Socioeconomic Factors Associated with Poor Prognosis in Patients with Alcoholic Liver Cirrhosis

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Abstract

Background: Alcohol liver cirrhosis is a life-threatening condition, especially if alcohol cessation is not accomplished. Past studies have shown that alcohol abuse is closely linked to low socioeconomic status and social marginalization. Public assistance (PA), or Seikatsu-hogo, a Japanese public assistance ensuring medical care to low-income population, was employed as a proxy for social marginalization. This study aims to investigate the prognostic effect of being a PA recipient on overall mortality in patients with alcoholic cirrhosis.

Methods: Patients diagnosed as alcoholic liver cirrhosis in a community hospital between 2006 to 2017 were included in this retrospective cohort study. Baseline demographics and mortality data were extracted from electronic health records. Cirrhosis severity at baseline was measured by mean model for end-stage liver disease (MELD) score and Albumin-Bilirubin (ALBI) score. Primary outcome was survival probability obtained by the Kapan Meier method and Cox proportional hazards regression.

Results: 244 participants were included, among which 62 were PA recipients. Baseline cirrhosis severity score was not different between the two groups. Incidence proportion for overall mortality was 48.4% and 31.9% for PA recipients and non-PA recipients, respectively (p=0.002). In cox regression model, adjusted for age, ALBI score and HCV infection, hazard ratio for PA reception was1.57 (95% CI: 0.97-2.5, p=0.06).

Conclusions: Being a PA recipient may be a poor prognostic factor of mortality in patients with alcoholic liver cirrhosis.

Introduction

Cirrhosis contributes to 85% of alcohol-related deaths worldwide [1]—3 million deaths annually according to World Health Organization[2]. A previous study has revealed that five-year mortality of alcoholic cirrhosis was 58%, with complications such as variceal bleeding and encephalopathy making the risk double-fold [3]. In Japan, annual age-standardized deaths from cirrhosis for men is 10.9 per 100 thousand individuals, and 67.8% is attributed to alcohol consumption [4].

Socioeconomic status (SES) refers to an individual's position in society; SES is established by a combination of educational, occupational, and economic criteria. SES, together with marital status, largely influences cirrhosis mortality. Regarding liver disease focusing on alcoholic etiology, a study from US have shown that patients with lower education, lower income, and unemployed had higher mortality than those better-off or employed[5]. In a study of Danish cirrhosis patients in which 85% of patients reported alcohol abuse, disabled pensioners, compared to employed, had 1.35 times higher mortality among cirrhosis patients in Denmark. Divorced had 1.22 times higher mortality than married [6]. In a study of cirrhosis from Sweden, in which 51% of cirrhosis was alcoholic, low- and middle-skilled workers, compared to professionals, had 1.85 times higher mortality [7].

Low SES individuals in Japan are warranted minimum living costs through a national Public Assistance (PA) system called Seikatsu- Hogo. PA system is the safety net of Japanese welfare system, thus those injured or sick without premium payment, or older population without sufficient pension benefits relies on PA programs [8]. PA consists of income security, employment support, and in-kind supply of medical and long-term care, financed by taxation. Therefore, Public Assistance beneficiaries can receive the same medical service as any other Japanese citizen, without any out-of-pocket payment. Previous studies in the US have shown that Medicaid and other health insurance schemes have contributed to improvements in access to health services, health status and quality of life in low-income populations[9,10]. However, no previous study up to our knowledge has investigated the prognostic effect of being a PA recipient in Japan.

Association between cirrhosis mortality and SES, especially employment and education, have been discussed. However, few have focused on alcoholic cirrhosis. Furthermore, up to our knowledge, previous studies have not taken clinical features such as cirrhosis severity and viral coinfection into account. Evidence regarding mortality of PA recipients in Japan is rare, and no previous study have revealed mortality hazard ratio of PA recipients in Japan. The aim of this study was therefore to investigate whether being a PA beneficiary was a poor prognostic factor for mortality in Japanese patients with alcoholic liver cirrhosis.

Materials And Methods

Study population and inclusion criteria

727 patients were diagnosed as liver cirrhosis (LC) in our institution during years 2006 to 2017. Our institution is a public hospital located in suburban area of Tokyo metropolitan area, with 376 beds and an outpatient ward. Etiology of LC was investigated by trained hepatologists by laboratory findings such as low Platelet and Albumin, and imaging test including ultrasound, computed tomography, or magnetic resonance image. 258 participants that had had history of excessive alcohol consumption and were diagnosed as alcoholic LC by the hepatologists were left. 12 patients that had only visited our outpatient ward once, and 2 that further medical record review revealed no presence of alcoholic LC were excluded from the analysis. Finally, a total of 244 patients were left and included for the present study. Inclusion and exclusion flowchart of participants is described in figure 1.

The research protocol was approved by Institutional Review Board of St Marianna University Hospital (approval number 4995).

Basic demographics

Basic demographics at point of diagnosis were obtained through medical record review. Age, sex, body mass index (BMI) calculated by height and weight, chief complaint at first hospital visit, and emergency hospitalization were recorded. Coexistence of viral hepatitis (HBV and HCV), and laboratory findings

including Asparate aminotransferase (AST), Alanine aminotransferase (ALT), Creatinine, total Bilirubin, Albumin, Prothrombin time- international normalized ratio (PT-INR), and Platelet count, were obtained from medical record review.

Liver cirrhosis severity was measured by MELD score [11] and albumin-bilirubin (ALBI) score [12]. MELD score is an objective scoring calculated by creatinine, total Bilirubin, Albumin and PT-INR [11]. Whether the discrimination power of MELD score in predicting mortality is superior to that of Child Pugh Score, a classical scoring for liver cirrhosis, is controversial; however, a systematic review in 2016 reports that MELD score is as reliable a prognostic score as the Child Pugh score [13]. A study conducted in 2019 reported ALBI to be the optimal predictor of mortality compared to MELD, MELD-Na and Child Pugh [14]. Furthermore, a study among Asians have reported that ALBI was provided particularly reliable prediction for short-term outcomes, whereas the MELD score was better in terms of assessing long-term outcomes [15]. Considering that Child Pugh scoring is rather subjective in terms of ascites and encephalopathy scoring, we employed the MELD and ALBI scores in the current study.

Regarding socioeconomic status, whether the participant was a PA beneficiary was obtained from insurance information in medical record. Residing alone and having no key person (a family member or someone in close relationship to contact in case of emergency) were other SES measurements obtained. Information on SES variables mentioned above were obtained from medical record of the participants.

Outcome measurements

The primary outcome for our study was survival time after diagnosis of alcoholic liver cirrhosis. The patients were followed until death, dropout or continuous outpatient visit at March 2020 or later, whichever came first. Data for those that death was not recorded (either dropped out or were continuing hospital visit) was handled as censored data.

As secondary outcome for our study, the incidence of ascites, esophageal varices, hepatocellular carcinoma (HCC), encephalopathy and spontaneous bacterial peritonitis (SBP) were obtained. Presence of abovementioned complications observed at our hospital at any point during follow up period was counted as positive.

Statistical analysis

Basic demographics were depicted using median and interquartile range, or by percentage, depending on whether the variable was linear or bivariate. In order to test differences between the two subgroups, Chi squared analyses were applied for binary variables. Mann Whitney U tests were applied for continuous variables since all continuous variables had non-normal distribution. We computed survival probabilities using the Kapan Meier method and used Cox proportional hazards regression to estimate hazard ratios. Using the Schoenfeld residuals, we determined that hazard ratios were constant over the follow-up time.

Mean survival time, survival rate at median follow-up, and five-year survival rate was obtained from survival curve for the two subgroups. Statistical difference of crude hazard ratio for being a PA recipient was obtained by Log rank test. Then, we included receiving PA, together with age, HCV infection, and ALBI score in one cox hazard model to obtain the adjusted hazard ratio. Significance level was set at the alpha value of 0.05. All statistical analysis was computed using STATA version 16 software (Stata Corporation, College Station, TX, USA).

Results

244 patients met our inclusion criteria, of whom 62 (26.1%) were PA recipients. 209 (80%) were men, and median age was 61.8 [60.3-63.3]. Median follow-up time was 819 days. During a total follow-up time of 9100 months of time at risk, 88 patients (33.6%) deceased. Basic demographics are shown in Table 1. Percentage of those living alone and those without a key person greatly differed between PA recipients and non-PA recipients—74.2% versus 28.6% ($p<0.001$), and 29.1% versus 7.1% ($p<0.001$), respectively. As for clinical parameters at time of diagnosis, mean MELD score and ALBI score was 8.19 [7.40-8.98] and -1.92 [-2.04- -1.83], among which neither was significantly different between the two subgroups. No participant had HBV infection, thus only coexistence of HCV infection is reported in our results table. 24.4% of overall patients required emergent admission during the study period. The most common chief complaint was asymptomatic liver dysfunction (34.0%). Other common symptoms were abdominal distension and edema (19.5%), fatigue and immobility (7.6%), gastrointestinal gastric and variceal bleeding (9.2%), among others (Supplementary table 1).

Table 1

basic demographics of the participants, described by median (25% to 75% interquartile range) or number (percentage). P value was obtained by Mann Whitney U-test for medians, and chi-squared analysis for percentages. Abbreviations: KP, key person; BMI, body mass index; DM, diabetes mellitus; HCV, hepatitis C virus; AST, asparate aminotransferase; ALT, alanine transaminase; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; PA, public assistance; n, number

		subgroup by public assistance		
	Overall (n=244)	Non-PA (n=182)	PA (n=62)	p value
Demographics				
Age	62 [54-70]	63 [54-72]	59 [53-67]	0.05
Male	209 (79.8%)	156 (85.7%)	53 (85.5%)	0.96
Living alone	98 (37.4%)	52 (28.6%)	46 (74.2%)	<0.001 **
No KP	31 (11.8%)	13 (7.14%)	18 (29.1%)	<0.001 **
Nursing care	63 (42.1%)	43 (23.6%)	20 (32.3%)	0.31
BMI	22.0 [19.7-24.5]	21.8 [19.7-24.6]	22.2 [20.3-24.4]	0.86
Presentation at first visit				
Diabetes Mellitus	70 (26.7%)	49 (26.9%)	21 (33.9%)	0.54
HCV infection	52 (19.8%)	31 (17.0%)	21 (33.9%)	0.005 **
AST	64 [38-105]	69 [40-107]	54 [34-97]	0.06
ALT	37 [24-63]	39 [26-66]	29 [21-52]	0.03*
Total Bilirubin	1.55 [0.9-3.00]	1.55 [0.9-3.0]	1.55 [0.9-2.8]	0.69
Albumin	3.5 [2.9-3.9]	3.5 [3.0-3.9]	3.5 [2.8-3.8]	0.53
PT-INR	1.09 [1.00-1.23]	1.08 [1.00-1.24]	1.11 [1.00-1.22]	0.92
Platelet	11.3 [8.0-16.1]	11.0 [7.9-16.6]	13.1 [9.2-16.0]	0.34
Cirrhosis severity at first visit				
MELD score	7.0 [3.0-12.0]	7.0 [3.0-12.0]	8.0 [4.0-13.0]	0.44
ALBI score	-2.03 [-2.48- -1.42]	-2.06 [-2.48- -1.42]	-1.97 [-2.50- -1.43]	0.65
ALBI Grade				
Grade	45 (17.2%)	32 (17.6%)	12 (21.0%)	0.78
Grade2	142 (54.2%)	108 (59.3%)	34 (54.8%)	

Grade3	19 (7.25%)	1 (0.55%)	0 (0%)	
Hospitalization				
Emergent	64 (24.4%)	46 (25.3%)	18 (29.0%)	0.577

Occurrence of primary and secondary outcomes are shown in Table 2. Mortality incidence proportion during the observed period was 33.6% overall, and 48.4% versus 31.9% (p=0.02) for PA recipients and non-PA recipients. The overall rate of treatment dropout was 18%; it did not differ between the subgroups. Death causes included liver-related causes such as HCC, acute on chronic liver failure and varices rupture. Occurrence of complications—ascites, varices, HCC, SBP and encephalopathy—were not different among the two groups.

Table 2

Primary and secondary outcomes for PA recipients and non-PA recipients. Abbreviations: CPA, cardiopulmonary arrest; HCC, hepatocellular carcinoma; SBP, spontaneous bacterial peritonitis; PA, public assistance; n, number.

		subgroup by public assistance		
	Overall (n=234)	Non-PA (n=173)	PA (n=61)	p value
Mortality				
Incidence proportion (%)	88 (33.6%)	58 (31.9%)	30 (48.4%)	0.02 *
median survival time	2104 [1589-3563]	2889 [1692 - N/A]	1559 [1589 -3563]	N/A
survival rate at median follow up (%)	75.3% [68.7-80.7]	76.6% [68.8-82.7]	69.9% [56.0 - 80.1]	0.28
five year survival rate	54.2% [45.6-62.0]	57.8% [47.7-66.6]	45.2% [29.2-60.6]	0.07
treatment adherence				
dropout rate	48 (18.3%)	38 (20.9%)	10 (16.3%)	0.08
death cause				
encephalopathy	11 (4.2%)	5 (2.7%)	6 (9.7%)	
HCC	14 (5.3%)	12 (6.6%)	2 (3.2%)	
HCC rupture	11 (4.2%)	11 (6.0%)	0	
liver failure	15 (5.3%)	10 (5.5%)	4 (6.5%)	
Other carci	7 (2.7%)	5 (2.8%)	2 (3.2%)	
SBP	2 (0.8%)	0	2 (3.2%)	
Sepsis/infection	4 (1.5%)	2 (1.1%)	2 (3.2%)	
Varix rupture	11 (4.2%)	6 (3.3%)	5 (8.1%)	
0thers	12 (4.6%)	7 (3.9%)	5 (8.1%)	
Complications				
ascites	203 (83.2%)	152 (83.5%)	51 (82.3%)	0.81
varix	147 (60.3%)	112 (61.5%)	35 (56.5%)	0.55
HCC	97 (39.8%)	73 (40.1%)	24 (38.7%)	0.87
SBP	17 (6.97%)	11 (6.04%)	6 (9.68%)	0.32
encephalopathy	66 (27.1%)	48 (26.4%)	18 (29.0%)	0.65

Figure 2 shows the Kaplan Meier survival estimates for the PA recipients and non-PA recipients. Log Rank test showed no significant difference in survival rate between the two groups (p=0.127). Median survival time were 51.9 months and 96.3 months for PA recipients and non-PA recipients, respectively.

Survival rate at median follow up (819 days) were 66.9% and 76.6%, respectively. Five-year survival rate was 45.2% and 57.8%.

Cox proportional hazard model was applied to calculate hazard ratio of PA recipients, adjusting for age, HCV infection and ALBI score. Results are shown in Table 3. PA recipients had higher risk compared to non-recipients with hazard ratio of 1.57 [CI: 0.97-2.53, p=0.06]. In the multivariable analysis, age and ALBI scores were independent predictors of mortality, with hazard ratio 1.04 [CI: 1.02-1.06, p<0.001] and 1.64 [CI: 1.28-2.10, p=0.001], respectively.

Table 3

Cox proportional hazard model of with age, HCV infection, ALBI and receiving PA included in the multivariate model. Abbreviations: HR, hazard ratio; 95 CI, 95 percent confidence intervals; HCV, hepatitis C virus; ALBI, Albumin-bilirubin; PA, public assistance.

	Cox HR	95 CI	p value
age	1.04	1.02-1.06	<0.001 **
HCV infection	1.3	0.80-2.12	0.29
ALBI score	1.64	1.28-2.10	0.001 **
receiving PA	1.57	0.97-2.53	0.06

Discussion

In this retrospective cohort study of 244 patients with alcoholic liver cirrhosis, we found that PA recipients tended to have higher hazard ratio for overall death than non- PA recipients after adjusting for age, HCV infection and ALBI score. Basic demographics such as BMI and concurrence of Diabetes Mellitus did not differ between the two groups; however, social isolation as measured by residing alone and having no key person were remarkably higher among the PA recipients. Baseline severity of liver dysfunction measured by MELD score and ALBI score, as well as proportion of patients requiring emergent hospitalization at first presentation were not higher among PA recipients.

Owing to the public assistance system, low-income individuals in Japan have no financial barriers to healthcare services. However, non-financial barriers such as upstream determinants of health that is closely related to low socioeconomic status, may lead to higher mortality in the poor despite the financial and medical assistance provided [16]. We hypothesized that if receiving PA and overall survival is not associated, low SES may not be homogenously associated with lower health status as in most countries, thanks to the assistance system in Japan. On the other hand, if PA beneficiaries' survival is relatively shorter, effect of low SES on mortality cannot be subsided by financial warrant.

Our study revealed a tendency of higher mortality among those receiving PA (adjusted HR 1.57 (95% CI 0.97-2.53, p=0.06)). Previous study by Jepsen et al has shown that poorer cirrhosis prognosis among divorced and unmarried, compared to married participants [6]. Our study concords with this result since PA recipients were more likely to be living alone or have no key person, and PA recipients tended to have poorer prognosis. This may be due to their lack of social support such as family members or workplace communities [17].

Furthermore, MELD score and need for emergent hospitalization did not differ among PA recipients and non-PA recipients at the point of diagnosis. Treatment dropout rate was also indistinguishable among the two groups. A literature review shows that socioeconomically deprived older population has worse access to care [18]. In our study, neither cirrhosis severity at the point of diagnosis nor dropout rate were different between PA recipients and non-PA recipients—in other words, healthcare access barrier was not observed at both point of diagnosis and at treatment continuum among cirrhosis patients that visited our hospital.

Our study has several clinical implications. Abovementioned results demonstrate that although neither cirrhosis severity at baseline nor dropout rate were different among the two groups, PA recipients had poorer prognosis. Several reasons for this health gap can be speculated, but one possible explanation may be that PA recipients experienced more hardship quitting alcohol. There is explicit evidence that shows strong relationship between alcohol-related death and low SES [1,19]. Although we couldn't measure severity of alcohol addiction in our study, it may be possible that PA recipients had lower alcohol cessation rate after diagnosis, probably due to family or social support. If so, clinicians should provide appropriate support for patients with alcoholic cirrhosis to improve their health-related behaviors. The results also imply that providing alcohol cessation information, and connecting low SES patients to social support such as mutual self-help groups may improve PA recipients' prognosis.

In our cox hazard model, hazard ratio for PA recipient was not statistically significant, although difference in mortality was conspicuous in the survival curve. We assume that this was due to lack of statistical power. As an attempt to decrease the number of censored data, we conducted a follow-up written survey to the 129 participants that were censored. We did not have the post address for 5 of the participants. Among 124 surveys sent, 65 of the address were invalid, thus we could not contact the patient. Only 20 had replied, and among them, 9 had agreed to participate in the survey. We assumed that there would be a selection bias to include the nine valid answers in our study, and that the population would not be homogenous with the medical record-based dataset. Therefore, we decided to exclude the follow-up survey results. The high percentage of uncontactable participants may be reflecting the social isolation of these population.

Other limitations to our study were that it was single-centered, and we did not have as much participants that would have enabled us to include more confounders in our multivariable analyses. We could not take into account comorbidities other than HCV infection; deaths may have occurred due to other critical illnesses. Also, we could only measure limited factors of SES, and more in-depth investigation on discrete

SES components is needed to unveil which upstream drivers of health is strongly affecting the prognosis of patients with cirrhosis.

Conclusion

Our study suggested that overall mortality of patients with alcoholic liver cirrhosis patients may be associated with low SES, which was measured by receiving PA. This association could not be explained by severity of cirrhosis at diagnosis nor dropout rate. Further study is needed to investigate the cause of higher mortality among the low SES population, and potential interventions to the disease burden.

Declarations

Ethics approval:

The research was approved by the Institutional Review Board of St Marianna University Hospital (approval number 4995).

Consent to participate:

Consent to participate was obtained by posting notices of the study in hospital bulleting and opting out.

Consent for publication:

not applicable

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests

Funding:

no funding was provided

Authors' contributions:

All authors contributed to study conceptualization and design. Data collection was performed by KM. Data curation was performed by MK. Data analysis was done by MK, KI and MH. Supervision was performed by TM. Manuscript was written and edited by MK, KI, MH, IM, TT and CO, then reviewed by all authors.

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not applicable

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Figures

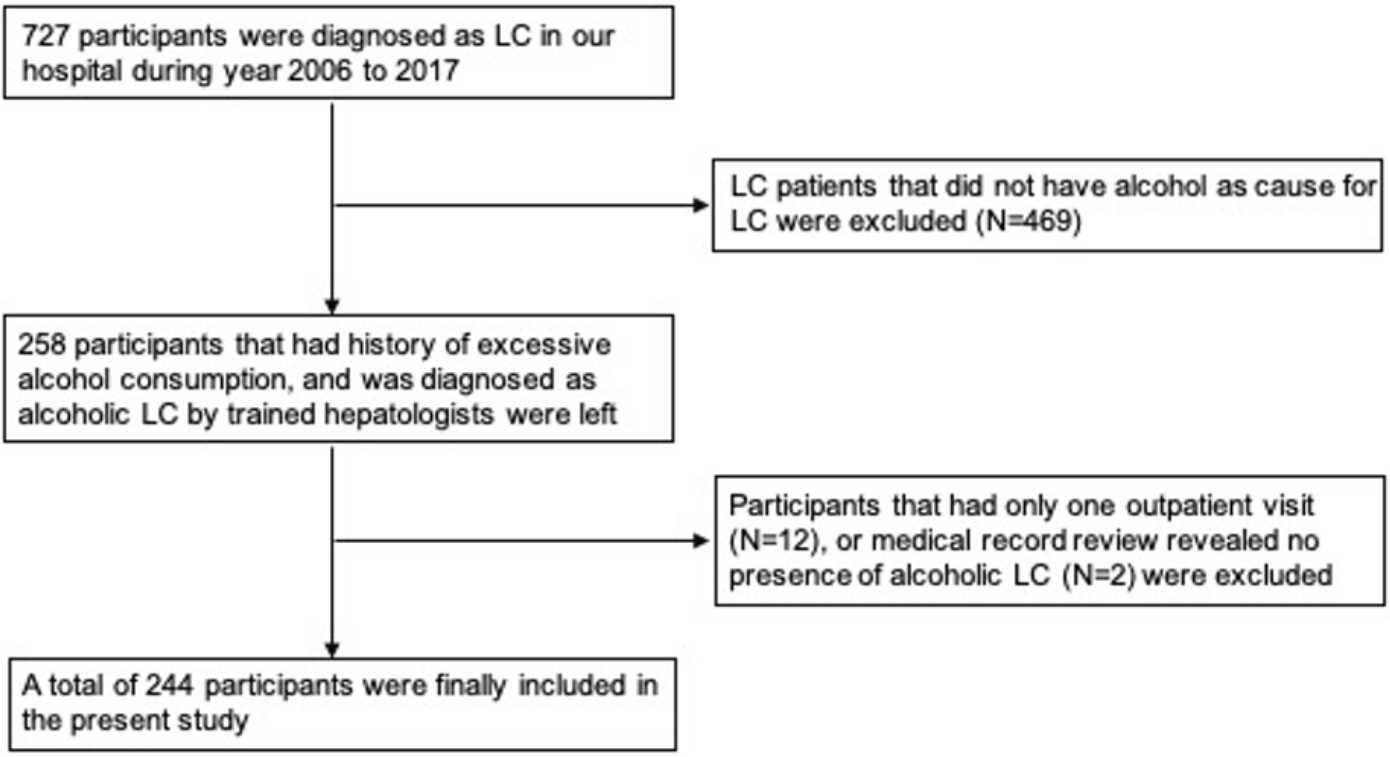

Figure 1

Inclusion and exclusion flowchart. Abbreviations: LC, liver cirrhosis

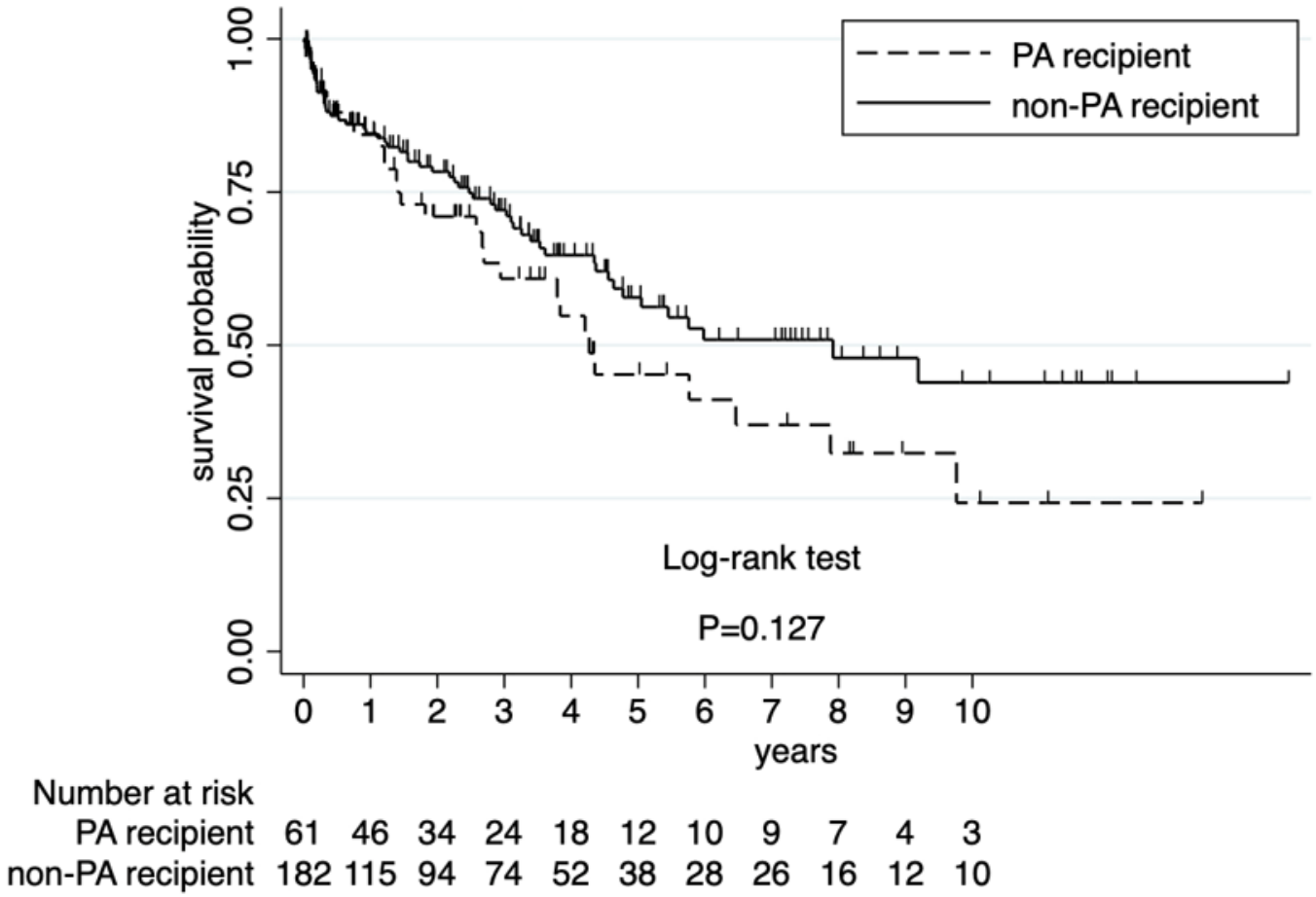

Figure 2

Survival curve for PA recipients and non-PA recipients. Abbreviations: PA, public assistance.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable1.docx