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Chronic Pain one to Five Years after Lung Transplantation

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ABSTRACT

Chronic bodily pain after lung transplantation has received little attention. Therefore, the aim was to provide a multidimensional assessment of self-reported chronic pain 1-5 years after lung transplantation and its relationship with self-reported psychological general well-being (PGWB) and self-efficacy. This multicenter, cross-sectional study is a part of the Swedish national study: Self-management after thoracic transplantation (SMATT). In total, 117 lung transplant recipients, all white, due for their yearly follow-up at one (n=35), two (n=28), three (n=23), four (n=20) or five years (n=11) after transplantation were included. Of these, 113 reported their pain on the Pain-O-Meter (POM), which provides information about pain intensity, quality, location, and duration. In addition, they responded to the PGWB instrument and the Self-Efficacy instrument for managing chronic disease. The prevalence of pain was 51% after 1 year, 68 % after 2 years, 69.5 % after 3 years, 75 % after 4 years and 54.5 % after 5 years. Women experienced higher pain intensity and worse sensory and affective burden than men. Psychological general well-being was the main factor that contributed to the experience of pain. Better perceived psychological well-being lowered the odds for pain, while higher self-efficacy reduced the probability of experiencing pain. Many of the lung recipients lacked pain treatment and were uncertain about the reasons behind their pain. Chronic bodily pain is a common and serious symptom up to five years after lung transplantation. Female lung recipients experience more pain and pain related illness than men.

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Introduction

Chronic pain has wide-ranging detrimental effects across various life-domains and also affects health related quality of life (HRQoL) after solid organ transplantation (SOT) (1-3). The rationale behind this study is that the extent to which lung recipients experience chronic bodily pain in the years after lung transplantation has received little attention in the literature.

Pain is a complication that might hamper self-management (4) due to decreased ability to cope with the physical and psychosocial consequences inherent in being a lung recipient. Self-efficacy, defined as the perceived capability of the lung recipient to perform a specific action required to achieve a concrete goal (5), might also be seriously limited.

After liver transplant, 26% of recipients stated that they suffered severe bodily pain (1) and in another cohort 18% reported pain in an extremity and 40% had arthralgia (6). Bone pain and fractures were also reported as the most significant non-immunological postoperative complication (7). Furthermore, deterioration in bone disease can lead to compression fractures of the vertebrae and pain (8). Kidney recipients treated with cyclosporine reported severe pain, restriction of movement, transient musculoskeletal pain, and a leg bone pain syndrome (9-12). Musculoskeletal-neurologic complaints and low back pain were prevalent following heart transplantation (13), and patients with at least mild pain after heart transplantation reported worse HRQoL than the general population and were less likely to be employed (3). Peripheral neuropathy is an undesirable complication after SOT with unexpected onset, rapid escalation of symptoms, lack of provider monitoring, and poor provider response to patient reported symptoms (14).

When discussing pain after SOT it is necessary to address Calcineurin-Inhibitor induced Pain Syndrome (CIPS), identified by Grotz et al., 2001 (15). In SOT recipients the overall incidence of the syndrome ranges from 1-17 % (16). The usual onset occurs 1 to 3 months after the introduction of Calcineurin Inhibitors (CIs) and the syndrome presents as symmetric bilateral pain in the lower extremities involving the bones of the feet, ankles, and knees. Mechanisms behind CIPS are lowered nociceptive pain thresholds due to the interruption in the function of 2-pore domain potassium channels (K2Ps) where the CIs eliminate the regulation of the K2Ps, leading to enhanced neuronal excitability (17). It has been suggested that the main mechanism may be the vasoconstrictive effect at the level of the bone marrow vasculature (16). CIPS is mainly presented in case studies of kidney recipients (18) and one lung recipient (19). Only one study reported CI induced headache among 74 patients following lung, liver, and bone marrow transplantation (20). Apart from the comprehensive pain assessment after kidney, heart, and liver transplantation (2), no other study has aimed to perform a multi-dimensional assessment of pain among SOT-recipients in general or lung recipients in particular. To our knowledge, this is the first comprehensive, multidimensional exploration of chronic pain after lung transplantation. Therefore, the aim of this study was to provide a multidimensional assessment of self-reported chronic pain 1-5 years after lung transplantation and its relationship with self-reported psychological general well -being (PGWB) and self-efficacy.

Methods

Study Population and Instruments

This multicenter, cross-sectional, cohort study is a part of the Swedish national study: Self-management after thoracic transplantation (SMATT). The inclusion criteria were being a lung recipient due for the annual follow-up 1-5 years after lung transplantation at either of the two Thoracic transplant centers in Sweden, Swedish speaking, mentally lucid, not hospitalized and without on-going rejection treatment with high doses of

steroids. The main reasons for exclusion were poor health status, declining participation, and language.

During the inclusion period, 204 lung recipients were due for their annual follow-up and thereby eligible for participation in this study. In total, 117 (57 %) were included at 1 yr. (n=35), 2 yrs. (n=28), 3 yrs. (n=23), 4 yrs. (n=20) and 5 yrs. (n=11) after lung transplantation. The patients could only be included once and 113 lung recipients (96 %), all white, completed the three measurement instruments.

In order to provide a multidimensional assessment of pain, the *Pain-O-Meter* (POM) (21-22) was used together with questions about how pain affects daily living. The POM provides information about pain intensity, sensation, location and duration. It consists of a 100 mm straight line, the POM-VAS, for indicating pain intensity. For each pain location the lung recipients (LuTx) were asked to indicate the pain intensity on the POM-VAS and a total score for each LuTx was calculated. There is also a list of sensory and affective words (pain descriptors), POM-WDS. These lists of pain descriptors were originally selected from the McGill Pain Questionnaire (MPQ). Eight of the 11 words on the Affective subscale of the POM (POM-Affective) were selected from the MPQ Affective subscale and the other 3 words were taken from the MPQ Miscellaneous subscale ("nagging", "agonizing", "torturing"). Patients indicate which of the 11 words may be used to describe their pain. All affective words POM-Affective were used in the Swedish version of the instrument: agonizing, annoying, troublesome, tiring, terrifying, miserable, sickening, nagging, killing, unbearable, and torturing. Each word has an assigned intensity value (range 1-5). Words such as unbearable, torturing, and killing have the highest intensity value, while annoying has a low value. Sensation could be described as numb, burning, stabbing, sharp or dull, with the highest intensity value for the word stabbing and the lowest for the word sharp. The sensory and affective scores are added together to form a total pain intensity score (PIS) for POM-WDS.

The LuTx were asked to answer the following open questions: When did the pain start?, How did the pain start?, Do you take any pain killers?, How does the pain affect your everyday life?, and What are your own thoughts about the reason behind the pain? This instrument has undergone testing for reliability and validity in different patient populations (21-22) and has been used previously among kidney, liver-, and heart recipients (2).

The *Psychological General Well-Being* (PGWB) instrument was used to explore psychological well-being or illness. It contains 22 items constituting six dimensions, i.e., anxiety, depressed mood, positive well-being, self-control, general health, and vitality. A normal sum score is considered to be between 100-105. A score below 100 indicates poorer psychological well-being, and women tend to score lower than men (23-24).

Self-efficacy was studied by the instrument *Self-Efficacy for managing chronic disease* developed by Stanford Patient Education Centre (25). Self-efficacy is measured by one homogenous factor made up of six statements with inter-item correlation values 0.78-0.90 and a Cronbach's Alpha of 0.92 (26).

Statistical Analysis and Ethics

The SPSS Statistics 23 (SPSS Inc., IBM Corporation, Armonk, N.Y., USA) was used for analyzing data, which were mainly ordinal. Single-scale ordered category data were summarized with medians and percentiles (P_{25}, P_{75}). The null hypotheses tested are presented together with the statistical analyses that were applied (Table 1). When applicable, values of $p < 0.05$ (two-tailed) were considered statistically significant. The steps in the analysis were as follows:

1. Explore proportions and describe the prevalence of pain, including pain locations, sensory and

Table 1. The hypothesis tested regarding pain, psychological general well-being, and self-efficacy.

Statistical analysis	Null hypothesis
Chi Square	There is no difference in the proportion of men and women who report pain. Lung recipients on CNI-treatment do not experience more pain than those not on CNI (e.g., rapamycin).
Mann Whitney U	There is no difference in pain intensity between men and women. There is no difference in psychological general well-being or self-efficacy between those with and without pain.
Spearman's rho	There is no relationship between pain intensity and psychological general well-being or self-efficacy.
Binary linear regression Logistic regression	Psychological general well-being or self-efficacy does not explain the pain prevalence.

affective components, consequences in everyday life, and personal explanation models.

2. Explore possible differences between two unpaired groups, e.g., men and women.
3. Explore possible relationships.
4. Analyze possible explanatory factors.

Permission to carry out the study was granted by the Regional Ethical Review Board of southern Sweden (D-nr. 2014-124). All participants gave their written informed consent and the information they provided was kept confidential and stored by the researchers in accordance with the Swedish personal data act; PuL-[1998:204] (27).

Results

Patient Characteristics

Indications for transplantation and medication among the 117 included lung recipients are shown in Table 2. The mean age of the pain free recipients was 53 years (SD 13.5) (range 22-70 years). Of the 113 recipients who answered all three instruments, 74 (65.5 %) reported pain, 40 women and 34 men with a mean age of 53 years (SD 12) (range 18-74 years). In the pain group, 71.6 % of the recipients were over the age of 50 years. In the group of patients younger than 50 years the prevalence of pain was 64.6 %, thus there was no significant difference between the two age groups. None of the patients were enrolled in a rehabilitation program at the time of their yearly follow-up

Outcomes

The prevalence of pain was 51% after 1 yr., 68 % after 2 yrs., 69.5 % after 3 yrs., 75 % after 4 yrs., and 54.5 % after 5 yrs. The proportion of recipients with pain did not differ between those on or not on CNIs (e.g., rapamycin).

The three most common pain locations were the chest, back, and legs (Table 3). Each recipient could report more than one pain location (range 1-7 pain locations). The pain most commonly started during the first hospital stay when the lung transplantation was performed or soon after discharge (32%). Among the patients with pain, 27 % developed chronic pain later than one year post transplantation, while 19 % already had pain pre-transplant. Finally, 0.5 % reported that they pain started in conjunction with a new disease and 21.5 % didn't answer this particular question.

Regarding the sensory aspect, the most common pain sensation was dull followed by stabbing or burning (Table 4). The three most common affective experiences of pain were annoying, troublesome, and tiring (Table 5). The pain experience affected everyday life in various ways with the most commonly reported consequence being inability to plan or perform the daily

Table 2. Indications for transplantation, medication and other relevant treatment variables among 117 lung transplant recipients 1-5 years after lung transplantation. Information about one patient is missing. Data regarding the type of graft in one patient are missing.

	N
Female/Male	59/58
Chronic obstructive pulmonary disease (COPD)	29
Lung fibrosis	24
Cystic fibrosis	19
Lack of Alpha 1- antitrypsin	19
Other	12
Pulmonary arterial hypertension	7
Emphysema	4
Bronchiectasis	3
Double lung	98
Single lung	18
Cyclosporine	61
Tacrolimus	45
Mycophenelate mofetil (MMF)	79
Azathioprine (AZA)	12
Steroids	63
Rapamycine	34

Table 3. Pain locations 1-5 years after lung transplantation (n=113) among 74 (65.5 %) lung recipients reporting pain. Each recipient could report more than one pain location (range 1-7 pain locations). The median number of pain locations was 3 (1 year), 2 (2 years), 2 (3 years), 3 (4 years) and 2 (5 years).

Pain location	1 year n=18	2 years n=19	3 years n=16	4 years n=15	5 year n=6	Total
Chest	6	10	5	5	1	**27**
Back	6	4	4	7	3	**24**
Legs	5	5	6	6	1	**23**
Feet	7	4	3	4	2	**20**
Hands	2	2	5	3	3	**15**
Shoulder/ neck	4	4	2	3	1	**14**
Head	4	2	3	3		**12**
Hip	3	4	1	3	1	**12**
Arms	2	5	4	1		**12**
Abdomen	2		3	4	1	**10**
Knee	4	3				**7**

Table 4. The sensory experience of pain 1-5 years after lung transplantation (n=113) among 74 lung recipients (65.5 %) reporting pain. Each recipient could report more than one sensory description.

Sensory words	1 year n=18	2 years n=19	3 years n=16	4 years n=15	5 years n=6	Total
Dull	22	17	18	20	4	**81**
Stabbing	7	8	9	9	2	**35**
Burning	7	10	3	5	1	**26**
Numb	1	2	8	6	2	**19**
Sharp		4	5	3	1	**13**

Table 5. The affective experience of pain 1-5 years after lung transplantation (n=113) among 74 (65.5%) lung recipients reporting pain. Each figure represents the number of times the affective experiences were reported. Each patient could report more than one affective word due to reporting more than one pain location.

Affective words	1 year n=18	2 years n=19	3 years n=16	4 years n=15	5 years n=6	Total
Annoying	25	19	24	15	2	**85**
Troublesome	16	10	6	13	3	**48**
Tiring	12		11	17	1	**41**
Nagging	4	5	7	11	1	**28**
Agonizing		5	8	2	2	**17**
Miserable	2	2	4	3		**11**
Torturing		5	3	2		**10**
Unbearable	2	4	3	1		**10**
Killing		2	2			**4**
Terrifying	1		2			**3**
Suffocating	1					**1**

occupation. The lung recipients with pain reported 13 different personal pain explanation models, the two most common being that they did not know why they had pain, and that the pain was caused by nerve injuries (Table 6).

Table 6. Consequences in everyday life among 74 lung recipients reporting pain. Each person could mention several consequences. There were 13 missing responses to this specific item.

	1 year n=17	2 years n=15	3 years n=11	4 years n=12	5 years n=5	Total
Limited daily occupation	8	6	5	1	2	**22**
No consequence	4	5	4	3	2	**18**
Somewhat impaired	3		1	4		**8**
Impaired ability to exercise	1	3	1	1		**6**
Fatigue			4	2		**6**
Sleeping problems	1	1	2	1	1	**6**
GI-symptoms		1	1	1		**3**
Mood			1	2		**3**
Negative effect on work/study			1			**1**
Inability to work/study			2			**2**

The pain intensity measured by the POM-VAS ranged from 0-28 cm, and a total VAS score was calculated for each lung recipient. The median POM-VAS was 4 cm (P_{25}=0; P_{75}= 9). The sensory and affective scores were added together to form a total pain intensity score (PIS) for POM-WDS, which ranged from 0 -112. The median PIS was 12 (P_{25}=0; P_{75}=28).

Lung recipients with pain experienced significantly lower psychological general well-being (PGWB) (p=0.021), more anxiety (p=0.047), more depression (p=0.003), and poorer general health (p<0.001) compared to lung recipients without pain. The lung recipients with pain also reported significantly lower self-efficacy (p=0.004).

Linear regression analysis revealed a significant relationship between overall PGWB and Pain Intensity Score (PIS) (Beta -0.481), where the overall PGWB contributes significantly to pain intensity (p=0.005). The overall PGWB seems to explain 21.6 % of the variance of PIS (R Square 0.216). There was also a significant relationship between self-efficacy and PIS (Beta -0.402) where self-efficacy contributes significantly to pain intensity (p≤0.001). Self-efficacy appears to explain 16.2 % of the variance of PIS (R Square 0.162). Thus PGWB seems to be a better predictor of the total PIS than low self-efficacy.

Gender Aspects of Pain

There were no significant differences in the proportions of men and women with pain. Of the participants with pain, 54.1 % were women and 45.9 % men. Among the women, 74.1 % reported pain compared to 59.6% of the men. There were significant differences between male and female lung recipients regarding POM-VAS (p=.010), POM-WDS (p=.015) and PIS (p=.006), where women experienced higher pain intensity as well as worse sensory and affective burden. Female recipients had 1.5 higher odds of experiencing pain when adjusted for PGWB, which was not significant (OR 1.503, 95 % CI 0.666-3.391). PGWB contributed significantly (p=0.028) to the prevalence of pain. Thus, the major factor contributing to lung recipients' pain is the overall psychological general well-being adjusted for gender. The higher the PGWB, the lower the odds of experiencing pain (OR 0.973, 95 % CI 0.950-0.977) when adjusted for gender. The analysis also showed that when perceived self-efficacy increases, the probability of experiencing pain is significantly (p=0.010) reduced (OR 0.747, 95 % CI 0.598 – 0.933).

Discussion :

The key findings in this study are:

- Chronic pain is very common in the first five years after lung transplantation ranging from 54.5-75 % of lung recipients.
- The most common pain locations are the chest, back, and legs.
- The pain reduces psychological general well-being and self-efficacy.
- Female lung recipients report higher pain intensity and worse sensory and affective burden than male lung recipients.

Chronic pain was more common than we could possibly have imagined. Moderate to severe persistent postsurgical pain occurred in 5-10 % of the patients in a Danish nationwide study of chronic pain after lung transplantation (28), which in turn was lower than that reported after non-transplant thoracotomy. The self-rated prevalence of generalized pain in the general Swedish population is 10-15 % (29-30). In total, 24 % of the population is living with persistent pain, i.e., lasting for more than 3 months, with an increased risk of various co-morbidities (31). For example, among persons with chronic pain the lifetime prevalence of depression is 58-86 % and anxiety 35-62 % (32). In the Regional database of care consumption in the south of Sweden about 3 % of the population is diagnosed with generalized pain each year. While such pain might be viewed as a specific disease per se, pain is also a common symptom of many other diseases including chronic conditions (33). Thus, the prevalence of pain among lung recipients is far above that of the general population, which constitutes an important aspect of long-term management after lung transplantation.

We did not explore the cause of the pain. However, the pain locations suggest multiple causes such as the incision, CIPS (especially pain in the hands, feet, joints, and head), and the side-effects of immunosuppressive drugs other than CNIs. The chest pain may be due to post thoracotomy pain syndrome (PTPS) that may have an incidence of more than 50 % (34) and be related to intra operative factors such as whether anterolateral thoracotomy or classic posterolateral thoracotomy was applied. The apparent etiology of PTPS is nerve damage and loss of superficial abdominal reflexes (34), thus it is noteworthy that in ten cases the personal models for explaining the pain involved nerve injury. None of these factors were explored in the present study, but will be analyzed in an ongoing prospective study. Due to the sensory descriptions in at least hands and feet it is reasonable to believe that we partly deal with neuropathic pain. For some time it has been recognized that inflammatory mediators released from immune cells can contribute several persistent pain states. Immune cell products might have a crucial role not just in inflammatory pain but also in neuropathic pain caused by damage to peripheral nerves or to the CNS (35). Accumulating evidence suggests that non-neuronal cells such as immune cells, glial cells, keratinocytes, cancer cells and stem cells play active roles in the pathogenesis and resolution of pain. Recent studies also suggest that bacterial infections regulate pain through direct actions on sensory neurons, and specific receptors are present in nociceptors to detect danger signals from infections (36). Since all the lung recipients were treated with CNIs more than one year our understanding is that the immunological condition caused by the anti-rejection treatment might be one reason behind the high prevalence of pain along with the occurrence of bacterial infections.

The findings reveal that 18 recipients experienced no consequences in their everyday life,

suggesting that it is possible to experience pain and still mange one's daily occupation without limitations. However, in a majority of cases chronic pain affects everyday life, which is supported by the Danish survey (28) where daily social activities were limited in 29-92 % of the participants and where more than half of the LuTx felt that their QoL was compromised due to pain. The consequences regarding HRQoL from our data are currently being analyzed and will be reported later.

In our study PGWB was reduced, but we do not know whether pain causes anxiety, depression, and poor general health or if reduced PGWB increases the experience of pain. The design does not permit any suggestions or conclusions regarding cause-effect. One concern is that self-efficacy was impaired among LuTX with pain. The ability to achieve certain goals is important for the experience of health and as self-efficacy is a pre-condition for self-management (37), the latter might also be limited by chronic pain. We argue that chronic pain after lung transplantation might hamper the recipient's ability to manage the symptoms, treatment, physical and psychosocial consequences, and life style changes inherent in living with the chronic condition of being a lung recipient.

As recommended in the consensus report on gender differences in pain and analgesia (38), we tested the pain experience in both sexes. Women with pain experienced significantly higher pain intensity and pain related illness than men with pain. Despite the lack of evidence, our understanding is that the differences in experienced pain intensity refer more to societal based gender phenomena than purely biological sex differences. The gender role might differ for female lung recipients and our findings suggest that both PGWB and self-efficacy affect the pain experience. It is well-established that there is a 2 to 6 fold greater prevalence and intensity of chronic pain syndromes in women compared to men (38). As women are more likely than men to have a history of clinical pain experiences and pain history influences pain perception, we argue that pre-transplant multi-dimensional pain assessment should be mandatory for all transplant candidates, but especially for female lung transplant candidates.

Methodological Considerations

The limitations of this study are the design and its retrospective nature. The investigation included data from the only two thoracic transplant centers in Sweden with different staffing conditions at the outpatient lung transplant clinic, which possibly affected the recruitment of participants during the study period. The slightly different approach to the care of these recipients in the pre, peri, and postoperative setting contributes to the heterogeneity of the study population. Although this heterogeneity might be considered a weakness, it can also be viewed as a strength because it may accurately represent the cross-section of patients undergoing lung transplantation in Sweden. As pain is a subjective sensation the data are self-reported and thus represent the inside perspective of the recipients' experience of pain. Consequently, this opens up the possibility of different interpretations of the items pertaining to pain and how pain intensity is rated by the study participants. However, these findings from our clinical research are probably more relevant to the relief of chronic pain after lung transplantation than those from studies involving laboratory animals or healthy, pain-free humans.

The POM has been used among various organ transplant recipients and is therefore known to work in this context. The POM includes both a mechanical VAS and two lists of pain descriptors also present in the MPQ (39). Especially the POM Affective scale has been shown to be adequately reliable, and sensitive to analgesic treatment (22, 39). It has also been shown to discriminate patients with acute myocardial infarction from patients with chest pain but no diagnosis of a myocardial infarction. On the down side, POM Affective scale may be less strongly related to other measures of affective disturbances e.g. measures of anxiety and

depression than the POM Sensory scale or the VAS measure of pain intensity on the POM (39).

Conclusion and Clinical Implications

This is the first multi-dimensional exploration of chronic pain after lung transplantation. It reveals that chronic bodily pain is a common and serious symptom for up to five years after lung transplantation. Female lung recipients experience more pain and pain related illness than men. Consequently, multi-dimensional pain assessment should be performed pre-transplant as well as regularly at follow-up after lung transplantation. It is also necessary to adopt a gender perspective. In addition to providing proper analgesia, an advanced nurse practitioner specialized in pain management and the use of complementary methods might be useful together with patient education aimed at relieving suffering and promoting healthy adaptation and self-efficacy despite pain.

Disclosure Statement

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