








Risk Factors for Mortality in Denim Sandblasters Silicosis: Selecting Candidate for Lung Transplantation

Türkan Nadir Öziş¹ , Nur Şafak Alıcı² , İbrahim Onur Alıcı³ , Dilek Ergün¹ , Emine Avcı⁴ ,
Nevin Tacı Hoca⁵ , Ömer Hınç Yılmaz⁶ 

¹Department of Pulmonology, Ankara Occupational Diseases Hospital, Ankara, Turkey

²Department of Occupational Medicine, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir, Turkey

³Department of Chest Diseases, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir, Turkey

⁴Department of Epidemiology, Dokuz Eylül University, İzmir, Turkey

⁵Department of Chest Diseases, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey

⁶Department of Toxicology, Ankara Occupational Diseases Hospital, Ankara, Turkey

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Abstract

OBJECTIVE: This study aimed to review the risk factors for silicosis together with survival analysis and a perspective for lung transplantation with data from a single center.

MATERIAL AND METHODS: We reviewed the medical records of denim sandblasters who were referred to our center between January 2006 and December 2011 and evaluated 219 patients with a history of denim sandblasting with a minimum follow-up period of 5 years until 2016. We analyzed several personal and occupational features, together with functional and radiologic data.

RESULTS: Of the 219 denim sandblasters, 107 (49%) had been diagnosed with silicosis. In the logistic regression analysis, the duration of exposure was the only independent risk factor for the development of silicosis, indicating a 9% increased risk of silicosis for every month of exposure ($p < 0.001$; odds ratio 1.09; 95% confidence interval 1.050–1.132). Of the patients, 7 (3%) died. A forced expiratory volume in the first second of $< 44\%$ and a forced vital capacity of $< 47\%$ were associated with an increased risk of mortality. Mortality was significantly higher in the international labor office category 3 patients, and 5-year survival rates of patients with A, B, and C lung opacities were 88%, 67%, and 25%, respectively.

CONCLUSION: Silicosis still kills young workers. Severe radiologic involvement and decreased lung volumes are related to mortality, and lung transplantation is the only therapeutic option.

KEYWORDS: Silicosis, pneumoconiosis, sandblasters, mortality, lung transplantation

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INTRODUCTION

Silicosis, which is one of the ancient diseases, still affects many workers throughout the world despite existing control programs. In Turkey, we have been living in an epidemic of silicosis for 15 years. The most unfortunate victims are likely the young workers of denim sandblasting. In the denim sandblasting sector, almost all workers were uninsured, and most of the workplaces were unregistered or unlicensed. The unregistered workers worked almost 10-hour days, 6 days a week, under poorly ventilated conditions without any personal protection [1]. Many workers died of the disease, and many more have become disabled [2].

Soon after the first cases of silicosis related to denim sandblasting were diagnosed in Erzurum [3], several reports and series have been published [1, 4-7]. The dying youth became a public issue and resulted in an initiation for an update and improvement in occupational laws, and in practice, all denim sandblasting facilities have been closed. However, unfortunately, the expected delayed effects of this terrible condition have continued.

Since March 2009, denim sandblasting using silica containing material has been banned in Turkey by the Ministry of Health, but only in the denim sector and not in other sectors. In our country, there is no specific silicosis surveillance system. Recently, especially after 2012, periodic examinations are legally mandated and suspected cases are sent to our center, which is 1 of the 3 occupational diseases hospital, by occupational physicians, other doctors, insurance system, or by individual application.

There are multiple studies conducted on this issue presenting the first cases in our country in the early 2000s [1-4]. This study aimed to present data involving denim sandblasters, with or without silicosis, to review the current situation and basic findings, survival data, and related risk factors. The data are remarkable as they involve a high number of cases with

Address for Correspondence: Nur Şafak Alıcı, Department of Occupational Medicine, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir, Turkey

E-mail: safak.alici@hotmail.com

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a relatively longer follow-up period. Together with the previous reports, this data focused on the clinical and radiological factors affecting survival and, therefore, demonstrate the possible factors related to mortality, which may guide the reader to select the appropriate patient for transplantation, which is the only treatment option for this deadly disease.

MATERIAL AND METHODS

Study Population and Study Procedure

We retrospectively reviewed the medical records of the denim sandblasters who were referred to our center between January 2006 and December 2011. Informed consent was obtained from all the subjects who participated in the study. All the patients with a history of denim sandblasting were included, and those with a history of tuberculosis were excluded. We evaluated 219 patients with a history of denim sandblasting with a minimum follow-up period of 5 years until 2016. We obtained vital status from our hospital records and the online death declaration system of the Turkish Health Ministry.

We compared demographic features, workplace exposure characteristics, and pulmonary functions of the patients with silicosis with those of workers with a history of silica exposure. The pulmonary function test (PFT) was carried out using a computerized spirometer [Vmax22; SensorMedics Corp., Yorba Linda, CA, USA]. We evaluated chest radiographs with the help of 2 certified pneumoconiosis radiograph readers. Any disagreement was resolved by consensus. We defined silicosis as related radiological signs (international labor office [ILO] classification of $\geq 1/0$) and radiological findings in high resolution computed tomography (HRCT) in a worker with an exposure to silica [8]. In patients with silicosis, ILO classification and HRCT features were noted at the first visit. We classified these patients as acute, accelerated, and chronic silicosis according to the exposure time of <5 years, 5–10 years, and >10 years [9]. We defined survival time as the time between the date of diagnosis and the date of death or the date of last contact at a control visit or call. All the deaths were attributed to silicosis or related complications.

Statistical Analysis

Descriptive findings were expressed as percent, mean \pm standard deviation, or median (minimum -maximum) values. Clinical characteristics were compared using t test, χ^2 test, and Fisher exact test between the groups. Kaplan-Meier survival curve and binary logistic regression test were used to determine the factors affecting survival. A p value of <0.05 was defined as statistically significant. The Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp.;

Armonk, NY, USA) was used to perform data analysis.

This study was approved by the Ethics Committee of Keçiören Training and Research Hospital (B.10.4.ISM.4.06.68.49).

RESULTS

All the participants in this study were sandblasters, not supervisors, and were no longer employed as sandblasters for more than 48 months at the time of evaluation. In total, 107 (49%) of them had been diagnosed with silicosis. The remaining 112 (51%) workers were free of radiological signs and enrolled as a control group with a history of denim sandblasting. The demographic features, smoking history, workplace exposure characteristics, and PFT results of all the workers are given in Table 1. The age at diagnosis and the time passed after the end of exposure were the same between the groups. However, patients with silicosis begin work at a younger age and are exposed to silica for a longer time, which in turn leads to longer latency periods. Smoking habits were not different between the groups, but the forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) values were lower in patients with silicosis. The decrease in the PFTs was found to be related to the presence of the disease. Of the patients, 3 (3%) were found to have concomitant active tuberculosis and were immediately referred to a tuberculosis clinic for treatment.

The results of the chest radiographs according to ILO classification are given in Table 2. The distribution was balanced between categories, but the percentage of newly diagnosed patients who were classified as category 2 and above was 69%. Similarly, large opacities were seen in 14% of the images, and 5% were C-type opacity.

Several features of the patients with silicosis are given in Table 3. There were no patients with acute silicosis, 39% of patients were classified as accelerated, and the remaining 61% as chronic disease. The patients were mostly symptomatic, and the most common symptoms were dyspnea (76%), chest pain (55%), cough (50%), and sputum production (49%). The findings on HRCT were reviewed, and the most common radiological findings were parenchymal micronodules (89%). Mediastinal and hilar lymphadenopathies (38%) and interlobular septal thickenings (23%) were the accompanying findings. Conglomerate masses and pleural thickening were detected in 17% and 13% of the patients, respectively.

There were several factors associated with silica exposure, which could be related to the development of silicosis. However, logistic regression analysis demonstrated that the duration of exposure was the only independent risk factor for the development of silicosis, indicating a 9% increased risk of silicosis for every month of exposure ($p < 0.001$; odds ratio [OR] 1.09; 95% confidence interval [CI] 1.050-1.132).

Among 107 patients with silicosis, 7 (3%) died of the disease over a median follow-up period of 5 years. In 7 patients, the mean survival after diagnosis was 32 ± 13 months (7-47). The mean age at the time of death was 29 years (25-40). All the patients died secondary to respiratory insufficiency. In patients who died of the disease, pulmonary functions were

MAIN POINTS

- Silicosis is common in denim sandblasters, and a prolonged exposure time to silica is the main risk factor.
- This study adds information about radiological involvement and decreased lung volumes, which are related to mortality.
- In patients with a high risk of mortality, lung transplantation should be considered.

Table 1. Comparative data on the features of denim sandblasters

	All workers	Silicosis	Silica exposed workers	p
Number of workers (n [%])	N: 219	107 (49%)	112 (51%)	
Median follow-up time (months)	60	62	57	NS*
Age at the time of diagnosis and evaluation (year±SD) (median/min-max)	27±6 (26/18-49)	26±4 (26/20-44)	28±7 (27/18-49)	NS*
Age at which started working (year±SD) (median/min-max)	18±6 (17/9-44)	17±4 (16/9-31)	20±6 (18/10-44)	<0.01*
Duration of exposure (months±SD) (median/min-max)	19±13 (16/6-96)	25±16 (24/6-96)	14±7 (12/6-42)	<0.001*
Time from the end of exposure (months±SD) (median/min-max)	107±31 (108/48-300)	108±27 (108/48-204)	108±35 (96/48-300)	NS*
Latency period (months±SD) (median/min-max)	127±37 (120/60-336)	134±34 (132/72-288)	120±39 (114/60-336)	<0.001*
Current smoker and ex-smoker	162 (74%)	79 (74%)	83 (73%)	NS**
Smoking (pack-year±SD) (median/min-max)	5.7±6.7 (4/0-54)	5.4±5.6 (4/0-25)	5.9±7.5 (5/0-54)	NS*
FEV1 (%±SD) (min-max)	76±22 (18-125)	72±21 (18-109)	79±23 (23-125)	<0.05*
FVC (%±SD) (min-max)	80±21 (22-119)	77±20 (25-116)	83±21 (22-119)	<0.05*
FEV1/FVC (%±SD) (min-max)	79±11 (43-100)	79±10 (44-100)	80±12 (43-100)	NS*
MEF25-75 (%±SD) (min-max)	66±29 (13-139)	62±25 (13-131)	70±32 (15-139)	NS*
DLCO (%±SD) (min-max)	93±21 (25-122)	89±22 (37-121)	97±19 (25-122)	NS*

* Mann-Whitney U test; ** chi-squared test; † independent sample t test; SD: standard deviation
 NS; p>0.05
 Significant p values are in bold

Table 2. ILO classification in patients with silicosis (n=107) (%)

Small opacities		
Category 1	1/0	6 (6)
	1/1	10 (9)
	1/2	17 (16)
Category 2	2/1	5 (5)
	2/2	20 (19)
	2/3	11 (10)
Category 3	3/2	3 (3)
	3/3	32 (30)
	3/+	3 (3)
Large opacities		
A		4 (4)
B		2 (2)
C		5 (5)

Table 3. Features of the patients with silicosis

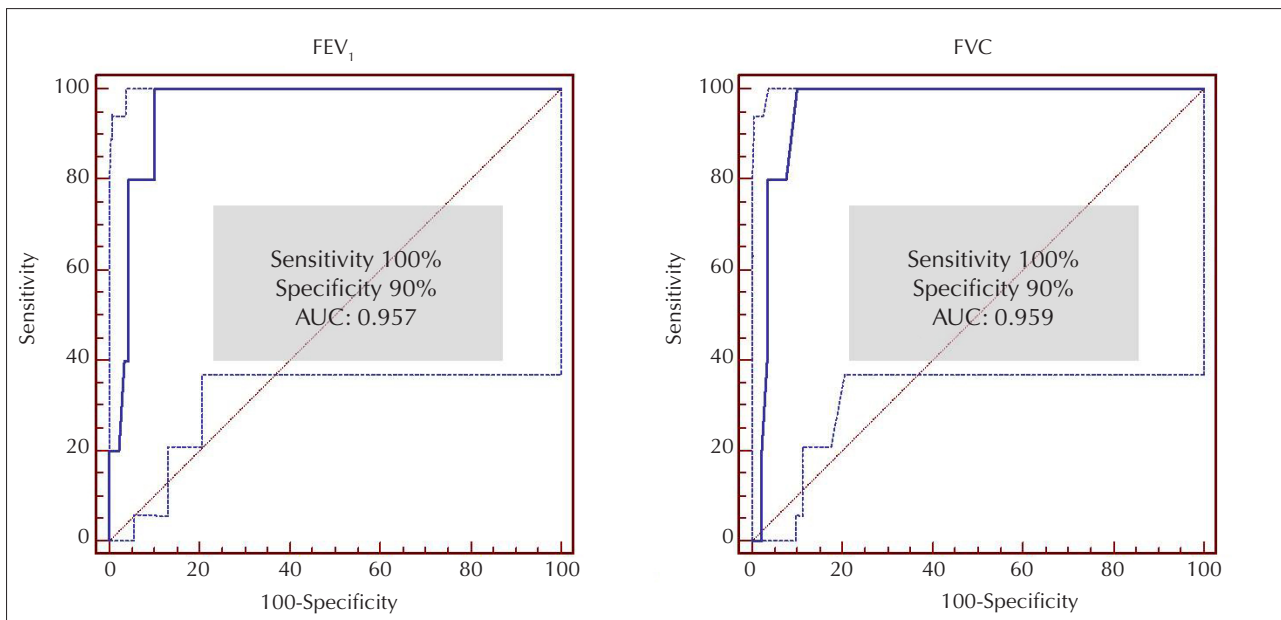
		n (%)
Classification	Acute silicosis	0 (0)
	Accelerated silicosis	42 (39)
	Chronic silicosis	65 (61)
Symptoms	Dyspnea	81 (76)
	Chest pain	59 (55)
	Cough	53 (50)
	Sputum	52 (49)
	Weight loss	45 (42)
	Wheezing	44 (41)
	Hemoptysis	5 (4)
HRCT findings (107 patients)	Micronodules	92 (89)
	Lymphadenopathy	40 (39)
	Interlobular septal thickening	24 (23)
	Reticular opacities	27 (26)
	Traction bronchiectasis	20 (19)
	Peribronchial thickening	20 (19)
	Conglomerate mass	17 (17)
	Pleural thickening	13 (13)
	Linear bands	4 (4)
	Cavitating mass	2 (2)
	Pneumothorax	1 (1)

poor; FEV1, FVC, and maximal expiratory flow (MEF)25-75 were significantly lower than in other patients (Table 4). In receiver operating characteristic (ROC) analysis, an FEV1 <44% was significantly related to mortality (p<0.001, sensitivity 100%, specificity 90%, area under the curve [AUC] 0.957 [0.894-0.988]). Similarly, an FVC <47% was a risk factor for mortality; corresponding p value, sensitivity, specificity, and AUC values were <0.001, 100%, 90%, and 0.959 (0.897-0.989), respectively (Figure 1). ROC analysis for MEF25-75 revealed a weaker effect, and 5-year survival for a MEF25-75 <38% was as high as 94%. However, the 5-year

Table 4. Comparison of pulmonary function tests of patients with silicosis according to the presence of mortality

	Died (n=7)	Living (n=100)	p
FEV1 (%±SD) (min–max)	32±9 (18–44)	75±19 (24–109)	0.001*
FVC (%±SD) (min–max)	36±5 (32–47)	79±19 (25–116)	0.001*
FEV1/FVC (%±SD) (min–max)	74±15 (49–90)	79±10 (44–91)	>0.05*
MEF25–75 (%±SD) (min–max)	27±8 (18–38)	64±24 (13–131)	0.001*
DLCO (%±SD) (min–max)	61±21 (46–76)	91±22 (37–121)	>0.05*
Category 3 (n [%])	5 (71)	33 (33)	<0.05**
Large opacity (n(%))	5 (71)	9 (9)	0.001**

* Mann-Whitney U test; **Pearson's Chi-squared test; SD: standard deviation
Significant p values are in bold

**Figure 1.** Receiver Operating Characteristic analysis of FEV1 and FVC for mortality

survival rates for an FEV1 <44% and an FVC <47% were 66% and 64%, respectively. However, these findings in PFTs could not be projected to the presence of symptoms, and no symptoms were found to be related to mortality.

As expected, the chest radiograph results according to ILO classification revealed that the workers who died of the disease were at least in categories 2 or 3, though mostly in category 3. With Kaplan-Meier analysis, mortality was significantly higher in ILO category 3 than in categories 1 and 2 ($p<0.05$) (Figure 2). The 5-year survival in categories 2 and 3 was 97% and 87%, respectively. Similarly, the presence of a large opacity was related to a poor outcome, and most of the workers who died had large opacities, mostly a C-type opacity (4/7, 57%). The Kaplan-Meier analysis revealed that the presence of a large opacity was significantly related to mortality ($p<0.001$) (Figure 3). The 5-year survival was significantly lower when a large opacity was present (98% vs 67%). The corresponding 5-year survival rates of patients with A, B, and C opacities were 88%, 68%, and 25%, respectively. The findings on HRCT have confirmed this data that having a conglomerate mass was significantly related to mortality ($p<0.001$).

DISCUSSION

The most important results of our study were functional and radiological findings that related to the 5-year survival. Akgün et al. [4] analyzed 157 individuals with a history of denim sandblasting and of 145 available chest radiographs, 77 (53%) demonstrated changes related to silicosis. Recently, they re-analyzed their patients after 4 years and reported that the prevalence of silicosis has increased to 96% [2]. In 2011, Bakan et al. [1] reported their data on silicosis in denim sandblasters. They had 32 patients who had been diagnosed with silicosis because of denim sandblasting, but they did not mention the total number of exposed individuals they had evaluated. In our study, we found the prevalence to be 49%, which is consistent with the previous data, but we could not follow the normal cases.

Denim sandblasting has become a public issue, as it results in the death of young people. They begin working when they are teenagers and die before 30. In the literature, the age at first exposure to sandblasting was under 16 years, and the mean age at diagnosis of silicosis was 23–31 years [1, 4]. Akgün et al. [4] have reported that the mean age of the patients who died during follow-up was 24 years. In our

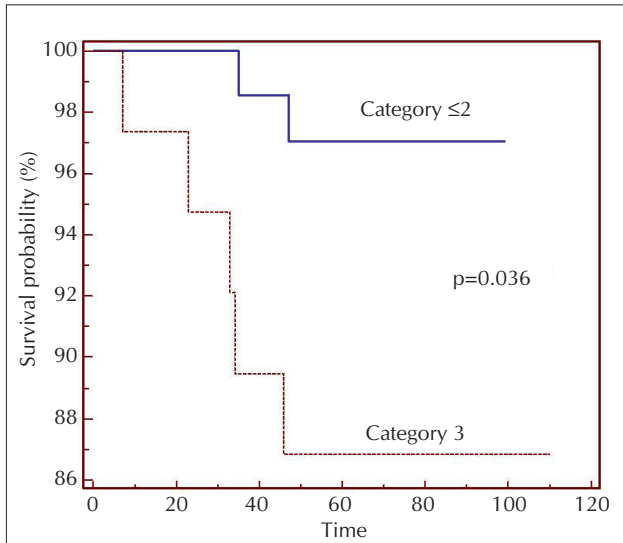


Figure 2. Kaplan-Meier Survival analysis comparing ILO categories ≤2 and 3

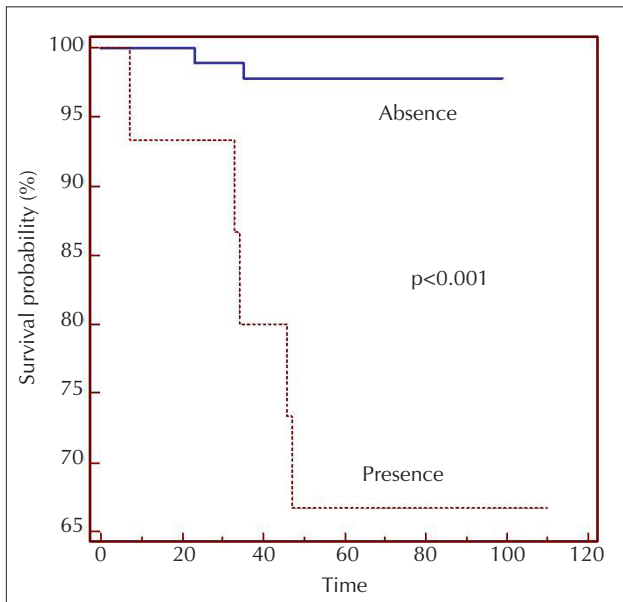


Figure 3. Kaplan-Meier Survival analysis comparing presence and absence of a large opacity

study, 7 patients died in 5 years, and most of them were under 35 years of age.

The total dose of silica is the main risk factor for the development of silicosis [10]. Nagelschmidt [11] previously reported that a total retained silica dose of 1-3 g was sufficient to cause silicosis. Denim sandblasting, in unregistered facilities, using non-standardized materials, under poorly ventilated circumstances, and without personal protection will definitely cause silicosis. As expected, our data revealed the duration of exposure as the main risk factor for silicosis in denim sandblasters. In their report, Akgün et al. [4] have found that the mean total exposure duration, duration since the last exposure, and the latency period were significantly higher in patients with silicosis and were 41 ± 23 , 44 ± 28 , and 86 ± 35 months, respectively. These data were consistent with other studies [1]. The duration of exposure was shorter, and

the time from the end of exposure to date of diagnosis was longer. Development of the disease in a shorter period may be related to the lack of adequate ventilation, although we did not have the data about respirable dust concentration and crystalline silica content of the air in the workplace. The lack of follow-up data and workplace visits and dust measurements are the main limitations of this study.

Silicosis is a destructive disease. It may result in a severely fibrotic lung and decreased lung volumes. As expected, PFTs (FEV1 and FVC) were worse in the silicosis group, despite similar smoking habits. This is consistent with the literature [1, 4]. Decreased and decreasing lung volumes are related to poor outcome and should be considered carefully.

Latency period is the defining factor between acute, accelerated, and chronic silicosis. No patients in our study were in the acute silicosis group despite the short and heavy exposure in denim sandblasting. The patients were mostly in the chronic silicosis group (61%). In their series, Bakan et al. [1] reported the percentages of acute and accelerated disease as 31% and 63%, respectively. This difference may be owing to delayed diagnosis, which is consistent with the advanced radiologic findings. The mortality in acute and accelerated silicosis was reported to be 40% and 10%, respectively, and the corresponding times to death after initial exposure were 6.4 years and 9.4 years, respectively [1]. From this point of view, our patients have rapidly progressed (similar to acute silicosis), although they have been classified as chronic disease.

Bakan et al. [1] reported that 6 (19%) of 32 patients died of the disease with the 5-year survival rate and mean survival time after diagnosis being 69% and 78 ± 8 months, respectively [1]. In their updated study, Akgün et al. [2] have reported the mortality rate to be 6%. The associated factors with mortality were an initial FEV1 $\leq 55\%$, an initial FVC $\leq 55\%$, and an initial diffusing capacity of the lungs for carbon monoxide $\leq 60\%$ [1], especially in acute and accelerated silicosis, where the volumes in PFTs markedly decreased in time until death. In our study, 7 (3%) patients died of the disease over a median follow-up period of 5 years. Similar to other studies, an FEV1 $< 44\%$ and an FVC $< 47\%$ were the main factors that were found to be related to mortality. In addition, the presence of severe radiologic findings, such as a higher category of profusions (category 3) and large opacities (especially C type), should be added to these factors.

According to above results, we believe that there are several patients with silicosis under the age of 30 years, and some of them are dead. The only therapeutic intervention for these patients is lung transplantation (LuTx) [12]. There are several small-sized studies on the success of LuTx in silicosis [13], but probably the most important one was a recent large retrospective analysis by Hayes et al. [14]. They have reviewed 7,227 patients who had undergone lung transplantation, of which 24 had silicosis and 29 had non-silicotic occupational diseases. In the Kaplan-Meier analysis, there was no difference in survival between silicosis, non-silicotic occupational diseases, and non-occupational lung diseases. Similarly, Singer et al. [13] reported the 6-month, 1-year, and 3-year

survival after LuTx in patients with silicosis as 86%, 86%, and 75%, respectively, which is comparable with referents (patients with LuTx of the US Organ Procurement and Transplantation Network Registry [OPTN-R], males aged 34-68 years, and body mass index 18-34), which was 89%, 84%, and 67%, respectively [13]. Silicosis is a rare indication for LuTx (0.7%) in developed countries but seems to be a prevalent option in our country [14]. As in other indications of LuTx, appropriate patient selection will decrease perioperative mortality and improve total survival. On the basis of the findings in our study and the data in the literature, a decreased FEV1 and FVC and/or rapidly decreasing volumes together with advanced radiologic involvement would be defined as a poor outcome, and these patients should be evaluated for LuTx. Sidney-Filho et al. [15] have aimed to determine the impact of LuTx on PFTs and survival among patients with end-stage silicosis. They compared spirometric and 6MWT values between the patients with silicosis and with and without LuTx. They observed significant increases in these values at follow-up in the patients who had LuTx ($p=0.036$ and $p=0.151$, respectively). They showed that LuTx offered significant benefits in terms of pulmonary function and survival compared with those for patients with end-stage silicosis and without LuTx [15].

It should be noted that the patients with silicosis commonly have areas of dystrophic calcification in the hilar lymph nodes and densely thickened pleura, which lead to several surgical problems during the exposure of hilum and dissection of the lung from the chest wall. In total, 13% of the patients in our study had pleural thickening, which is not uncommon. There are several studies about the radiologic patterns in silicosis, which show pleural involvement as a serious problem with a prevalence of 34%-58% [16-18]. Conglomerate masses and lymphadenopathies are common and may be related to malignancy; therefore, a bronchoscopy or percutaneous biopsy should be done [16]. Similarly, active tuberculosis may complicate silicosis and could be present in as high as 13% of the patients [1]. In our study, accompanying tuberculosis was present in 3% of the patients. Thus, tuberculosis should be excluded in patients with silicosis during the pre-transplant evaluation. Because of these changes, during the transplantation process, there may be some challenges during the procedure. Jaubert et al. [19] grouped patient with LuTx by occupational lung diseases (OLD) and non-OLD as control. A total of 17 patients (57%) with OLD required intraoperative support with either extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass ($p=0.02$) and 5 (17%) required delayed chest closure ($p=0.05$), which was more frequent than in matched controls. In addition, the operative time was significantly longer in patients with OLD ($p=0.03$). Despite these factors, there were no significant differences in immediate postoperative outcomes, including mechanical ventilator support, postoperative ECMO, and tracheostomy. Chronic lung allograft dysfunction and long-term survival were also similar between the patients and controls. The authors have emphasized that OLDs should not preclude LuTx. Rosengarten et al. aimed to analyze the survival experience following LuTx among patients with silicosis. They observed that the survival advantage was statistically not significant (hazard

ratio 0.6; 95% CI 0.24-1.55) for those undergoing LuTx for silicosis relative to patients with idiopathic pulmonary fibrosis undergoing LuTx [20].

The main limitation of this study was the lack of follow-up data. We only had follow-up data of diagnosed cases. Silicosis can develop or progress after the end of exposure in normal but exposed workers; and thus, the number of patients who develop silicosis after end of exposure can affect the prevalence. We did not follow the normal cases. We had only 7 patients die and did not have the follow-up data on deceased workers and so could not perform an analysis. There is no surveillance system in our country, and we were not able to identify everyone who worked in sandblasting in the area of study. We could not obtain the measurements of dust exposures, which was another limitation of this study.

In conclusion, without institutional preventive measures, personal protection, and surveillance examinations, occupational hazards will continue to cause premature deaths. Silicosis among denim sandblasters is a prototype of an uncontrolled industry in the developing world. The cumulative amount of exposure is the main risk factor for the development of silicosis. Decreased and decreasing lung functions with severe radiologic abnormalities are the main factors related to mortality. LuTx may be an option for advanced disease, and with careful patient selection, the outcomes will be similar to common indications for LuTx.

Ethics Committee Approval: This study was approved by the Ethics Committee of Keçiören Training and Research Hospital (B.10.4.ISM.4.06.68.49).

Informed Consent: Informed consent was obtained from all the subjects who participated in the study.

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