplant center (miles) was significantly greater for patients who were evaluated as inpatient or not evaluated compared with those who were evaluated in the clinic (52 [IQR, 24–179] for clinic versus 72 [IQR, 23–228] for inpatient versus 86 [IQR, 29–250] for those not evaluated, $P < 0.01$; Table 1).

Candidates Evaluated for LT

Among the 1792 patients who initiated LT evaluation in the clinic, a total of 622 (34.7%) were ultimately waitlisted. Among the 265 patients evaluated as an inpatient, 76 (28.7%) were waitlisted. **Table S1** (**SDC,** http://links.lww.com/TXD/A751) demonstrates baseline characteristics of the patients who initiated evaluation in the clinic, stratified by waitlist status. The most common reason for not being waitlisted was denial (due to medical or nonmedical ineligibility) or clinical improvement (61%; N = 714), followed by death (21%; N = 244), and then withdrawal or inability to contact patient (10%; N = 118), as shown in **Table S2** (**SDC,** http://links.lww.com/TXD/A751).

Table 2 shows the univariate and multivariable logistic regression models of the association between ADI and LT waitlisting for the cohort evaluated in the clinic. We found that candidates from more disadvantaged neighborhoods (higher ADI quartile) had an increasingly lower probability

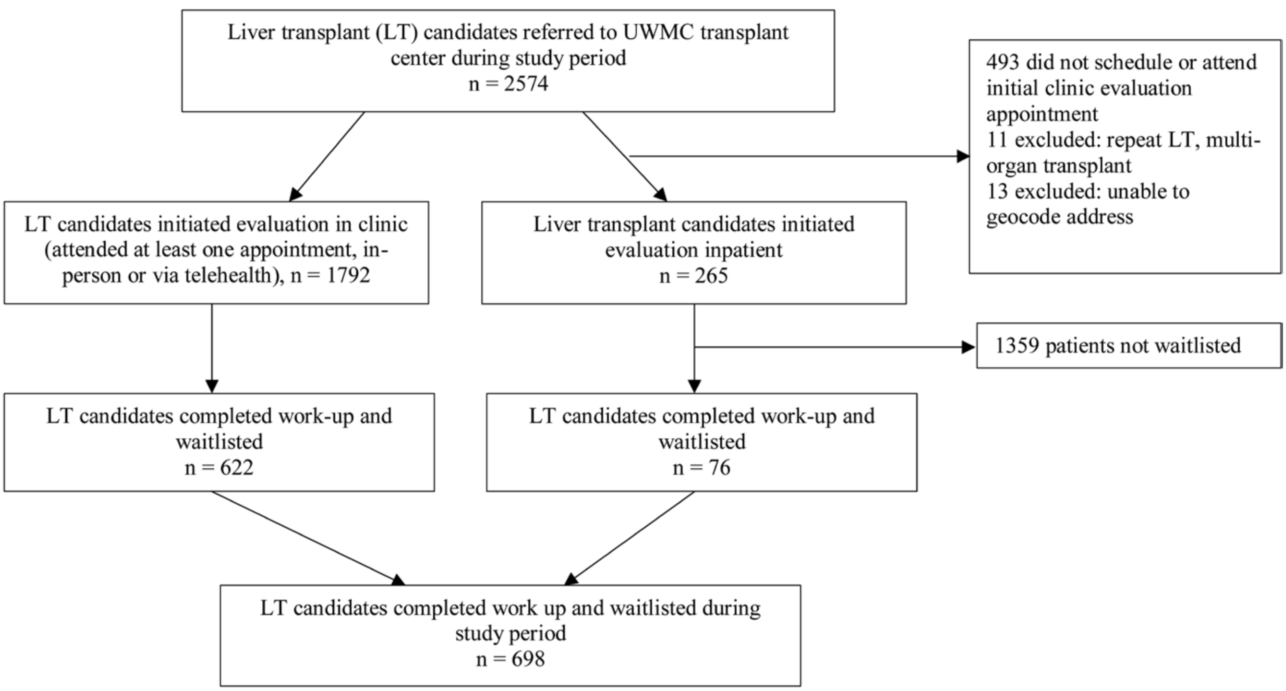

FIGURE 2. Liver transplant candidates included and excluded from study.

TABLE 1.

Baseline characteristics of referral population, stratified by clinic evaluation vs inpatient evaluation vs not seen

Variables	Overall (N = 2550)	Clinic (N = 1792)	Inpatient (N = 265)	Not seen[a] (N = 493)	*P*[b]
Area deprivation index	33 (21–47)	32 (21–46)	32 (21–47)	34 (23–49)	0.20
ADI quartiles					0.80
Q1	639 (25%)	463 (26%)	67 (25%)	109 (22%)	
Q2	671 (26%)	465 (26%)	72 (27%)	134 (27%)	
Q3	620 (24%)	437 (24%)	61 (23%)	122 (25%)	
Q4	620 (24%)	427 (24%)	65 (25%)	128 (26%)	
Age, y	58 (49, 64)	58 (49, 64)	52 (40, 61)	58 (49, 64)	<0.01
Sex					
Male	1462 (57%)	1047 (58%)	123 (46%)	292 (59%)	<0.01
Female	1088 (43%)	745 (42%)	142 (54%)	200 (41%)	
Marital status					<0.01
Married/partnered	1340 (53%)	1038 (58%)	121 (46%)	181 (37%)	
Divorced/widowed	445 (17%)	348 (19%)	45 (17%)	52 (11%)	
Single	518 (20%)	335 (19%)	91 (34%)	92 (19%)	
Unknown	247 (9.7%)	71 (4.0%)	8 (3.0%)	168 (34%)	
Race and ethnicity					<0.01
White	1637 (64%)	1221 (68%)	185 (70%)	231 (47%)	
Asian	111 (4.4%)	76 (4.2%)	17 (6.4%)	18 (3.7%)	
Black	51 (2.0%)	34 (1.9%)	5 (1.9%)	12 (2.4%)	
Hispanic	199 (7.8%)	152 (8.5%)	16 (6.0%)	31 (6.3%)	
AI/AN	111 (4.4%)	77 (4.3%)	24 (9.1%)	10 (2.0%)	
Multiracial or other	32 (1.3%)	20 (1.1%)	4 (1.5%)	8 (1.6%)	
Unknown	409 (16%)	212 (12%)	14 (5.3%)	183 (37%)	
Primary language					<0.01
English	2336 (92%)	1662 (93%)	245 (92%)	429 (87%)	
Spanish	86 (3.4%)	61 (3.4%)	8 (3.0%)	17 (3.4%)	
Other	71 (2.8%)	50 (2.8%)	9 (3.4%)	12 (2.4%)	
Unknown	57 (2.2%)	19 (1.1%)	3 (1.1%)	35 (7.1%)	
Insurance					<0.01
Private	1285 (50%)	919 (51%)	129 (49%)	237 (48%)	
Public	1240 (49%)	868 (48%)	131 (49%)	241 (49%)	
Unknown	25 (1.0%)	5 (0.3%)	5 (1.9%)	15 (3.0%)	
Education					<0.01
≤High school	813 (32%)	678 (38%)	98 (37%)	37 (7.5%)	
>High school	798 (31%)	705 (39%)	64 (24%)	29 (5.9%)	
Unknown	939 (37%)	409 (23%)	103 (39%)	427 (87%)	
Employment					<0.01
Yes	577 (23%)	452 (25%)	68 (26%)	57 (12%)	
No	1483 (58%)	1192 (67%)	161 (61%)	130 (26%)	
Unknown	490 (19%)	148 (8.3%)	36 (14%)	306 (62%)	
ESLD diagnosis					
AIH	66 (2.6%)	52 (2.9%)	9 (3.4%)	5 (1.0%)	
ALD	907 (36%)	683 (38%)	101 (38%)	123 (25%)	
Cancer	13 (0.5%)	9 (0.5%)	0 (0%)	4 (0.8%)	
Cholestatic liver disease	143 (5.6%)	117 (6.5%)	12 (4.5%)	14 (2.8%)	
MASH	313 (12%)	256 (14%)	22 (8.3%)	35 (7.1%)	
Viral hepatitis	485 (19%)	397 (22%)	27 (10%)	61 (12%)	
Other	424 (17%)	256 (14%)	80 (30%)	88 (18%)	
Unknown	199 (7.8%)	22 (1.2%)	14 (5.3%)	163 (33%)	
Diabetes mellitus					<0.01
Yes	675 (26%)	537 (30%)	53 (20%)	85 (17%)	
No	1628 (64%)	1220 (68%)	196 (74%)	212 (43%)	
Unknown	247 (9.7%)	35 (2.0%)	16 (6.0%)	196 (40%)	
Hypertension					<0.01
Yes	685 (27%)	528 (29%)	55 (21%)	102 (21%)	
No	1559 (61%)	1216 (68%)	188 (71%)	155 (31%)	
Unknown	306 (12%)	48 (2.7%)	22 (8.3%)	236 (48%)	

(Continued)

TABLE 1.
Continued

Variables	Overall (N = 2550)	Clinic (N = 1792)	Inpatient (N = 265)	Not seen[a] (N = 493)	P[b]
Cardiovascular disease					<0.01
Yes	176 (6.9%)	141 (7.9%)	10 (3.8%)	25 (5.1%)	
No	2037 (80%)	1588 (89%)	228 (86%)	221 (45%)	
Unknown	337 (13%)	63 (3.5%)	27 (10%)	247 (50%)	
Previous abdominal surgery					<0.01
Yes	851 (33%)	729 (41%)	57 (22%)	65 (13%)	
No	1269 (50%)	956 (53%)	169 (64%)	144 (29%)	
Unknown	430 (17%)	107 (6.0%)	39 (15%)	284 (58%)	
Hepatocellular carcinoma					<0.01
Yes	450 (18%)	381 (21%)	12 (4.5%)	57 (12%)	
No	1427 (56%)	1103 (62%)	189 (71%)	135 (27%)	
Unknown	673 (26%)	308 (17%)	64 (24%)	301 (61%)	
MELD	16 (12–22)	15 (11–20)	31 (24–37)	19 (12–24)	<0.01
Unknown	485	113	39	333	
Ascites					<0.01
Yes	1538 (60%)	1210 (68%)	173 (65%)	155 (31%)	
No	677 (27%)	527 (29%)	68 (26%)	82 (17%)	
Unknown	335 (13%)	55 (3.1%)	24 (9.1%)	256 (52%)	
Portal vein thrombosis					<0.01
Yes	117 (4.6%)	97 (5.4%)	8 (3.0%)	12 (2.4%)	
No	2051 (80%)	1620 (90%)	227 (86%)	204 (41%)	
Unknown	382 (15%)	75 (4.2%)	30 (11%)	277 (56%)	
Encephalopathy					<0.01
Yes	1152 (45%)	894 (50%)	163 (62%)	95 (19%)	
No	1014 (40%)	831 (46%)	70 (26%)	113 (23%)	
Unknown	384 (15%)	67 (3.7%)	32 (12%)	285 (58%)	
Variceal bleed history					<0.01
Yes	294 (12%)	224 (12%)	28 (11%)	42 (8.5%)	
No	1883 (74%)	1501 (84%)	206 (78%)	176 (36%)	
Unknown	373 (15%)	67 (3.7%)	31 (12%)	275 (56%)	
Distance from center, miles	57 (25–213)	52 (24–179)	72 (23–228)	86 (29–250)	<0.01

[a]n (%); median (interquartile range).
[b]Pearson's chi-square test and Kruskal-Wallis rank-sum test.
ADI, area deprivation index; AI/AN, American Indian/Alaska Native; AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; ESLD, end-stage liver disease; MASH, metabolic dysfunction–associated steatohepatitis; MELD, model for end-stage liver disease.

of being waitlisted after being seen in the clinic, compared with candidates from the lowest quartile ADI (least disadvantaged) neighborhoods (ADI quartile 2 [Q2]: odds ratio [OR], 0.77; 95% confidence interval [CI], 0.59-1.00; Q3: OR, 0.69; 95% CI, 0.53-0.91; and Q4: OR, 0.64; 95% CI, 0.49-0.85). This relationship persisted for candidates from ADI Q3 (OR, 0.70. 95% CI, 0.52-0.94) and ADI Q4 (OR, 0.63; 95% CI, 0.46-0.86) after adjusting for medical factors in model 2.

In model 3, after adjusting for both medical and individual sociodemographic factors, this relationship persisted for candidates from ADI Q4 (OR, 0.72; 95% CI, 0.52-0.99). Among the sociodemographic factors, those associated with an increased probability of LT waitlisting included having greater than a high school education (OR, 1.56; 95% CI, 1.17-2.07) and being employed at the time of initiating LT evaluation (OR, 1.66; 95% CI, 1.27-2.15). Marital status of divorced/widowed or single were both associated with a lower probability of LT waitlisting compared with being married/partnered (OR, 0.66; 95% CI, 0.48-0.89 and OR, 0.54; 95% CI, 0.40-0.74, respectively). In model 3, which adjusted solely for sociodemographic factors without the medical factors, the effect of ADI on LT waitlisting was significantly attenuated.

Interaction effects between covariates were tested for, and none were found. Similar results were found in our sensitivity analysis treating ADI as a continuous exposure (**Table S3, SDC,** http://links.lww.com/TXD/A751). In our fully adjusted model 4, we also found that for every 10-y increase in age was associated with a lower likelihood of waitlisting (OR, 0.86; 95% CI, 0.75-0.98), and male sex was associated with an increased likelihood of waitlisting (OR, 1.90; 95% CI, 1.47-2.45).

We performed similar analyses in the inpatient evaluation cohort and found that ADI was not associated with LT waitlisting in both the univariate and multivariable models (ADI Q2: OR, 0.90; 95% CI, 0.30-2.69; Q3: OR, 1.06; 95% CI, 0.33-3.45; and Q4: OR, 1.37; 95% CI, 0.37-5.12).

Mediation Analysis

Baseline characteristics of patients initiating evaluation in the clinic, stratified by caregiver support status (yes, no, or unknown), are shown in **Table S4** (**SDC,** http://links.lww.com/TXD/A751). The median ADI was 31 for patients with caregiver support versus 34 for those with unknown support and 37 for those without support. Patients with caregiver support were more likely to be married/partnered than those with no or unknown support ($P < 0.001$).

TABLE 2.

Univariate and multivariable logistic regression models of liver transplant waitlisting

	Model 1 (ADI alone)				Model 2 (ADI + medical factors)				Model 3 (ADI + sociodemographic factors)				Model 4 (ADI + medical + sociodemographic factors)			
Variables	Estimate	95% CI		Estimate	Estimate	Estimate		Estimate	Estimate	95% CI		*P*	Estimate	95% CI		*P*
Area deprivation index																
ADI Q1	Ref				Ref				Ref				Ref			
ADI Q2	0.77	0.59	1.00	0.05	0.79	0.59	1.06	0.11	0.87	0.66	1.15	0.32	0.87	0.64	1.18	0.36
ADI Q3	0.69	0.53	0.91	0.01	0.70	0.52	0.94	0.02	0.82	0.61	1.10	0.18	0.79	0.58	1.08	0.13
ADI Q4	0.64	0.49	0.85	<0.01	0.63	0.46	0.86	<0.01	0.78	0.58	1.06	0.11	0.72	0.52	0.99	0.04
Age[a]					0.86	0.77	0.96	0.01	0.90	0.81	0.99	0.04	0.82	0.73	0.93	<0.01
Sex (male)					1.95	1.55	2.47	<0.01	1.59	1.29	1.97	<0.01	1.82	1.43	2.32	<0.01
Medical factors																
Cause of ESLD																
Cholestatic liver disease					Ref								Ref			
AIH					0.81	0.39	1.68	0.57					1.04	0.48	2.21	0.93
ALD					0.30	0.19	0.47	<0.01					0.36	0.22	0.57	<0.01
Cancer					0.12	0.02	0.69	0.02					0.14	0.03	0.78	0.03
MASH					0.41	0.25	0.69	<0.01					0.42	0.24	0.71	<0.01
Other					0.29	0.18	0.48	<0.01					0.31	0.19	0.53	<0.01
Viral hepatitis					0.29	0.18	0.46	<0.01					0.36	0.22	0.59	<0.01
Comorbidities																
Diabetes					1.29	0.99	1.67	0.06					1.35	1.02	1.77	0.03
Hypertension					0.85	0.66	1.10	0.21					0.87	0.68	1.12	0.29
CVD					0.22	0.13	0.38	<0.01					0.23	0.13	0.40	<0.01
Prior abdominal surgery					1.00	0.80	1.26	0.97					1.04	0.83	1.31	0.72
HCC					3.06	2.20	4.25	<0.01					2.98	2.15	4.14	<0.01
ESLD complications																
MELD					1.04	1.02	1.06	<0.01					1.03	1.01	1.05	<0.01
Ascites					0.91	0.69	1.19	0.48					0.93	0.70	1.22	0.59
PVT					1.48	0.95	2.32	0.08					1.37	0.86	2.17	0.19
Encephalopathy					2.27	1.78	2.90	<0.01					2.57	1.98	3.34	<0.01
Variceal bleed history					0.33	0.23	0.49	<0.01					0.32	0.22	0.47	<0.01
Sociodemographic factors																
Education (>HS)									1.47	1.12	1.92	<0.01	1.56	1.17	2.07	<0.01
Employment (yes)									1.50	1.18	1.90	<0.01	1.66	1.27	2.15	<0.01
Insurance (public)									0.85	0.69	1.06	0.14	0.94	0.75	1.19	0.63
Marital status																
Married/partnered									Ref				Ref			
Divorced/widowed									0.63	0.48	0.83	<0.01	0.66	0.48	0.89	0.01
Single									0.60	0.45	0.80	<0.01	0.54	0.40	0.74	<0.01
Race and ethnicity																
White									Ref				Ref			
Asian									1.53	0.87	2.68	0.14	1.52	0.82	2.81	0.18
Black									0.76	0.35	1.64	0.49	0.73	0.32	1.66	0.46
Hispanic									1.02	0.66	1.56	0.94	1.03	0.64	1.65	0.90
AI/AN									1.01	0.58	1.77	0.96	0.92	0.50	1.68	0.77
Multiracial or other									0.87	0.33	2.27	0.78	0.83	0.30	2.32	0.72
Primary language																
English									Ref				Ref			
Spanish									1.50	0.77	2.92	0.23	1.39	0.67	2.87	0.38
Other									0.91	0.46	1.80	0.79	0.92	0.43	1.97	0.84
Distance from transplant center[b]									0.97	0.94	1.01	0.11	0.98	0.95	1.01	0.24

[a]For every 10-y increase.
[b]For every 100 miles.
ADI, area deprivation index; AI/AN, American Indian/Alaska Native; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; CI, confidence interval; CVD, cardiovascular disease; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; HS, high school; MASH, metabolic associated steatohepatitis; MELD, model for end-stage liver disease; PVT, portal vein thrombosis; Q, quartile; Ref, reference.

TABLE 3.

Analysis of caregiver support as potential mediator of the association between area deprivation index and liver transplant waitlisting

Area deprivation index quartile		Unadjusted		Adjusted[a]	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Direct effects	Q1	Ref		Ref	
	Q2	0.83 (0.65-1.05)	0.13	0.92 (0.71-1.19)	0.53
	Q3	0.79 (0.61-1.01)	0.07	0.92 (0.70-1.23)	0.57
	Q4	0.79 (0.61-1.02)	0.07	0.95 (0.72-1.26)	0.71
Indirect effects	Q1	Ref		Ref	
	Q2	0.93 (0.84-1.04)	0.19	0.99 (0.89-1.09)	0.80
	Q3	0.88 (0.78-0.99)	0.03	0.96 (0.87-1.06)	0.42
	Q4	0.81 (0.72-0.92)	<0.001	0.90 (0.80-1.01)	0.06

[a]Adjusted for potential confounders of the exposure-mediator and mediator-outcome relationships (education, employment status, and insurance type).
CI, confidence interval; OR, odds ratio; Ref, reference.

Among patients residing in the least disadvantaged areas (ADI Q1), 74.5% had caregiver support compared with 63.7% of those in the highest disadvantage areas (ADI Q4; **Table S5, SDC,** http://links.lww.com/TXD/A751). Among those with caregiver support, 53.3% were waitlisted from ADI Q1 compared with 45.2% from Q4. Among those with no or unknown social support, 4.2% were waitlisted from ADI Q1, 2.9% from Q2, 4.3% from Q3, and 5.2% from Q4.

In unadjusted mediation analysis, caregiver support was a significant mediator of the association between highest neighborhood socioeconomic disadvantage (ADI Q3 and Q4) and waitlisting (OR, 0.88; 95% CI, 0.78-99 for Q3, $P = 0.03$ and OR, 0.81; 95% CI, 0.72-92; $P < 0.001$ for Q4; Table 3). However, once we adjusted for the potential confounders of the exposure-mediator and mediator-outcome relationships, caregiver support was no longer a significant mediator with OR of 0.96 (95% CI, 0.87-1.06; $P = 0.42$) for Q3 and OR of 0.90 (95% CI, 0.80-1.01; $P = 0.06$) for Q4. The direct effects of ADI on waitlisting were not significant at any quartile of ADI in unadjusted or adjusted mediation analyses.

A sensitivity mediation analysis was performed by excluding 355 individuals with unknown caregiver support (**Table S6, SDC,** http://links.lww.com/TXD/A751), and again, caregiver support was not a significant mediator in adjusted analyses.

Given the potential for caregiver support to serve as a moderator, we lastly conducted a formal interaction analysis, which found no significant interaction between ADI and caregiver support.

DISCUSSION

In this study, we found that, among individuals who initiated evaluation in the LT clinic, those residing in neighborhoods of greatest socioeconomic disadvantage were significantly less likely to be waitlisted for LT after adjusting for individual clinical and sociodemographic factors. This association was not significant for those evaluated inpatients, where evaluation is often expedited and barriers to follow-up and completion of steps in the evaluation process are no longer present. These findings suggest a potential role for ADI to serve as an initial marker to prompt more individualized assessment and support early in the outpatient LT evaluation process. In our mediation analysis, caregiver support was not a significant mediator of this relationship, suggesting the need to identify other potentially modifiable mediators.

The lack of association between ADI and initiation of evaluation in our study differs from prior research by Strauss et al,[16] which found that individuals from high ADI areas were at higher risk of not initiating evaluation postreferral,[16] suggesting that there may be geographic variation in upstream factors that contribute to patient referral for LT evaluation. At our center, patients who did not initiate evaluation in the clinic tended to live farther from the transplant center. Similarly, patients who were evaluated inpatient were more likely to live farther away from the transplant center than those who initiated evaluation in the clinic. Being farther from the transplant center may also exacerbate challenges in securing caregiver support, given the burden of travel and removal from one's community and life obligations that posttransplant caregiving demands. Outreach clinics and telemedicine are 2 ways to make pre- and posttransplant care more accessible for these remote communities. For example, our hepatology division staffs a Liver Clinic in Spokane, WA, which serves the communities of eastern Washington as well as Idaho and Montana, thereby improving care access and reducing travel burden for these largely rural communities.

Among patients initially seen in the LT clinic, residence in the highest ADI neighborhood was associated with a 28% lower odds of being waitlisted for LT after adjusting for individual medical and sociodemographic variables, as well as distance from the transplant center, although those adjustments attenuated the effect. This finding is consistent with recent work demonstrating that composite measures of neighborhood disadvantage (such as ADI and social vulnerability index) may be associated with a lower probability of waitlisting.[16-18] We add to the validity of these findings by adjusting for a more extensive collection of individual confounders than other studies, including education, employment, insurance type, race and ethnicity, marital status, and primary language.

Finally, in our mediation analysis, we focused on caregiver support as a potentially modifiable, routinely collected factor, which we hypothesized to lie on the causal pathway between ADI and reduced odds of waitlisting. We found that caregiver support was not a significant mediator of the relationship between ADI and LT waitlisting. Our results showed that among those with identified caregiver support, LT waitlisting rates were still lower among those from highest versus least disadvantaged areas; this gradient was not present among those without or with unknown caregiver support. Formal interaction analysis did not find caregiver support to be a moderator of the relationship between ADI and waitlisting.

The effect of ADI on LT waitlisting may be mediated through other unmeasured variables, such as individual HRSN, which were not available for this study and merit future investigation. For example, in the study by Basu et al,[25] residence in high ADI areas has been associated with individuals having more HRSN, such as transportation barriers and housing insecurity, which may hinder the completion of the evaluation process, but these needs must still be ascertained on an individual level to avoid ecological fallacy.

Our findings suggest that an intervention focused on expanding caregiver support (eg, paid support for caregivers) is unlikely to close the gap in disparities in LT waitlisting related to neighborhood ADI. Nonetheless, ADI may serve as a potential screening tool to identify patients at risk of not progressing through the LT process. ADI is readily available from a patient's 9-digit zip code and can easily be integrated into the electronic medical record. A transplant center can then provide comprehensive outreach and assessment to individuals identified as at-risk. This may also help a transplant center optimize the use of limited resources for more equitable care. Identified HRSN and other barriers to evaluation completion and waitlisting could then be addressed by a dedicated "subteam" of the transplant team, including a social worker and financial counselor, who would develop expertise in caring for this population. To inform such interventions, more research—particularly qualitative in nature—is needed to better understand and describe the facilitators and barriers to waitlisting experienced by this population.

Our study has several strengths. Although our study was based at a single center, we were able to collect data on a large cohort of patients (>2000) from a multiple state referral region. In addition, through manual chart review, we were able to extract individual sociodemographic data, including education level, employment status, and presence of caregiver support, which enabled us to assess the interplay between neighborhood-level and individual sociodemographic factors in our analysis, an important gap in the literature, as well as assess a potential mediator.

We acknowledge several limitations of our study. First, the median ADI of our referred cohort was 33, lower than the national average at the 50th percentile, which may reflect that the Pacific Northwestern region of the United States tends to skew toward a slightly lower ADI compared with other regions of the United States. However, this finding may also reflect lower rates of LT referral from high ADI areas, an important finding that has been demonstrated in prior work.[26] Despite our average ADI being slightly lower than the national, our ADI still varied widely from a minimum of 2 to a maximum of 99, and we affirm findings found in other parts of the United States about the association between ADI and waitlisting, suggesting that these are not merely regional trends but generalizable findings.[16] Second, despite manual chart review, missingness of social variables and complications of liver disease remained high. We therefore used multiple imputations to address missingness. Furthermore, we cannot account for residual confounding attributable to individual- and neighborhood-level characteristics not captured in the electronic medical record, such as individual income, individual social needs, sociocultural beliefs and preferences surrounding transplant, and others. These limitations in terms of individual-level sociodemographic data reinforce our assertion that, for now, an easily attainable social marker such as ADI may facilitate support for patients who are at risk of not advancing in the transplant process. The amount of missing data among those who have not been evaluated or were denied early has been a frequently cited limitation[17] and argues for the need to have a standardized approach to collect SDOH data and form a national registry, especially among patients who have been referred for LT. Next, we did not conduct an empirical test to compare social worker evaluations across ADI or other sociodemographic factors to assess for different degrees of implicit and interpersonal bias, which may influence transplant listing. Fourth, we did not collect additional detailed information about the type of caregiver support (such as multiple versus one caregiver(s), friend versus family member support, financial stability of caregivers, etc). Finally, as our study was single-center, our findings may not be generalizable to other transplant centers' patient populations. Each transplant center should take into account the regional distribution of their referral population's ADI and independently decide what ADI cutoff to use for screening. Nonetheless, our study identifies an important inequity in the care for patients from neighborhoods with high socioeconomic disadvantage.

In conclusion, our findings emphasize that to make LT more equitable, we must work to redesign a system in which the levels of support offered in the transplant process can be individualized and personalized to the needs of the patient. Implementing programmatic changes to better support individuals living farther from transplant centers and living in high ADI areas will advance the care we provide to ensure that more patients can be successfully waitlisted, transplanted, and thrive posttransplant. Future studies with more robust individual data on HRSN are needed to advance the identification of modifiable factors, and more qualitative research is needed to elicit patient and community perspectives on the challenges faced in succeeding with LT evaluation, waitlisting, transplantation,[17] and posttransplant care[27] to inform future interventions.

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