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History of cigarette smoking and heart transplant outcomes

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ABSTRACT

Background: Active cigarette smoking (CS) is a contraindication for Orthotopic Heart Transplantation (OHT) with a recommendation that HT candidates be free from CS for at minimum 6 months prior to HT. Animal studies have shown that a history of CS is associated with increased risk of allograft rejection, but few studies have examined the association of past CS and HT outcomes. **Methods:** Data were analyzed from HT recipients captured in the United Network for Organ Sharing (UNOS) transplant registry. Adults aged 18–79 who underwent HT from 1987 to 2018 and with data for all covariates (N = 32,260) were included in this study. The cohort was categorized by past smoking history (CS vs non-CS). Post-transplant outcomes of interest included survival, graft failure, treated rejection, malignancy and hospitalization for infection. Baseline characteristics were compared between the two groups using the chi-squared analysis. Unadjusted associations between CS and patient survival were determined using the Kaplan-Meier estimations and confounding was addressed using multivariable Cox proportional hazards models. **Results:** HT recipients with a history of CS were older (55 vs 50, p = <0.0001), more likely to be Caucasian (75.7 vs 62.3, p = <0.0001), male (81.7 vs 68.2, p =< 0.0001), and diabetic (27.4 vs 24.4, p =< 0.0001). CS was associated with significantly worse survival (HR: 1.23, p < 0.0001). A history of CS was also associated with increased risk of acute rejection (OR: 1.20, p < 0.0001), hospitalization for infection (OR:1.24, p < 0.0001), graft failure (OR:1.23, p < 0.0001) and post-transplant malignancy (OR:1.43, p < 0.0001). **Conclusion:** A history of CS is associated with increased risk of adverse events post OHT.

1. Introduction

The adverse health effects of cigarette smoking (CS) are well-known, with studies demonstrating an increased risk of cardiovascular, neurologic, and pulmonary disease [1–5]. Specifically, CS confers an increased risk of developing coronary artery disease and congestive heart failure, through the promotion of inflammation, vasomotor dysfunction, atherogenesis, and thrombosis. In turn, sequelae of these diseases can ultimately necessitate orthotopic heart transplantation (OHT) [1,6]. Subsequently, among OHT recipients, these same processes may lead to the development of cardiac allograft vasculopathy, rejection, and decreased graft survival [1].

Despite major advances in OHT, allograft rejection remains a leading cause of morbidity and mortality. According to The International Society for Heart and Lung Transplantation, between 2004 and 2010, 19% of heart transplant recipients reported one or more clinically significant acute rejection episodes during the first year after transplant. As demonstrated in animal models, exposure to cigarette smoke pre-transplant is associated with increased allograft rejection and reduces survival by 33% to 57% [7]. Potential mechanisms include heightened systemic inflammation, alloimmune activation, and consequent myocardial and vascular destruction [8]. Additional studies suggest stimulation of T or B cell memory, suppression of Tol-DC development, or downregulation of Treg cell numbers may also play a role [9].

Few studies have evaluated the impact of a pre-OHT history of CS on post OHT outcomes, with the majority being small single center studies. Therefore, questions remain as to whether a history of CS engenders worse outcomes [9–12]. In our study, we seek to

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investigate the long-term outcomes in post heart transplant recipients with a history of CS.

2. Methods

2.1. Study population

The study population was derived from OHT recipients captured in the United Network for Organ Sharing (UNOS) registry. The UNOS registry represents a multicenter collaboration designed to capture waitlist, transplant, and post-transplant data, in order to improve future transplant outcomes. The registry has been capturing transplant outcomes since its inception in 1987 to current date.

2.2. Patient selection

Included in this analysis were adults aged 18 years and older, who underwent OHT from 1987 to 2018. Patients were categorized based on pre-OHT smoking history. Those with a history of cigarette smoking were classified as CS, and those without a history of cigarette smoking were classified as non-CS. CS history was obtained by the transplanting center. At time of enrollment in the UNOS registry smoking history was recorded (History of cigarette use "yes" or "no"), and duration of abstinence was also collected. Transplant recipient history of CS was defined as responding yes to any variable measuring cigarette usage while non-CS was defined as responding no to any history of cigarette use. CS was further categorized by length of abstinence from smoking for sub-group analysis.

Covariates were derived based on clinical relevance and included graft failure, diabetes, ethnicity, sex, age, BMI, ischemic time, and serum creatinine level. Individuals who were missing data on smoking history or any of the covariates were excluded from the analysis.

2.3. Outcomes

The primary outcome was post-transplant all-cause mortality. Secondary outcomes included hospitalizations for treated rejection, hospitalization for infection, graft failure, and post-transplant malignancy (Fig. 1).

2.4. Statistical analysis

All statistical analyses were performed using SAS version 9.4 (Cary, NC, USA). Baseline characteristics were compared between the two groups using the Chi-squared test and Student's *t* test for categorical and continuous variables, respectively. Unadjusted associations between CS history and patient survival were determined using the Kaplan-Meier estimations and confounding was addressed using multivariable Cox proportional hazards models. This study was approved by the Institutional Review Board of Northwestern University Feinberg School of Medicine.

3. Results

3.1. Baseline characteristics

Among 62,588 patients in the registry, 32,257 (51.5%) underwent OHT from 1987 to 2018 and had complete data for all covariates. 18,330 (56.8%) patients had a history of CS. Baseline characteristics are shown in Table 1. HT recipients with a history of CS were more likely to be older, Caucasian, male, diabetic, and have a donor with a history of cigarette smoking ($p < 0.0001$). They had higher BMI and shorter ischemic time ($p < 0.0001$) (Table 1).

3.2. Survival

The median survival time for the entire study population was 4404 days (Fig. 2). Unadjusted one-year (88.4% vs 90.1%, five-year (74.4% vs 79.1%), and ten-year (54.8 vs 65.3%) survival were all significantly worse for patients with a history of CS ($p < 0.0001$) (Fig. 3). In the multivariable model, a history of CS in the recipient (HR:1.23, CI:1.18,1.29, $p < 0.0001$) and donor (HR 1.13, CI 1.08–1.19, $p =< 0.001$) was a significant predictor of survival (Table 2).

3.3. Treated rejection

A history of CS in the transplant recipient was associated with increased risk of being hospitalized and treated for acute rejection (OR:1.20, CI: 1.11, 1.31, $p < 0.0001$) (Table 3).

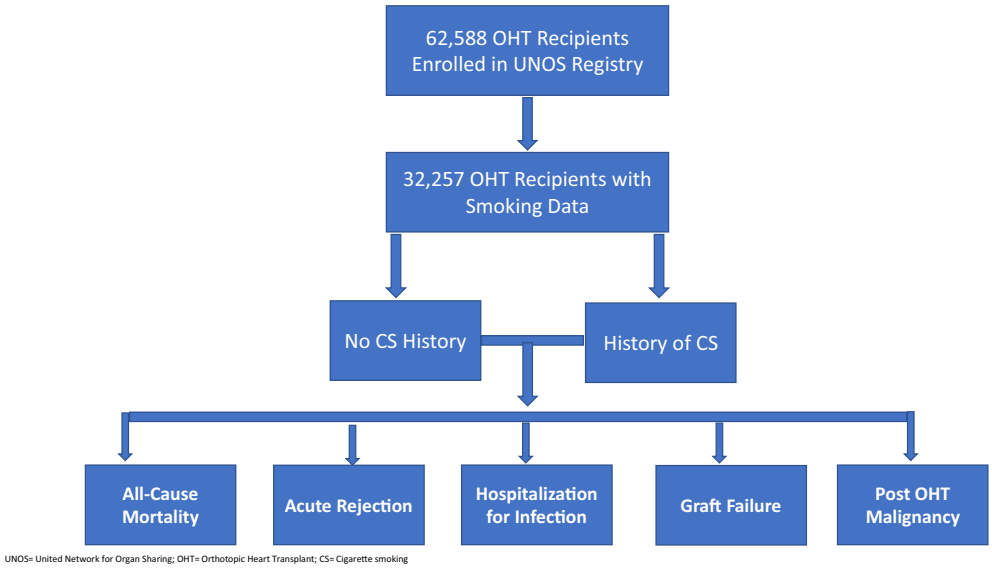

Fig. 1. Study population and outcomes of interest.

Table 1
Patient demographics by smoking history.

	Smoking history (%)	No smoking history (%)	p-value
Age (mean yrs ± SD)	55.0 ± 10.2	50.4 ± 13.9	<0.0001
Gender (%)			<0.0001
Male	14,983 (81.7)	9503 (68.2)	
Female	3347 (18.3)	4424 (31.8)	
Ethnicity (%)			<0.0001
Caucasian	13,866 (75.7)	8678 (62.3)	
African American	2901 (15.8)	3206 (23.0)	
Hispanic	1088 (5.9)	1380 (9.9)	
Other	475 (2.6)	663 (4.8)	
Donor Smoker	6113 (33.65)	1822 (13.24)	<0.0001
BMI (mean ± SD)	27.1 ± 4.7	26.8 ± 5.0	<0.0001
Diabetes (%)	5023 (27.4)	3395 (24.4)	<0.0001
Ischemic time (mean hrs ± SD)	3.1 ± 1.0	3.2 ± 1.1	<0.0001
Serum Creatinine ± SD	1.37 ± 0.97	1.39 ± 1.1	0.1079

Yrs = years; Hrs = hours; BMI = body mass index.

3.4. Infectious hospitalization

A history of CS in the transplant recipient was associated with increased risk of hospitalization for infection (OR:1.24, CI: 1.15,1.33, p < 0.0001) (Table 3).

3.5. Graft failure

A history of CS in the transplant recipient was associated with increased risk of graft failure (OR:1.23, CI:1.16, 1.30, p < 0.0001) (Table 3).

3.6. Post-Transplant malignancy

A history of CS in the transplant recipient was associated with increased risk of post-transplant malignancy (OR:1.43, CI:1.33, 1.55, p < 0.0001) (Table 3).

3.7. Duration of smoking abstinence

Of those with a history of CS, 11,224 had complete data available on abstinence period and were included in the sub-group analysis (Table 4.)

Compared to non-CS, CS was associated with increased risk of all-cause mortality. CS abstinence between 0 and 12 months was associated with the highest likelihood of mortality compared to non-CS (HR 1.36, CI 1.26, 1.48, p < 0.0001). This likelihood decreased with longer abstinence periods, 13–60 months (HR 1.30, CI 1.19, 1.42, p= <0.0001), >60 months (HR 1.1, CI 1.03, 1.18, p = 0.0017) (Table 5) (Fig. 4).

CS was associated with increased risk of hospitalization for rejection. This risk was highest in those that abstained between 0 and 12 months (OR 1.5, CI 1.33, 1.73, p= <0.0001), followed by those who were smoke free for 13–60 months (OR 1.2, CI 1.07, 1.42, p = 0.004). There was no statistical difference in those who abstained from smoking for > 60 months (OR 1.04, CI 0.93, 1.16, p = 0.45) compared to non-CS (Table 5).

Graft failure was highest in the CS group that abstained from 0 to 12 months (OR 1.45, CI 1.31, 1.60, p =< 0.0001), followed by those with an abstention period between 13 and 60 months (OR 1.38, CI 1.2, 1.5, p =< 0.0001), and those with an abstinence period > 60 months (OR 1.12, CI 1.04, 1.21, p = 0.0018).

OHT recipients with a history of CS that abstained from CS between 0 and 12 months has the highest risk of post-transplant malignancy compared to non-CS recipients (OR 1.22, CI 1.05, 1.41, p = 0.008). No statistical differences were seen in those who abstained between 13 and 60 months (OR 1.03, CI 0.87, 1.21, p = 0.71), and those who abstained > 60 months (OR 1.09, CI 0.96, 1.21, p = 0.20) compared to non-CS recipients.

4. Discussion

In this multicenter analysis of 32,257 patients captured in the UNOS registry we reported the following major findings. A history of CS was associated with: (1) decreased post-transplant patient

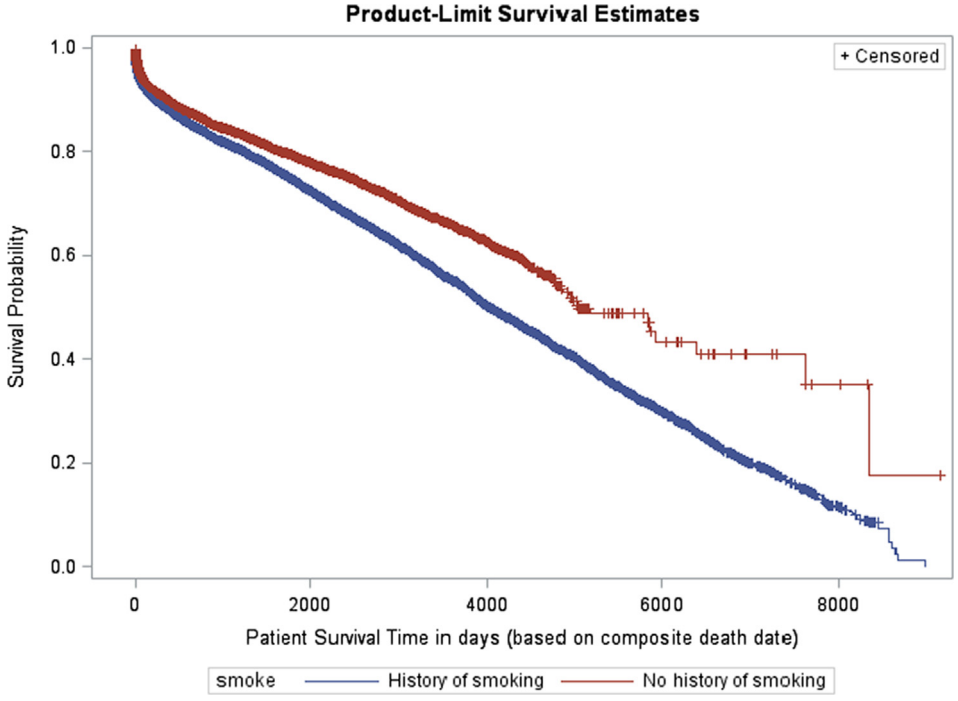

Fig. 2. Survival time by smoking status.

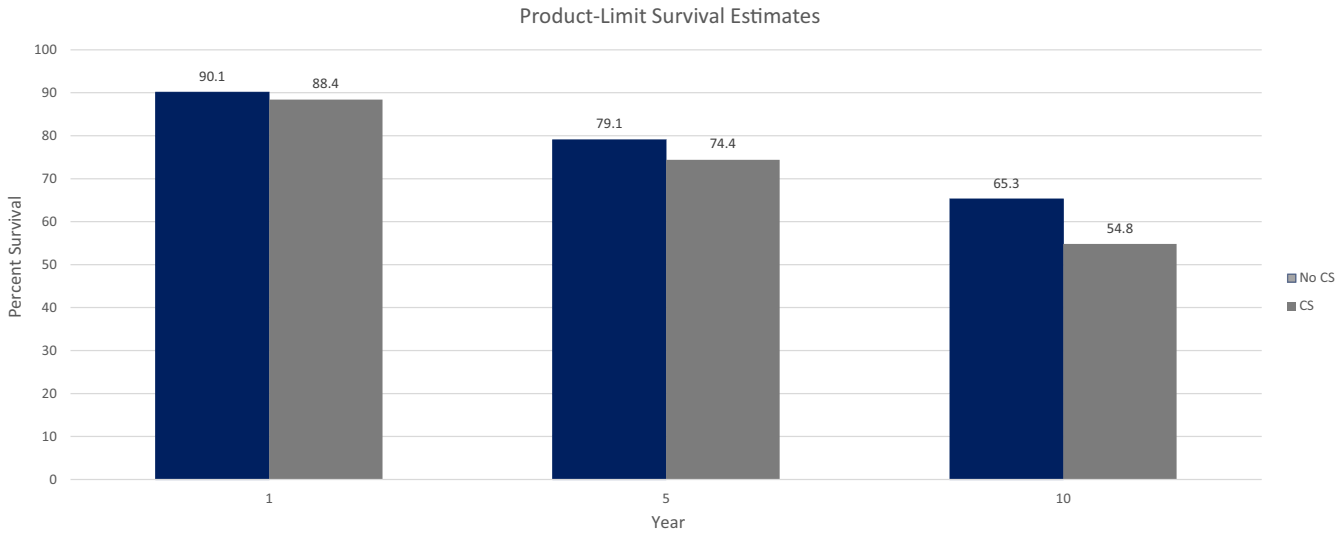

Fig. 3. Survival (1, 5, and 10 year survival p =< 0.0001).

Table 2
Maximum likelihood estimates for survival analysis.

Parameter	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazardratio	95% Hazard ratio confidence limits
CS	0.20223	0.02485	66.2092	<0.0001	1.224	(1.166, 1.285)
Age	0.00379	0.0009511	15.8997	<0.0001	1.004	(1.002, 1.006)
Black	0.20019	0.02682	55.7348	<0.0001	1.222	(1.159, 1.288)
Hispanic	0.01406	0.04071	0.1193	0.7298	1.014	(0.936, 1.098)
Other ethnicity	−0.07328	0.06351	1.3314	0.2486	0.929	(0.821, 1.053)
Female	0.08537	0.02414	12.5073	0.0004	1.089	(1.039, 1.142)
Donor smoker	0.12737	0.02514	25.6729	<0.0001	1.136	(1.081, 1.193)
Diabetes	0.2119	0.02285	86.0262	<0.0001	1.236	(1.182, 1.293)
BMI	0.00952	0.00215	19.5529	<0.0001	1.01	(1.005, 1.014)
Serum creatinine	0.03118	0.00569	30.0387	<0.0001	1.032	(1.02, 1.043)
Ischemic time	0.0811	0.00917	78.2674	<0.0001	1.084	(1.065, 1.104)
Transplant year	−0.01354	0.00228	35.1832	<0.0001	0.987	(0.982, 0.991)
HLA mismatch level	0.02556	0.00919	7.7343	0.0054	1.026	(1.008, 1.045)

Table 3
Adjusted odds ratios for secondary outcomes.

Outcome	OR	Confidence interval	P-value
Treated rejection	1.21	(1.11, 1.31)	<0.0001
Infectious hospitalization	1.18	(1.09, 1.27)	<0.0001
Graft failure	1.22	(1.15, 1.29)	<0.0001
Post-transplant malignancy	1.35	(1.25, 1.47)	<0.0001

OR = Odds Ratio.

Table 4
Cigarette smoking abstinence period categories.

Abstinence period	Frequency	Percent	Cumulativepercent
Never smoked	13,927	55.37	55.37
>60 Months	6468	25.72	81.09
13–60 Months	2225	8.85	89.94
0–12 Months	2471	9.82	99.76
Current smoker	60	0.24	100

survival (1, 5, and 10 years), (2) increased risk of hospitalization for acute rejection and infection, (3) increased risk of graft failure, (4) increased risk of post-transplant malignancy, and (5) a history of cigarette smoking in the donor was associated with increased risk of post-transplant mortality.

Our findings add to the current body of research that has substantiated prior CS as an independent risk of morbidity and mortality in patients undergoing OHT. Dellgren et al in a cohort study of 595 Scandinavian OHT patients, found that a history of smoking was a significant predictor of long-term mortality [13]. Sánchez-Lázaro et al in a retrospective analysis of 288 OHT patients transplanted in a single center in Spain similarly reported that a pre-OHT history of CS was associated with decreased survival post OHT a disparity that increased over time [10]. Our study is the largest reported to date, and the only large-scale study to be performed in a heterogeneous population.

4.1. Infection

Infections are common complications following OHT with a reported one year incidence of 22% and 5 year cumulative incidence of 85% [14]. Over time and with reduction of immunosuppression, the risk of infection decreases in OHT patients [15]. Known risk factors for infection post OHT include age, African American race, perioperative induction, intensity of immunosuppression, early graft failure, and perioperative intubation [15,16]. In our study we showed that those with a history of CS prior to OHT were at increased risk of post OHT infection. The mechanism in which CS increases infectious risk is multifactorial. CS induces structural changes in the respiratory tract including fibrosis, inflammation, increased permeability and decreased mucocillary clearance [17]. Studies suggest that CS alters cellular concentration of CD4 + cells which are necessary for B cell proliferation and antibody response [17]. Studies have also shown that Polymorphonuclear leukocytes in the peripheral blood of CS have depressed

Table 5
CS abstinence period outcomes.

Survival	HR	CI	p-value
Current smoker	1.159	0.729, 1.842	0.5338
0–12 months	1.366	1.26, 1.481	<0.0001
13–60 months	1.303	1.194, 1.422	<0.0001
>60 months	1.108	1.039, 1.18	0.0017
Treated rejection	**OR**	**CI**	**p-value**
Current smoker	1.667	0.812, 3.423	0.1642
0–12 months	1.523	1.339, 1.731	<0.0001
13–60 months	1.233	1.07, 1.422	0.0039
>60 months	1.042	0.937, 1.16	0.4475
Graft status	**OR**	**CI**	**p-value**
Current smoker	1.13	0.638, 2.002	0.6755
0–12 months	1.45	1.312, 1.602	<0.0001
13–60 months	1.387	1.247, 1.543	<0.0001
>60 months	1.128	1.046, 1.217	0.0018
Malignancy	**OR**	**CI**	**p-value**
Current smoker	0.863	0.365, 2.042	0.7375
0–12 months	1.222	1.054, 1.417	0.008
13–60 months	1.031	0.873, 1.218	0.7197
>60 months	1.091	0.981, 1.214	0.1079
Infection	**OR**	**CI**	**p-value**
Current smoker	0.518	0.222, 1.208	0.1278
0–12 months	1.045	0.913, 1.197	0.5214
13–60 months	0.916	0.787, 1.065	0.2535
>60 months	1.071	0.964, 1.189	0.204

OR = Odds Ratio.
HR = Hazard Ratio.

migration and chemotaxis response compared to non CS [17]. Further studies are required to understand the exact mechanism of a history of CS and infection in transplant patients.

4.2. Malignancy

Malignancy is a cause of long term morbidity and mortality post transplantation [18,19]. The incidence of malignancy 10 years after OHT is approximately 20% [20]. OHT patients on immunosuppression are at 2–4 folds higher risk of manifesting malignancies compared to the general population [21]. As immunosuppression therapies lead to increased survival after transplantation, the complications of prolonged immunosuppression become more significant. The literature on the influence of smoking on tumor development shows an increased risk of development of De Novo malignancies [2,3,22]. Post-transplant malignancy is a cause of long-term morbidity and mortality in OHT recipients, this study identifies a subset of patients at increased risk and will aid in implementing early surveillance.

4.3. Rejection and graft failure

The increased risk of acute rejection and graft failure seen in our study belies the smoker's paradox. Acute rejection accounts for only 11% of deaths during this time period, but is thought to be an important contributor to graft failure [23]. The exact mechanism in which CS leads to allograft rejection has not been well elucidated. Khanna et al in an animal study demonstrated that pre-transplant smoke exposure was associated with allograft rejection and increased pro-inflammatory cytokines such as interleukin-1, Interleukin-6, interferon gamma, and tumor necrosis factor-alpha [7]. It has been postulated that CS may lead to systemic inflammation and oxidative stress in the pre-transplant period that progresses into the post-transplant period resulting in graft injury [7,24].

4.4. Effects of abstaining from cigarette smoking and transplant outcomes

The deleterious effects of cigarette smoking are commonly known and have been presented in this current study. OHT patients with a history of CS are at higher risk of post-transplant mortality, malignancy, graft failure, and hospitalizations for acute rejection and infection. Our study demonstrates that duration of abstinence matters. In our analysis a dose response effect appears to be present (Fig. 4). OHT recipients who have abstained from

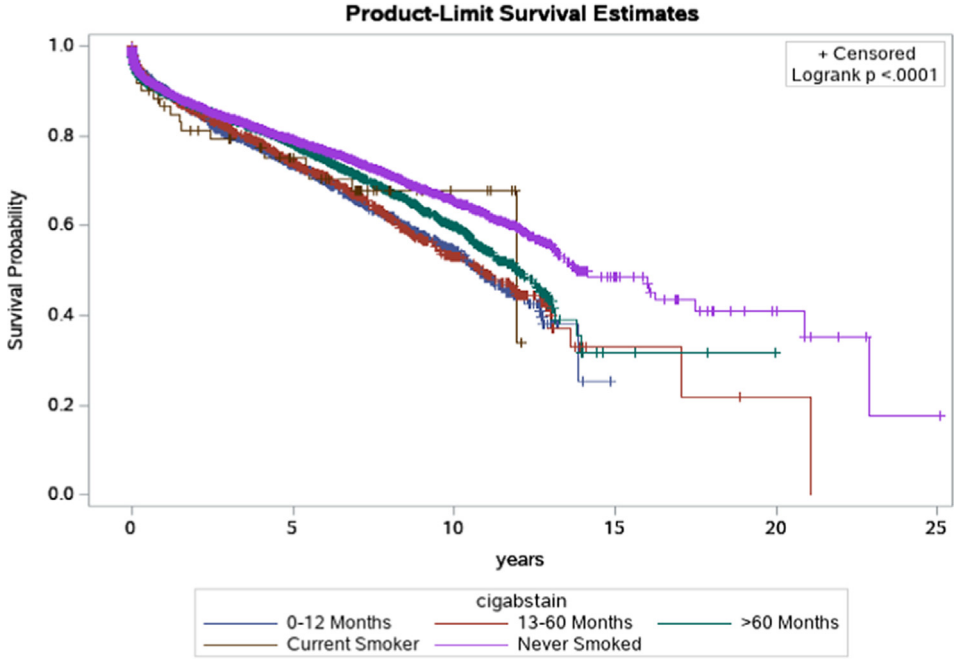

Fig. 4. Survival by length of abstinence from cigarette use.

smoking for 12 months or less are at increased risk of mortality, treated rejection, graft failure, and post-transplant malignancy compared to OHT recipients who have longer duration of smoking abstinence. We included current smokers in our analysis and found no difference in outcomes compared to nonsmokers. This finding is likely do to the very small portion of post OHT registrants identified as current smokers. The very small population size is too small to detect a statistically significant effect.

The ISHLT considers active tobacco smoking (within 6 months of transplantation) a relative contraindication to transplantation [25]. The findings of this study show that a 6-month moratorium prior to OHT does not completely absolve a patient of post-transplant adverse events associated with CS. Our study further adds to the emerging body of work demonstrating increased risk of morbidity and mortality after OHT in individuals who have had a history of CS [26]. A history of CS should be considered in pre-transplant risk counseling, and post-transplant medical surveillance. The findings in this study should further aid in smoking cessation efforts in patients post OHT.

5. Limitations

The limitations of this study are those inherently associated with registry/database analysis and include data validity, selection bias, and unmeasured behavior. The validity of registry data is dependent on accuracy of data entry. Transplant centers are responsible for entering data on patients pre-transplant and post-transplant. This process does lend itself to data entry error. In this study we utilized the UNOS registry to assess long-term outcomes of OHT recipients with a pre-transplant history of CS. This study only included registry participants who had complete data on smoking history, which accounted for >50% of the participants captured within the registry, however a significant portion of the population was excluded from analysis. Additionally, the rate of smoking relapse post-transplant has been measured to range from 12.0 to 32.5% of those who smoked pretransplant [27–30]. Recidivism was not measured in this registry and therefore could not be factored into this analysis. Despite the limitations of the study, our findings are consistent with several small-scale studies.

6. Conclusions

In conclusion, our results demonstrate that a pre transplant history of smoking is associated with increased mortality and post-transplant adverse events. As such, it is an important historical factor that should be considered during pre-transplant risk counseling, and post-transplant adverse event surveillance. Further studies into length of abstinence and transplant outcomes is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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