DE GRUYTER OPEN

10.1515/sjph-2016-0005 Zdrav Var 2016; 55(1): 29-35

Zmeškal M, Králíková E, Kurcová I, Pafko P, Lischke R, Fila L, Valentová Bartáková L, Fraser K. Continued smoking in lung transplant patients: a cross sectional survey. Zdrav Var 2016; 55(1): 29-35.

# CONTINUED SMOKING IN LUNG TRANSPLANT PATIENTS: A CROSS SECTIONAL SURVEY

## NADALJNJE KAJENJE PRI PACIENTIH PO PRESADITVI PLJUČ: PRESEČNA ŠTUDIJA

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Received: Mar 23, 2015
Accepted: Sep 03, 2015

Original scientific article

**ABSTRACT**

**Introduction.** Smoking is associated with a higher incidence of post-lung transplantation complications and mortality. Prior to inclusion on the lung transplant waiting list in the Czech Republic, patients are supposed to be tobacco free for at least 6 months. Our aim was to determine the prevalence of smoking, validated by urinary cotinine, among patients post lung transplantation and prior to inclusion on the transplant waiting list.

**Methods.** Between 2009 and 2012, we conducted a cross-sectional survey of urinary cotinine to assess tobacco exposure in 203 patients in the Lung Transplant Program in the Czech Republic. We measured urinary cotinine in 163 patients prior to inclusion on the transplantation waiting list, and 53 patients post bilateral lung transplantation.

**Results.** 15.1% (95% CI 0.078 to 0.269) of all lung transplant recipients had urinary cotinine levels corresponding to active smoking; and a further 3.8% (95% CI 0.007 to 0.116) had borderline results. Compared to patients with other diagnoses, patients with COPD were 35 times more likely to resume smoking post- transplantation (95% CI 1.92 to 637.37, p-value 0.016). All patients who tested positive for urinary cotinine levels were offered smoking cessation support. Only one Tx patient sought treatment for tobacco dependence, but was unsuccessful.

**Conclusion.** Smoking resumption may be an underrecognized risk for lung transplantation recipients, particularly among patients with chronic obstructive pulmonary disease. More rigorous screening, as well as support and treatment to stop smoking among these patients are needed.

**Keywords:** smoking, transplantation, lung

***IZVLEČEK***

***Uvod**. Kajenje po presaditvi pljuč je povezano z višjo incidenco komplikacij in stopnjo umrljivosti. Pacienti pred vključitvijo na čakalno listo za presaditev pljuč v Češki republiki ne smejo kaditi vsaj 6 mesecev. Naš cilj je določiti prevalenco kajenja, potrjeno s stopnjo kotinina v urinu, pri pacientih po presaditvi pljuč in pred vključitvijo na čakalno listo za presaditev.*

***Metode**. Med 2009 in 2012 smo izvedli presečno študijo o vsebnosti kotinina v urinu, da bi za 203 paciente, vključene v program za presaditev pljuč v Češki republiki, ocenili izpostavljenost tobaku. Vsebnost kotinina smo izmerili pri 163 pacientih pred vključitvijo na čakalno listo za presaditev in pri 53 pacientih za obojestransko presaditev pljuč.*

***Rezultati**. 15,1% (95 Cl 0,078 do 0,269) vseh pacientov za presaditev pljuč je imelo stopnjo kotinina v urinu, ki je kazala na aktivno kajenje; nadaljnjih 3,8% (95% Cl 0,007 do 0,116) pa je beležilo mejne vrednosti. V primerjavi s pacienti z drugimi diagnozami imajo pacienti s kroničnimi obstruktivnimi pljučnimi boleznimi 35-krat večjo verjetnost, da bodo nadaljevali s kajenjem po presaditvi (95% Cl 1,92 do 637,37, p-vrednost 0,016). Vsem pacientom, ki so imeli pozitivne stopnje vsebnosti kotinina v urinu, je bila ponujena pomoč za opustitev kajenja. Samo en pacient je obiskoval zdravljenje od odvisnosti od tobaka, a je bil neuspešen.*

***Zaključek**. Nadaljevanje s kajenjem je morda premalo poudarjeno kot tveganje za paciente po presaditvi pljuč, še posebej med pacienti s kronično obstruktivno pljučno boleznijo. Potrebno je bolj temeljito presejanje, kot tudi podpora in zdravljenje za opustitev kajenja pri teh pacientih.*

***Ključne besede**: kajenje, transplantacija, pljuča*

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## 1 INTRODUCTION

Cigarette smoking is the single greatest modifiable risk factor for death and illness due to lung disease (1). The benefits of smoking cessation are well established. Despite advances in medical therapy, lung transplantation (Tx) remains the best treatment option for patients with end-stage lung disease. The demand for lung transplantation greatly exceeds availability, yet developing rigorous selection criteria and methods to identify suitable transplant recipients continues to present unique challenges.

Patients who actively abuse drugs, alcohol or use tobacco products are routinely excluded from Tx waiting lists (WL), until they have been abstinent for at least 6 months. Among patients with alcoholic liver disease, many programs require a minimum of 6 months of abstinence from alcohol before placement on the transplant waiting list (2). Similar to alcohol dependence, tobacco dependence is a chronic disease characterized by relapse and remission (3). Pharmacological treatment combined with intensive counseling has been shown to improve smoking cessation rates (4-6). While the risk of smoking on post lung Tx outcomes have not yet been adequately described (7), evidence in liver, heart and renal Tx patients suggest that smoking is associated with higher incidence of post-Tx complications and mortality (8-13). Despite efficacy of current cessation therapies, compliance among transplant recipients is often poor, with 10-40% returning to smoking post- Tx (7). Few centres actively screen patients for tobacco exposure or offer cessation support to patients, particularly post Tx (8). Many centres rely on self-reported smoking status, which has previously been shown to be unreliable. (13-15).

Despite the severity of their illness and the knowledge that quitting would have important long-term benefits, many patients continued to smoke (15-17). This may not be due to the lack of motivation to stop smoking, but rather a matter of dependence for these patients (18). Furthermore, despite lung Tx candidates' reliable self-reported disclosure of active smoking, it is unlikely that their survival may depend on inclusion on the Tx WL. Due to the limited number of suitable donors and the high demand for Tx, it is important that centres are able to detect patients who deceptively report smoking behaviour in order to select patients who will have the best outcomes long term. The aim of this study was to determine the prevalence of smoking among patients post lung Tx, as well as prior to inclusion on the Tx WL, and to offer treatment of tobacco dependence to smokers. The only lung Tx center in the Czech Republic is located at the University Hospital in Motol. The centre has performed about 20 lung Tx per year since 1997. To date, physicians in the Czech Republic have relied solely on self-reported smoking status. This study is the first to measure urinary cotinine levels prior to inclusion on the Tx-WL and post lung-Tx among patients in the Czech Republic.

## 2 METHODS

Between January 2009 and April 2012, we conducted a cross sectional survey of urinary cotinine levels to assess tobacco smoke exposure in 203 patients in the Lung Transplant Program. The purpose was to biochemically validate self-reported smoking status in these patients and determine if ongoing screening might be necessary. All patients had been diagnosed with end-stage lung disease and were cared for by the Department of Pneumology, 2nd Faculty of Medicine, Charles University in Prague, and the University Hospital in Motol, Czech Republic.

Urine samples were obtained from patients at routine visits. 163 patients were tested prior to inclusion on the lung transplant WL. 53 patients were tested post-Tx as bi-lateral lung recipients cared for by Lung Transplant Centre, 3rd Department of Surgery, 1st Faculty of Medicine, Charles University in Prague, and Motol University Hospital, Czech Republic. 13 patients were tested both prior to inclusion on the WL and post-Tx.

Prior to inclusion on the Tx-WL, patients had to meet the following criteria: the terminal state of pulmonary disease with expectancy survival of 12-18 months; the dependence of oxygen inhalation from oxygenator; and exhaustion of all other conservative treatment options. Patients had to meet standard criteria for specific diagnoses and avoid all absolute contraindications, including: malignant tumor, progressive neuromuscular disease, severe systemic disease or infection (HIV, hepatitis B or C), multi organ failure, ideal body weight < 70% or > 130%, long term corticoids treatment > 20mg Prednisone/ day, smoking or drug use during last six months, acute infection, psychosocial instability, or diabetes mellitus with organ complications. Other relative contraindications included: age > 65, the need for invasive ventilation, cardiac disease, or renal disease with creatinine clearance < 50mg/ml/min. Prior to inclusion on the WL, all patients in our sample met the inclusion criteria, but only had to prove they had been smoke-free during the last 6 months. All patients were advised to avoid active and passive smoking. This was validated by a negative urinary cotinine result, which was an obligatory parameter for the inclusion on the transplant WL. Among patients who had a positive or borderline result, passive smoking was discussed, and they were tested again at subsequent visits. All patients were asked about the use of nicotine replacement therapy

or nicotine in other forms (none reported). Two patients reported using electronic cigarettes.

Between January 2009 and April 2012, all lung Tx recipients and patients prior to inclusion on the Tx-WL were eligible to be included in the study. All post-Tx patients were tested for urinary cotinine as a part of annual Tx follow up. The data including demographic characteristics and diagnosis was obtained from patients' charts (see Table 1). This study was approved by the ethics committee at University Hospital in Motol, Czech Republic.

Urinary cotinine (COT) was measured as a marker of smoking. Urinary cotinine levels (COT) were assessed by semiquantitatively urine enzyme immunoassay (DRI® Cotinine Assay, Microgenics Corporation, Fremont, CA, USA) (18, 19). Based on urinary cotinine levels, patients were categorized as positive (≥ 500 ng/ml), negative (< 50 ng/ml), or borderline (50-499 ng/ml), according to their level of tobacco exposure. In the case of a positive or borderline result, the measure was confirmed by LC-MS/MS (Applied Biosystems, 3200 Q Trap®, Singapore, Singapore) (19-24). Patients with a borderline or positive result were tested again at subsequent visits. Previously established urinary cotinine cut-off points were used to categorize patients as negative, borderline or positive for tobacco smoke expose (24). These cutoffs were established by Zielińska-Danch et al. (2007) to distinguish non-smokers, passive and active smokers (24). A brief cessation intervention (up to 10 minutes) was conducted with all smokers, as well as the recommendation to visit the Centre for Tobacco-Dependence.

Statistical analyses were performed using MedCalc for Windows, version 12.4.0 (MedCalc Software, Mariakerke, Belgium). For post-Tx patients and patients prior to inclusion on the WL, means and standard deviations were calculated for continuous variables, whilst frequencies and percentages were calculated for the categorical variables.

## 3 RESULTS

The majority of patients in both observed groups suffered from chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis. Patients with Cystic Fibrosis were on average 25.6 years younger than patients with other diagnoses (Table 1).

**Table 1.** Demographic characteristics of lung transplant recipients' post-transplantation and prior to the inclusion on the transplant waiting list in the Czech Republic 2009-2012.

| Characteristics | Pre-WL (N=163) | Post-Tx (N=53) |
|---|---|---|
| **Gender (% male)** | 67% | 62% |
| **Age (years) (mean ± SD)** | | |
| CF group | 30.66 ± 10.90 | 28.68 ± 8.81 |
| Non-CF group | 56.28 ± 8.69 | 54.38 ± 8.88 |
| **Medical Diagnosis (%)** | | |
| COPD group | 69 (42.3%) | 26 (49.1%) |
| Non-COPD group | 94 (57.7%) | 27 (50.9%) |

CF; Cystic Fibrosis; Pre-WL; pre-wait list; Post-Tx; post-transplant; COPD; Chronic Obstructive Pulmonary Disease

Among patients prior to the inclusion on the Tx waiting list, 4.9% (8/163) had at least one positive urinary cotinine test corresponding to active smoking (Table 2). Two patients reported using electronic cigarettes. Another 6.1% of patients (10/163) had borderline results, and the test was repeated. In the case of positive or repeated borderline tests, patients were not included to the WL until they had been smoke-free (negative test for urinary cotinine) for at least 6 months. Prior to inclusion on the Tx-WL, all patients were tested for cotinine in urine.

The prevalence of positive urinary cotinine among patients post-Tx was 15.1% (8/53). An additional 3.8% of post-Tx patients (2/53) had borderline results. One year post-Tx, 80% of all patients were tested for urinary cotinine during the observed period at a median of 1.4 (0.95 – 2.64) years. There was no known selection bias.

**Table 2.** Urinary cotinine concentrations of lung transplant (Tx) patients post-Tx and prior to the inclusion on the waiting list in the Czech Republic 2009-2012. 80% of all patients one year post-Tx were tested in the observed period.

| Urinary cotinine concentrations (ng/ml) | Pre-WL (N=163) | Post-Tx (N=53) |
|---|---|---|
| **Negative** (< 50 ng/ml) | 89.0% (145/163) 95% CI 0.821 to 0.921 | 81.1% (43/53) 95% CI 0.685 to 0.893 |
| **Borderline** (50 ≤ X < 500 ng/ml) | 6.1% (10/163) 95% CI 0.033 to 0.108 | 3.8% (2/53) 95% CI 0.007 to 0.116 |
| **Positive** (≥ 500 ng/ml) | 4.9% (8/163) 95% CI 0.025 to 0.094 | 15.1% (8/53) 95% CI 0.078 to 0.269 |

Pre-WL; pre-wait list; Post-Tx; post-transplant

Regarding patients' positive and borderline urinary cotinine levels, corresponding to active smoking, the prevalence of cotinine was consistently higher among patients with COPD at both time points, compared to patients with other diagnoses (Table 3). All patients who tested positive for urinary cotinine levels were offered smoking cessation support, but only one Tx patient sought treatment for tobacco dependence at the Centre for Tobacco Dependent. That patient did not quit smoking.

**Table 3.** The comparison of urinary cotinine levels among patients with COPD & Emphysema and patients with other diagnoses post-lung Tx and prior to inclusion on the Tx waiting list.

| Urinary cotinine levels | COPD-group (n= 94) | Non-COPD group (n=122) |
|---|---|---|
| **Pre-WL** | | |
| Negative (< 50 ng/ml) | 81.2% (56/69) | 94.7% (89/94) |
| Positive and Borderline (≥ 50 ng/ml) | 18.8% (13/69) | 5.3% (5/94) |
| Odds ratio | 4.13 | |
| 95% CI | 1.40 to 12.22 | |
| P-value | 0.010 | |
| **Post-Tx** | | |
| Negative (< 50 ng/ml) | 61.5% (16/26) | 100% (27/27) |
| Positive and Borderline (≥ 50 ng/ml) | 38.5% (10/26) | 0% (0/27) |
| Odds ratio | 35.00 | |
| 95% CI | 1.92 to 637.37 | |
| P-value | 0.016 | |

COPD; Chronic Obstructive Pulmonary Disease, Post-Tx; post-transplant, Pre-WL; pre-wait list

Post-Tx, the prevalence of smoking resumption was 15% (8/53), based on positive urinary cotinine levels. The highest prevalence post-Tx was among patients with COPD, with 38.5% (10/26) having positive or borderline urinary cotinine levels corresponding with active smoking. All patients who tested positive for urinary cotinine levels were offered smoking cessation support.

The odds of smoking resumption was not different for men or women. There was a trend towards women tending to be more likely to have a positive or borderline urinary cotinine result prior to the inclusion on the Tx WL, but the difference was not significant.

The odds of smoking resumption were higher among patients with COPD, compared to patients with other diagnoses, at both time points. Prior to inclusion on the WL, the odds of smoking resumption was 4.13 times higher among patients with COPD (Table 3), and 35 times higher post-Tx, compared to patients with other diagnoses.

## 4 DISCUSSION

Our most remarkable finding was the high prevalence of smoking resumption post-Tx, particularly among patients with COPD. Despite the fragility of their condition, 15% of all tested lung Tx recipients had urinary cotinine levels corresponding to active smoking; a further 3.8% had borderline results. Compared to patients with other diagnoses, patients with COPD were 35 times more likely to resume smoking post-Tx.

Our findings are similar to those of Vos et al. who found that 11% of lung Tx recipients self-reported smoking resumption post transplantation (8). Similarly, the prevalence was higher (23%) among patients with emphysema due to COPD (8). Risk factors, including shorter cessation period prior to transplantation, lower socioeconomic status, exposure to second-hand smoke, emphysema, and death of a spouse were all associated with a higher likelihood of smoking resumption post-Tx (8). In a group of 331 lung Tx patients, Ruttens et al. found that the prevalence of post-Tx smoking was 12%, and they identified peer group smoking as an important risk factor for smoking resumption (25).

Over a period of 13 years, Botha et al. covertly assessed smoking habits among cardiac transplant patients. They found that 27% tested positive for urinary cotinine levels corresponding to active smoking at least once post transplant; 15% tested positive repeatedly (12). Post cardiac transplantation, smoking shortened median survival and was the most significant determinant of overall mortality (12). Among liver transplant recipients, Lee et al. found that 12% self-reported smoking resumption post surgery (27). Bright et al. similarly found that 17% of liver transplant recipients' self-reported ongoing tobacco use (28). They also found that self-reported smoking behaviour was not the most reliable measure, as 11% of liver transplant recipients who denied tobacco use, had serum cotinine levels that corresponded to active smoking (28). Among renal transplant recipients, Nguyen et al. found that 34% of patients with serum cotinine levels corresponding to active smoking, claimed to be non-smokers (13).

Ensuring that candidates are abstinent prior to transplantation is important, but this is only half of the equation. Few centres actively screen patients for tobacco exposure or offer cessation support to patients,

particularly post transplantation (8). Until 2008, the Pneumology Clinic and the Lung Transplant Centre in Prague relied solely on patients' self-reported smoking status. No further validation was deemed necessary, as those patients were considered to be too ill to continue smoking. We found that 4.9% of transplant candidates prior to inclusion on the WL tested positive for urinary cotinine levels corresponding to active smoking; a further 6.1% had borderline results. Those findings clearly speak to the degree of nicotine dependence among some patients, the need for active screening, and the importance of offering an ongoing smoking cessation support to patients both pre- and post-Tx.

Despite the fact that patient compliance with cessation measures is often poor, this problem may be perpetuated by a number of factors. Beyond self-reported smoking status, few centers actively screen for tobacco use, or collect a comprehensive smoking history on their patients. Factors, such as the duration of abstinence period, quit attempts, the age of initiation, demographics, behavioural and psycho- sociological factors have all been shown to influence cessation (29, 30). The implementation of a more rigorous screening program will help centres identify patients who may benefit from an ongoing cessation support, and those patients who may be the most promising candidates for Tx.

To date, pharmacological treatment for nicotine withdrawal symptoms combined with intensive counseling have been shown to improve quit rates (4-6). Our findings underscore the need for physicians to proactively address smoking behaviour and screen patients for smoking at each visit. Unfortunately, many physicians are ill prepared to talk to their patients about smoking and, therefore, do not intervene (31). While physicians need support, information and training to effectively intervene, there is also the need for a reliable system of tobacco treatment centres, where patients can be referred to in order to receive the specialized cessation support they need.

Limitations of the current study include: a small sample size (dictated by the number of lung Tx in the Czech Republic, which is around 20 per year) and the availability of sociodemographic characteristic (e.g. socioeconomic status, marital status, stress/ anxiety, depression, etc.), as well as more detailed information about patients' smoking histories (e.g. quit attempts, the duration of abstinence, the age of initiation, smoking frequency, the degree of nicotine dependence, etc.). Without proper screen protocols in place, the medical staff cannot proactively identify patients who may have relapsed, or refer them to appropriate cessation supports. Another limitation is that only 80% of all patients were tested one year post-TX in the observed period. Despite results of a pilot study that showed the importance of an ongoing screening, testing may not have been perceived as a priority by staff, and, in some cases, samples were never collected. In some cases, patients did not show up for follow-up visits, or there were issues relating to handling and processing samples.

All biochemical tests can trigger false results. In the case of urinary cotinine, the use of nicotine replacement therapy or ingestion of nicotine in any form will result in a positive test, even though the patient may have quit smoking. In the case of a false positive result, the patient should be questioned about any tobacco smoke exposure in more detail, and another test should be conducted at a subsequent visit. All patients in the study were asked about the use of nicotine replacement therapy or the use of nicotine in any form; none was reported. Two patients reported using electronic cigarettes. The biological cutoffs used included a range that would account for even higher levels of exposure to environmental tobacco smoke, so there is little likelihood of a false positive result due to passive smoking. A false negative result is also possible in the case where enough time has passed for cotinine to be eliminated from the patient's system prior to the test, but this result is not likely in heavy smokers.

Despite the fragility of their condition, smoking continues to be an issue for many patients with end stage lung disease. The prevalence of smoking among patients post lung Tx, as well as prior to the inclusion on the Tx-WL, provides evidence that an ongoing screening is necessary to detect smoking resumption. The implementation of routine screening protocols may help centers identify those candidates who are likely to have the best outcomes post transplantation.

## CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist. There was no financial relationship with any organization that might have an interest in the submitted work, or other relationship or activity that could appear to have influenced the submitted work. Authors do not have any financial conflict of interest arising from involvement with organisations that seek to provide help with, or promote, recovery from addiction.

## FUNDING

Funding support for this study came from the Ministry of Health, Czech Republic - conceptual development of research organization, University Hospital in Motol, Prague, Czech Republic, 00064203, and Project PRVOUK P28/1LF/2 of Charles University in Prague, Czech Republic.

**ETHICAL APPROVAL**

The study was approved by the ethics committee at the University Hospital in Motol, Czech Republic (Reference No.: EK – 735/13).

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