Impact of a Prohibitive Versus Restrictive Tobacco Policy on Liver Transplant Candidate Outcomes

Alisa Likhitsup ,[1] Ammar Hassan,[1] Jessica Mellinger,[1] Frederick Askari,[1] Gerald S. Winder,[2] Naba Saeed ,[4] Christopher J. Sonnenday,[3] Pratima Sharma,[1] and Robert J. Fontana[1]

[1]Division of Gastroenterology and Hepatology and Department of [2]Psychiatry and [3]Surgery, University of Michigan, Ann Arbor, MI; and [4]Department of Internal Medicine, Beaumont Hospital, Dearborn, MI

Tobacco use has been associated with poorer outcomes after liver transplantation (LT). Our study examined the effect on LT listing outcomes of a newly implemented policy prohibiting the use of all tobacco products compared with a prior restrictive policy. 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. The mean age of the 2694 LT candidates was 54 ± 11 years, 60% were male, and the mean Model for End-Stage Liver Disease (MELD) score was 15 ± 7. Although the proportion of LT candidates who were smokers was significantly higher in era 2 (33% versus 23%; $P < 0.005$), the proportion of smokers listed for LT remained stable (13% versus 17%; $P = 0.25$). However, there were more smokers excluded for ongoing tobacco use in era 2 compared with era 1 (9.6% versus 4.4%; $P = 0.001$). Factors independently associated with LT listing included a diagnosis of hepatocellular carcinoma, being married, private insurance, absence of psychiatry comorbidity, and absence of tobacco, marijuana, or opiate use but evaluation during era 2 was not associated with LT listing. However, the median time to listing significantly increased over time, especially in smokers (from 65 to 122 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 ($P < 0.05$). In conclusion, 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 waiting list for smokers who were eventually listed was significantly longer due to the need to achieve complete tobacco cessation.

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Liver transplantation (LT) is a lifesaving intervention for patients with decompensated cirrhosis and other forms of liver failure. However, because of 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 an increased risk of infections as well as 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]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALD, alcoholic liver disease; CI, confidence interval; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; NS, not significant; OR, odds ratio; SUD, substance-use disorder.

Address reprint requests to Alisa Likhitsup, M.D., Division of Gastroenterology and Hepatology, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48109. Telephone: 816-932-4655; FAX: 816-932-7920; Email: alikhitsup@gmail.com

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Our program implemented a prohibitive tobacco use policy on August 1, 2013, wherein all LT candidates were 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 among smokers being evaluated for LT and a longer time to listing among the smokers who are eventually listed.

Patients and Methods

PATIENT COHORT

The University of Michigan institutional review board priorly approved this retrospective chart-review study. All adult LT candidates over 18 years of age evaluated at the University of Michigan from January 1, 2010, to March 1, 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, sex, 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 comorbidities, and prior substance use–related treatments were collected. Toxicology screening at the initial LT evaluation and other prelisting 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 1, 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 from self or family member or by detectable serum or urine metabolites. Urine cotinine was used to screen for active nicotine use, whereas 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 included urine amphetamine, cocaine, opiate, oxycodone, benzodiazepines, and barbiturates to screen for illicit substance use. The frequency of substance use interventions, including referral to tobacco consultation

Alisa Likhitsup designed the study, provided data collection and statistical analysis, and drafted the manuscript. Ammar Hassan and Naba Saeed provided data collection. Jessica Mellinger, Frederick Askari, and Gerald S. Winder designed the study and reviewed the manuscript. Christopher J. Sonnenday reviewed the manuscript. Pratima Sharma provided statistics consultation and reviewed the manuscript. Robert J. Fontana designed the study, provided data analysis, supervised the study, and drafted and reviewed the manuscript.

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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 listing), 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 variables were expressed as percentages. The baseline characteristics at the time of LT evaluation were compared using an 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 listing). A simple linear regression analysis was used to predict the proportion of liver disease diagnosis and the time to listing based on the year of evaluation. We used multivariate logistic regression analysis to assess the candidate factors associated with listing status and the time-to-listing period (≥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 the Kaplan-Meier method stratified by smoking status and log-rank analysis. SPSS, version 25.0 (IBM Corp., Armonk, NY) was used for all analyses.

Results

PATIENT CHARACTERISTICS

From January 1, 2010, to March 1, 2017, 3045 adults underwent LT evaluation. In total, 351 patients were excluded from the analysis, including 24 living donor evaluations, 6 patients with incomplete data, and 321 duplicate evaluations. Among the remaining 2694 patients, 1344 underwent LT evaluation in era 1 and 1350 underwent LT evaluation in era 2 (Fig. 1).

The clinical characteristics of the patients are shown in Table 1. The mean age of the 2694 patients was 54 ± 11 years, 60% were male, and 84% were Caucasian. Interestingly, the number of smokers was significantly higher in era 2 compared with era 1 (33% versus 23%; $P < 0.005$). Overall, smokers were significantly younger compared with nonsmokers 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 nonsmokers in era 2 (14 ± 7 versus 15 ± 7; $P = 0.008$), and it was also lower than the MELD scores of the era 1 smokers (14 ± 7 versus 15 ± 8; $P = 0.03$). 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

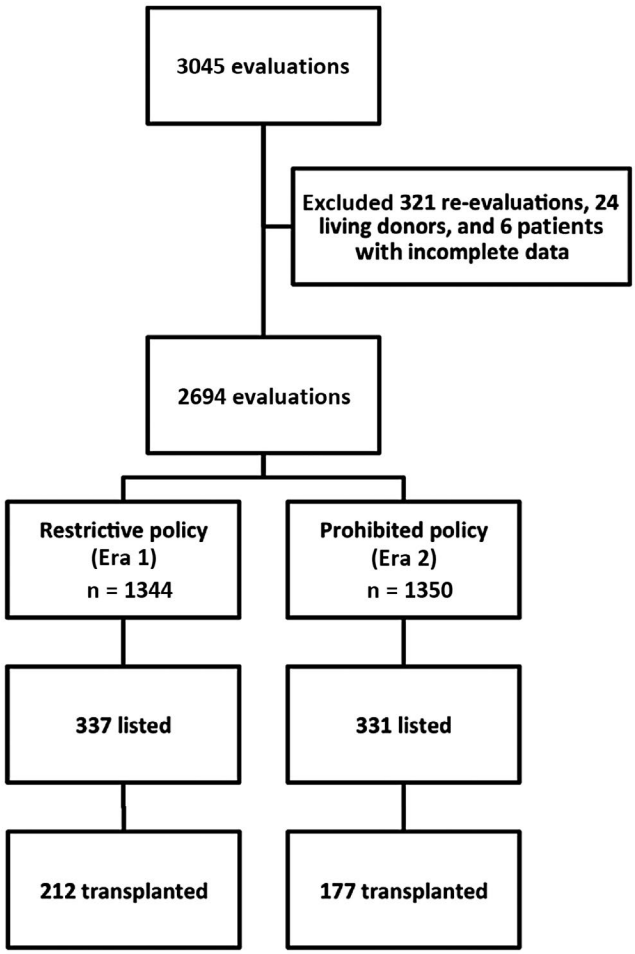

FIG. 1. LT candidates included in this study. Among the 1344 LT candidates in era 1, 337 were listed for LT. Among the 1350 LT candidates in era 2, 331 were listed for LT. As of June 1, 2017, a total of 212 and 177 candidates underwent transplantation during era 1 and era 2, respectively.

TABLE 1. Clinical Characteristics of 2694 Patients Evaluated for LT Stratified by Smoking Status and Era

	Era 1 (n = 1344)			Era 2 (n = 1350)			*P* Value*	
Variables	Smokers (n = 315)	Nonsmokers (n = 1029)	*P* Value	Smokers (n = 452)	Nonsmokers (n = 898)	*P* Value	Smokers	Nonsmokers
Age at evaluation, years	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
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	10	<0.05†	5	18	<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 substance use history								
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 psychiatric 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
Opiate 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

NOTE: Data are given as mean ± standard deviation or as percentages.
*P value for era 1 versus era 2.
†Univariate analysis $P < 0.05$.
‡Calculated MELD score, not MELD-sodium.

liver disease significantly changed with the proportion of patients with ALD significantly increasing in era 2 (27% to 34%; $P < 0.05$), whereas viral hepatitis decreased (37% to 29%; $P < 0.05$) (Fig. 2). A simple linear regression analysis was used to predict proportion of liver disease diagnosis based on the year of evaluation. Each year an increase in referral for evaluation was associated with a 2.8% decrease in the proportion of LT candidates with viral hepatitis ($\beta = -0.028$ [95% confidence interval [CI], –0.037 to –0.018]; $P < 0.001$), 2% increase in ALD ($\beta = 0.02$ [95% CI, 0.007-0.03]; $P = 0.007$), and 1.0% increase in nonalcoholic steatohepatitis (NASH; $\beta = 0.01$ [95% CI, 0.002-0.019]; $P = 0.03$). 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 (84% versus 63% and 86% versus 64%), marijuana (35% versus 17% and 42% versus 18%), opiate (25% versus 9% and 26% versus 13%), and other illicit substance use (18% versus 8% and 25% versus 8%) compared with nonsmokers ($P < 0.005$). In addition, the rates of lifetime marijuana (42% versus 35%) and illicit substance use (25% versus 18%) was higher in smokers in era 2 compared with era 1, although lifetime opiate use increased in nonsmokers in era 2 (13% versus 9%; $P < 0.05$; Table 1).

As expected, smokers reported more frequent history of alcohol (37% versus 20% and 49% versus 27%), marijuana (16% versus 5% and 26% versus 8%), opiate (23% versus 7% and 23% versus 12%), and illicit substance use (1.9% versus 0.3% and 2.7% versus 0.3%) within the 12 months before LT evaluation compared with nonsmokers ($P < 0.005$). In era 2, the reported history of alcohol and marijuana use within 12 months increased in both smokers (era 1 to era 2, 37% to 49% and 16% to 26%, respectively) and nonsmokers (era 1 to era 2, 20% to 27% and 5% to 8%, respectively), whereas reported history of opiate use within 12 months increased in nonsmokers only (era 1 to era 2, 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 with nonsmokers ($P < 0.005$). In addition, all of these rates significantly increased in era 2 compared with era 1 in both smokers and nonsmokers ($P < 0.005$; 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 with nonsmokers, but the 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 2 eras. Both smokers and nonsmokers received more interventions for various SUDs in era 2 versus era 1, including substance-use counseling, psychology or psychiatry referral (46% versus 31% in smokers and 21% versus 11% in nonsmokers; $P < 0.005$). In addition, smokers received more SUD pharmacotherapy compared with nonsmokers, but there was no significant difference between the 2 eras (Table 1).

LT EVALUATION OUTCOMES

Although the proportion of candidates listed for LT were similar in both eras (25% versus 24%; $P = 0.14$), a significantly lower proportion of smokers versus nonsmokers were listed in both eras (13% versus 28% in era 1 and 17% versus 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 with era 1 (4.4% versus 9.6%; $P = 0.001$; Table 2). Interestingly, the median time to listing was similar in the smokers and nonsmokers in era 1 (65 versus 81 days; $P = 0.59$). However, the median time to listing significantly increased in the era 2 smokers compared with the nonsmokers (122 versus 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 nonsmoker patients over the entire time of this study (Fig. 3). In an unadjusted linear regression analysis, every year increase in referral for evaluation was associated with a 6.1-day increase in time to listing on average ($\beta = 0.51$ [95% CI, 0.178-0.842], $P = 0.003$ for all LT candidates; $\beta = 1.176$ [95% CI, 0.399-1.954], $P = 0.004$ for smokers; and $\beta = 0.453$ [95% CI, 0.095-0.811], $P = 0.01$ for nonsmokers). On multivariate analysis,

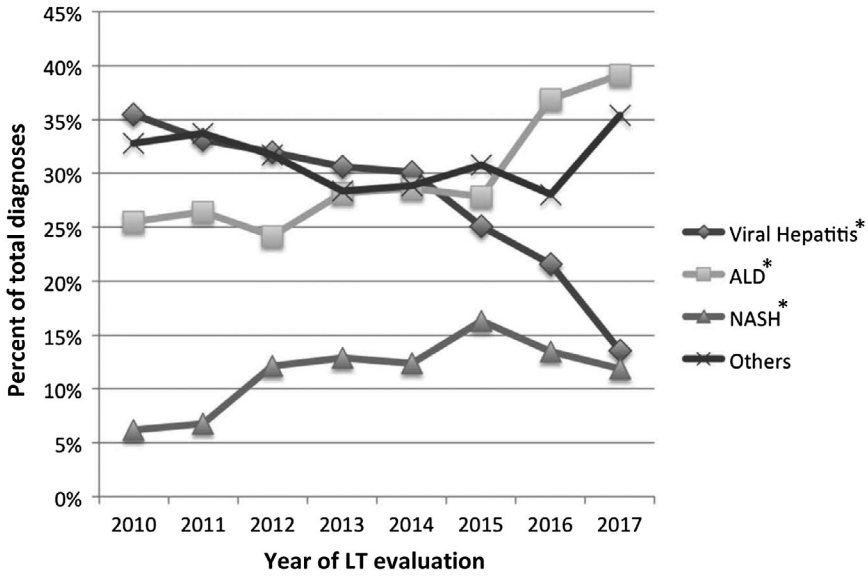

FIG. 2. Liver disease diagnoses among LT candidates seen from 2010 to 2017. Over time, the proportion of LT candidates with ALD and NASH significantly increased while the proportion with viral hepatitis decreased ($P < 0.001$). *$P < 0.05$.

TABLE 2. Selection Outcomes Stratified by Eras and Smoking Status

	Era 1 (n = 1344)			Era 2 (n = 1350)			*P* Value*	
	Smokers (n = 315)	Nonsmokers n = 1029)	*P* value	Smokers (n = 452)	Nonsmokers (n = 898)	*P* Value	Smokers	Nonsmokers
Selection results, listed	52 (17)	285 (28)	<0.005†	61 (13)	270 (30)	<0.005†	0.25	0.25
Time to listing, days	65 (0-342)	81 (0-519)	0.59	122 (0-481)	105 (0-546)	0.014†	0.001†	<0.005†
Reason not listed								
Clinically too well	89 (28)	252 (24)	0.18	106 (23)	202 (22)	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

NOTE: Data are given as median (range), mean ± standard deviation, or n (%).
*P value for era 1 versus era 2.
†Univariate analysis $P < 0.05$.
‡Calculated or exceptional MELD score, not MELD-sodium.

a diagnosis of HCC, being married, male sex, higher MELD score, absence of prior SUD-related health or legal consequences, absence of psychiatric comorbidities, 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 a 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

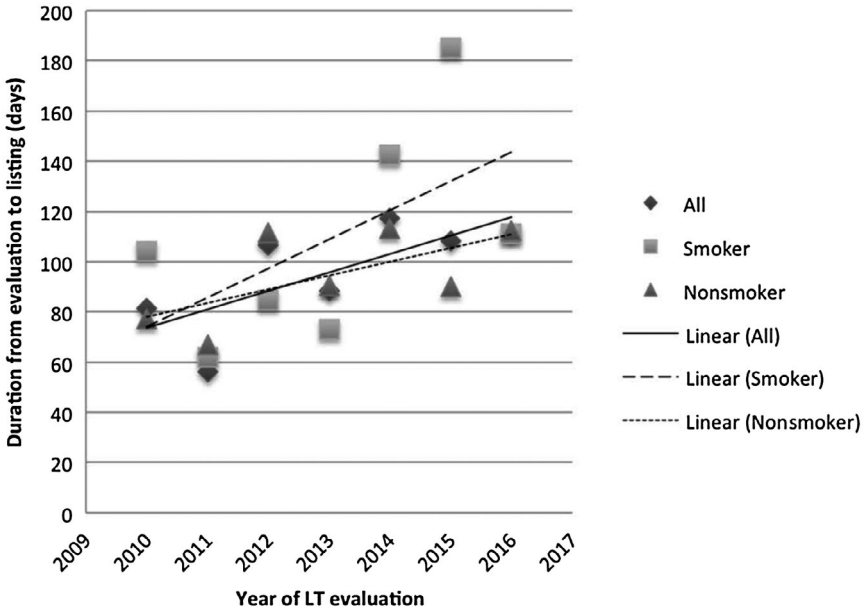

FIG. 3. Days from evaluation to listing among LT candidates seen from 2010 to 2017. Using a linear regression analysis, the median time to listing significantly increased for the overall cohort ($P = 0.003$), smokers ($P = 0.004$), and nonsmokers ($P = 0.01$).

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 (Supporting Table 1).

TRANSPLANT OUTCOMES

In era 1, 8 (2.4%) of the 337 listed patients were removed from the waiting list due to alcohol (n = 4), tobacco (n = 3), or marijuana (n = 1) use. In era 2, 13 (3.9%) of the 331 listed patients were removed from the waiting list due to either alcohol (n = 6), tobacco (n = 6), or marijuana (n = 1) use. There was no difference in the rate of wait-list 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 with era 1 (41% versus 65%; $P = 0.01$), presumably due to lead-time bias. The median (range) time of follow-up after listing was 2191 (3-3025) days in era 1 smokers, 1873 (0-3038) days in era 1 nonsmokers, 882 (154-1638) days in era 2 smokers, and 772 (4-1696) days in era 2 nonsmokers (Table 4). The mean MELD score at transplantation in nonsmokers increased in era 2 (25 versus 23; $P = 0.008$), whereas there was no difference between smokers (Table 2).

TABLE 3. Factors Associated With Being Listed for LT Among 2694 LT Candidates

Variable	OR*	95% CI	*P* Value
Sex, 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 comorbidity	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.

GRAFT AND PATIENT SURVIVAL

From era 1, 212 listed patients had undergone LT, whereas 177 of the era 2 patients had undergone LT. In era 2, 20 patients were excluded from the graft and

TABLE 4. Posttransplant Outcomes Stratified by Era and Smoking Status

	Era 1 (n = 212)			Era 2 (n = 157)*			*P* Value†	
Outcomes	Smokers (n = 34)	Nonsmokers (n = 178)	*P* Value	Smokers (n = 23)	Nonsmokers (n = 134)	*P* Value	Smokers	Nonsmokers
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	100.0	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‡	100.0	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

NOTE: Data are given as median (range) or percentage.
*20 patients were excluded due to incomplete survival data.
†*P* value for era 1 versus era 2.
‡Univariate analysis $P < 0.05$.

patient survival outcome analysis due to survival data was not available at the time of this analysis. The median follow-up time after 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 among smokers and nonsmokers in both eras (Table 4).

A 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 rates in smokers were similar to nonsmokers (88% versus 88% graft survival and 88% versus 87% patient survival; $P > 0.05$). However, during a median follow-up time of 2191 (3-3025) days in smokers and 1873 (0-3038) days in nonsmokers, the graft survival was significantly lower in smokers compared with nonsmokers (73.5% versus 89.7%; $P = 0.01$). In contrast, overall patient survival was slightly lower in the smokers but not significantly different than the nonsmokers (70.6% versus 78.7%; $P = 0.30$; Table 4). Using a Kaplan-Meier analysis, the unadjusted graft survival rate was significantly lower in smokers compared with nonsmokers ($P = 0.04$), but no significant difference in patient survival was noted ($P = 0.40$; Fig. 4). Although the cumulative incidence of graft loss was significantly higher in era 1 smokers compared with nonsmokers, the causes of graft loss were similar (Supporting Table 2).

Discussion

Cigarette smoking is a well-recognized cause or cofactor 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 United States, an estimated 480,000 annual deaths are attributed to cigarette smoking and secondhand exposure.[11] In 2016, 37.8 million or 15.5% of US adults were current cigarette smokers. The highest prevalence of tobacco use is among men and those aged 25-64 years.

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

The rate of biliary complications after LT was 92% higher in active smokers compared with lifetime nonsmokers (hazard ratio, 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 with those without a smoking history (17.8% versus 8%). Smoking cessation for 2 years or more before LT significantly reduced the risk of vascular complications after LT (13.5% versus 4.8%).[3] Although

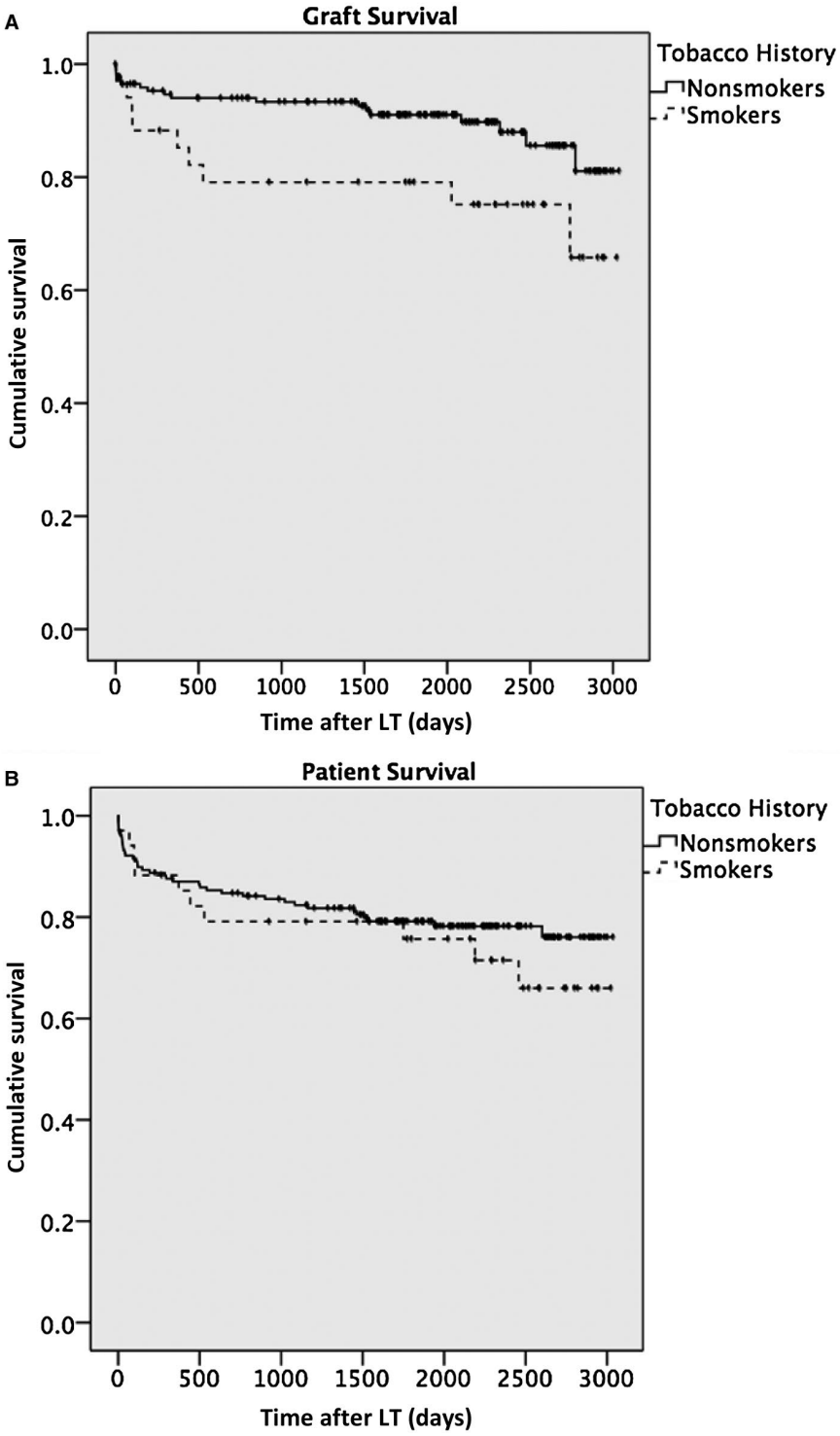

FIG. 4. Kaplan-Meier curve of patient and graft survival. Among the 212 LT recipients from era 1, smokers had a significantly lower rate of (A) graft survival ($P = 0.04$), although (B) overall survival was not different ($P = 0.40$).

there are 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 waiting list. In addition, all smokers in our program are referred to formal tobacco cessation programs, many of which use adjuvant bupropion or varenicline 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 before LT, 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 after LT.[14-18] Smoking has also been associated with increased overall cardiovascular- and sepsis-related mortality in LT recipients.[19] McConathy et al. also reported that smokers had a longer mean length of stay and higher hospital costs compared with nonsmokers, 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 nonsmokers in era 1, but with more prolonged follow-up, both patient and graft survival were significantly lower for the smokers (Table 4; Fig. 4). However, the causes of death appear to be qualitatively similar in the 2 groups (Supporting Table 2).

Our data showed that the prevalence of lifetime tobacco use was higher in era 2 patients compared with era 1 patients (62% versus 41%). According to previous studies, approximately 60% of LT candidates reported a lifetime history of cigarette smoking with the percentage as high as 75% among 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 a 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 1 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 screening for cotinine, a metabolite of nicotine, to monitor for ongoing tobacco use and to 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 it was highest among ALD patients at 58%.[24] However, we did not have these post-LT data available for analysis in our cohort.

Recent substance use remains a significant concern for LT programs and contributes to the decision to list or not to 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 before 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, and 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 with the prior era (13% versus 17%; $P = 0.25$) despite an increase in the proportion of smoking LT candidates (33% versus 23%; $P < 0.005$). As expected, there was an increase in the proportion of smokers who were excluded from transplant listing due to continued tobacco use after the policy implementation (4.4% versus 9.6%; $P = 0.001$; Table 2). Furthermore, the median time-to-listing period increased significantly after implementation of the policy (Table 2). The time-to-listing period lengthened modestly (30 days) among patients without a history of recent tobacco use (within the past 12 months) but was more prominent (60 days) in the patients with a 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, not having children, and lower levels of education were all independently associated with a longer time to wait listing (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 nonsmokers (Fig. 3), which may have been, in part, due to the evolving demographics of LT candidates at 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 who frequently require more extensive pretransplant medical evaluation (Fig. 2). In addition, the proportion of patients with Medicaid insurance, psychiatric comorbidities, and lower levels of family support and education have significantly increased over time, and they frequently require more resources and time to be cleared for LT listing.[11]

There are several important limitations of our study. First, all of the data were retrospectively abstracted

from a single center, and consecutive cohorts of patients were compared with each other rather than with contemporaneous cohorts. However, we note that United Network for Organ Sharing 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 of 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 interviews 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 observed deaths both before and after LT 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 who improved after LT, outcomes will be realized in the prior smokers who can sustain tobacco cessation after LT as reported by others.[3,4]

In conclusion, cigarette smoking puts LT candidates at an increased, but preventable, risk of 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 who were eventually listed for LT compared with our prior restrictive policy. However, the time to LT listing significantly increased among the initial smoker LT candidates who were eventually listed in era 2 compared with era 1. This latter observation may have been due to the increasing proportion of patients with smoking, SUD, and psychiatric comorbidities 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 after LT.

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