Individual and neighborhood socioeconomic status in the prediction of liver transplantation among patients with liver disease

A population-based cohort study in Taiwan

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Abstract

Given the fact that >80% of liver transplantations (LTs) were living donor liver transplantation (LDLT) in Taiwan, we conducted this study to assess whether patients with lower socioeconomic status are subject to a lower chance of receiving hepatic transplantation.

This was a cohort study including 197,082 liver disease patients admitted in 1997 to 2013, who were at higher risk of LT. Personal monthly income and median family income of living areas were used to indicate individual and neighborhood socioeconomic status, respectively. Cox proportional hazard model that considered death as a competing risk event was used to estimate subdistribution hazard ratio (sHR) of LT in association with socioeconomic status.

Totally 2204 patients received LT during follow-up, representing a cumulative incidence of 1.12% and an incidence rate of 20.54 per 10^4 person-years. After adjusting for potential confounders, including age, sex, co-morbidity, location/urbanization level of residential areas, we found that patients with < median monthly income experienced significantly lower incidence of LT (aHR = 0.802, 95% confidence interval (CI) = 0.717–0.898), but those with >- median monthly income had significantly elevated incidence of LT (aHR = 1.679, 95% CI = 1.482–1.903), as compared to those who were not actively employed. Additionally, compared to areas with the lowest quartile of median family income, the highest quartile of median family income was also associated with significantly higher incidence rate of LT (aHR = 1.248, 95% CI = 1.055–1.478).

Higher individual and neighborhood socioeconomic status were significantly associated with higher incidence of LT among patients with higher risk of LT.

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, DDLT = deceased donor liver transplantation, ELSD = end-stage liver disease, HbsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LDLT = living donor liver transplantation, LT = liver transplantation, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, SES = socioeconomic status.

Keywords: cohort studies, liver transplantation, propensity score, socioeconomic status

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1. Introduction

Mounting evidence has suggested lower rates of access to liver transplantation (LT) among racial minorities, older, single, divorced, immigrants, and patients with lower income or inadequate insurance.[1–4] The reasons for such lower access to LT in these disadvantaged or lower socioeconomic status (SES) people could be multifaceted. A lower SES was found to be associated with lower waiting list registration rates for LT; and wait-list mortality was higher for the public insurance group than for the private insurance group.[5] Additionally, many patients with lower SES were residents of less developed areas, who usually have to face multiple financial and physical barriers to health care access. For example, they need to travel long distances for health care which also adds difficulty in receiving follow-up care.[6,7] Moreover, maintaining or expanding access to LT and the subsequent care is often threatened by the high cost of care, which also poses challenging to poor patient populations.[8]

Despite the above findings, most of the previous studies of the association between SES and prevalence rate of LT came from Western societies, whose context could be different from what has been observed in Taiwan at least on the following aspects.

First, unlike Western societies where most LT were deceased donor liver transplantation (DDLT) are common, there was widespread acceptability of the idea of living donor liver transplantation (LDLT) in East Asia, including Taiwan where more than 80% of LT are LDLT.[9] Additionally, according to Taiwan Human Organ Transplant Act, patients with end-stage liver disease (ESLD) can received liver organ from their adult (>=18 years) relatives who are no more than fifth degree of kinship.[10] This context could make unequal chance of LT for patients in need.

Second, due to the current regionally based allocation system in most Western nations, some patients list for and are transplanted away from home in regions with shorter waits and higher transplant rates. Such geographic disparity in availability of LT causes the dilemma of lower socioeconomic status, multiple listing, and death on the liver transplant waiting list.[11] Although there is also urban–rural difference for the residential areas of Taiwan, there is little barrier against accessibility to health care for most Taiwanese people mainly due to a relatively small area of Taiwan (394 km (245 mi) long, 144 km (89 mi) wide and has an area of 35,883 km^2 (13,855 mi^2). A convenient transportation system further effectively removes physical barriers against LT in areas away from home.

Third, Taiwan launched its National Health Insurance (NHI) program in 1995, which covers nearly all local residents. Such universal health insurance coverage greatly benefits several disadvantaged populations, such as children, elderly people, and non-working adults, who may receive health care at a reasonable cost.[12] The implementation of NHI program is thus expected to effectively remove the financial barriers to LT.

For such unique context mentioned above, Taiwan is a good setting for further examining the relationship between socioeconomic status and prevalence of LT. We hypothesized that there is still socioeconomic inequality in incidence of LT among patients with liver diseases.

2. Methods

2.1. Source of data and study design

The National Health Insurance Research Database (NHIRD) of Taiwan contains a large data size with complete and valid information of diagnoses and procedures in patients admitted. This retrospective cohort study was conducted using the NHIRD of Taiwan, which used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to define diseases and procedures.[13] We listed the ICD-9-CM codes of procedures and diseases described in this study in Supplementary Table S1, http://links.lww.com/MD/C870. Access to NHIRD was approved by the Review Committee of the National Health Research Institutes. Informed consents from study participants are waived as all study subjects included in the NHIRD are anonymous.

2.2. Identification of study cohort

We used a retrospective cohort study design in this study. A total number of 1,971,811 patients were admitted, between 1997 and 2013, for treatment or operation of various liver diseases. These patients did not have histories of LT. Details of these liver diseases and operations were listed in Supplemental Table S1, http://links.lww.com/MD/C870. Because not all patients admitted for liver diseases and operations are at potential risk of LT, we managed to calculate propensity score in an attempt to include only those who had higher chance of performing LT. Using LT as the dependent variable, we used multiple logistic regression model to calculate probability of performing LT. The independent variables included in the probability prediction model included liver diseases and operations shown in Supplemental Table S1, http://links.lww.com/MD/C870, as well as demographic characteristics, selected co-morbidity, locations of residences, and socioeconomic status presented in Table 1 and Supplemental Table S2, http://links.lww.com/MD/C870.

Supplemental Table S3, http://links.lww.com/MD/C870. The distribution of patients admitted for treatment or operation of various liver diseases and percentage of LT, according to different percentiles of propensity score. A higher propensity score is indicative of greater chance of receiving LT. More than 98.97% (2,968/2,999) of LTs were performed in patients with propensity scores >=50th percentile. The proportion decreased to 91.53%, 73.49%, 56.22%, and 21.97% for the >=75th, >=90th, >=95th, and >=99th percentile, respectively. We used the Youden index to determine that the 90th percentile was the optimal cut-off point[14] of propensity score, which may maximize the sensitivity and specificity of risk prediction. Thus, all patients (n=197,082) with a propensity score greater than 90th (i.e., 0.00341) were included as the study cohort in this study. The c-static for the multiple logistic regression was estimated at 0.79, suggesting a satisfactory level of model discrimination.

2.3. Measures of socioeconomic status

In this study, we used monthly income to indicate a person's SES. The amount of insurance premier in NHI program has been determined according to individual beneficiary's monthly income, which has been frequently used as an indicator of individual's SES.[15,16] Neighborhood SES was defined by the averaged median household income in each of 316 city districts or townships all over Taiwan in 1997–2003.[17] Both personal monthly income and median family income were determined for the year of index date. For a patient who had different monthly incomes in the year of index date, we calculated the mean monthly income for this patient.

2.4. Follow-up, end-point, and covariates

All 197,082 study subjects were followed from the date (i.e., index date) of his/her first hospitalization for treatment or

Table 1

Numbers and prevalence of liver transplantation according to characteristics of study subjects.

Characteristics	No. of patients (%)	No. of person-years observed	No. of patients with LT	Incidence rate of LT (per 10^4 person-years)
Total	197082 (100.00%)	1073157.71	2204	20.54
Demographics				
Sex				
Male	147101 (74.64%)	777616.90	1659	21.33
Female	49981 (25.36%)	295540.81	545	18.44
Age, years				
18−<45	55588 (28.72%)	367793.36	349	9.49
45–54	33209 (17.16%)	187069.13	904	48.32
55–64	41256 (21.32%)	199398.23	810	40.62
>=65	63496 (32.81%)	292526.51	91	3.11
Missing	3533		50	
Co-morbidity				
Liver cancer				
No	97072 (49.25%)	648484.24	831	12.81
Yes	100010 (50.75%)	424673.47	1373	32.33
Liver tumor				
No	174383 (88.48%)	964289.88	1923	19.94
Yes	22699 (11.52%)	108867.82	281	25.81
Hepatitis				
No	848 (0.43%)	3232.73	0	0
Yes	196234 (99.57%)	1069924.97	2204	20.60
Decompensated liver cirrhosis				
No	106312 (53.94%)	666820.97	1006	15.09
Yes	90770 (46.06%)	406336.73	1198	29.48
Liver surgery				
No	164916 (83.68%)	882427.83	1677	19.0
Yes	32166 (16.32%)	190729.87	527	27.63
Heart disease				
No	189501 (96.15%)	1018652.61	2102	20.64
Yes	7581 (3.85%)	54505.10	102	18.71
Renal disease				
No	164984 (83.71%)	907760.32	1810	19.94
Yes	32098 (16.29%)	165397.38	394	23.82
Hypertension				
No	160660 (81.52%)	844154.59	1771	20.98
Yes	36422 (18.48%)	229003.12	433	18.91
Diabetes mellitus				
No	140413 (71.25%)	732450.42	1454	19.85
Yes	56669 (28.75%)	340707.28	750	22.01
Albumin disorder				
No	194773 (98.83%)	1059903.50	2169	20.46
Yes	2309 (1.17%)	13254.21	35	26.41
Coagulopathy				
No	181938 (92.32%)	992078.84	1802	18.16
Yes	15144 (7.68%)	81078.86	402	49.58
Thrombocytopenia				
No	163303 (82.86%)	865470.74	1429	16.51
Yes	33779 (17.14%)	207686.97	775	37.32
Splenomegaly				
No	189776 (96.29%)	1026187.23	2034	19.82
Yes	7306 (3.71%)	46970.48	170	36.19
Alcoholism				
No	183015 (92.86%)	978071.08	2032	20.78
Yes	14067 (7.14%)	95086.63	172	18.09
Drug addiction				
No	196525 (99.72%)	1069129.34	2199	20.57
Yes	557 (0.28%)	4028.36	5	12.41
Propensity score[*]				
<Q1	47715 (24.21%)	302562.91	219	7.24
Q1−<Q2	50589 (25.67%)	291282.91	297	10.20
Q2−<Q3	49372 (25.05%)	224420.15	500	22.28
>=Q3	49406 (25.07%)	254891.74	1188	46.61

(continued)

Table 1

(continued).

Characteristics	No. of patients (%)	No. of person-years observed	No. of patients with LT	Incidence rate of LT (per 10^4 person-years)
Locations of residences				
Urbanization level				
Urban	45660 (23.21%)	257413.81	616	23.93
Satellite	57834 (29.40%)	315669.42	662	20.97
Rural	93236 (47.39%)	496782.27	916	18.44
Missing	352		10	
Geographic location				
Northern	72822 (37.02%)	411613.16	927	22.52
Central	40998 (20.84%)	224890.91	567	25.21
Southern	75646 (38.45%)	394466.11	645	16.35
Eastern and remote	7264 (3.69%)	38895.33	55	14.14
Missing	352		10	
Measures of socioeconomic status				
Monthly income†				
Dependents	46481 (23.59%)	243014.40	499	20.53
<Median	118096 (59.94%)	637733.19	1061	16.63
>=Median	32449 (16.47%)	191606.54	644	33.61
Missing	56		0	
Median family income‡				
<Q1	14165 (8.78%)	69715.37	153	21.95
Q1−<Q2	23927 (14.83%)	120930.76	248	20.51
Q2−<Q3	37584 (23.29%)	191540.16	456	23.81
>=Q3	85673 (53.10%)	464750.90	1163	25.02
Missing	35733		184	

* Propensity score: Q1=0.0043, Q2=0.0059, and Q3=0.0106
† Median=21,900 NTD (1 USD ≅ 30 NTD)
‡ Q1=447,000, Q2=477,000, and Q3=528,000 New Taiwan Dollars (NTD); 1 USD ≅ 30 NTD.
LT=liver transplantation.

operation of various liver diseases in 1997–2013 to the occurrence of LT, based on the medical orders (liver organ receipt: 75022B 75021B, 75020B) and LT operation codes (ICD-9-CM, 50.5X, V59.6, V42.7, or V42.9), death, or end of 2013. During the follow-up period, 2204 patients received LT, representing a cumulative LT incidence of 1.12%. Figure 1 illustrates the study patients' enrollment and follow-up.

To avoid confounding, information of a number of potential risk factors for LT was also retrieved from the NHI medical claims and registries of beneficiaries at baseline, namely, prior to and on the index date. These potential confounders included age, sex, selected co-morbidity of liver disease (see Supplemental Table S1, http://links.lww.com/MD/C870), and geographic locations/urbanization level of residence. The geographic location was defined as the northern, central, southern, and eastern parts of Taiwan. The categorization of urbanization level was based on the classification scheme proposed by Liu et al[18] who classified all 316 cities and townships of Taiwan into 7- ordered levels of urbanization according to various indicators, including population density, proportion of residents with college or higher education, percentage of elderly (>65 years) people, proportion of the agricultural workforce, and number of physicians per 105 people. Adjustment for the geographic locations and level of urbanization may help reduce the presence of an urban-rural difference in accessibility to medical health services in Taiwan.[19]

2.5. Statistical analysis

Person-years from index date to the occurrence of LT, death, or end of 2013 was calculated for each study patient. We then calculated the overall and specific incidence rate of LT, according to various characteristics of study patients. We then conducted Cox proportional hazard regression models to estimate the hazard ratios (HRs) of LT in association with patient's individual and neighborhood socioeconomic status. Since there was a large number of deaths that occurred during follow-up, the potential effect of competing mortality should be taken into account to estimate the relative hazard.[20] By taking death as a competing risk event and LT the outcome event of interest, sub-distribution hazard ratios (sHRs) were estimated using the method proposed by Fine and Gray.[21] Multivariate regression analyses were sequentially constructed. The first model was established by adjusting the propensity score; then, selected co-morbidity associated with liver disease was additionally adjusted. The full model will further adjust for patients' age, sex, and location/urbanization level of residential areas.

Missing information on the variables analyzed in this study was not managed due to only very few of them. All statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC). A P-value <.05 was considered statistically significant.

3. Results

Over 1,073,157.71 person-years of follow-up, 2204 patients received LT, representing a prevalence rate of 20.54 per 10^4 person-years. Male patients had a slightly higher LT incidence rate than females (21.33 vs 18.44 per 10^4 person-years). Compared to middle-aged patients (40.62–48.32 per 10^4 person-years), those younger than 45 years (9.49 per 10^4
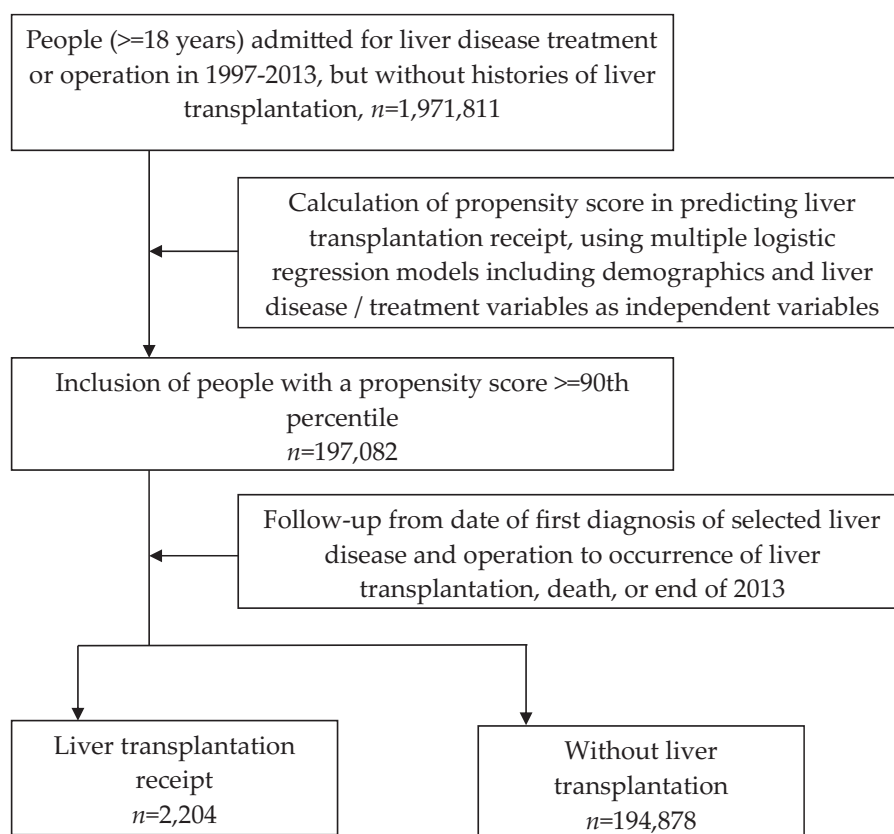
Figure 1. Flowchart of study patients' enrollment and follow-up.

person-years) and 65 years and older (3.11 per 10^4 person-years) had much lower incidence rate of LT. Patients with co-morbidity related to liver disease were found to consistently experience higher incidence of LT, except those with hypertension, alcoholism, and drug addiction (Table 1).

There is a gradient relationship between urbanization level and LT incidence, where patients living in the urban areas had the highest incidence rate of LT (23.93 per 10^4 person-years), followed by those from satellite city districts/townships (20.97 per 10^4 person-years) and rural areas (18.44 per 10^4 person-years). Compared to southern, eastern, and remote areas, northern and central parts (more developed) of Taiwan also had higher incidence rates of LT. With respect to personal monthly income, patients who had higher than median monthly income had twice prevalence rate of LT than those who had monthly income lower than median (33.61 vs 16.63 × 10^4 person-years). Additionally, the highest LT incidence rate was also observed in patients with the highest quartile of neighborhood median family income (25.02 × 10^4 person-years). The prevalence rate for the patients in the other 3 quartiles were lower at 23.81 × 10^4 person-years (Q2-<Q3), 20.51 × 10^4 person-years (Q1−<Q2), and 21.95 × 10^4 person-years (<Q1) (Table 2).

Table 2

Competing risk regression analyses of measures of socioeconomic status in predicting liver transplantation receipt.

	Subdistribution hazard ratios (sHRs) of liver transplantation receipt			
Measures of socioeconomic status	Crude estimates (95% CI)	Model 1[*] (95% CI)	Model 2[†] (95% CI)	Model 3[‡] (95% CI)
Monthly income[§]				
Dependents (ref.)	1.000	1.000	1.000	1.000
<Median	0.830 (0.746–0.923)	0.825 (0.742–0.918)	0.953 (0.854–1.063)	**0.802 (0.717–0.898)**
>=Median	1.879 (1.672–2.112)	1.824 (1.622–2.052)	2.174 (1.924–2.456)	**1.679 (1.482–1.903)**
Median family income of residential city/township[ǁ]				
<Q1	1.000	1.000	1.000	1.000
Q1−<Q2	0.951 (0.777–1.163)	0.958 (0.783–1.173)	0.945 (0.772–1.155)	0.952 (0.778–1.164)
Q2−<Q3	1.130 (0.941–1.357)	1.130 (0.940–1.359)	1.112 (0.926–1.335)	1.107 (0.922–1.329)
>=Q3	1.272 (1.075–1.505)	1.267 (1.069–1.502)	1.263 (1.067–1.495)	**1.248 (1.055–1.478)**

[*] Adjustment for propensity score

[†] Adjustment for propensity score and selected co-morbidity

[‡] Adjustment for propensity score, selected co-morbidity, age, and sex

[§] Median = 21,900 NTD (1 USD ≅ 30 NTD)

[ǁ] Q1 = 447,000, Q2 = 477,000, and Q3 = 528,000 New Taiwan Dollars (NTD); 1 USD ≅ 30 NTD.

Results from Cox regression models with sequential adjustment for potential confounders were similar. The full mode (i.e., Model 3) indicated that compared to dependents (not actively employed), patients with < median monthly income experienced significantly lower incidence rate of LT [aHR = 0.802, 95% confidence interval (CI) = 0.717–0.898], but those with >= median monthly income had significantly elevated prevalence rate of LT (aHR = 1.679, 95% CI = 1.482–1.903). Compared to those living in areas with lowest quartile of median family income (reference group), only those in the highest quartile showed significantly higher incidence rate of LT (aHR = 1.248, 95% CI = 1.055–1.478). Those who lived in areas with median family income within the inter-quartile range (i.e., Q1 – <Q3) showed no significant difference in LT incidence, in comparison with the reference group (Table 2).

4. Discussion

Even with a context different from that of Western society, this study still observed an inverse association between personal and neighborhood SES status and incidence of LT in Taiwan. Liver disease patients with higher incomes or living in areas with the highest quartile of median family income were observed to have significantly higher incidence rate of LT. Such findings are unlikely to be accounted by a number of known factors that may influence the chance of LT receipt, including demographic characteristics, live disease related co-morbidity, and rural–urban difference in accessibility to healthcare.

Although our study findings are essentially similar to what have been observed in studies of Western societies, interpretations of study findings might not be exactly the same as explanations commonly made in previous studies due to dissimilar context. Because more 80% of LT are LDLT in Taiwan,[9] and the donors of liver organ must be close relatives of patients, the chance of LT may not be equal for all ESLD patients in Taiwan. For examples, patients without relatives eligible for liver organ donations are forced to register with the waitlist for DDLT, for which the time-to-LT is much longer than receiving LDLT.

An earlier Taiwanese study showed a clustering of viral hepatitis in families of patients with chronic liver diseases, likely due to infection and common genetic origins.[22] Yu et al[23] analyzed a total of 671 first-degree relatives of HBsAg-positive hepatocellular carcinoma (HCC) cases in Taiwan, who were from 165 simplex families defined as having only one HCC case and 72 multiplex families with more than one case, and found that familial aggregation of HCC in HBsAg carriers is associated with familial clustering of liver cirrhosis. A recent Taiwanese study also suggested different genetic susceptibility between familial and sporadic HBV-related HCC.[24] Such family clustering in liver disease might have limited the availability of living donors for lower SES patients with ESLD in Taiwan. Additionally, a multiple-nation study demonstrated that socioeconomic indicators are strong predictors of hepatitis A seroprevalence rates in the Middle East and North Africa, where the prevalence of viral hepatitis A was higher among lower SES populations.[25] The review by Chak et al[26] also indicated that social, cultural, and language barriers may prevent effective implementation of interventions for screening and treatment of chronic hepatitis B and C. Disadvantaged people were particularly vulnerable to lack of such interventions. Because of higher prevalence of liver disease in families with lower SES, the ESLD patients from lower SES families might face considerable lack of potential family donors. Given the fact that the prevalence of HBsAg in the general population of

Taiwan was the highest in the world (approximately 11%–20%) before the launch of the universal hepatitis B vaccination in 1984,[27] such problem could be even more imperative in Taiwan

The other reason that could possibly explain our findings is poor survival of the liver disease patients with lower SES. Although we managed to consider liver disease related co-morbidity in the regression model, this way of doing may not fully account for the risk factors that may influence survival. A recent review of studies conducted Singapore where there is also little physical barrier to accessibility of health care, like Taiwan, also observed disparity in health in association with SES. This review found that people staying in public rental housing were associated with poorer health status and outcomes, mainly through lower participation in health screening, preferred alternative medicine practitioners to Western-trained doctors for primary care, and lower utilization of primary care.[28] This review highlights the importance of health behavior and health literacy in explaining the SES related health disparity. A poor survival rate of patients with lower SES for reasons other than co-morbidity related disease burden could be responsible, at least to some extent, for the lower LT prevalence noted among patients with lower SES in our studies.

One of the strengths involved in this study was that this is the first study to investigate the relationship between SES and receipt of LT under Taiwan's specific context. While LDLT quickly became the predominant form of LT in most Asian countries, it did not find such widespread acceptance in the Western societies. Such differences are primarily due to cultural, religious, and political reasons.[29] Additionally, this study was based on Taiwan's NHI claim data, which provides complete information of all LT, which makes the estimations of LT incidence valid. On the other hand, this study was limited by inadequate consideration of liver disease severity. The SES disparities in LT prevalence could be due to dissimilarity of disease severity or necessity between people with lower and higher SES. However, we managed to minimize such residual confounding by adjusting propensity score and co-morbidity in the regression models. One major limitation of our study was that generalizability of our study results could be limited as the context in Taiwan is different from that of Western society. Taiwan is relatively small in its land, so that the regional variation in transplant rates is expected to be small. In addition, under the universal health insurance coverage of all Taiwanese residents, the disadvantaged populations, such as children, elderly people, and nonworking adults may receive health care at a reasonable cost, which greatly increases the chance of LT for those disadvantaged populations.

In conclusion, our study noted that higher individual and neighborhood socioeconomic status were significantly associated with higher prevalence rates of LT. Although findings from this study are of lesser clinical implications, reallocation of medical resources that may improves the availability of LT for those end-stage liver disease patients should be considered by health policy makers in Taiwan.

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