Chronic Pain After Lung Transplantation and Its Impact on Quality of Life: A 4-Year Follow-up

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ABSTRACT

Aiming to investigate the prevalence of chronic pain and its impact on quality of life of lung transplantation (LTx) recipients, we performed a transversal study collecting data using a standard interview model in 2 different periods: first, in 2016 we studied LTx recipients after 3 to 11 months of the transplantation; and second, in 2019, we studied the same patients after 39 to 55 months of transplantation surgery. The chosen questionnaires were the Brief Pain Inventory and Short-Form Health Survey. Chronic pain was identified in 47.2% of the analyzed recipients at the initial interview and in 40.7% at the second evaluation. In both periods, the domain quality of life was the most affected in contrast to functional capacity, which was the least affected. On the first analysis, a moderate negative correlation was found between pain intensity and functional capacity domains (-0,42/$P = .010$), pain (-0,46/$P = .005$), and mental health (-047/$P = .004$); meanwhile, the second survey showed a moderate/high negative correlation for most of the domains, except for the mental health (-0,036/$P = .120$). We conclude that the prevalence of chronic pain after LTx is high, and the pain intensity had a moderate negative correlation with domains such functional capacity, mental health, and pain at the first analysis in contrast to the moderate/high negative correlation for almost every domain, except mental health, at the second analysis.

LUNG transplantation (LTx) is a well-known modality of treatment to improve the quality of life (QOL) and survival of patients with end-stage lung diseases, which are refractory to the conventional treatments [1,2]. For the success of this procedure, pain control is an essential factor of postoperative (PO) care, which can alter the recovery of these patients because some PO complications are strictly related to inadequate analgesia or difficulty with effectively coughing, deep breathing, and expectoration, which can lead to hypoxia, secretions retaining, pneumonia, and acute respiratory failure. Moreover, sufficient evidence exists in the literature that the proper analgesic management of acute pain can reduce the risk of chronic pain development [3,4].

The PO or posttraumatic chronic pain is defined for its persistence after the normal healing process beyond 3 months of the initial insult (including traumatic injury, surgery, or even burn injuries) [5].

Of all surgical procedures, studies demonstrate that patients who are submitted to surgical intervention in the

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thoracic wall have an increased risk of developing chronic pain (14% to 83% of cases) in comparison to other groups [6.7]. Focusing on LTx recipients, the few published studies report a prevalence of 49% to 59% of pain after 3 months of the procedure [8,9].

The high prevalence of chronic pain after LTx alerts us of the necessity of an accurate evaluation and special care in this group because their analgesic control is difficult and can lead to functional, psychological, social, and behavioral impairment, affecting their QOL and alienating them from their routine activities [10,11]. Because the diagnosis of chronic pain remains a challenge for the health care team, evaluation tests are important to humanized care and in planning proper interventions [12].

One of the goals of pain management is QOL improvement. Studies prove that the occurrence of pain is associated with a decrease in QOL in LTx recipients [8,13]. Therefore, in addition to evaluating the prevalence of PO pain after LTx, it is interesting to investigate the impact of this symptom in QOL with the aim of developing strategies to minimize these damages.

Our hypothesis is that the prevalence of chronic pain is high after LTx and that there is a correlation between the pain and the decrement QOL of these patients; thus, the goals of this study are defining the prevalence of chronic pain and its impact on QOL of LTx recipients.

METHODS

We performed an observational transversal study, approved by the Research Ethics Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (1.329.526), and all participants signed an informed consent before assessment.

The population of the study was compounded by lung transplanted patients. The data were collected in 2 different PO periods: the first analysis, in 2016, studied patients after 3 to 11 months of LTx surgery; and the second analysis, in 2019, evaluated patients after 39 to 55 months of LTx surgery.

The chosen instruments for evaluation were the Brief Pain Inventory (BPI), the Short-Form Health Survey (SF-36), and another formulary developed by the authors for collection of data referent to sociodemographics, clinical aspects before LTx, and intraoperative information. After signing the informed consent form, the patient was instructed regarding the evaluation instruments, and he or she (or guardian) filled out the instruments without the participation of the researchers so that there was no interference in the results.

The BPI instrument was developed to provide information about pain intensity and its interference on QOL. It results in a multidimensional, short, and easy-to-understand score, which was translated and adapted to Brazilian Portuguese [14]. It comprises 15 items, subdivided in 2 parts: first an evaluation of pain intensity (8 items) and second an evaluation of pain interference in QOL (7 items; general activities, humor, ability to walk, ability to sleep, ability to work, relationships with other people, and enjoying life). Pain intensity is assessed by the patient with reference to the past 24 hours on a numerical scale from 0 (no pain) to 10 (as strong as imaginable). Interference in aspects of life is also assessed on a numerical scale from 0 (no interference) to 10 (complete interference).

The SF-36, used to assess QOL after LTx, is the most used instrument in critically ill patients in international studies and is also adapted and validated for the Brazilian culture [15]. SF-36 evaluates 8 domains: functional capacity (10 items), physical aspects limitation (4 items), pain (2 items), general health status (5 items), vitality (4 items), social aspects (2 items), emotional aspects (3 items), and mental health (5 items), and provides a comparative assessment between current health conditions and 1 year earlier. It presents a final score from 0 to 100 (obtained by the Raw Scale calculation), where 0 corresponds to the worst general health condition and 100 to the best health state.

In addition to these data, we verified, in the pain control group's registration files of the institution, the information about pain at rest and movement in the second PO and seventh PO, by using the numerical verbal scale (NVS) to quantify daily pain. It is a 1-dimensional scale (evaluates only 1 pain dimension) and aims to measure pain intensity in numerical values of 0 (no pain) and 10 (maximum pain imaginable). It has an accurate pain expression and is easy to use. This scale does not necessarily require the patient to have eye contact with the scale; it can simply be spoken to him or her, making it possible and simple for illiterate or visually impaired individuals [16].

After collection, all data were stored in a data bank (Excel, Microsoft, Redmond, Wash, United States). Qualitative sociodemographic characteristics were informed in absolute frequencies (n) and relative frequencies (%), and the quantitative variables were presented as mean, standard deviation (SD) or median, and interquartile range according to its distribution. Tests for statistical inferences used were the Mann-Whitney U test, Kruskal-Wallis test, and Pearson correlation. It was considered a significant P value of $< .05$. For statistical analysis, we used Statistical Package for the Social Sciences (SPSS), version 18.0 (SPSS Inc., Chicago, Ill, United States).

RESULTS

The inclusion of patients occurred between June 2015 to October 2016. In this period, 41 LTx were performed; of these, 5 patients died before completing the third month of transplantation, thus the initial evaluation consisted of 36 patients. In the second analysis, 9 patients died during the follow-up, and therefore the final sample included 27 patients.

In sociodemographic analysis, there was a predominance of female sex, and the mean age was 36 years. Most of these patients (69.4%) had a history of past surgical procedures before LTx, and of these 5.6% were thoracic surgeries. Regarding medication use, 27.8% of patients reported using drugs to treat anxiety and depression, and no patient was on opioids. Pretransplant pain was reported in 38.9% of patients. The mean waiting time for transplantation was 21.1 months (Table 1).

Most of the patients (88.9%) underwent bilateral transplantation, and the main surgical access was the bithoracotomy (83.3%). The mean chest tubes duration was 14.1 days, and 30.6% of patients had some type of PO complication like exploratory laparotomy due to bowel obstruction (11.1%), graft dysfunction or acute cellular rejection (8.3%), arrhythmia (5.6%), acute ischemic stroke (2.8%) and altered level of consciousness (2.8%) (Table 2).

Table 1. Distribution of Lung Transplantation Recipients According to Sociodemographic Characteristics

Variable	n	%
Sex (female/male)		
First analysis (after 3-11 months of LTx)	21/15	58.3/41.7
Second analysis (after 39-55 months of LTx)	18/9	66.6/33.4
Age in years, mean (SD)		
First analysis	36.2 (14.4)	
Second analysis	37.7 (15.1)	
Arterial hypertension	7	19.4
Diabetes mellitus	4	11.1
Depression/anxiety	10	27.8
Sedentary lifestyle	18	50
Previous surgery	25	69.4
Previous thoracic surgery	2	5.6
Waiting time in months, mean (SD)	21.1 (12.1)	
Lung transplantation indication		
Bronchiolitis/bronchiectasis	11	30.5
Cystic fibrosis	10	27.8
Lung emphysema	5	13.9
Lung fibrosis	3	8.4
COPD	2	5.5
Lymphangioleiomyomatosis	2	5.5
Airway burn injury	1	2.8
Silicosis	1	2.8
Berylliosis	1	2.8

Abbreviations: COPD, chronic obstructive pulmonary disease; LTx, lung transplantation; SD, standard deviation.

For acute PO pain, according to NVS, the mean intensity of rest pain in the second PO was 1.8 ± 2.4 and 3.8 ± 2.8 for movement-evoked pain. In the seventh PO, there was a reduction of the mean pain score at rest to 1.2 ± 2.1, and movement-evoked pain remained the same values (3.8 ± 2.8). All transplanted recipients used a patient-controlled analgesia (PCA) pump, generally administered through epidural route (75%), with a solution containing fentanyl, 0.05 mg/mL, and bupivacaine, 5 mg/mL, diluted in 200 mL of normal saline, or intravenous route (25%), with a solution containing morphine, 0.5 mg/mL, diluted in 95 mL of normal saline. The daily dose received, independent of the administration route, changed according to the patient pain and PCA pump programming. Aside from the PCA, all patients received multimodal analgesia with nonopioid drugs and other adjuvants. The duration of PCA pump was variable because it is the institution's routine to maintain this analgesia until the chest tubes are removed.

Evaluating chronic pain in the post-transplant outpatient return performed between 3 and 12 months (analysis 1), 47.2% of the patients reported pain, and of these, 64.7% reported mild pain intensity and 35.3% reported moderate to severe pain. In the second analysis, 40.7% of patients still had pain. The mean intensity of pain evaluated with BPI at first return was 1.9 ± 2.7 and 1.5 ± 2.4 at the second evaluation. Comparing the mean scores of pain (BPI) according to sex, women presented more intense pain than men (2.2 vs 1.5) however without statistical significance ($P = .715$). Patients with prior surgical intervention presented an inferior mean pain intensity compared with those without previous surgery (1.5 vs 2.8; $P = .057$). The remaining clinical characteristics did not influence pain intensity.

Assessing the surgical procedure aspects, we identified an association between the surgical access and functional capacity and physical aspects limitation. Patients submitted to posterolateral access presented greater impairment in the functional capacity domain (63.3%), followed by the anterolateral access (66.7%) and bithoracotomy (88.5%), and the difference between the groups was significant ($P = .037$). Regarding physical limitation aspects domain, patients submitted to anterolateral (25.0%) and posterolateral (50.0%) thoracotomies presented greater impairment in comparison to bithoracotomy (80.8%), and the difference between the groups was statistically significant ($P = .020$). In addition, patients undergoing posterolateral thoracotomy observed more intense pain (5.0%) than patients undergoing bithoracotomy (1.6%) or anterolateral thoracotomy (1.7%), without statistical significance difference ($P = .368$).

Table 2. Distribution of Lung Transplantation Recipients According to Surgical Characteristics and Surgical Outcomes

Variable	n	%
Intraoperative		
Lung transplantation modality		
Unilateral	4	11.1
Bilateral	32	88.9
Surgical access		
Bithoracotomy	30	83.3
Anterolateral thoracotomy	3	8.3
Posterolateral thoracotomy	3	8.3
Surgical time in hours, mean (SD)	8.6 (1.6)	
Anesthetic time (in hours)	11.8 (1.8)	
Cardiopulmonary bypass	4	11.1
Ischemic time right side in minutes mean (SD)	363.3 (94)	
Ischemic time left side in minutes mean (SD)	383.7 (104.3)	
Postoperative		
Mechanic ventilation duration in minutes mean (SD)	2046.7 (1726.7)	
Chest tube duration in days, mean (SD)	14.1 (5.2)	
Complications	11	30.6
Exploratory laparotomy (acute bowel obstruction)	4	11.1
Primary graft dysfunction/acute cellular rejection	3	8.3
Arrhythmia	2	5.6
Acute ischemic stroke	1	2.8
Altered level of conscience	1	2.8
Acute cellular rejection	9	25
Hospitalization time in days, mean (SD)	25.2 (11.4)	
Lung transplantation survival in months, mean (SD)	4.6 (2.4)	

Abbreviation: SD, standard deviation.

Table 3. Mean Scores of Domains in Short-Form Health Survey 36

Domains	Mean (SD)		P Value
	Analysis 1	Analysis 2	
Functional capacity	84.6 (18.0)	76.1 (26.6)	.070
Physical aspects limitation	73.6 (40.5)	68.5 (44.7)	.389
Pain	73.3 (24.6)	61.7 (29.2)	.036
General health status	73.5 (13.5)	60.0 (24.4)	.011
Vitality	76.3 (19.4)	63.7 (26.4)	.007
Social aspects	76.0 (29.0)	69.9 (28.8)	.042
Emotional aspects	77.8 (39.0)	66.6 (45.3)	.589
Mental health	76.1 (20.6)	67.7 (25.3)	.083

Abbreviation: SD, standard deviation.

Regarding QOL, the results of both evaluations were equal. The domains of pain (73.3-61.7; $P = .036$) and general health (73.5-60; $P = .011$) were the most affected by pain, with significant results. Functional capacity was the domain that experienced the least pain interference (84.6-76.1; $P = .070$) (Table 3). In addition, in the second evaluation, there was a reduction in scores (Raw Scale) in all domains, showing a worsening of the general state over the years. Considering the correlation between pain intensity and QOL domains (SF-36), in the first analysis, there was a moderate and significant negative correlation among pain intensity and functional capacity domains (r = -0.42; $P = .010$), pain (r = -0.46; $P = .005$), and mental health (r = -0.47; $P = .004$), whereas in the second analysis, we found a significant moderate or high negative correlation in most domains, except mental health (Table 4). A weak negative correlation was found between age and the functional capacity domain (r = -0.34; $P = .043$) and a moderate negative correlation between age and the social aspects domain (r = - 0.43; $P = .010$). The correlation between transplantation time and the functional capacity domain was positive and moderate (r = 0.42; $P = .011$), and the correlation between transplantation time and social aspects was positive and weak (r = 0.34; $P = .045$).

DISCUSSION

Studies pointed out that some alterations of the painful sensory pathways postsurgical trauma can be prevented through correct acute pain management [17,18]. Multimodal analgesia combines different medications that act through variable pain pathways with additive effects and seem to interfere adequately on the complex pain transmission [18]. The combination of drugs, in addition to contemplating several inhibitory effects of the pathophysiology of pain, also promotes reductions in their side effects [18,19]. However, the prevention of chronic pain after surgical procedures should be done not only by the anesthesiologist, but also by the surgical team, who should always choose surgical techniques that allow a lower risk for the development of this complication [18].

PO analgesia in our study was performed in 75% of the cases with epidural PCA with catheter maintenance until chest tube removal. This analgesic method has increasingly been shown to be effective in controlling pain in LTx patients, reducing the risk of pneumonia, reducing length of stay in the intensive care unit, and minimizing opioid usage [20,21]. In addition, the low pain intensity reported by patients (mean NVS 3.8 ± 2.8) may be a reflection of epidural analgesia. A previous study has shown that epidural analgesia is superior to intravenous analgesia in controlling acute pain and in reducing the incidence and intensity of chronic pain after thoracotomy [22].

Considering the prevalence of chronic pain among the analyzed patients, this study shows that 47.2% of this group experienced chronic pain after LTx, corroborating the results presented by other studies, which demonstrated a prevalence of 49% and 59% in this population [8,9]. Nonetheless, research with post-transplantation pain is still scarce, and our study is the first to be performed in Brazil with this focus.

Regarding the limitations of our study, the instrument of evaluation, the population's culture, and the period after LTx can affect the results obtained. In addition, we had a limited period to include participants for the analysis, different from other studies like one Canadian study (which included 96 patients from 1989 to 2202) and another French study (which included 143 patients from 2008 to 2011).

In this research, although women had more intense pain, no significant difference was found in the pain intensity between sexes. Previous studies in postthoracotomy patients showed that women reported more pain than men and that female sex was a predictor of higher pain levels ($P = .02$) [7,23]. These data suggest that, compared with men, women present higher sensitivity to pain, leading not just to a higher level of PO acute pain but also suggesting a higher prevalence of PO chronic pain [7,23].

Regarding the type of surgical incision, patients submitted to posterolateral thoracotomy presented more severe pain (5.0%), worse functional capacity (63.3%), and significant limitation in physical aspects (50.0%). A study has

Table 4. Correlation Between Pain Intensity and Quality of Life Domains (Short-Form Health Survey 36)

Domains	Analysis 1		Analysis 2	
	Pearson Correlation	P Value	Pearson Correlation	P Value
Functional capacity	−0.42*	.010	−0.736†	< .001
Physical aspects limitation	−0.29	.086	−0.473*	.013
Pain	−0.46†	.005	−0.541*	.004
General health status	−0.19	.263	−0.657†	< .001
Vitality	−0.29	.081	−0.557†	.003
Social aspects	−0.12	.474	−0.565†	.002
Emotional aspects	−0.22	.202	−0.510†	.007
Mental health	−0.47†	.004	−0.306	.120

*Correlation is significant when $P < .05$.
†Correlation is significant when $P < .01$.

shown that 17% of patients undergoing thoracotomy had persistent PO pain [13]. Another study, which evaluated pain intensity comparing posterolateral and anterolateral thoracotomy, showed that patients undergoing posterolateral thoracotomy had more severe pain, coinciding with our results [14]. Several factors contribute to these findings such as sectioning of the skin, muscles, and pleura; retraction of muscles, ligaments, parietal pleural; intercostal nerve damage by surgical retractors and chest drains; and, occasionally, rib fractures. Research has shown that patients undergoing posterolateral thoracotomy had a higher degree of intercostal injury, confirmed by the loss of abdominal reflexes, decreased amplitude of somatosensory potentials, and a large increase in the sensory threshold for tactile perception and pain [24].

Among the various objectives of LTx, the most important are to reduce disability, increase survival, and improve QOL [25]. A study found significant improvement in the QOL indices after 3 months of transplantation compared with pretransplantation measures [26]. However, a limitation of this study was the impossibility to get data related to patients' previous QOL to compare pre- and posttransplant status.

Our study demonstrated that the SF-36 domain that experienced the least interference in both periods of PO follow-up was functional capacity (84.6-76.1); whereas sleep (73.3-61.7) and general health status (73.5-60) were the domains with the greatest impairment. We also noted a reduction of scores (Raw Scale) in all domains, showing a worsening of the general state over the years. No studies were found in the literature that evaluated the impact of pain on QOL in this way, and further investigation is needed on the subject.

The first data analysis of the present study also showed a moderate negative correlation between pain (BPI) and the domains of functional capacity, pain, and mental health. The second analysis demonstrated moderate or high significant negative correlation in most domains, except for mental health.

A research evaluating patients undergoing thoracotomy concluded that those who experienced pain faced worse QOL scores, and the most affected areas by this symptom were: sleep, work, and walking ability, varying in moderate to severe grades (40%-55%) [4]. The effects of pain on daily living activities were also assessed by another study, in which 54% of patients who reported PO pain experienced a reduction in their QOL and 57% reported sleep disturbance [13]. Other authors state that the presence of pain results in a significant impact on the prevalence of depression in late PO LTx patients [4]. These studies found pain interference in different domains of QOL from those found in our study.

CONCLUSION

The prevalence of chronic pain in patients after LTx was high and was not associated with sociodemographic, clinical, and surgical variables. During the periods evaluated, the most affected QOL domain was pain and the least affected was the functional capacity. These findings are important because they address a specific and poorly studied population regarding pain and QOL. However, further studies are needed to better understand these aspects and to propose strategies that minimize the occurrence of pain and contribute improving the QOL of these patients.

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