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Article type : Original Articles

A Prohibitive Tobacco Use Policy does not reduce the Proportion of Smokers Listed for Liver Transplantation

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Short title: Prohibitive versus restrictive tobacco policy

Keywords: liver disease, liver transplantation, patient selection, tobacco use, and substance use.

Abbreviations:

AASLD, *American Association for the Study of Liver Disease;*

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/LT.25497

ALD, alcoholic liver disease;

CTP, Child Turcotte Pugh;

HCC, hepatocellular carcinoma;

LT, Liver transplantation;

MELD, *Model for End-Stage Liver Disease;*

NAFLD, non-alcoholic fatty liver disease;

ns, not significant;

OR, odd ratio;

SUD, substance use disorder.

Grant or financial support: None

Disclosure: AL, AH, NS, JM, FA, GSW, CJS, and PS report no relevant conflicts.

RJF: receives grant support from Abbvie, BMS, and Gilead. He also does consulting for Alnylam pharmaceuticals.

Authorship: A Likhitsup, study design, data collections, statistical analysis, manuscript drafting; A Hassan, data collection; J Mellinger, study design, manuscript review; F Askari, study design, manuscript review; GSW, study design, manuscript review; NS, data collection; CJS, manuscript review; P Sharma, statistic consultation, manuscript review; RJF, study design, data analysis, supervise study, manuscript drafting and review.

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ABSTRACT

Introduction: Tobacco use has been associated with poorer outcomes after liver transplantation (LT). Our study examined the effect of a newly implemented policy prohibiting use of all tobacco products compared to a prior restrictive policy on LT listing outcomes. **Methods**: Medical records of consecutive

adult patients evaluated for LT from January 2010 to July 2013 (Era-1, n=1344) and August 2013 to March 2017 (Era-2, n=1350) were reviewed. The proportion of LT candidates listed was the primary outcome. **Results:** The mean age of the 2694 LT candidates was 54 ± 11 years, 60% were male, and the mean MELD score was 15 ± 7. Although the proportion of LT candidates that were smokers was significantly higher in era-2 (33% vs 23%, p< 0.005), the proportion of smokers listed for LT remained stable (13% vs 17%, p= 0.25). However, there were more smokers excluded for ongoing tobacco use in era-2 compared to era-1 (9.6% vs 4.4%, p= 0.001). Factors independently associated with LT listing included a diagnosis of HCC, being married, private insurance, absence of psychiatry co-morbidity, and absence of tobacco, marijuana or opiate use but not evaluation during era-2. However, the median time-to-listing significantly increased over time, especially in smokers (92 to 155 days; p=0.001) and this trend was independently associated with evaluation during era-2, a lower MELD score, not having children and a lower level of education (p < 0.05). **Conclusions:** Despite an increasing incidence of active smokers being referred for LT evaluation, the proportion of smoker candidates listed for LT was unchanged after instituting our prohibitive tobacco use policy. However, the time to get on the waitlist amongst smokers that were eventually listed was significantly longer due to the need to achieve complete tobacco cessation.

INTRODUCTION

Liver transplantation (LT) is a life-saving intervention for patients with decompensated cirrhosis and other forms of liver failure. However, due to the ongoing shortage of donor organs, candidate selection presents unique ethical issues. The principles of organ allocation are utility (maximize benefit), justice (fair distribution of access to transplantation) and respect of individual autonomy. Active abuse of alcohol, illicit substances, and certain psychosocial behaviors such as poor compliance, inadequate social support and uncontrolled psychiatric disorders are generally considered relative to absolute contraindications to LT[1].

Tobacco use is a well-recognized risk factor for heart and lung disease, stroke, peripheral vascular disease, cancer, and other causes of death in the general population.[2] Active smokers also

have increased risk of infections, biliary and vascular complications after LT.[3-5] Although the American Association for the Study of Liver Diseases (AASLD) practice guideline recommends that tobacco consumption should be prohibited in all LT candidates, a recent study showed substantial variation in tobacco use policies among LT centers. [6, 7]

Our program implemented a prohibitive tobacco use policy on August 1, 2013 wherein all LT candidates are required to abstain completely from tobacco as well as alcohol, marijuana, and other illicit substances. Prior to the implementation of this prohibitive tobacco use policy, only LT candidates with coronary artery disease and lung disease were required to stop using tobacco products (Restrictive policy). The aim of this study was to examine the impact of this policy change on LT listing outcomes with the hypothesis that the prohibitive policy would be associated with a lower overall rate of LT listing amongst smokers being evaluated for LT and a longer time to listing amongst the smokers who are eventually listed.

METHODS

Patient cohort

The University of Michigan Institutional Review Board approved this retrospective chart-review study. All adult LT candidates over 18 years of age evaluated at the University of Michigan from January 1st, 2010 to March 1st, 2017 were included. Pediatric, living donor, repeat evaluations, and patients with missing data were excluded. All patients were evaluated by a multidisciplinary team of hepatologists, surgeons, and social workers. Data were abstracted from electronic medical records.

Data collection

Abstracted demographic features included patient age, gender, race, etiology of liver disease, Model for End-Stage Liver Disease (MELD) score (at evaluation, listing, and transplant), and insurance, employment, and marital status. Tobacco, alcohol and illicit substance use history were coded as never used, remote use (more than 12 months ago), and current user or any use within the past 12 months before evaluation. History of prior substance use related health or legal consequences, psychiatric co-morbidities and prior substance use related treatments were collected. Toxicology screening at the initial LT evaluation and other pre-listing test results were collected and analyzed.

Definitions

The period from January 1, 2010 to July 31, 2013, when only patients with coronary artery disease and lung disease were required to stop smoking, was defined as era-1 (restrictive tobacco). In contrast, the period from August 1, 2013 to March 1st, 2017, when all LT candidates were required to abstain completely from tobacco products was defined as era-2 (prohibited tobacco). During both eras, patients were encouraged to stop using tobacco products and asked to sign a substance use contract that prohibited them from drinking alcohol, using marijuana, or taking other illicit substances. There was no minimum duration of tobacco abstinence required but a negative urine tobacco metabolite test was required prior to listing. In addition, other aspects of the substance use contract and policy in our center were not changed with implementation of the prohibitive policy. Patients who violated the substance use policy were either removed from the waiting list or required to complete substance use rehabilitation and reactivated for LT only after having negative toxicology screens.

Patients with a history of tobacco use within the past 12 months were categorized as smokers. An active smoker was determined by disclosure to staff by self or family member, or detectable serum or urine metabolites. Urine cotinine was used to screen for active nicotine use while urinary anabasine was used to confirm active cigarette use in patients receiving nicotine replacement therapy.[8] Serum ethanol, phosphatidylethanol and urine ethyl glucuronide were used to screen for alcohol use in patients with alcoholic liver disease (ALD).[9] Active marijuana use was confirmed by a positive urine cannabinoid screen. Other toxicology screens include urine amphetamine, cocaine, opiate, oxycodone, benzodiazepines, and barbiturate to screen for illicit substance use. The frequency of substance use interventions including referral to tobacco consultation service, psychology or psychiatry, and substance use pharmacotherapy were collected.

Outcome measures

The LT selection outcome included being listed for LT, time from initial LT evaluation to listing (time-to-list) and the reasons for patients being excluded from LT listing. Graft and patient survival data were collected at 1-year and last available follow up until June 30, 2018.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variable were expressed as percentages. The baseline characteristics at the time of LT evaluation were compared using independent sample T-test for continuous variables and Chi-square tests for categorical data. The primary outcomes were either being listed or not listed and the time from evaluation to listing (time-to-list). A simple linear regression analysis was used to predict the proportion of liver disease diagnosis and time-to-listing based on the year of evaluation. We used multivariable logistic regression analysis to assess the candidate factors associated with listing status and time-to-list (≥ 90 days). These models were adjusted for age, policy, MELD score, presence of hepatocellular carcinoma (HCC), insurance status, marital status, substance use history, prior substance use disorder (SUD) consequences, and psychiatric comorbidities. We performed subgroup analysis in era-1 comparing the patient and graft survival using Kaplan-Meier method stratified by smoking status and log rank analysis. SPSS 25.0 (IBM Corp, Armonk, NY) was used for all analyses.

RESULTS

Patient characteristics

From January 1, 2010 to March 1st, 2017, 3,045 adults underwent LT evaluation. 351 patients were excluded from the analysis including 24 living donor evaluations, 6 patients with incomplete data, and 321 duplicate evaluations. Amongst the remaining 2694 patients, 1,344 underwent LT evaluation in Era-1 and 1,350 underwent LT evaluation in Era-2. (**Figure 1**)

The mean age of the 2,694 patients was 54 ± 11 years, 60% were male, and 84% were Caucasian (**Table 1**). Interestingly, the number of smokers was significantly higher in era-2 compared to era-1 (33% vs 23%, $p < 0.005$). Overall, smokers were significantly younger compared to non-smokers in both eras ($p<0.005$). The mean MELD score of the entire cohort was 15 ± 7. The mean MELD score of smokers was lower than the non-smokers in era-2 and also lower than the MELD scores of the era-1 smokers; 14±7 vs 15±8 ($p=0.03$) and 15±7 ($p=0.008$). In both eras, smokers were more likely to have ALD, HCC, and viral hepatitis as the causes of their liver disease. The underlying causes of liver disease significantly changed with the proportion of patients with ALD significantly increasing in era-2 (27 to

34%, p<0.05), while viral hepatitis decreased (37 to 29%; p<0.05). A simple linear regression analysis was used to predict proportion of liver disease diagnosis based on the year of evaluation. Each year increase in referral for evaluation was associated with a 2.8% decrease in the proportion of LT candidates with viral hepatitis (β=-0.028 [(-0.037)-(-0.018)]; p<0.001), 2% increase in ALD (β=0.02 [0.007-0.03]; p=0.007) and 1.0% increase in NASH (β=0.01 [0.002-0.019]; p=0.03) (**Figure 2**). Furthermore, smokers in both eras were significantly more likely to have Medicaid insurance, be unemployed and less likely to be married (p < 0.005).

Substance use and psychiatric history

In both eras, smokers reported more lifetime history of alcohol (86 vs 64%), marijuana (42 vs 18%), opiate (26 vs 13%), and other illicit substance use (25 vs 8%) compared to non-smokers (p<0.005). In addition, the rates of lifetime marijuana (42 vs 35%) and illicit substance use (25 vs 18%) was higher in smokers in era-2 compared to era-1, while lifetime opiate use increased in non-smokers in era-2 (13 vs 9%; p<0.05) (Table 1).

As expected, smokers reported more frequent history of alcohol (49 vs 27%), marijuana (26 vs 8%), opiate (23 vs 12%) and illicit substance use (2.7 vs 0.3%) within the 12 months before LT evaluation compared to non-smokers (p<0.005). In era-2, the reported history of alcohol and marijuana use within 12 months increased in both smokers (37 to 49% and 16 to 26%) and non-smokers (20 to 27% and 5 to 8%), while reported history of opiate use within 12 months increased in non-smokers only (7 to 12%; p=0.003) (Table 1).

Smokers also reported more health or legal consequences related to substance use, SUD treatment experience, underlying psychiatric comorbidities, and psychiatric medication use compared to non-smokers (p<0.005). In addition, all of these rates significantly increased in era-2 compared with era-1 in both smokers and non-smokers (p<0.005) (**Table 1**).

Toxicology results and interventions

Smokers in both eras were significantly more likely to have toxicology testing completed as part of their LT evaluation compared to non-smokers but rates were high in all groups (**Table 1**). Although alcohol, tobacco, and marijuana metabolites were more frequently detected in smokers in both eras

(p<0.05), there was no difference seen between the two eras. Both smokers and non-smokers received more interventions for various SUD in era-2 versus era-1 including substance use counseling, psychology or psychiatry referral (46 vs 31% in smokers and 21 vs 11% in non-smokers; p<0.005). In addition, smokers received more SUD pharmacotherapy compared to non-smokers but there was no significant difference between the two eras (**Table 1**).

Liver Transplant evaluation outcomes

Although the proportion of candidates listed for LT were similar in both eras (25% vs 24%, p=0.14), a significantly lower proportion of smokers versus non-smokers were listed in both eras (13 vs 28% in era-1 and 17 vs 30% in era-2; p<0.005) (**Table 2**). The proportion of patients not listed for being clinically too well, medical issues, and other reasons were similar in both eras. However, the proportion of smokers excluded for ongoing tobacco use was significantly higher in era-2 compared to era-1 (4.4% vs 9.6% p=0.001) (**Table 2**). Interestingly, the median time to listing was similar in the smokers and non-smokers in era-1 (65 vs 81 days, p=0.59). However, the median time to listing significantly increased in the era-2 smokers compared to the non-smokers (122 vs 105 days, p =0.01) (**Table 2**). In reviewing these data more carefully, the temporal trend of time to listing was increasing in both smokers and non-smoker patients over the entire time of this study (**Figure 3**). In an unadjusted linear regression analysis, every year increase in referral for evaluation was associated with 6.1 days increase in time to listing on average; (β=0.51 [0.178-0.842]; p=0.003 for all LT candidates, β=1.176 [0.399-1.954]; p=0.004 for smokers, and β=0.453 [0.095-0.811]; p=0.01) for non-smokers.

On multivariate analysis, a diagnosis of HCC, being married, male gender, higher MELD score, absence of prior SUD-related health or legal consequences or psychiatric co-morbidities and absence of tobacco, marijuana or opiate use within 12 months were predictive factors for an LT candidate being listed (**Table 3**). Predictive factors associated with the time to listing exceeding 90 days include presence of prior SUD-related health or legal consequences, presence of any substance use within 12 months and screening positive for tobacco or marijuana metabolites. In contrast, being evaluated in era-1, higher MELD score, having children and a higher education level were all significantly associated with a shorter evaluation time (**supplemental Table 1**).

Transplant outcomes

In era 1, 8 (2.4%) of the 337 listed patients were removed from the waitlist due to alcohol (4), tobacco (3), or marijuana (1) use. In era 2, 13 (3.9%) of the 331 listed patients were removed from the waitlist due to either alcohol (6), tobacco (6), or marijuana (1) use. There was no difference in the rate of waitlist removal due to substance use between the 2 eras (p = 0.58)

The proportion of smokers undergoing LT during follow-up decreased in era-2 compared to era-1 (41 vs 65%; P=0.01), presumably due to lead-time bias. The median time of follow-up after listing was 2191 (3-3025) days in era-1 smokers, 1873 (0-3038) days in era-1 non-smokers, 882 (154–1638) days in era-2 smokers and 772 (4-1696) days in era-2 non-smokers (**Table 4**). The mean MELD score at transplantation in non-smokers increased in era-2 (25 vs 23, p=0.008) while there were no differences amongst smokers (**Table 2**).

Graft and patient survival

At the time of this analysis, 212 listed patients from era-1 had undergone LT while 157 of the era-2 patients had undergone LT. The median follow-up time post-LT was 1923 (0 – 3038) days in Era 1 and 796 (4 – 1696) days in era-2 (p<0.05). The 1-year graft and patient survival rates were 88% and 87%, respectively in era-1 and 96% and 96%, respectively in era-2. The 1-year patient and graft survival rates were similar amongst smokers and non-smokers in both eras (**Table 4**)**.**

Subgroup analysis for LT outcome in era-1 patients was performed to evaluate associations between smoking status and graft or patient survival. The 1-year graft and patient survival in smokers were similar to non-smokers (88 vs 88% graft survival and 88% vs 87% patient survival; p>0.05). However, during a median follow-up time of 2,191 (3 -3025) days in smokers and 1,873 (0 – 3038) days in non-smokers, the graft survival was significantly lower in smokers compared with non-smokers (73.5 vs 89.7%; p=0.01). In contrast, overall patient survival was slightly lower in the smokers but not significantly different than the non-smokers (70.6 vs 78.7%; p=0.30) (**Table 4**). Using Kaplan-Meier analyses, unadjusted graft survival rate was significantly lower in smokers compared to non-smokers (p=0.04), but no significant difference in patient survival was noted (p=0.40) (**Figure 4**). Although the cumulative incidence of graft loss was significantly higher in era-1 smokers compared to non-smokers, the causes of graft loss were similar (See supplemental Table 2).

DISCUSSION

Cigarette smoking is a well-recognized cause or co-factor for a variety of diseases, including heart disease, stroke, peripheral vascular disease, lung disease, and many types of cancer.[2] Tobacco use is responsible for over 6 million annual deaths worldwide with many of these deaths occurring in younger adults.[10] In the U.S., an estimated 480,000 annual deaths are attributed to cigarette smoking and second hand exposure.[11] In 2016, 37.8 million or 15.5% of U.S. adults were current cigarette smokers. The highest prevalence of tobacco use is among men and those aged 25 to 64 years.

In cirrhotic patients, tobacco consumption is a major risk factor for both bone and kidney disease.[12] Cirrhotic smokers are also more likely to have ascites and encephalopathy at LT referral compared to non-smokers.[13] Mangus et al. reported that current and previous smokers were more likely to have HCC in their explant compared to lifetime non-smokers (25%, 29% vs 18%, $p<0.001$).[14] Our data also demonstrated a trend towards more frequent HCC among smokers compared to non-smokers in both eras 1 and 2 ($P>0.05$).

The rate of biliary complications after LT was 92% higher in active smokers compared with lifetime non-smokers (HR 1.92, 95% CI 1.07-3.43).[4] The incidence of post-LT hepatic arterial thrombosis or stenosis is increased in patients with a history of cigarette smoking compared to those without a smoking history (17.8% vs 8%). Smoking cessation for 2 years or more pre-LT significantly reduced the risk of vascular complications post-LT (13.5% vs 4.8%).[3] Although there is insufficient data to support how long LT candidates should be abstinent from tobacco before LT listing, we require that all smokers have repeatedly negative urine metabolite screens on 2 consecutive occasions before placing them on the waitlist. In addition, all smokers in our program are referred to formal tobacco cessation programs many of which use adjuvant buproprion or varencline treatment to help achieve tobacco abstinence. In addition, smokers with active anxiety or depressive symptoms are frequently referred to psychiatry to help them achieve sustained abstinence from tobacco preLT but further studies are needed on the optimal approach. Many published studies have also shown that smoking is associated with a higher

risk of malignancy post-LT. [14-18] Smoking has also been associated with increased overall, cardiovascular-related and sepsis-related mortality in LT recipients.[19] McConathy et al. also reported that smokers had a longer mean length of stay and hospital charges compared to non-smokers although 1-year survival was the same. [13] Similar to these studies, our data showed that 1-year graft and patient survival were comparable between smokers and non-smokers in Era-1 but with more prolonged follow-up both patient and graft survival were significantly lower in the smokers (**Table 4**, **Figure 4**). However, the causes of death appear to be qualitatively similar in the two groups (**Supplemental Table 2**)

Our data shows that the prevalence of lifetime tobacco use was higher in the era-2 compared to era-1 patients (62% vs 41%) (**Table 1**). According to previous reports, approximately 60% of LT candidates report a lifetime history of cigarette smoking with the percentage as high as 75% amongst ALD patients. [20, 21] Among the smokers, one-third to one-half achieved abstinence from tobacco while waiting for LT [20]. Among our patients with lifetime smoking history, 23% of patients in era-1 and 42% of patients in era-2 stopped smoking for more than 12 months before the evaluation. In one recent study, the reliability of patient self-reported tobacco use in LT candidates was high, but a 10% deception rate was identified. [22] As a result, many centers perform urinary cotinine screening, a metabolite of nicotine, to monitor for ongoing tobacco use and increase the reliability of detection.[23] In our cohort, the estimated deception rate was 6-7% when using urine cotinine screening. Following LT, the reported rate of tobacco relapse was 40%, and highest among ALD patients at 58%.[24]. However, we did not have these postLT data available for analysis in our cohort.

Recent substance use remains a significant concern for liver transplant programs and contributes to the decision to list or not list a patient for transplantation. A survey study in 2015 showed that most LT programs have a policy on tobacco use (75%), most centers required cessation pre-LT (84%), and all centers encouraged attempts at tobacco cessation.[7] However, smoking was considered an absolute contraindication to LT in only 15% of LT programs, while 62% of the programs reported offering LT for current smokers.[6]

In our study, we hypothesized that implementation of a prohibitive tobacco use policy in August 2013 would lead to fewer smokers being listed for LT and a more prolonged time to listing from initial

evaluation. Contrary to our expectations, there was no significant difference in the proportion of smokers listed for LT after the prohibitive policy was implemented compared to the prior era (13% vs 17%, p=0.25) despite an increase in the proportion of smoking LT candidates (33% vs 22%, $p < 0.005$). As expected, there was an increase in the proportion of smokers that were excluded from transplant listing due to continued tobacco use after the policy implementation (4.4% vs 9.6%, p=0.001) (**Table 2**). Furthermore, the median "time-to-listing" increased significantly after implementation of the policy (**Table 2**). The time-to-listing lengthened modestly (30 days) amongst patients without history of recent tobacco use (within the past 12 months) but was more prominent (60 days) in the patients with history of recent tobacco use. We attribute the increase in evaluation time to the need to treat comorbid SUD and psychiatric illnesses as well as the need to achieve complete tobacco cessation. In our multivariate model, the prohibitive policy era (era-2), a lower MELD score, absence of children and lower levels of education were all independently associated with a longer time to waitlisting **(Table 3**). However, we note that there was a significant increase in the time to listing already ongoing in Era-1 for both smokers and non-smokers (**Figure 3**) which may have been, in part, due to the evolving demographics of LT candidates in our center. For example, the median age of our LT candidates continues to increase and there are a larger proportion of patients with ALD and NASH being referred that frequently require more extensive pretransplant medical evaluation (**Figure 2**). In addition, the proportion of patients with Medicaid insurance, psychiatric co-morbidities, and lower levels of family support and education have significantly increased over time which frequently require more resources and time to be cleared for LT listing. [11]

There are several important limitations of our study. Firstly, all of the data were retrospectively abstracted from a single center and consecutive cohorts of patients were compared to each other rather than contemporaneous cohorts. However, we note that UNOS and others have also reported a recent increase in the proportion of adult LT candidates with ALD and NASH being referred and listed for LT enhancing the face validity and generalizability to our findings. [25, 26] Assessment of tobacco use was also gleaned from retrospective review of medical and social work notes and did not involve direct patient interview using a standardized instrument. Furthermore, our post-LT outcome data must be cautiously interpreted and may reflect lead-time bias due to the shorter duration of follow-up in the era-2 versus era-1 LT recipients. Lastly, the number of deaths both pre and post-LT observed

was small limiting our power and ability to make definitive conclusions regarding risk factors for mortality. _However, we anticipate that with more prolonged follow-up of LT recipients in era-2 that improved postLT outcomes will be realized in the prior smokers who can sustain tobacco cessation postLT (3,4).

In conclusion, cigarette smoking places LT candidates at increased, but preventable, risks including graft loss, malignancy and premature deaths. Thus, it is medically justified to completely prohibit tobacco use in all LT candidates as recommended by the AASLD. Our study found that implementation of a prohibitive tobacco use policy did not impact the proportion of initial smoker candidates that were eventually listed for LT compared to our prior restrictive policy. However, the time to LT listing significantly increased amongst the initial smoker LT candidates who were eventually listed in era-2 compared to era-1. This latter observation may have been due to the increasing proportion of patients with smoking, SUD, and psychiatric co-morbidities being referred for LT evaluation in era-2 (**Table 1**). Going forward all LT candidates should be counseled regarding the need for tobacco cessation as soon as possible to improve their likelihood of getting listed for LT and to experience more favorable outcomes post-LT.

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Figure legends

Figure 1. Liver Transplant candidates included in this study. Amongst the 1344 LT candidates in era-1, 337 were listed for liver transplantation. Amongst the 1350 LT candidates in era-2, 331 were listed for LT. As of June 1st, 2017, 212 and 177 candidates had been transplanted from era-1 and era-2, respectively.

Figure 2. Liver disease diagnoses amongst liver transplant candidates seen from 2010 to 2017. Over time, the proportion of LT candidates with ALD and NASH significantly increased while the proportion with viral hepatitis decreased ($p < 0.001$).

Figure 3. Days from evaluation to listing amongst liver transplant candidates seen from 2010 to 2017. Using linear regression analysis, the median time to listing significantly increased in the overall cohort (p=0.003), smokers (p=0.004), and non-smokers (p=0.014).

Figure 4. Kaplan-Meier curve of patient and graft survival. Amongst the 212 liver transplant recipients from era-1, smokers had a significantly lower rate of A) graft survival (p=0.04) while B) overall survival was not different (p=0.4)

Figure 1:

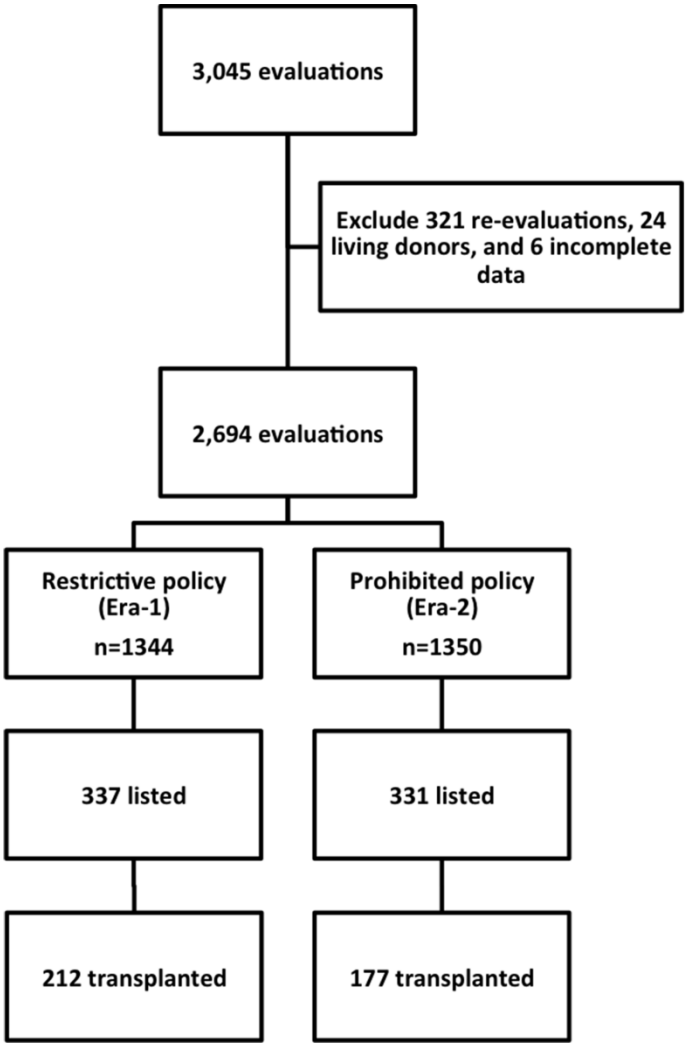


Figure 2:

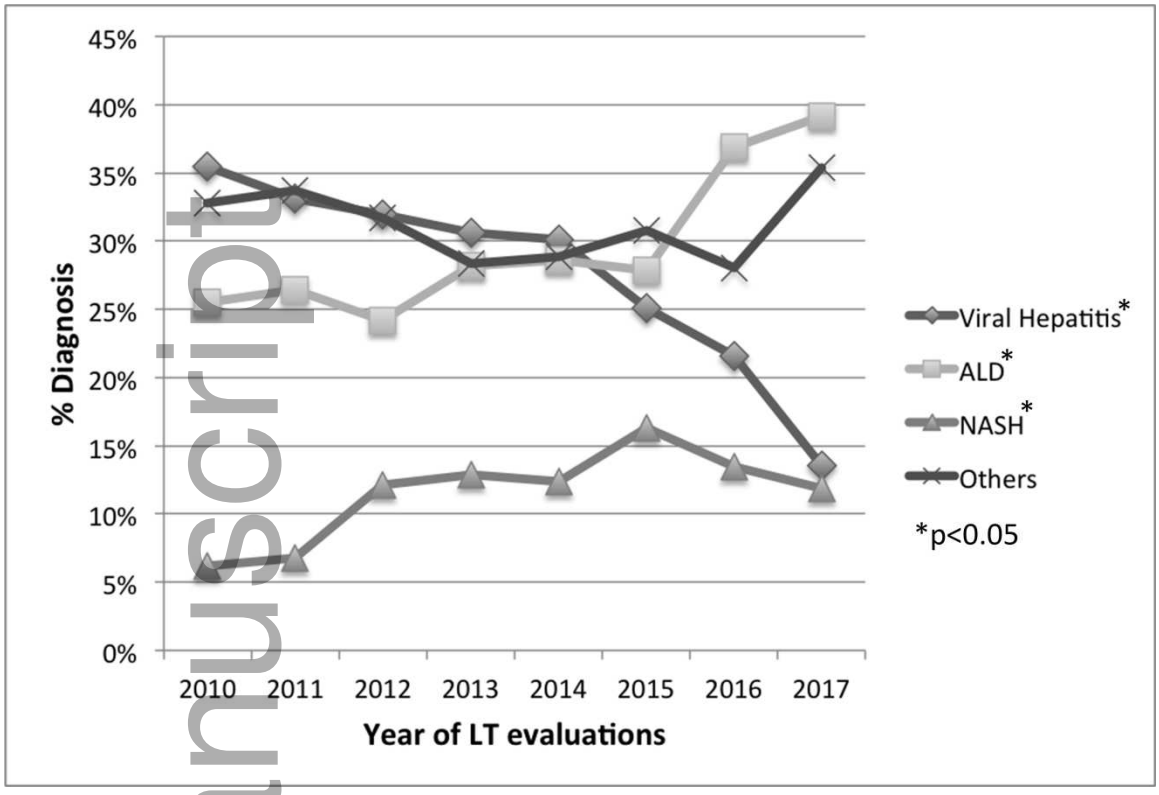


Figure 3

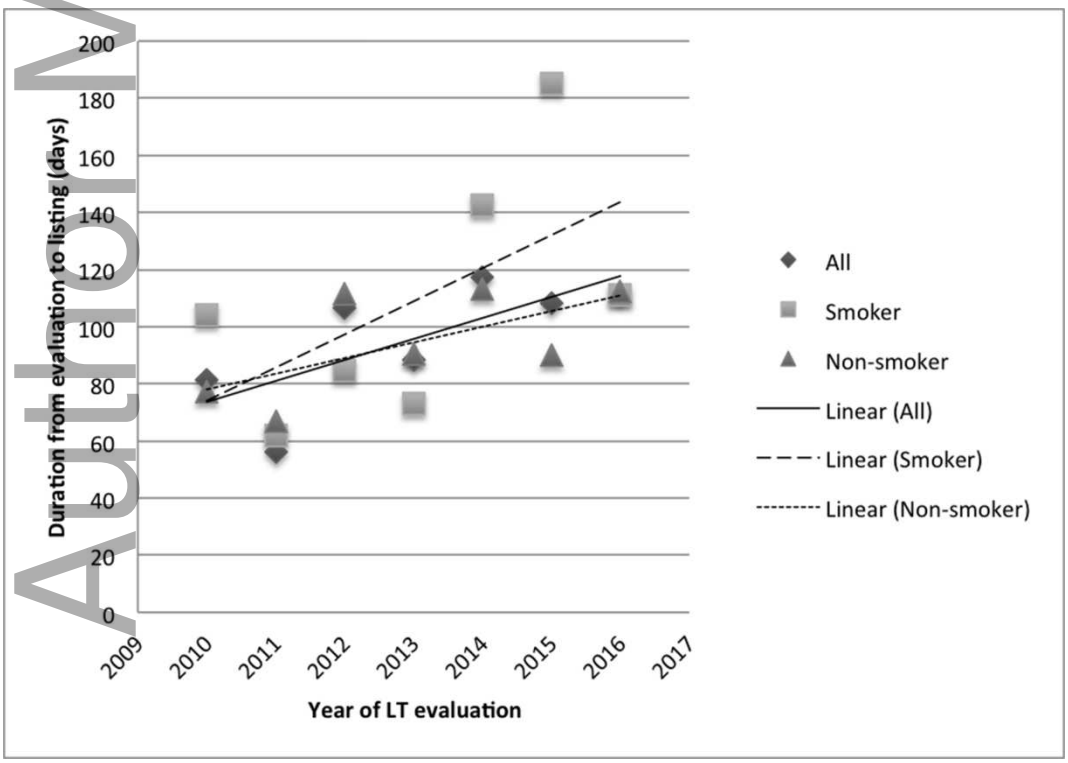
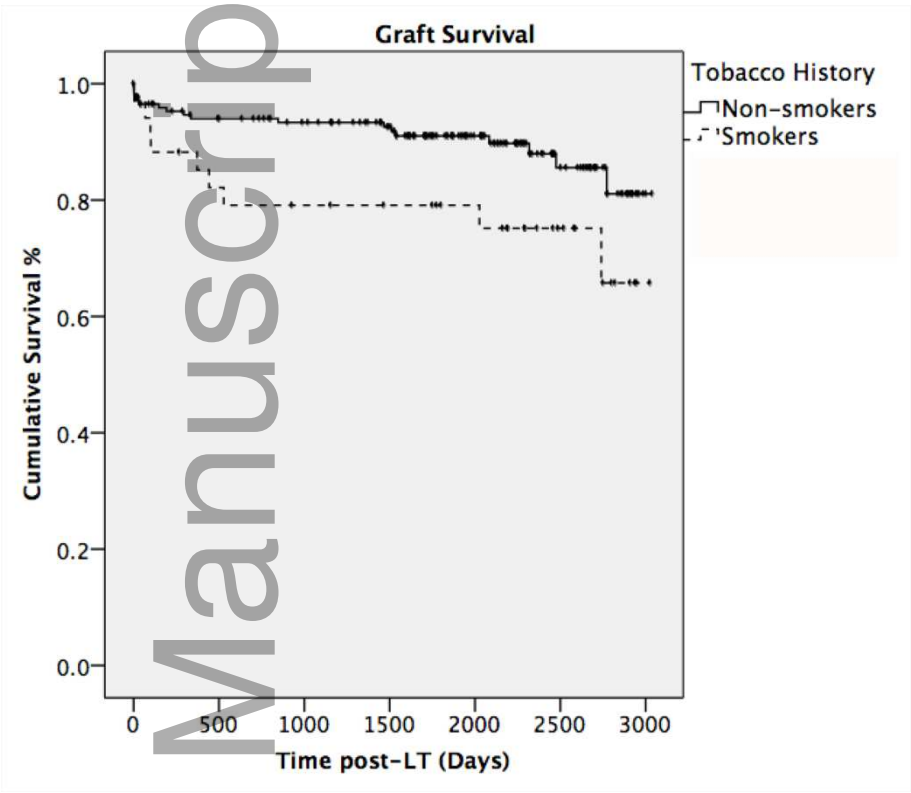


Figure 4.

A)



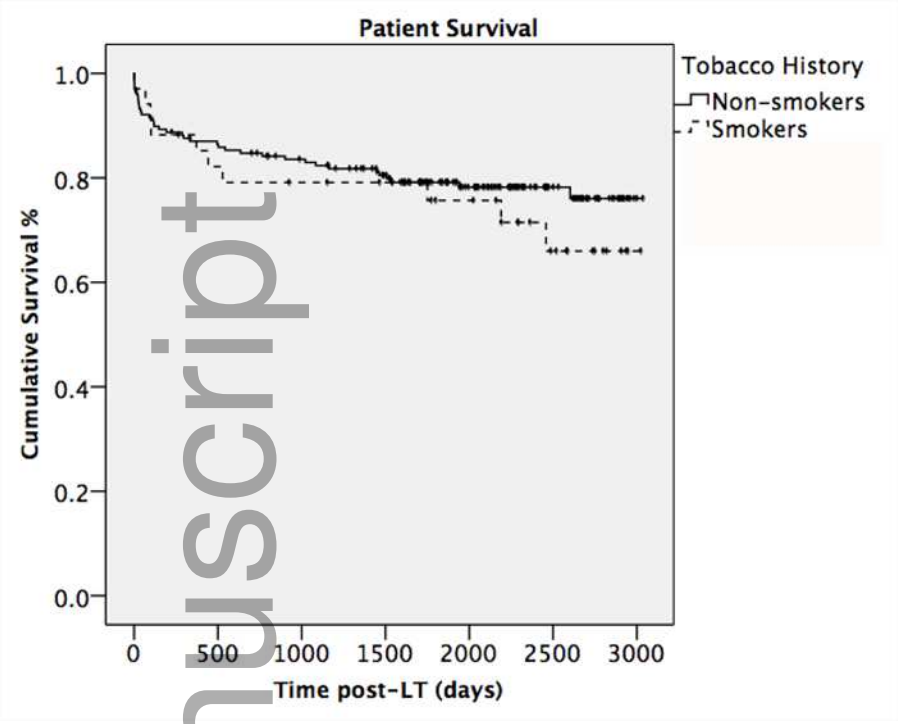


Table 1. Clinical characteristics of 2694 patients evaluated for LT stratified by smoking status and era.

Variables	**Era-1** (n=1344)			**Era-2** (n=1350)			*p-value***	
	Smokers (n=315)	**Non-smokers** (n=1029)	*p-value*	**Smokers** (n=452)	**Non-smokers** (n=898)	*p-value*	**Smokers**	**Non-smokers**
Age at evaluation (year)	51 ± 10	54 ± 11	<0.005*	52 ± 10	56 ± 12	<0.005*	0.12	0.001*
Sex (% male)	62	56	0.06	60	60	0.98	0.56	0.08
Race (% white)	83	82	0.51	84	86	0.05	0.42	0.12
Mean MELD# score at evaluation	15 ± 8	15 ± 8	0.53	14 ± 7	15 ± 7	0.008*	0.03*	0.64*
Diagnosis (%)								
Viral hepatitis	45	29	<0.05*	37	21	<0.05*	<0.05*	<0.05*
ALD	31	24	<0.05*	40	27	<0.05*	<0.05*	<0.05*
NASH	3	11	<0.05*	6	19	<0.05*	<0.05*	<0.05*
Others	21	37	<0.05*	18	34	<0.05*	ns	ns
Presence of HCC (%)	15	11	0.08	13	10	0.05	0.39	0.20
Insurance status (% Medicaid)	27	12	<0.005*	39	18	<0.005*	0.001*	<0.005*
Education level (% college or higher)	52	57	0.14	58	64	0.04*	0.11	0.002*
Employment status (% unemployed)	60	52	0.02*	68	53	<0.005*	0.02*	0.69
Marital status (% married)	53	68	<0.005*	48	63	<0.005*	0.15	0.02*
Parental status (% has children)	74	80	0.02*	81	82	0.5	0.03*	0.24
Reported history of (%)								
Lifetime tobacco use	100	23	<0.005*	100	42	<0.005*	ns	<0.005*
Lifetime alcohol use	84	63	<0.005*	86	64	<0.005*	0.34	0.65

Lifetime marijuana use	35	17	<0.005*	42	18	<0.005*	0.04*	0.48
Lifetime opiate use	25	9	<0.005*	26	13	<0.005*	0.82	0.02*
Lifetime other illicit substance use	18	8	<0.005*	25	8	<0.005*	0.02*	0.59
Tobacco use within 12 months	100	-	<0.005*	100	-	<0.005*	ns	ns
Alcohol use within 12 months	37	20	<0.005*	49	27	<0.005*	0.001*	0.001*
Marijuana use within 12 months	16	5	<0.005*	26	8	<0.005*	0.001*	0.009*
Opiate use within 12 months	23	7	<0.005*	23	12	<0.005*	0.97	0.003*
Illicit substance use within 12 months	1.9	0.3	<0.005*	2.7	0.3	<0.005*	0.5	0.87
Presence of psychiatry comorbidity (%)	32	18	<0.005*	48	29	<0.005*	<0.005*	<0.005*
On psychiatry medications (%)	21	11	<0.005*	31	23	0.002*	<0.005*	<0.005*
Prior SUD health/legal consequences (%)	11	5	<0.005*	27	10	<0.005*	<0.005*	<0.005*
Prior SUD treatment (%)	17	7	<0.005*	30	12	<0.005*	<0.005*	<0.005*
Toxicology screen								
Toxicology screening (% test completed)	79	70	0.007*	80	72	0.001*	0.97	0.58
Alcohol metabolites (% positive)	5	1.9	0.02*	8	3.4	0.002*	0.14	0.08
Tobacco metabolites (% positive)	61	6	<0.005*	55	7	<0.005*	0.14	0.36
Marijuana metabolites (% positive)	15	7	<0.005*	17	8	<0.005*	0.40	0.18
Opiates metabolites (% positive)	31	18	<0.005*	22	17	0.05	0.01*	0.78
Other illicit substances metabolites (% positive)	2.8	1.4	0.14	3.1	2.2	0.4	0.84	0.26
Counseling/referral	31	11	<0.005*	46	21	<0.005*	<0.005*	<0.005*
SUD Pharmacotherapy	1.5	0	0.004*	2.2	2	<0.005*	0.53	0.26

univariate analysis p< 0.05.p-value compared era-1 vs era-2. #Calculated MELD score, not MELD-Na.*

ALD, alcoholic liver disease, HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis; ns, not significant; SUD, substance use disorder

Table 2. Selection outcomes stratified by eras and smoking status.

	Era-1 (n=1344)			**Era-2** (n=1350)			*p-value***	
	Smokers (n=315)	**Non-smokers** (n=1029)	*p-value*	**Smokers** (n=452)	**Non-smokers** (n=898)	*p-value*	**Smokers**	**Non-smokers**
Selection results (% listed)	52 (17)	285 (28)	<0.005*	61 (13)	270 (30)	<0.005*	0.25	0.25
Median time to list (days)	65 (0–342)	81 (0-519)	0.59	122 (0-481)	105(0-546)	0.014*	0.001*	<0.005*
Reason not listed; n (%)								
Clinically too well	89 (28)	252 (25)	0.18	106 (24)	202 (23)	0.69	0.13	0.30
Deceased	10 (3)	43 (4)	0.42	27 (6)	68 (8)	0.28	0.75	0.001*
Medical issue	58 (18)	217 (21)	0.3	54 (12)	186 (21)	<0.005*	0.01*	0.84
Alcohol use	45 (14)	104 (10)	<0.04*	62 (14)	88 (10)	<0.03*	0.82	0.82
Tobacco use	14 (4.4)	6 (0.6)	<0.005*	50 (9.6)	2 (2.2)	<0.005*	0.001	0.22
Other substance use	8 (3)	18 (2)	0.37	10 (2.2)	23 (2.6)	0.69	0.76	0.21
Others	39 (12)	104 (10)	0.46	82 (18)	59 (6)	0.51	0.93	0.08
Transplanted (% of listed)	34 (65%)	178 (62%)	0.69	25 (41%)	152 (56%)	0.03*	0.01*	0.14
Mean MELD# score at LT	24 ± 6	23 ± 6	0.17	25 ± 6	25 ± 6	0.43	0.51	0.008

**Univariate analysis p< 0.05. **p-value compared era-1 vs. era-2. #Calculated or exceptional MELD score, not MELD-Na*

LT, liver transplantation; MELD, Model for End-stage Liver Disease.

Table 3. Factors associated with being listed for LT amongst 2694 LT candidates

Variable	Odd ratio*	95% CI, low value	95% CI, high value	*P-value*
Male	1.24	1.02	1.53	0.04
Higher MELD score at evaluation	1.03	1.02	1.04	<0.005
Married	1.59	1.27	1.99	<0.005
Medicaid insured	0.48	0.36	0.65	<0.005
Presence of HCC	2.48	1.85	3.33	<0.005
Absence of prior SUD health/legal consequences	1.48	1.00	2.16	0.04
Absence of psychiatric co-morbidity	1.43	1.12	1.82	0.004
Absence of tobacco use within 12 months	1.43	1.02	2.02	0.04
Absence of marijuana use within 12 months	1.53	1.01	2.33	0.04
Absence of opioid use within 12 months	3.72	2.3	6.02	<0.005

**Adjusted for age, policy, MELD score, presence of HCC, insurance status, marital status, substance use history, prior consequences, and psychiatry comorbidity.*

CI, Confidence Interval; HCC, hepatocellular carcinoma; SUD, substance use disorder.

Table 4. Post-transplant outcomes stratified by era and smoking status.

Outcomes	**Era-1** (n=212)			**Era-2** (n=157[#])			*p-value***	
	Smokers (n=34)	**Non-smokers** (n=178)	*p-value*	**Smokers** (n=23)	**Non-smokers** (n=134)	*p-value*	**Smokers**	**Non-smokers**
Median post-LT follow up (days)	2191 (3-3025)	1873 (0-3038)	0.14	882 (154-1638)	772 (4-1696)	0.78	0.005*	<0.005*
1-year graft survival (%)	88.2	88.2	0.99	100	94.8	0.26	0.08	0.04*
1-year patient survival (%)	88.2	87.1	0.85	95.7	95.5	0.98	0.33	0.01*
Overall graft survival (%)	73.5	89.7	0.01*	100	96	0.32	0.006*	0.03*
Overall patient survival (%)	70.6	78.7	0.30	92	95.4	0.47	0.04*	<0.005

**Univariate analysis p< 0.05. **p-value compared era-1 vs. era-2.*

[#]20 patients were excluded due to incomplete survival data.

LT, liver transplantation.

Table 1. Clinical characteristics of 2694 patients evaluated for LT stratified by smoking status and era.

Variables	**Era-1** (n=1344)			**Era-2** (n=1350)			*p-value***	
	Smokers (n=315)	**Non-smokers** (n=1029)	*p-value*	**Smokers** (n=452)	**Non-smokers** (n=898)	*p-value*	**Smokers**	**Non-smokers**
Age at evaluation (year)	51 ± 10	54 ± 11	<0.005*	52 ± 10	56 ± 12	<0.005*	0.12	0.001*
Sex (% male)	62	56	0.06	60	60	0.98	0.56	0.08
Race (% white)	83	82	0.51	84	86	0.05	0.42	0.12
Mean MELD[#] score at evaluation	15 ± 8	15 ± 8	0.53	14 ± 7	15 ± 7	0.008*	0.03*	0.64*
Diagnosis (%)								
Viral hepatitis	45	29	<0.05*	37	21	<0.05*	<0.05*	<0.05*
ALD	31	24	<0.05*	40	27	<0.05*	<0.05*	<0.05*
NASH	3	11	<0.05*	6	19	<0.05*	<0.05*	<0.05*
Others	21	37	<0.05*	18	34	<0.05*	ns	ns
Presence of HCC (%)	15	11	0.08	13	10	0.05	0.39	0.20
Insurance status (% Medicaid)	27	12	<0.005*	39	18	<0.005*	0.001*	<0.005*
Education level (% college or higher)	52	57	0.14	58	64	0.04*	0.11	0.002*
Employment status (% unemployed)	60	52	0.02*	68	53	<0.005*	0.02*	0.69
Marital status (% married)	53	68	<0.005*	48	63	<0.005*	0.15	0.02*
Parental status (% has children)	74	80	0.02*	81	82	0.5	0.03*	0.24
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Lifetime tobacco use	100	23	<0.005*	100	42	<0.005*	ns	<0.005*
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Lifetime other illicit substance use	18	8	<0.005*	25	8	<0.005*	0.02*	0.59
Tobacco use within 12 months	100	-	<0.005*	100	-	<0.005*	ns	ns

Alcohol use within 12 months	37	20	<0.005*	49	27	<0.005*	0.001*	0.001*
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Deceased	10 (3)	43 (4)	0.42	27 (6)	68 (8)	0.28	0.75	0.001*
Medical issue	58 (18)	217 (21)	0.3	54 (12)	186 (21)	<0.005*	0.01*	0.84
Substance use	59 (19)	110 (11)	<0.005*	112 (25)	90 (10)	<0.005*	0.05	0.63
Others	28 (9)	196 (10)	0.46	41 (9)	72 (8)	0.51	0.93	0.08
Transplanted (% of listed)	34 (65%)	178 (62%)	0.69	25 (41%)	152 (56%)	0.03*	0.01*	0.14
Mean MELD[#] score at LT	24 ± 6	23 ± 6	0.17	25 ± 6	25 ± 6	0.43	0.51	0.008

**Univariate analysis p< 0.05. **p-value compared era-1 vs. era-2. [#]Calculated or exceptional MELD score, not MELD-Na*

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Presence of HCC	2.48	1.85	3.33	<0.005
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Overall graft survival (%)	73.5	89.7	0.01*	100	96	0.32	0.006*	0.03*
Overall patient survival (%)	70.6	78.7	0.30	92	95.4	0.47	0.04*	<0.005

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[#]20 patients were excluded due to incomplete survival data.

LT, liver transplantation.

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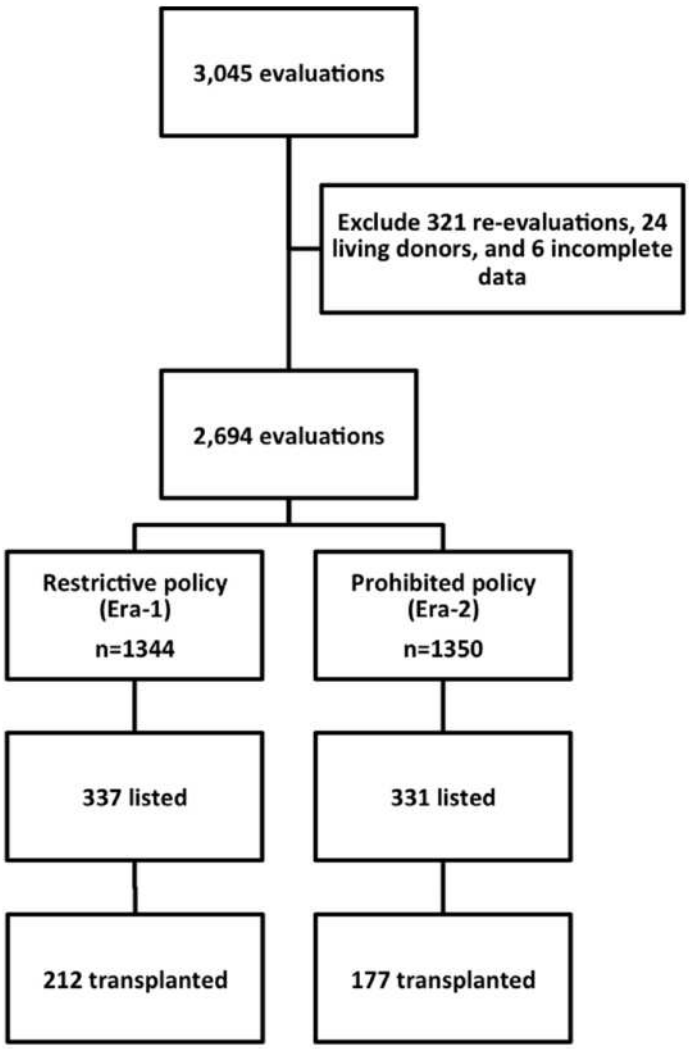

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Figure 2:

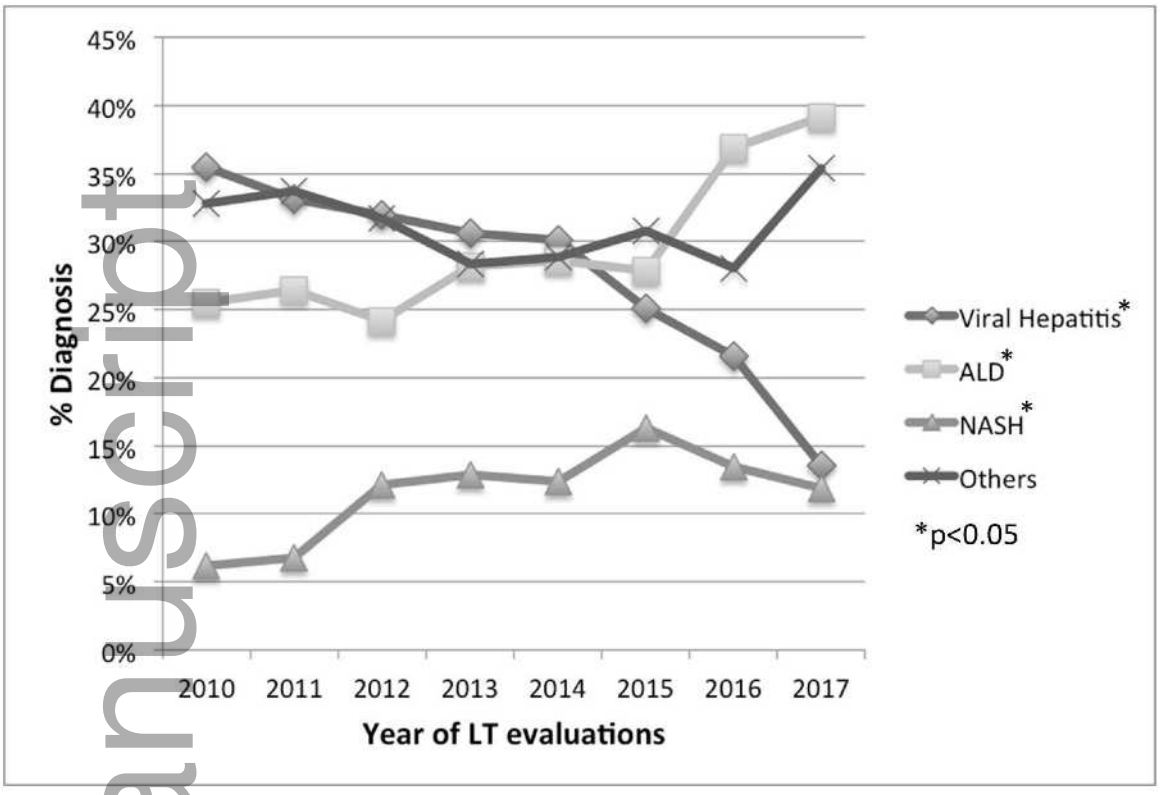

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Figure 3.

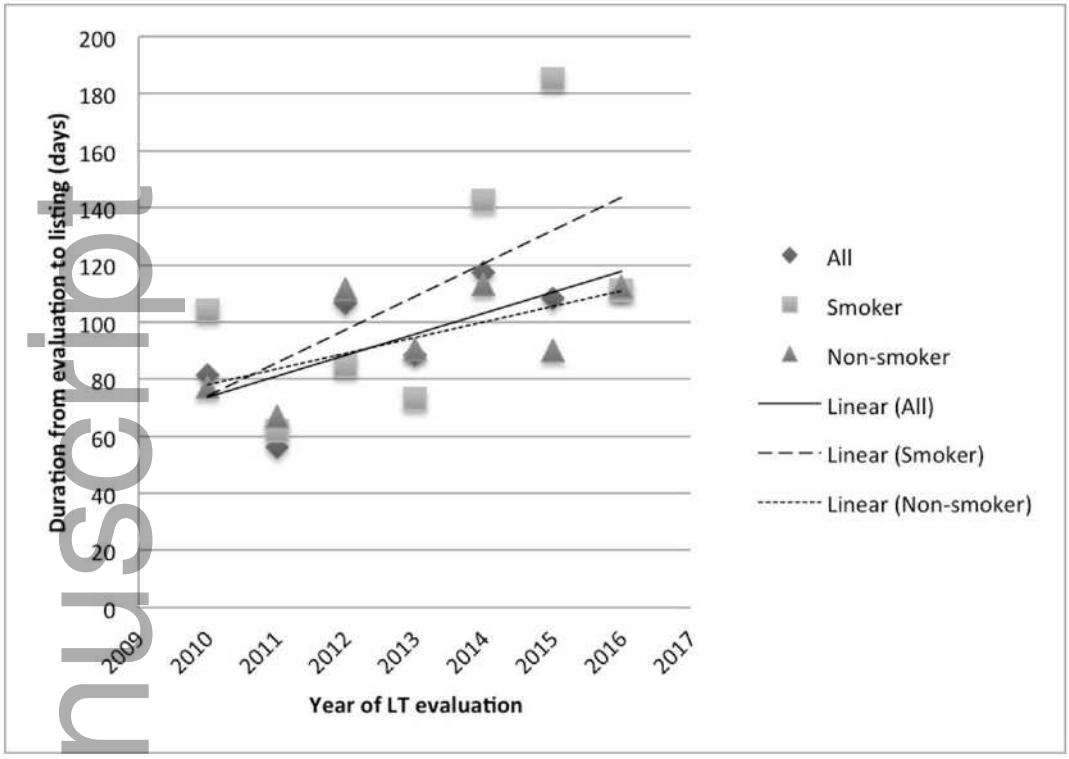

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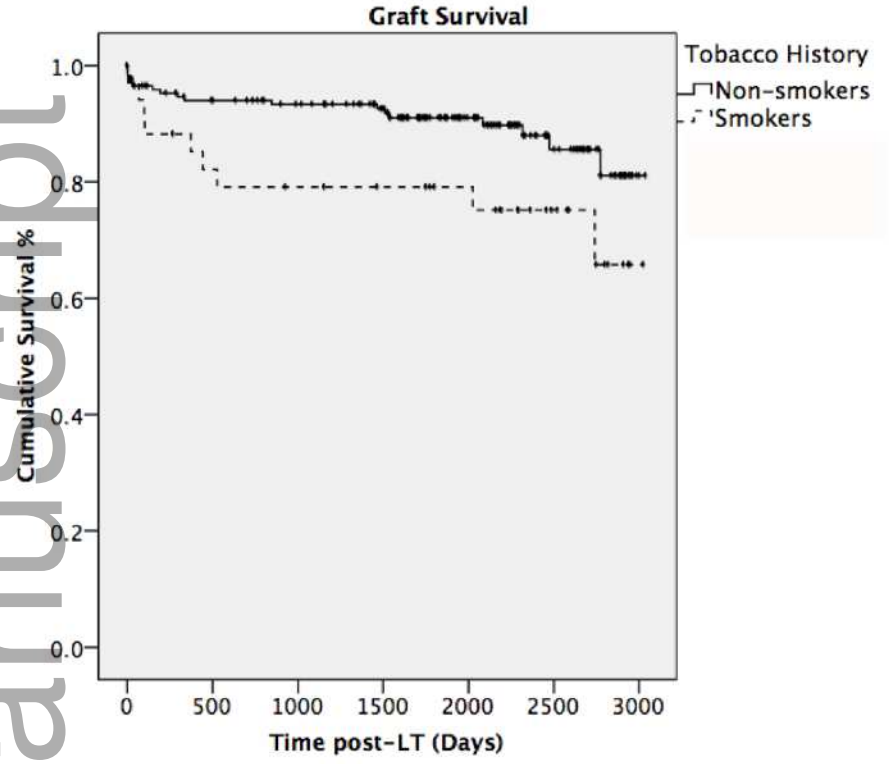
Figure 4.

A)



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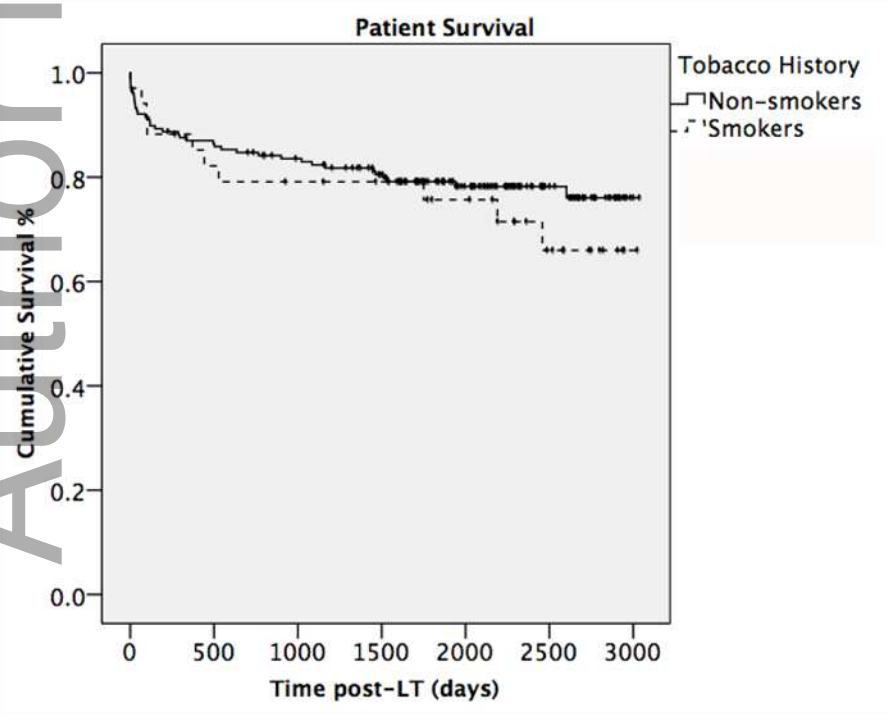

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