



HAL
open science

Prevalence, Characteristics and Preoperative Predictors of Chronic Pain After Double-Lung Transplantation: A Prospective Cohort Study

Quentin Laurent, Mireille Michel-Cherqui, Barbara Szekely, Matthieu Glorion, Édouard Sage, Julie Trichereau, Marc Fischler, Julien Fessler, Morgan Le Guen

► To cite this version:

Quentin Laurent, Mireille Michel-Cherqui, Barbara Szekely, Matthieu Glorion, Édouard Sage, et al.. Prevalence, Characteristics and Preoperative Predictors of Chronic Pain After Double-Lung Transplantation: A Prospective Cohort Study. *Journal of Cardiothoracic and Vascular Anesthesia*, 2022, 36 (2), pp.500-509. 10.1053/j.jvca.2021.07.041 . hal-04360594

HAL Id: hal-04360594

<https://hal.science/hal-04360594v1>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Prevalence, characteristics and preoperative predictors of chronic pain after double-lung transplantation: A prospective cohort study

Quentin Laurent, MD,¹ Mireille Michel-Cherqui, MD,¹ Barbara Szekely, MD,¹

Matthieu Glorion, MD,² Edouard Sage, MD, PhD,² Julie Trichereau, MSc,³

Marc Fischler, MD,¹ Julien Fessler, MD,¹ Morgan Le Guen, MD, PhD,¹

¹ Department of Anesthesiology and Pain Management Clinic, Hôpital Foch, 92150 Suresnes, France
and Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

² Department of Thoracic Surgery and Lung Transplantation, Hôpital Foch, Suresnes, France and
Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

³ Department of Clinical Research and Innovation, Hôpital Foch, 92150, Suresnes, France

Corresponding author: Marc Fischler, MD, Department of Anesthesiology, Hôpital Foch, 40 rue
Worth, 92150 Suresnes, France. E-mail: m.fischler@hopital-foch.com. Phone: 0033 1 46 25 24 42
(Business telephone) – 0033 6 09 68 78 54 (Mobile). Fax: 0033 1 46 25 240 88

E-mail addresses of each author:

Quentin Laurent: quentin0.laurent@gmail.com

Mireille Michel-Cherqui: m.michel-cherqui@hopital-foch.com

Barbara Szekely: b.szekely@hopital-foch.com

Matthieu Glorion: m.glorion@hopital-foch.com

Edouard Sage: e.sage@hopital-foch.com

Julie Trichereau: j.trichereau@hopital-foch.com

Marc Fischler: m.fischler@hopital-foch.com

Julien Fessler: j.fessler@hopital-foch.com

Morgan Le Guen: m.leguen@hopital-foch.com

Declarations of interest: none in the relation with the present work

Funding source : . This work was supported by the Clinical Research Department of Hôpital Foch and by a grant from the Association “Vaincre la Mucoviscidose” (VLM; contract N° TP0904) which was not involved in the conduct of the study or development of the submission.

INTRODUCTION

Over the years, striking changes have transformed anesthesia, leading to new challenges. Because of the improved survival of lung transplant patients, which reaches about 70% at 5 years,¹ their anesthetic management must take into consideration the risk of development of chronic pain and its consequences, notably an impaired quality of life. Pain is a common problem in patients who are candidates for, or have undergone, lung transplantation. Accordingly, nearly half of the patients awaiting lung transplantation had pain² and post-transplant pain prevalence has been evaluated in up to 20% to 80% of patients.³⁻⁸

Thoracic surgical procedures are at high risk of developing severe persistent postsurgical pain, particularly caused by nerve injury related to the incision.⁹ However it is difficult to demonstrate a direct link between incision-related nerve injury cause by the thoracotomy and post-surgical neuropathic pain.¹⁰ Furthermore, in lung transplantation, surgical incisions may vary depending on teams and patients, going from sternotomy to double anterior thoracotomy, or clamshell thoracotomy. Chronic pain has also been suggested to be associated with decreased lung function and increased mortality after lung transplantation in a single-center cohort study.¹ Many patient characteristics have been identified as risk factors for chronic post-surgical pain such as gender, age or genetic traits, but also the existence of preoperative pain and psychosocial factors.^{11, 12}

We carried out this study to specify the prevalence and the characteristics of-the chronic pain, whether neuropathic or not, evaluated at the sixth postoperative month after a double-lung transplantation and to search for preoperative personal factors associated with the development of chronic pain.

METHODS

This retrospective analysis of a prospective single-center database was approved by the institutional review board of the French Society for Anesthesia and Intensive Care (IRB 00010254 - 2018 - 121). All participants provided written informed consent that their data be used for research purposes.

Participants

Patients were recruited when registering on the waiting list for double-lung transplantation in our institution (Foch Hospital, 92150 Suresnes, France) from August 2008 to October 2013. Exclusion criteria were age below 18, an unstable condition at registration requiring the high emergency lung transplantation program,¹³ and multiorgan transplantation.

Study design

We used a database prospectively completed in real time during consultations with a **pain-certified anesthesiologist** before lung transplantation and six months after surgery. This term refers to an anesthesiologist with a 2-year university degree in acute and chronic pain medicine.

Procedure and data collection

Preoperative assessment

A thorough and rigorous preoperative assessment using validated scales was performed during a two-day hospital stay required before registration on the waiting list and described in a prior study of the cohort.² Briefly, it comprised a 45-min interview and physical examination and a questionnaire completed by the patient and the investigator.

The questionnaire contained an evaluation of pain including its existence with a closed-ended question (“Do you suffer regularly from one or several kinds of pain?”). Patients are defined “with pain”, as opposed to a “pain free” patient, if they answered this question positively and if their pain intensity score was superior to 3 on a 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (most

severe pain imaginable). Intensity of pain was evaluated using this scale with current pain, maximal pain in the last 8 days, and average pain in the last 8 days. Location of pain was specified using diagrams of the body (chest, upper back, lower back, head, abdomen, limbs, joints), and answers to a questionnaire on pain location and circumstances (pain related to scars, to previous surgery, and to procedures like tracheal endoscopy).

Sensory and affective components of pain were evaluated using 16 adjectives describing pain (“Questionnaire Douleur Saint-Antoine (QDSA”, a French adaptation of the McGill Pain Questionnaire¹⁴) associated with a verbal scale of intensity. A “moderate” to “severe” answer was considered positive for each qualification. Neuropathic pain was clinically detected using the “Douleur Neuropathique en 4 questions” (DN4) if the score was 4 or above on 10 questions.¹⁵

Anxiety and depression were assessed with the French version of the Hospital Anxiety and Depression Scale (HADS). An anxiety score or a depression score above 7 on this 14-item scale was considered as indicative of a clinical diagnosis of anxiety or depression.¹⁶

The interference between pain and quality of life was evaluated with subscales including mood, walking ability, normal work, relations with other people, and enjoyment of life. The intensity of each subscale was rated on a scale of 0 to 10 (0 being no symptoms, 10 being the worst possible severity).

Finally, current life, current health and comfort were assessed on a 7-point Likert scale from “totally satisfied” to “totally unsatisfied”.

Pharmacologic pain management was noted according to the World Health Organization analgesic scale in its 1997 edition. Only medication taken on a regular basis was recorded. Nonpharmacologic treatments including relaxation, hypnosis, transcutaneous electric nerve stimulation, active physical therapy, and reconditioning, were recorded as “absent” or “present”.

Lung transplantation procedure

Surgery consisted in a sequential double-lung transplantation performed through two anterolateral thoracotomies. Our standardized anesthetic management has been previously described¹⁷ and can be found on the web site “<http://anesthesie-foch.org/protocoles-anesthesie>”. Briefly, the anesthetic protocol combined total intravenous anesthesia with thoracic epidural analgesia unless contraindicated (refusal of the patient, hemostasis disorder, technical difficulty). Inhaled nitric oxide was

systematically administered. Peripheral veno-arterial extracorporeal membrane oxygenation was **utilized** mainly in cases of severe intraoperative respiratory or hemodynamic failure and rarely planned in cases of severe pulmonary hypertension. At the end of surgery an evaluation was performed to determine whether to decrease respiratory and hemodynamic support (extracorporeal membrane oxygenation, inhaled nitric oxide) or to extubate the patient in the operating room if possible.

Postoperative Analgesia

Postoperative analgesia after lung transplantation was standardized. An epidural catheter was inserted in the absence of contraindication. Epidural analgesia was initiated before surgical incision with a fractionated injection of levobupivacaine 0.25% (6 mL or 8 mL if the height was greater than 170 cm) associated with sufentanil (15-20 µg). Then the infusion was continued during surgery with 0.125% levobupivacaine and 0.25 µg/mL sufentanil at 5 mL/h. In case of patient refusal or contraindication to epidural catheter, an intravenous morphine injection was administered when the surgery ended. During the surgery, systemic analgesia was started for all patients with a multimodal analgesia protocol combining mild analgesics (acetaminophen 1 g, nefopam 20 mg) and a co-analgesic (ketamine 0.15 mg/kg).

Later, when the patient was awake, postoperative epidural analgesia was delivered via a patient-controlled device. Patients received a continuous infusion with 0.125% levobupivacaine and 0.125 µg/mL sufentanil at 5 mL/h plus a patient-controlled bolus of 3 mL of the same solution on demand with a lockout time of 20 min. If the patient was sedated, epidural analgesia was delivered by continuous infusion with the same solution. In patients without patient-controlled devices postoperative pain could be managed by morphine 1 mg/mL delivered through patient-controlled analgesia (bolus: 1-2 mL, lockout interval: 7 min). Standardized multimodal analgesia protocol was continued for all patients with mild analgesics (acetaminophen 3-4 g/day, nefopam 80-120 mg/day, and if necessary, tramadol 200 mg/d) and a co-analgesic (ketamine 0.2-0.5 mg/kg 1-4/day).

Usually, the epidural catheter was removed at day 5. Epidural to intravenous or oral switch therapy was established according to the patients' needs and status with morphine or oral long-acting/short-

acting morphine (20-30 mg twice a day and 10 mg four to six times a day respectively). Medication was prescribed depending on the patients' comorbidities.

Postoperative assessment

Six months after the transplantation, a second pain assessment was undertaken during the usual 1 or 2-day follow-up hospital stay with the same medical examination and the same questionnaire.

Statistical Analysis

Quantitative variables were presented as medians (interquartile range) and categorical variables as numbers (percentages). Percentages are given according to the number of data collected. To identify predictive factors of postoperative pain, comparison was made between preoperative characteristics and postoperative pain with Chi² test for categorical variables and with the Mann-Whitney test for quantitative variables. Then a logistic analysis univariate was realized and OR and CI 95% were reported. A multivariate logistic analysis included all factors associated with postoperative pain with $p < 0.20$ in the univariate model was performed. Backward stepwise selection was used to perform a final multivariate model. All statistical analyses were performed using the Software SAS V.9.4 (SAS) and a two-sided test with $p < 0.05$ was considered as significant.

RESULTS

Patients

Two hundred and thirty-one patients received a double-lung transplantation from August 2008 to October 2013. Of them, forty-eight patients met one or several criteria for exclusion. Nineteen patients died during the first six postoperative months. Among the 164 patients alive 6 months after surgery, 72 undertook the postoperative pain assessment (**Figure 1**).

Characteristics of all patients at inclusion

Main characteristics of all patients at inclusion are shown in **Table 1**. Among 72 patients, 43 (59.7%) were women and 29 (40.3%) were men. Primary diagnosis was cystic fibrosis for 41 (56.9%), emphysema for 19 (26.3%) and fibrosis for 7 (9.7%). Among the responders, 39 (54.9% of the responders) were assessed as anxious and 21 (29.6%) were assessed as depressive.

Preoperative prevalence and pain characteristics

Forty-two (58.3%) patients were considered **to suffer from pain** if they answered “yes” to the question “Do you suffer regularly from one or several kinds of pain?” or **if** they reported a numerical response scale > 3. Among the responders, 11 (27.5%) of these patients had moderate to severe pain (NRS > 5) on average, 28 (38.3%) presented multiple pain and two (5.0%) had neuropathic pain. They mostly had back pain (59.5%), headache (50.0%) and joint pain (40.4%) (data not shown). Twenty-seven (84.4%) pain patients took analgesics frequently or daily but only three (9.1%) took opioid analgesics; eight (19.5%) used complementary therapies for pain relief (**Table 2**).

Postoperative prevalence and pain characteristics

Forty-nine (68.0%) patients had pain six months after surgery using the same definition as at inclusion. Among the **patients suffering from chronic pain** who responded to the questionnaire, 25

(52.1%) reported moderate to severe (NRS > 5) maximal pain and eight (16.7%) reported moderate to severe average pain. Twenty-eight (59.6%) reported multiple locations of pain and 13 (26.5%) had neuropathic pain. Among the responders, 42 (100.0%) took analgesics frequently or daily but only four (9.1%) consumed opioid analgesics; 11 (23.4%) used complementary therapies for pain relief (**Table 3**). They mostly reported back pain (51.0%), pain along the surgical scar (44.8%) and thoracic pain (38.7%) (data not shown).

Psychosocial impact of pain six months after the double-lung transplantation

Anxiety and depression questionnaires (HADS) showed significantly higher scores in patients with pain who responded to the questionnaire ($p=0.02$ and $p=0.001$), and more patients with pain were anxious (46.9% vs 17.4%, $p=0.02$) or depressed (22.4% vs 0.0%, $p=0.01$). Patients with pain presented more difficulties for walking, work, and sleep ($p=0.03$, $p=0.02$ and $p=0.02$). However, patients with and without pain did not really vary in terms of satisfaction with their current life and current health state (**Table 4**).

Preoperative predictive risk factors of postoperative pain

Comparison of preoperative patient factors between those who did not develop chronic pain and those who did show that numerous factors are similar between them: age, initial pulmonary disease, diabetes, level of activity, levels of depression and mood, quality of life regardless of the type of information provided, and characteristics of pain treatment. In the univariate analysis, of interest is the fact that female gender and anxiety score are slightly different between groups (OR 2.68 [0.97-7.42], $p=0.05$ and OR 1.1 [0.99-1.30], $p=0.06$ respectively). Only presence of preoperative pain (OR 4.5 [1.57-13.14], $p=0.005$) and a maximal numeric rating scale of pain >3 (OR 3.5 [1.15-10.46], $p=0.03$) are significantly different between patients who will develop chronic pain and others while the neuropathic characteristic of the preoperative pain has a similar prevalence between these groups (**Table 5**). Finally, the backward stepwise selection of the multivariate logistic regression identified that the maximal preoperative pain score is the only independent predictor of postoperative pain in

lung transplant recipients (OR 1.23 [1.02–1.49] p=0.03).

DISCUSSION

Our study investigating pain 6 months after lung transplantation found that prevalence of chronic pain was 68% with mostly a mild intensity and about 25% of neuropathic component in patients with pain. These patients were more frequently anxious or depressed and reported **greater worsening** of their quality of life than pain free patients. Intensity of maximal pain eight days before the preoperative assessment was the only independent risk factor for 6-month postoperative pain.

The prevalence of chronic pain after lung transplantation is variously reported. Earlier studies have reported a prevalence ranging from 18% to 75%³⁻⁸ with, in general, a frequency around 50%.^{3, 6, 8} Inconsistency of reported prevalence of pain after lung transplantation could be explained by different types of incision among teams (sternotomy, double anterior thoracotomy, or clamshell thoracotomy. the pain assessment tools (numeric rating scale,^{4, 7} Brief Pain Inventory,^{3, 8} or Organ Transplant Symptom and Well-being Instrument⁶) and a large disparity of time period between surgery and pain assessment (from 2 months⁵ to 5 years⁶). Our result is in the high range of the literature data since 68% of our patients complained of pain 6 months after transplantation. This is consistent with the 70% prevalence found in the most similar study in terms of way of assessment (NRS) and waiting period (6-12 months).⁷

Chronic postoperative pain after lung transplant is mostly reported as low or moderate.^{4, 5} However, contrary results have also been reported with more than half of transplanted patients having moderate to severe pain³ and one in two pain patients taking opioids.⁵ **Different ways of assessment and non-homogeneous intensity bounds and various kinds of evaluated pain (current, average, maximal, etc...) account for these disparate observations.** Our patients manifested mild levels of average pain (with a parallel low consumption of potent opioids), which is in accordance with the literature.^{4, 6, 7} After hospital discharge, levels of pain tend to decrease,^{5, 8} therefore it can be argued that the sooner pain is measured, there is an increased probability of finding high levels of pain.³ Also, potent opioid use is a poor indicator of pain intensity, since it does not necessarily imply severe pain presence.⁵

Data about the neuropathic component of pain after lung transplantation are scarce. Some studies showed that a large proportion of patients with pain had sensory abnormalities^{4, 7} but a definitive diagnostic of neuropathic pain was not performed. In our study, we used an accepted evaluation method (DN4) and found a lower incidence of definite neuropathic pain of 26%. In fact, sensory disturbances are not always associated with neuropathic pain since it can be caused by nerve damage without pain.⁷

Finally, numerous studies report quality of life and psychological state after lung transplantation;^{18, 19} only a few examined their relationship with pain. In fact, there is a strong interaction between pain and anxiety and depression. Depressed patients complain of pain more often than controls and their pain is more intense and prolonged.²⁰ Conversely, the presence of pain in depressed patients is associated with a more severe and more difficult to treat depressive symptomatology.²¹ Lung recipients with pain reported lower well-being quantified by local score (Organ Transplant Symptom and Well-being instrument)⁶ or classic index (SF-36).⁸ Data on psychologic consequences of pain are less clear, three months after surgery, patients with and without pain did not differ in terms of state anxiety but differ in trait anxiety, and mental health scores are not statistically different.³ A more psychological study conducted by psychiatrists found higher postoperative pain in patients with a history of depression or anxiety.⁵ In our study, despite a low intensity of pain, patients with pain were more anxious or depressed and presented more difficulties for walking, work and sleep. It is close to interferences found in the literature where these three activities were also affected.³ However, our patients expressed the same satisfaction about their current life and their current health state. This is only apparently paradoxical given the many elements that characterize the life of a lung transplant recipient with its better and worse periods: the respiratory functional outcome, the adverse effects of immunosuppressive drugs, and the potential complications.

An important topic of our study was to investigate preoperative factors predictive of chronic postoperative pain. The development of chronic postoperative pain is a complex process and predictive factors (preoperative, intraoperative and postoperative) are not entirely understood.¹¹ Numerous studies have investigated risk factors for chronic post thoracotomy pain and have found,

among others, patient-related factors (young age, female gender, genetic characteristics, pre-existing pain at surgery, anxiety, depression, stress, low social support), surgical factors (type and duration of surgery, nerve damage), and extent of acute postoperative pain.⁹ Most of these factors are non-modifiable while the link between chronic postsurgical pain and intraoperative nerve damage, demonstrated by experimental studies,²² can be **reduced** by a change in surgical technique.^{23, 24}

This suggests that patient-related factors are involved in the development of chronic pain after lung transplantation⁷ but data are scarce and contradictory. Female gender,⁸ postoperative depression and postoperative use of opioids,⁵ lung emphysema³ or rare lung pathologies⁵ were found to be related to the development of chronic postoperative pain. But other studies reported no predictive factors.^{6, 7} Our study did not find any of these risk factors, and the only independent predictor for the presence of pain 6 months after lung transplantation was the preoperative maximal pain score. One notable point is the influence of gender on the occurrence of chronic pain, a predictive factor found in many studies. This factor was not found in our study, but it is likely analysis of a larger group of patients would have found it.

Some strengths of the present study can be outlined: its prospective design with identical pain evaluation before and after lung transplantation, the examination of quality-of-life indicators and their relationship with pain, the exploration of predictive risk factors. However, it does have some limitations. First, 92 patients alive six months after their transplantation were lost to **follow-up**; this high number could **be due to** several reasons: the geographical distance of some patients whose post-transplant follow-up is provided in a center close to their home, the refusal of other patients to participate in this evaluation, and, sometimes, the unavailability of investigators. We studied a large proportion of cystic fibrotic patients and no patients suffering from primary pulmonary hypertension and used a local standardized procedure. We focused in this study on preoperative factors and consequently we did not include intraoperative variables, use of epidural analgesia whose preventive role on the development of chronic pain is disputed,²⁵ and postoperative factors related to patients' health and particularly lung complications and function. It is regrettable that we did not use standardized questionnaires assessing quality of life, but we preferred to analyze certain aspects of it.

Finally, due to complex administrative reasons, this study reports the clinical evolution of patients transplanted around ten years ago. However, its results remain relevant since the surgical and anesthetic practice is still transposable to the present time, even though the indications for transplantation have changed recently with the possibility of improvement in some cystic fibrotic patients permitted by elexacaftor-tezacaftor-ivacaftor combination therapy.²⁶ Consequently, future studies are needed to be in adequation with the evolution of recipients' characteristics.

Conclusion

The prevalence of post-operative pain is high after double-lung transplantation. While its intensity is mild, it has significant repercussions on mental health and quality of life. The maximum level of pre-operative pain is associated with the presence of 6-month postoperative pain; this confirms its deleterious role and the need for effective management combining analgesics and non-pharmacologic techniques.

REFERENCES

1. Khush KK, Potena L, Cherikh WS, et al: The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: 37th adult heart transplantation report-2020; focus on deceased donor characteristics. *J Heart Lung Transplant* 39:1003-1015, 2020
2. Michel-Cherqui M, Ley L, Szekely B, et al: Prevalence and characteristics of pain in patients awaiting lung transplantation. *J Pain Symptom Manage* 49:548-554, 2015
3. Girard F, Chouinard P, Boudreault D, et al: Prevalence and impact of pain on the quality of life of lung transplant recipients: a prospective observational study. *Chest* 130:1535-1540, 2006
4. Wildgaard K, Iversen M, Kehlet H: Chronic pain after lung transplantation: a nationwide study. *Clin J Pain* 26:217-222, 2010
5. Farquhar JM, Smith PJ, Snyder L, et al: Patterns and predictors of pain following lung transplantation. *Gen Hosp Psychiatry* 50:125-130, 2018
6. Forsberg A, Claëson M, Dahlman GB, et al: Pain, fatigue and well-being one to five years after lung transplantation - a nationwide cross-sectional study. *Scand J Caring Sci* 32:971-978, 2018
7. Petersen PL, Bredahl P, Perch M, et al: Chronic pain after bilateral thoracotomy in lung transplant patients. *Scand J Pain* 19:271-277, 2019
8. Loxe SC, de Mello LS, Camara L, et al: Chronic Pain After Lung Transplantation and Its Impact on Quality of Life: A 4-Year Follow-up. *Transplant Proc* 52:1388-1393, 2020
9. Wildgaard K, Ravn J, Kehlet H: Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. *Eur J Cardiothorac Surg* 36:170-180, 2009
10. Guastella V, Mick G, Soriano C, et al: A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. *Pain* 152:74-81, 2011

11. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. *Lancet* 367:1618-1625, 2006
12. Reddi D, Curran N: Chronic pain after surgery: pathophysiology, risk factors and prevention. *Postgrad Med J* 90:222-227; quiz 226, 2014
13. Roux A, Beaumont-Azuar L, Hamid AM, et al: High Emergency Lung Transplantation: dramatic decrease of waiting list death rate without relevant higher post-transplant mortality. *Transpl Int* 28:1092-1101, 2015
14. Boureau F, Luu M, Doubrère JF: Comparative study of the validity of four French McGill Pain Questionnaire (MPQ) versions. *Pain* 50:59-65, 1992
15. Bouhassira D, Attal N, Alchaar H, et al: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114:29-36, 2005
16. Bjelland I, Dahl AA, Haug TT, et al: The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 52:69-77, 2002
17. Felten ML, Moyer JD, Dreyfus JF, et al: Immediate postoperative extubation in bilateral lung transplantation: predictive factors and outcomes. *Br J Anaesth* 116:847-854, 2016
18. Shahabeddin Parizi A, Krabbe PFM, Verschuuren EAM, et al: Patient-reported health outcomes in long-term lung transplantation survivors: A prospective cohort study. *Am J Transplant* 18:684-695, 2018
19. Zhu X, Liang Y, Zhou H, et al: Changes in Health-Related Quality of Life During the First Year in Lung Transplant Recipients. *Transplant Proc* 53:276-287, 2021
20. Bair MJ, Robinson RL, Katon W, et al: Depression and pain comorbidity: a literature review. *Arch Intern Med* 163:2433-2445, 2003
21. Kroenke K, Shen J, Oxman TE, et al: Impact of pain on the outcomes of depression treatment: results from the RESPECT trial. *Pain* 134:209-215, 2008
22. Zhang R, Schwabe K, Krüger M, et al: Electro-physiological evidence of intercostal nerve injury after thoracotomy: an experimental study in a sheep model. *J Thorac Dis* 9:2461-2465, 2017

23. Cerfolio RJ, Price TN, Bryant AS, et al: Intracostal sutures decrease the pain of thoracotomy. *Ann Thorac Surg* 76:407-411, 2003
24. Cerfolio RJ, Bryant AS, Patel B, et al: Intercostal muscle flap reduces the pain of thoracotomy: a prospective randomized trial. *J Thorac Cardiovasc Surg* 130:987-993, 2005
25. Richebe P, Capdevila X, Rivat C: Persistent Postsurgical Pain: Pathophysiology and Preventative Pharmacologic Considerations. *Anesthesiology* 129:590-607, 2018
26. Middleton PG, Mall MA, Dřevínek P, et al: Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med* 381:1809-1819, 2019

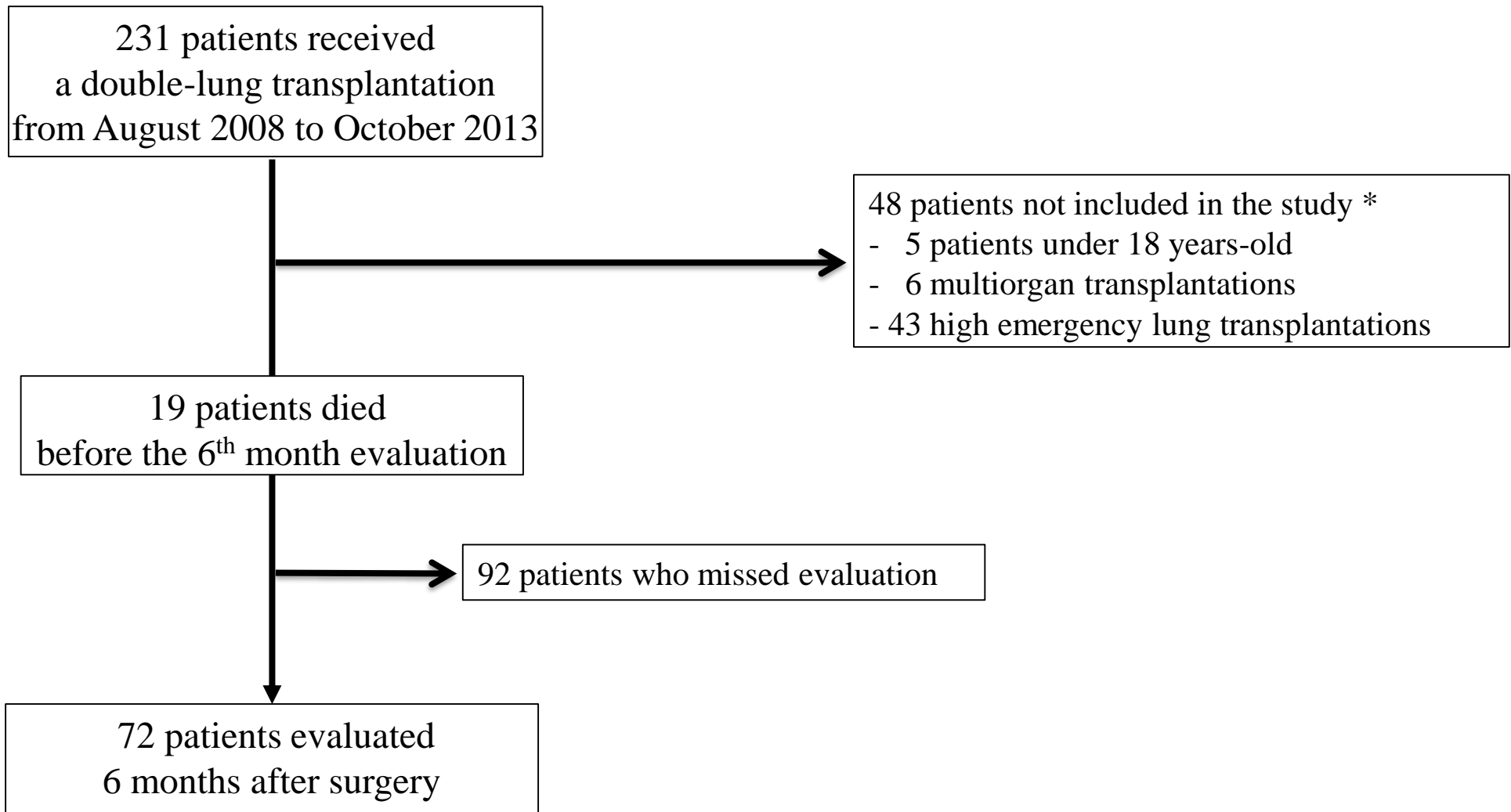


Figure 1

Table 1. Characteristics of all patients at inclusion

Variables	
Demographic characteristics {72}	
Female/male gender, no of patients	43/29 (59.7/40.3)
Age, years	37 [22]
Diagnosis, no of patients	
Cystic fibrosis	41 (56.9)
COPD/Emphysema	19 (26.3)
Fibrosis	7 (9.7)
Other diagnosis	4 (5.5)
Diabetes, no of patients {72}	18 (25.0)
Activity, no of patients {54}	
Work	19 (30.2)
Physical ability	17 (25.4)
Psychological state	
Anxiety {71}	
Anxiety score	8 [7]
Anxiety score >7, no of patients	39 (54.9)
Depression {71}	
Depression score	5 [4]
Depression score >7, no of patients	21 (29.6)
Mood, no of patients {66}	
Slight worsening	45 (68.2)
Moderate worsening	14 (21.2)
Severe worsening	7 (10.6)
Quality-of-life indexes	
Ability to walk, no of patients {67}	
Slight worsening	39 (58.2)
Moderate worsening	10 (14.9)
Severe worsening	18 (26.9)

Table 1. Characteristics of all patients at inclusion (continued)

Normal work, no of patients {66}	
Slight worsening	34 (51.6)
Moderate worsening	16 (24.2)
Severe worsening	16 (24.2)
Relations with other people, no of patients {66}	
Slight worsening	48 (72.7)
Moderate worsening	12 (18.2)
Severe worsening	6 (9.1)
Sleep, no of patients {67}	
Slight worsening	38 (56.7)
Moderate worsening	21 (31.3)
Severe worsening	8 (11.9)
Enjoyment of life, no of patients {66}	
Slight worsening	56 (84.8)
Moderate worsening	6 (9.1)
Severe worsening	4 (6.1)
Current health state, no of patients {39}	
Satisfactory	3 (7.7)
Moderately satisfactory	7 (17.9)
Unsatisfactory	29 (74.4)
Current life, no of patients {39}	
Satisfactory	13 (33.3)
Moderately satisfactory	7 (17.9)
Unsatisfactory	19 (48.7)
Comfort, no of patients {38}	
Satisfactory	21 (55.3)
Moderately satisfactory	9 (23.7)
Unsatisfactory	8 (21.0)

Values are presented as number (%) and median [interquartile range]. The no of values are presented as { }. Percentages are given according to the data collected.

Table 2. Preoperative pain characteristics of the 42 painful patients

Variables	
At least 2 pain locations, no of patients {41}	28 (38.3)
Pain intensity, numerical rating scale (NRS)	
Current NRS {41}	2 [4]
Current NRS >3, no of patients	11 (26.8)
Current NRS >5, no of patients	8 (19.5)
Average NRS {40}	3 [5]
Average NRS > 3, no of patients	17 (42.5)
Average NRS > 5, no of patients	11 (27.5)
Maximal NRS {40}	5 [3]
Maximal NRS > 3, no of patients	31 (77.5)
Maximal NRS > 5, no of patients	19 (47.5)
Neuropathic component {40}	
DN4 score	0 [1]
DN4 \geq 4, no of patients	2 (5.0)
Pain treatment, no of patients	
Chronic or daily use of analgesics {32}	27 (84.4)
Use of non-opioids or weak opioids analgesics {41}	31 (75.6)
Use of potent opioid analgesics {33}	3 (9.1)
Use of complementary therapies {41}	8 (19.5)

Values are presented as number (%) and median [interquartile range]. The no of values are presented as { }. Percentages are given according to the data collected.

NRS: Numeric rating scale, a single 11-point numeric scale, with 0 representing one pain extreme (e.g., “no pain”) and 10 representing the other pain extreme (e.g., “pain as bad as you can imagine” and “worst pain imaginable”).

DN4: Neuropathic pain is diagnosed when in the questionnaire the patient answered “yes” to at least four responses of ten of the DN4 questionnaire.

Table 3. Pain characteristics of the 49 painful patients at the 6th postoperative month

Variables	
At least 2 pain locations {47}	28 (59.6)
Pain intensity, numerical rating scale (NRS)	
Current NRS {48}	2 [3]
Current NRS >3, no of patients	11 (22.9)
Current NRS >5, no of patients	4 (8.3)
Average NRS {45}	2 [3]
Average NRS > 3, no of patients	19 (42.2)
Average NRS > 5, no of patients	8 (16.7)
Maximal NRS {48}	6 [4.5]
Maximal NRS > 3, no of patients	36 (75.0)
Maximal NRS > 5, no of patients	25 (52.1)
Neuropathic component {49}	
DN4	2 [3]
DN4 ≥ 4, no of patients	13 (26.5)
Pain treatment, no of patients	
Chronic or daily use of analgesics {42}	42 (100.0)
Use of non-opioids or weak opioid analgesics {47}	28 (59.6)
Use of potent opioid analgesics {44}	4 (9.1)
Use of complementary therapies {47}	11 (23.4)

Values are presented as number (%) and median [interquartile range]. The no of values are presented as { }. Percentages are given according to the data collected.

NRS: Numeric rating scale, a single 11-point numeric scale, with 0 representing one pain extreme (e.g., “no pain”) and 10 representing the other pain extreme (e.g., “pain as bad as you can imagine” and “worst pain imaginable”).

DN4: Neuropathic pain is diagnosed when in the questionnaire the patient answered “yes” to at least four responses of ten of the DN4 questionnaire.

Table 4. Psychosocial impact of pain six months after the double-lung transplantation

	Patients with postoperative pain (n=49)	Postoperative pain-free patients (n=23)	p
Anxiety	{49}	{23}	
Anxiety score	7 [7]	4 [5]	0.02
Anxiety score >7, no of patients	23 (46.9)	4 (17.4)	0.02
Depression	{49}	{23}	
Depression score	3 [6]	1 [2]	0.001
Depression score >7, no of patients	11 (22.4)	0 (0.0)	0.01
Mood, no of patients	{49}	{21}	0.09
Slight worsening	35 (71.4)	20 (95.2)	
Moderate worsening	12 (24.5)	1 (4.8)	
Severe worsening	2 (4.1)	0 (0.0)	
Quality-of-life indexes, no of patients			
Ability to walk	{48}	{21}	0.03
Slight worsening	29 (60.4)	19 (90.5)	
Moderate worsening	10 (20.8)	2 (9.5)	
Severe worsening	9 (18.8)	0 (0.0)	
Normal work	{48}	{21}	0.02
Slight worsening	28 (58.3)	19 (90.5)	
Moderate worsening	13 (27.1)	2 (9.5)	
Severe worsening	7 (14.6)	0 (0.0)	
Relations with other people	{49}	{21}	0.10
Slight worsening	39 (79.6)	21 (100.0)	
Moderate worsening	7 (14.3)	0 (0.0)	
Severe worsening	3 (6.1)	0 (0.0)	

Table 4. Psychosocial impact of pain six months after the double-lung transplantation (continued)

	Patients with postoperative pain (n=49)	Postoperative pain-free patients (n=23)	p
Sleep	{49}	{21}	0.02
Slight worsening	31 (63.3)	20 (95.2)	
Moderate worsening	13 (26.5)	1 (4.8)	
Severe worsening	5 (10.2)	0 (0.0)	
Enjoyment of life	{48}	{21}	0.06
Slight worsening	39 (81.2)	21 (100.0)	
Moderate worsening	8 (16.7)	0 (0.0)	
Severe worsening	1 (2.1)	0 (0.0)	
Current health state	{40}	{15}	0.29
Satisfactory	29 (72.5)	14 (93.3)	
Moderately satisfactory	7 (17.5)	1 (6.7)	
Unsatisfactory	4 (10.0)	0 (0.0)	
Current life	{40}	{15}	0.11
Satisfactory	27 (67.5)	14 (93.3)	
Moderately satisfactory	6 (15.0)	1 (6.7)	
Unsatisfactory	7 (17.5)	0 (0.0)	
Comfort	{39}	{15}	0.04
Satisfactory	22 (56.4)	14 (93.3)	
Moderately satisfactory	11 (28.2)	1 (6.7)	
Unsatisfactory	6 (15.4)	0 (0.0)	

Values are presented as number (%) and median [interquartile range]. The no of values are presented as { }. Percentages are given according to the data collected.

Table 5. Preoperative factors of patients with postoperative pain and of postoperative pain-free patients

	Patients with postoperative pain (n=49)	Postoperative pain-free patients (n=23)	OR [CI95%]	p
Demographic characteristics	{49}	{23}		
Female gender, no of patients	33 (67.3)	10 (43.5)	2.68 [0.97-7.42]	0.05
Age, years	38 [22]	31.5 [25]	1.01 [0.97-1.05]	0.50
Diagnosis, no of patients				0.79
Cystic fibrosis	28 (57.1)	13 (56.5)	1	
Emphysema	13 (26.5)	5 (21.7)	1.2 [0.35-4.10]	
Fibrosis	5 (10.0)	2 (8.7)	1.2 [0.20-6.79]	
Other diagnosis	3 (6.1)	3 (13.0)	0.5 [0.08-2.62]	
Diabetes , no of patients	11 (22.4) {49}	7 (30.4) {49}	1.5 [0.50-4.60]	0.47
Activity , no of patients				
Work	14 (31.1) {45}	5 (27.8) {18}	1.2 [0.35-3.93]	0.79
Physical ability	35 (76.1) {46}	15 (71.4) {21}	1.3 [0.40-4.08]	0.68
Psychological state				
Anxiety	{49}	{22}		
Anxiety score	9 [6]	5.5 [6]	1.1 [0.99-1.30]	0.06
Anxiety score >7, no of patients	17 (34.7)	5 (22.7)	1.8 [0.57-5.75]	0.32
Depression	{49}	{22}		
Depression score	6 [4]	5 [4]	1.1 [0.96-1.33]	0.12
Depression score >7, no of patients	5 (10.2)	0 (0.0)	NA	0.31
Mood, no of patients	{47}	{19}		0.23
Slight worsening	30 (63.8)	15 (78.9)	NA	
Moderate worsening	10 (21.3)	4 (21.0)	NA	
Severe worsening	7 (14.9)	0 (0.0)	NA	

Table 5. Preoperative factors of patients with postoperative pain and of postoperative pain-free patients (continued)

	Patients with postoperative pain (n=49)	Postoperative pain-free patients (n=23)	OR [CI95%]	p
Quality-of-life indexes, no of patients				
Ability to walk	{47}	{20}		0.70
Slight worsening	26 (55.3)	13 (65.0)	1	
Moderate worsening	7 (14.9)	3 (15.0)	1.2 [0.26-5.27]	
Severe worsening	14 (29.8)	4 (20.0)	1.7 [0.48-6.39]	
Normal work	{46}	{20}		0.33
Slight worsening	21 (45.6)	13 (65.0)	1	
Moderate worsening	13 (28.3)	3 (15.0)	2.7 [0.64-11.25]	
Severe worsening	12 (26.1)	4 (20.0)	1.8 [0.49-6.99]	
Relations with other people	{46}	{20}		0.19
Slight worsening	33 (71.7)	15 (75.0)	NA	
Moderate worsening	7 (15.2)	5 (25.0)	NA	
Severe worsening	6 (13.1)	0 (0.0)	NA	
Sleep	{47}	{20}		0.15
Slight worsening	23 (48.9)	15 (75.0)	1	
Moderate worsening	17 (36.2)	4 (20.0)	2.8 [0.78-9.86]	
Severe worsening	7 (14.9)	1 (5.0)	4.6 [0.51-40.95]	
Enjoyment of life	{46}	{20}		0.33
Slight worsening	39 (84.8)	17 (85.0)	NA	
Moderate worsening	3 (6.5)	3 (15.0)	NA	
Severe worsening	4 (8.7)	0 (0.0)	NA	
Current health state	{29}	{10}		0.29
Satisfactory	1 (3.4)	2 (20.0)	1	
Moderately satisfactory	5 (17.2)	2 (20.0)	5 [0.27-91.51]	
Unsatisfactory	23 (79.3)	6 (60.0)	7.7 [0.59-99.48]	

Table 5. Preoperative factors of patients with postoperative pain and of postoperative pain-free patients (continued)

	Patients with postoperative pain (n=49)	Postoperative pain-free patients (n=23)	OR [CI95%]	p
Current life	{29}	{10}		0.82
Satisfactory	9 (31.0)	4 (40.0)	1	
Moderately satisfactory	5 (17.2)	2 (20.0)	1.1 [0.15-8.37]	
Unsatisfactory	15 (51.8)	4 (40.0)	1.7 [0.33-8.37]	
Comfort	{28}	{10}		0.08
Satisfactory	13 (46.4)	8 (80.0)		
Moderately satisfactory	9 (32.1)	0 (0.0)		
Unsatisfactory	6 (21.4)	2 (20.0)		
Pain				
Preoperative pain, no of patients	34 (70.8) {48}	8 (34.8) {23}	4.5 [1.57-13.14]	0.005
At least 2 pain locations, no of patients	25 (53.2) {47}	8 (36.4) {22}	2.0 [0.70-5.63]	0.19
Pain intensity, numeric rating scale (NRS)				
Current NRS, no of patients	1 [(3) {47}]	0 [0] {22}	1.3 [0.98-1.80]	0.06
Current NRS >3	11 (23.4)	1 (4.5)	6.4 [0.77-53.28]	0.08
Current NRS >5	8 (17.0)	1 (4.6)	4.3 [0.5 – 36.8]	0.18
Average NRS, no of patients	2 [5] {47}	0 [1] {21}	1.2 [0.95-1.47]	0.14
Average NRS > 3	15 (31.9)	3 (14.3)	2.8 [0.72-11.04]	0.14
Average NRS > 5	9 (19.2)	3 (14.3)	1.42 [0.34-5.89]	0.63
Maximal NRS, no of patients	4 [7] {46}	0 [4] {22}	1.2 [1.02-1.45]	0.03
Maximal NRS > 3	26 (56.5)	6 (27.3)	3.5 [1.15-10.46]	0.03
Maximal NRS > 5	17 (37.0)	3 (13.6)	3.7 [0.96-14.42]	0.06
Neuropathic component	{47}	{22}		
DN4	0 [1]	0 [0]	1.2 [0.77-1.95]	0.40
DN4 ≥ 4, no of patients	2 (4.3)	1 (4.5)	0.93 [0.08-10.88]	0.96

Table 5. Preoperative factors of patients with postoperative pain and of postoperative pain-free patients (continued)

	Patients with postoperative pain (n=49)	Postoperative pain-free patients (n=23)	OR [CI95%]	p
Pain treatment, no of patients				
Chronic or daily use of analgesics	32 (88.9) {36}	13 (86.7) {15}	1.2 [0.20-7.56]	0.82
Use of non-opioids or weak opioid analgesics	29 (61.7) {47}	10 (45.4) {22}	1.9 [0.69-5.39]	0.21
Use of potent opioid analgesics	35 (94.6) {37}	14 (93.3) {15}	1.2 [0.10-14.91]	0.86
Use of complementary therapies	10 (21.3) {47}	2 (9.1) {22}	1.2 [0.54-13.56]	0.23

Values are presented as number (%) and median [interquartile range]. The no of values are presented as { }. Percentages are given according to the data collected.

NRS: Numeric rating scale, a single 11-point numeric scale, with 0 representing one pain extreme (e.g., “no pain”) and 10 representing the other pain extreme (e.g., “pain as bad as you can imagine” and “worst pain imaginable”).

DN4: Neuropathic pain is diagnosed when in the questionnaire the patient answered “yes” to at least four responses of ten of the DN4 questionnaire.