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The effect of smoking on biliary complications following liver transplantation

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Summary

We sought to estimate the effect of smoking on the biliary complication rate following orthotopic liver transplantation. We retrospectively evaluated the records of liver transplant recipients at our center from July 1, 1999 to October 26, 2007. Using Cox proportional hazards models, we estimated the time to the earliest biliary complication (leak or stricture) based on smoking exposure, as active, former, or lifetime nonsmoker, adjusting for other clinical factors. Overall, 409 liver transplant recipients were evaluated. The overall biliary complication rate was 37.7% (n = 154). Biliary complications included 66 anastomotic leaks, 60 anastomotic strictures, and 28 nonanastomotic lesions. ERCP was the primary diagnostic modality (n = 112). 18.1% of liver transplant recipients were active smokers (n = 74) and 42.8% were former smokers (n = 175). Active smokers were at greatest risk for biliary complications on unadjusted analysis (P = 0.022). After multivariable adjustment, active smokers had a 92% higher rate of biliary complication rates compared with lifetime nonsmokers (HR 1.92, 95% CI 1.07–3.43), but no difference was noted in the rate of complication resolution. Smoking clearly portends a significant risk of biliary complications following liver transplantation. Smoking status should be clearly defined when evaluating transplant candidacy and in counseling patients with cirrhosis.

Introduction

The scarcity of deceased donors in the United States and the desire to obtain the best outcome for each potential liver transplant recipient make candidate evaluation a challenging endeavor, and centers are required to weigh a multitude of clinical and psychosocial factors to place the best candidates on the waiting list. Patient use of tobacco is among these factors, and is exceedingly common, with 33.6% of liver transplant candidates self-reporting themselves as active or former smokers [1]. Smoking has important clinical implications for patients, and financial consequences for transplant centers.

We have previously shown that liver transplant candidates at our institution have similar waiting list and post-transplant survival regardless of smoking status at the time of evaluation or transplant [1]. While smoking may not affect the survival of potential liver candidates, the majority of the literature suggests that smoking portends a significant risk of cardiovascular, pulmonary, and malignancy-related morbidity [2–8]. Patients, clinicians, and insurance providers all have a vested interest in minimizing post-transplant smoking-related morbidity.

Postoperative biliary leaks and strictures are a major source of morbidity following deceased donor and living donor liver transplantation. These complications occur in 18–36% of liver transplant procedures, and require complex and expensive management strategies to identify, control, and reconstitute the biliary drainage system [9–35]. The key to preventing these complications is to understand their driving mechanism. One potential mechanism responsible for biliary leaks and strictures

may arise from corruption of the biliary microvasculature, which is largely perfused by the hepatic arterial system. Smoking is known to create a thrombogenic environment in the vasculature, vasoconstriction and failure of oxygen delivery. In addition, hepatic artery thrombosis is associated with the development of biliary complications [36–39]. These deleterious effects may impede the healing of the biliary anastomosis, leading to a leak, stricture, or both.

In this study of over 400 liver transplant recipients over an 8-year period at our center, we sought to understand the effect of smoking on biliary complications following liver transplantation. We hypothesized that active and former smokers would have a significantly increased rate of biliary complications compared with lifetime nonsmokers, after adjusting for other relevant clinical covariates. By understanding the effect of smoking on biliary complications following liver transplantation, clinicians may be able to better select candidates for the procedure, decrease overall morbidity and mortality in a vulnerable patient population, and inform smoking cessation strategies for patients and programs.

Methods

Patient cohort

We retrospectively reviewed the records of all adult patients who underwent orthotopic liver transplantation at our center between July 1, 1999 and October 26, 2007 with adequate smoking history. A total of 409 patients had adequate smoking history. Pediatric, living donor, partial graft, and combined liver/kidney transplant recipients were excluded from the analysis. No patient underwent ABO incompatible transplants. All data were collected from our institutional electronic medical record and from a prospectively collected institutional transplant database. Clinical data were collected on all transplant recipients, including demographics, Model for End-Stage Liver Disease (MELD) score, indication for transplantation, cold ischemia time, type of biliary anastomosis, the use of a biliary stent at transplant, donor demographics, donor cause of death, donor type, and cytomegalovirus (CMV) serology and other factors.

Definition of smoking behaviors and definitions of outcomes

Smoking status was determined from the review of all clinical encounters the subject had at our center during transplant evaluation up to the time of transplantation, and was self-reported by all recipients. Likewise, smoking cessation was recorded based on the self-report of the transplant recipient. All patients in the cohort had clearly defined smoking status based on the review of their records. The study period spanned from the date of liver transplant to the most recent follow-up or death. We defined smoking behaviors in the following manner:

Active smoker: Liver transplant recipients who were actively smoking cigarettes within 3 months of their liver transplant.

Former smoker: A patient with a history of smoking but had quit at least 3 months prior to liver transplantation.

Lifetime nonsmoker: Patients who denied smoking cigarettes at any point in their lifetime.

In addition, we also attempted to record the number of pack-years of smoking for all active and former smokers. These data were missing in 10% of active and former smokers.

The primary outcome of interest was the first occurrence of a biliary complication, defined as any anastomotic or nonanastomotic leaks or strictures diagnosed clinically or radiographically by endoscopic retrograde cholangiopancreatogram (ERCP), percutaneous transhepatic cholangiogram (PTC), or magnetic resonance cholangiopancreatogram (MRCP), or through a combination of these tests. At our center, the decision to pursue biliary imaging for diagnostic or therapeutic purposes is based solely on the clinical judgment of a multidisciplinary group of transplant providers that include surgeons and hepatologists. These studies are initiated when biliary sepsis or biliary obstruction is suspected based on physical symptoms, signs, or laboratory testing. Because of the great availability of these imaging techniques and the significant risk in delaying diagnosis, our threshold is low in pursuing these studies in general. In this analysis, all biliary complications that occurred following liver transplantation were included in the analysis until the end of follow-up.

Statistical analysis

Our primary exposure variable was smoking behavior, defined as active, former, or life-time nonsmoker, and our primary outcome of interest was the time to the first biliary complication, either leak or stricture. Patient demographics, diagnoses, and other clinical details were compared based on smoking behavior using analysis of variance or chi-square where appropriate. For biliary complications, the Kaplan–Meier method was used to estimate event rates over time. The log-rank test was used to compare biliary complication rates based on smoking history. To evaluate the specific effect of smoking on biliary complication outcomes in the context of other clinical variables, a multivariable Cox proportional-hazards model was constructed to risk-adjust our estimate of the

time to the first biliary complication, with smoking history as the primary exposure. Models were constructed with smoking as a categorical variable based on history and as a continuous variable based on total pack-years. The adjustment covariates included recipient and donor demographics, diagnosis, previous transplant, MELD score at transplant, year of transplant, donor and recipient CMV status, coronary artery disease, diabetes mellitus, transplant surgeon, donor type (donation after cardiac death vs. brain death), donor cause of death, cold ischemia time, anastomosis type (biliary-enteric, choledocho-choledochostomy), and the use of a biliary stent at transplant. The occurrence of hepatic artery thrombosis was also included in the model as a time-dependent covariate, meaning the effect of hepatic artery thrombosis on biliary complications is not present at baseline, i.e. its effect may begin after it has occurred in the at-risk period. Secondary analyses included evaluating the effect of smoking on the rate of biliary complication resolution using a similar model structure. Each model was censored at death or at the end of follow-up (July 31, 2009). Covariates were included in the model based on a significant effect on univariate analysis or on potential biologic plausibility.

The study was approved by the local Institutional Review Board. STATA version 10.0 (Stata Corp, College Station, TX, USA) was used to complete all statistical analyses. Statistical significance was defined at a P value of 0.05.

Results

Baseline characteristics, smoking behavior, and detection of biliary complications

The retrospective cohort was comprised of 409 liver transplant recipients over an 8-year period at our center. 60.9% of liver transplant recipients were either active ($n = 74$, 18.1%) or former smokers ($n = 175$, 42.8%). Table 1 displays the clinical differences between patients based on their smoking behaviors. Former smokers were older than active and lifetime nonsmokers. Active smokers had a higher proportion of males than the other groups. MELD scores at transplant were similar for active, former, and nonsmokers, but trended toward higher MELD scores in the nonsmoking group. Only a small minority of the patients in the cohort were transplanted prior to 2003. There were significant differences in the distribution of smoking behaviors by diagnosis. Active and former smokers predominated the hepatitis, alcoholic cirrhosis, and hepatocellular carcinoma diagnosis groups (all, $P < 0.01$). Repeat transplant rates were similar across smoking groups. CMV seropositivity prior to transplant was similar across the cohort. With regard to donor factors, donor age was similar across the cohort, but active smokers received a significantly higher proportion of allografts from male donors. There were no differences with regard to the causes of donor death or donation after cardiac death based on recipient smoking behavior. Former smokers had higher rates of CMV-seropositive donors compared with the other groups. Transplant-related characteristics were fairly similar across groups. Cold ischemia time, the use of biliary stents, and rates of postoperative hepatic artery thrombosis were respectively similar, regardless of smoking status at transplant. The biliary anastomosis was duct-to-duct in the vast majority of all cases, and was applied in active smokers more often than in other groups.

At the end of follow-up, 37.7% of liver transplant cases had a biliary complication ($n = 154$). Of the 154 patients with biliary complications, 42.9% initially had anastomotic leaks, 39% had anastomotic strictures, and <10% had nonanastomotic biliary lesions. Nine per cent presented with diffuse intrahepatic strictures. Table 2 displays the distribution of the initial biliary complications and the method of diagnosis by smoking behavior. Overall, there were no statistically significant differences in the types of initial biliary complications based on smoking behavior at transplantation on univariate analysis. Anastomotic leaks were proportionally more common in the active smokers, and strictures were equally distributed across the cohort. Of the evaluations performed to diagnose biliary complications, 63.6% were identified by ERCP and 31.3% were diagnosed using a PTC approach. Nineteen patients required both ERCP and PTC, related to failed endo-biliary stent placement. Few complications were identified by MRCP alone, or clinical diagnosis alone. Four complications were diagnosed during a re-operation and a subsequent PTC was placed. One late complication was initially diagnosed by MRCP, was subsequently verified and treated with a subsequent PTC. Active smokers were more readily identified using ERCP than the other modalities, in comparison with the other two groups.

Influence of smoking on biliary complication rates following liver transplantation

Significant differences were noted in the incidence of biliary complications based on smoking behavior at the time of transplant. While active smokers made up <20% of the cohort, more than half of them (51.4%) had developed a biliary complication compared with 33.7% and 35.6% of the former and nonsmoker groups, respectively (Fig. 1) ($P = 0.025$). Figure 2 displays the cumulative incidence of biliary complications over time for liver transplant recipients. Active smokers had a significantly higher rate of

Table 1. Clinical and demographic characteristics of 409 liver transplant recipients by smoking behavior at transplantation.

Variable	Active smoker (*n* = 74)	Former smoker (*n* = 175)	Nonsmoker (*n* = 160)	*P*-value
Recipient factors				
Age at transplant (year) (SD)	49.3 ± 8.3	53.6 ± 7.8	48.8 ± 12.2	<0.001
Sex (% male)	54 (73.0)	123 (70.3)	84 (52.5)	0.001
Race (% black)	6 (8.6)	9 (5.3)	12 (7.8)	0.539
Mean MELD Score	20.2 ± 7.7	19.7 ± 6.7	21.7 ± 8.5	0.051
Pack-years of smoking (*n*) (SD)	28.8 ± 15.4	24.6 ± 17.2	0 ± 0	0.303
Year of transplant				
1999 (*n* = 3)	0 (0)	1 (0.6)	2 (1.3)	0.586
2000 (*n* = 24)	5 (6.8)	11 (6.3)	8 (5.0)	
2001 (*n* = 33)	8 (10.8)	13 (7.4)	12 (7.5)	
2002 (*n* = 65)	7 (9.5)	28 (16.0)	30 (18.8)	
2003 (*n* = 68)	16 (21.6)	23 (13.1)	29 (18.1)	
2004 (*n* = 69)	16 (21.6)	28 (16.0)	25 (15.6)	
2005 (*n* = 60)	5 (6.8)	31 (17.7)	24 (15.0)	
2006 (*n* = 68)	13 (17.6)	32 (18.3)	23 (14.4)	
2007 (*n* = 19)	4 (5.4)	8 (4.6)	7 (4.4)	
Diagnosis				
Hepatitis B/C (*n* = 201)	53 (71.6)	100 (57.1)	48 (30.0)	<0.001
ETOH Cirrhosis (*n* = 102)	30 (40.5)	51 (29.1)	21 (13.1)	<0.001
HCC (*n* = 44)	7 (9.5)	28 (16.0)	9 (5.6)	0.009
Cryptogenic (*n* = 46)	6 (8.1)	21 (12.0)	19 (11.9)	0.640
Other (*n* = 109)	4 (5.4)	30 (17.1)	75 (46.9)	<0.001
Re-transplant (*n* = 26)	3 (4.1)	8 (4.6)	15 (9.4)	0.132
CMV status (% positive)	46 (62.2)	119 (68.0)	89 (55.6)	0.083
Donor factors				
Donor age (year) (SD)	37.0 ± 16.8	37.3 ± 15.5	39.1 ± 15.7	0.764
Donor sex (% male)	56 (75.7)	130 (74.3)	95 (59.4)	0.005
Donor cause of death				
Anoxia (*n* = 5)	1 (1.4)	3 (1.7)	1 (0.6)	0.211
Cardiovascular (*n* = 9)	4 (5.4)	4 (2.3)	1 (0.6)	
Cerebrovascular (*n* = 155)	26 (35.1)	64 (36.6)	65 (40.6)	
Trauma (*n* = 159)	24 (32.4)	67 (38.3)	68 (42.5)	
Other (*n* = 16)	19 (25.7)	37 (21.1)	25 (15.6)	
Donation after cardiac death (*n* = 14)	4 (5.4)	5 (2.9)	5 (3.1)	0.579
Donor CMV status (% positive)	19 (25.7)	60 (34.9)	65 (40.6)	0.034
Transplant factors				
Cold ischemia time (min)	491.9 ± 144.5	493.9 ± 163.6	520.9 ± 183.9	0.312
Initial anastomosis type at a transplant				
Choledochodochostomy (*n* = 356)	70 (94.6)	162 (92.6)	124 (77.5)	<0.001
Roux-en-Y biliary-enteric (*n* = 49)	4 (5.4)	12 (6.9)	33 (20.6)	
Other (*n* = 4)	0 (0)	1 (0.6)	3 (1.9)	
Biliary stent in operating room (*n* = 115)	21 (28.4)	52 (29.7)	42 (26.3)	0.779
Hepatic artery thrombosis (*n* = 30)	3 (4.1)	10 (5.7)	7 (4.4)	0.111

Values within parenthesis are in percentage.

biliary complications compared with lifetime nonsmokers ($P = 0.022$). Former and lifetime nonsmokers had a relatively similar risk of biliary complications over time (p=ns). Of the 154 biliary complications, 136 (88.3%) occurred within 6 months of liver transplantation, seven (4.5%) occurred between 6 and 12 months after transplantation, seven (4.5%) occurred in the second year after transplant, and an additional four (2.7%) occurred after 2 years post-transplant.

After multivariable risk-adjustment for donor, recipient, and transplant factors, active smokers had a nearly twofold greater risk of biliary complications compared with lifetime nonsmokers (HR 1.92, 95% CI 1.07–3.43) (Fig. 3). Former smokers did not have a significantly different risk of biliary complications compared with the lifetime nonsmokers (HR 1.05, 95% CI 0.64–1.74). When considering smoking history as a continuous variable, an increase in smoking burden by a single pack-year was not

Table 2. Diagnostic and therapeutic approach to initial biliary complications by smoking behavior.

	Number of cases with biliary complications				
Type of biliary complication	Total cases with complications (n = 154)	Active smokers (n = 38)	Former smokers (n = 59)	Nonsmokers (n = 57)	P-value
Anastomotic leak	66	19 (50)	19 (32.2)	28 (49.1)	0.382
Anastomotic stricture	60	13 (34.2)	25 (42.4)	22 (38.6)	
Nonanastomotic leak	9	3 (7.9)	4 (6.8)	2 (3.5)	
Nonanastomotic strictures	5	0 (0.0%)	4 (6.8)	1 (1.8)	
Diffuse intrahepatic strictures	14	3 (7.9)	7 (11.9)	4 (7.0)	
Diagnostic approach	Total evaluations (n = 176)	Active smokers (n = 41)	Former smokers (n = 72)	Nonsmokers (n = 64)	P-value
ERCP Diagnosis/Treatment	112	31	42	39	0.010
PTC Diagnosis/Treatment	55	8	25	22	0.470
MRCP diagnosis	2	0	2	0	0.261
Operative diagnosis/Surgical Treatment	7	2	3	3	0.872

Values within parenthesis are in percentage.

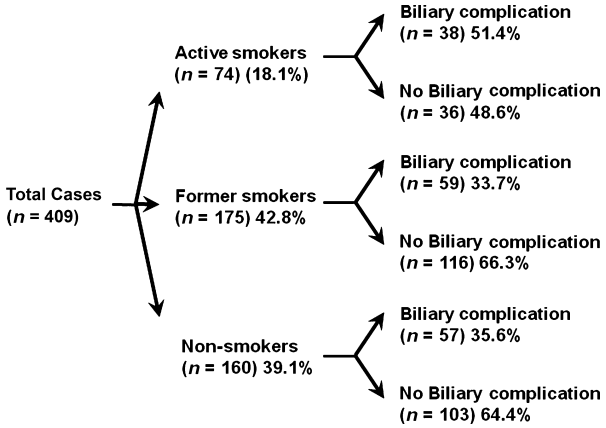

Figure 1 The development of biliary complications in a cohort of 409 liver transplant recipients based on smoking status. This figure displays the clinical trajectory of 409 liver transplant recipients at our center over an 8-year period. Eighteen per cent of liver transplant recipients were active smokers at the time of transplantation. A greater proportion of active smokers developed a biliary complication after liver transplant compared with former and lifetime nonsmokers.

associated with a significantly increased risk of biliary complications. The remaining significant covariates are displayed in Table 3. No recipient factor was significantly predictive of biliary complication rates. Recipient factors including age, sex, race, diagnosis, MELD score, co-morbidities, and CMV status were not significantly predictive of biliary complication rates. Each year increase in donor age increased the risk of biliary complications by 2% (HR 1.02, 95% CI 1.01–1.03). Donor sex, cause of death, donation after cardiac death, or donor CMV sero-positivity, respectively, were not significantly associated with increased risk of biliary complications after multivariable adjustment, respectively. Neither the year of transplantation nor the surgeon was significantly associated with an increased risk of biliary complications. Cold ischemia time was not associated with an increased risk-adjusted biliary complication rate, when analyzed continuously or categorically. However, hepatic artery thrombosis had a significant effect on the risk of biliary complications – the occurrence of this complication was associated with a 14% increase in biliary complication risk (HR 1.14, 95% CI 1.06–1.21). The management of the bile duct at initial transplant was also not predictive of a future biliary complication – neither choledochocholedochostomy, Roux-en-Y biliary-enteric configuration, nor temporary biliary exteriorization was associated with increased biliary complication rates post-transplant. However, the use of a biliary stent significantly decreased the risk-adjusted biliary complication rate by more than 60% (HR 0.39, 95% CI 0.22–0.67). An interaction analysis to determine the effect of stent utilization on patients in each smoking group revealed that stent use significantly altered the rate of developing a biliary complication in active smokers to the point that the biliary complication rates were similar across all groups (active vs. nonsmokers: HR 2.60, 95% CI 0.70–9.72, P = 0.155).

Of the 154 biliary complications noted at the end of follow-up, 73.4% (n = 113) had resolved at the end of follow-up. There were no significant differences in the proportion of resolved biliary complications by smoking status on univariate analysis (active smokers 78.9%, former smokers 71.2%, lifetime nonsmokers 71.9%, P = 0.67). In a subgroup analysis of those with biliary leaks or strictures, using a multivariable time-to-resolution model, neither active smoking at the time of transplant

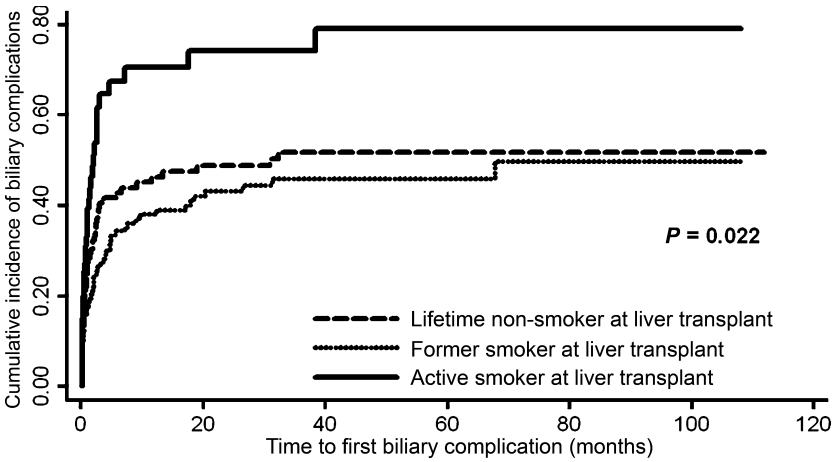

Figure 2 Biliary complication rates by smoking status in liver transplant recipients. Using the Kaplan–Meier method, the cumulative incidence of biliary complications was significantly higher among active smokers compared with both former smokers and lifetime nonsmokers.

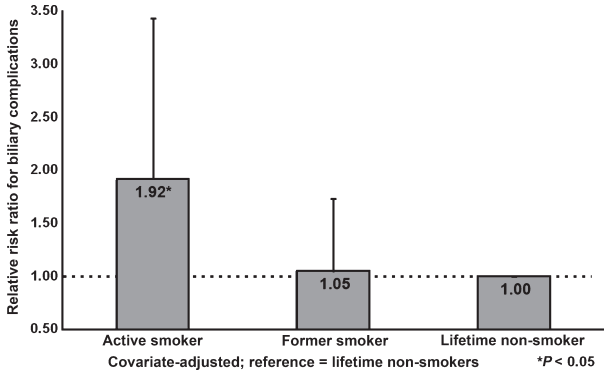

Figure 3 Adjusted relative risk ratios of biliary complications by smoking status in liver transplant recipients. After adjusting for recipient demographics, donor characteristics, diagnosis, disease severity, and surgical factors, the risk of developing a biliary complication was 92% higher for active smokers compared with lifetime nonsmokers. Former smokers notably had a similar risk of biliary complications as their nonsmoking counterparts.

Table 3. Significant predictors of biliary complications following liver transplantation on multivariate analysis.

Variable	Hazard ratio	Confidence interval		*P*-value
Recipient characteristics				
Smoking behavior				
Active smoker at transplant	1.92	1.07	3.43	0.028
Former smoker at transplant	1.05	0.64	1.74	0.838
Lifetime nonsmoker at transplant	1.00	Ref	Ref	Ref
Donor characteristics				
Donor age				
1 year increase	1.02	1.01	1.04	0.049
Transplant characteristics				
Use of a biliary stent	0.39	0.22	0.67	0.001
Hepatic artery thrombosis*	1.14	1.06	1.24	<0.001

*Time varying covariate.

nor other factors were associated with any significant differences in the rate of biliary complication resolution.

Discussion

Cigarette smoking is altogether too common in the general population, but particularly among liver transplant candidates [1], and is associated with a significantly increased risk of post-transplant biliary complications after adjusting for a plethora of confounding factors. Most biliary leaks and strictures developed relatively early following transplant, and were related to the anastomosis. Active smoking within 3 months of a liver transplant was associated with the greatest risk of morbidity from the bile duct, even after adjusting for several recipient, donor, and transplant characteristics. Former smokers seemed to be protected from this risk, demonstrating a similar adjusted rate of biliary complications as that of nonsmokers.

Several recent studies have evaluated the effect of smoking on post-transplant outcomes, but have not addressed biliary complications directly. We have previously demonstrated that 2-year post-transplant mortality is similar for smokers and nonsmokers, with some differences arising in long-term survival [1]. Leithead and colleagues in Edinburgh have recently evaluated their outcomes from a 4-year series of 132 liver transplant recipients. Their work indicates an increased risk of overall, cardiovascular-specific, and sepsis-specific mortality with smoking [40]. Other recent studies have demonstrated that smoking is associated with inferior long-term cardiovascular and oncologic outcomes following liver transplantation [2,4,5,41–44]. With regard to perioperative outcomes, smoking was also associated with increased resource utilization and hospital charges following liver transplantation in a series of 65 liver transplants over a 2-year period at the University of Kentucky [45]. Based

on these reports, it is clear that smoking has significant implications on short- and long-term postliver transplant outcomes.

One of the most notable findings in our analysis related to the placement of a biliary stent in the operating room and its effect on subsequent complications. Biliary stents were significantly protective from biliary leaks or strictures, which has been previously reported by our group [9]. The interaction between active smoking and stent use revealed no significantly increased risk of biliary complications. While our study may not have had sufficient statistical power to evaluate this interaction more precisely, the benefit noted across the entire population in the multivariable models seems to favor a mitigating effect of intraoperative stent placement in transplant recipients who smoke. While we do not uniformly use biliary stents during liver transplantation, we have seen significant improvements in biliary complications when it is applied and we now place an internal biliary stent in most cases [9]. However, this practice must be further studied in a randomized controlled fashion to assess its prospective validity.

The biologic effect of smoking on post-transplant biliary complications is not specifically understood, but is likely related to the effects of smoking on the microvasculature of the bile duct. The nicotine and tar in cigarettes are known to be thrombogenic and cause vasoconstriction by inhibiting endothelial nitric oxide pathways and other processes [7–9]. Pungpapong *et al.* [7] have demonstrated that smoking was associated with postliver transplant arterial vascular complications, including hepatic artery thrombosis. Smoking may create an environment of relative ischemia in the biliary tissue, which leads to poor or improper healing. Based on our models, the risk of developing a biliary complication was 13% higher after hepatic artery thrombosis occurred. Strategies to prevent arterial vascular complications in liver transplantation may therefore improve the outcomes of the biliary anastomosis as well.

Our findings are subject to some limitations. The estimation of actual smoking exposure is difficult, particularly in heavy smokers who have been smoking for a long time, as it is based on self-reported data during transplant-related clinical visits with a physician. In both active and former smokers, this may lead to recall bias from both patients and providers. Pack-year smoking history is how we generally quantify smoke exposure clinically, but this has not been validated for research purposes. Our categorical definition of smoking behavior may obfuscate any potential increased risk of biliary complications among former smokers who quit relatively recently before their transplant. Technical factors in creation of the biliary anastomosis are also of concern. We attempted to account for this by adjusting for the surgeon who did the procedure, which was not significant, but it is impossible to include extensive operative detail in an observational study with this model design. In addition, our study design has an inherent risk of confounding and selection bias. We attempted to account for several sources of bias using multivariable time-to-event analysis, which improves any bias related to variable follow-up or the development of new risk factors, such as hepatic artery thrombosis, over time. It is possible that other variables and missing data, such as donor smoking history or incomplete smoking historical data in our cohort, may affect our results. We were limited also by the patients where smoking data were specifically noted in the clinical documentation. We did not focus on the risk factors for specific types of biliary complications, such as a predisposition toward leaks or strictures. Our previous work on this topic has clearly demonstrated a significant risk for biliary strictures in those who previously had biliary leaks [9]. Another limitation may be related to the classification of stent usage. The type of stent used in the course of the study was not uniform. The study period included an era where we used the so-called 'Turcotte tube', which was a trans-cystic duct biliary stent. We have previously shown that these were associated with a greater leak rate versus the internal biliary stents [9]. Despite the inclusion of these 'higher risk' stents, the protective effect of stent utilization is significant, suggesting that our latter stent use – using an internal pediatric feeding tube – is extremely effective. Similarly, the overall rates of biliary complications and hepatic artery thrombosis are notable and may be higher than in other centers. Confidently, we feel that the high rates are related to an aggressive approach to diagnosis and management. We feel that early diagnosis prevents much of the morbidity of a biliary complication. Thus, the majority of our patients undergo a cholangiogram and liver ultrasound during the postoperative period. Any evidence of biliary leak or stricture intervened upon was thus coded as a complication in the manuscript. This approach to biliary complications probably results in the high rates noted and should not affect the overall conclusions of the study. With regard to hepatic artery thrombosis, our analysis expands several years of follow-up and our definition included early and late arterial complications, which may have affected the rates observed in the study. Within this context, however, our study represents one of the largest and detailed treatments of the effect of smoking on surgical complications following liver transplantation.

The morbidity for patients with a biliary complication is undoubtedly significant, but transplant centers and payers may bear considerable economic hardships by selecting smokers for liver transplantation [46]. These

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costs may arise directly from facility and professional fees related to clinical interventions, and, in the future, may also come from a loss of potential patient referrals. In the US, transplant outcomes for graft and patient survival for each center are documented and tracked by federal mandate in order to ensure transparency and the long-term success of clinical transplantation. Currently, complications such as biliary leaks or strictures are not tracked on a national scale or reported to the public. It is conceivable that surgical and other complications may contribute to composite metrics used to evaluate center performance. The risk for patients, centers, and payers is clearly great in this context, and it may grow in the future.

Our study clearly demonstrates that one of the most important interventions in pretransplant care to decrease biliary complications following liver transplantation is smoking cessation. While the benefits may not extend to a mortality benefit given the already high mortality risk in the population [1], we have demonstrated a clearly important association between active smoking and biliary complications, while being a former smoker seemed to attenuate biliary morbidity risk to a great extent. Our findings should not necessarily be used as the sole criteria to block registration on a liver transplant waiting list, as the decision to perform a transplant on a smoker with cirrhosis should be based on a detailed clinical evaluation of the individual patient and patient choice. Our studies on this topic, as well as several well-designed retrospective studies, do suggest that the aggressive use of smoking cessation programmes in liver transplant centers may have far-reaching benefits. Transplant center and payer investment in smoking cessation initiatives for liver transplant candidates seem to have significant promise in preventing down-stream posttransplant complications and achieving improved patient outcomes.

Authorship

AMK: study conception, design, data collection, analyses, manuscript production, critical review. DNR: data collection, analyses, manuscript production. SPP: data collection, analyses, manuscript production. DSL: data collection, analyses, critical review. FB – data collection, analyses, manuscript production, critical review. RJL: study design, manuscript production, critical review. THW: study design, manuscript production, critical review. MJE: study conception, design, analyses, manuscript production, critical review.

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