Received: 20 October 2022 | Revised: 25 February 2023 | Accepted: 15 March 2023

DOI: 10.1111/odi.14569

ORAL DISEASES Leading in Oral, Maxillofacial, Head & Neck Medicine WILEY

ORIGINAL ARTICLE

Influence of dental status on outcome after lung transplantation

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Abstract

Introduction: Poor oral hygiene can cause infections and inflammatory diseases. Data on its impact on outcome after lung transplantation (LuTX) is scarce. Most transplant centers have individual standards regarding dental care as there is no clinical guideline. This study's objective was to assess LuTX-listed patient's dental status and determine its effect on postoperative outcome.

Methods: Two hundred patients having undergone LuTX from 2014 to 2019 were selected. Collected data comprised LuTX-indication, periodontal status, and number of carious teeth/fillings. A preoperative panoramic dental X-ray and a dentist's consultative clarification were mandatory.

Results: 63.5% had carious dental status, differing significantly regarding TX-indication ($p < 0.001$; ILD: 41.7% vs. CF: 3.1% of all patients with carious teeth). Mean age at the time of LuTX differed significantly within these groups. Neither preoperative carious dental status nor periodontitis or bone loss deteriorated post-LuTX survival significantly. No evidence was found that either resulted in a greater number of deaths related to an infectious etiology.

Conclusion: This study shows that carious dental status, periodontitis, and bone loss do not affect post-TX survival. However, literature indicates that they can cause systemic/pulmonary infections that deteriorate post-LuTX survival. Regarding the absence of standardized guidelines regarding dental care and LuTX, we strongly recommend emphasizing research in this field.

KEYWORDS
CF, COPD, dental status, ILD, infection, lung transplantation, oral hygiene, panoramic dental X-ray, tooth extraction

Maximilian Vorstandlechner and Katharina T. Obermeier contributed equally to this study, thus both are considered to be first author of the publication.

1 | INTRODUCTION

For some pulmonary diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), hypersensitivity pneumonitis (HP), and other rare lung conditions, lung transplantation (LuTX) may represent the only remaining curative therapeutic approach when other treatment options are exhausted (Gottlieb et al., 2014). Not only the transplantation (TX) itself but also especially the years of illness, the procedure for listing, the preparation for surgery, the follow-up, and immunosuppressive therapy are a great physical and psychological challenge for patients (Goldbeck et al., 2014). Among the feared complications of TX and the subsequent necessary lifelong immunosuppressive therapy are infectious diseases of viral, bacterial, or even parasitic origin. Infection under immunosuppression can progress into sepsis and thus potentially life-threatening diseases (Napolitano, 2018).

The urogenital system, long-term airway intubation, central venous lines, and chronic wounds are among others to be considered as potential gateways for harmful germs to spread (Gotts & Matthay, 2016). However, the oral cavity and teeth can be an underrated infectious focus (Aas et al., 2005). Bacteria can spread via defects in the oral mucosa (Wilson et al., 2007) or swallowing of infested saliva. Aspiration poses a threat of continuously spreading bacteria due to the direct link of the oral cavity to the respiratory tract (Svanes et al., 2018; Whiteson et al., 2014). As shown before in other studies, oral hygiene, dental, and periodontal status seem to have an influence on pulmonary infections such as pneumonia and COPD (Paju & Scannapieco, 2007). Guggenheimer et al. (2005) could even show by performing a nationwide survey in the US, that 27% of the surveyed centers reported posttransplant sepsis cases linked to dental infections.

As far as periodontal disease is concerned, previous studies have already shown that it can have a systemic impact on the body. Cullinan & Seymour describe the association of periodontal disease, systemic inflammation, and atherosclerosis, as there were oral bacteria found in coronary plaques (Cullinan & Seymour, 2013). Furthermore, if left untreated, periodontitis can result in the spreading of gram-negative bacteria throughout the body and consequently lead to bacteremia and sepsis (Herrera et al., 2000; Sato et al., 2021).

Even though assessment of patients' dental status and subsequent treatment is considered to be a mandatory prerequisite for solid organ transplantation in most transplantation centers (Guggenheimer et al., 2003) and the ISHLT recommends an annual dental checkup for patients on the waiting list for a cardiac transplant (HTX) (Mehra et al., 2006), there are no general or practical clinical guidelines available regarding LuTX. A survey performed by Ziebolz et al. (2011), showed that 89% of the participating transplant centers demanded preoperative assessment of the dental status, of whom only 67% were in contact with the patients' dentist. Furthermore, best to our knowledge, there is barely any preexisting data for patients' outcome after LuTX considering the preoperative dental status and its influence on post-TX survival.

2 | AIM/OBJECTIVE

The aim of this study was to collect data on preoperative dental status, periodontal disease, and bone loss in order to assess the overall condition of patients' oral cavity and to find out if there is an influence on postoperative survival and outcome. In addition, indications for TX and their relative diagnosis-related groups were identified to examine the effect of the underlying condition on the dental status.

We hypothesized that factors contributing to a bad overall condition of the oral cavity such as carious dental status, periodontal disease, and bone loss as a sign of an ongoing in-depth infection, altogether in connection with an impaired immune response post-TX, could facilitate the spreading of potentially harmful bacteria and fungi on a direct pathway into the respiratory tract by aspiration or as a systemic infection.

3 | MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the Ludwig Maximilian University Hospital of Munich, Germany (Munich, Germany; Project-Nr.: 22–0466). The present retrospective cohort study includes 200 patients, who underwent LuTX in our hospital during a 6-year period from 2014 to 2019. Only patients who had a preoperative panoramic dental X-ray, that has been conducted in our department, and patients with a valid follow-up have been included. All patient records, comprising doctors' notes, discharge papers, radiographs, survival data, and data of death were reviewed retrospectively. Overall, data were collected on dental status, number of (root) fillings, number of teeth extractions, periodontal status, bone loss of the jawbone, and caries infestation.

The extent of bone loss and resorption was evaluated according to the following method. Radiographic-based periodontal bone loss (PBL) method radiographic examination followed the standardized protocol by Rydén et al. (2016). Third molars were excluded, resulting in a possible maximum of 28 teeth. Dental implants were not examined. The PBL was assessed by measuring the total root length (distance from the tooth's apex to the cementoenamel junction) and the total bone height (distance from the tooth's apex to the marginal bone crest), in each tooth. For these measurements, the arithmetic mean was then calculated and used as a measure of proportion (%). Based on the PBL, in percentage, patients were then divided into different groups: Healthy periodontium (PBL ≥ 70%) and severe periodontitis (PBL < 70%).

Additionally, we investigated preknown diseases, the condition indicating TX, date of surgery, cause of death, and survival time. For data analysis, all patients were considered for the survival analysis. Censoring was made automatically by performing statistical analysis.

3.1 | Statistical analysis

Statistical analysis was conducted using R Studio Version 1.3.1093 (Free Software Foundation). Normally distributed data were

presented using mean ± standard deviation (SD). Non-normal distributed data were illustrated by depicting median and interquartile range. All patients underwent survival analysis by performing Kaplan–Meier estimator. Statistical significance was defined as $p < 0.05$. Comparison of mean values of two groups was done by performing the *t*-test. ANOVA with Bonferroni post-hoc (Tukey) test was used for comparing multiple mean values. The influence of the underlying diagnosis leading to TX, patients' gender, age at TX, caries, periodontal status, and bone loss was examined.

To identify the strongest risk factors for a deteriorated rate of survival and subsequently patients' death among the listed above, we used a logistic regression model and chi() test.

4 | RESULTS

4.1 | Study population

Overall 200 patients were included in this study. Mean follow-up time was 2.3 ± 1.7 years with a maximum of 5.9 years. One hundred and eleven patients were male (55.5%), 89 patients female (44.5%). The mean age at the time of TX was 52.4 ± 11.8 years with a range from 20 to 69 years. On an annual average, 33.3 ± 11.3 patients (range from 22 to 53) received a new organ from a deceased donor, of which most had an ILD as an underlying condition (37.5%; 75 patients).

In order to achieve adequate immunosuppression and avoid graft failure (GF), patients received a combination of a calcineurin inhibitor (Tacrolimus), Mycophenolat-Mofetil (MMF), and prednisolone as post-TX immunosuppressive medication. Postoperatively, all patients were initially admitted to the intensive care unit (ICU) and, after successful weaning and extubation, transferred to the general ward. Throughout the hospital stay further examinations were performed to look for signs of early lung allograft rejection, including pulmonary function tests (PFT) and bronchoscopy with transbronchial biopsy (TBB).

Fifty-two patients (26.0%) died during follow-up time. The observed survival rates were 94.5% after 90 days, 85.7% after 1 year, and 56.1% after 5 years. We investigated the most common causes of death after LuTX, identifying multi organ failure (MOF) as the most frequent cause, accounting for 32.7% (17 patients) of all deaths, followed by GF (10 patients; 19.2%).

4.2 | Overview of teeth's condition

All patients received a preoperative panoramic dental X-ray. On average, each patient had 22.9 ± 9.7 teeth (range from 0 to 32) preoperatively. Mean total tooth count in COPD patients as depicted in Table 1 was significantly reduced in comparison to other groups. Figure 1 shows the indication for LuTX in relation to a carious dental record.

The apical abnormalities in panoramic X-ray were also evaluated. In total 30 patients (15%) showed apical radiolucency most likely to be compatible with apical granuloma. In eight patients (4%), radiopacity was found and most likely to be interpreted as sclerosis. Due to the retrospective design of the study, no histopathological examination results are available for these lesions of the jaw.

Overall 127 patients (63.5%) had carious lesions with a mean of 3.3 ± 2.4 teeth affected per patient (range from 0 to 15). Thirty-one of 48 patients, hence 64.6% of all patients suffering from COPD, suffered from decayed dental status, being surpassed only by ILD-patients (53 of 75 cases, 70.1%). By contrast, carious lesions in patients with CF were only found in 30.1% within this particular, diagnosis-related group. We could show that the underlying diagnosis for LuTX related significantly to a carious dental status ($p = 0.01$).

In addition to the underlying disease affecting patients' dental status, age also played a major role in developing carious lesions. Mean age at the time of TX differed from 58.2 ± 7.3 years (COPD) and 56 ± 7.5 years (ILD) to 30.6 ± 6.2 years (CF) as illustrated in Figure 2. We divided patients according to their age into groups of a 10-year period. Results showed that increasing age is related to a poorer dental status. People aged 61–70 had the highest rate of carious teeth at 78.0% (46 of 59), compared with 14.3% (3 of 18) in the group of 21–30-year-olds. The same applies to periodontitis (88 patients, 44.0%, with a mean of 1.8 ± 3.1 teeth affected). The age group from 61 to 70 years old had a significantly higher number of periodontitis cases (34 of 59; $p < 0.01$) compared with other age groups. A statistically significant relation between the underlying condition and periodontitis was not to be found. Regarding bone loss, there was no significant difference noticeable in age or diagnosis-related groups.

All three seem to have an influence on each other. Performing chi-square testing, we could show that patients with signs of bone loss and periodontitis at the same time are more likely to also suffer from decayed dental status ($p < 0.01$).

Survival analysis, performed by using Kaplan–Meier estimator, regarding dental status ($p = 0.86$), periodontal status ($p = 0.73$), and bone loss ($p = 0.59$) as illustrated in Figure 3a–c, showed no statistically significant effect on patients' survival and outcome compared to their respective reference group. Regarding preoperatively performed dental treatment, the mean number of fillings was 9.2 ± 6.3 (range from 0 to 30) and each patient had on average 1.9 ± 2.2 root fillings (range from 0 to 16). The number of preoperative fillings or dental restorations did not show any impact on survival post-TX.

4.3 | Smoking

Seventy eight patients had a history of smoking with an average of 28.4 ± 3.6 pack years. The patient group with the highest number of former smokers was COPD patients (95.8%; 46 of 48). The percentage of former smokers in this particular group was found to be significantly higher ($p < 0.001$) than in patient groups with other underlying conditions. The same appears to be the case for elderly patients, as the number of smokers differed significantly ($p < 0.01$) according to their age, peaking in age group

TABLE 1 Underlying condition indicating lung transplantation.

	Overall	CF	COPD	ILD	HP/LAM	GF	PH	Sarc.	Other	*p*-Value
Patients *n* (%)	200 (100.0%)	17 (8.5%)	48 (24.0%)	75 (37.5%)	24 (12.0%)	11 (5.5%)	10 (5.0%)	6 (3.0%)	9 (4.5%)	
Age (mean)	52.4 ± 11.8	**30.6 ± 6.2**[a]	58.2 ± 7.3	56.6 ± 7.5	52.0 ± 11.3	45.5 ± 13.5	42.8 ± 14.1	52.2 ± 4.9	48.0 ± 10.5	
Teeth (mean)	22.9 ± 9.7	29.2 ± 7.76	**16.1 ± 10.1**[b]	23.9 ± 9.3	24.5 ± 6.7	22.8 ± 10.9	29.3 ± 4.1	28.8 ± 1.7	23.1 ± 8.4	
Pat. with fillings *n* (%)	174 (87.0%)	8 (47.0%)	42 (87.5%)	71 (94.7%)	22 (91.7%)	9 (81.1%)	9 (90.0%)	6 (100.0%)	7 (77.8%)	0.06
Fillings (mean)	9.2 ± 6.3	4.7 ± 6.2	8.8 ± 6.3	10.4 ± 5.9	10.3 ± 6.4	8.2 ± 6.4	7.6 ± 5.6	13.2 ± 6.1	8.4 ± 7.7	
Pat. with caries, *n* (%)	127 (63.5%)	4 (23.5%)	31 (64.4%)	53 (68.0%)	17 (70.8%)	5 (45.5%)	5 (50.0%)	5 (83.3%)	7 (77.8%)	**0.01**
Teeth affected (mean)	3.3 ± 2.4	2.8 ± 1.5	4.1 ± 3.2	3.0 ± 1.9	3.4 ± 2.6	2.6 ± 1.1	2.8 ± 1.6	5.0 ± 2.4	2.1 ± 0.9	
Periodontitis-Pat., *n* (%)	79 (39.5%)	1 (5.9%)	20 (41.7%)	30 (40.0%)	12 (50.9%)	5 (45.5%)	2 (20.0%)	2 (33.3%)	7 (77.8%)	**0.02**
Teeth affected (mean)	4.5 ± 3.5	2.0 ± 0	4.6 ± 5.4	4.4 ± 2.3	5.2 ± 2.2	1.8 ± 1.1	4.5 ± 5.0	3.0 ± 1.4	6.1 ± 4.2	
Bone-loss-Pat., *n* (%)	41 (20.5%)	1 (5.9%)	8 (16.7%)	19 (25.3%)	6 (25.0%)	2 (18.2%)	1 (10.0%)	0 (0.0%)	4 (44.4%)	0.22
Smokers, *n* (%)	78 (39.0%)	2 (11.8%)	46 (95.8%)	21 (28.0%)	3 (12.5%)	3 (27.3%)	0 (0.0%)	1 (16.7%)	2 (22.2%)	**<0.001**
Pack years (mean)	28.4 ± 3.6	6.0 ± 0	33.0 ± 2.8	22.2 ± 1.2	15.3 ± 0	40.5 ± 0.6	0.0	25.0 ± 0	0.0	
CLAD, *n* (%)	35 (17.5%)	1 (5.9%)	9 (18.8%)	20 (26.7%)	1 (4.2%)	3 (27.3%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0.06
Time to CLAD (years; mean)	1.8 ± 1.2	0.2 ± 0	2.0 ± 1.6	1.9.	0.1 ± 0	1.4 ± 0.4	NA	1.7 ± 0	NA	

Note: Values are illustrated as number (*n*) or percentage of patients (%) or mean ± standard deviation (mean ± sd). Bold font was chosen to highlight significant differences.

Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; LAM, lymphangioleiomyomatosis; LTR, lung transplant rejection; LuTX, lung transplantation; Pat., patient(s); PH, pulmonary hypertension; Sarc., sarcoidosis.

[a] $p < 0.0001$ (vs. COPD, ILD, LTR, sarcoidosis), $p = 0.014$ (vs. PH).

[b] $p < 0.0001$ (vs. CF, ILD, PH); $p = 0.02$ (vs. sarcoidosis).

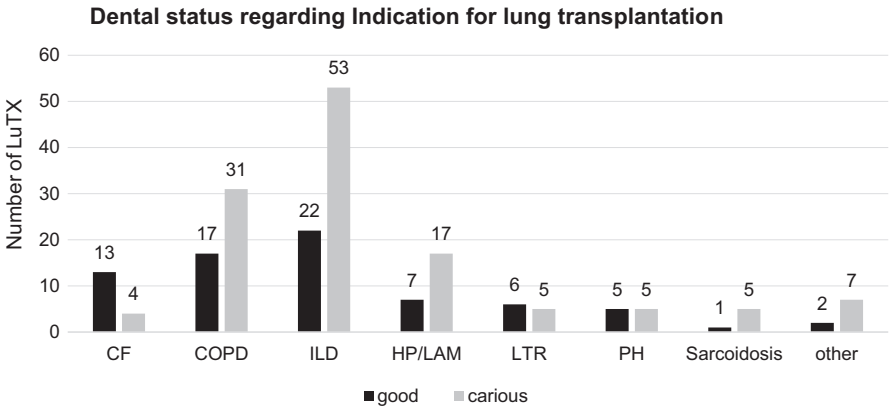

FIGURE 1 Dental status was examined pretransplant. Values are illustrated as absolute numbers. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; LAM, lymphangioleiomyomatosis; GF, graft failure; LuTX, lung transplantation; PH, pulmonary hypertension.

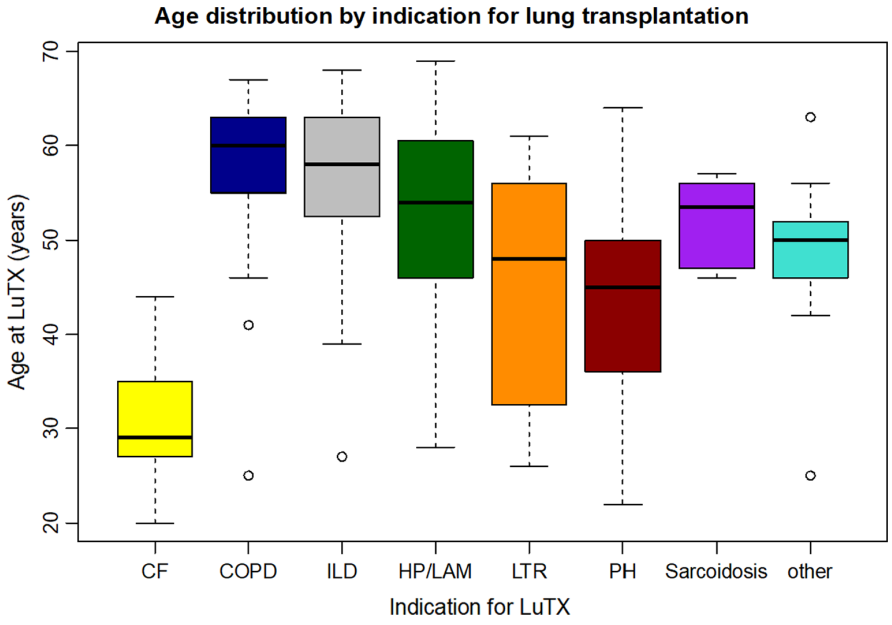

FIGURE 2 Boxplot; mean age at time of lung transplantation by indication (years). CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; LAM, lymphangioleiomyomatosis; GF, graft failure; LuTX, lung transplantation; PH, pulmonary hypertension.

61–70 (49.2%, 29 of 59). In comparison, only 19.7% (13 of 66) of the patients younger than 50 years at the time of TX reported having a history of smoking. However, smoking showed no significant effect on patients' dental status ($p = 0.97$). Survival analysis, comparing patients being exposed to tobacco in the past to a nonsmoking reference group, showed a trend ($p = 0.11$) toward a deteriorated survival for former smokers in the long-term follow-up after LuTX (Figure 3d).

4.4 | Corticosteroids

To see if there was a connection between the intake of corticosteroids and the extent of bone loss in the panoramic dental X-ray, we checked patients' medical records on preoperative intake of prednisone, which was often necessitated by the underlying condition such as COPD or ILD. One hundred and ten of 200 patients (55.0%) were prescribed prednisone at a mean dose of 6.7 ± 8.0 milligrams as permanent medication, most of which suffering from ILD (42.7%; 47 of 110). Preoperative oral intake of corticosteroids showed no influence on bone loss.

4.5 | Chronic lung allograft dysfunction (CLAD)

Of the 200 patients participating in the study, 35 (17.5%) witnessed a decreasing forced expiratory volume in 1 s (FEV1) when performing pulmonary function tests, eventually resulting in bronchiolitis obliterans syndrome (BOS) during follow-up after LuTX. Mean time to onset of BOS was 1.8 ± 1.2 years. Regarding the question if there was any factor potentially influencing the development of BOS, there was no association with the condition of the oral cavity pre-TX, smoking or the preoperative intake of corticosteroids. Nevertheless, it became apparent that the underlying disease seemed to play a role; however, not significantly ($p = 0.06$), as retransplantation (re-TX) due to preceding GF favored the onset of BOS. 27.0% of patients having undergone re-TX, necessitated by developing GF prior to their second LuTX, developed BOS after re-TX at some point. It

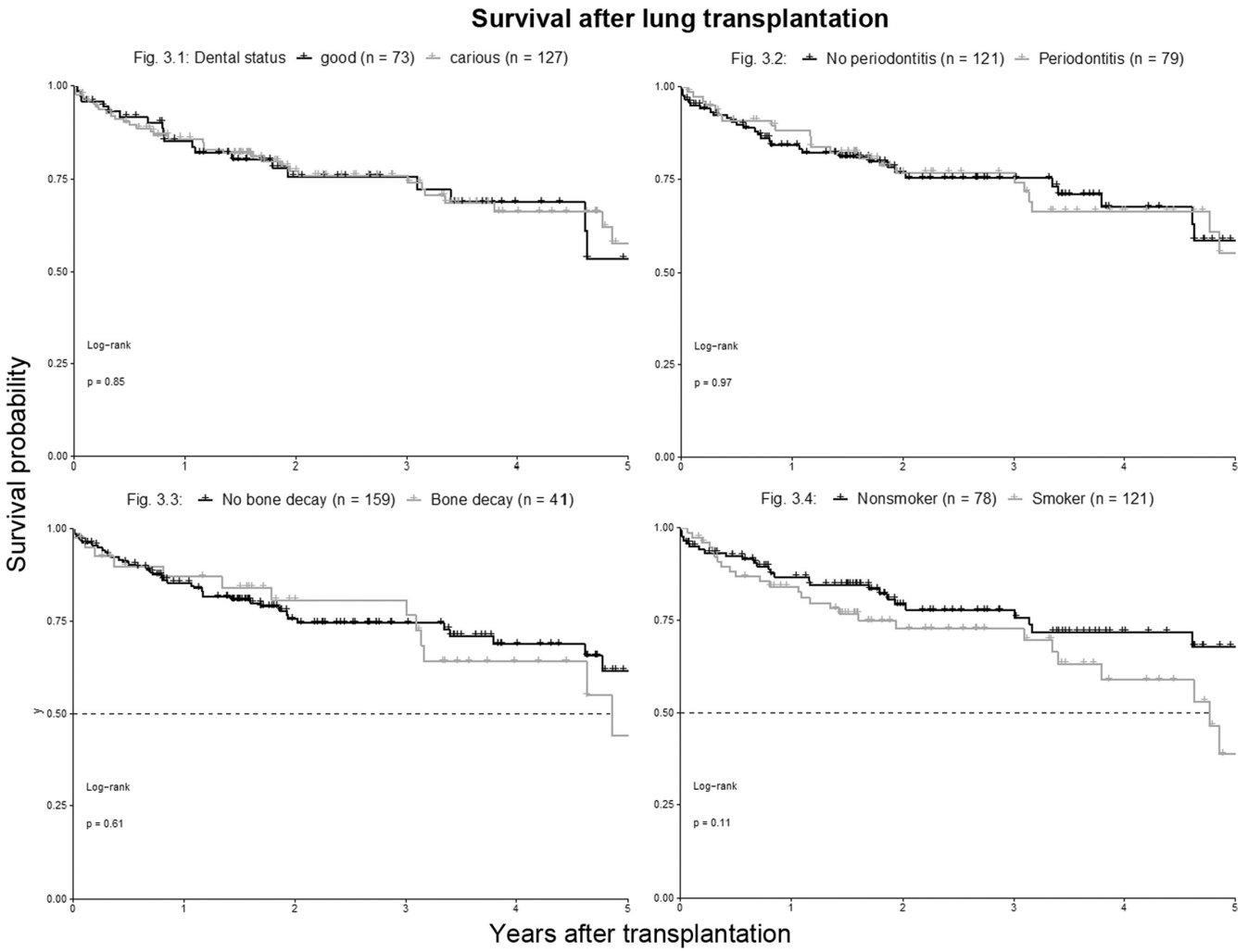

FIGURE 3 Kaplan–Meier estimator, 5-year survival curves. (a) Dental status; (b) periodontitis; (c) bone loss; (d) smoking.

has to be taken into consideration that the small sample size (GF; $n = 11$) can lead to a distorted result.

5 | DISCUSSION

Given the very specialized nature of lung transplantations in the field of medicine and the fact that there are only a few transplant centers on a nation- and European-wide scale performing this delicate procedure, data on patients having received a donor lung is scarce. Literature review shows that there was only very little research performed on dental status, condition of the oral cavity and their association with the outcome after LuTX. Best to our knowledge, up to this point there was no research performed on the question regarding the influence of preoperative dental and periodontal status on postoperative survival after LuTX.

Our study shows that oral hygiene is insufficient prior to TX. A high number of patients on the waiting list for a donor lung is likely to have carious dental status and show signs of periodontal problems. Especially in certain groups like COPD- or ILD-patients, a significant number of people suffering from decayed dental status was to be found. Trying to figure out the reasons for this insufficiency in health of the oral cavity, we came up with two possible explanations.

First of all, there seems to be missing awareness for the association between the condition of the oral cavity and teeth and its effect on systemic diseases like infections and atherosclerosis. Especially in the case of recipients of donor organs, existing literature already points out the lack of information regarding "oral health and SOT" as Ziebolz et al. could show in a survey performed in 2011. Only a minor fraction of patients interviewed, reported to have received comprehensive information concerning this topic (Ziebolz et al., 2011) and the subsequent assumed increase of risk in odontogenic infections in transplant patients (Melkos et al., 2005). Secondly, the absence of a general clinical guideline or consensus concerning pre- and post-operative dental care and management of oral health issues, impedes a standardized approach for involved doctors in a field, where interdisciplinary collaborative work between the transplant team, physicians and dentists plays a crucial role to ensure the best possible medical care.

Retrospective analysis of the underlying survival data in our study shows that there was no significant influence on the probability of post-TX survival in association with the preoperative dental and periodontal status and the degree of bone loss. But even though the survival curves are neither statistically significant for periodontitis ($p=0.73$) nor for bone loss ($p=0.59$), there was a slight trend noticeable for the two to have a negative effect on survival probability. A weakness of the study is that the bone lesions could not be histopathologically diagnosed due to the retrospective design. Prospective studies involving submission of the tissue, diagnosis and their influence on survival considering the WHO classification of odontogenic tumors 2022 should be performed.

On a side note, it should be mentioned that the collected data comes from patients treated in a transplant center, where every patient is required to see a dentist before primary surgery as a prerequisite to TX. If this was not the case, dental and periodontal status could be worse, possibly leading to a deteriorated outcome as studies suggest that TX-patients who underwent preoperative dental treatment had a lower incidence of graft rejections or postoperative infectious complications (Melkos et al., 2005).

6 | CONCLUSION

In conclusion, this study shows deficits in the condition of the oral cavity before LuTX. The original hypothesis could not be confirmed, as there was no significant influence of the preoperative dental and periodontal status on the outcome and survival after LuTX. Nevertheless, it was revealed that there was definitely a lack of unified clinical guidelines for oral health before and after TX.

Research showed that only single center studies have been performed so far. As multiple authors have described before, the lack of general clinical guidelines, the individuality of the center standards in pre- and post-TX patient care and the different setup and type of studies conducted so far, makes it difficult to draw comparisons and conclusions. Consequently, further prospective multicenter studies should be conducted, as this could be an effort to increase the sample size of patients undergoing this very rarely performed and delicate procedure. We concur that interdisciplinary joint effort between the transplant team of surgeons and specialists for internal medicine, the physician and the treating dentist should be emphasized. Early and thorough education of patients before and after TX regarding the association of oral health and lung transplantation could be a relatively uncomplicated and simple measure to improve the outcome after LuTX and eliminate one risk factor. In order to meet this need, standardized collaborative guidelines regarding the pre- and post-operative management of oral health should be established, empowering all health-care personnel involved in the process of TX to provide the best possible medical care.

AUTHOR CONTRIBUTIONS

MV and KTO contributed equally to this study, thus both are considered to be first author of the publication; substantial contribution to concept, design, conduct, analysis, and interpretation of the study. Concept/design: MV, KTO. Data collection: Maximilian Vorstandlechner, KTO, CPS, JMF, RAH, SM, TV, IM, RT. Data interpretation: MV, KTO, TK, WS. Statistics: MV. Critical revision: TK, WS.

ACKNOWLEDGEMENTS

We would like to thank Alma Sisic (Transplantation Center Munich (LMU)) for her contribution to our study by providing crucial data. Additionally, we are grateful for Rainer Miksch's (MD) and Mareen Braunstein's (MD) support and interest in our study.

CONFLICT OF INTEREST STATEMENT

All of the authors involved and mentioned above have reported no conflict of interest and agreed to the submission of the underlying manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING INFORMATIONS

The authors of this study have no sources of funding to disclose.

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How to cite this article: Vorstandlechner, M., Obermeier, K. T., Schneider, C. P., Fertmann, J. M., Smolka, W., Michel, S., Veit, T., Irlbeck, M., Tomasi, R., Hatz, R. A., & Kauke, T. (2023). Influence of dental status on outcome after lung transplantation. *Oral Diseases*, *00*, 1–8. https://doi.org/10.1111/odi.14569