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Psychological Adjustment to Lung Transplantation

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Dedicated to the lung transplant patients

Hope is the thing with feathers

Hope is the thing with feathers
That perches in the soul,
And sings the tune without the words,
And never stops at all,

And sweetest in the gale is heard;
And sore must be the storm
That could abash the little bird
That kept so many warm.

I've heard it in the chillest land,
And on the strangest sea;
Yet, never, in extremity,
It asked a crumb of me.

Emily Dickinson, 1861

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Abstract

Lung transplantation (LTx) is an effective treatment for end-stage lung failure. Despite great advances in transplant medicine over the last few decades, LTx does not result in complete recovery of health, as transplant recipients continue to be confronted by various health problems that must be psychologically processed and overcome. Many suffer from frequent emotional distress and psychological disorders that can negatively influence their ability to cope with their new organ, negatively impacting both their adherence to immunosuppressive therapy and health-related quality of life (HRQoL). Therefore, it is both clinically and scientifically relevant to assess the postoperative HRQoL and mental health of LTx recipients to identify those at risk for poor post-transplant outcomes and to improve patients' symptom experience.

This manuscript consists of three studies that review psychological adjustment to lung transplantation in terms of HRQoL and psychosocial outcomes via three different approaches. Study 1 is a systematic review of the literature to compile and interpret the evidence on measures to assess HRQoL and psychological outcomes following LTx, summarizing psychological outcomes in studies published between 1994 and 2013. Of 371 articles, 63 studies were selected for final review. Considerable heterogeneity was found in methodology, operational concepts and applied outcome measures in the existing literature on HRQoL and psychological outcomes after LTx. Nevertheless, eligible studies generally point to significant improvements in both mental health and HRQoL post-transplant. A huge opportunity for future research lies in the development of guidelines to aid in the selection of outcome measures to assess psychological outcomes of lung transplant recipients.

The second study investigated the psychosocial outcome trajectories of 40 lung transplant recipients related to psychological distress and HRQoL over their first six months post-transplant. Three distinctive clusters were identified: (1) patients with optimal postoperative trajectories (35%); (2) patients with good postoperative trajectories (42%); and (3) patients with poor postoperative trajectories (23%). The last group tended to be older, to suffer from more severe disease, to have more co-morbid conditions, and to have had a prolonged ICU and/or hospital stay. Disease severity, length of stay, and HRQoL two weeks post-transplant were strong predictors of psychological distress and impaired HRQoL at six months of follow-up. The results underscore the psychosocial needs of patients with poor post-transplant trajectories.

The third study qualitatively analyzed patient experiences with transplantation and their adjustment to normal life within the first six months post-transplant. ‘Physical benefits’, ‘fear of rejection’, ‘gratitude towards the donor’, and ‘side effects’ were the most frequently named themes with respect to the transplantation process, new lungs, donor and medication regimen. Most themes remained unchanged over time. While comments about ‘intensive care unit delirium’ and ‘worries regarding donated organ quality’ diminished significantly over time, mentions of ‘restrictions in everyday life’ increased significantly. Gender comparison revealed only marginal differences in the response categories. Improvements in physical function during the early postoperative phase may be limited by the onset of clinical complications, fear of rejection and infections, medication side effects, and restrictions in everyday life.

Generally, studies on HRQoL and psychological outcomes after lung transplantation have been limited by lost to follow-up, cross-sectional designs, small sample sizes and, great variability in the use of validated and non-validated outcome measures, such that

comparisons between different studies are difficult. One area of future research is the development of consensus guidelines to aid in the selection of outcome measures to assess HRQoL and psychological outcomes among LTx patients. In addition, longitudinal studies, including pre- vs. post-transplant assessment with adequately-sized samples are needed to further investigate outcome profiles and identify additional outcome predictors in these patients.

Zusammenfassung

Die Lungentransplantation ist eine effektive Therapiemethode für Patienten mit fortgeschrittenen Lungenerkrankungen im Endstadium. Trotz den unbestreitbaren medizinischen Fortschritten, die in den letzten Jahren stattgefunden haben, führt eine Lungentransplantation nicht zu einer vollständigen gesundheitlichen Genesung. Lungentransplantierte Patienten bleiben weiterhin mit verschiedenen gesundheitlichen Problemen konfrontiert, die sie psychisch verarbeiten und bewältigen müssen. Viele lungentransplantierte Patienten leiden unter anhaltendem emotionalen Distress oder sogar an psychischen Störungen, die den Umgang mit dem neuen Organ erschweren und die Therapieadhärenz für die notwendigen immunsupressiven Medikamente und die Lebensqualität beeinträchtigen können. Es ist deshalb von klinischer und wissenschaftlicher Relevanz, die Lebensqualität und psychische Gesundheit von lungentransplantierten Patienten zu untersuchen, um Patienten mit schlechten post-operativen Verläufen rechtzeitig identifizieren und die psychischen Beschwerden behandeln zu können.

Dieses Manuskript umfasst drei Studien, welche die psychische Verarbeitung einer Lungentransplantation im Sinne von Lebensqualität und psychosozialen Aspekten anhand von drei unterschiedlichen Ansätzen untersuchen. Die erste Studie umfasst einen systematischen Review, welcher die verwendeten psychometrischen Instrumente zur Untersuchung der gesundheitsbezogenen Lebensqualität und der psychischen Gesundheit nach einer Lungentransplantation bewertet. Der Artikel fasst Studien zusammen, die zwischen 1995 und 2013 veröffentlich wurden. Von 371 Artikeln wurden 63 Studien in die Übersichtsarbeit eingeschlossen. In der vorhandenen Literatur über Lebensqualität und psychische Gesundheit nach einer Lungentransplantation wurde eine beträchtliche

Heterogenität in der Methodik, operationalen Konzepten und angewendeten psychometrischen Instrumenten gefunden. Die eingeschlossenen Studien weisen jedoch einheitlich auf eine signifikante Verbesserung der psychischen Gesundheit und der Lebensqualität nach einer Lungentransplantation hin. Ein künftiger Forschungsbereich liegt in der Entwicklung von Richtlinien hinsichtlich der Auswahl von psychometrischen Testinstrumenten zur Beurteilung der psychologischen Outcomes nach einer Lungen Transplantation.

Die zweite Studie untersuchte bei 40 lungentransplantierten Patienten postoperative Verläufe hinsichtlich psychischen Distress und Lebensqualität während den ersten sechs Monaten nach der Transplantation. Es konnten drei unterschiedliche Clustertypen identifiziert werden: Patienten mit 1) ausserordentlich guten postoperativen Verläufen (35%), 2) guten postoperativen Verläufen (42%) und 3) schlechten postoperativen Verläufen (23%). Patienten mit schlechten postoperativen Verläufen waren typischerweise älter, schwerer erkrankt, litten unter mehr Komorbiditäten und wiesen eine längere Hospitalisation sowohl auf der Intensivstation als auch auf der Normalstation auf. Der Schweregrad der Erkrankung, die Länge der Hospitalisation und die gesundheitsbezogenen Lebensqualität zwei Wochen nach der Transplantation waren wichtige Prädiktoren für psychischen Distress und Lebensqualität 6 Monaten nach der Transplantation. Unsere Resultate unterstreichen den psychosozialen Behandlungsbedarf von Patienten mit schlechten postoperativen Verläufen.

Die dritte Studie untersuchte mittels einer qualitativen Datenanalyse die subjektive Wahrnehmung einer Lungentransplantation und die Rückkehr in den Alltag innert der ersten sechs Monate nach der Transplantation. ‚Verbesserung der körperlichen Belastbarkeit', ‚Angst vor Abstossung', ‚Dankbarkeit dem Spender gegenüber', und ‚Nebenwirkungen' waren die häufigsten genannten Themen hinsichtlich der Transplantation, der neuen Lunge, dem Spender und der Medikamente. Die meisten Themen blieben über die Zeit unverändert. Während Aussagen bezüglich Delirium auf der Intensivstation und Sorgen bezüglich Qualität des neuen Organs über die Zeit abnahmen, nahmen Äusserungen hinsichtlich Einschränkungen im Alltag über die Zeit signifikant zu. Geschlechtsvergleichende Analysen zeigten nur marginale Unterschiede in Bezug auf die Antwortkategorien. Die Verbesserung des körperlichen Wohlbefindens nach einer Lungentransplantation kann durch das Auftreten von medizinischen Komplikationen, Angst vor Abstossung und Infektionen, Nebenwirkungen der Medikamente und Einschränkungen im Alltag beeinträchtigt sein.

Bisherige Studien zur Untersuchung der Lebensqualität und psychischen Gesundheit von lungentransplantierten Patienten sind häufig durch methodische Schwächen wie *lost to follow-up*, Querschnittstudiendesigns, kleine Stichprobengrössen und eine hohe Variabilität der verwendeten Testinstrumente, die den Vergleich zwischen den Studien erschwert, limitiert. Künftige Studien sollten auf die Entwicklung von Richtlinien, die eine Auswahl von Testinstrumenten zur Erfassung der Lebensqualität und psychischen Gesundheit nach einer Lungentransplantation vereinfachen, fokussieren. Zudem sind weitere Längsschnittstudien mit prä- versus postoperativen Untersuchungen und genügend grossen Stichproben notwendig, um postoperative Verläufe und Verlaufsprädiktoren zuverlässig identifizieren zu können.

Table of contents

List of abbreviation

BDI	Beck Depression Inventory
BOS	Bronchiolitis Obliterans Syndrome
BODE-index	Body-mass index, obstruction, dyspnea, exercise capacity index in chronic obstructive pulmonary disease
CF	Cystic fibrosis
CLAD	Chronic lung allograft dysfunction
COPD	Chronic obstructive pulmonary disease
DBD	Donation after brain death
DCD	Donation after circulatory determination of death
ECMO	Extracorporeal membrane oxygenation
EQ-5D	The EuroQoL five dimensions Health-Related Quality of Life questionnaire
FVC	Forced vital capacity
FEV1	Forced expiratory volume in one second
F-SoZu	Short Form Social Support Questionnaire
HADS	Hospital Anxiety Depression Scale
HRQoL	Health-related quality of life
ICU	Intensive care unit

ILD	Interstitial lung disease
IPF	Interstitial pulmonary fibrosis
ISHLT	International Society for Heart and Lung Transplantation
LOS	Length of hospital stay
LTx	Lung transplantation
pLTx	Post lung transplantation
NHP	Nottingham Health Profile
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SCL-K-9	Symptom Checklist short version-9
SF-36	Short Form Health Survey
SOAS	Swiss Organ Allocation System
STAI	State-Trait Anxiety Inventory

1 Introduction

Lung transplantation (LTx) has become an established therapeutic option to extend survival, reduce disability and improve health-related quality of life (HRQoL) in selected patients with end-stage pulmonary diseases of different etiologies (Dierich et al., 2013). Although survival rates among adult lung transplant recipients have increased remarkably over the years, due to enhanced surgical techniques and postoperative care, long-term rates are still inferior to those achieved with other solid organ transplants (Krueger, Berutto, & Aubert, 2011). Acute and chronic allograft rejection and infections involving a transplanted graft that is in direct contact with open air constitute the main postoperative challenges (Inci, Schuurmans, Boehler, & Weder, 2013).

Traditionally, the main outcome of interest with any lung transplant procedure has been patient survival. With improved survival rates, however, post-transplant health-related quality of life (HRQoL) has become an important component of any evaluation of benefits (Anyanwu, McGuire, Rogers, & Murday, 2001). Furthermore, lung transplant recipients represent a heterogeneous group, and therefore do not necessarily experience the same survival benefits or exhibit the same post-transplant trajectories. Moreover, throughout the transplant process, lung transplant patients undergo complex physical and psychological changes that can cause a range of psychosocial issues that affect physical function, mental health, social roles and relationships, as well as adherence to medication (Rosenberger, Dew, DiMartini, DeVito Dabbs, & Yusen, 2012).

Psychological aspects of transplantation have been investigated and documented extensively, commonly addressing HRQoL, mental health, social functioning and symptom experiences. Results from previous research generally demonstrate considerably improved HRQoL and psychological function in lung transplant recipients relative to their pre-transplant period (Kugler et al., 2005; Limbos, Joyce, Chan, & Kesten, 2000; Santana, Feeny, Jackson, Weinkauf, & Lien, 2009). However, numerous methodological problems limit the reliability and generalizability of findings in the literature and affect the ability to draw well-supported conclusions regarding the effect of lung transplantation on HRQoL. These limitations include the use of small cohorts, retrospective data collection, cross-sectional study designs, survivor bias, and the heterogeneous use of psychometric instruments to assess psychological outcomes after LTx (Finlen Copeland, Vock, Pieper, Mark, & Palmer, 2013). Prospective studies with large enough samples are few in the field of lung transplantation, and data obtained in larger studies often included cohorts with different organ transplants that potentially obscure results among lung transplant recipients.

To address these limitations, this thesis contributes the existing literature by presenting 1) a systematic review of the application of psychometric instruments to assess health-related quality of life and psychological outcomes following lung transplantation; 2) a six-month observational study investigating psychological distress and quality of life; and 3) a qualitative analysis exploring patients' experience with their transplant and adjustment to normal life over the first six months post-transplant.

2 Theoretical framework

This chapter first summarizes the most important cornerstones in the development of transplant medicine. Secondly, medical and ethical issues relating to lung transplantation are outlined; and thirdly, the most important psychosocial consequences of lung transplantation are highlighted.

2.1 History of lung transplantation

The first contribution to organ transplant history was made by Vladimir Petrovich Demikhov (1916 – 1998), a Russian scientist who, by means of animal experiments in the 1930s through 1950s, demonstrated that transplantation procedures were technically feasible (Blumenstock & Lewis, 1993). The next major breakthrough was made by James Hardy at the University of Mississippi in 1963. He performed the first human lung transplant; however, his patient survived for only 18 days after transplantation, rapidly succumbing to renal failure (Hardy, Webb, Dalton, & Walker, 1963). Over the following twenty years, multiple further attempts at lung transplantation failed due to infection, acute rejection and the excessive toxicity of inadequately immunosuppressive drugs (Lynch & Ross, 2006). In 1972, however, a new immunosuppressant drug called *cyclosporine* was developed and found to be a promising means to attenuate allograft rejection (Borel, Feurer, Magnee, & Stahelin, 1977). Subsequently, in 1983, the Toronto Lung Transplant Group performed the first successful long-term single lung transplant in a patient with pulmonary fibrosis. Twenty-six months after transplantation, the patient was reported to be in good health, leading a normal life and working regularly. That patient eventually died of renal failure seven years after transplantation. This successful case report demonstrated that unilateral lung transplantation was possible in selected patients with end-stage lung disease (Toronto Lung Transplant Group, 1986).

In summary, over the past sixty years, remarkable advances have been made in the field of transplant medicine. What started in the early twentieth century as animal experiments has progressed to effective high-tech clinical practice (De Perrot et al., 2004). Today, lung transplantation is regarded worldwide as a mainstay of therapy for many patients with life-threatening pulmonary disease (Banner, Polak, & Yacoub, 2003).

2.2 Lung transplantation in Switzerland

2.2.1 Facts and figures of lung transplantation

To date, more than 47’000 adult lung transplants have been reported worldwide to the Registry of the International Society for Heart and Lung Transplantation (ISHLT) (Yusen et al., 2014). Meanwhile, in Switzerland since 1992, more than 700 lung transplants have been performed (Swisstransplant, 2015a). In Switzerland, there are two transplant centers, which perform lung transplantation. One is located at the University Hospital of Zurich, the other one at the University Hospital of Lausanne. Overall patient survival has progressively improved, such that today, one-, three-, and five-year survival rates of 87%, 75% and 69%, respectively, have been achieved at the University Hospital of Zurich, rates comparable to those achieved at high-volume programs internationally (Inci et al., 2013). One of the key challenges in lung transplantation is the limited availability of donor organs for lung transplantation. Switzerland has one of the lowest *post mortem* donation rates among European countries, and as a consequences, many patients die while awaiting organ transplant (Immer, 2015). Background data on the lung transplant-related characteristics of Swiss patients are presented for the year 2014 in Table 1.

Table 1. Key data regarding lung transplantation in Switzerland

Lung transplant-related characteristics	[d]
Number of patients on lung waiting-list	122
Number of lung transplanted patients	56
Average time on waiting-list	465
Deceased patients on waiting-list	6.6%
Nr. of imported lungs organs	8

Note: Data provided by the 2014 Annual Report of the Swiss National Foundation for Organ Donation and Transplantation (Swisstransplant, 2015b).

2.2.2 Organ procurement for lung transplantation

In Switzerland, most organs donated for lung transplantation are retrieved from primary or secondary brain-dead donors with sustained circulation (heart-beating donors). Donation after brain death (DBD) is possible when cerebral functions are totally and irreversibly abolished due to some lesion or injury affecting the brain (Spaight, Weiss, Keel, & Immer, 2013). Furthermore, since 2011, organ donation after circulatory determination of death (DCD or non-heart-beating donors) is being increasingly accepted in Switzerland to partly compensate for the general shortage of organs suitable for transplantation. In Switzerland, the procuring of organs from DCD donors is strictly regulated and only permitted, if cardiocirculatory arrest occurs within 60 minutes after cessation of life-sustaining treatment, followed by brain death diagnosis after 10 minutes of documented circulatory arrest. However, organ procurement from DCD donors is a demanding procedure and only performed in highly specialized centers, so that the number of DCD donors remains relatively low. The diagnosis of death in view of organ donation is strictly regulated by the Swiss Academy of Medical Sciences (SAMS) and governed by the Swiss Transplantation Law (Immer, 2015).

2.2.3 Ethical aspects of lung transplantation

Over the past few decades, technological accomplishments in the understanding of immunologic responses to foreign tissues, the technology of organ preservation, immune suppression and surgical procedures, have opened up further possibilities for organ transplantation, resulting in an ever-increasing need for transplantable organs (Mahoney, 2001). However, rapid developments in transplant medicine have raised many ethical, moral and policy concerns. Among the many questions raised have been whether the criterion of ‘brain death’ is an ethically-acceptable definition of death; how best to procure more organs; how to fairly distribute limited resources; where to set medical limits; what kind of medical conditions should be treated and which should not, despite the medical possibilities; and whether all transplants should be covered by public funds (Shelton & Balint, 2001).

Today, the shortage of available organs and the distribution of limited sources constitute the main ethical problems for cadaveric organ transplantation, causing heated discussions over what measures ought to be taken to increase the available supply (Quante & Wiedebusch, 2006). Explanations for the organ shortage can be divided into two categories: the complexity of the medical system and individuals' willingness for organ donation. Results from previous studies demonstrated that countries with established organ donor centers that outreach to larger population groups perform a greater number of transplants (Horton & Horton, 1991; Matesanz & Dominguez-Gil, 2007). However, willingness to donate also depends on individual attitudes, social structures, cultural practices and religious beliefs (McGlade & Pierscionek, 2013). It has been suggested that unusually high fear and anxiety concerning one's own death can deter people from behaviors that confront them with their own mortality (Lester, 2005). Furthermore, there is evidence that serious doubts about the criteria used to determine death dissuade people from becoming organ donors (DuBois & Anderson, 2006). Moreover, the concept of brain death, which constitutes the legal definition of death, has been frequently misunderstood in the population. This misconception holds people back from considering organ donation (Anker & Feeley, 2010; Siminoff, Mercer, & Arnold, 2003).

In summary, doubts associated with organ transplantation based on misinformation, misunderstandings, and mistrust can decrease organ donation rates (Dubois, 2010). Despite major public campaigns among medical personnel and the general public, the supply of organs for transplantation remains far short of demand. Consequently, in Switzerland, a nationwide intense debate about possible incentives to encourage individuals to donate has been ignited. Different solutions have been discussed. Among them is to treat individuals willing to donate preferentially when it comes to receiving a transplant; to offer gifts when someone fills out a donor card; and providing monetary reimbursement in cases of living donation. To date, none of the named possibilities have come into force (BAG, 2015). Further improving knowledge regarding organ donation, the methods available for registration, and the regulations that govern the process of organ donation could help to remove significant barriers and encourage more individuals to donate their organs (McGlade & Pierscionek, 2013).

2.2.4 Transplantation act

In Switzerland, organ transplantation is bound by medical-ethical guidelines, which determine under which conditions organ, tissues and cells can be used for transplantation. These guidelines have been established to prevent the improper handling of organs in the context of human transplantation medicine, and to protect human dignity, privacy and health. The most important regulations stated in the Federal Council Decree 2007 are the following (The Federal Assembly of the Swiss Confederation, 2014, pp. 3-18):

- Criteria for death and determination of death: “a person is dead if the functions of his or her brain, including the brain stem, have ceased irreversibly” (by definition: brain death) (Art. 9).
- Organ transplantation is free of charge and therefore, trade involving human tissues is prohibited (Art. 6 and 7).
- Switzerland practices a soft opt-in solution: utilizing the organs of a deceased person is only allowed “if the person has consented before his or her death to their removal” or if the person’s relatives have expressed agreement (Art. 8).

- Allocation of organs is followed by principles of equality and fairness (Art. 17) in consideration of four criteria: 1) the medical urgency of transplantation; 2) the medical benefits of transplantation; 3) the waiting time; and 4) equal opportunity (in particular for individuals reliant on a graft with rare physiological characteristics (Art 18).
- Confidentiality of data: confidentiality merits protection. “The data must accordingly be treated confidentially” by assuring anonymity of the recipient to (the relatives of) the donor and of the donor to the recipient (Art 57 and 58).

2.2.5 Swiss organ allocation system

In Switzerland, the allocation of organs is navigated by a web-based computer program called the *Swiss Organ Allocation System* (SOAS), which contains relevant data on potential recipients on the Swiss waiting list, as well as data on all available donors. By means of these provided data, the system prioritizes registered transplant candidates based on the following criteria: 1) medical urgency, 2) domicile in Switzerland, 3) medical purpose, and 4) priority (e.g. blood group), 5) waiting time (Swisstransplant, 2015a).

2.2.6 The Swiss Transplant Cohort Study

Similar to other national or international transplant registries (e.g. the Scientific Registry of Transplant Recipients (SRTR) in the US; the Heidelberg-based Collaborative Transplant Study (CTS) in Europe; the Australian and New Zealand Dialysis and Transplant (ANZDATA) registry, the Swiss Transplant Cohort Study (STCS) aims at systematically monitor transplant outcomes of solid organ transplantation (e.g. heart, lung, liver, kidney) in Switzerland to evaluate the quality, effectiveness and efficiency of transplantation. The STCS is a multi-center cohort study, which has collected prospectively data from all, transplant centers in Switzerland since 01.05.2008. The main objectives of the STCS are the followings (STCS, 2015):

- To improve knowledge about the progress and complications following transplantation in all Swiss transplant centers and of all transplanted organs.
- To identify efficacy and side effects of the treatment.
- To study the relationship with concomitant disease, psychological and social factors.
- To analyze the influence of genetic factors on the progress after transplantation.
- To examine the response to treatment and the occurrence of side effects.

All transplant patients who got transplanted in Switzerland and have given their consent are considered to be eligible for inclusion. Data are collected longitudinally, before transplantation, 6 months and 12 months after transplantation and thereafter yearly. The study period is indefinite (STCS, 2015).

2.3 Referral for lung transplantation

Today, lung transplantation is accepted as a viable treatment option for selected patients with diverse end-stage pulmonary disorders, who either are not or are no longer responding to maximal medical therapy, or for whom no effective medical therapy exists. According to the most recent Registry Report of the International Society for Heart and Lung Transplantation (ISHLT) (Yusen et al., 2014), the main indications for lung transplantation between 1995 and 2013 were chronic obstructive pulmonary disease (COPD, 33%); followed by interstitial lung disease (ILD, 24%), which includes idiopathic pulmonary fibrosis (IPF); and cystic fibrosis (CF, 16%). Referral for lung transplantation assessment is warranted when patients have less than 50% two- to three-year predicted survival. As the demand for donor lungs far exceeds the supply, the waiting time for a suitable donor organ is steadily increasing. Survival on a waiting list depends on the waiting time, the underlying diagnosis, and donor availability. Waiting times tend to be longer for small candidates and for recipients with a blood group other than AB (Orens et al., 2006).

2.3.1 Absolute and relative contraindications

Potential candidates need to be well-informed regarding the procedure and its health implications, and they must demonstrate adequate health behaviors and willingness to adhere to guidelines from healthcare professionals. To screen for contraindications, prior to active listing potential candidates are sent for complex medical and psychosocial assessments performed by a multidisciplinary team to determine whether they meet the selection criteria for lung transplantation. This screening process helps to identify factors in a person's life that could cause difficulties for them during the waiting period, during recovery, and/or postoperatively (Hook & Lederer, 2012). The psychosocial assessment screens potential candidates for mental and psychosocial health issues, their use and abuse of alcohol, and their decisional capacity, motivation for transplantation, and coping skills for dealing with chronic disease (Lanuza & McCabe, 2001). If a patient successfully meets the selection criteria, he or she is added to the transplant waiting list. Absolute and relative contraindications are listed in Figure 2. Single relative contraindications are seldom considered prohibitive. Someone with multiple relative contraindications is generally rejected for transplantation (Inci et al., 2013).

Absolute contraindications to transplant

- Malignancy in the last 2 years. In general, a 5-year disease-free interval is prudent
- Untreatable advanced dysfunction of another major organ system (e.g. heart, liver or kidney)
- Acute medical instability including, but not limited to, acute sepsis, myocardial infarction, and liver failure
- Incurable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C and human immunodeficiency virus
- Class II or III obesity (body mass index [BMI] ≥ 35.0 kg/m^2)
- Significant chest wall/ spinal deformity
- Documented nonadherence or inability to follow through with medical therapy
- Absence of an adequate or reliable social support system
- Substance addiction (e.g. alcohol, tobacco or narcotics) that is either active or within the last 6 months

Relative contraindications to transplant

- Age older than 65 years
- Class I obesity (body mass index [BMI] exceeding 30kg/m^2)
- Severe or symptomatic osteoporosis
- Extensive prior chest surgery with lung resection
- Critical or unstable clinical condition (e.g. shock, mechanical ventilation or extracorporeal membrane oxygenation)
- Colonization with highly resistant or highly virulent bacterial, fungi or mycobacteria
- Other medical conditions that have not resulted in end-stage organ damage (e.g. diabetes mellitus, systemic hypertension, epilepsy, central venous obstruction, peptic ulcer disease, or gastroesophageal reflux)

Figure 1. Absolute and relative contraindications to lung transplantation adapted by Weill et al. (2015, pp. 3-4). The list is not intended to include all possible clinical scenarios but rather to highlight common areas of concern.

2.3.2 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by chronically-poor airflow. Main symptoms include shortness of breath, cough, and excessive sputum production. Typically, airflow limitation is progressive. The most common cause of COPD is tobacco smoking, together with numerous other factors like air pollution and genetic determinants (Decramer, Janssens, & Miravitlles, 2012). Presently, COPD is the fourth leading cause of death worldwide, but the World Health Organization (WHO) predicts that this disease will become the third leading cause by 2030 unless urgent action is taken to reduce underlying risk factors, in particular tobacco use (WHO, 2015). Referral for transplantation for COPD should only be considered when patients continue to deteriorate even with optimal medical and surgical therapy, including smoking cessation, maximal bronchodilator treatment, rehabilitation, long-term oxygen therapy, and endoscopic or surgical lung volume reduction (Orens et al., 2006). Compared to other end-stage lung diseases, COPD patients have a relatively good transplant prognosis (Inci et al., 2013).

2.3.3 Interstitial lung disease

Interstitial lung disease (ILD) refers to a diverse group of lung diseases that involve inflammation and fibrosis of the alveoli, distal airways and septal interstitium of the lungs. The term idiopathic pulmonary fibrosis is used to describe an interstitial lung disease for which no obvious cause can be identified (hence, idiopathic) (Raghu et al., 2011). Inhaled substances such as dust or other particles in the air, and exposure to molds, gases or fumes, but also autoimmune diseases can be responsible for some types of ILD (King, 2005). Typically, the patient suffers from progressive breathlessness, lung crackles, and a diffusely-abnormal chest radiograph (Raghu et al., 2011). Prolonged ILD may result in idiopathic pulmonary fibrosis (IPF). IPF results from scarring of lung tissue and is characterized by a progressive decline in lung function and worsening dyspnea. IPF patients have a poor prognosis and experience the highest mortality rate while on the waiting list (Christie et al., 2012).

2.3.4 Cystic fibrosis

Cystic fibrosis (CF) is a genetic disorder that primarily affects the lungs, but also the pancreas, liver, kidneys and intestine. Long-term complications include difficulties with breathing and coughing up sputum as a consequence of frequent lung infections. Other symptoms include, among others, sinus infections, poor growth, clubbing of fingers and toes, and infertility in males (O'Sullivan & Freedman, 2009). Interestingly, cystic fibrosis is most common among residents of northern Europe, among whom the disease occurs in approximately 1 in 3’000 newborns (Walters & Mehta, 2007). As there is no cure for cystic fibrosis, lung infections are treated with antibiotics (Hofer et al., 2009). Ultimately, lung transplantation is the only treatment option that allows advanced CF patients to obtain normal respiratory health. Good post-transplant outcomes, in terms of prolonged survival and improved health-related quality of life, have been reported worldwide (Meachery et al., 2008).

2.4 Diathesis-stress model as an explanation for the development of distress in lung transplant recipients

Current research in psychosocial transplant medicine seeks to assess the relationship between illness and distress and what variables may influence this association. Specific questions that have been addressed are what factors are associated with distress and with the individual’s ability to cope and adapt successfully with lung transplantation and whether distress has an impact on outcomes following transplantation (Dew et al., 2012; Phillips, Burker, & White, 2011).

One theoretical model that may explain the development of distress in lung transplant patients, is the diathesis-stress model (Zubin & Spring, 1977). This model assumes that specific types of psychopathology arise from a combination of vulnerability (diathesis) in the context of life stress (Monroe & Simons, 1991). The term diathesis derives from the Greek and is conceptualized as a disposition or vulnerability, including genetic, psychological, biological or situational factors (Ingram & Luxton, 2005). Stress can be defined as a significant life event that disrupts the equilibrium of a person’s life (Lazarus & Folkman, 1984). The diathesis-stress model describes a dose-response relationship, suggesting that if the combination of the diathesis and the stress exceeds a threshold, the person is likely to develop a disorder. This model is also useful for the purpose to describe why some individuals who go through stressful live events are more vulnerable to develop a disorder than others (Ingram & Luxton, 2005). Protective factors are critical when considering the interaction of diatheses and stress because they can mitigate major stressors. Examples of protective factors include particular personal traits, a supportive peer network, and individual and social competences (Ingram & Price, 2001). Translating this model to the experience of a lung transplantation, the diathesis includes predispositional factors, such as genetic, biological, cognitive or interpersonal variables, while stress refers to the transplant evaluation, waiting period, perioperative recovery and adjustment to life as a transplant recipient.

In the following, the diathesis-stress model is used as a conceptual framework to understand patients’ response to lung transplantation and relative adaptation to life as a lung transplant recipient.

2.5 The waiting period for lung transplantation

2.5.1 Mental health of lung transplant candidates

Transplant candidates and recipients are confronted with a great number of stressors throughout the process of transplant evaluation, the waiting period, the period of peri-operative recovery, and both early and long-term after transplantation (Figure 2), all of which can adversely affect global quality of life, mental health, social roles, relationships, and health maintenance behaviors (Rosenberger, Dew, DiMartini, et al., 2012). Waiting for a transplant can be an intensely agonizing and stressful time for both patients and caregivers (Naef & Bournes, 2009; Yelle, Stevens, & Lanuza, 2013).

Transplant-specific events	Periods	Health Issues	Psychosocial Issues	Interventions
Evaluation for transplant ↓	**Waiting for donor lung**	- Continued deterioration of lung function - Acute health crisis - Hospitalizations - Treatment for end stage lung disease and sequelae	- Stress of transplant evaluation - Stage of acceptance of need for transplant - Uncertainty about waitlist outcome - Quality of life decrements - Psychological distress	- Cognitive-behavioral therapy to improve quality of life and reduce psychological distress
Transplant surgery ↓	**Perioperative recovery**	- Improvements in lung function - Sequelae of major surgery	- Hospital stay obscures realistic expectations of caregiving	
Hospital discharge ↓	**Adjustment to life as a transplant recipient**	- New medications side effects	- Optimism of post-operative 'honeymoon' obscures participation in self-care regimen	
First anniversary ↓	**Early years post-transplant**	- Acute graft rejection - Infection - Re-hospitalization - Physical rehabilitation - Chronic post-operative pain	- Disappointment about slower pace of functional improvement - Changing family dynamics - Quality of life improvements - Adherence to self-care regimen - Psychological distress - Caregiver burden	- Physical activity rehabilitation to improve physical functioning and quality of life - Self-monitoring and decision support aid to improve adherence and communication with transplant team
Five-year anniversary ↓	**Long-term post-transplant**	- Chronic graft rejection - New health problems - Sequelae of long-term immunosuppression	- Burden of additional health problems - Quality of life changes - Return to work - Caregiver burden	- Mindfulness-based stress reduction to reduce psychological distress
Ten-year anniversary				

Figure 2. Examples of events and stressors that contribute to different phases of the transplantation experience as well as interventions that have demonstrated efficacy in reducing the impact of these stressors (Rosenberger, Dew, DiMartini, et al., 2012, pp. 519).

Usually, lung transplant candidates are in a highly-critical state of physical health, associated with a marked reduction in their vitality and quality of life (Chen et al., 2011). Shortness of breath, limited physical fitness, frequent hospitalizations, and oxygen dependency are the most distressing symptoms reported by end-stage respiratory patients, which in turn, can cause severe psychological distress (Lanuza et al., 2012). Stressors associated with the transplant procedure include fear of surgery, worry about changes to future life plans, financial strains, and ambivalent feelings with respect to treatment options (Rosenberger, Dew, DiMartini, et al., 2012).

Adjustment disorders with anxiety and mood disturbances and simultaneously reduced HRQoL relative to norms are common among candidates awaiting surgery, presumably due to their poor underlying medical condition, including their symptoms of dyspnea, hyperventilation and feebleness that can trigger anxiety and distress (Feltrim et al., 2008; Limbos et al., 2000). Prevalence rates for anxiety and mental disorders are high, reportedly ranging from 21% to 55% (Chen et al., 2011; Craven, 1990; Najafizadeh et al., 2009). Consequently, it is not surprisingly that lung transplant candidates often are in need of medical and psychosocial support. Fortunately, favorable results have been achieved using cognitive behavioral interventions aimed at improving coping skills, quality of life, mood symptoms and relationships with caregivers (Rodrigue, Baz, Widows, & Ehlers, 2005).

2.5.2 The lived experience of waiting

Most challenging for transplant candidates and their caregivers might be the balancing act between being in a life-threatening situation, accompanied by feelings of uncertainty and ambiguity, and the hope that their well-being will improve and suffering dissipate (Rosenberger, Dew, DiMartini, et al., 2012). Patients on a waiting list for organ transplantation describe their situation as uncomfortable, unpleasant, irritating, frustrating and threatening: ”It’s like living with a time bomb and watching the sand in the hourglass run out” (Bunzel, Wollenek, & Grundbock, 1992). Thoughts about death became prominent as people became more ill: ”God, if I don’t get the transplant, I wonder how long I can survive?” (Flynn, Daiches, Malpus, Yonan, & Sanchez, 2013). One patient waiting for lung transplantation described being on a waiting list as living from day to day, feeling both miserable and yet hopeful, always wondering when “the phone call” is going to come, and making plans for “after the operation” (Thomsen & Jensen, 2009). Another lung transplant candidate reported that “I have no choice, but to accept that my family and I must simply put our lives on hold until after the transplant surgery” (Naef & Bournes, 2009).

2.6 The early years after lung transplant

Most patients experience a rapid change in health soon after transplantation. Because of the transplantation, patients transition quickly from life with minimal lung function and maximal restrictions to life with normal lung function, no dyspnea, and more energy (Rosenberger, Dew, DiMartini, et al., 2012). Notwithstanding, it usually takes several years for patients to fully adjust to their new life situation after their transplant (Langer, 2015).

2.6.1 Health-related quality of life of lung transplant recipients

Health-related quality of life is an important outcome measure to assess the effectiveness of lung transplantation. The World Health Organization (WHO) defines quality of life as “individuals perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment" (WHO, 1997, pp. 1). The term 'health-related quality of life' (HRQoL) is a multidimensional construct and reflects the health and disease-related aspects of quality of life. The concept of HRQoL incorporates domains that include physical, psychological, and social functioning (WHOQOL group, 1993). HRQoL measurement quantifies the impact of disease and treatments on daily life and well-being in a formal and standardized way (Yusen, 2009).

Within transplant medicine, a considerable number of outcome studies have demonstrated significant improvements in HRQoL following lung transplantation relative to the pre-transplant period (Gerbase, Spiliopoulos, Rochat, Archinard, & Nicod, 2005; Kunsebeck et al., 2007; Vermeulen et al., 2004). Quality of life benefits can already be observed within the first six months of a transplant and appear to remain stable for a period of three to five years (Limbos et al., 2000; Santana et al., 2009). This improvement in HRQoL after LTx are primarily related to considerably better physical function, increased vitality, fewer restrictions in social and leisure activities, more energy, and less pain and discomfort relative to pre-transplant levels (Lanuza et al., 2012; Vermeulen et al., 2003). Only few authors have investigated predictors of HRQoL outcomes after transplantation. Predictors for poor post-transplant HRQoL outcomes included a single lung transplant, older age at the time of transplantation, and recurrent infections (Kugler et al., 2005). The onset of bronchiolitis obliterans syndrome (BOS) (Santana, Feeny, Ghosh, & Lien, 2012), side effects from immunosuppressant medication (Smeritschnig et al., 2005), and pain (Girard et al., 2006) also significantly reduced post-transplant HRQoL. In contrast, results on other potential outcome predictors, including gender, psychiatric history, longer waiting times for transplantation, haven been contradictory and were supported only by single studies (Dew et al., 2012; Gerbase et al., 2005). Further research is warranted to investigate predictions of postoperative complications and reduced post-transplant HRQoL.

2.6.2 Mental health of lung transplant recipients

During the early postoperative phase, delirium is common among lung transplant candidates, mostly due to hypoxia (Hafliger, 2005). However, its prevalence and prognostic significance have not been systematically investigated. There are only few studies indicating that the occurrence of delirium in lung transplant recipients was associated with poorer pre-transplant cognitive functioning and longer hospital stays (Smith et al., 2014; Smith et al., 2015). Although lung transplant recipients report significantly better mental health than transplant candidates, anxiety, depression and adjustment disorders occur frequently in patients within the first year after transplantation with prevalence rates up to 30% (Dew et al., 2012; Kugler et al., 2013). Evidence also supports associations between pre-transplant risk factors and post-transplant mental health, including female gender, a longer wait for transplantation, and having poor caregiver support as major risk factors for the onset of anxiety and depression post-transplant (Dew et al., 2012). However, surprisingly few studies exist that investigated onset rates and risk factors for psychiatric disorders in lung transplant recipients. This is an important research gab as studies on other solid organ transplantation indicated psychiatric morbidity as a predictor for negative long-term outcomes (DiMartini et al., 2011; Rosenberger, Dew, Crone, & DiMartini, 2012). The impact of psychiatric conditions on the morbidity and mortality of lung transplant recipients remains inconclusive and further research is warranted to investigate these associations among a broader range of psychiatric predictors.

2.6.3 Adherence to medication regimen in lung transplant recipients

Non-adherence to immunosuppressive therapy is a common problem in the treatment of solid organ transplant recipients, with severe consequences for the patient’s health, including acute rejection and mortality. Adherence is defined as “the extent to which a person’s behavior –

taking medication, following a diet, and/ or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" (WHO, 2003). The prevalence of non-adherence reported in the context of organ transplantation ranges widely, between 20% and 50% (Chisholm, 2002; Dew et al., 2007; Germani et al., 2011). Furthermore, pre-transplant medication non-adherence is predictive of post-transplant non-adherence with immunosuppressives (De Geest et al., 2014), and post-transplant non-adherence increases over time (Dew et al., 2007; Germani et al., 2011). However, non-adherence rates differ greatly between different organ groups. In lung transplant recipients, non-adherence to immunosuppressive therapy is comparable to that observed among heart transplant patients, and superior to what is seen among liver or kidney transplant patients (De Geest et al., 2014; Dew et al., 2008; Goetzmann et al., 2008).

The World Health Organization (WHO, 2003) proposes five interacting dimensions affecting medication adherence: 1) social/economic factors; 2) the health-care system; 3) condition-related factors; 4) therapy-related factors; and 5) patient-related factors. These five dimensions of adherence are summarized in Figure 3. In one literature review (Dew et al., 2007), non-Caucasian ethnicity, poorer social support, and poorer perceived health were the most consistently-observed determinants of non-adherence to medical regimens after solid organ transplantation. Further psychosocial variables that appear to influence immunosuppressive non-adherence in organ recipients are younger age (Bosma, Vermeulen, Verschuuren, Erasmus, & van der Bij, 2011), poor social and family support (Chisholm, 2002; Hugon et al., 2014), social isolation (Germani et al., 2011), a low internal locus of control (Burker, Evon, Galanko, & Egan, 2005), and a difficult doctor-patient relationship (Dew et al., 2007). Non-adherent transplant patients also tend to have lower perceptions about the necessity of medications, weaker beliefs that their medication will prevent rejection and greater concerns about potential harm resulting from their medication than adherers

(Kung, Koschwanez, Painter, Honeyman, & Broadbent, 2012). Given the negative consequences of non-adherence to medical regimens on clinical outcomes, the behavioral dimension of transplant patient management deserves increased attention, both in research and clinical practice. Efforts to implement adherence-enhancing interventions to encourage proper medication-taking behavior are an important component of post-transplant care (De Geest, Dobbels, Fluri, Paris, & Troosters, 2005).

Social/ economic factors	**Health-care system**	**Condition-related factors**	**Therapy-related factors**	**Patient-related factors**
Young age Low educational level Lack of social support Unstable living conditions High medication cost	Difficult provider-patient relationship Poor provider's communication skills Disparity between health beliefs of the health care provider and patient Lack of positive reinforcement from the health care provider Incomprehensible patient information materials	Chronic disease Symptom severity Psychiatric disorders (e.g. depression, anxiety) Mental retardation	Complexity of medication regime (dose, mastery of techniques) Duration of therapy Lack of immediate benefit of therapy Actual or perceived unpleasant side effects Treatment interferes with lifestyle/ requires sign. behavioral changes	Lack of knowledge about the disease Insufficient understanding why medication is needed No perceived benefits of treatment Lack of motivation Fear of possible averse effects/ dependence Frustration with health care provider Stress, anxiety, depression substance abuse

Figure 3. Five dimension of adherence to long-term therapies according to WHO (WHO, 2003, pp. 27-30).

2.7 Long-term outcomes after lung transplantation

In subsequent years following transplantation, patients tend to become more stable and secure dealing with medical and psychosocial issues and usually shift their focus towards reestablishing normalcy in everyday life. Yet, lung transplant recipients often remain chronically ill and the risk of medical complications remains (Goetzmann et al., 2010). Major long-term complications that survivors of lung transplantation develop include chronic rejection and medical complications that arise as a consequence of immunosuppressive therapy, like renal failure, diabetes, cardiovascular complications like hypertension and atherosclerosis, osteoporosis, and malignancies like skin cancer and lympho-proliferative disorders (Yusen et al., 2014). Only few longitudinal studies have investigated long-term outcomes of HRQoL after lung transplantation. Based upon these results, it appears that, beyond 5 years after transplantation, HRQoL outcomes become less predictable. There are many lung transplant recipients who ultimately start to experience a decline across several dimensions of HRQoL, largely due to an increase in co-morbid conditions and the onset of chronic rejection reaction (Rutherford et al., 2005; Vermeulen et al., 2003). Besides, these long-term post-transplant complications are associated with an increased risk of emotional distress and reduced social function (Rutherford et al., 2005). Future investigations may address these limitations of prior research by examining determinants of post-transplant HRQoL through prospective longitudinal study designs.

2.8 Mental processing of lung transplantation

2.8.1 Theoretical concepts

Despite the potential of lung transplantation to prolong life and to improve health-related quality of life, the psychological processes associated with solid organ transplantations largely remain unknown. To date, only a few studies have been published investigating the mental processing of organ transplants. Most of these studies have relied on psychoanalytic concepts to explain what goes on psychologically in patients after they receive their new organ. Since the early nineteen seventies, which is when the first successful organ transplantations occurred, some investigators have utilized psychoanalytic methods to study the psychological implications of organ transplantation in depth, though this has primarily been among kidney transplant recipients (Lefebvre, Crombez, & LeBeuf, 1973; Muslin, 1971, 1972). In this context, organ integration refers to the mental process of experiencing the transplanted organ as part of the person's self and not as part of the deceased donor or as a foreign object (Boothe, Boehler, & Goetzmann, 2013). In postmortem donation, as is the case in lung transplantation, the psychological processing includes not only the incorporation of an organ extracted from someone else's body, but also the fact that the organ was donated by someone who is now deceased; in other words, for lung transplant recipients to live, someone else had to die. In this sense, lung transplantation becomes an extreme experience that raises philosophical questions regarding one's identity of self and the meaning of life (Quintin, 2013).

In accordance with the psychoanalytic conceptualizations of organ integration proposed by Muslin (1972) and Lefebvre et al. (1973), Neukom, Corti, Boothe, Boehler, and Goetzmann (2012) introduced a psychodynamic model to describe the psychological processes that occur in lung transplant patients relative to their organ donor. This proposed model has three stages. In the first, called *the foreign body stage*, self-representation is consistent with donor representation, while the lung remains externalized. In this initial phase of mental processing, the recipient identifies subconsciously with the unknown donor. In the second stage, *the transitional stage,* the donor and the lung become transitional; i.e., both the lung and donor can be experienced simultaneously as both foreign and part of the recipient. This means that the lung is perceived to belong to both the donor and the recipient. In the final stage, which is called *the stage of complete internalization,* the graft becomes progressively integrated into the patient's own body image, and thus is gradually accepted as part of the patient's self. In contrast, the donor is moved progressively into an external position and is increasingly represented as foreign and distinct from oneself.

2.8.2 Empirical findings

To date, only a few authors have empirically examined the mental processing of lung transplant patients. For instance, Goetzmann et al. (2009) reported that 90% of 76 lung transplant patients viewed their new lungs as a part of themselves, while 66% mentioned frequently thinking about their lung donor, but fewer than 20% believed that they had adopted any of the donor's characteristics. Complementarily, Neukom et al. (2012) examined the relationship between lung transplant recipients and their unknown deceased donors. Almost all of the study subjects expressed concern over the questions of whether and how they were connected with their donor; but only a minority (20%) admitted to having latent feelings of guilt related to the deceased donor. Furthermore, Goetzmann et al. (2009) found that poor organ integration predicted low rates of adherence to treatment and strong feelings of guilt, and that high ratings of donor identification predicted higher levels of psychological distress. In addition, patients' worries concerning the transplant were significantly associated with patient feelings of distress (Goetzmann et al., 2010). Conversely, mental processing of the transplant was found to be favorable when the graft was perceived as part of the patient's own body (Goetzmann et al., 2009), and when the patient managed to view the donor as external (Boothe et al., 2013).

In conclusion, the findings briefly outlined above suggest that undergoing transplantation represents a physical and psychological challenge that can essentially modulate a patient's self-concept and body image. Although these psychological theories regarding the processing of a lung transplant are preliminary and few in numbers, they contribute to a deeper understanding of the transplant experience. Further investigation is needed, however, to confirm and elaborate on these theories. Employing qualitative methods could generate further insights into the psychological adjustments to life that occur in lung transplant recipients, and the emotional difficulties they face.

2.9 Rationale

Lung transplantation is the only available therapy for patients with end-stage pulmonary diseases of different etiologies when other alternative treatment options are no longer effective (Hofer et al., 2009). The shortage of suitable donor organs in Switzerland demands that patients are selected for lung transplantation only if they are likely to experience a survival benefit of the procedure (Hook & Lederer, 2012). However, approximately 20% of lung transplant recipients die within the first year after lung transplantation (Inci et al., 2013), indicating, that the patient evaluation and selection criteria for lung transplantation failed to identify those at high risk for severe early complications. Although the majority of patients experience considerably improved psychological well-being and quality of life after transplantation, a small proportion of patients experience no significant improvement in their health-related quality of life (Yusen, 2011). Typically, most investigators have looked at post-transplant outcomes of the entire study group and subgroup analysis for detecting patients with poor post-transplant outcomes have rarely been performed. Lastly, the lung transplant procedure is associated with complex ongoing medical and psychological challenges for patients that start prior to surgery and continue long beyond the first year of survival (Rosenberger, Dew, DiMartini, et al., 2012). In this perspective, ongoing research of long-term post-transplant outcomes after lung transplantation is both of clinical and scientific relevance to evaluate outcomes of lung transplantation, to identify those patients with poor post-transplant HRQoL-trajectories, to determine factors that are predictive for postoperative complications and to sustain and increase gains related to this procedure by providing psychosocial interventions.

3 Empirical work

3.1 Aims and hypotheses

The overall aims of this thesis were to evaluate health-related quality of life (HRQoL) and psychological outcomes after lung transplantation and to investigate psychological adjustment to lung transplantation within the first six months post-transplant. To achieve this, three separate but related studies were conducted using three distinct methodological approaches. The first study was a systematic review of the literature analyzing HRQoL outcomes of lung transplantation and the study designs and methodology adopted; the second and third were a prospective longitudinal study identifying patients at risk for poor postoperative outcomes and a longitudinal qualitative study examining the patients' experience with their transplant and adjustment to normal life, respectively. In the following section, the three studies are introduced briefly, together with each study's rationale and aims.

3.1.1 A systematic review of health-related quality of life and psychological outcomes following lung transplantation

The issues of health-related quality of life (HRQoL) and psychological outcomes following lung transplantation have been investigated in a number of outcome studies. A variety of assessment instruments have been suggested for measuring psychological health outcomes after transplantation, but only a small number of investigators have systematically evaluated the strengths and limitations of these measures. Moreover, the interpretation of quality of life outcomes related to transplantation is often affected by methodological limitations, such as bias and unmeasured confounding that might hinder the generalizability of results. We addressed this knowledge gap via a systematic literature review focusing on empirical research articles assessing HRQoL and psychological outcomes in adult lung transplant recipients. The objectives of this review were 1) to determine which validated self-report instruments are being used in the literature to assess HRQoL and psychological outcomes after lung transplantation; 2) to explore the study designs and methodology used; 3) to review the instruments and outcomes that have been utilized most frequently; and 4) to provide recommendations for selecting appropriate outcome measures. By systematically analyzing post-transplant outcomes regarding HRQoL and psychological outcomes, identifying understudied thematic areas and knowledge gaps for future research, this study provided an important bases for the following two empirical work.

3.1.2 Psychological distress and quality of life in lung transplant patients. A six months observational study

Lung transplantation aims not merely to prolong recipients' lives and reduce disability, but also to improve health-related quality of life (HRQoL). However, lung transplant recipients are a heterogeneous group, and do not necessarily experience the same improvements in health status. In the medical literature, the post-transplant HRQoL trajectories of lung transplant recipients and predictors of post-transplant HRQoL are not well described. An improved understanding of the magnitude and durability of HRQoL following lung transplantation has important clinical and research implications. To bridge the existing research gaps, the aims of this study were threefold: 1) to assess psychosocial outcome trajectories in lung transplant recipients related to psychological distress and HRQoL over the first six months post-transplant, 2) to identify patients with poor post-transplant trajectories, and 3) to determine potential predictors of psychological distress and poor HRQoL at six months post-transplant. It was hypothesized that HRQoL will improve within the first six months post-transplant but that not all patients will show the same degree of HRQoL improvements after lung transplantation.

3.1.3 Early postoperative adjustment to lung transplantation. A longitudinal qualitative study

While several published studies have focused on the quantitative assessment of post-transplant HRQoL, only a few have qualitatively examined the experience of transplantation and the impact this procedure has on patients' everyday lives. Qualitative data analysis is generally considered a powerful tool for studying the complexities of human experiences within a specific research field (Anderson, 2010). Our aim in this last study was, therefore, to delve deeper into patients' experiences with their transplant and adjustment to normal life within the first six months of the procedure utilizing a qualitative approach. We used semi-structured interviews to specifically explore the thoughts, feelings and attitudes of lung transplant recipients with respect to the transplantation process, their new lungs, the organ donor, and their medication regimen over their first six months post-transplant. A more comprehensive understanding of the issues that patients consider important in the early postoperative phase could improve clinical decision-making and interventions. It was hypothesized that the frequency of comments of most codes will diminish within the first six months post-transplant and that gender differences in response rate can be observed.

4 Empirical work 1

A systematic review of health-related quality of life and psychological outcomes following lung transplantation

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4.1 Abstract

Background: Lung transplantation (LTx) aims to reduce physical disability and mental distress, extend survival, and improve health-related quality of life (HRQoL). This systematic review aimed 1) to augment evidence regarding measures to assess HRQoL and psychological outcomes following lung transplantation (LTx), and 2) to summarize HRQoL and psychological outcomes after LTx.

Methods: Validated and standardized instruments with well-known psychometric properties used for assessing HRQoL and psychological outcomes after LTx were identified by means of comprehensive literature searches of Psychinfo and Medline/PubMed, up through March 2014, using the following search terms in various combinations: lung transplantation, physical functioning, symptom experience, mental health, anxiety, depression, distress, social functioning, life satisfaction, and health-related quality of life.

Results: The search strategy identified 371 titles and abstracts. Of these, 279 were retrieved for further assessment and 63 papers selected for final review. Thirty-nine studies were found for HRQoL, 15 for physical functioning, 5 for mental health, and 4 for social functioning. A total of 50 psychometric instruments were encountered.

Conclusions: Considerable heterogeneity exists in methodology, operational concepts and applied outcome measures in the existing literature on HRQoL and psychological outcomes after LTx. Nevertheless, those studies generally point to significant improvements in both mental health and HRQoL post transplant. Further research clearly is warranted utilizing consistent outcome measures, including LTx-specific measures, and longitudinal study designs.

Study registration: PROSPERO CRD42013006204.

4.2 Introduction

Among the multiple aims of lung transplantation (LTx), the most important are to reduce disability, extend survival, and improve health-related quality of life (HRQoL) (Kugler et al., 2007; Munro, Holland, Bailey, Button, & Snell, 2009; Rodrigue, Baz, Kanasky, & MacNaughton, 2005). Traditionally, patient survival has been the primary LTx outcome measured. With improved survival rates, however, post-transplant HRQoL has become an important component of any evaluation of benefits. Furthermore, lung transplant patients within different diagnostic groups do not necessarily experience the same survival benefits or exhibit the same post-transplant trajectories (Yusen et al., 2014). Therefore, it is clinically important to assess postoperative HRQoL and mental health, as well as to identify those patients at risk for poor post-transplant outcomes.

In transplant medicine, a variety of assessment instruments have been suggested, though there is no standard inventory to formally evaluate health-related quality of life (HRQoL) or psychological outcomes after lung transplants. An overview of existing self-report diagnostic instruments would assist researchers and clinicians in choosing the most appropriate psychometric instruments for assessing post-transplant outcomes in lung transplant populations. However, as yet, only a small number of authors have evaluated the relative merits of specific outcome screening instruments after organ transplantation of any kind (Cleemput & Dobbels, 2007; Goetzmann, Klaghofer, Spindler, et al., 2006; Klaghofer et al., 2008; Singer et al., 2013; Yusen, 2011). A comprehensive systematic review was presented by Singer et al., (2013) which thematically assessed published studies of HRQoL in lung transplant patients. However, scientific articles on mental and psychosocial health of LTx-recipients were not considered in this report. To address this knowledge gap, this paper systematically focuses on published empirical studies of HRQoL and psychological outcomes among adult lung transplant recipients. According to the definition of health, which was mandated by the World Health Organization as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO, 1948), we directed our analyses towards the three HRQoL-domains physical functioning, mental health, and social functioning. We considered this multidimensional approach essential to adequately evaluating the postoperative clinical management of adult lung transplant recipients. Moreover, these three HRQoL-domains have generally been considered when investigating postoperative outcomes after solid organ transplants (Cleemput & Dobbels, 2007; De Geest et al., 2013; Dew et al., 2000).

The overall purposes of this systematic review were 1) to determine which validated self-report instruments are being used to assess HRQoL and psychological outcomes after lung transplantation; 2) to explore the study designs adopted for the eligible studies; 3) to review outcomes among those instruments that have been utilized most frequently; and 4) to provide recommendations for selecting appropriate outcome measures.

4.3 Methods

By systematic literature review, validated and standardized outcome measures with well-known psychometric properties were identified that had been applied to evaluate HRQoL and psychological outcomes following lung transplants. Data extraction and the study review process were conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2010). In accordance with these guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42013006204).

4.3.1 Search strategy

A comprehensive literature search was performed to identify scientific studies that included at least one measure of HRQoL and/or psychological outcome after lung transplantation. For the purposes of this review, physical functioning was defined in terms of the level of physical activity in daily life, symptom experiences (pain), and the physical side effects of immunosuppressant medication. Mental health was considered the patient's levels of anxiety, depression and/or psychological distress; and social functioning was characterized in terms of the patient's quality of relationships, social support, and level of life satisfaction. A systematic search of electronic databases, including Psychinfo and Medline/PubMed, was conducted from inception to March 2014. Keywords used for the search included lung transplantation, physical functioning, symptom experience, mental health, anxiety, depression, distress, social functioning, life satisfaction, and health-related quality of life.

4.3.2 Eligibility criteria

English- and German-language studies were eligible if they examined any form of HRQoL or psychological outcome of lung transplant recipients, in terms of physical functioning, psychological functioning, and/ or social functioning using standardized validated instruments. Considered for inclusion were also studies on pre- versus post-comparison of lung transplant patients. Only studies involving patients who were adults (≥ 18 years old) at the time of lung transplantation were included. Studies were excluded if they involved solely lung transplant candidates (i.e. patients referred for lung transplant), pediatric lung transplant recipients, or recipients of additional solid organ transplants, such as stem cells, bone marrow, liver, kidney, heart or heart-lung. Moreover, systematic reviews, meta-analyses, qualitative studies, and case-study investigations were excluded, as were unpublished manuscripts, Master's or Doctoral theses, books and book chapters, studies for which only abstracts were available, and studies for which data collection methods were not adequately reported.

4.3.3 Data selection and extraction

The first stage of paper selection was based upon titles and abstracts. Full-text articles were obtained for all abstracts meeting the inclusion criteria for further evaluation, and for articles that could not be rejected with certainty. The reference lists of papers meeting the eligibility criteria were screened for additional relevant papers that may have been missed by our electronic searches. Two researchers (A.S. and M.T.) independently evaluated the selection of eligible papers following the inclusion and exclusion criteria. In cases of disagreement, consensus was achieved by discussion. The process of study selection is outlined in Figure 4. The evaluation of data was processed by means of qualitative description. Results were summarized in tables and presented in a narrative form.

4.4 Results

The search strategy identified 371 titles and abstracts. Of these, 279 were retrieved for further assessment and 63 papers selected for inclusion in the final review. All eligible articles were published between 1994 and 2013.

4.4.1 Study characteristics

Study designs used in the 63 eligible studies were not always reported clearly. The majority of the papers (54%) used a cross-sectional study design that predominantly assessed lung transplant patients twelve months postoperative or later (68%). The duration of follow-up ranged from six months to 8.5 years post transplant. The average sample size across all studies was 80.1 (range: 10 - 287) participants. Examination of the studies that described participants' age ranges revealed an average participant age of 46.1 years (age range: 29 – years). Fifty-two percent of the participants across the 63 studies were male. The most frequent underlying diagnosis for lung transplantation was chronic obstructive pulmonary disease (COPD) (37.8%), followed by cystic fibrosis (35.6%) and idiopathic pulmonary fibrosis (17.7%). Nine percent of the patients suffered from primary pulmonary hypertension and 19.9% suffered from some other disease. The studies included in the review are summarized in Table 2.

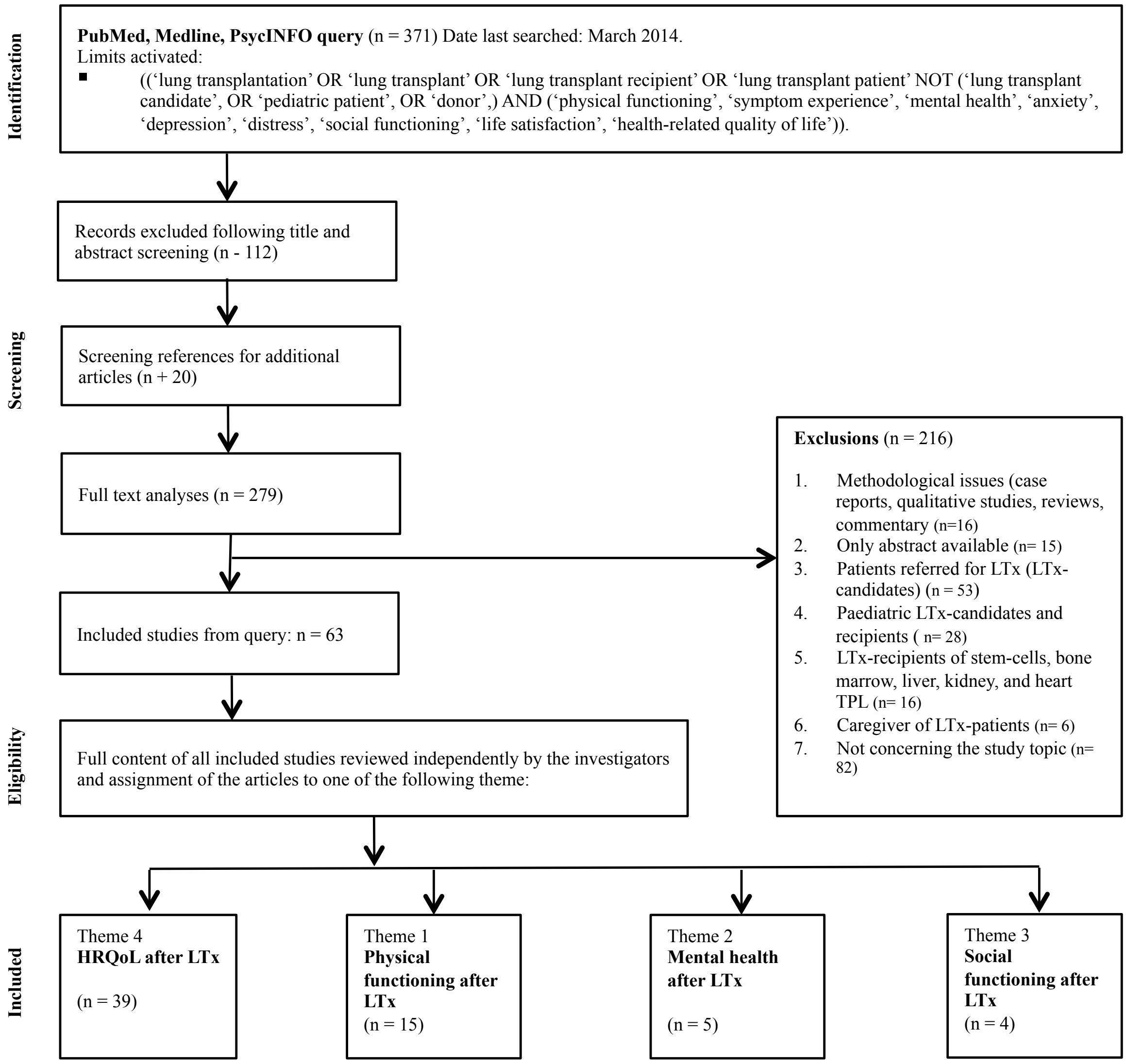

Figure 4. Search retrieval process

4.4.2 Outcome measures

All studies included in our analysis used at least one psychometric instrument. A variety of outcome measures were administered: 50 different psychometric measures in total. Of 13 different HRQoL outcome measures identified, the 36-Item Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992) was the most commonly used (19 studies). Standardized questionnaires were rarely used to evaluate physical functioning-related issues, like pain or symptom occurrence; only seven standardized questionnaires were encountered. Physical functioning was more commonly assessed by means of one or more exercise tolerance tests. The most frequent self-reported instrument applied to measure physical functioning was the Karnofsky Performance Status Scale (seven studies) (Karnofsky & Burchenal, 1949). Twenty-one different outcome measures were identified assessing mental health, the most frequently-used measure being the State-Trait Anxiety Inventory (STAI; 9 studies) (Spielberg & Vagg, 1980), followed by the Hospital Anxiety Depression Scale (HADS; 8 studies) (Zigmond & Snaith, 1983). Six different instruments rated social function, the most often used instrument being the Short-Form Social Support Questionnaire (F-SoZu) (Sommer & Fydrich, 1998); however, this was utilized in only three studies. The psychometric instruments used in the eligible studies to assess HRQoL and psychological outcomes of lung transplant recipients are summarized in Table 3.

4.4.3 HRQoL and psychological outcomes after LTx

Health-related quality of life after LTx

The majority of the studies (n = 32) investigating HRQoL after lung transplantation demonstrated a significant improvement in almost all HRQoL domains, except pain, within the first three years post-transplant (Finlen Copeland et al., 2013; Gerbase et al., 2005; Kunsebeck et al., 2007; Vermeulen et al., 2004). Some authors even reported the HRQoL of transplant recipients to become comparable to that of the general population (Stavem et al., 2000; Vermeulen, van der Bij, Erasmus, & TenVergert, 2007). More specifically, improvements in SF-36 domains were primarily related to better overall general health, physical health, vitality, and social functioning, fewer role limitations due to physical health, and total HRQoL (Archonti et al., 2004; Cohen, Littlefield, Kelly, Maurer, & Abbey, 1998; Limbos, Chan, & Kesten, 1997; Limbos et al., 2000; Rodrigue, Baz, Kanasky, et al., 2005; Rutherford et al., 2005; Stavem et al., 2000). Improvements reported in the Nottingham Health Profile (NHP) domains within the first 12 months post transplant included gains in mobility, energy, sleep, and activities of daily life, as well as less dyspnea (TenVergert et al., 1998; Vermeulen et al., 2003; Vermeulen et al., 2004). Gender differences in HRQoL improvements post transplant were revealed by three different studies (Limbos et al., 1997; Rodrigue, Baz, Kanasky, et al., 2005; Santana et al., 2012) in which women reported more frequent and problematic post-surgery symptoms and a lower percentage gain in HRQoL than men.

Longitudinal studies of HRQoL

Only a small number of studies was identified examining HRQoL in patients surviving more than three years post-transplant (Kugler et al., 2005; Rutherford et al., 2005; Stavem et al., 2000; Vermeulen et al., 2003). As such, the trajectory beyond three years post-transplant appears to remain uncertain, mostly due to the lack of data. At 38 months post-surgery, Stavem et al. (2000) reported significantly better scores in all SF-36 domains. In contrast, Vermeulen et al. (2003), investigating recipients 55 months post-transplant, observed a decline in several dimensions of HRQoL due to an increase in co-morbid conditions and the incidence of bronchiolitis obliterans syndrome (BOS). Similarly, in patients living 5 to 6 years with their allograft, Kugler et al. (2005) noted significantly reduced HRQoL across all subscales, except social functioning; reduced HRQoL was associated with BOS. Finally, Rutherford et al. (2005) reported significantly lower scores for the SF-36 parameters physical functioning, role-emotional, and general health, as well as considerably lower energy and social functioning among lung transplant recipients surviving 10 years postoperatively, relative to the normative population.

Predictors of HRQoL after LTx

BOS was the strongest determinant of physical health status, its presence associated with reduced energy, mobility and well-being (Kugler et al., 2005; Santana et al., 2012; Vermeulen et al., 2003; Vermeulen et al., 2007). Additionally, the side effects of immunosuppressants significantly impaired HRQoL (Smeritschnig et al., 2005). In a similar vein, pain was found to significantly reduce HRQoL and to increase depressive symptoms (Girard et al., 2006). However, pain was more prevalent in older recipients with unilateral transplants and in those with emphysema (Girard et al., 2006; Vasiliadis, Collet, & Poirier, 2006). Further predictors of poor HRQoL were cystic fibrosis, a single lung transplant, older age at the time of transplantation, and recurrent infections (Kugler et al., 2005). Only a single study failed to identify a negative influence of incidence BOS or poor FEV1 recovery (forced expiratory volume in 1 second) on subjective HRQoL after LTx (Gerbase et al., 2005). Perceived social support was positively associated with HRQoL and psychological well-being (Archonti et al., 2004). Lastly, an older study by Cohen et al. (1998) revealed sleep disturbances as a mediator between pre-transplant anxiety and post-transplant adjustment and HRQoL.

4.4.4 Physical functioning after LTx

Pain

The prevalence of postsurgical pain in LTx-recipients was 49% three months after transplantation in a study investigating health-related outcomes (Girard et al., 2006). Characteristically, patients with pain were older, more likely to have undergone a unilateral transplant, and more likely to have emphysema. According to Girard et al. (2006), 28% never used analgesics to control pain, whereas 38% used analgesics irregularly and 34% used them on a daily basis. Thirty-nine months postoperatively, 18% of transplant recipients reported persistent pain and, of those, 71% admitted to using a mild analgesic (Wildgaard, Iversen, & Kehlet, 2010). Patients with postsurgical pain also experienced pain in some other part of their body. The majority experienced pain when carrying heavy bags, working, and performing other strenuous activities, but also while driving, cooking, doing office work, and sitting down for more than 30 minutes. Pain was perceived to interfere with life in roughly 50% of the respondents with pain, while sleep and HRQoL were disturbed in 57% and 54%, respectively (Wildgaard et al., 2010).

Physical symptoms experienced after LTx

Post-transplant, patients reported improved shortness of breath with activity 3, 9 and 12 months after LTx and at rest, and less fatigue three months post-transplant. Despite these significant improvements, new symptoms occurred post-operatively, including distressful nausea, changes in taste, tremors, vomiting, stomach pain, and burning or numbness in the hands and/or feet, three and six months after surgery (Lanuza et al., 2012). Similar observations were reported by Dobbels et al. (2008) and Kugler et al. (2007). Both authors reported tremors (70%), hirsutism (68%), a Cushingoid appearance (39%), and muscle weakness (32%) as the most frequently-reported symptoms three months after the transplant.

Furthermore, women and younger patients reported significantly more frequent bodily symptoms and greater levels of symptom-induced distress than men (Dobbels et al., 2008; Kugler et al., 2007). Patients, and especially men suffering from adverse drug effects, admitted often attempting to reduce medication-related sides effect by postponing their medication intake (30%), or by either dropping (8%) or reducing doses (9%) (Kugler et al., 2007). Olfactory performance was significantly below average in randomly selected outpatient LTx-recipients (Irani et al., 2010).

Impact of physical symptom experience on mental health and HRQoL

The experience of physical symptoms negatively influenced HRQoL across all dimensions (Kugler et al., 2007). Immunosuppression-induced adverse effects negatively influenced patient perceptions of HRQoL. Patients with BOS mentioned significantly more restrictions in the NHP dimensions of physical mobility and energy; this effect was noted 7, 19, 25, and 31 months after surgery. Moreover, physical symptoms negatively impacted mental health (Kugler et al., 2007). Correspondingly, the average BDI score was higher among patients with pain (Girard et al., 2006). Similarly, patients with BOS reported significantly more depressive symptoms and anxiety, both one and two years after the transplant (Van Den et al., 2000). Also, the new-onset of diabetes after LTx was associated with psychological strain (Kugler et al., 2007). However, state anxiety was not different in patients with versus without pain (Girard et al., 2006). Conversely, patients with depressive symptoms tended to experience greater symptom occurrence and higher levels of symptom-related distress (Dobbels et al., 2008).

4.4.5 Mental health of LTx-recipients

The most common psychiatric disorders found in lung transplant recipients that occurred primarily within the first year post-transplant were major depression (26-30%), panic disorder, adjustment disorders, and generalized anxiety disorders (Dew et al., 2012). Two studies found that pre-transplant depressive disorders did not predict survival after transplantation (Evon, Burker, Galanko, Dedert, & Egan, 2010; Woodman et al., 1999).

Longitudinal studies of mental health outcomes after LTx

Only one long-term study was identified that investigated mental health as long as 55 months after lung transplantation. According to Vermeulen et al. (2003), improvements in most mental health dimensions, including lower anxiety and depression levels and improved well-being, were apparent until approximately 43 months after the transplant. However, beyond 43 months, patients again started to experience increased anxiety and depression levels and reported lower levels of well-being, mostly due to renal failure, diabetes, drug-treated hyperlipidemia, and the onset of BOS.

Predictors of mental health

Pre-transplant risk factors for the onset of anxiety and depression during the first two years after transplant included a combination of pre-transplant psychiatric history, female gender, a longer wait for transplantation, early post-transplant health problems, and psychosocial characteristics - like poorer caregiver support and avoidant coping (Dew et al., 2012). However, psychiatric diagnosis pre-transplant did not appear to worsen post-surgical survival (Evon et al., 2010; Woodman et al., 1999).

4.4.6 Social functioning after lung transplantation

Only three eligible studies addressed the psychosocial health of lung transplant recipients (Archonti et al., 2004; De Vito Dabbs et al., 2013; Goetzmann et al., 2005). Social support was found to be positively associated with HRQoL and inversely associated with levels of depression; and, when social support was perceived as positive, the risk of psychopathology was reduced (Archonti et al., 2004). While patient self-esteem was significantly related to social support (Goetzmann et al., 2005), low self-care agency was associated with significantly poorer caregiver relationship quality and more psychological distress. Accordingly, the quality of caregiver relationships was a significant predictor of postsurgical anxiety and depression (De Vito Dabbs et al., 2013).

4.4.7 Psychometric properties of articles included

The quality of the reporting and extent of psychometric assessment of the outcome measures varied. Relatively few studies (n= 7) indicated the psychometric properties of the instruments used in the lung transplant population (see Table 3), with Cronbach's alpha ranging between .65 and .96. In the eligible studies, no transparence was given regarding any *a priori* power calculation to estimate the required sample size to satisfy study objectives.

4.4.8 Major limitations of eligible studies

Severe methodological limitations were encountered in almost all eligible studies, including selection/survivor bias (90%), the use of cross-sectional versus longitudinal designs (56%), heterogeneous group/confounding variables (46%), missing data (22%), small sample sizes (19%) that limited both statistical power and generalizability, short follow-up time (16%), and the lack of control/comparison groups (12%) (see Table 2).

Table 2. Summary of studies included in the review

	Author, date	**Title**	**Study design**	**Sample Size**	**Outcome measures**	**Outcome**	**Methodological limitations**
HRQoL	Anyanwu et al., 2001	Assessment of quality of life in lung transplantation using a simple generic tool.	Cross-sectional study design (candidates vs. recipients 6M – 3 yr after LTx)	255	EQ-5D	61% of LTx-candidates reported extreme problems in at least one EQ-5D-dimension compared with 20% of single und 4% of bilateral LTx-recipients ≥ 3yr post-transplant. EQ-5D was a simple method for deriving a single utility value for HRQoL and was responsive to changes after LTx.	Confounding variables (heterogeneous population) Cross-sectional study design Survivor bias
	Archonti et al., 2004	Physical quality of life and social support in patients on the waiting list and after a lung transplantation.	Cross-sectional study design (candidates vs. recipients 5 – 47M after LTx)	20	BDI F-SoZu SF-36	Sign. improvements post LTx were observed in physical functioning, vitality, health perception and social functioning. The perceived support correlated negatively with the level of depression.	Cross-sectional study design Small study cohort Survivor bias Confounding variables (heterogeneous population)
	Buschbach et al., 1994	Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis	Retrospective study design (12,14, 16M after LTx)	6	Karnofsky Performance Index NHP VAS	The preliminary results suggested that the improvements of quality of life for patients with cystic fibrosis after bilateral lung transplantation was comparable to the improvement of quality of life after heart transplantation.	Small study sample Retrospective study design Survivor bias
	Cohen et al., 1998	Predictors of quality of life and adjustment after lung transplantation.	Cross-sectional study design (candidates vs. LTx-recipients > 6M)	60	BDI BPI (Basic Personality Inventory) MHI SF-36 STAI	Anxiety and psychopathology were found to predict post-transplant adjustment; greater pre-transplant anxiety predicted worse post-transplant HRQoL. Subjective sleep disturbances were associated with poorer adjustment and HRQoL.	Cross-sectional study design Confounding variables (heterogeneous population) Missing data Survivor bias
	Eskander et al., 2011	BODE index and quality of life in advanced chronic obstructive pulmonary disease before and after lung transplantation	Prospective longitudinal study design (before vs. ± 4M pLTx)	112	SGRQ SF-36 VAS	BODE was directly associated with SGRQ and inversely related to all other HRQoL measures ($p < 0.05$). Early post-transplant improvements in HRQoL were also seen across the spectrum of BODE scores from 5 to 10.	Short follow-up time Selection bias
	Finlen Copeland et al., 2013	Impact of Lung Transplantation on Recipient Quality of Life	Multicenter, prospective randomized longitudinal study (3, 6, 9, 12M after LTx)	131	SF-36	Over the first year after lung transplantation, the SF-36 Physical Component Score significantly increased whereas the Mental Component score did not change from baseline.	Missing data Survivor bias Short follow-up time
	Gerbase et al., 2005	Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome.	Longitudinal follow-up study for 2 years after LTx	44	FEV1 SGRQ VAS 6MWD	Sign. improvements on the FEV1, 6MWD and SGRQ were observed after LTx. Increased risk for patients with single LTx for lower FEV1 and increased risk for BOS was observed.	Selection bias Missing data

Gerbase et al., 2008	Long-term Health-related Quality of Life and Walking Capacity of Lung Recipients With and Without Bronchiolitis Obliterans Syndrome.	Prospective longitudinal study followed (3, 6, 9, 12, 18, 24M after LTx)	58	Record of clinical complications SGRQ 6MWD	BOS was a sign. predictor of lower SGRQ and reduced time free of clinical complications, but not of 6MWT.	Survivor bias, Missing data Confounding variables (heterogeneous group)
Girard et al., 2006	Prevalence and Impact of Pain on the Quality of Life on Lung Transplant Recipients.	Cross-sectional study design; > 3M after LTx	96	BDI BPI (Brief Pain Inventory) SF-36 STAI	The prevalence of pain in LTx-recipients was 49%. Patients with pain were older, more likely to have undergone unilateral LTx, and more likely to have emphysema. BDI was higher for patients with pain. No sign. difference was found regarding anxiety. Pain-free patient had sign. higher physical component score in the SF-36.	Cross-sectional study design Confounding variables (heterogeneous group) Survival bias
Goetzmann et al., 2008	Psychological response and quality of life after transplantation: a comparison between heart, lung, liver and kidney recipients.	Cross-sectional study design (≤ 20 yr after LTx)	76	SF-36 TxEQ	72% of patients developed a feeling of responsibility for the received organ. Conscious feelings of guilt and shame were harbored by only a minority of patients. Lung transplant patients showed significantly better adherence and worry less about their transplant.	Cross-sectional study design Selection bias Missing data
Gross et al., 1995	Long-term health status and quality of life outcomes of lung transplant recipients.	Prospective follow up study (before and 6 and 12M after LTx)	18	IWB Karnofsky Performance Index MOS 20	While LTx-candidates reported poor day-to-day functioning, LTx-recipients were able to carry on normal activities (although with symptoms) but required occasional assistance from others. Also, LTx-recipients reported better functioning on the Karnofsky index and in every MOS dimension (p<.001).	Short follow-up time Confounding variables (variance in follow-up time and sample size pre vs. post-transplant) Selection bias
Ihle et al., 2011	Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: a prospective, randomized study.	Cross-sectional study design: inpatient rehabilitation program vs. medical standard therapy (4.5 ± 3.5yr after LTx)	60	Cardiopulmonary exercise testing SF-36 SGRQ Quality of Life Profile for Chronic Diseases questionnaire 6MWD	Both group sing. improved their maximal exercise capacity. In both study groups, HRQoL tended to improve. Sign. correlations were found for exercise capacity and HRQoL scales.	Cross-sectional study design Confounding variables (temporal variation in data collection) Selection bias Lack of control group
Irani et al., 2006	Lung transplant recipients holding companion animals: impact on physical health and quality of life.	Cross-sectional study design	89	FLZM HADS LOT F-SoZu	In lung transplant recipients keeping pets the frequency of somatic complications was not higher compared to lung transplant recipients without pets. After LTx, pets were associated with a better HRQoL.	Cross-sectional study design Survival / selection bias

Kugler et al., 2005	Health-related quality of life in two hundred-eighty lung transplant recipients.	Cross-sectional study design, including LTx-recipients from 3 to 14yr after LTx.	280	Quality of Life Profile for Chronic Diseases	Sign. reduced HRQoL was reported by patients living 5 to 6 yr with the allograft for all subscales, except for social functioning and was associated with incidence of BOS. CF-patients, patients with single LTx and patients of older age showed sign. decreased physical ability ratings.	Non-randomized retrospective study design Confounding variables (heterogeneous group)
Kugler et al., 2007	Symptom experience after lung transplantation: impact on quality of life and adherence	Cross-sectional study design, including LTx-recipients ≥ 3M after LTx	287	Quality of Life Profile for Chronic Diseases Self-developed questionnaire with 91 items regarding adherence and symptom experience	Women and younger patients reported a significantly higher level of symptom experience compared with their counterparts respectively. Symptom experiences negatively influenced HRQoL in all dimensions. Those who described experiencing adverse effects reported significantly more ‘‘drug holidays’’.	Cross-sectional study design Selection bias Confounding variables (heterogeneous study group: single vs. bilateral LTx)
Kunsebeck et al., 2007	Quality of life and bronchiolitis obliterans syndrome in patients after lung transplantation.	Cross-sectional study design post LTx (> 1yr post LTx)	119	BAI Center for Epidemiologic Studies-Depression Scale SF-12 Zerssen List of Complaints	41% of LTx-recipients developed BOS at 5.6 yr after LTx. Actuarial freedom from BOS was 90% at 1 yr, 80% at 3 yr, and 60% at 5yr after LTx. Recipients with BOS reported sign. lower well-being and HRQoL than those without BOS. Body functioning was mostly affected by BOS.	Cross-sectional study design Selection bias Confounding variables (heterogeneous group: single vs. bilateral LTx)
Lanuza et al., 2000	Prospective study of functional status and quality of life before and after lung transplantation.	Longitudinal, repeated measure design (before, 1M and 3M after LTP)	10	BSI SIP-136 The General Health/QOL Rating Scale	Post-transplant, patients reported sign. improvement with physical strength, current health, and HRQoL. Dramatic improvements in pulmonary function (FVC, FEV1 at 25 to 75%) were observed. The total number of psychological problems did not decrease sign. over time.	Short-follow up time Small sample size
Limbos et al., 1997	Quality of life in female lung transplant candidates and recipients.	Cross-sectional study design (> 6M after LTx)	34	BCSC DSFI HADS RSEC SF-36	No differences were found for emotional-well-being, role limitations due to emotional health and social functioning. Significant differences were found between pre and post body satisfaction scores. The Pre group reported higher sex drive. 52% of the LTx-recipients scored below the 10th percentile in overall sexual functioning.	Cross-sectional study design Selection bias Small sample size Lack of comparison group
Limbos et al., 2000	Psychological functioning and quality of life in lung transplant candidates and recipients.	Cross-sectional study design (> 6M post LTx; candidates vs. recipients)	73	BSI BCSC DSFI HADS RSES SF-36 VAS	Post LTx-patients had sign. better score on the SF-36 subscales physical health, role limitations and social functioning, visual analog scale, BSI, HADS. Many patients continued to experience impairments in psychological functioning.	Cross-sectional study design Confounding variables (variance in sample size: 36 candidates vs 73 recipients) Selection/ survival bias

Lobo et al., 2004	Estimation and comparison of derived preference scores from the SF-36 in lung transplant patients. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation.	Cross-sectional study design (≥ 6M post LTx)	99	CES-D *Scale* DS IIRS PS (Pulmonary Scale) SDS SF-36 VAS	Three practical methods of deriving preference scores form existing SF-36 data (1. Fryback et al., 2. Nichol et al., 3. Brazier et al.) were compared. Any of the 3 methods would detect differences in health states between groups. All 3 methods provide compatible findings and yield scores with good construct validity.	Cross-sectional study design Selection bias
Matthees et al., 2001	Use of complementary therapies, adherence, and quality of life in lung transplant recipients	Cross-sectional study design (≥ 6M post LTx)	99	Self-report measure of medication adherence SDS	The majority used at least 1 form of complementary and alternative medicine (CAM). Prayer, support groups and relaxation techniques were the most common. CAM users were adherent to their transplant regimen. Education, high symptom burden, female sex, and depression symptoms were associated with various types of CAM use.	Cross-sectional study design Survival/ selection bias Confounding variables (heterogeneous study groups: comparison group was small; n = 11)
Rodrigue et al., 2005	Does lung transplantation improve health-related quality of life? The University of Florida experience.	Repeated measure design (before and ≥ 6M after LTP)	66	FEV1 SF-36 TSFQ 6MWD	Significant improvements of HRQoL, FEV1 and 6MWD after LTx. Patient with longer time since LTx reported more frequent and problematic symptoms commonly associated with immunosuppression.	Selection bias Confounding variables (heterogeneous study group: comorbidities, medical condition)
Rodrigue et al., 2006	Are there sex differences in health-related quality of life after lung transplantation for chronic obstructive pulmonary disease?	Repeated measure design. HRQoL before and after LTx (≥ 6M after LTx)	37	FEV1 SF-36 TSFQ 6MWD	Substantial improvements in HRQoL, lung function, physical endurance for most patients. Women reported more frequent and problematic symptoms and a lower percentage gain in HRQoL than men.	Selection bias
Rutherford et al., 2005	Functional status and quality of life in patients surviving 10 years after lung transplantation.	Cross-sectional study design (10 yr post TPL.)	28	SF-36	29% of patients survived > 10 yr post LTx. Long-term survival after LTx was characterized by an absence or delayed development of BOS, low iatrogenic morbidity and a preserved mental, but reduced physical health status.	Survival/ selection bias Small sample size
Santana et al., 2009	Improvement in health-related quality of life after lung transplantation.	Prospective longitudinal study (before, 3 and 6M after LTx)	36	HADS HUI3 Morisky's and Godin's Questionnaire	The mean overall HUI3 scores were lower for LTx-candidates than recipients at 6M post LTx. Sign. results were found for HADS post-transplant. After 6M, LTx-recipients were more adherent to medication.	Small sample size Selection/ survival bias

Santana et al., 2012	Patient-reported outcome 2 years after lung transplantation: does the underlying diagnosis matter?	Cross-sectional study at 2yr post LTx	214	HUI3	COPD and CF-patients displayed moderate, while pulmonary fibrosis and pulmonary arterial hypertension patients displayed severe disability. COPD-Patients had the worst pain level whereas patients with pulmonary fibrosis and the worst emotion and cognition levels. BOS was the most important determinant of physical health status (p = .003).	Cross-sectional study design Selection/ Survival bias
Shih et al., 2002	The context framing the changes in health-related quality of life and working competence before and after lung transplantation: one-year follow-up in Taiwan	Prospective longitudinal study design (pre and 1, 3, 6, 12M after LTx)	8	VAS	Significant improvements in HRQoL after transplantation. The most evident improvement in HRQoL of LTx recipients occurred between 1 and 3 months post-transplant.	Small sample size Survival /selection bias Short follow-up time
Smeritschnig et al., 2005	Quality of life after lung transplantation: a cross-sectional study.	Cross-sectional study (> 3M post LTx)	94	HADS-D SF-36 SGRQ	All LTx-recipients showed better scores in SGRQ and enhanced HRQoL. HADS and SF-36 did not differ sign. compared with published normative data. Side effects of immunosuppression were sign. influencing HRQoL.	Cross-sectional study design Selection bias
Stavem et al., 2000	Health-related quality of life in lung transplant candidates and recipients.	Cross-sectional study design (candidates vs. recipients on average 38M post LTx.	31	HADS SF-36 SGRQ VAS 6MWD	SGRQ and SF-36 in all dimension except pain, showed sign. better scores post-transplant.	Cross-sectional study design Confounding variables (heterogeneous study groups: 15 candidates vs. 31 recipients) Selection bias
Tegtbur et al., 2004	Quality of life and exercise capacity in lung transplant recipients.	Cross-sectional study design (7 ± 2M after LTx)	27	Cardiopulmonary exercise Standardized German Quality of life profile for chronic disease self-rating questionnaire	Subjective HRQoL in physical, psychological and social domains did not differ from values of the general population. The HRQoL physical domain correlated sign. with exercise capacity.	Cross-sectional study design Selection bias Small sample size
Ten Vergert et al., 1998	The effect of lung transplantation on health-related quality of life: A longitudinal study.	Prospective longitudinal study (before and 1, 4, 7, 13 and 19M post LTx)	24	ADL IWB Karnofsky Performance Index NHP STAI ZUNG	Before LTx, patients reported major restrictions in mobility and energy, low level of well-being and depressive symptoms. Pre-tansplant patients reported difficulties in performing ADL and in taking care of themselves. 4M post-LTx, patients reported improvements in mobility, energy, sleep, ADL and dyspnea. Improvements were maintained in the following 15M.	Small sample size Selection/ survival bias Missing data

Ten Vergert et al., 2001	Quality of life before and after lung transplantation in patients with emphysema versus other indications.	Prospective longitudinal design (before and 4, 7, 13, 25 M after LTx)	42	IWB Karnofsky Performance Index NHP STAI ZUNG	Before transplantation, both groups reported major restrictions on the dimensions energy and mobility of the NHP, low experienced well-being, depressive symptoms, and high dyspnea. 4M after LTx, most HRQoL-domains improved sign. in both groups. Improvements were maintained in the following 21M.	Selection/ survival bias Short follow-up time
Van den Berg et al., 2000	Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life.	Cross-sectional comparison & longitudinal analysis (4M, 7M, and every 6M post-transplant until 49M)	27	IWB NHP STAI ZUNG	BOS reported sign. more restrictions on the dimension physical mobility and energy of the NHP at 7, 19, 25, 31M. Patient with BOS reported statistically sign. more depressive symptoms and anxiety 1 and 2 yr after LTx.	Cross-sectional study design Small sample size Selection/ survival bias
Vasiliadis et al., 2006	Health-related quality of life determinants in lung transplantation.	Cross-sectional cohort study (LTx-candidates vs. recipients)	34 vs 71	SF-36 Determinants associated with LTx (age, type of LTx, lung disease, hospitalization, days in hospital (LOS), infections)	LTx was positively associated with all HRQoL domains. Clinically meaningful effects on physical HRQoL domains were observed with disease, type of transplant received and hospital stay. Gender played a role in mental health.	Cross-sectional study design Confounding variables (heterogeneous group: 34 candidates vs. 71 recipients) Selection/ survival bias
Vermeulen et al., 2003	Long-term quality of life in patients surviving at least 55 months after lung transplantation.	Cross-sectional & longitudinal design (55M after LTx)	28	IWB Karnofsky Performance Index NHP STAI ZUNG Questionnaire concerning lung-specific problems Questions reg. activities of daily life	Until app. 43M after LTx, sign. improvements on most dimension of NHP, Karnofsky-Index, anxiety and depression, well-being, walking without dyspnea, activities of daily life could be performed without help by most patients. After 43M patients experiences more dyspnea, anxiety, depression and lower level of well-being.	Cross-sectional study design Selection/ survival bias Small sample size for longitudinal study design
Vermeulen et al., 2004	Improved quality of life after lung transplantation in individuals with cystic fibrosis.	Prospective longitudinal design (1, 4, 7, and then every 6 M after LTx until 31M after LTx)	35	IWB Karnofsky Performance Index NHP STAI ZUNG	Between 1-4M after LTx, NHP, ZUNG & Karnofsky Index improved, and STAI and IWB occurred even within the reference value in both groups. Significant better scores in NHP dimension mobility 4M and sleep 13M post-LTx for CF-patients in contrast to non-CF patients.	Selection/ survival bias Small sample size
Vermeulen et al., 2004	The effect of bronchiolitis obliterans syndrome on health related quality of life.	Longitudinal follow-up study (pre vs. 1, 4, 7 and then every 6M after LTx)	29	IWB NHP STAI ZUNG	HRQL was negatively affected by the onset of BOS. After the onset of BOS, STAI scores remained stable and close to the value of the general population. ZUNG scores were significantly higher after the onset of BOS, and patients experienced a lower level of well being than the general population.	Selection/ survival bias Missing data Small sample size

	Vermeulen et al., 2007	Long-term health-related quality of life after lung transplantation: different predictors for different dimensions.	Longitudinal follow-up study (pre vs. 1, 4, 7 and then every 6M after LTx)	140	NHP STAI ZUNG	The presence of BOS, age and pre-transplant scores were sign. for energy and mobility post-transplant. Regarding mobility, gender seemed to be an additional predictor. BOS was a predictor for anxiety and depression, and age was a predictor for anxiety.	Selection/ survival bias Missing data
	Vermeulen et al., 2008	Pre-transplant quality of life does not predict survival after lung transplantation.	Prospective longitudinal study (pre vs. 1, 4, 7, and every 6M after LTx)	200	IWB Karnofsky Performance Scale NHP SDS-Zung STAI	Survival rates at 1, 3, 5 yr were 85%, 73%, and 69%. Pre-transplant HRQoL measures were unfavorable compared with values for the general population. No sign. predictors for survival after LTx were found.	Selection/ survival bias Missing data
Physical functioning	Dierich et al., 2013	The influence of clinical course after lung transplantation on rehabilitation success.	Prospective longitudinal study (group comparison: > vs. <42 days LOS; follow-up 42 days later	138	ADL FEV1 PWR (peak work rate) SF-36 VC (vital capacity) VO2max (maximum oxygen uptake) 6MWD	FVC, FEV1, 6MWD, ADL and HRQoL improved in each cohort.	Non-controlled, non-randomized study Selection bias Confounding variables (heterogeneous study groups)
	Dobbels et al., 2008	Measuring symptom experience of side-effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale.	Cross-sectional pilot study; > 3M post LTx (validation study of the 45-item MTSOSD)	84	MTSOSD-59R	The clarity of instructions and items has significantly improved compared to the previous version. Female patients showed a tendency toward higher symptom occurrence and sign. higher symptom distress compared to men. Patients with depressive symptoms had sign. higher symptom occurrence and higher symptom distress compared with patients without depressive symptoms.	Short follow-up time
	Gerbase et al., 2008	Long-term Health-related Quality of Life and Walking Capacity of Lung Recipients With and Without Bronchiolitis Obliterans Syndrome.	Prospective longitudinal study followed for 5.6 ± 2.9 yr after LTx	58	Record of clinical complications SGRQ 6MWD	BOS was a sign. predictor of lower SGRQ and reduced time free of clinical complications, but not of 6MWT.	Survivor bias, Missing data Confounding variables (heterogeneous study group)
	Girard et al., 2006	Prevalence and Impact of Pain on the Quality of Life on Lung Transplant Recipients.	Cross-sectional study; > 3M after LTx	96	BDI BPI SF-36 (STAI	The prevalence of pain in LTx-recipients was 49%. Patients with pain were older, more likely to have undergone unilateral LTP, and more likely to have emphysema. BDI was higher for patients with pain. No sign. difference was found regarding anxiety. Pain-free patient had sign. higher physical component score in the SF-36.	Cross-sectional study design Confounding variables (heterogeneous study group) Survival bias

Goetzmann et al., 2005	Psychosocial situation and physical health in 50 patients > 1 year after lung transplantation.	Cross-sectional study design (after ≥ 12M post LTx	48	F-SoZu HADS RSES	The overall degree of anxiety and depression of LTx-patients was comparable to standard sample of an average population. Male LTx-patients were sign. more depressed than female recipients. Self-esteem was higher than in clinical comparison sample.	Cross-sectional study design Selection/ survival bias
Ihle et al., 2011	Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: a prospective, randomized study.	Cross-sectional study design: inpatient rehabilitation program vs. medical standard therapy (4.5 ± 3.5 yr after LTx).	60	Cardiopulmonary exercise testing SF-36 SGRQ Quality of Life Profile for Chronic Diseases questionnaire 6MWD	Both group sing. improved their maximal exercise capacity. In both study groups, HRQoL tended to improve. Sign. correlations were found for exercise capacity and HRQoL scales.	Cross-sectional study design Confounding variables (temporal variation in data collection) Selection bias Lack of control group
Irani et al., 2010	Olfactory performance before and after lung transplantation: quantitative assessment and impact on quality of life.	Cross-sectional study design	70	FLZM HADS Sniffin' Sticks for olfactory performance	Patients <55 yr had a lower olfactory performance both before and after LTx. General life satisfaction, health life satisfaction, and depression were sign. better in LTx-recipients. Better olfactory performance was sign. associated with better HRQoL before and after LTx.	Cross-sectional study design Selection bias Confounding variables (variance in sample size: 22 candidates vs. 70 recipients)
Kugler et al., 2007	Symptom experience after lung transplantation: impact on quality of life and adherence.	Cross-sectional study design, ≥ 3M after LTx	287	Quality of life profile for Chronic Diseases	Women and younger patients reported a significantly higher level of symptom experience compared with their counterparts respectively. Symptom experiences negatively influenced HRQoL in all dimensions. Those who described experiencing adverse effects reported significantly more ‘‘drug holidays’’.	Cross-sectional study design Selection bias Confounding variables (heterogeneous study group: single vs. bilateral LTx)
Langer et al., 2009	Physical Activity in Daily Life 1 Year After Lung Transplantation.	Cross-sectional study (> 12M post LTx)	22	Activity monitors SF-36 6MWD	Steps, standing time and moderate-intensity activity of LTx-recipients were reduced by 43%, 29% and 66% relative to controls. Daily sedentary time was increased by 30%.	Cross-sectional study design Small sample size Selection bias Confounding variables (heterogeneous study group: 7 single vs 15 bilateral LTx)
Langer et al., 2012	Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial.	Randomized control study. 3M of supervised exercise training vs. control group with no intervention. Follow-up 1yr after LTx.	40	Exercise training 3 times weekly during 3 months (walking, stair climbing, cycling about 90') 6MWD	Sign. improvements in quadriceps fore, 6MWD and self-reported physical functioning in intervention group.	Cross-sectional study design Selection bias

	Lanuza et al., 2012	A longitudinal study of patients' symptoms before and during the first year after lung transplantation.	Prospective, repeated measure design (pre vs. 1, 3, 6, 12M post LTx)	78	TSI	Post-transplant sign. improvements in most frequent occurring and most distressing pre-transplant symptoms (e.g. shortness of breath with activity). Marked increases in frequency and distress of new symptoms (e.g. tremor).	Selection bias Missing data Short follow-up time
	Maury et al., 2008	Skeletal muscle force and functional exercise tolerance before and after lung transplantation: a cohort study.	Prospective longitudinal study (2.8M before LTx and 1.8 M and 3 M after LTx)	36	Lung function Skeletal muscle force (Quadriceps force) 6MWD	26 Patients showed skeletal muscle weakness before LTx. The number of days in intensive care unit was sign. related to the observed deterioration in muscle force after LTx. Rehabilitation improved 6MWD and muscle force significantly (<.05), even though the evolution was less in female compared to male subjects.	Selection bias Missing data Short follow-up time
	Munro et al., 2009	Pulmonary Rehabilitation Following Lung Transplantation.	Prospective, repeated measure design 1, 2 and 3M after LTx.	36	FEV1 SF-36 6MWD	Sign. improvements in 6MWD, FEV1, FVC and all SF-36 domains.	Short follow-up time Small sample size Selection bias Lack of control group
	Van den Berg et al., 2000	Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life.	Cross-sectional comparison & longitudinal analysis; 4M, 7M, and then every 6M post-transplant until 49M	27	IWB NHP STAI ZUNG	BOS reported sig more restrictions on the dimension physical mobility and energy of the NHP at 7, 19, 25, 31M. Patient with BOS reported statistically sign. more depressive symptoms and anxiety 1 and 2 yr after LTx. The increase in reported restriction occurred simultaneously with the development of BOS.	Cross-sectional design Confounding variables (heterogeneous study groups) Selection/ survival bias
	Wildgaard et al., 2010	Chronic Pain After Lung Transplantation. A Nationwide Study.	Cross-sectional study design (mean 39M after LTx)	79	McGill Pain Questionnaire	18% reported persistent pain. 71% of LTx-patients with postsurgical pain also had pain from another part of the body. Postsurgical pain was associated with sign. impaired HRQoL. 73% of LTx-patients experienced sensory disturbances.	Cross-sectional study design Confounding variables (temporal variation in data collection)
Mental health	Dew et al., 2012	Onset and risk factors for anxiety and depression during the first 2 years after lung transplantation.	Longitudinal study with assessments at 2, 7, 12, 18, 24M	178	SCID	Pre-transplant risk factors for mental illness after LTx included pre-transplant psychiatric history, female gender, longer wait for transplant, early post-transplant health problems and psychosocial characteristics (poorer caregiver support, avoidant coping).	Selection/ survival bias Missing data Small sample size
	Evon et al., 2010	Depressive symptoms and mortality in lung transplant.	Prospective, longitudinal design	124	BDI	Depressive symptoms pre-transplant did not predict survival after transplantation. Depressive symptoms pre-transplant did not predict survival after LTx.	Selection/ survival bias Missing data

	Goetzmann et al., 2010	Lung function, sociodemographic characteristics, and psychological reaction to transplant associated with chronic stress among lung recipients.	Cross-sectional study (≥ 3M post LTx)	76	TICS TxEQ Physical and sociodemographic conditions (lung function, BOS, working status, parenting)	Chronic stress after LTx was significant lower than that in a normal community sample. Stress levels were not related to the time since transplantation. Worries concerning transplant were sign. associated with the patient's chronic stress.	Cross-sectional study design Selection bias
	Goetzmann et al., 2010	Distress and alexithymia in lung recipients – psychosocial strains and associations with chronic allograft dysfunction.	Cross-sectional design (≥3M after LTx)	76	SCL-K-9 TAS-20 Physical health (FEV1, exhaled nitric oxide, comorbidity)	Levels of distress and alexithymia were sign. higher in LTP-recipient than in a normal community sample. A positive correlation between BOS and distress was found. Distress was a predictor for new-onset BOS 1 yr after LTx. No sign. correlations were found between alexithymia and physical parameters.	Cross-sectional study design Selection bias Confounding variables (temporal variation in data collection)
	Woodman et al., 1999	Psychiatric Disorders and Survival After Lung Transplantation.	Longitudinal study (1yr after LTx)	30	PACT SCID	Recipients with a history of anxiety and depression were more likely to survive 1 year (80%). No significant differences in recipients without a psychiatric history in term of rejection reaction, BOS or noncompliance with treatment.	Short follow-up time Selection/ survival bias Confounding variables (heterogeneous study group)
Social functioning	Archonti et al., 2004	Physical quality of life and social support in patients on the waiting list and after a lung transplantation.	Cross-sectional study design (candidates vs. recipients 5 – 47M after LTx)	20	BDI F-SoZu SF-36	Sign. improvements post LTx were observed in physical functioning, vitality, health perception and social functioning. The perceived support correlated negatively with the level of depression.	Cross-sectional study design Small study cohort Survivor bias Confounding variables (heterogeneous population)
	DeVito et al., 2003	Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation.	Cross-sectional study design (2 - 17M post LTx)	50	SCL-90-R SCID-DSM-III-R SIP The 7-item Sense of Mastery Scale WCCL	Elevated depressive and anxiety symptoms, a low sense of mastery, and the presence of concurrent medical complications were each associated with increased number of physical symptoms and physical impairment level.	Cross-sectional study design Selection bias Confounding variables (temporal variation in data collection)
	DeVito et al., 2013	Quality of recipient-caregiver relationship and psychological distress are correlates of self-care agency after lung transplantation.	Cross-sectional study design (with LTx-recipients of max. 1yr post LTx)	111	DAS Health Locus of Control Scale. PSCA SCL-90-R	Patients with low self-care agency reported significantly poorer quality of caregiver relationship. The recipient-caregiver relationship was sign. associated with self-care agency.	Cross-sectional study design Selection bias Confounding variables (temporal variation in data collection)
	Goetzmann et al., 2005	Psychosocial situation and physical health in 50 patients > 1 year after lung transplantation.	Cross-sectional study design (after ≥ 12M post LTx	48	F-SoZu HADS RSES	The overall degree of anxiety and depression of LTx-patients was comparable to standard sample of an average population. Male LTx-patient were sign. more depressed than female recipients. Self-esteem was higher than in clinical comparison sample.	Cross-sectional study design Selection/ survival bias

Note. BOS = bronchiolitis obliterans syndrome; CF = cystic fibrosis; BODE = Body mass index, Obstruction, Dyspnea, Exercise. The BODE-index predicts the risk of death in patients with chronic obstructive pulmonary disease (COPD), and is used to identify candidates for lung transplantation; FVC = forced vital capacity; FEV1 = Forced expiratory volume in 1 second; HRQoL = health related quality of life; LTx = lung transplantation; pLTx = post lung transplantation; 6MWD = 6-min walking distance test. Abbreviations for test instruments are given in Table 3.

Table 3. Instruments used in eligible studies for assessing HRQoL and psychological outcomes after LTx.

	Instrument	Acronym	Author	Instruments utilized by (ID reference)	Cronbach's α
HRQoL	Body Cathexis Scale	BCSC	Secord and Jourard, 1953	Limbos et al., 1997	not reported
				Limbos et al 2000	not reported
	EuroQuol Health Utility and Health-related Quality of Life questionnaire	EQ-5D	EuroQol Group, 1990	Anyanwu et al., 2001	not reported
	Health Utilities Index Mark 3	HUI3	Feeny et al., 2002	Santana et al., 2009	not reported
				Santana et al., 2012	not reported
	Index of Well-Being	IWB	Campbell, 1976	Gross et al., 1995	not reported
				Ten Vergert et al., 1998	not reported
				Ten Vergert et al., 2001	not reported
				Van den Berg et al., 2000	not reported
				Vermeulen et al., 2003	not reported
				Vermeulen et al., 2004	not reported
				Vermeulen et al., 2008	not reported
	Medical Outcome Study Health Survey	MOS 20	Steward et al., 1989	Gross et al., 1995	.81 - .91
	Nottingham Health Profile	NHP	Hunt et al, 1985	Buschbach et al., 1994	not reported
				Ten Vergert et al., 1998	not reported
				Ten Vergert et al., 2001	not reported
				Van den Berg et al., 2000	not reported
				Vermeulen et al., 2003	not reported
				Vermeulen et al., 2004	not reported
				Vermeulen et al., 2007	not reported
				Vermeulen et al., 2008	not reported
	Quality of life profile for Chronic Diseases	PLC	Siegrist et al, 1996	Ihle et al., 2011	not reported
				Kugler et al., 2005	not reported
				Kugler et al., 2007	not reported
				Tegtbur et al., 2004	not reported
	Sickness Impact Profile 136 items	SIP-136	Bergner et al., 1981	DeVito et al., 2003	.86
				Lanuza et al., 2000	.92
	St George's Respiratory Questionnaire	SGRQ	Jones et al., 1991	Eskander et al., 2011	not reported
				Gerbase et al., 2005	not reported
				Gerbase et al., 2008	not reported
				Ihle et al., 2011	not reported
				Smeritschnig et al., 2005	not reported
				Stavem et al., 2000	not reported
	The General Health Questionnaire	GHQ	Goldberg and Hillier, 1978	Lanuza et al., 2000	.82
	The 12-Item Short Form Health Survey	SF-12	Ware et al., 1996	Kunsebeck et al., 2007	not reported
	The 36-Item Short Form Health Survey	SF-36	Ware and Sherbourne, 1992	Archonti et al., 2004	not reported
				Cohen et al 1998	not reported
				Eskander et al., 2011	not reported
				Finlen Copeland et al., 2013	not reported
				Girard et al 2006	not reported
				Goetzmann et al., 2008	not reported
				Ihle et al 2011	not reported
				Langer et al, 2009	not reported
				Limbos et al., 1997	not reported
				Limbos et al., 2000	not reported
				Lobo et al., 2004	not reported
				Munro et al 2009	not reported
				Rodrigue et al., 2005	not reported
				Rodrigue et al., 2006	not reported
				Rutherford et al., 2005	not reported
				Smeritschnig et al., 2005	not reported
				Stavem et al., 2000	not reported
				Vasiliadis et al., 2006	not reported
	Health Status Visual Analog Scale	VAS	The EuroQol Group, 1990	Buschback et al., 1994	not reported
				Gerbase et al., 2005	not reported
				Eskander et al., 2011	not reported
				Limbos et al., 2000	not reported
				Lobo et al., 2004	not reported
				Shih et al., 2002	not reported
Physical functioning	Brief Pain Inventory	BPI	Cleeland, 1989	Girard et al., 2006	not reported
	Dyspnea Assessment with visual analogue scale		Noseda et al., 1992	Stavem et al., 2000	NA

	Dyspnea Scale	DS	Comstock et al., 1979	Lobo et al., 2005	NA
	Karnofsky Performance Status Scale	Karnofsky-Index	Karnofsky and Burchenal, 1949	Buschbach et al., 1994	not reported
				Gross et al., 1995	not reported
				Ten Vergert et al., 1998	not reported
				Ten Vergert et al., 2001	not reported
				Vermeulen et al., 2003	not reported
				Vermeulen et al., 2004	not reported
				Vermeulen et al., 2008	not reported
	McGill Pain questionnaire	MPQ	Melzack, 1975	Wildgaard et al., 2010	not reported
	Modified Transplant Symptom Occurrence and Distress Scale 59-Revised	MTSOSD-59R	Moons et al., 2001	Dobbels et al., 2008	not reported
	Sniffin' Sticks Test for olfactory performance	SST	Hummel et al., 1997	Irani et al., 2010	NA
	Transplant Symptom Frequency Questionnaire	TSFQ	McNaughton et al., 1998	Rodrigue et al., 2006	not reported
	Transplant Symptom Inventory	TSI	Moons et al., 2001	Lanuza et al., 2012	.91 - .96
	Zerssen List of Complaints	Zerssen	Zerssen et al., 1976	Kunsebeck et al., 2007	not reported
Mental health	Basic Personality Inventory	BPI	Kroner et al., 1991	Cohen et al., 1998	not reported
				Girard et al., 2006	not reported
	Beck Anxiety Inventory	BAI	Beck and Steer, 1993	Kunsebeck et al., 2007	not reported
	Beck Depression Inventory	BDI	Beck, 1972	Archonti et al., 2004	not reported
				Cohen et al., 1998	not reported
				Evon et al., 2010	not reported
				Girard et al., 2006	not reported
	Brief Symptom Inventory	BSI	Derogatis and Spencer, 1982	Lanuza et al., 2000	.73 - .80
				Limbos et al., 2000	not reported
	Centre for Epidemiologic Studies-Depression Scale	CES-D	Radloff, 1977	Kunsebeck et al., 2007	not reported
				Lobo et al., 2004	not reported
	Derogatis Sexual Functioning Inventory	DSFI	Derogatis, 1975	Limbos et al., 1997	not reported
				Limbos et al., 2000	not reported
	Hospital Anxiety Depression Scale	HADS	Zigmond and Snaith, 1983	Goetzmann et al., 2005	not reported
				Irani et al., 2006	not reported
				Irani et al., 2010	not reported
				Limbos et al., 1997	not reported
				Limbos et al., 2000	not reported
				Santana et al., 2009	not reported
				Smeritschnig et al., 2005	not reported
				Stavem et al., 2000	not reported
	Illness Intrusion Rating Scale	IIRS	Devins et al., 1994	Lobo et al., 2004	not reported
	Mental Health Inventory	MHI	Ware et al., 1987	Cohen et al., 1998	not reported
	Psychiatric Assessment of Candidates for Transplantation	PACT	Olbrisch and Levenson, 1989	Woodmann et al., 1999	not reported
	Rosenberg Self-Esteem Scale	RSES	Rosenberg, 1965	Goetzmann et al., 2005	not reported
				Limbos et al., 1997	not reported
				Limbos et al., 2000	not reported
	Symptom Distress Scale	SDS	McCorkle et al., 1998	Lobo et al., 2004	not reported
				Matthees et al., 2001	not reported
	Screening Subscale of Chronic Stress of the Trier Inventory for the Assessment of Chronic Stress	TICS	Schultz et al, 2004	Goetzmann et al., 2010	.92
	State-Trait Anxiety Inventory	STAI	Spielberg et al, 1980	Cohen et al 1998	not reported
				Girard et al 2006	not reported
				Ten Vergert et al., 1998	not reported
				Ten Vergert et al., 2001	not reported
				Van den Berg et al., 2000	not reported
				Vermeulen et al., 2003	not reported
				Vermeulen et al., 2004	not reported
				Vermeulen et al., 2007	not reported
				Vermeulen et al., 2008	not reported

	Symptom Checklist 90-Revised	SCL-90-R	Derogatis, 1997	DeVito et al., 2003	not reported
				DeVito et al., 2013	.83 - .92
				Goetzmann et al., 2010	not reported
	The Life Orientation Test	LOT	Scheier and Carver, 1985	Irani et al., 2006	not reported
	The Structured Clinical Interview for DSM-III-R	SCID (DSM-III-R)	Spitzer, 1992	DeVito et al., 2003	not reported
				Dew et al., 2012	not reported
				Woodmann et al., 1999	not reported
	Toronto Alexithymia Scale	TAS-20	Bagby and Parker, 1994	Goetzmann et al., 2010	not reported
	Transplant Effects Questionnaire	TxEQ	Ziegelmann et al., 2002	Goetzmann et al., 2008	.65 - .92
				Goetzmann et al., 2010	not reported
	The Ways of Coping Checklist	WCCL	Neacsiu et al., 2010	DeVito et al., 2003	not reported
	ZUNG Self-Rating Depression Scale)	ZUNG-SDS	Zung, 1965	Ten Vergert et al., 1998	not reported
				Ten Vergert et al., 2001	not reported
				Van den Berg et al., 2000	not reported
				Vermeulen et al., 2003	not reported
				Vermeulen et al., 2004	not reported
				Vermeulen et al., 2007	not reported
				Vermeulen et al., 2008	not reported
Social functioning	Activity of daily living	ADL	Katz et al., 1963	Dierich et al., 2013	not reported
				Ten Vergert et al., 1998	not reported
	Dyadic Adjustment Scale	DAS	Spanier, 1976	DeVito et al., 2013	.86
	Evaluation of the short-form social support questionnaire)	F- SoZu	Sommer and Fydrich, 1998	Archonti et al., 2004	not reported
				Goetzmann et al., 2005	not reported
				Irani et al., 2006	not reported
	Multidimensional Health Locus of Control Scale	MHLC Scale	Wallton et al., 1978	DeVito et al., 2013	.78
	Perception of Self-Care Agency	PSCA	Hansen and Bickel et al, 1985	DeVito et al., 2013	.95
	Questions on Life Satisfaction	FLZM	Henrich and Herschbach, 2000	Irani et al., 2006	not reported
				Irani et al., 2010	not reported

Note. Cronbach’s alpha as a measure of reliabilty of the instruments in LTx-population. *NA* = not applicable.

4.5 Discussion

4.5.1 Principal findings

We identified 63 studies, amongst which there were 50 different instruments used to evaluate HRQoL and psychological outcomes after lung transplants. These tools covered four distinct dimensions: HRQoL, physical functioning, mental health, and social functioning. A heterogeneous assortment of test instruments was encountered; but rarely were transplant-specific test instruments used, even though lung-specific questionnaires have been developed (Jones, Baveystock, & Littlejohns, 1989; Jones, Quirk, Baveystock, & Littlejohns, 1992). While generic instruments are designed to assess overall physical, psychological and social function, they fail to address the unique emotional and behavioral concerns of transplant recipients, and might not be sensitive enough to screen for transplant-specific issues (Cleemput & Dobbels, 2007). Furthermore, the heterogeneity of the applied test instruments rendered comparisons between studies difficult. In short, there are no guidelines to indicate which outcome measures are most appropriate for assessing HRQoL and psychological outcomes following lung transplantation. Moreover, severe methodological limitations of the studies included in this review significantly hampered the interpretation of HRQoL and psychological outcome data. Consistent with other literature findings, selection bias, survival bias due to high mortality rates, loss of subjects during data collection, and inability to control for confounding variables, such as heterogeneous groups, temporal variation in data collection, or underlying comorbidities, were the most frequent identified constraints. Additionally, small samples sizes, missing data or the lack of prospective longitudinal study designs limited the results of many of the studies (Yusen, 2009, 2011).

4.5.2 HRQoL

Among the four investigated psychosocial domains, HRQoL was the most frequently addressed, being evaluated in 39 of the papers. In transplant medicine, HRQoL has been widely accepted as an important outcome measure (Stavem et al., 2000). Appraising the articles, assessing HRQoL collectively demonstrates considerable postoperative improvement in HRQoL among lung transplant recipients, relative to their pre-transplant baseline. This finding has been reported in other reviews that have focused on HRQoL after lung transplantation (Rosenberger, Dew, DiMartini, et al., 2012; Singer et al., 2013). Although transplant recipients' HRQoL levels are typically lower than the general population's (Santana et al., 2009; Smeritschnig et al., 2005), they generally still report better physical function, fewer restrictions in social and leisure activities, more energy, and less discomfort than pre-operatively (Limbos et al., 1997). Moreover, the benefits of improved physical and psychosocial HRQoL appear to remain stable for a period of three to five years after the transplant (2006; Kugler et al., 2010; Rodrigue, Baz, Kanasky, et al., 2005; Stavem et al., 2000; TenVergert et al., 1998; Vermeulen et al., 2003). However, evidence of maintained benefits within the physical and psychosocial HRQoL domains beyond five years is generally lacking, so that the outcome trajectories of these patients five to ten years following their transplants remain ambiguous. Based upon the few long-term longitudinal studies that have been published, it appears that, over the long-term, lung transplant recipients ultimately start to experience a decline across several dimensions of HRQoL, largely due to an increase in co-morbid conditions and the onset of BOS (Kugler et al., 2005; Rutherford et al., 2005; Vermeulen et al., 2003). These findings are supported by one-, three-, and five-year survival rates of 79%, 64% and 53%, respectively (Christie et al., 2012).

Some investigators attempted to determine if gender differences exist in HRQoL outcomes in response to lung transplantation. Three studies suggest that, relative to men, women experience more frequent and severe symptoms and a lower percentage gain in HRQoL (Limbos et al., 1997; Rodrigue & Baz, 2006; Santana et al., 2012; Vermeulen et al., 2007). Alternative theories have been proposed to explain these gender differences. For instance, it has been hypothesized, that the higher levels of psychological distress observed in female lung transplant patients may not be due to gender-specific vulnerabilities, but rather due to culturally-driven gender biases in symptom reporting, with females generally more willing to report psychological distress and males tending towards the denial and rationalization of feelings (Rankin, 1990; Sokol, Folks, Herrick, & Freeman, 1987). However, the small number of studies reporting on gender differences in HRQoL makes the interpretation of these findings difficult. Focusing on predictors of HRQoL following transplantation, a number of studies have consistently shown that BOS, the adverse effects of immunosuppressant medications, and pain significantly reduce HRQoL and increase depressive symptoms (Kugler et al., 2005; Santana et al., 2012; Vermeulen et al., 2003). In contrast, results regarding FEV1, the underlying diagnosis, patient gender and age, and recurrent infections as predictors of HRQoL following lung transplantation have been contradictory, with each variable supported by only a single study. Further empirical research is clearly warranted to examine whether these factors do, in fact, play a determinative role in HRQoL outcomes, along with research to explore the various mechanisms affecting HRQoL following lung transplants.

4.5.3 Physical functioning

Significant improvements from pre-transplant symptoms were reported by several authors (Dierich et al., 2013; Langer et al., 2012; Lanuza et al., 2012). In particular, physical function tended to improve over the first several months (Munro et al., 2009), and males tended to be more likely to report improvements than females (Maury et al., 2008). However, despite successful health gains, many lung transplant recipients suffered from new symptoms, like postsurgical pain, the adverse effects of immunosuppressants, and the onset of BOS that interfered with both HRQoL and mental health (Dobbels et al., 2008; Girard et al., 2006; Van Den et al., 2000). Hence, interventions designed to improve physical functioning are important in post-transplant rehabilitation. Considerable success has been achieved by both in- and out-patient rehabilitation programs, with physical improvements lasting as long as nine months (Langer et al., 2012). Moreover, inpatient rehabilitation improved physical function even more impressively in patients with an extended length of stay (Dierich et al., 2013).

4.5.4 Mental health

Thus far, there is no conclusive evidence with respect to the degree that mental health is affected following lung transplantation. Overall, the studies included in this review indicate that a considerable number of lung transplant recipients suffer from psychological distress and mental health problems, including a variety of psychiatric diagnoses like depression, and both anxiety and adjustment disorders. Moreover, in the long-term, mental health appears to ultimately decline, even if gains are achieved in the short term. There are even fewer data on potential predictors of impaired mental health, with only one study addressing this issue (Dew et al., 2012). In this paper, several predictors were named, but evidence from other studies is lacking. As a result of the few articles identified in which mental health was an outcome of interest, no clear conclusions can be drawn with regard to mental health following lung transplantation. Accordingly, further studies that are consistent in their selection of psychometric instruments are required.

4.5.5 Psychosocial health

Although the quality of relationships with one’s primary caregiver, spouse and family are assumed to exert an influential impact upon psychological well-being throughout the peri-operative recovery period and one’s long-term adjustment to post-transplant life (Rosenberger, Dew, DiMartini, et al., 2012), only three studies on psychosocial health were identified in our review. The psychological well-being of lung transplant recipients was reported to be similar to that of the normal general population (Goetzmann et al., 2005). Additionally, lung transplant recipients were found to have high levels of self-care agency (De Vito Dabbs et al., 2013).

The evaluation of psychosocial issues within the care and treatment of the chronically ill is of both clinical and social relevance. As a matter of course, hospitals are continuously seeking to decrease hospital stays as a cost-cutting measure, and family care-givers are simultaneously being handed more and more responsibility for providing daily care to the chronically ill, a responsibility that is increasingly expanding the caregivers’ burdens. Thus, interventions designed to reduce psychological distress and strengthen the quality of relationships in both transplant recipients and their caregivers are indispensable.

4.5.6 Strengths and limitations of this review

This review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Study selection followed clear inclusion and exclusion criteria. Furthermore, two independent reviewers carefully assessed the selection of eligible studies. A limitation of our study is the potential for selection bias when identifying and reviewing evidence for each article selected for this review. In this regard, we excluded all studies that evaluated HRQoL and psychological outcomes of lung transplant candidates (i.e. patients referred for lung transplant), pediatric transplant recipients, and patients who had received additional solid organ transplants. This restricted selection of studies might have biased our results, and certainly limits their generalizability. Further limitations are the small number of studies for almost all subcategories of HRQoL and psychological outcomes following lung transplant, as well as the variability that was apparent in study outcomes, study design, and study populations, so that drawing conclusions was difficult. Finally, we also excluded articles not published in either English or German, and research studies that utilized a strictly qualitative approach.

4.5.7 Implications for practice and future research

Overall, increasing attention has been paid to assessing the HRQoL and psychological outcomes of lung transplant recipients. However, a great assortment of validated and non-validated outcome measures, as well as many different study designs, has been used, all in the absence of any gold standards or consensus guidelines. Comparing research findings between different studies is rendered difficult because of the extreme variability that exists. Moreover, because of limited sample sizes and the extreme diversity of outcome measures between studies, insufficient data currently exist to justify any measures over others for use in future studies within transplant medicine.

Based upon our review, we suggest that a huge opportunity for future research lies in the development of guidelines to aid in the selection of outcome measures to assess psychological outcomes of lung transplant patients. We also recommend the development of transplant specific HRQoL-measures that concisely target physical symptoms and functional well-being, including pain and any adverse effects of immunosuppressants, similar to what has been adopted for research on cancer patients (Webster, Cella, & Yost, 2003). Finally, we suggest that the emphasis of further research should be on prospective longitudinal studies with large enough samples, accounting for survival bias and confounding variables to allow for the identification of predictors of both good and poor transplant outcomes.

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Author contributions

AS was responsible for drafting the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor. RK, KK and JJ were consultants and provided advice during the conception and design of the project. All authors critically revised the paper for important intellectual content. JJ obtained the funding.

Conflict of Interest

The authors have no conflicts of interest to declare.

5 Empirical work 2

Post-transplant outcome-trajectories of psychological distress and quality of life in lung transplant recipients. A six months observational study

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5.1 Abstract

Background: It is crucial to evaluate the psychosocial trajectories of lung transplant recipients to identify patients who experience no significant improvement in health-related quality of life (HRQoL) and, thus, require additional psychosocial care.

Objectives*:* To (1) assess psychosocial outcome trajectories in lung transplant recipients related to psychological distress and HRQoL during the first six months post-transplant; (2) identify patients with poor psychosocial trajectories; and (3) determine potential outcome predictors regarding psychological distress and HRQoL at six months post-transplant.

Methods: A total of 40 patients were examined for psychological distress (SCL-K-9) and HRQoL (EQ-5D) during their first six months post-transplant. Hierarchical cluster analyses were performed to identify distinct types of postoperative outcome trajectory. Correlational analyses examined medical and psychosocial predictors of the outcome at 6 months post-transplant.

Results: Three distinctive clusters were identified, summarizing either (1) patients with optimal postoperative trajectories (35%), (2) patients with good postoperative trajectories (42%), and (3) patients with poor postoperative trajectories (23%). The latter tended to be older, to suffer from more severe disease, to have more co-morbidities, and to have had a prolonged ICU and/or hospital stay. Disease severity, length of stay and EQ-5D two weeks post-transplant were strong predictors of psychological distress and impaired HRQoL at six months of follow-up.

Conclusion: Results underscore the psychosocial needs of patients with poor post-transplant trajectories. Further longitudinal research with larger subject samples is needed to further investigate outcome profiles of these patients and identify additional outcome predictors.

5.2 Background

Lung transplantation is an established therapeutic option for end-stage lung disease, yielding successful outcomes in carefully selected patients characterized by reduced disability, extended survival and improved health-related quality of life (HRQoL) (Kugler et al., 2007; Munro et al., 2009; Rodrigue, Baz, Kanasky, et al., 2005). To date, more than 47’000 adult lung transplants have been reported worldwide to the Registry of the International Society for Heart and Lung Transplantation (ISHLT) (Yusen et al., 2014), while in Switzerland since 1992, more than 700 lung transplants have been performed (Swisstransplant, 2013). During the last years, overall patient survival has progressively improved, and today, one-, three-, and five-year survival rates of 84%, 71% and 66.5%, respectively have been achieved in Zurich, comparable to results of international high-volume programs (Inci et al., 2013).

To date, studies on psychosocial outcomes following transplantation have primarily compared the postoperative HRQoL-trajectories of different types of solid organ transplantation (Goetzmann et al., 2008; Myaskovsky et al., 2006; Pinson et al., 2000). In these studies, recipients of different solid organ transplants did not share the same HRQoL-trajectories. In particular, the HRQoL-outcomes of lung transplant recipients appeared to be inferior to those receiving other solid organs (Kugler et al., 2010; Pinson et al., 2000). Interestingly, most studies look at the entire group, and do not distinguish between patients with improved postoperative HRQoL and patients with similar or worse quality of life compared to their pre-transplant scores.

Understanding the predictive impact of psychosocial and medical variables on postoperative HRQoL could be useful when making choices regarding therapy. Although previous research has identified associations between psychosocial and medical characteristics and post-transplant HRQoL, the predictors of post-transplant HRQoL are still not well described for lung transplant patients. Only very few consistent data regarding predictive factors for post-transplant HRQoL exists (Butler et al., 2003). In general, studies on predictors of post-transplant HRQoL in lung recipients demonstrate that bronchiolitis obliterans syndrome (BOS), the most common form of chronic lung allograft dysfunction (CLAD), the adverse effects of immunosuppressant medications, and pain significantly reduce HRQoL and increase depressive symptoms (Santana et al., 2012; Vermeulen et al., 2003; Vermuelen, van der Bij, Erasmus, & TenVergert, 2007). In contrast, results on other potential outcome predictors - including age, gender, psychiatric history, longer waiting times for transplantation, and forced expiratory volume in one second (FEV1) – have been contradictory and supported only by single studies (Dew et al., 2012; Gerbase et al., 2005; Kugler et al., 2005; Rodrigue, Baz, Kanasky, et al., 2005).

In light of the above, it is of clinical relevance to assess the psychosocial health of lung transplant patients to identify those at risk for unfavorable postoperative outcomes and make more informed therapeutic choices to enhance patients' symptom experience. The main objectives of the current study were therefore: (1) to determine the post-transplant trajectories of lung transplant recipients over the first six months post transplant in terms of psychological distress and HRQoL; (2) to identify those lung recipients with poor postoperative trajectories; and (3) to assess potential short-term predictors and their impact upon psychological distress and HRQoL. This subject has clinical relevance with respect to the treatment of patients who undergo lung transplantation but fail to experience any improved quality of life.

5.3 Methods

5.3.1 Participants

Between January 2012 and April 2014, 72 lung transplants were performed at the Transplant Center at the University Hospital of Zurich, Switzerland. All patients who received transplants over this time period were considered to be eligible for inclusion, unless they were: (i) younger than 18 years of age, (ii) unable or unwilling to provide informed consent, or (iii) unable or unwilling to complete questionnaires in German. Forty-four consecutive adult lung transplant recipients qualified for the study. During data collection, four subjects unexpectedly withdrew from participations for medical or personal reasons (e.g., feeling overwhelmed by hospital routines and preparations for discharge, distressed, overly-tired, and/or short of time). One patient had to be excluded due to critical health conditions and repeated hospitalizations to the intensive care unit (ICU). The final sample included 40 patients (Figure 5).

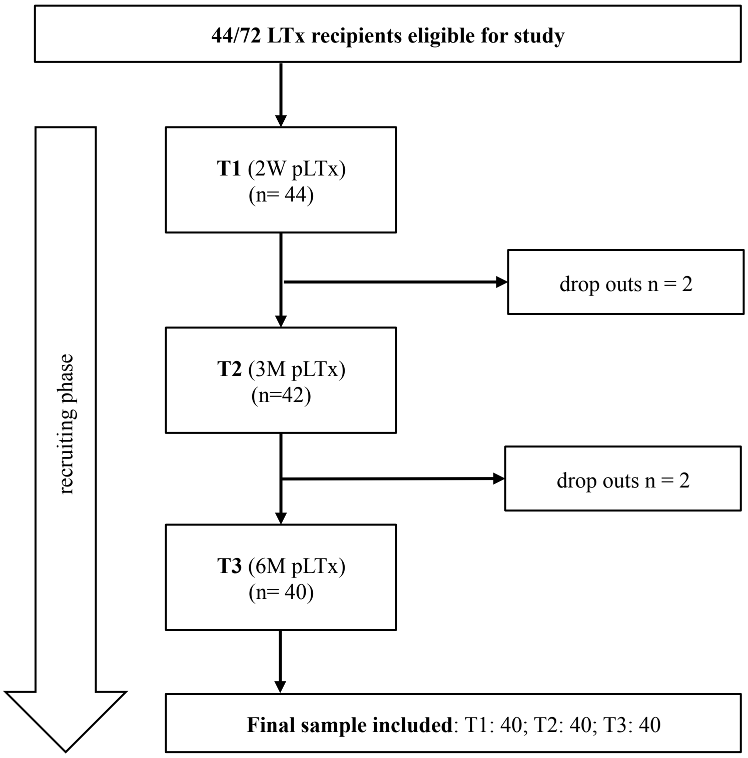

Figure 5. Flowchart showing patient recruitment

5.3.2 Design and Procedures

In this prospective, longitudinal study, 40 lung transplant recipients were examined at three different measurement time points (T1: two weeks; T2: three months; T3: six months after transplantation) to capture HRQoL changes over the first six postoperative months. Following approval by the Ethics Committee of the Canton of Zurich, Switzerland, all patients provided written informed consent prior to their participation. Eligible patients were asked to complete the same battery of questionnaires at every data collection point. While the initial assessment at T1 was performed during hospitalization, the follow-up assessments at T2 and T3 typically were conducted during regular transplant clinic out-patient visits at the University Hospital Zurich. Few patients were still hospitalized or admitted to hospital due to complications at T2 or T3. Demographic and medical data were retrieved from patient medical records. Medical data included the underlying diagnosis/indication for transplantation, the presence of co-morbid conditions, the time on the waiting list, the number of days spent in the ICU after transplantation, the length of hospital stay (LOS), and the mortality rate over the course of the data collection phase.

5.3.3 Measures

The Symptom Checklist (SCL-K-9)

The German version of the Symptom Checklist-Short form (SCL-K-9) was used to assess overall psychological distress (Klaghofer & Braehler, 2001). The SCL-K-9 (Rosen et al., 2000) is comprised of nine items, each rated on a five-point Likert scale ranging from 0 (not at all) to 4 (very strong). According to the original global severity index (GSI), a mean score (0- 4) for the nine items was computed, with higher values indicating greater distress (the community-based standard value = .41). The SCL-K-9 is highly correlated with the original SCL-90-R (Franke, 1995) and offers similarly good psychometric properties and sensitivity to change, with a Cronbach's alpha of .87. In our clinical sample, internal consistency of the SCL-K-9 over the three measurement points was good, with Cronbach's alpha ranging from .75 to .84.

EuroQuol (EQ-5D)

All study subjects completed the EQ-5D, a 5-item self-administered survey instrument that measures HRQoL (EuroQol Group, 1990; Hinz, Klaiberg, Brahler, & Konig, 2006). The questionnaire covers five dimensions of health: 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. For each dimension, patients selected one of three graded responses, indicating no problems, some problems, or severe problems with the activity. A single global EQ-5D score (range 0 - 100) was generated by use of the sum model as describe by Hinz et al. (Hinz et al., 2006) (community-based standard value = 91.7). The EQ-5D is used in studies to assess psychotherapeutic treatment, where it has been shown to be valid, sensitive to change, and responsive in improvements in mental health. In the current study, the EQ-5D demonstrated acceptable to good internal consistency over the three data collection points, with Cronbach's alpha ranging between .60 and .76. The lower level of internal consistency observed across the different outcome measures might be explained by the high level of homogeneity in our clinical sample.

Additionally, we used a pre-transplant co-morbidity index developed by Barrios et al. (2014), consisting of ten extra-pulmonary co-morbidities that may have negatively impacted short- and long-term postoperative trajectories. This comorbidity index included the following factors: 1) BMI >30 kg/m2, 2) osteoporosis, 3) insulin-dependent diabetes, 4) arterial hypertension, 5) cardiac disease, 6) chronic liver disease, 7) diverticulosis, 8) gastroesophageal reflux, 9) history of malignancy, and 10) psychiatric disorders. The comorbidity index was computed by summing up the number of comorbidities for each patient. Values between 0 and 10 were possible.

5.3.4 Statistical analysis

The Statistical Package for the Social Sciences (SPSS, version 22.0) was used to perform all statistical analyses, with a two-tailed probability value of .05 considered statistically significant (Corp, 2013). Descriptive statistics were reported as means and standard deviations, or as counts and percentages. Hierarchical cluster analysis was performed to generate homogeneous groups within complex data sets. We used squared Euclidean distance as a proximity measure and Ward's minimum variance agglomerative method to determine different post-transplant trajectories (Ward, 1963) based on six variables (SCL-K-9 global severity index and EQ-5D score measured at T1, T2 and T3). All these variables were standardized prior to clustering. The clustering process starts with the same number of clusters as cases, and reduces the number of clusters step-wise using dissimilarities or distances between objects; that is, combining those clusters whose combination results in a minimum increase in the total within-group sum of squares. If a point is reached whereby clusters are combined that are dissimilar, the within-group sum of squares noticeably increases (as can be seen in the agglomeration schedule). The number of clusters prior to this rapid increase in the agglomeration coefficient is considered the natural grouping scheme (Hair & Black, 2000). However, it must be taken into account that this analysis was exploratory in nature, and that the choice of the number of cluster to extract is somewhat arbitrary. Patients' characteristics were compared between the cluster groups using one-way ANOVA, with Bonferroni post hoc test to identify statistically-significant differences between specific cluster groups. Moreover, to generate some appreciation regarding the clinical significance of our results, effect sizes (Eta^2 for interval scalded variables and

Cramer's V for categorical variables) were computed according to Cohen (Cohen et al., 1998). Values for Eta2 are categorized as small (0.01), intermediate (0.06), or large (.14) while for Cramer's V, a value of .1 is considered a small effect, .3 a medium effect and .5 a large effect. Pearson correlation coefficients were calculated to identify relevant predictor variables of psychological distress (SCL-K-9) and HRQoL (EQ5D) six months post-transplant.

Table 4. Demographic and medical data of LTx-recipients

Variables	**40 LTx-Recipients n (%)**
Male gender	22 (55)
Median age (range)	50 (20 - 68)
Education level	
Elementary	7 (17)
Secondary	21 (53)
Tertiary	12 (30)
Married	17 (43)
Indication for LTx	
COPD	15 (38)
Cystic Fibrosis	13 (33)
Idiopathic Pulmonary Fibrosis	7 (17)
Others	5 (12)
ECMO-use	13 (33)
Bilateral LTx	40 (100)
Retransplant	2 (5)
Average time on wait list (d)	270.5 (10 - 992)
Days in ICU (mean; range)	4 (2 – 29)
Weeks in hospital pLTx (mean; range)	4.5 (3 – 14)

Note. LTx = lung transplantation; pLTx = post-transplant; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

5.4 Results

5.4.1 Demographic characteristics

Detailed patient demographics and clinical characteristics are summarized in Table 4. The median age at the time of transplantation was 50 years (range 20 to 68). Of the 40 patients, 55% were men and 43% were married. With respect to employment status, 45% were not working prior to transplant for health reasons, while 20% were already retired. Thirty-eight percent of the patients had been diagnosed with chronic obstructive pulmonary disease (COPD), which was the main indication for transplantation in our clinical sample, followed by cystic fibrosis in 33%. Six months after transplantation, all 40 patients were still alive.

5.4.2 Cluster analysis

The agglomeration coefficients generated by cluster analysis revealed a demarcation point between three- and four-cluster solutions, suggesting that a four-cluster solution best distinguished the post-transplant trajectories (Table 5). However, a four-cluster solution produced one cluster with only two patients. For statistical reasons, we therefore decided for a three-cluster solution. An inspection of the clustering tree (dendrogram) in Figure 6 indicates a three-cluster solution as appropriate. The resultant three-cluster solution generated relatively well-sized postoperative psychosocial trajectories, labeled according to their most distinguishing characteristics (Figure 7). Cluster characteristics are displayed in Table 6. In this study, the terms ‘trajectories’ and ‘clusters’ are used as synonyms.

Cluster A synthesizes those patients with optimal postoperative trajectories (n = 17; 42%) in terms of a high EQ-5D and low SCL-K-9 score within two weeks of surgery. While EQ-5D further improved over the three data collection points, SCL-K-9 decreased progressively. At six months post-transplant, these patients reported HRQoL levels comparable to those of a community-based sample (EQ-5D value of 91.7) (Hinz et al., 2006) and small but not significantly elevated SCL-K-9-values. Cluster B includes transplant recipients with good postoperative trajectories (n= 14; 35%), characterized by considerable reduced EQ-5D and high SCL-K-9 scores two weeks after surgery, but significant improvements in EQ-5D and SCL-K-9 at 6 months. EQ-5D-values at six months of follow-up were slightly lower than those of the healthy norm population. Cluster C incorporates transplant recipients with poor postoperative trajectories (n= 9; 23%), with both a low EQ-5D and high SCL-K-9 score two weeks after transplantation, and only a small gain in EQ-5D while SCL-K-9 scores remained steadily elevated over the remainder of the first six months of follow-up.

Table 5. Re-formed agglomeration table

No of clusters	**Agglomeration last step**	**Coefficients this step**	**Change**
2	234.100	151.886	82.214
3	151.886	111.244	40.642
4	111.244	97.966	13.278
5	97.966	85.793	12.173
6	85.793	75.342	10.451

Note. A clear demarcation point seems to be between three and four cluster solutions, suggesting that a four-clusters solution best distinguished the cases.

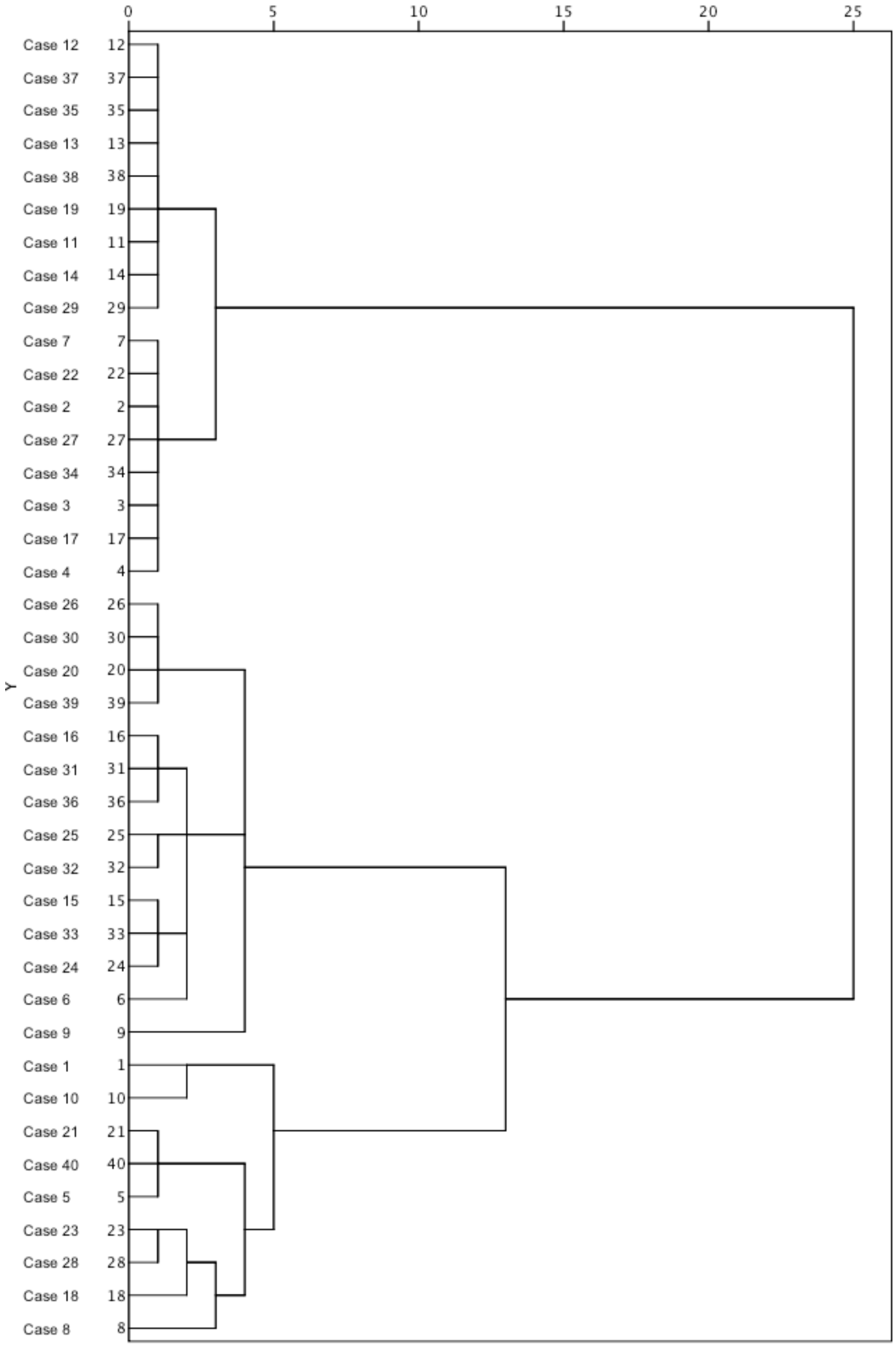

Figure 6. The dendrogram generated by the cluster analysis. Each patient (n = 40) begins as single clusters and step-by-step the most similar clusters are progressively joined together resulting at the end of the process in a single cluster grouping all the patients. The distance along the x-axis represents a measure of similarity between the patients. A low value here indicates a low heterogeneity within the groups.

5.4.3 Predictor analyses of post-transplant trajectory

For predictor analyses to distinguish the three postoperative trajectories, the following demographic, clinical and psychosocial characteristics were included: sex, age, underlying diagnosis, disease severity, time on the waiting list, extracorporeal membrane oxygenation (ECMO) use, comorbidities number of days in the ICU and LOS following transplantation (Table 7). The median comorbidity index value across the 40 patients was 2 and ranged between 0 and 4 comorbidities. Thirty-five percent of the transplant recipients suffered from three or more comorbidities. Significant inter-group differences were identified only for LOS with a large effect size ($eta^2 = .53$). No significant cluster differences were evident for all other investigated variables. However, medium to large effect sizes were found for age ($eta^2 = .07$), disease severity ($eta^2 =.13$), comorbidities ($eta^2 =.06$), and number of days in ICU ($eta^2 = .08$), indicating that relative to patients with either optimal or good postoperative trajectories, those with poor postoperative trajectories tended to be older, to suffer from considerably more severe disease, to have more co-morbid conditions, and to have spent longer periods of time in the ICU and hospital. No meaningful inter-cluster differences were identified for patient gender, underlying diagnosis, time on waiting list or ECMO-use prior to transplantation.

5.4.4 Predictor analyses for psychological distress and HRQoL six months post-transplant

Table 8 presents the results of correlation analyses used to identify associations between each potential outcome predictor and both the level of psychological distress (SCL-K-9) and HRQoL score (EQ-5D) six months post-transplant. Significant associations with the SCL-K-9 score at T3 were evident for disease severity ($r= .39$; $p= .001$); length of hospital stay ($r= .44$; $p= .005$) and the EQ-5D score at T1 ($r= -.37$; $p= .02$).

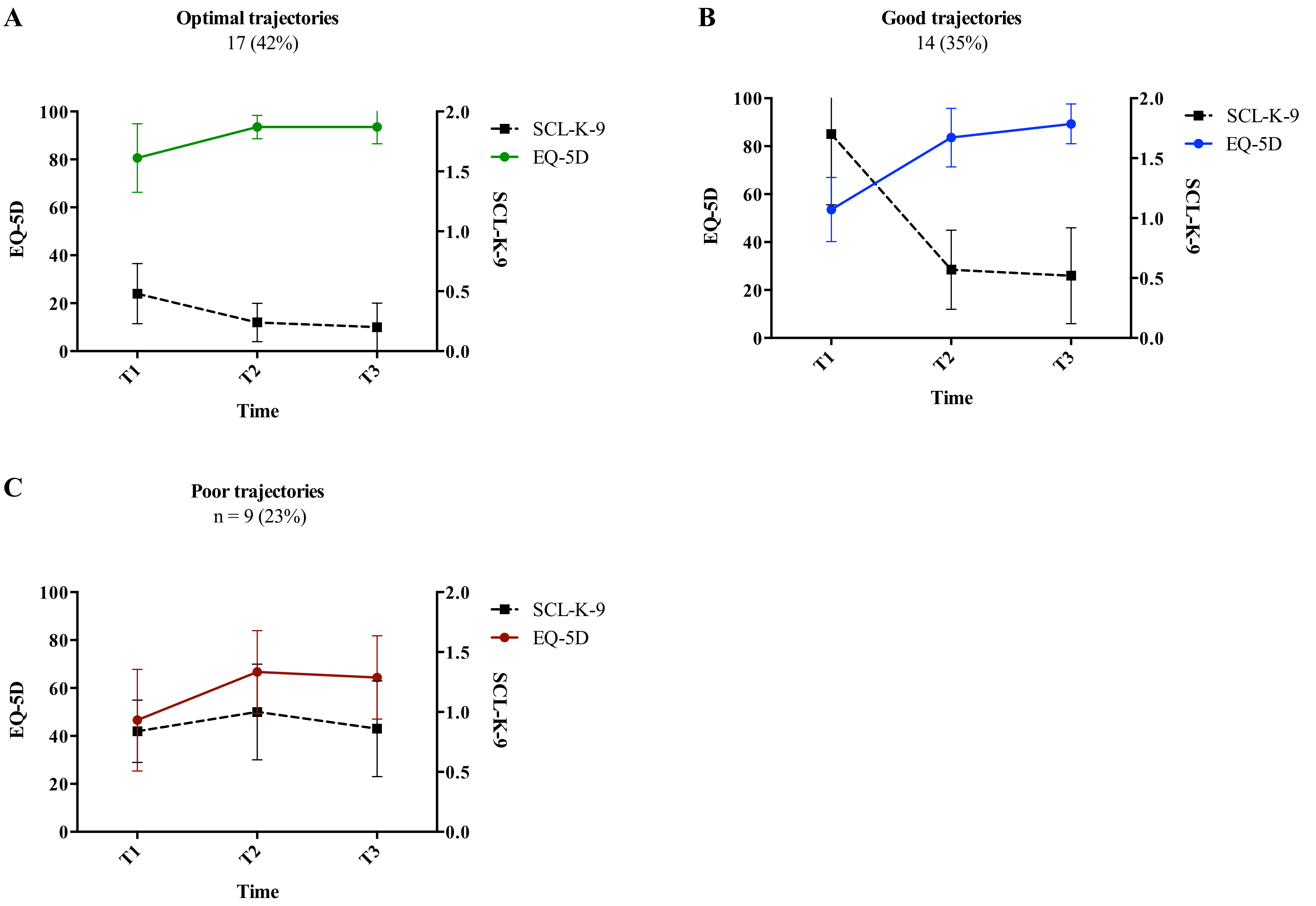

Figure 7. Post-transplant trajectories in lung transplant recipients

Table 6. Clusters' characteristics

	Optimal trajectories (A) *n* = 17 (42%)		**Good trajectories (B)** *n* = 14 (35%)		**Poor trajectories (C)** *n* = 9 (23%)		Between groups				
	M	*SD*	*M*	*SD*	*M*	*SD*	df	*F*	*p*	*Bonferroni post hoc test*	*p*
T1 SCL-K-9	.5	.2	1.7	.6	.8	.3	2	37.2	<.001	A vs. B A vs. C B vs. C	<.001 .105 <.001
T1 EQ-5D	80.6	14.3	53.6	13.4	46.7	21.1	2	17.9	<.001	A vs. B A vs. C B vs. C	<.001 <.001 .937
T2 SCL-K-9	.2	.2	.6	.3	1.0	.4	2	21.2	<.001	A vs. B A vs. C B vs. C	.008 <.001 .004
T2 EQ-5D	93.5	4.9	83.6	12.2	66.7	17.3	2	16.7	<.001	A vs. B A vs. C B vs. C	.058 <.001 .004
T3 SCL-K-9	.2	.2	.5	.4	.9	.4	2	13.3	<.001	A vs. B A vs. C B vs. C	.027 <.001 .042
T3 EQ-5D	93.5	7.0	89.3	8.3	64.4	17.4	2	23.8	<.001	A vs. B A vs. C B vs. C	.814 <.001 <.001

Note. M = mean; SD = standard deviation; df = degrees of freedom; *F* = ANOVA F-test statistic; *p* = level of significance.

Table 7. Sociodemographic and medical characteristics of the 3 clusters in 40 lung transplant recipients

	Optimal trajectories (A)		**Good trajectories (B)**		**Poor trajectories (C)**			
	n = 17 (42%)		n = 14 (35%)		n = 9 (23%)			
	M	*SD*	*M*	*SD*	*M*	*SD*	effect sizes	*p-values*
Sex							.17[a]	.551[a]
*male	11	27.5%	7	17.5%	4	10 %		
*female	6	15%%	7	17.5%	5	12.5%		
Age	46.5	16.6	44.2	13.9	54.6	15.4	.07[b]	.286[b]
Underlying Diagnosis							.34[a]	.160[a]
COPD	9	22.5%	3	7.5%	3	7.5%		
CF	6	15%	6	15%	1	2.5%		
IPF	2	5%	2	5%	3	7.5%		
Other	0	0	3	7.5%	2	5%		
Disease severity	1.8	.6	1.9	.3	2.3	.5	.13[b]	.075[b]
Time on waiting list	258.3	288.5	313.4	210.4	226.7	77.9	.02[b]	.700[b]
*ECMO-use	6	15%	4	10%	3	7.5%	.08[a]	.883[a]
Comorbidities	1.7	1.2	1.8	1.3	2.3	1.1	.06[b]	.386[b]
Nr. of days in ICU pLTx	5.8	5.5	5.9	4.6	10.4	11.0	.08[b]	.210[b]
LOS	4.4	1.4	4.6	1.4	9.6	3.6	.53[b]	<.000[b]

Note. *values stated with n(%).

[a] Chi-square test for comparison of nominal or dichotomized variables and Cramer's V for computing effect sizes.

[b] *F*-test for multiple comparison ANOVA with continuous variables and Eta^2 for computing effect sizes.

Statistical Significance: $p < 0.05$.

Disease severity, scaled 1 – 3. Higher value indicates higher disease severity.

Abbreviations: COPD = chronic obstructive pulmonary disease; CF = cystic fibrosis; IPF = interstitial pulmonary fibrosis; LOS = length of stay in weeks.

Table 8. Predictor analyses for psychological distress and HRQoL six months post-transplant

Medical factors	**T3 SCL-K-9** (n = 40)	**T3 EQ-5D** (n = 40)
Age	.25	-.20
*Sex	-.13	-.12
Disease severity	.39*	-.42**
Time on waiting list	-.02	.24
ECMO-use	-.02	.29
Comorbidities	.16	-.05
Nr. of days in ICU	.11	-.36*
LOS	.44*	-.72**
T1 EQ-5D	-.37*	.39*

*p ≤ .05; **p ≤ .01; ***p ≤ .001.

*Statistical relationship computed by Spearman Correlation.

Sex: 1 = male; 2 = female.

The following variables were significantly correlated with T3 EQ-5D: disease severity (*r*= -.42; *p*= .006); number of days in the ICU (*r*= -.36; *p*=.02); length of hospital stay (*r*= -.72; *p*= .001) and T1 EQ-5D (*r*= .39; *p*= .01).

5.5 Discussion

The aim of this prospective longitudinal study was to assess psychological distress and HRQoL trajectories in lung transplant recipients over the first six months following their transplantation, to identify those with poor postoperative trajectories and to explore potential outcome-related predictors and their impact upon psychological distress and HRQoL during the study period.

We performed hierarchical cluster analysis – a useful statistical tool to classify subjects into homogeneous subgroups based upon similar characteristics – so as to identify distinctive post-transplant trajectories for psychological distress and HRQoL over those first six postoperative months. Our data revealed a three-cluster solution, distinguishing transplant recipients manifesting optimal, good and poor postoperative trajectories. Transplant recipients with optimal postoperative trajectories (42%) reported surprisingly high HRQoL levels and notably low levels of psychological distress shortly after transplantation, and by six months post-transplant, their reported HRQoL and stress levels were similar to healthy population values. Those patients with good trajectories (35%) experienced impaired HRQoL and elevated stress levels two weeks after transplantation, but by three months follow-up reported significantly increased HRQoL and significantly reduced psychological distress. This group of patients benefitted most from lung transplant surgery by demonstrating substantial improvements in HRQoL dimensions and levels of psychological distress over the first six months following transplantation relative to the other two cluster groups. Finally, almost a quarter of our clinical sample (23%) showed poor postoperative trajectories, suffering from elevated stress levels that continued to remain high over the first six months post-transplant, and experiencing only slightly increased HRQoL that remained low throughout the six-month observation period. These results indicate that lung transplant recipients respond in different ways to their surgery and that quality of life gain after transplantation varies greatly from patient to patient. The majority of patients appear to cope very well, while others seem to struggle postoperatively. For many patients, the transplantation itself, as well as the ICU stay, might be perceived as a traumatic stressor that can decrease HRQoL and trigger mental distress (Baranyi, Krauseneck, & Rothenhausler, 2013). Additionally, the rehabilitation period can vary greatly from patient to patient. Given lung recipient’s own history of lung disease plus enduring functional impairments and symptom distress post-transplant, may negatively affect the patient’s HRQoL perception (Dew et al., 2012). Furthermore, the concept of resilience might explain at least some of the different responses to transplantation. For instance, previous studies in transplant medicine illustrated that a high degree of resilience and self-efficacy (Schumacher, Sauerland, Silling, Berdel, & Stelljes, 2014) as well as social support (Archonti et al., 2004; De Vito Dabbs et al., 2013), are essential to successful coping with the transplant experience. The early identification of lung transplant patients with poor postoperative trajectories is therefore critical to initializing adequate outpatient psychiatric therapy or psychosocial support to thereby reduce psychological distress and enhance quality of life.

As a second analytical step, we sought to identify differences between the cluster groups and thereby detect those with poor post-transplant trajectories. Our patients with poor postoperative HRQoL generally were older, more likely to suffer from more severe disease and more co-morbid conditions, and more likely to have had prolonged ICU and hospital stays. Previous studies have suggested a negative impact of co-morbidities on HRQoL after lung transplants (Kugler et al., 2005; Vermeulen et al., 2003). Our results are consistent with these findings, indicating that clinical complications (e.g., greater disease severity, a higher number of co-morbidities, and longer hospital stays) are associated with progressive quality of life deterioration over the early post-transplant period. With regards to demographic variables, in the psychosocial transplant literature, reduced HRQoL-gains have been commonly described in older lung transplant recipients, presumably because older patients have less energy and reserves to cope with the taxing postoperative period than those who are younger (Vasiliadis et al., 2006; Vermuelen et al., 2007). On the other hand, researchers have reported significant gender differences in overall HRQoL, reflecting better outcomes in men (Rodrigue & Baz, 2006; Santana et al., 2012), notwithstanding, we did not observe this.

Lastly, we explored potential predictors of psychological distress and poor HRQoL six months after transplantation. In particular, disease severity, the number of days spent in the ICU and hospital as well as self-reported HRQoL two weeks post-transplant predicted impaired HRQoL at six months of follow-up. Meanwhile, disease severity, length of hospital stay and self-reported HRQoL two weeks post-transplant significantly predicted level of psychological distress at six months. Age, gender, time on the waiting list, pre-operative ECMO-use, and the number of co-morbid conditions failed to predict six-month levels of psychological distress or HRQoL. Prospective studies on potential short-term outcome predictors and their impact upon psychological distress and HRQoL are lacking; therefore, direct comparisons with our data are impossible. However, our findings are similar to those of an earlier cross-sectional cohort study investigating HRQoL determinants among patients between one and five years since their lung transplant, suggesting that lung disease and events leading to hospitalization negatively affect most of the SF-36 (Short Form Health Survey) domains, while other variables like age, gender and FEV1 exert little to no influence on HRQoL (Vasiliadis et al., 2006).

Taken together, among the investigated predictor variables, disease severity, the length of hospital stay and self-reported HRQoL two weeks post-transplant were the strongest predictors of both impaired HRQoL and elevated psychological distress six months after transplantation. Our results indicated that the post-transplant psychological distress and HRQoL appear to be influenced in the early postoperative phase predominantly from medical rather than psychosocial factors. Elevated psychological distress and impaired HRQoL in the early postoperative phase can have a persistent negative impact upon long-term mental health and HRQoL (Goetzmann et al., 2010). Thus, psychosocial care for those transplant recipients suffering from elevated stress levels and impaired HRQoL is of great importance.

5.5.1 Study strengths and limitations

Strengths of the current study include our investigation of a lung transplant population treated exclusively by the transplant centre using a prospective, longitudinal study design, as well the use of a rigorous statistical methodology to identify distinct cluster groups, and the utilization of validated outcome measures with well-known psychometric properties. Potential limitations include the relatively small study sample. Due to the small sample, our results lack statistical power, meaning that the results of our cluster analyses were presented only descriptively. Moreover, we surveyed lung transplant recipients over a relatively short period of time (only six months). The follow-up of lung transplant recipients over several years would add further insights into the development of post-transplant psychosocial trajectories and outcome predictors. Although our findings should be interpreted with caution due to these limitations, we believe that our study provides realistic and valid predictors for early postoperative psychosocial trajectories and outcomes.

5.5.2 Conclusions

The psychosocial care of transplant recipients who suffer from emotional distress is critical to maximizing recovery and outcomes. The assessment of post-transplant psychological distress and HRQoL in terms of trajectories instead of considering only outcomes at discrete time points is beneficial in identifying patients who experience no significant postoperative improvement in HRQoL. However, since we only studied patients for six months, additional longitudinal research with larger samples remains necessary to clarify the long-term post-transplant trajectories of these patients and to identify other potentially important outcome predictors.

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Author contributions

AS was responsible for drafting the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor. JJ and RK were consultants and provided advice during the conception and design of the project. All authors critically revised the paper for important intellectual content. JJ obtained the funding.

Conflict of Interest

The authors have no conflicts of interest to declare.

6 Empirical work 3

Early postoperative adjustment to lung transplantation A longitudinal qualitative study

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6.1 Abstract

Background: Understanding the impact of transplantation on patients' perceived well-being is crucial to guide supportive psychosocial interventions. However, little attention has been paid to the individual patients' experiences with lung transplantation.

Aim: To gain a more comprehensive view of patients' experiences with transplantation and their adjustment to normal life within the first six months post-transplant.

Methods: Forty lung transplant patients were interrogated at three different measurement time points (T1: two weeks; T2: three months; and T3: six months post-transplant) using semi-structured interviews to address their thoughts, feelings and attitudes with respect to the transplantation process, their new lungs, the organ donor, and their medication. Interviews were analyzed by means of qualitative content analysis as per Mayring.

Results: 'Physical benefits', 'fear of rejection', 'gratitude towards the donor' and 'side effects' were the most frequently named themes with respect to the transplantation process, new lungs, donor and medication regimen. Most themes remained unchanged over time. While the frequency of comments about intensive care unit delirium and worries regarding donated organ quality decreased significantly over time, mentions of restrictions in everyday life increased significantly. Gender comparisons revealed only marginal differences in the response categories.

Conclusions: Improvements in physical function during the early postoperative phase may be limited by the onset of clinical complications, fear of rejection and infections, medication side effects, and restrictions in everyday life. Listening attentively to patients, addressing their concerns in a timely fashion, and actively psychological intervening when mental health problems arise are crucial for the effective management of lung transplant patients.

6.2 Introduction

Lung transplantation (LTx) is an established therapeutic option that extends survival and improves health-related quality of life (HRQoL) in selected patients with end-stage lung disease (Dierich et al., 2013; Kugler et al., 2005). The majority of lung transplant recipients experience a dramatic improvement in their underlying health condition, particularly over the first few months after transplantation (Lanuza, Lefaiver, Mc Cabe, Farcas, & Garrity, 2000). Improvements primarily include overall general health, physical health, vitality, and social functioning, with patients experiencing fewer role limitations due to physical health relative to their pre-transplant level of function (Archonti et al., 2004; Cohen et al., 1998; Limbos et al., 1997; Limbos et al., 2000; Rodrigue, Baz, Kanasky, et al., 2005; Rutherford et al., 2005; Stavem et al., 2000). However, even in patients with successful clinical outcome, lung transplantation does not lead to the complete recovery of health and is frequently associated with long-term medical complications, including graft dysfunction, recurrent infections, and the side effects of immunosuppressive drugs that affect approximately 40% of LTx patients (Inci et al., 2013). In addition, mental health problems commonly occur, including depressive disorders, adjustment disorders, and generalized anxiety disorders with prevalence rates up to 30% (Dew et al., 2012; Goetzmann, Irani, Schwegler, Stamm, Bricman, et al., 2010). These medical and psychological complications contribute to limitations in physical fitness, and can negatively influence a patient's ability to cope with their new graft, their adherence to pharmacologic therapy, and their postoperative HRQoL (De Perrot et al., 2004; Xu et al., 2012).

The lung transplant procedure creates complex ongoing medical and psychological challenges for patients, starting prior to surgery and extending far beyond the first year of survival. After transplantation, patients must follow a strict medical regimen and are expected to perform a variety of health-promoting behaviors. These medical routines are often perceived as stressful and disruptive, because they interfere with daily activities and patients' interests (Xu et al., 2012).

Qualitative data analyses based on patient narratives could provide valuable insights into post-transplant adjustments following lung transplantation. Presently, few studies have been published that qualitatively examined the subjective experience of lung transplantation. Accessible qualitative studies addressing patients' transplant experiences have investigated the psychological processing of transplantation (Goetzmann et al., 2009), feelings of guilt and relationships with the donor (Neukom et al., 2012), symptom experiences and reactions to the threat of rejection (De Vito Dabbs et al., 2004), post-transplant compliance behaviors (Goetzmann, Moser, et al., 2006), and patient experiences with education and support after transplantation (Ivarsson, Ekmehag, & Sjoberg, 2013). However, these studies were preliminary and hampered by methodological limitations, including the use of small study samples and restrictions in data collection (e.g. no tape recording, temporal distortion in data collection).

The underlying aim of this prospective qualitative study was to provide a comprehensive view of patients' postoperative experiences with their transplant and adjustments to normal life during the first six months following transplantation. We hypothesized that a deeper understanding of the themes that emerge within the early postoperative phase and how lung transplant patients cope with their post-transplant situation may help professionals to respond more competently to patients' needs, especially to those who suffer from increased emotional distress post-operatively.

6.3 Methods

6.3.1 Patients

Between January 2012 and April 2014, 72 lung transplants were performed at the Transplant Center at the University Hospital of Zurich, Switzerland. All patients who received lung transplants over this time period were considered eligible for inclusion, unless they were: (i) younger than 18 years of age, (ii) unable or unwilling to provide informed consent, or (iii) unable or unwilling to complete questionnaires in German. Forty-four consecutive adult LTx recipients qualified for the study. During data collection, 3 subjects unexpectedly withdrew from participation for medical or personal reasons (e.g., feeling overwhelmed by hospital routines and preparations for discharge, distressed, overly-tired, and/or short of time). One patient had to be excluded due to critical health conditions and repeated admissions to the intensive care unit (ICU). The final sample included 40 patients. Interview data were supplemented with demographic and clinical information obtained from medical records.

6.3.2 Procedures

The patients were interviewed at three different time points (T1: two weeks; T2: three months; and T3: six months post-transplant) regarding their thoughts, feelings and attitudes with respect to the transplantation process itself, the new lungs they had received, the organ donor, and the medication they had been prescribed post-transplantation. While the first interview at T1 was performed during the initial hospitalization, the follow-up interviews at T2 and T3 typically were conducted during regular transplant clinic out-patient visits at the University Hospital Zurich. A few patients either still were hospitalized or had been readmitted to hospital due to complications at T2 or T3. All patients provided written informed consent prior to their participation. The patients were informed about their right to withdraw from the survey at any time. The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland.

6.3.3 Data collection

Eligible patients were invited to participate in a semi-structured interview. The interviews were conducted by three different investigators (A.B., V.H., A.S.) who worked either as a psychiatrist or clinical psychologist in the Department of Consultation-Liaison Psychiatry at the University Hospital of Zurich. All interviews were tape-recorded and then transcribed verbatim (A.S.). The interviews lasted, on average, 20 minutes (range 10 to 30 minutes). The core questions asked in the semi-structured interview are listed in Table 9.

Table 9: Questions in the semi-structured interview

Interview questions	
1	What thoughts, feelings and attitudes do you have with respect to the transplantation process itself?
2	What thoughts, feelings and attitudes do you have with respect to the new lung(s)?
3	What thoughts, feelings and attitudes do you have with respect to the organ donor?
4	What thoughts, feelings and attitudes do you have with respect to your current medication regimen?

Note. These broad interview questions were supplemented by appropriate open-ended questions.

6.3.4 Data analysis

Qualitative analysis

The 120 interviews (40 patients; 3 data collection points) were analyzed by qualitative content analysis as per Mayring (2008), using the qualitative data analysis software ATLAS.ti, version 5.2 (atlas.ti, 2015). Mayring's (2008) qualitative content analysis is one of the most frequently used qualitative methodological approaches in social research in German-speaking countries.

In the present study, four main categories were defined deductively from the semi-structured interviews. They were: ‘the lung transplantation procedure itself’, ‘the new lungs’, ‘the donor’, and ‘the medication regimen’. One author rated the interviews (A.S.). Using the research questions, text material was analyzed by stepwise inductive construction of coding categories (codes), which were then assigned to the main categories. After 10% of the text material was analyzed, the codes were re-evaluated and revised (N.D.; L.G.). The number of responses determined the relevance of each code. Inter-rater reliability of the defined codes was evaluated (N.D.), by rating a random sample of 20% of the quotations that had previously been coded by the first author. In cases of disagreement, consensus was achieved by discussion and adjustment of the codes. Inter-rater reliability was calculated as Cohen’s kappa across all main categories. The two code assignment ratings achieved excellent inter-rater reliability, as indicated by Cohen’s kappa values ranging between .89 and .97 (category LTx: .97; category new lungs: .92; category donor: .95; category medication regimen: .89).

Quantitative analysis

Qualitative analysis was followed by quantitative analysis to examine the frequency of mentioned codes and changes in the response categories over time. The data consisted of binary variables (mentioned: 1; not mentioned: 0) for each unique code identified during qualitative analysis. The Statistical Package for the Social Sciences (SPSS, version 22.0) was used to perform all statistical analyses, with any two-tailed probability value less than .05 considered statistically significant (IBM Corp, 2013). Descriptive statistics were reported as median and range, or as counts and percentages, as appropriate. To test for changes between the three data collection points (T1-T3), Cochran’s Q test and McNemar’s test were used to identify statistically-significant differences between the time points. Gender comparisons were conducted via Fisher’s exact test.

6.4 Results

6.4.1 Sample characteristics

Participants included 21 male and 19 female lung transplant recipients with a median age at the time of transplantation of 52 years (range 20 to 68). Of the 40 patients, 43% were married. With respect to employment status, 45% were not working prior to their transplant for health reasons, while 20% were already retired. The main indication for transplantation in our clinical sample was chronic obstructive pulmonary disease (COPD; 38%), which was followed by cystic fibrosis in 30%. Six months after transplantation, all 40 patients were still alive. Demographic and clinical characteristics are summarized in Table 10.

Table 10: Demographic and clinical characteristics of lung transplant (LTx) recipients

Variables	**40 LTx recipients n (%)**
Male gender	21 (53)
Median age (range)	52 (20 - 68)
Education level	
Elementary	6 (15)
Secondary	25 (63)
Tertiary	9 (22)
Married/ in partnership	29 (73)
Primary indication for LTx	
COPD	15 (38)
Cystic Fibrosis	12 (30.0)
Idiopathic Pulmonary Fibrosis	8 (20.0)
Others	5 (12)
Bilateral LTx	40 (100)
Time on waiting list (d) (median; range)	224 (10 - 992)
Days in the ICU (median; range)	4 (2 – 29)
Weeks in hospital pLTx (median; range)	4 (3 – 14)

Note. LTx = lung transplantation; pLTx = post-transplant; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.

6.4.2 Qualitative data

Text analysis revealed six codes for the theme ‘transplantation’, four codes for the theme ‘new lungs’, five codes for the theme ‘donor’, and seven codes for the theme ‘medication regimen’. The identified codes and categories are described and exemplified with patient quotations below.

Thoughts, feelings and attitudes about the transplantation process itself

Thoughts, feelings and attitudes about transplantation can be encompassed by the themes ‘physical benefits’, ‘physical complaints’, ‘psychological distress’, ‘psychological benefits’, ‘coping strategies that could positively affect recovery’, and ‘ICU delirium’.

I. Physical benefits

With respect to the transplantation procedure, ‘physical benefits’ was the category most often mentioned by patients (T1: 75%; T2: 83%; T3: 73%). Patients spoke about how the transplantation had saved their life and frequently associated the lung transplantation event with prolonged survival, a second chance at living, or a gift of life. Furthermore, physical benefits encompassed significant improvements in physical function, vitality and health perceptions, such as being able to breathe again, being able to walk without supplementary oxygen, generally having more energy for conducting day-to-day activities, and being able to participate in sporting activities like hiking, riding a bicycle and playing tennis, or to play music. Many patients expressed relief about no longer suffering from respiratory distress, coughing or always having mucus in their lungs.

‘It is crazy how quickly one forgets how bad it was before transplantation… I was no longer mobile; I could not feed myself; drinking was difficult; and going to the toilet required an enormous effort… I had to refuse to do many enjoyable things. My life was restricted by my

poor physical condition, which included shortness of breath, fatigue and difficulty exercising. Now I can breathe without being exhausted, I can walk without getting short of breath, and can speak or laugh simultaneous with walking. It is simply marvelous that today I can pursue hobbies, walking outside in nature, riding a bike...'

II. Physical complaints

Despite significant physical benefits, patients also reported numerous physical complaints (T1: 58%; T2: 60%; T3: 48%). The most frequent were pain and discomfort, feeling pressure at the incision site, nausea, fatigue, feebleness, muscle weakness, poor digestion, diarrhea, and recurrent infections. A few patients disclosed having subsequently been diagnosed with cancer, diabetes or hypertension.

'It bothers me that I am still not physically fit. Even though I train regularly, I lack muscle strength and quickly get exhausted. I am very tired and need a lot of rest. After a busy day, I am so tired that I can hardly do anything.'

III. Psychological distress

Records indicated that psychological adjustment to transplantation was associated with considerable psychological distress (T1: 48%; T2: 30%; T3: 38%), including feelings of being overwhelmed, helplessness, lack of control, nervousness, and being worried about complications or organ failure. Common characteristics of the difficulty to adjust to the postoperative situation were depressed mood, anxiety, emotional disturbances, and sleep difficulties. Psychological distress also occurred because of the prolonged rehabilitation process, major side effects of medication, social isolation for fear of infections, insecurity in physical symptom recognition and in dealing with medication, and repeated hospital admissions.

‘Physically, I am in good condition. However, when I became able to leave the hospital and go home, suddenly I found myself suffering from a number of fears. I had great difficulties structuring and organizing my daily life. I quickly felt distressed and overwhelmed doing things that used to be easy for me. My wife worked full-time and could not be with me all day. I was not able to cope with the situation at home and felt like I was going crazy. So I let myself be hospitalized again.’

A few patients expressed distress due to still being on sick leave while in good physical condition. Those patients felt bored staying at home all day and not having meaningful activities to engage in.

IV. Psychological benefits

In addition to physical improvements, psychological benefits were observed following lung transplantation (T1: 33%; T2: 38%; T3: 28%). Typically, after surgery, patients felt elated and experienced a sense of relief and satisfaction with their steadily-improving lung function. In particular, psychological benefits were related to gains in mobility, autonomy, self-care and usual activities, as well as in reduced psychological distress and anxiety. Likewise, patients were happy to again be able to take care of their family and to engage in social and cultural activities and pursue hobbies.

‘*Thanks to the transplant, I can again provide care for my family. At the time I was sick, I always felt I was a bad mother. This feeling bothered me deeply ... Before transplantation, I had no energy at all and had to tell my children that they had to look after themselves or that they had to go somewhere alone. Today, I thoroughly enjoy that I can be there for my family. But I also enjoy that I can be independent again; that I can meet friends and go to parties.’*

Prior to transplant, physical impairments resulted frequently in feelings of low self-confidence and withdrawal from social life. After lung transplantation, some patients reported to have experienced a boost in self-confidence: '*Because I can speak without getting out of breath and generally have more energy, it is much easier for me to approach to people and I feel more like going out'*.

V. Coping strategies promoting recovery

A small proportion of patients mentioned various coping strategies that might have positively affected their recovery and adjustment to post-transplant life (T1: 28%; T2: 18%; T3: 28%). Among adaptive cognitive coping styles, adopting a positive life orientation, focusing on the future and not thinking too much about possible complications were highlighted.

'From the very first, I decided not to think too much about the transplant and possible complications. I simply take each day as a gift. There are few people who wonder what I will do when my new lungs stop working. I tell them that I don't want to discuss such an eventuality. I will not allow myself to harbor such negative thoughts. I live with the transplant from day to day, being thankful for every good moment I can have with my new lungs.'

Other coping strategies were based on problem-focused, information-seeking or social support-seeking behaviors, like promoting information about organ donation and providing donor cards to friends and working colleagues, and talking about their experiences with other transplant patients and thus supporting each other. Only a few patients mentioned a change in their emotional reactions, like being much calmer in stressful situations. In general, any meaningful activity – like attending a course, returning to work, enjoying one's family and garden, going on holidays, and holding one's pet, facilitated the recovery and resumption of normal life.

VI. ICU delirium

Memories of intensive care unit (ICU) delirium were reported by only a minority of patients (T1: 23%; T2: 5%; T3: 10%). Patients described their delirium states as ‘dreamlike experience’, ‘a delirious condition between half-asleep and half-awake’, ‘crazy dreams’, ‘nightmares’, ‘fantasies, and ‘illusions’. The contents of hallucinations were primarily lost orientation, distorted feelings, chaotic thoughts, diffuse fears, and feeling threatened. Subjects described their delusions as ‘perfectly real’. Some believed that their hallucination happened at the exact moment of transplantation.

‘The hallucination started with a beautiful dream; there was wonderful music and everyone was happy. But then, an evil woman came to kill me. I was fastened to the bed. I couldn’t move or defend myself. I was terribly afraid; it was an awful feeling to be so helpless…’

Thoughts, feelings and attitudes about the new lungs

The category ‘new lungs’ contained four subcategories: ‘fear of transplant rejection’, ‘fantasies regarding new lungs’, ‘satisfaction with new lungs’, and responsibilities for the new lungs’.

I. Fear of transplant rejection

The most frequently mentioned theme with respect to the category ‘new lungs’ was ‘fear of transplant rejection’ (T1: 53%; T2: 45%; T3: 55%), which also included the fear of infections, fear of losing the graft, and fear of requiring a second transplant. The majority of patients anticipated that, sooner or later, their transplant would be rejected.

‘I do not know how the future looks like. I do not know if my body will reject the transplant or when. I only hope that good lung function can be maintained for a long time and that I have few medication side effects and little to no evidence of rejection. However, the latent fear of

rejection is always present. Every time I need to go to the clinic to check my numbers (e.g., oxygen levels, spirometry testing, pulmonary function tests, and blood tests), I worry about my health, even though I am feeling well. It is confusing, because you cannot rely on how your body feels; you can never be certain…'

The threat of organ rejection was associated with better symptom recognition and reporting. Most patients reported paying great attention to symptoms. However, many patients described insecurity in how to interpret their symptoms, because the symptoms associated with rejection often were identical to those related to everyday illnesses (cold, the flu, etc.). This ambiguity with symptom recognition resulted in health-concerns, careful illness behavior, and the fear of making mistakes.

II. Fantasies regarding the new lungs

About one third of the patients mentioned fantasies regarding the new lungs (T1: 40%; T2: 38%; T3: 35%) with respect to their body image and identity. Approximately one third of the patients reported that they perceived the new lungs to be part of themselves (T1: 28%; T2: 35%; T3: 28%) and used statements like 'the lungs belong to me', 'the lungs became part of me', or 'I have fully adopted the lungs'. While one patient gave the new lungs a name (*'the new lungs are my Empress, so I call them Sissi'*), another patient said that she had accepted the new lungs as part of herself and that she therefore did not need to give them a name. She added that she did not give too much thought to her new lungs. She just lived with them. Two patients had the feeling that their lungs had been repaired instead of replaced (T1: 5%; T2: 3%; T3: 3%).

‘The advantage is that you cannot see the transplant. If I had the hand of a Chinese woman, I would be constantly reminded that I carry something foreign. But I cannot see the lungs, so I can live with the idea that my old lungs simply got cleaned.’

A minority of patients mentioned perceiving their new lung(s) as a foreign object (T1: 8%; T2: 5%; T3: 3%), though this feeling tended to decrease over time. They made statements like: ‘the lungs are something new’, ‘as of yet, the lungs have not arrived’, ‘the lungs need to get used to my body’, and ‘this represents a dynamic process that takes awhile’. Thoughts regarding the new organ spontaneously transferred to the donor and to the fact that they were alive because someone else had died.

III. Satisfaction with the new lungs

The patients who reported ‘satisfaction with the new lungs’ were mostly patients who had experienced optimal postoperative trajectories without complications or recurrent infections. This might also explain why this code was named by only a small proportion of patients (T1: 18%; T2: 35%; T3: 20%).

IV. Responsibility for the new lungs

A few patients expressed feelings of responsibility for their new lungs (T1: 13%; T2: 8%; T3: 10%) and reported perceiving the new lungs as ‘a gift’, as ‘something of particular value’ that they have to take care of and look after.

‘My thoughts mainly revolve around my new lungs. Everything I do, I do out of respect for my new lungs. I do hope that everything goes well and that the lungs remain working for a long time. I am therefore very committed to taking the best care of myself and paying

attention to any abnormal changes I feel. It is equally important to me that I work closely with the transplant team to monitor my condition.'

Thoughts, feelings and attitudes about the donor

Analysis of the 'thoughts, feelings and attitudes about the donor' category resulted in five codes, which included 'gratitude', 'thoughts regarding the bereaved', 'fantasies regarding the donor', 'dealing with the donor's death', and 'worries regarding the donated organ's quality'.

I. Gratitude

Of all the codes, 'gratitude' was the most frequently mentioned (T1: 83%; T2: 88%; T3: 80%). The vast majority of patients expressed deep feelings of gratitude for the donor's generosity and for the opportunities the new organ(s) had given them. Patients spoke about the donor as '*an angel who saved my life'*, or *'someone who gave me my life back, the most precious gift anyone can give…'*. Patients frequently expressed their gratefulness to the donors by taking good care of the organ or by thinking of the donor when celebrating the anniversary of their transplantation.

'Especially on my birthday, but also on the anniversary of my transplant, I think of the donor and I realize that I would not have become this old without the donor's lungs. I am grateful to the donor that he donated his organs so I feel obligated to take care of my new organ and do everything I can to keep the lungs going'.

Despite feelings of gratitude, many patients felt that there was no purpose to them having further thoughts about the donor: *'I am thankful to the donor, but otherwise do not concern myself with thoughts about them'.*

II. Thoughts regarding the bereaved

The most frequently mentioned code in this category was ‘thoughts regarding the bereaved’ (T1: 25%; T2: 35%; T3: 33%) who were undoubtedly in mourning. Similar to their thoughts about the donor, the patients expressed feelings of gratefulness towards the relatives for having agreed to the removal of their loved one’s organs, while simultaneously acknowledging the difficulties inherent in making this decision *(‘I think the bereaved family needs a lot of strength to decide, at the last moment, whether an organ should be donated’*). Many patients would like to return the favor by writing an anonymous thank-you letter to the bereaved family: *‘Maybe it would be nice for the bereaved family to hear that someone is grateful for the donated lungs. I have three children who fully need me’.* Simultaneously, patients felt sympathy for the bereaved: *‘I often think of the bereaved family. While I have had this transplant for six months, it is only six months ago that the donors’ relatives suffered a significant loss. This is definitely not easy’.*

III. Fantasies regarding the donor

A small percentage of patients (T1: 30%; T2: 30%; T3: 23%) spoke about their speculations with respect to the donor. They wondered about the donors’ gender, age and personality, as well as the circumstances surrounding the donor’s death. Driven by curiosity, a few patients researched the newspaper to identify fatal accidents and thereby discover more about the donor’s death.

Only a few patients felt somehow connected to the donor (T1: 13%; T2: 8%; T3: 10%) and described their relationship as ‘*a sensation of relatedness’, ‘congeniality of souls’, ‘having something in common’* or *‘he continues to live through me and I continue to live through him’.*

Only two patients thought about having adopted the donor's characteristics (T1: 0; T2: 5%; T3: 3%): *'Since I have had the new lungs, I am simply thrilled to go shopping. My friends tell me jokingly that I received the lungs from a former shopping queen', or 'Since I have had this transplant, I have had a craving for black coffee. I keep wondering if this has something to do with my new lungs'.*

IV. Dealing with the donor's death

There were two different types of response related to the donor's death (T1: 25%; T2: 15%, T3: 18%). One group of patients (35%) was affected by feelings of sadness and latent feelings of guilt regarding the donor's death, and expressed emotional difficulties accepting that the donor had to die so they could get the organ. *'Shortly after transplantation, I reflected on this for a long time — that someone had to die so I could continue to live. Only after many discussions with my caregiver did I come to understand that the donor had to die anyway, regardless of whether I received the lungs or not'.* The other group of patients (28%) presented themselves as detached from any emotional involvement with the donor's death and reasoned that *'the donor had to die anyway'*; '*it was not my fault that the donor had to die'*; or *'I assume that the donor consented to donating organs after his death'.*

V. Worries regarding donated organ quality

While at T1, six patients talked about being worried regarding the quality of the donated organ, at T2 and T3 only one patient mentioned these fears (T1: 18%; T2: 3%, T3: 3%). The fears were related to thoughts like '*I hope the donor lived a healthy life and I've received healthy lungs'*, or *'especially uncertainty about who the donor was, whether he had taken care of himself, whether he had led a healthy life or whether he has smoked, bother me. After* *all, the new lungs are a foreign object inside my body; I do not know the lungs and I did not know the donor'.*

Thoughts, feelings and attitudes about the medication regimen

I. Side effects

The code 'side effects' had the highest rates of mention (T1: 78%; T2: 75%; T3: 78%) within the category 'thoughts, feelings and attitudes about the medication regimen'. Numerous side effects were named, including nausea, vomiting, change in taste, stomach pain, gastrointestinal complaints, hirsutism, Cushingoid appearance, weight gain, and swelling. In addition, neurotoxic effects of immunosuppression were reported, like tremors, headaches, light sensitivity, restlessness, neuropathy (burning and numbness in hands/feet), insomnia, and mood swings.

In the early postoperative phase, patients were most concerned about dealing with the nausea and vomiting caused by their new medication.

'In the beginning, I had to take the medications two or even three times because I vomited them all up. Even thinking about the medication, I had to throw up. I had troubles accepting that I have to take so many drugs'.

Side effects that frequently were reported later in the postoperative period were tremors, swelling, and weight loss or weight gain.

'I suffer from severe tremors. I cannot pour a mug without spilling. The tremors sometime drive me crazy. I would like to take less cyclosporine, but that could be the final blow for my transplant.'

Concerns also related to long-term adverse effects and damage to other organs, as well as at the mercy of physicians. '*The feeling of being at the mercy of the transplant team, without being involved in decisions, makes me feel helpless. Sometimes I feel like a passenger in a plane, but worse'*. Metaphorical concepts of treatment included the idea that drugs attack and destroy one's body. Patients referred to drugs as *'little bombs', 'an enormous load of chemistry', 'a necessary evil', and 'an unresolved dilemma'*.

II. Benefits of medical treatment

Despite the many complaints resulting from medical treatment, most patients were aware of the importance and necessity of their drugs (T1: 73%; T2: 60%; T3: 68%). Mentioned advantages of the medical treatment were: *'the medical treatment ensures that the lung is not rejected'*; *'thanks to the medication, I am doing fine'*; *'the drugs give me a chance to survive, a chance to live'*; *'without the drugs, the transplant won't work*'; and *'they are protection against infections and rejection'*.

III. Restrictions in everyday life

Feeling restricted in everyday life as a consequence of the strict medical regimen and side effects increased significantly over time and was most pronounced at T2 and T3 (T1: 43%; T2: 70%, T3: 65%). On one hand, restrictions referred to the large number of medications required and the strict dosing schedule: *'My everyday life must comply with that strict drug schedule. I don't feel free anymore; my life is determined by my medication regimen'*. On the other hand, for many patients, following the medication regimen implied not only an expenditure of time but also organizational responsibilities. Additionally, some felt that their required adherence to strict diets was somehow an invasion into their everyday life.

'Sometimes it is very hard to follow the medication regimen, and taking the medication is very time-consuming. I get up at 8.00 a.m.; I measure my blood glucose and take my medication. Then I need a break to recover from nausea. I then continue with my inhalers. It isn't until about 11 a.m. that I'm done with the whole program. Furthermore, I have to follow a strict diet: eating cheese, eggs or raw meat is prohibited. In addition to that, the many follow-up appointments restrict my everyday life. Sometimes I feel time pressured. I also feel restricted in my private life. For instance, I cannot spontaneously go out for dinner with my husband because I have to be home in time to take my medications; and, when I want to go on holiday, I have to plan carefully what I need to bring. I have to think not only of my pills, but also my inhalers, the blood pressure meter, the home spirometer, the cold box for the medication… this is just tedious.'

IV. Adherence to medication

The code 'adherence to the medication regimen' included statements regarding attitudes and intentions, beliefs and satisfaction relating to the medication as well as perceived behavioral control of the prescribed intake of medication. Slightly more than one third of the patients rated their adherence to their medication regimen as good (T1: 38%; T2: 35%; T3:43%). Sustained motivation for regular medication intake stemmed from the belief that the medications were imperative for their survival (*'the medications are indispensible to life'*), but also from a sense of commitment and responsibility towards the donor and the transplant team *('I feel obliged to take care of the matter, mainly out of respect for the donor, but also for the transplant team'*). Patients also admitted that they had *'accepted the fact of taking medication all (their) life'*, and that taking medication had become routine: *'the medications are as much a part of my life as the daily brushing of teeth'*; '*the medication became part of my life*'.

Only a very small minority of patients admitted to having missed a dose of medication, taken drug holidays, postponed drug intake, or failed to follow a dietary program or health behavior (T1: 3%; T2: 3%, T3: 5%).

'The medications make me feel depressed, so I frequently postpone them… And the inhaler causes nausea and shortness of breath and scrapes my throat. Therefore, instead of daily, I inhale every five days.'

V. Coping strategies to manage the medication regimen

Coping strategies related to the management of medication were mentioned only by a minority of patients, but the reported use of such strategies increased over time (T1: 5%; T2: 18%; T3: 20%). Principally, two different coping styles were observed: on one hand, adaptive cognitive coping styles were used, characterized by cognitive flexibility in terms of modifying one's way of thinking and distancing oneself from the problem of medications (*'I don't want the medication to determine my life, I'd rather focus on things I could not do anymore before the* transplant'; and *'the medications don't cause any problems; I have accepted them as part of the game'*). On the other hand, patients adopted problem-focused strategies or tricks to make the handling of medications easier and more pleasant (*'I take the medication together with a yoghurt'; 'I have shifted the drugs so I only have to take them twice a day'; and 'I always try to do something useful or something I like while I have to use the inhaler. Usually, I read the newspaper or watch the news').*

VI. Insecurities dealing with medical treatment

Insecurities dealing with medical treatment were largely restricted to T1 and only mentioned by a few patients (T1: 8%; T2: 0; T3: 3%).

'When I have a migraine and throw up, I become worried because I don't know whether or not my body has already absorbed the drugs. I always have doubts about whether I should take them once again. I worry and wonder: how bad is this now?'

6.4.3 Quantitative analysis

The frequency of responses and changes over time are shown in Table 11, and the rank orders of response categories are depicted in Figure 8. The most frequently-mentioned codes with respect to the categories 'lung transplant', 'new lungs', 'donor' and 'medication regime' were 'physical benefits' (T1: 75%; T2: 83%, T3: 73%), 'fear of rejection' (T1: 53%; T2: 45%; T3: 55%), 'gratitude' (T1: 83%; T2: 88%; T3: 80%), and 'side effects (T1: 78%, T2: 75%, T3: 78%), respectively. Significant changes in response frequencies over the three data time points were identified only for 'ICU delirium' (*Cochran's* $Q = 6.000$; $p = .05$), 'worries regarding donated organ quality' (*Cochran's* $Q = 8.000$; $p = .02$), and 'restrictions in everyday life' (*Cochran's* $Q = 6.462$; $p = .04$). While response rates for 'ICU delirium' (T1 vs. T2: $p = .04$; T1 vs. T3: $p = .23$; T2 vs. T3: $p = .69$) and worries regarding donated organ quality' (T1 vs. T2: $p = .07$; T1 vs. T3: $p = .07$; T2 vs. T3: $p = 1.000$) diminished over time, rates for 'restrictions in everyday life' increased (T1 vs. T2: $p = .04$; T1 vs. T3: $p = .09$; T2 vs. T3: p = .81). Gender comparisons revealed only marginal differences in response rates, with women more frequently mentioning coping strategies with respect to recovery at T1 ($p = .05$) and more side effects at T2 ($p = .04$) than men.

6.5 Discussion

Using qualitative content analysis, we found 'physical benefits', 'fear of organ rejection', 'gratitude', and 'medication side effects' to be mentioned most frequently within the predefined categories ‘lung transplant’, ‘new lungs’, ‘donor’ and ‘medication regimen’, respectively. Interestingly, the response rates, by category, hardly changed over time, indicating that most themes that patients were concerned about initially remained unchanged over the first six postoperative months.

Table 11: Changes in response categories over time

	T1 n = 40		**T2 n = 40**		**T3 n = 40**		**Test statistics**	
Category LTx	*n*	*%*	*n*	*%*	*n*	*%*	*Cochran’s Q*	*p*
Physical benefits	30	75	33	83	29	73	2.000	.37
Physical complaints	23	58	24	60	19	48	1.750	.42
Psychological distress	19	48	12	30	15	38	3.083	.21
Psychological benefits	13	33	15	38	11	28	1.412	.49
Coping strategies promoting recovery	11	28	7	18	11	28	1.600	.45
*ICU delirium	9	23	2	5	4	10	6.000	**.05**
Category new lungs								
Fear of transplant rejection	21	53	18	45	22	55	1.083	.58
Fantasies regarding new lungs	16	40	15	38	14	35	.273	.87
Satisfaction with new lungs	7	18	14	35	8	20	4.526	.10
Responsibility for new lungs	5	13	3	8	4	10	.667	.72
Category donor								
Gratitude	33	83	35	88	32	80	.933	.63
Thoughts regarding the bereaved	10	25	14	35	13	33	1.625	.44
Fantasies regarding donor	12	30	12	30	9	23	.900	.64
Dealing with donors’ death	10	25	6	15	7	18	1.529	.47
*Worries regarding donated organ quality	7	18	1	3	1	3	8.000	**.02**
Category medication regimen								
Side effects	31	78	30	75	31	78	.118	.94
Benefits of medical treatment	29	73	24	60	27	68	1.407	.50
*Restrictions in everyday life	17	43	28	70	26	65	6.462	**.04**
Adherence to medication	15	38	14	35	17	43	.519	.77
Coping strategies to manage medication regimen	2	5	7	18	8	20	5.636	.06
Non-adherence to medication regimen	1	3	1	3	2	5	.667	.72
Insecurities dealing with medication treatment	3	8	0	0	1	3	3.500	.17

Analyses over time conducted by means of Cochran’s Q test for categorical variables.

*McNemar test was used to identify statistically-significant differences between the time points.

ICU delirium: T1 vs. T2: p = .04*;* T1 vs. T3: *p* = .23*;* T2 vs. T3: *p* = .69

Worries regarding quality of donated organ: T1 vs. T2: *p* = .07; T1 vs. T3: *p* = .07; T2 vs. T3: *p* = 1.000

Restrictions in everyday life: T1vs T2: *p* = .04; T1 vs. T3: *p* = .09; T2 vs. T3: *p* = .81

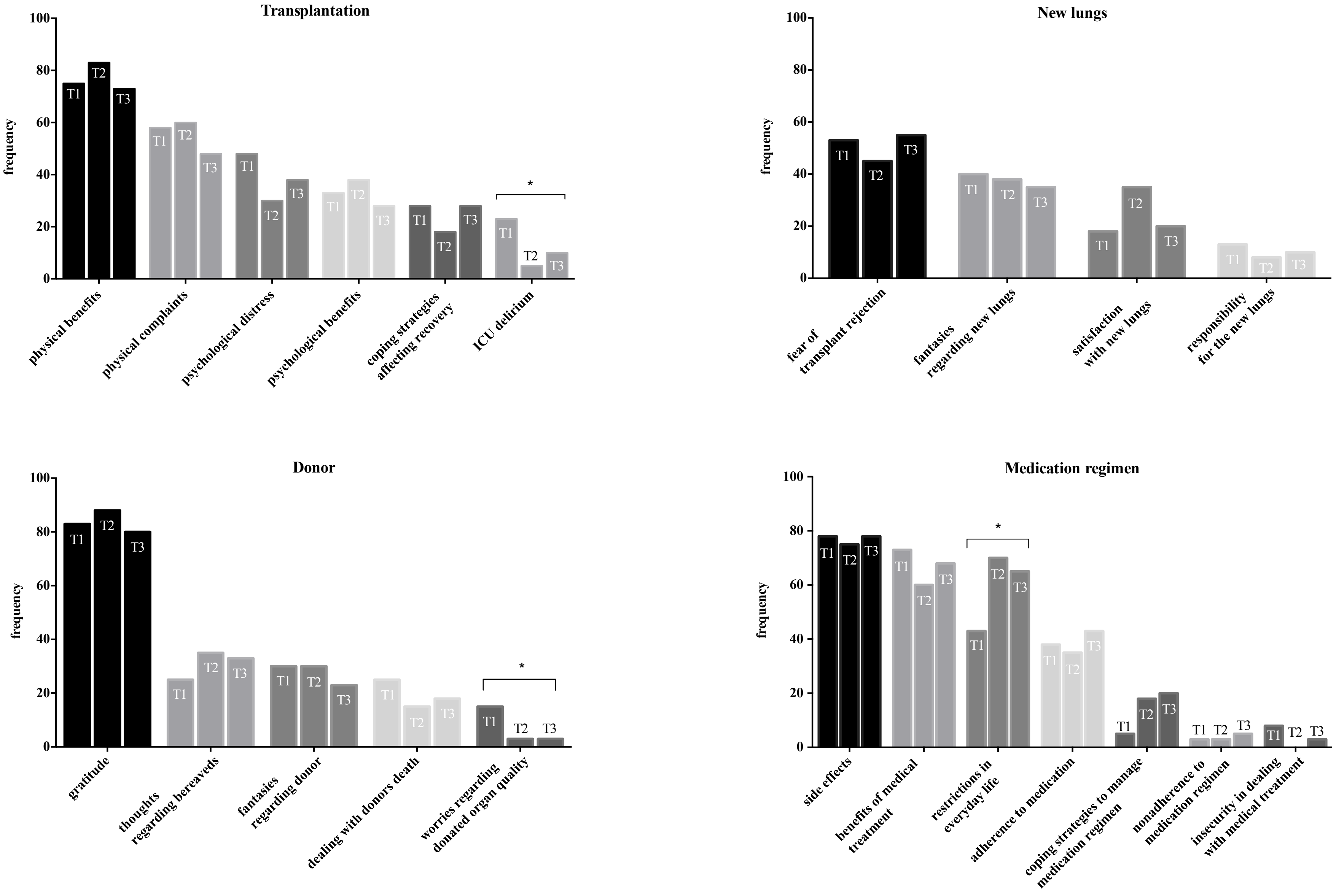

Figure 8: Frequency and rank order of response categories. *Note:* * indicates statistically significant difference.

Only three response categories changed in the frequency of mention over those first six months. While thoughts about ICU delirium and worries regarding donated organ quality decreased significantly within the first three months, concerns about restrictions in everyday life increased over six months. The lengthy process required for recovery and adjustment to transplantation, which typically spans several years, might explain the relative absence of change over time. At six months post-transplant, patients are only starting to resume their normal daily routines (Rosenberger, Dew, DiMartini, et al., 2012). Also notable in our results is that, contrary to other investigations that found women to experience more frequent problematic symptoms and lower gains in HRQoL than men (Kugler et al., 2007; Rodrigue & Baz, 2006), we encountered only marginal gender differences with respect to psychological adjustments to transplantation. By reason of lack of statistical significance over time and between the genders, for this paper, it is more fruitful to consider the content of the respective response categories qualitatively.

6.5.1 The transplantation process

In line with a number of other, already-published outcome studies (Finlen Copeland et al., 2013; Kunsebeck et al., 2007; Vermeulen et al., 2004), the majority of narrations indicated a positive impact of lung transplantation on health status and well-being. Patients acknowledged marked improvements in their physical function, vitality, mobility, level of autonomy, and self-care, and reduced psychological distress and anxiety. This being said, physical complaints were mentioned almost as often as physical benefits. The main physical issues were nausea, fatigue, feebleness, gastrointestinal disorders, and recurrent infections. Adjusting to new stresses associated with post-transplant life can trigger mental health problems (Rosenberger, Dew, DiMartini, et al., 2012). Consistent with other studies that identified elevated risks of mental health problems and psychological distress in lung transplant recipients (Dew et al., 2012; Kugler et al., 2007; Limbos et al., 2000), 30% of the patients in our sample reported features of psychological distress. In our study cohort, psychological distress within the first six months post-transplant was primarily linked to feelings of being overwhelmed, sensing a loss of security, feeling anxious at the time of discharge, having latent feelings of guilt over knowing that some other person had to die for them to receive their organ, worries about the threat of infections and organ failure, severe medication side effects, and perceived significant restrictions in everyday life.

Adopting active coping mechanisms can help one to deal with the stress-related experiences of transplantation, especially during the early postoperative phase (Nilsson, Forsberg, Lennerling, & Persson, 2013). In our study, the number of patients who mentioned coping strategies was surprisingly low. However, those respondents who used coping tended to use positive coping strategies (to promote positive well-being). In particular, these patients brought up problem-focused, information-seeking, and social-support seeking coping strategies. The training of pre- and post-transplant coping skills is important, as there is evidence that the use of problem-focused coping strategies positively influences post-transplant outcomes (Golfieri et al., 2007).

Even though ICU delirium following transplantation is commonly experienced in lung transplant recipients (Smith et al., 2015), in our study, only a small minority of patients (23%) reported the experience of delirium in their narrations, indicating that most patients seemed to remember little to none of their time in the ICU. Consistent with other findings on ICU delirium in transplant patients (DiMartini, Dew, Kormos, McCurry, & Fontes, 2007; Flynn et al., 2013), the main themes of ICU dreams were ‘feelings of threat’ and ‘fears about death’, both of which might reflect the patients’ uncertainty, lack of control, lack of trust, and presence of constant agony pre-transplant. Moreover, thoughts about ICU delirium diminished significantly over the first six months post-transplant. Although a few reports have been published suggesting that individuals can be adversely affected by transplant and ICU experiences (DiMartini et al., 2007; Flynn et al., 2013), our accounts revealed no evidence of psychological difficulties following the ICU stay.

6.5.2 New lungs

In our patient sample, 'fear of transplant rejection' was one of the most prevalent concerns post-transplant (more than 50% of all patients), resulting in illness behavior, fear of making mistakes, and social isolation. During postoperative management, the transplant team plays a pivotal role by communicating confidence via the regular monitoring of each patient's health condition. At the same time, being reliant on the transplant team interfered with many patients' desires for independence and self-reliance. On the other hand, to prevent infections and rejection, patients must assume some level of responsibility for attentively watching for changes in their condition, precociously reporting symptoms, and recognizing their shared responsibility with the transplant team, so as to achieve an acceptable quality of life within the limits imposed by their illness (De Vito Dabbs et al., 2004).

When asked about their thoughts and feelings towards their new lungs, many patients mentioned having 'adopted' the new organ. While most patients believed that the new organ had become a part of them and, thus, reasoned not needing to think further about the lungs, a minority of patients regarded their new lung as a 'foreign object' or as their 'own lungs that were repaired'.

6.5.3 Donor

Our transplant recipients were characteristically deeply grateful to their donors. However, about half of the patients emphasized not having any further thoughts about the donor and viewed the transplantation as a mechanical and rational process. In contrast, however, a few patients mentioning continuous speculations about the donor or the lung(s) (as mentioned above), like divining the donor's personality or figuring out what relationship they might still have with the donor. Some patients felt connected to the donor; others wondered whether they had adopted some of the donor's characteristics; and still others felt that their new organ was continuing to live within them. Likewise, a few patients had worries regarding the quality of their donated organ, perceiving the new lung(s) as something foreign, and being unable to comprehend their origin. According to Goetzmann et al. (2004), patients' fantasies and speculations about their new lungs or the lung donor represent a coping mechanism, similar to dreams, that helps them to process their transplant experience and mentally integrate the graft into their own body image. A more philosophical explanation was given by Quintin (2013), who assumed that the act of thinking and having fantasies related to the experience of organ transplantation enables patients to gain a greater understanding of what is entailed and, thus, give it meaning. As such, speculating and fantasizing about the new lungs and donor, is a way for them to come to terms with the transplant experience. Our patient narratives underscored how undergoing lung transplantation is a complex physical and psychological challenge that can substantially affect both a patient's self-identity and perceived meaning of life.

6.5.4 Medication regimen

Life-long maintenance of a complex medical regimen is crucial to preventing acute and chronic rejection and the loss of the lung allograft. Unfortunately, many of these medications have severe side effects and thus can induce considerable morbidity, thereby impacting the patient's physical function (Finlen Copeland et al., 2013). Suffering from side effects was mentioned by the majority of our study sample. Consistent with the literature, our analysis revealed that side effects arising from the immunosuppressive treatment ranged from transient to permanent and varied in the level of psychological distress they produced (Rosenberger, Dew, DiMartini, et al., 2012). One positive finding is that, despite the frequency of side effects mentioned, most patients understood the importance of following the immunosuppressive regimen as prescribed, and that failure to take immunosuppressive medications could be life-threatening.

Strict adherence to medications is particularly important for lung transplant patients, due to the high risk of infections and the potential for either acute or chronic rejection. With regular follow-up visits in the outpatient clinic, the majority of lung transplant patients exhibited good adherence over their first six months post-transplant (De Geest et al., 2014; Dew et al., 2007). Non-adherence to their medication regimen was admitted by just two patients.

Similar to De Vito et al. (2004), our analysis revealed that early post-transplant adjustment was predominantly affected by severe side effects, fears of organ rejection, and restrictions in everyday life. At some point, patients typically come to the realization that they have replaced one disease for another. Despite the many restrictions arising from transplantation, it is crucial for them to identify ways to live as normal as possible. Developing coping strategies can be important in dealing with the challenges of their onerous medical regimen. Only 20% of our patients reported using coping strategies to facilitate their medical regimen. Our results underscore the importance of interventions to improve adherence to self-care and proper medication-taking behaviors post transplant (De Geest et al., 2005).

6.5.5 Study limitations and strengths

The findings reported here must be interpreted taking into consideration certain methodological limitations. First among these is the risk of subjectivity in the interpretation of answers. Using an independent rater to assess the accuracy of the codes chosen minimized this risk of bias. A second limitation of our study was the potential for selection bias, as we only included patients who were physically and mentally fit enough to attend the interviews. Furthermore, some participants appeared to have difficulties articulating their experiences with transplantation or responding to the questions posed. Given the study's qualitative design, however, our findings are not meant to 'accurately' represent the experience of all lung transplant patients. Notwithstanding, we assume that our findings will have relevance for other transplant centers. Study strengths were the use of a prospective, qualitative study design with a relatively large sample without any drop-outs.

6.5.6 Conclusions and implications for clinical practice

The themes identified here, related to the experience of lung transplantation and adjustment to life as a transplant recipient, should increase healthcare-giver awareness of the many physical, psychological, social and behavioral challenges transplant recipients are confronted with during the early postoperative period. Improvements in physical function during the early postoperative phase may be limited by the onset of clinical complications, fear of rejection and infections, medication side effects, and restrictions in everyday life. Understanding this may help healthcare providers to enhance their practice, via listening attentively to patient narratives, addressing patient concerns in a timely fashion, and initiating active and/or pro-active interventions when mental health problems arise and start to adversely impact their patients' quality of life. Psychological support is of great importance to facilitate the early postoperative management.

Further qualitative research is required, considering the first 2-3 years after LTx, to elucidate the impact of lung transplantation on patients' wellbeing in the long-term.

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7 General discussion

The underlying purpose of this thesis was to evaluate health-related quality of life and psychological outcomes after lung transplantation and to investigate psychological adjustment to lung transplantation within the first six months post-transplant. Taken together, by employing three different research methodologies, the findings of the three empirical works contained herein contribute a more holistic understanding to the growing body of literature in transplant medicine.

In this chapter, the main results of the studies are briefly summarized and a general discussion of the results is offered, including the strengths and limitations of this three-part research project as a whole, suggestions for future research, and conclusions drawn by synthesizing the combined results.

7.1 Summary of the results

Empirical work 1: A systematic review of health-related quality of life and psychological outcomes following lung transplantation

The primary objectives of this systematic review were to assess the assortment of self-report instruments used to assess HRQoL and psychological outcomes following lung transplantation, to explore the study designs and methodology adopted for the eligible studies, to review the outcomes of instruments that have been applied most frequently, and to provide suggestions regarding which instruments to use. Our results revealed considerable heterogeneity in the approaches, methodologies and outcome measures utilized in published studies on HRQoL and psychological outcomes after lung transplantation. Methodological limitations potentially biased conclusions regarding the effects of lung transplantation on quality of life, such limitations including missing data, selection bias, small sample sizes, and the exclusion of patients who either had died or were too unwell to participate. Relatively few studies assessed HRQoL and psychological outcomes longitudinally within the same study sample. On the other hand, studies consistently identified significant post-transplant improvements in both mental health and HRQoL.

Empirical work 2: Psychological distress and quality of life in lung transplant recipients. A six months observational study

The overall purpose of this study was to evaluate outcome trajectories in lung transplant patients with respect to psychological distress and quality of life within the first six months post transplant, to identify patients with poor postoperative trajectories, and to determine potential predictors of psychological distress and poor HRQoL six months after transplantation. Hierarchical cluster analysis revealed three patient clusters, discriminating between transplant recipients with optimal (35%), good (42%) and poor (23%) postoperative trajectories. Patients with poor postoperative trajectories tended to be older, to have suffered from more severe lung disease, to have more co-morbid conditions, and to have had a more prolonged ICU and/or hospital stay. We also found disease severity, length of hospital stay, and self-reported HRQoL two weeks post transplant to be significant predictors of psychological distress and HRQoL at six months of follow-up.

Empirical work 3: Early postoperative adjustment to lung transplantation. A longitudinal qualitative study

By qualitative data analysis, we aimed to explore patients' experiences with their transplant and adjustment to normal life within the first six months after surgery. More specifically, semi-structured interviews were conducted to investigate patients' thoughts, feelings and attitudes with respect to the transplantation process, their new lungs, the organ donor, and their medication regimens two weeks, three months and six months postoperatively. Via content analysis, we identified 'physical benefits', 'fear of rejection', 'gratitude' and 'medication side effects' as the issues most frequently mentioned over those first six postoperative months. Out of 22 coding categories of responses identified, only three changed significantly, in terms of frequency of mention, over that time. While comments about 'ICU delirium' and 'worries regarding donated organ quality' significantly decreased over those six months, those regarding 'restrictions in everyday life' increased. Only marginal differences in frequency of the coding categories were noted between the genders.

7.2 Discussion of the results

The systematic review of 63 studies identified important outcome measures and methodological approaches that have been utilized previously to evaluate psychological outcomes and HRQoL after lung transplantation. Most importantly, the literature consistently confirmed meaningful improvements in HRQoL following lung transplants, those improvements primarily reflected as enhanced physical function, increased vitality, more energy, less pain and discomfort, and fewer restrictions in social and leisure activities. Furthermore, the most important improvements in HRQoL were observed within the first year post transplant and remained stable for up to five years. Although a body of research already existed on psychological outcomes and HRQoL after lung transplantation, our review of the literature revealed noticeable methodological limitations that might affect the interpretation of those prior results. Consistent with findings from another review, by Yusen et al. (2009, 2011), previous study limitations included small sample sizes, missing data, selection bias, loss of subjects to follow-up due to deterioration of health status or exclusion of deaths. Furthermore, longitudinal studies, which are important to survey the degree and stability of improvements following lung transplantation, were conducted only by a relatively small number of investigators (13 different first authors). In addition, a great number of different outcome measures were applied in the absence of any guidelines, which limits the comparability of these results. Finally, transplant-specific outcome measures were rarely used, despite being critical to identifying transplant-specific issues like the adverse effects of immunosuppressant medication, pain or adherence to medication regimen. Better outcome instruments are required that more adequately picture the effectiveness of lung transplantation and improvements in post-transplant HRQoL. Furthermore, the use of standardized test instruments is essential to reduce heterogeneity and to facilitate comparability of results among different studies.

To date, studies on psychosocial outcomes following transplantation have primarily compared postoperative trajectories combining patients with a variety of solid organ transplants. Interestingly, most investigations focused on the average value of HRQoL and did not distinguish between favorable and poor postoperative outcome trajectories. To broaden the scope of HRQoL research in the field of transplant medicine, the second study in this thesis sought to assess post-transplant HRQoL and psychological distress in terms of trajectories, rather than just considering outcomes at discrete time points. To achieve this objective, HRQoL and psychological outcomes were investigated in 40 lung transplant recipients over the first six months since surgery. It is important to note that our results are in line with the broad body of literature in demonstrating significantly improved HRQoL over the first six postoperative months. Consistent with our hypothesis, most patients experienced either a good or optimal postoperative trajectory. However, a quarter of patients had a poor postoperative trajectory, suffering from elevated distress and substantially impaired quality of life, with no significant improvement over time. Hence, a considerable proportion of patients might not benefit from transplantation, from a quality of life perspective. This result is alarming, given that depression and psychological distress appear to significantly increase the risk of mortality after transplantation (Havik et al., 2007; Sirri et al., 2010). Risk factors for poor postoperative outcomes after lung transplantation are not well described in the literature. Analyzing our three different cluster groups - optimal, good and poor outcome - for medical and sociodemographic differences, we found that patients with a poor postoperative trajectory tended to be older, more likely to suffer from more severe pre-operative lung disease and more co-morbid conditions, and more likely to have prolonged ICU and hospital stays. These results are in accordance with those of other studies that identified older age (Inci et al., 2015; Vasiliadis et al., 2006; Vermeulen et al., 2007) and the presence of co-morbid conditions (Kugler et al., 2005; Vermeulen et al., 2003) as independent risk factors for diminished outcomes after lung transplantation. Similar to Inci et al. (2015), gender, time on the waiting list and underlying diagnosis failed to predict mortality. Improving health-related quality of life is an important goal of lung transplantation. However, predictors of HRQoL outcomes are also not well understood. Addressing this knowledge gap, our study found that pre-operative lung disease severity, length of hospital stay, and self-reported HRQoL two weeks post-transplant were the strongest predictors of both high-level psychological distress and impaired HRQoL at the time of the six-month postoperative evaluation. Our results emphasize the need for new pre-transplant predictors of poor early post-transplant outcomes that can help to identify candidates with high risk for severe complications, reduced quality of life and mortality after lung transplantation. Furthermore, the effect of exercise training, education and psychosocial support in patients with poor postoperative HRQoL-trajectories should be further explored.

The qualitative study provided novel insights into how patients experience lung transplants and adjust to normal life over their first six postoperative months. The most-frequently mentioned themes within the categories ‘transplantation process’, ‘new lungs’, ‘the donor’ and ‘medication regimen were ‘physical benefits’, ‘fear of rejection’, ‘gratitude towards the donor’, and ‘side effects’, respectively. Contrary to our expectations, most themes that concerned patients immediately after surgery remained unchanged in the prominence over time. One possible explanation for the relative absence of change over time is the lengthy process required for recovery and adjustment to transplantation, which typically spans several years. At six months post-transplant, patients are only starting to resume their normal daily routines (Rosenberger, Dew, DiMartini, et al., 2012). Although seemingly inconsistent with findings in the current literature demonstrating gender differences in HRQoL after lung transplantation (Kugler et al., 2007; Rodrigue & Baz, 2006), our results revealed only marginal gender differences, suggesting that gender does not play a major role in how patients process the transplant experience. Consistent with quantitative studies on HRQoL outcomes post lung transplant (Finlen Copeland et al., 2013; Kugler et al., 2007; Smeritschnig et al., 2005), we found that improvements in physical function during the early postoperative phase were offset by clinical complications, fear of rejection, medication side effects, and restrictions in everyday life. Even though these aspects might be well-known to practitioners, this study extends prior work by presenting narratives that comprehensively depict patient experiences. Analyzing these narratives, it becomes evident that lung transplantation is a life-changing event that affects many physiological, psychological, social and behavioral aspects of a person's life. The themes related to lung transplant identified in this study have direct clinical implications and should increase healthcare-givers awareness of the many challenges transplant recipients must confront within the first six months after their surgery. Postoperative recovery and returning to normalcy is a demanding process that requires considerable time and energy. To facilitate this journey to relative normalcy, healthcare providers must act as both mediators and providers of information and support. The number of authors who have employed qualitative methods to explore psychological outcomes after lung transplantation is still few even though qualitative research is an important prerequisite for providing important insights of psychological adjustment to lung transplantation (Singer & Singer, 2013). Further longitudinal qualitative research is required to investigate the patients' well-being and experience with their transplant 2 or 3 years after transplantation.

7.3 Limitations

Despite the significant contributions mentioned above, there are several limitations that should be considered when interpreting our data. Specific limitations have already been discussed in the discussion section of each paper, and I will refrain from reiterating them here. Rather, I will make some cautionary remarks about the limitations of this thesis in its entirety.

First, the small number of patients included in our studies limited our ability to perform subgroup analysis, as we did to compare the three cluster groups, and was therefore under-powered. Results from the cluster analysis are therefore exploratory in nature and need to be confirmed in bigger subject samples.

Second, data were collected over a short postoperative observation period. The early post-transplant period is predominantly characterized by rehabilitation, close monitoring of health status, the introduction of new medications with potential side effects, and the distinct possibility of early re-hospitalization. Six months after transplantation may be too short for patients to have achieved optimal pulmonary recovery. As such, longer follow-up times may be required to more accurately document HRQoL outcomes, including the risks and benefits of lung transplantation. Additionally, relative to cross-sectional studies, prospective longitudinal studies remain few in number when reviewing the current medical literature and definitely constitute a niche for further research.

Third, no pre-operative reference values were considered during study design, even though such information would have been important as an aid to predicting postoperative outcomes.

Fourthly, data were extracted from a single medical center, which inherently limits the generalizability of our results to other contexts, since the community or health center itself might have biased patient responses to some extent.

Other important methodological limitations resulted from our inability to control for confounding variables like the underlying diagnosis, and the presence of co-morbid pre- and post-transplant medical conditions. Also, selection bias is inherent when interviewing only surviving patients or patients who are fit enough to participate in a study (e.g., including only those patients with completed data sets might have resulted in a better HRQoL estimates than actually characterized by our patients overall). Lastly, the loss of subjects during the course of follow-up – for reasons like psychological distress, fatigue and other health complications

– is a common problem when conducting prospective longitudinal studies in lung transplant recipients.

7.4 Future research

To determine the overall outcomes of lung transplantation, future research should include pre- versus post-transplant assessments, embedded within a prospective longitudinal study with patient samples large enough to allow for more extensive empirical analysis. Most suitable would be to implement some sort of standard assessment, investigating patients from the time of entry into the transplant system until death or other removal from the transplant system.

A further huge opportunity for future research lies in the development of guidelines to aid in the selection of outcome measures to assess psychological outcomes after lung transplantation. The use of consistent outcome measures in transplant medicine would reduce heterogeneity and facilitate comparisons between different studies. Adopting transplant specific HRQoL-measures is also highly recommended, such as measures that screen for physical symptoms like the potential adverse effects of immunosuppressants but also quantify the degree of disability, in terms of activities of daily living and self-care.

The identification of powerful pre-transplant predictors for poor postoperative outcomes in terms of reduced HRQoL and mortality are important to improve overall outcomes of lung transplantation and to avoid futile transplantation.

Although HRQoL outcomes have been researched extensively in transplant medicine, the question of whether the benefits of lung transplantation outweigh its potential harm remains largely unacknowledged. Better tools are required for measuring post-transplant

HRQoL. Addressing this issue, Yusen (2011) suggested integrating outcome instruments that assess both survival and quality of life. By considering the risks and benefits of lung transplantation, including longevity, symptom experiences, everyday function, and other components of HRQoL, a quality-adjusted survival value could be computed that more adequately demonstrates the effectiveness of this treatment.

The use of subgroup analysis rather than considering outcomes at discrete time points are highly recommended to detect those patients who did not experienced any improvements in HRQoL after lung transplantation.

Finally, only a small number of investigators have investigated mental health among lung transplant recipients. The reasons for ongoing psychological difficulties in lung transplant recipients are not completely understood and warrant further study. Even though the physical health of lung transplant recipients has improved significantly, the unpredictability of outcomes and patient feelings of lack of control may continue to adversely influence emotional health and raise levels of anxiety (Dew et al., 2012). Employing qualitative data analysis could yield a deeper understanding of the transplant experience, as well as the concerns, symptoms and emotional difficulties associated with this procedure.

7.5 Conclusion

The over-riding purpose of this thesis was to comprehensively investigate patients' psychological adjustment to lung transplantation, in terms of psychological outcomes and HRQoL. The present results are important given the growing body of scientific literature demonstrating that lung transplantation confers clinically meaningful and statistically significant improvements in HRQoL in patients suffering from end-stage pulmonary disease

(Finlen Copeland et al., 2013; Santana et al., 2012; Singer & Singer, 2013). HRQoL improvements essentially concern physical domains and largely transpire within the first six months post transplant (Kugler et al., 2010). In contrast, beyond the first year after transplantation, HRQoL outcomes become less predictable. Larger longitudinal studies with large enough subject samples are required to better assess the long-term effects of transplantation on HRQoL.

Given the scarcity of available donor organs, it has become increasingly important to determine factors that are predictive of who is most likely to benefit from lung transplantation in terms of extended survival and improved HRQoL (Evon et al., 2010). Although lung transplant candidates are selected according to relative and absolute contraindications, approximately 20% of lung transplant patients die within the first year after transplantation (Inci et al., 2013). Therefore, new factors need to be identified that more powerful can predict the risk for severe early post-transplant complications (Hook & Lederer, 2012).

To date, many conceptual and methodological limitations persist in the scientific literature that render comparisons between studies difficult and weaken the ability to draw conclusions concerning the effects of lung transplantation on HRQoL. These limitations include survivorship bias, losses to follow-up, predominant use of cross-sectional study designs, and small sample sizes.

The findings of this thesis underscore the need to develop guidelines for outcome instrument selection and thereby reduce study heterogeneity. Once a special transplant interest group has identified those instruments that best measure HRQoL outcomes in lung transplant recipients, these instruments could be used to integrate HRQoL data by default into existing registries, as is currently being done to some degree within the Swiss Transplant

Cohort Study (STCS) (De Geest et al., 2013). Doing so could help to reduce sample size limitations and biases that result from single-center studies. Such a standardized assessment could also improve efforts to quantify the impact of lung transplantation on HRQoL (Yusen, 2011).

Although lung transplantation dramatically improves most patients' physical function and quality of life, they remain confronted by a variety of health problems, including the risk of organ rejection, side effects of immunosuppressants, various medical co-morbidities, and mental health problems like anxiety and depression (Lanuza et al., 2012). Adjusting to life as a transplant recipient requires acceptance of ongoing medical illness and continued reliance on caregivers. To identify those patients with clinically significant distress and impaired HRQoL post-transplant, healthcare providers ought to conduct early, comprehensive diagnostics as part of their routine clinical practice, so mental distress symptoms can be treated rapidly and HRQoL improved. Support groups and psychosocial interventions are critical to sustaining and increasing gains related to transplantation, to optimizing adherence with medical regimens, and to decreasing patients' symptom experiences (Rosenberger et al., 2012).

References

Anderson, C. (2010). Presenting and evaluating qualitative research. *American Journal of Pharmaceutical Education, 74*(8), 141.

Anker, A. E., & Feeley, T. H. (2010). Why families decline donation: the perspective of organ procurement coordinators. *Progress in Transplantation, 20*(3), 239-246.

Anyanwu, A. C., McGuire, A., Rogers, C. A., & Murday, A. J. (2001). Assessment of quality of life in lung transplantation using a simple generic tool. *Thorax, 56*(3), 218-222.

Archonti, C., D'Amelio, R., Klein, T., Schafers, H. J., Sybrecht, G. W., & Wilkens, H. (2004). Physical quality of life and social support in patients on the waiting list and after a lung transplantation. *Psychotherapie Psychosomatik Medizinische Psychologie, 54*(1), 17-22. doi: 10.1055/s-2003-812589

atlas.ti. (2015). Software for Qualitative Data Analysis. Retrieved 03.04.2015 http://atlasti.com

BAG. (2015). Bundesamt für Gesundheit (BAG). Ethik in der Transplantationsmedizin Retrieved 25.02.2015 http://www.bag.admin.ch/transplantation/10023/index.html?lang=de

Banner, N., R, Polak, J., M, & Yacoub, M. (2003). *Lung Transplantation*. Cambridge, United Kingdom: Cambridge University Press.

Baranyi, A., Krauseneck, T., & Rothenhausler, H. B. (2013). Overall mental distress and health-related quality of life after solid-organ transplantation: results from a retrospective follow-up study. *Health and Quality of Life Outcomes, 11*, 15. doi: 10.1186/1477-7525-11-15

Blumenstock, D. A., & Lewis, C. (1993). The first transplantation of the lung in a human revisted. *The Annals of Thoracic Surgery, 56*, 1423-1424.

Boothe, B., Boehler, A., & Goetzmann, L. (2013). The other in me. Organ transplantation as a relatoinal experience. *PSYCHE, 2*, 120-143.

Borel, J. F., Feurer, C., Magnee, C., & Stahelin, H. (1977). Effects of the new anti-lymphocyte peptide cyclosporin A in animals. *Immunology, 32*, 1017-1025.

Bosma, O. H., Vermeulen, K. M., Verschuuren, E. A., Erasmus, M. E., & van der Bij, W. (2011). Adherence to immunosuppression in adult lung transplant recipients: prevalence and risk factors. *Journal of Heart and Lung Transplantation, 30*(11), 1275-1280. doi: 10.1016/j.healun.2011.05.007

Bunzel, B., Wollenek, G., & Grundbock, A. (1992). Psychosocial problems of donor heart recipients adversely affecting quality of life. *Quality of Life Research, 1*(5), 307-313.

Burker, E. J., Evon, D. M., Galanko, J., & Egan, T. (2005). Health locus of control predicts survival after lung transplant. *Journal of Health Psychology, 10*(5), 695-704. doi: 10.1177/1359105305055326

Busschbach, J. J., Horikx, P. E., van den Bosch, J. M., Brutel de la Riviere, A., & de Charro, F. T. (1994). Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. *Chest, 105*(3), 911-917.

Butler, J., McCoin, N. S., Feurer, I. D., Speroff, T., Davis, S. F., Chomsky, D. B., . . . Pinson, C. W. (2003). Modeling the effects of functional performance and post-transplant comorbidities on health-related quality of life after heart transplantation. *Journal of Heart and Lung Transplantation, 22*(10), 1149-1156.

Chen, L., Huang, D., Mou, X., Chen, Y., Gong, Y., & He, J. (2011). Investigation of quality of life and relevant influence factors in patients awaiting lung transplantation. *Journal of Thoracic Disease, 3*(4), 244-248. doi: 10.3978/j.issn.2072-1439.2010.08.03

Chisholm, M. A. (2002). Enhancing transplant patients' adherence to medication therapy. *Clinical Transplantation, 16*(1), 30-38.

Christie, J. D., Edwards, L. B., Kucheryavaya, A. Y., Benden, C., Dipchand, A. I., Dobbels, F., . . . Hertz, M. I. (2012). The Registry of the International Society for Heart and Lung

Transplantation: 29th adult lung and heart-lung transplant report-2012. *Journal of Heart and Lung Transplantation, 31*(10), 1073-1086. doi: 10.1016/j.healun.2012.08.004

Cleemput, I., & Dobbels, F. (2007). Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date. *Pharmacoeconomics, 25*(4), 269-286.

Cohen, L., Littlefield, C., Kelly, P., Maurer, J., & Abbey, S. (1998). Predictors of quality of life and adjustment after lung transplantation. *Chest, 113*(3), 633-644.

Corp, I. (2013). *IBM SPSS Statistics for Windows, Version 22.0*. Armonk, NY: IBM Corp.

Craven, J. (1990). Psychiatric aspects of lung transplant. The Toronto Lung Transplant Group. *Canadian Journal of Psychiatry, 35*(9), 759-764.

De Geest, S., Burkhalter, H., Berben, L., Bogert, L. J., Denhaerynck, K., Glass, T. R., . . . Schmidt-Trucksass, A. (2013). The Swiss Transplant Cohort Study's framework for assessing lifelong psychosocial factors in solid-organ transplants. *Progress in Transplantation, 23*(3), 235-246. doi: 10.7182/pit2013250

De Geest, S., Burkhalter, H., Bogert, L., Berben, L., Glass, T. R., & Denhaerynck, K. (2014). Describing the evolution of medication nonadherence from pretransplant until 3 years post-transplant and determining pretransplant medication nonadherence as risk factor for post-transplant nonadherence to immunosuppressives: the Swiss Transplant Cohort Study. *Transplant International, 27*(7), 657-666. doi: 10.1111/tri.12312

De Geest, S., Dobbels, F., Fluri, C., Paris, W., & Troosters, T. (2005). Adherence to the therapeutic regimen in heart, lung, and heart-lung transplant recipients. *European Journal of Cardiovascular Nursing, 20*(5 Suppl), S88-98.

De Perrot, M., Chaparro, C., McRae, K., Waddell, T. K., Hadjiliadis, D., Singer, L. G., . . . Keshavjee, S. (2004). Twenty-year experience of lung transplantation at a single center: influence of recipient diagnosis on long-term survival. *The Journal of Thoracic and Cardiovascular Surgery, 127*(5), 1493-1501. doi: http://dx.doi.org/10.1016/j.jtcvs.2003.11.047

De Vito Dabbs, A., Dew, M. A., Stilley, C. S., Manzetti, J., Zullo, T., McCurry, K. R., . . . Iacono, A. (2003). Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation. *Journal of Heart and Lung Transplantation, 22*(11), 1268-1275.

De Vito Dabbs, A., Hoffman, L. A., Swigart, V., Happ, M. B., Dauber, J. H., McCurry, K. R., & Iacono, A. (2004). Striving for normalcy: symptoms and the threat of rejection after lung transplantation. *Social Science and Medicine, 59*(7), 1473-1484. doi: 10.1016/j.socscimed.2004.01.013

De Vito Dabbs, A., Terhorst, L., Song, M. K., Shellmer, D. A., Aubrecht, J., Connolly, M., & Dew, M. A. (2013). Quality of recipient-caregiver relationship and psychological distress are correlates of self-care agency after lung transplantation. *Clinical Transplantation, 27*(1), 113-120. doi: 10.1111/ctr.12017

Decramer, M., Janssens, W., & Miravitlles, M. (2012). Chronic obstructive pulmonary disease. *Lancet, 379*(9823), 1341-1351. doi: 10.1016/s0140-6736(11)60968-9

Dew, M. A., DiMartini, A. F., De Vito Dabbs, A., Myaskovsky, L., Steel, J., Unruh, M., . . . Greenhouse, J. B. (2007). Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation, 83*(7), 858-873. doi: 10.1097/01.tp.0000258599.65257.a6

Dew, M. A., Dimartini, A. F., De Vito Dabbs, A., Zomak, R., De Geest, S., Dobbels, F., . . . McCurry, K. R. (2008). Adherence to the medical regimen during the first two years after lung transplantation. *Transplantation, 85*(2), 193-202. doi: 10.1097/TP.0b013e318160135f

Dew, M. A., DiMartini, A. F., DeVito Dabbs, A. J., Fox, K. R., Myaskovsky, L., Posluszny, D. M., . . . Toyoda, Y. (2012). Onset and risk factors for anxiety and depression during the first 2 years after lung transplantation. *General Hospital Psychiatry, 34*(2), 127-138. doi: 10.1016/j.genhosppsych.2011.11.009

Dew, M. A., Switzer, G. E., DiMartini, A. F., Matukaitis, J., Fitzgerald, M. G., & Kormos, R. L. (2000). Psychosocial assessments and outcomes in organ transplantation. *Progress in Transplantation, 10*(4), 239-259; quiz 260-231.

Dierich, M., Tecklenburg, A., Fuehner, T., Tegtbur, U., Welte, T., Haverich, A., . . . Gottlieb, J. (2013). The influence of clinical course after lung transplantation on rehabilitation success. *Transplant International, 26*(3), 322-330. doi: 10.1111/tri.12048

DiMartini, A., Dew, M. A., Chaiffetz, D., Fitzgerald, M. G., Devera, M. E., & Fontes, P. (2011). Early trajectories of depressive symptoms after liver transplantation for alcoholic liver disease predicts long-term survival. *American Journal of Transplantation, 11*(6), 1287-1295. doi: 10.1111/j.1600-6143.2011.03496.x

DiMartini, A., Dew, M. A., Kormos, R., McCurry, K., & Fontes, P. (2007). Posttraumatic stress disorder caused by hallucinations and delusions experienced in delirium. *Psychosomatics, 48*(5), 436-439. doi: 10.1176/appi.psy.48.5.436

Dobbels, F., Moons, P., Abraham, I., Larsen, C. P., Dupont, L., & De Geest, S. (2008). Measuring symptom experience of side-effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale. *Transplant International, 21*(8), 764-773. doi: 10.1111/j.1432-2277.2008.00674.x

Dubois, J. M. (2010). The ethics of creating and responding to doubts about death criteria. *Journal of Medicine and Philosophy, 35*(3), 365-380. doi: 10.1093/jmp/jhq021

DuBois, J. M., & Anderson, E. E. (2006). Attitudes toward death criteria and organ donation among healthcare personnel and the general public. *Progress in Transplantation, 16*(1), 65-73.

Eskander, A., Waddell, T. K., Faughnan, M. E., Chowdhury, N., & Singer, L. G. (2011). BODE index and quality of life in advanced chronic obstructive pulmonary disease before and after lung transplantation. *Journal of Heart and Lung Transplantation, 30*(12), 1334-1341. doi: 10.1016/j.healun.2011.06.006

EuroQol Group. (1990). EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy, 16*(3), 199-208.

Evon, D. M., Burker, E. J., Galanko, J. A., Dedert, E., & Egan, T. M. (2010). Depressive symptoms and mortality in lung transplant. *Clinical Transplantation, 24*(5), E201-206. doi: 10.1111/j.1399-0012.2010.01236.x

Feltrim, M. I., Rozanski, A., Borges, A. C., Cardoso, C. A., Caramori, M. L., & Pego-Fernandes, P. (2008). The quality of life of patients on the lung transplantation waiting list. *Transplantation Proceedings, 40*(3), 819-821. doi: 10.1016/j.transproceed.2008.02.035

Finlen Copeland, C. A., Vock, D. M., Pieper, K., Mark, D. B., & Palmer, S. M. (2013). Impact of lung transplantation on recipient quality of life: a serial, prospective, multicenter analysis through the first posttransplant year. *Chest, 143*(3), 744-750. doi: 10.1378/chest.12-0971

Flynn, K., Daiches, A., Malpus, Z., Yonan, N., & Sanchez, M. (2013). 'A post-transplant person': Narratives of heart or lung transplantation and intensive care unit delirium. *Health, 18*(4), 352-368. doi: 10.1177/1363459313501356

Franke, G. H. (1995). *SCL-90-R. Die Symptomcheckliste von Derogatis - Deutsche Version. Manual.* Göttingen: Beltz.

Gerbase, M. W., Spiliopoulos, A., Rochat, T., Archinard, M., & Nicod, L. P. (2005). Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. *Chest, 128*(3), 1371-1378. doi: 10.1378/chest.128.3.1371

Gerbase, M. W., Soccal, P. M., Spiliopoulos, A., Nicod, L. P., & Rochat, T. (2008). Long-term health-related quality of life and walking capacity of lung recipients with and without bronchiolitis obliterans syndrome. *Journal of Heart and Lung Transplantation, 27*(8), 898-904. doi: 10.1016/j.healun.2008.04.012

Germani, G., Lazzaro, S., Gnoato, F., Senzolo, M., Borella, V., Rupolo, G., . . . Burra, P. (2011). Nonadherent behaviors after solid organ transplantation. *Transplantation Proceedings, 43*(1), 318-323. doi: 10.1016/j.transproceed.2010.09.103

Girard, F., Chouinard, P., Boudreault, D., Poirier, C., Richard, C., Ruel, M., & Ferraro, P. (2006). Prevalence and impact of pain on the quality of life of lung transplant recipients: a prospective observational study. *Chest, 130*(5), 1535-1540. doi: 10.1378/chest.130.5.1535

Goetzmann, L. (2004). "Is it me, or isn't it?" - transplanted organs and their donors as transitional objects. *The American Journal of Psychoanalysis, 64*(3), 279-289. doi: 10.1023/B:TAJP.0000041262.36839.fd

Goetzmann, L., Irani, S., Moser, K. S., Schwegler, K., Stamm, M., Spindler, A., . . . Klaghofer, R. (2009). Psychological processing of transplantation in lung recipients: a quantitative study of organ integration and the relationship to the donor. *British Journal of Health Psychology, 14*(Pt 4), 667-680. doi: 10.1348/135910708x399447

Goetzmann, L., Irani, S., Schwegler, K., Stamm, M., Bricman, R., Buddeberg, C., . . . Boehler, A. (2010). Distress and alexithymia in lung recipients - psychosocial strains and associations with chronic allograft dysfunction. *Swiss Medical Weekly, 140*(25-26), 382-387. doi: smw-12770

Goetzmann, L., Irani, S., Schwegler, K., Stamm, M., Spindler, A., Bricman, R., . . . Klaghofer, R. (2010). Lung function, sociodemographic characteristics, and psychological reaction to transplant associated with chronic stress among lung recipients. *Anxiety, Stress and Coping, 23*(2), 213-233. doi: 10.1080/10615800903038882

Goetzmann, L., Klaghofer, R., Spindler, A., Wagner-Huber, R., Scheuer, E., & Buddeberg, C. (2006). The "Medication Experience Scale for Immunosuppressants" (MESI): initial results for a new screening instrument in transplant medicine. *Psychotherapie Psychosomatik Medizinische Psychologie, 56*(2), 49-55. doi: 10.1055/s-2005-867060

Goetzmann, L., Klaghofer, R., Wagner-Huber, R., Halter, J., Boehler, A., Muellhaupt, B., . . . Buddeberg, C. (2006). Quality of life and psychosocial situation before and after a lung, liver or an allogeneic bone marrow transplant. *Swiss Medical Weekly, 136*(17-18), 281-290. doi: 2006/17/smw-11362

Goetzmann, L., Moser, K. S., Vetsch, E., Klaghofer, R., Naef, R., Russi, E. W., . . . Boehler, A. (2006). What do patients think after a lung transplantation about their self, lung and social network? A quantitative analysis of categorical interview data. *GMS Psycho-Social-Medicine, 3*, Doc03.

Goetzmann, L., Ruegg, L., Stamm, M., Ambuhl, P., Boehler, A., Halter, J., . . . Klaghofer, R. (2008). Psychosocial profiles after transplantation: a 24-month follow-up of heart, lung, liver, kidney and allogeneic bone-marrow patients. *Transplantation, 86*(5), 662-668. doi: 10.1097/TP.0b013e3181817dd7

Goetzmann, L., Sarac, N., Ambuhl, P., Boehler, A., Irani, S., Muellhaupt, B., . . . Klaghofer, R. (2008). Psychological response and quality of life after transplantation: a comparison between heart, lung, liver and kidney recipients. *Swiss Medical Weekly, 138*(33-34), 477-483. doi: 2008/33/smw-12160

Goetzmann, L., Scheuer, E., Naef, R., Vetsch, E., Buddeberg, C., Russi, E. W., & Boehler, A. (2005). Psychosocial situation and physical health in 50 patients > 1 year after lung transplantation. *Chest, 127*(1), 166-170. doi: 10.1378/chest.127.1.166

Golfieri, L., Lauro, A., Tossani, E., Sirri, L., Dazzi, A., Zanfi, C., . . . Pinna, A. D. (2007). Coping strategies in intestinal transplantation. *Transplantation Proceedings, 39*(6), 1992-1994. doi: 10.1016/j.transproceed.2007.05.051

Gross, C. R., Savik, K., Bolman, R. M., 3rd, & Hertz, M. I. (1995). Long-term health status and quality of life outcomes of lung transplant recipients. *Chest, 108*(6), 1587-1593.

Hafliger, S. (2005). A primer on solid organ transplant psychiatry. In *A. A. W. B. Wyszynski* (Ed.), *Manual of psychiatric care for the medically ill.* Arlington: VA: American Psychiatric Publishing.

Hair, J. F., & Black, W. C. (2000). Cluster analysis. *In Reading and Understanding More Multivariate Statistics. L.G. Grimm, P.R. Yarnold, eds.* (pp. 147-205). Washington DC: American Psychological Association.

Hardy, J. D., Webb, W. R., Dalton, M. L., & Walker, G. R. (1963). Lung homotransplantation in man. Report of the initial case. *Journal of the American Medical Association, 186*, 1065-1074.

Havik, O. E., Sivertsen, B., Relbo, A., Hellesvik, M., Grov, I., Geiran, O., . . . Gullestad, L. (2007). Depressive symptoms and all-cause mortality after heart transplantation. *Transplantation, 84*(1), 97-103. doi: 10.1097/01.tp.0000268816.90672.a0

Hinz, A., Klaiberg, A., Brahler, E., & Konig, H. H. (2006). The Quality of Life Questionnaire EQ-5D: modelling and norm values for the general population. *Psychotherapie Psychosomatik Medizinische Psychologie, 56*(2), 42-48. doi: 10.1055/s-2005-867061

Hofer, M., Benden, C., Inci, I., Schmid, C., Speich, R., Weder, W., & Boehler, A. (2009). True survival benefit of lung transplantation for cystic fibrosis patients: the Zurich experience. [Journal Article]. *The Journal of Heart and Lung Transplantation, 28*(4), 334-339. doi: 310.1016/j.healun.2008.1012.1025.

Hook, J. L., & Lederer, D. J. (2012). Selecting lung transplant candidates: where do current guidelines fall short? *Expert Review of Respiratory Medicine, 6*(1), 51-61. doi: 10.1586/ers.11.83

Horton, R. L., & Horton, P. J. (1991). A model of willingness to become a potential organ donor. *Social Science and Medicine, 33*(9), 1037-1051.

Hugon, A., Roustit, M., Lehmann, A., Saint-Raymond, C., Borrel, E., Hilleret, M. N., . . . Allenet, B. (2014). Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. *Transplantation, 98*(2), 222-228. doi: 10.1097/tp.0000000000000221

IBM Corp. (2013). *IBM SPSS Statistics for Windows, Version 22.0*. Armonk, NY: IBM Corp.

Ihle, F., Neurohr, C., Huppmann, P., Zimmermann, G., Leuchte, H., Baumgartner, R., . . . Behr, J. (2011). Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: a prospective, randomized study. *Journal of Heart and Lung Transplantation, 30*(8), 912-919. doi: 10.1016/j.healun.2011.02.006

Immer, F. F. (2015). Organ donation after circulatory death in Switzerland: slow but constant progress. *Swiss Medical Weekly, 145*, w14062. doi: 10.4414/smw.2015.14062

Inci, I., Schuurmans, M., Ehrsam, J., Schneiter, D., Hillinger, S., Jungraithmayr, W., . . . Weder, W. (2015). Lung transplantation for emphysema: impact of age on short- and long-term survival. *European Journal Cardio-Thorac Surgery*. doi: 10.1093/ejcts/ezu550

Inci, I., Schuurmans, M. M., Boehler, A., & Weder, W. (2013). Zurich University Hospital lung transplantation programme: update 2012. *Swiss Medical Weekly, 143*, w13836. doi: 10.4414/smw.2013.13836

Ingram, R. E., & Luxton, D. D. (2005). Vulnerability-Stress Models. In B. L. H. Hanking & J. R. Z. Abela (Eds.), *Development of Pschopathology: A vulnerability stress perspecitve* (pp. 32-44). New Yorks: Sage.

Ingram, R. E., & Price, J. M. (2001). *Vulnerability to psychopathology: Risk across the lifespan*. New York: Guilford Press.

Irani, S., Mahler, C., Goetzmann, L., Russi, E. W., & Boehler, A. (2006). Lung transplant recipients holding companion animals: impact on physical health and quality of life. *American Journal of Transplantation, 6*(2), 404-411. doi: 10.1111/j.1600-6143.2005.01168.x

Irani, S., Thomasius, M., Schmid-Mahler, C., Holzmann, D., Goetzmann, L., Speich, R., & Boehler, A. (2010). Olfactory performance before and after lung transplantation: quantitative assessment and impact on quality of life. *Journal of Heart and Lung Transplantation, 29*(3), 265-272. doi: 10.1016/j.healun.2009.07.016

Ivarsson, B., Ekmehag, B., & Sjoberg, T. (2013). Patients' experiences of information and support during the first six months after heart or lung transplantation. *European Journal of Cardiovascular Nursing, 12*(4), 400-406. doi: 10.1177/1474515112466155

Jones, P. W., Baveystock, C. M., & Littlejohns, P. (1989). Relationships between general health measured with the sickness impact profile and respiratory symptoms, physiological measures, and mood in patients with chronic airflow limitation. *The American Review of Respiratory Disease, 140*(6), 1538-1543. doi: 10.1164/ajrccm/140.6.1538

Jones, P. W., Quirk, F. H., Baveystock, C. M., & Littlejohns, P. (1992). A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *The American Review of Respiratory Disease, 145*(6), 1321-1327. doi: 10.1164/ajrccm/145.6.1321

Karnofsky, D., & Burchenal, J. (1949). The clinical evaluation of chemotherapeutic agents in cancer. *In Evaluation of chemotherapeutic agents* (pp. 191 - 205). New York: Columbia University Press.

King, T. E., Jr. (2005). Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *American Journal of Respiratory and Critical Care Medicine, 172*(3), 268-279. doi: 10.1164/rccm.200503-483OE

Klaghofer, R., & Braehler, E. (2001). Construction and validation of a shor form of the SCL-90-R. *Zeitschrift für Klinische Psychologie, Psychiatrie und Psychotherapie, 49*(2), 115-124.

Klaghofer, R., Sarac, N., Schwegler, K., Schleuniger, M., Noll, G., Muellhaupt, B., . . . Goetzmann, L. (2008). Questionnaire on emotional response after organ transplantation: German validation of the Transplant Effect Questionnaire (TxEQ-D). *Zeitschrift für Psychosomatische Medizin und Psychotherapie, 54*(2), 174-188. doi: 10.13109/zptm.2008.54.2.174

Krueger, T., Berutto, C., & Aubert, J. D. (2011). Challenges in lung transplantation. *Swiss Medical Weekly, 141*, w13292. doi: 10.4414/smw.2011.13292

Kugler, C., Fischer, S., Gottlieb, J., Tegtbur, U., Welte, T., Goerler, H., . . . Strueber, M. (2007). Symptom experience after lung transplantation: impact on quality of life and adherence. *Clinical Transplantation, 21*(5), 590-596. doi: 10.1111/j.1399-0012.2007.00693.x

Kugler, C., Fischer, S., Gottlieb, J., Welte, T., Simon, A., Haverich, A., & Strueber, M. (2005). Health-related quality of life in two hundred-eighty lung transplant recipients. *Journal of Heart and Lung Transplantation, 24*(12), 2262-2268. doi: 10.1016/j.healun.2005.07.005

Kugler, C., Gottlieb, J., Warnecke, G., Schwarz, A., Weissenborn, K., Barg-Hock, H., . . . Haller, H. (2013). Health-related quality of life after solid organ transplantation: a prospective, multiorgan cohort study. *Transplantation, 96*(3), 316-323. doi: 10.1097/TP.0b013e31829853eb

Kugler, C., Tegtbur, U., Gottlieb, J., Bara, C., Malehsa, D., Dierich, M., . . . Haverich, A. (2010). Health-related quality of life in long-term survivors after heart and lung transplantation: a prospective cohort study. *Transplantation, 90*(4), 451-457. doi: 10.1097/TP.0b013e3181e72863

Kung, M., Koschwanez, H. E., Painter, L., Honeyman, V., & Broadbent, E. (2012). Immunosuppressant nonadherence in heart, liver, and lung transplant patients: associations with medication beliefs and illness perceptions. *Transplantation, 93*(9), 958-963. doi: 10.1097/TP.0b013e31824b822d

Kunsebeck, H. W., Kugler, C., Fischer, S., Simon, A. R., Gottlieb, J., Welte, T., . . . Strueber, M. (2007). Quality of life and bronchiolitis obliterans syndrome in patients after lung transplantation. *Progress in Transplantation, 17*(2), 136-141.

Langer, D. (2015). Rehabilitation in Patients before and after Lung Transplantation. *Respiration*. doi: 10.1159/000430451

Langer, D., Burtin, C., Schepers, L., Ivanova, A., Verleden, G., Decramer, M., . . . Gosselink, R. (2012). Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *American Journal of Transplantation, 12*(6), 1584-1592. doi: 10.1111/j.1600-6143.2012.04000.x

Langer, D., Gosselink, R., Pitta, F., Burtin, C., Verleden, G., Dupont, L., . . . Troosters, T. (2009). Physical activity in daily life 1 year after lung transplantation. *Journal of Heart and Lung Transplantation, 28*(6), 572-578. doi: 10.1016/j.healun.2009.03.007

Lanuza, D. M., Lefaiver, C., Mc Cabe, M., Farcas, G. A., & Garrity, E., Jr. (2000). Prospective study of functional status and quality of life before and after lung transplantation. *Chest, 118*(1), 115-122.

Lanuza, D. M., Lefaiver, C. A., Brown, R., Muehrer, R., Murray, M., Yelle, M., & Bhorade, S. (2012). A longitudinal study of patients' symptoms before and during the first year after lung transplantation. *Clinical Transplantation, 26*(6), E576-589. doi: 10.1111/ctr.12002

Lanuza, D. M., & McCabe, M. A. (2001). Care before and after lung transplant and quality of life research. *American Association of Critical-Care Nurses: Clinical Issues, 12*(2), 186-201.

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and copig*. New Yorks: Springer.

Lefebvre, P., Crombez, J. C., & LeBeuf, J. (1973). Psychological dimension and psychopathological potential of acquiring a kidney. *Canadian Psychiatric Association Journal, 18*(6), 495-500.

Lester, D. (2005). Organ donation and the fear of death. *Psychological Reports, 96*(3 Pt 1), 769-770. doi: 10.2466/pr0.96.3.769-770

Limbos, M. M., Chan, C. K., & Kesten, S. (1997). Quality of life in female lung transplant candidates and recipients. *Chest, 112*(5), 1165-1174.

Limbos, M. M., Joyce, D. P., Chan, C. K., & Kesten, S. (2000). Psychological functioning and quality of life in lung transplant candidates and recipients. *Chest, 118*(2), 408-416.

Lobo, F. S., Gross, C. R., & Matthees, B. J. (2004). Estimation and comparison of derived preference scores from the SF-36 in lung transplant patients. *Quality of Life Research, 13*(2), 377-388.

Lynch, J., P, & Ross, D., J. (2006). *Lung and Heart-Lung Transplantation* (Vol. 217). New York: Taylor and Francis Group.

Mahoney, J. D. (2001). Should we adopt a market strategy to organ donation. In W. Shelton (Ed.), *The Ethics of Organ Transplantation* (pp. 65-88). Published online.

Matesanz, R., & Dominguez-Gil, B. (2007). Strategies to optimize deceased organ donation. *Transplantation Reviews, 21*, 177-188.

Matthees, B. J., Anantachoti, P., Kreitzer, M. J., Savik, K., Hertz, M. I., & Gross, C. R. (2001). Use of complementary therapies, adherence, and quality of life in lung transplant recipients. *Heart and Lung, 30*(4), 258-268. doi: 10.1067/mhl.2001.116135

Maury, G., Langer, D., Verleden, G., Dupont, L., Gosselink, R., Decramer, M., & Troosters, T. (2008). Skeletal muscle force and functional exercise tolerance before and after lung transplantation: a cohort study. *American Journal of Transplantation, 8*(6), 1275-1281. doi: 10.1111/j.1600-6143.2008.02209.x

Mayring, P. (2008). *Qualitative Inhaltsanalyse*. Weinheim und Basel: Beltz Verlag.

McGlade, D., & Pierscionek, B. (2013). Can education alter attitudes, behaviour and knowledge about organ donation? A pretest-post-test study. *BMJ Open, 3*(12), e003961. doi: 10.1136/bmjopen-2013-003961

Meachery, G., De Soyza, A., Nicholson, A., Parry, G., Hasan, A., Tocewicz, K., . . . Corris, P. A. (2008). Outcomes of lung transplantation for cystic fibrosis in a large UK cohort. *Thorax, 63*(8), 725-731. doi: 10.1136/thx.2007.092056

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Internatoinal Journal of Surgery, 8*(5), 336-341. doi: 10.1016/j.ijsu.2010.02.007

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychological Bulletin, 110*(3), 406-425.

Munro, P. E., Holland, A. E., Bailey, M., Button, B. M., & Snell, G. I. (2009). Pulmonary rehabilitation following lung transplantation. *Transplantation Proceedings, 41*(1), 292-295. doi: 10.1016/j.transproceed.2008.10.043

Muslin, H. L. (1971). On acquiring a kidney. *The American Journal of Psychiatry, 127*(9), 1185-1188.

Muslin, H. L. (1972). The emotional response to the kidney transplant: the process of internalization. *Canadian Psychiatric Association Journal, 17*(2), Suppl 2:SS3-.

Myaskovsky, L., Dew, M. A., McNulty, M. L., Switzer, G. E., DiMartini, A. F., Kormos, R. L., & McCurry, K. R. (2006). Trajectories of change in quality of life in 12-month survivors of lung or heart transplant. *American Journal of Transplantation, 6*(8), 1939-1947. doi: 10.1111/j.1600-6143.2006.01395.x

Naef, R., & Bournes, D. A. (2009). The lived experience of waiting: a Parse method study. *Nursing Science Quarterly, 22*(2), 141-153. doi: 10.1177/0894318409331932

Najafizadeh, K., Ghorbani, F., Rostami, A., Fard-Mausavi, A., Lorgard-Dezfuli-Nejad, M., Marashian, S. M., . . . Masjedi, M. R. (2009). Depression while on the lung transplantation waiting list. *Annals of Transplantation, 14*(2), 34-37.

Neukom, M., Corti, V., Boothe, B., Boehler, A., & Goetzmann, L. (2012). Fantasized recipient-donor relationships following lung transplantations: a qualitative case analysis based on patient narratives. *The International Journal of Psychoanalysis, 93*(1), 117-137. doi: 10.1111/j.1745-8315.2011.00496.x

Nilsson, M., Forsberg, A., Lennerling, A., & Persson, L. O. (2013). Coping in relation to perceived threat of the risk of graft rejection and Health-Related Quality of Life of organ transplant recipients. *Scandinavian Journal of Caring Sciences, 27*(4), 935-944. doi: 10.1111/scs.12007

O'Sullivan, B. P., & Freedman, S. D. (2009). Cystic fibrosis. *Lancet, 373*(9678), 1891-1904. doi: 10.1016/s0140-6736(09)60327-5

Orens, J. B., Estenne, M., Arcasoy, S., Conte, J. V., Corris, P., Egan, J. J., . . . Glanville, A. R. (2006). International guidelines for the selection of lung transplant candidates: 2006 update - a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *Journal of Heart and Lung Transplantation, 25*(7), 745-755. doi: 10.1016/j.healun.2006.03.011

Phillips, K. M., Burker, E. J., & White, H. C. (2011). The roles of social support and psychological distress in lung transplant candidacy. *Progress in Transplantation, 21*(3), 200-206.

Pinson, C. W., Feurer, I. D., Payne, J. L., Wise, P. E., Shockley, S., & Speroff, T. (2000). Health-related quality of life after different types of solid organ transplantation. *Annals of Surgery, 232*(4), 597-607.

Quante, M., & Wiedebusch, S. (2006). Overcoming the shortage of transplantable organs: ethical and psychological aspects. *Swiss Medical Weekly, 136*(33-34), 523-528. doi: 2006/33/smw-11303

Quintin, J. (2013). Organ transplantation and meaning of life: the quest for self fulfilment. *Medicine, Health Care and Philosophy, 16*(3), 565-574. doi: 10.1007/s11019-012-9439-z

Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., . . . Schunemann, H. J. (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine, 183*(6), 788-824. doi: 10.1164/rccm.2009-040GL

Rankin, S. H. (1990). Differences in recovery from cardiac surgery: a profile of male and female patients. *Heart and Lung, 19*(5 Pt 1), 481-485.

Rodrigue, J. R., & Baz, M. A. (2006). Are there sex differences in health-related quality of life after lung transplantation for chronic obstructive pulmonary disease? *Journal of Heart and Lung Transplantation, 25*(1), 120-125. doi: 10.1016/j.healun.2005.02.005

Rodrigue, J. R., Baz, M. A., Kanasky, W. F., Jr., & MacNaughton, K. L. (2005). Does lung transplantation improve health-related quality of life? The University of Florida experience. *Journal of Heart and Lung Transplantation, 24*(6), 755-763. doi: 10.1016/j.healun.2004.04.012

Rodrigue, J. R., Baz, M. A., Widows, M. R., & Ehlers, S. L. (2005). A randomized evaluation of quality-of-life therapy with patients awaiting lung transplantation. *American Journal of Transplantation, 5*(10), 2425-2432. doi: 10.1111/j.1600-6143.2005.01038.x

Rosen, C. S., Drescher, K. D., Moos, R. H., Finney, J. W., Murphy, R. T., & Gusman, F. (2000). Six- and ten-item indexes of psychological distress based on the Symptom Checklist-90. *Assessment, 7*(2), 103-111.

Rosenberger, E. M., Dew, M. A., Crone, C., & DiMartini, A. F. (2012). Psychiatric disorders as risk factors for adverse medical outcomes after solid organ transplantation. *Current Opinion in Organ Transplantation, 17*(2), 188-192. doi: 10.1097/MOT.0b013e3283510928

Rosenberger, E. M., Dew, M. A., DiMartini, A. F., DeVito Dabbs, A. J., & Yusen, R. D. (2012). Psychosocial issues facing lung transplant candidates, recipients and family caregivers. *Thoracic Surgery Clinics, 22*(4), 517-529. doi: 10.1016/j.thorsurg.2012.08.001

Rutherford, R. M., Fisher, A. J., Hilton, C., Forty, J., Hasan, A., Gould, F. K., . . . Corris, P. A. (2005). Functional status and quality of life in patients surviving 10 years after lung transplantation. *American Journal of Transplantation, 5*(5), 1099-1104. doi: 10.1111/j.1600-6143.2004.00803.x

Santana, M. J., Feeny, D., Ghosh, S., & Lien, D. C. (2012). Patient-reported outcome 2 years after lung transplantation: does the underlying diagnosis matter? *Journal of Patient Related Outcome Measures, 3*, 79-84. doi: 10.2147/prom.s32399

Santana, M. J., Feeny, D., Jackson, K., Weinkauf, J., & Lien, D. (2009). Improvement in health-related quality of life after lung transplantation. *Canadian Respiratory Journal, 16*(5), 153-158.

Schumacher, A., Sauerland, C., Silling, G., Berdel, W. E., & Stelljes, M. (2014). Resilience in patients after allogeneic stem cell transplantation. *Supportive Care in Cancer, 22*(2), 487-493. doi: 10.1007/s00520-013-2001-6

Shelton, W., & Balint, J. (2001). Preface *In The Ethics of Organ Transplantation* (pp. xi-xiii). Published online.

Shih, F. J., Tsao, C. I., Lin, M. H., & Lin, H. Y. (2002). The context framing the changes in health-related quality of life and working competence before and after lung transplantation: one-year follow-up in Taiwan. *Transplantation Proceedings, 34*(7), 2801-2806.

Siminoff, L. A., Mercer, M. B., & Arnold, R. (2003). Families' understanding of brain death. *Progress in Transplantation, 13*(3), 218-224.

Singer, J. P., Chen, J., Blanc, P. D., Leard, L. E., Kukreja, J., & Chen, H. (2013). A thematic analysis of quality of life in lung transplant: the existing evidence and implications for future directions. *American Journal of Transplantation, 13*(4), 839-850. doi: 10.1111/ajt.12174

Singer, J. P., & Singer, L. G. (2013). Quality of life in lung transplantation. *Seminars in Respiratory and Critical Care Medicine, 34*(3), 421-430. doi: 10.1055/s-0033-1348470

Sirri, L., Potena, L., Masetti, M., Tossani, E., Magelli, C., & Grandi, S. (2010). Psychological predictors of mortality in heart transplanted patients: a prospective, 6-year follow-up study. *Transplantation, 89*(7), 879-886. doi: 10.1097/TP.0b013e3181ca9078

Smeritschnig, B., Jaksch, P., Kocher, A., Seebacher, G., Aigner, C., Mazhar, S., & Klepetko, W. (2005). Quality of life after lung transplantation: a cross-sectional study. *Journal of Heart and Lung Transplantation, 24*(4), 474-480. doi: 10.1016/j.healun.2003.12.013

Smith, P. J., Rivelli, S., Waters, A., Reynolds, J., Hoyle, A., Flowers, M., . . . Blumenthal, J. A. (2014). Neurocognitive changes after lung transplantation. *Annals of the American Thoracic Society, 11*(10), 1520-1527. doi: 10.1513/AnnalsATS.201406-232OC

Smith, P. J., Rivelli, S. K., Waters, A. M., Hoyle, A., Durheim, M. T., Reynolds, J. M., . . . Blumenthal, J. A. (2015). Delirium affects length of hospital stay after lung transplantation. *Journal of Critical Care, 30*(1), 126-129. doi: 10.1016/j.jcrc.2014.09.010

Sokol, R. S., Folks, D. G., Herrick, R. W., & Freeman, A. M., 3rd. (1987). Psychiatric outcome in men and women after coronary bypass surgery. *Journal of Psychosomatics, 28*(1), 11-16.

Sommer, G., & Fydrich, T. (1998). *Soziale Unterstützung. Diagnostik, Konzepte, F-SOZU. Materialie Nr. 22*. Tübingen: Deutsche Gesellschaft für Verhaltenstherapie.

Spaight, C., Weiss, J., Keel, I., & Immer, F. (2013). Variation in Organ Donation Rates in Switzerland: Prospective Cohort Study of Potential Donors (SwissPOD). Study Report.

Spielberg, C. D., & Vagg, P. R. (1980). *The factor structure of the state-trait anxiety inventory* (Vol. 7). New York: Hemisphere/Wiley.

Stavem, K., Bjortuft, O., Lund, M. B., Kongshaug, K., Geiran, O., & Boe, J. (2000). Health-related quality of life in lung transplant candidates and recipients. *Respiration, 67*(2), 159-165. doi: 29480

STCS. (2015). The Swiss Transplant Cohort Study. Study description. Retrieved 24.05.2015 http://www.stcs.ch/about/study-description

Swisstransplant. (2013). Swiss Transplant Annual Report 2013. Swiss National Fondation for organ donation and transplantation. Retrieved from http://www.swisstransplant.org/pdf/Jahresbericht-Swisstransplant-2013-de.pdf

Swisstransplant. (2015a). Swiss National Foundation for organ donation and transplantation. Organ Allocation. Retrieved 23.02.2015 http://www.swisstransplant.org/l4/organ-donation-transplantation/organ-donation-transplantation-donor-recipient-allocation-coordination-wait-list.php

Swisstransplant. (2015b). Swisstransplant Annual Report 2014. Retrieved from http://www.swisstransplant.org/l1/organspende-organ-transplantation-zuteilung-koordination-warteliste-statistiken.php?dl=1&datei=P34840-SWT-Jahresbericht-dt-abz2-2.pdf

Tegtbur, U., Sievers, C., Busse, M. W., Pethig, K., Warnecke, G., Kugler, C., . . . Niedermeyer, J. (2004). Quality of life and exercise capacity in lung transplant recipients. *Pneumologie, 58*(2), 72-78. doi: 10.1055/s-2003-812526

TenVergert, E. M., Essink-Bot, M. L., Geertsma, A., van Enckevort, P. J., de Boer, W. J., & van der Bij, W. (1998). The effect of lung transplantation on health-related quality of life: a longitudinal study. *Chest, 113*(2), 358-364.

TenVergert, E. M., Vermeulen, K. M., Geertsma, A., van Enckevort, P. J., de Boer, W. J., van der Bij, W., & Koeter, G. H. (2001). Quality of life before and after lung transplantation in patients with emphysema versus other indications. *Psychological Reports, 89*(3), 707-717. doi: 10.2466/pr0.2001.89.3.707

The Federal Assembly of the Swiss Confederation. (2014). 810.21 Federal Act on the Transplantation of Organs, Tissues and Cells (Transplantation Act). Retrieved 23.02.2015 http://www.admin.ch/ch/e/rs/810_21/index.html

Thomsen, D., & Jensen, B. O. (2009). Patients' experiences of everyday life after lung transplantation. *Journal of Clinical Nursing, 18*(24), 3472-3479. doi: 10.1111/j.1365-2702.2009.02828.x

Toronto Lung Transplant Group. (1986). Unilateral lung transplantation for pulmonary fibrosis. Toronto Lung Transplant Group. *The New England Journal of Medicine, 314*(18), 1140-1145. doi: 10.1056/nejm198605013141802

Van Den, B. J., Geertsma, A., van Der, B. W., Koeter, G. H., de, B. W., Postma, D. S., & ten, V. E. (2000). Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life. *American Journal of Respiratory and Critical Care Medicine, 161*(6), 1937-1941. doi: 10.1164/ajrccm.161.6.9909092

Vaquero Barrios, J. M., Redel Montero, J., & Santos Luna, F. (2014). Comorbidities impacting on prognosis after lung transplant. *Archivos de Bronconeumología, 50*(1), 25-33. doi: 10.1016/j.arbres.2013.11.010

Vasiliadis, H. M., Collet, J. P., & Poirier, C. (2006). Health-related quality of life determinants in lung transplantation. *Journal of Heart and Lung Transplantation, 25*(2), 226-233. doi: 10.1016/j.healun.2005.08.008

Vermeulen, K. M., Ouwens, J. P., van der Bij, W., de Boer, W. J., Koeter, G. H., & TenVergert, E. M. (2003). Long-term quality of life in patients surviving at least 55 months after lung transplantation. *General Hospital Psychiatry, 25*(2), 95-102.

Vermeulen, K. M., van der Bij, W., Erasmus, M. E., Duiverman, E. J., Koeter, G. H., & TenVergert, E. M. (2004). Improved quality of life after lung transplantation in individuals with cystic fibrosis. *Pediatric Pulmonology, 37*(5), 419-426. doi: 10.1002/ppul.20009

Vermeulen, K. M., Groen, H., van der Bij, W., Erasmus, M. E., Koeter, G. H., & TenVergert, E. M. (2004). The effect of bronchiolitis obliterans syndrome on health related quality of life. *Clinical Transplantation, 18*(4), 377-383. doi: 10.1111/j.1399-0012.2004.00174.x

Vermeulen, K. M., van der Bij, W., Erasmus, M. E., & TenVergert, E. M. (2007). Long-term health-related quality of life after lung transplantation: different predictors for different dimensions. *Journal of Heart and Lung Transplantation, 26*(2), 188-193. doi: 10.1016/j.healun.2006.11.006

Vermeulen, K. M., TenVergert, E. M., Verschuuren, E. A., Erasmus, M. E., & van der Bij, W. (2008). Pre-transplant quality of life does not predict survival after lung transplantation. *Journal of Heart and Lung Transplantation, 27*(6), 623-627. doi: 10.1016/j.healun.2008.03.011

Walters, S., & Mehta, A. (2007). Epidemiology of cystic fibrosis. In M. Hodson, D. Geddes, & A. Bush (Eds.), *Cystic fibrosis, 3rd edn.* (pp. 21-45). London: Edward Arnold.

Ward, J. H. (1963). Hierarchical Grouping to Optimize an Objective Function. *Journal of the American Statistical Association, 58*(301), 236-244.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473-483.

Webster, K., Cella, D., & Yost, K. (2003). The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health and Quality of Life Outcomes, 1*, 79. doi: 10.1186/1477-7525-1-79

Weill, D., Benden, C., Corris, P. A., Dark, J. H., Davis, R. D., Keshavjee, S., . . . Glanville, A. R. (2015). A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *Journal for Heart and Lung Transplantation, 34*(1), 1-15. doi: 10.1016/j.healun.2014.06.014

WHO. (1948). World Helath Organization. Constitution in basic documents. Geneva: WHO.

WHO. (1997). World Health Organization. WHOQOL. Measuring Quality of life. Retrieved 15.05.2015, from WHOQOL group http://www.who.int/mental_health/media/68.pdf

WHO. (2003). World Health Organisation. Adherence to long-term therapies. Evidence for action.

WHO. (2015). Worl health statistic 2015. Burden of COPD. Retrieved 18.02.2015 http://www.who.int/respiratory/copd/burden/en/

WHOQOL group. (1993). Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). *Quality of Life Research, 2*(2), 153-159.

Wildgaard, K., Iversen, M., & Kehlet, H. (2010). Chronic pain after lung transplantation: a nationwide study. *The Clinical Journal of Pain, 26*(3), 217-222. doi: 10.1097/AJP.0b013e3181b705e4

Woodman, C. L., Geist, L. J., Vance, S., Laxson, C., Jones, K., & Kline, J. N. (1999). Psychiatric disorders and survival after lung transplantation. *Journal of Psychosomatics, 40*(4), 293-297. doi: 10.1016/s0033-3182(99)71221-1

Xu, J., Adeboyejo, O., Wagley, E., Aubrecht, J., Song, M. K., Thiry, L., & Dabbs, A. D. (2012). Daily burdens of recipients and family caregivers after lung transplant. *Progress in Transplantation, 22*(1), 41-47; quiz 48.

Yelle, M. T., Stevens, P. E., & Lanuza, D. M. (2013). Waiting narratives of lung transplant candidates. *Nursing Researach and Practice, 2013*, 794698. doi: 10.1155/2013/794698

Yusen, R. D. (2009). Technology and outcomes assessment in lung transplantation. *Proceedings of the American Thoracic Society, 6*(1), 128-136. doi: 10.1513/pats.200809-102GO

Yusen, R. D. (2011). Survival and quality of life of patients undergoing lung transplant. *Clinics in Chest Medicine, 32*(2), 253-264. doi: 10.1016/j.ccm.2011.02.006

Yusen, R. D., Edwards, L. B., Kucheryavaya, A. Y., Benden, C., Dipchand, A. I., Dobbels, F., . . . Stehlik, J. (2014). The Registry of the International Society for Heart and Lung Transplantation: Thirty-first Adult Lung and Heart-Lung Transplant Report-2014; Focus Theme: Retransplantation. *Journal of Heart and Lung Transplantation, 33*(10), 1009-1024. doi: 10.1016/j.healun.2014.08.004

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361-370.

Zubin, J., & Spring, B. (1977). Vulnerability--a new view of schizophrenia. *Journal of Abnormal Psychology, 86*(2), 103-126.

Index of Tables

Theoretical framework

Study 1

Study 2

Study 3

Index of Figures

Theoretical framework

Study 1

Study 2

Study 3

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Publications and Abstracts

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Seiler, A., Klaghofer, R., Martin-Soelch, Ch., & Jenewein, J. Psychological adjustment after lung transplantation. *Journal of Psychosomatic Research*: 76(6), 514

Conference Talks and Poster Presentations

03/2015	*Psychological distress and quality of life after lung transplantation. Results from a six months observational study*. TNT Seminar. Hot Topics in Transplantation. University Hospital Zurich, Switzerland *(oral presentation)*
07/2014	*Psychological Adjustment after Lung Transplantation*. European Association of Psychosomatic Medicine (EAPM). Sibiu, Ro *(oral presentation)*
12/2013	Tag der Forschung der Psychiatrie und der Kinder- und Jugendpsychiatrie. Psychiatrische Universitätsklinik Zürich *(poster presentation)*
07/2013	European Association of Psychosomatic Medicine (EAPM). Cambridge, UK (*poster presentation)*

Workshops

03/ 2015	*Besonderheiten in der konsiliarpsychiatrischen Behandlung von Herz- und Lungentransplantierten Patienten*. Moderne Psychosomatik – und ihr Bezug zur K+L Psychiatrie. Swiss Society of Consultation-Liaison Psychiatry

Annina Julia Seiler, Zurich, Mai 2015

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich meine Dissertation selbständig und ohne unzulässige fremde Hilfe verfasst habe und sie noch keiner anderen Fakultät vorgelegt habe.

Annina Julia Seiler, Mai 2015