

## **International Society of Heart and Lung Transplantation**

### **Pulmonary Transplantation Quality of Life Workforce Annotated Bibliography of Health Related Quality of Life in Lung Transplantation**

The manuscripts making up this annotated bibliography are organized thematically. There are seven original themes and an eighth theme for review articles and editorials.

#### **Theme I. Determinants of HRQL**

#### **Theme II. Psychosocial factors in HRQL**

#### **Theme III. Comparisons of HRQL before and after lung transplantation**

#### **Theme IV. Long-term longitudinal studies of HRQL in lung transplant recipients**

#### **Theme V. The effect of therapies and interventions on HRQL**

#### **Theme VI. Instrument validation and methodology**

#### **Theme VII. HRQL as a predictor of clinical outcomes**

#### **Theme VIII. Reviews and Editorials**

#### **Theme I. Determinants of HRQL**

- 1) Pinson, C.W., et al., *Health-related quality of life after different types of solid organ transplantation*. Ann Surg, 2000. **232**(4): p. 597-607. [PMID: 10998658](#).

This study assessed psychosocial outcomes (HRQoL, anxiety, depression, social support, and work performance) 354 patients after kidney (n=165), liver (n=53), heart (n=24), and lung (n=112) transplantation at 2, 6, 12, and 24 months. Physical and Psychosocial Component Scales for the entire sample showed a marginal decrease until 24 months after transplantation. Overall, HRQoL increased for all organ types with differing trajectories. Liver patients reported the lowest HRQoL benefit for the majority of the physical ( $P \leq 0.01$ ) and psychosocial ( $P \leq 0.01$ ) subscales. Anxiety (17.4%) and depression (13.8%) were prevalent in the overall sample. Depression symptoms impaired HRQoL outcomes in both SF-36 components and unemployment impacted the SF-36 psychosocial outcomes. Regular screening for depression symptoms may diminish psychologic disorders and distress after transplantation and thus may further improve outcomes.

- 2) van den Berg, J., et al., *Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life*. Am J Respir Crit Care Med, 2000. **161**(6): p. 1937-41. [PMID: 10852770](#).

This study examines the relationship between HRQL and BOS after lung transplant. Subjects completed surveys at 4, 7, and then every 6 months post-transplant. HRQL and other patient-reported outcomes were assessed by the Nottingham Health Profile, State-trait Anxiety Inventory (STAI), Zung Self-Rating Depression Scale, and Index of Well-Being (IWB). The study design was

complex including both cross-sectional and longitudinal components and varying numbers of subjects at each time point (range 27-72). Patients who developed BOS reported significant restrictions on physical mobility at 7, 19, 25 and 31 months post-transplant, more depression and anxiety at 13 and 25 months post-transplant, and reduced well-being at 13, 19 and 25 months post-transplant, compared to those who did not develop BOS. After development of BOS, patients reported increased anxiety but not depression.

- 3) Anyanwu, A.C., et al., *Assessment of quality of life in lung transplantation using a simple generic tool*. *Thorax*, 2001. **56**(3): p. 218-22. [PMID: 11182015](#).

This study evaluated the EQ-5D as a measure of quality of life before and after lung transplant by administering the EQ-5D survey cross-sectionally to 87 pre-transplant and 255 post-transplant patients from four lung transplant centers in the United Kingdom. Mean EQ-5D scores were compared between various types of transplant recipients (single, bilateral and heart-lung) and between various epochs (before transplant, 0-6 months, 7-18 months, 19-36 months, and more than 36 months post-transplant). Better scores were found post-transplant than pre-transplant and worse scores were found in recipients of single compared to bilateral lung transplant. The authors concluded that the EQ-5D is responsive to changes in quality of life across various lung transplant groups and can be used as an aggregate HRQL value to study outcomes.

- 4) Vermeulen, K.M., et al., *The effect of bronchiolitis obliterans syndrome on health related quality of life*. *Clin Transplant*, 2004. **18**(4): p. 377-83. [PMID: 15233813](#).

This was a retrospective cohort study of lung transplant recipients who had at least 18 months of follow up after the diagnosis of BOS grade 1 or higher, or biopsy-confirmed obliterative bronchiolitis. Out of 181 transplant recipients, 70 developed BOS and 29 were included in the study. HRQL measures mailed at regular intervals included the generic Nottingham Health Profile (NHP), the State-Trait Anxiety Inventory (STAI), the Self-Rating Depression Scale (SDS) and the Index of Well-Being (IWB). Prior to the onset of BOS, HRQL values were similar to the general population except for higher depression scores. BOS was associated with a worsening in the energy and mobility domains of the NHP, and worsening SDS and IWB. Activity restriction and dyspnea also increased after the onset of BOS.

- 5) Gerbase, M.W., et al., *Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome*. *Chest*, 2005. **128**(3): p. 1371-8. [PMID: 16162731](#).

This study compared long-term health-related quality of life (HRQL) in single (n=14) and bilateral (n=30) lung recipients pre and annually post-transplant. The SGRQ and the VAS ( $r = 0.812$ ;  $p < 0.0001$ ), the SGRQ and the 6MWT ( $r = 0.610$ ;  $p < 0.0001$ ), and the SGRQ and the FEV1 ( $r = 0.523$ ;  $p < 0.0001$ ) were significantly correlated in all patients. Significant improvements on the FEV1, 6MWT, and SGRQ were observed after transplant in both single and bilateral LTx recipients. Increased risk for the development of bronchiolitis obliterans syndrome (BOS) [relative risk, 2.86; 95% confidence interval, 1.22 to 6.67;  $p = 0.03$ ] and significantly lower FEV1 values were observed in patients following a single compared to bilateral procedures ( $p < 0.01$ ). In contrast, the 6MWT and the SGRQ scores were not significantly different between recipients of single and double LTx. The same patterns of results were observed in comparisons between single and bilateral lung recipients with prior pulmonary emphysema. Despite poorer FEV1 recovery and increased risk of BOS after LTx, single recipients had comparable long-term exercise tolerance and quality-of-life scores as patients

who received bilateral transplants. These results suggest the limited influence of functional performance on objective and subjective markers of HRQL recovery after LTx.

- 6) Kugler, C., et al., *Health-related quality of life in two hundred-eighty lung transplant recipients*. J Heart Lung Transplant, 2005. **24**(12): p. 2262-8. [PMID: 16364880](#).

In this cross-sectional study the authors aimed to compare HRQL in 280 lung transplant recipients with 155 healthy controls. They also aimed to evaluate transplant recipient HRQL correlation with age, gender, social support, type of transplant (single, bilateral, heart-lung), post-transplant time, BOS grade, and pre-transplant diagnoses. HRQL was measured using the Quality of Life Profile for Chronic Diseases (PLC). The PLC includes Physical Abilities, Relaxation Capabilities, Positive Moods, Negative Moods, Contact Capabilities and Social Functioning subscales. The authors found HRQL subscale scores were similar between healthy controls and lung transplant recipients except for the Social Functioning subscale. In that scale, lung transplant recipients reported better HRQL than health controls. Subjects surviving greater than 5 years after transplant reported significantly poorer health-related quality of life relative to other transplant patients in all subscales except Social Functioning. These subjects also had a high incidence of BOS, which was associated with lower HRQL scores. BOS, cystic fibrosis, single-lung transplantation, older age and recurrent infections were all associated with worse scores on the Physical Ability subscale. Subjects with episodes of infection or rejection scored lower in Relaxation Capability and Social Functioning subscales.

- 7) Singer, L.G., et al., *Determinants of health utility in lung and heart-lung transplant recipients*. Am J Transplant, 2005. **5**(1): p. 103-9. [PMID: 15636617](#).

This was a cross-sectional study of the determinants of standard gamble utility for current health in 90 stable lung and heart-lung transplant recipients of whom 34 had BOS. Candidate predictor variables included age, sex, indication for transplant, type of transplant, time since transplant, BMI, arterial pO<sub>2</sub>, creatinine clearance, number of medications, presence of BOS and risk attitude. The overall median utility was 0.88 (IQR 0.50-0.99). Female sex, absence of BOS, better renal function and longer time since transplantation were associated with higher utility scores on multivariate analysis.

- 8) Girard, F., et al., *Prevalence and Impact of Pain on the Quality of Life of Lung Transplant Recipients*. Chest, 2006. **130**(5): p. 1535-1540. [PMID: 17099034](#).

This cross-sectional study aimed to assess the impact and extent of pain in 96 lung transplant recipients at least 3 months after transplant. Subjects were evaluated for pain, anxiety, quality of life, and depression by the Brief Pain Inventory (BPI), State-Trait Anxiety Inventory (STAI), SF-36 and Beck Depression Inventory (BDI) respectively. 47 subjects (49%) reported pain related to transplant surgery or other transplant related treatments. Subjects reported pain at various body sites but most frequently identified the thoracotomy incision. Depression scores were higher and trait anxiety scores were slightly higher for subjects with pain than without, while state anxiety scores did not differ between those with or without pain. Subjects without pain scored higher on the physical component summary score (PCS) of the SF-36, though mental component summary (MCS) scores were comparable between those with and without pain.

- 9) Ricotti, S., et al., *Determinants of quality of life after lung transplant: an Italian collaborative study*. Monaldi Arch Chest Dis, 2006. **65**(1): p. 5-12. [PMID: 16700187](#).

This was a multicenter cross-sectional study of health-related quality of life in 129 stable Italian lung transplant recipients, of whom 18 (14%) had BOS. HRQL instruments included the SF-36, General Health Questionnaire (GHQ) which measures psychiatric disturbance, and SGRQ. They examined associations with a number of clinical factors as well as six minute walk and dyspnea (using visual analog scale and Borg scale before and after 6MW). Age, exertional dyspnea, osteoporosis and recent acute rejection were associated with the SF-36 physical component summary score (PCS) on bivariate analysis with only exertional dyspnea reaching significance on multivariate analysis.

- 10) Rodrigue, J.R. and M.A. Baz, Are there sex differences in health-related quality of life after lung transplantation for chronic obstructive pulmonary disease? *J Heart Lung Transplant*, 2006. **25**(1): p. 120-5. [PMID: 16399540](#).

The authors investigated whether HRQL in lung transplant recipients vary with respect to sex differences. 37 patients (20 males and 17 females), originally diagnosed with COPD, were assessed before and after lung transplantation at varying points in each patient's course. Measures of assessment included the Short Form-36 Health Survey (SF-36), Transplant Symptom Frequency Questionnaire (TSFQ), FEV1, and 6-minute walk test. Results showed that there are indeed sex differences in HRQL outcomes. Women reported more frequent symptoms than men, despite a more significant improvement in lung function, as well as a different set of symptom presentations than men. HRQL gains were more substantial for men than women.

- 11) Kugler, C., et al., *Symptom experience after lung transplantation: impact on quality of life and adherence*. *Clinical Transplantation*, 2007. 21(5): p. 590-596. [PMID: 17845632](#).

This single center cross-sectional cohort study evaluated symptom experiences (frequency and distress), adherence, and quality-of-life (QOL) in 287 of 308 surviving lung and heart-lung transplant recipients. The study found an association between immunosuppression and significant adverse effect symptom frequency and distress. Symptom experiences negatively influenced QOL and adherence, though the most frequently experienced symptoms did not necessarily have the greatest impact on perceived distress. Women and younger recipients (<40 yr) reported a significantly higher level of symptom experience compared with their counterparts. Recipients reported using strategies to reduce adverse effects that consisted of postponing medication intake, dropping doses, and reducing doses. The study demonstrated a significant association between patients' perceptions of immunosuppression-related symptom experiences and QOL and adherence.

- 12) Langer, D., et al., *Physical activity in daily life 1 year after lung transplantation*. *J Heart Lung Transplant*, 2009. **28**(6): p. 572-8. [PMID: 19481017](#).

This cross-sectional study compared physical activity, physical function and HRQL in 22 lung transplant recipients between 12 and 24 months after transplant with 22 healthy age and gender-matched controls. Physical activity was measured by two activity monitors which recorded daily walking time, daily steps, standing time, sedentary time, and time spent in activities of at least moderate intensity. Tests of functioning included pulmonary tests of maximal inspiratory volume, maximal expiratory volume, maximal workload and oxygen consumption during cycle ergometer test. Muscle strength was tested by handgrip and quadriceps isometric tests. Endurance was measured by 6 minute walk distance (6MWD). HRQL was assessed with the SF-36, physical component summary (PCS) and mental component summary (MCS) scores. Average physical

activity levels of recipients were lower than those of healthy controls across all measures. Lung transplant recipients also manifested significantly lower maximal workload, maximal oxygen consumption, quadriceps strength, and 6MWD than healthy controls. SF-36 PCS scores were lower than those of the normative population. All measures of physical activity demonstrated moderate to good correlations with the SF-36 PCS. The daily steps measure was also significantly with 6MWD, quadriceps force, and maximum workload.

- 13) Irani, S., et al., *Olfactory performance before and after lung transplantation: Quantitative assessment and impact on quality of life*. The Journal of Heart and Lung Transplantation, 2010. **29**(3): p. 265-272. [PMID: 19783170](#).

This cross-sectional study tested olfactory ability before and after transplantation and its association with life satisfaction, psychological status and baseline characteristics. 22 subjects were evaluated before transplant and 70 were evaluated after transplant (range: 24 to 88 months after transplant surgery). Olfactory performance was measured by a test that calculated a threshold, discrimination and identification (TDI) score. Life satisfaction was assessed by Questions on Life Satisfaction Modules (FLZM) including two modules for general and health-related life satisfaction. Psychological status was assessed by the Hospital Anxiety Depression Scale (HAD) including anxiety and depression subscales. Demographics included age, gender, underlying diagnosis of cystic fibrosis (CF) or chronic obstructive pulmonary disease, bronchiolitis obliterans (BOS) score and time after transplant for subjects assessed after transplant. Olfactory performance was not associated with-transplant status or time after transplant. Female gender was associated with better olfactory performance whereas an underlying diagnosis of CF and age younger than 55 years was associated with worse performance. Better olfactory performance was significantly associated with better HRQL and less depression and anxiety regardless of transplant status.

- 14) Wildgaard, K., M. Iversen, and H. Kehlet, *Chronic pain after lung transplantation: a nationwide study*. Clin J Pain, 2010. **26**(3): p. 217-22.

The authors evaluated chronic pain in 79 transplant recipients. Of these, a total of 14 patients who reported persistent postsurgical pain were administered three measures: a numeric rating scale (NRS) of 0-10 applied to a variety of questions about pain, the McGill Pain questionnaire, and a drawing of a torso on which subjects were asked to shade in the affected area. Overall, 14 patients (18%) reported persistent post-surgical pain; of these, 8 reported moderate pain and 4 reported severe pain. Strenuous physical activities, work and carrying heavy bags were the activities associated most highly with pain. Other results included pain characteristics, pain over a variety of activity levels and daily activities, pain on various locations on the body, and use of pain medications.

- 15) Santana, M.J., et al., *Patient-reported outcome 2 years after lung transplantation: does the underlying diagnosis matter?* Patient Relat Outcome Meas, 2012. **3**: p. 79-84. [PMID: 23204877](#).

This study aimed to assess the impact of demographics, clinical characteristics and complications on health status and disability in subjects surviving at least two years after lung transplantation. The authors conducted a cross-sectional study of 214 lung transplant recipients at least two years after transplant. Health status and disability were measured using the Health Utilities Index Mark 3 (HUI3). The HUI3 includes dimension scores for ambulation, dexterity, cognition, emotion, pain and discomfort as well as an overall score. Demographics included age, sex, education, employment,

and underlying diagnoses. Clinical characteristics included incidence of comorbidities, transplant type, time since transplant, BOS and CMV infection. The authors found that underlying diagnoses of COPD or CF were associated with moderate disability and diagnoses of pulmonary fibrosis or pulmonary hypertension were associated with severe disability. Women reported worse overall HUI3 scores than men. They also reported worse scores in ambulation, emotion and cognition than men, however, they reported less pain. Using random-effect models holding time since transplant as a random variable and age, sex, underlying diagnoses, BOS and CMV infection as fixed variables, they found that BOS determined health status, while the other variables did not.

- 16) Chen, F., et al., *Lung allocation score and health-related quality of life in Japanese candidates for lung transplantation*. *Interact Cardiovasc Thorac Surg*, 2015. **21**(1): p. 28-33. [PMID 25888341](#).

This study examined the Lung Allocation Score's (LAS) ability to predict mortality and the relationship between LAS score and HRQL. HRQL measures were administered in 102 Japanese lung transplant candidates between 2009 and 2013. Measurements included pulmonary function, 6 minute walk distance, Medical Outcomes Study SF-36 (MOS SF-36), and St. George's Respiratory Questionnaire (SGRQ). The Hospital Anxiety and Depression Scale was also administered to assess psychological status. Dyspnea was measured using the modified Medical Research Council (mMRC) dyspnea scale. LAS score was found to be significantly related to mortality ( $P = 0.0026$ ), but other physiological measurements such as pulmonary function and 6MWD were not. Multivariate analyses demonstrated that LAS was less significantly related to SGRQ than dyspnea and psychological status. LAS did seem to be a predictor of mortality in Japanese lung transplantation candidates and LAS was also significantly related to certain dimensions of HRQL (i.e. dyspnea and psychological status).

## **Theme II. Psychosocial factors in HRQL**

- 1) Cohen, L., et al., *Predictors of quality of life and adjustment after lung transplantation*. *Chest*, 1998. **113**(3): p. 633-44. [PMID: 9515836](#).

This study tested psychological predictors of health-related quality of life, physical health and psychological adjustment after transplant using both cross-sectional and longitudinal cohorts. In the cross-sectional study the authors assessed 17 transplant candidates and 60 transplant recipients. In the longitudinal study, they evaluated 107 subjects before transplant, following 32 of them after transplant. Psychological measures of adjustment and mental health included the Basic Personality Inventory (BPI), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI) and Mental Health Inventory (MHI). HRQL was assessed with SF-36. Other measures included the Multidimensional Health Locus of Control Scales, Cardiac Symptoms Inventory, Sleep Disturbance Questionnaire and a background questionnaire. Psychological status before transplant was not associated with infections, rejection episodes, BOS development, FEV1 or length of survival after. High trait anxiety levels before transplant predicted worse sleep disturbances and worse HRQL afterward. Sleep disturbances were associated with worse mental health, state anxiety, pulmonary and cardiac symptoms and HRQL scores in mental health, role emotional and social functioning.

- 2) Stilley, C.S., et al., *Psychological symptom levels and their correlates in lung and heart-lung transplant recipients*. *Psychosomatics*, 1999. **40**(6): p. 503-9. [PMID: 10581979](#).

This cross-sectional study examined psychological status, psychosocial factors and HRQL in lung (n=36) and heart-lung (n=14) transplant recipients between 2.5 and 17 months after transplant.

Psychological distress was measured by the Symptom Checklist-90 (SCL-90). Psychosocial factors potentially affecting psychological distress were measured by the Self-Esteem Scale, Sense of Mastery Scale, questions on health-related worry, a social support questionnaire, and the Sickness Impact Profile (SIP). Psychiatric diagnoses were assessed by the Structured Clinical Interview for DSM-III-R, and the Renard Diagnostic Interview. Overall quality of life was measured by the Campbell Sense of Well-Being Scale. Subjects had significantly higher levels of anxiety and lower levels of hostility compared to normative population scores. 26.5% of subjects showed depression and 34.7% showed anxiety on the SCL-90 depression and anxiety subscales, significantly higher than the 16% expected rate of scores above one standard deviation over the mean. Lung transplant recipients had significantly higher rates of depression than heart-lung transplant recipients. A personal history of depression or anxiety before transplant correlated with greater psychological distress after transplant. Other factors associated with psychological distress included lower social support (the social support questionnaire), lower mastery (Sense of Mastery Scale), higher health concern (health-related worry questions) and greater difficulty with activities of daily living (SIP).

- 3) Limbos, M.M., et al., *Psychological functioning and quality of life in lung transplant candidates and recipients*. Chest, 2000. **118**(2): p. 408-16. [PMID: 10936133](#).

This cross-sectional study compared overall quality of life, psychological functioning, body satisfaction, self-esteem and sexual functioning between 36 lung transplant candidates and 73 recipients. A survey battery was administered including the SF-36, visual analog scale of overall quality of life, Brief Symptoms Inventory (BSI), Hospital Anxiety and Depression Scale (HAD), Body Cathexis Scale, Rosenberg Self-Esteem Scale (RSES), and Derogatis Sexual Functioning Inventory (DSFI). Post-transplant subjects reported better general health, physical health, psychological health, body satisfaction, and self-esteem than pre-transplant subjects. The emotional health and emotional role limitations on the SF-36 were not significantly different between subjects before and after transplant. Sexual functioning was similar between pre and post groups and within the normative range of healthy adults. Both pre and post-transplant groups reported higher anxiety, depression, and body image and self-esteem issues than normative population scores.

- 4) Kurz, J.M., *Desire for control, coping, and quality of life in heart and lung transplant candidates, recipients, and spouses: a pilot study*. Prog Transplant, 2001. **11**(3): p. 224-30. [PMID: 11949467](#).

In this study, 25 dyads of patients and their spouses were administered structured surveys aimed at examining desire for control, coping strategies and quality of life. Nine pre-transplant and 16 post-transplant dyads were administered the Desire for Control (DC) Scale, Family Crisis Oriented Personal Evaluation Scale (FCOPES) and Quality of Life index (QLI). Quality of life scores between post-transplant patients and spouses were significantly correlated and quality of life in the health and functioning subscale for pre-transplant patients were significantly worse than all other groups. In pre-transplant spouses, desire for control was inversely correlated with use of coping strategies. Desire for control from spouses was also inversely correlated with desire for control from patients, in both pre and post-transplant dyads.

- 5) Kollner, V., et al., *Posttraumatic stress disorder and quality of life after heart or lung transplantation*. Transplant Proc, 2002. **34**(6): p. 2192-3. [PMID: 12270360](#).

This cross-sectional study aimed to compare three measures for post-traumatic stress disorder (PTSD) in thoracic transplant recipients. They evaluated 82 subjects after heart (n = 72), lung (n=8) and heart-lung (n=2) transplantation for PTSD using two diagnostic tools, the Structured Clinical Interview for DSM IV (SCID) and the Impact of Event Scale (IES-R), and a screening questionnaire, the

scale for posttraumatic stress symptoms (PTSS 10). They also assessed HRQL with the SF-36. Subjects ranged from 4 to 86 months after transplant (mean 32.3 months). 28 of these subjects reported transplantation or heart or lung disease as their most severe life event, while the remaining 54 described another event or no event as being most severe. The IES-R, PTSS 10 and SCID showed different results, in which some subjects demonstrated PTSD features on one instrument but not another. The PTSS 10 was an insufficient screening tool; it failed to recognize 50% of the cases diagnosed by the SCID. SF-36 mental component summary scores were worse in subjects diagnosed with PTSD by the SCID, while scores for subjects without PTSD were close to that of normative population scores.

- 6) De Vito Dabbs, A., et al., *Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation*. *J Heart Lung Transplant*, 2003. **22**(11): p. 1268-75. [PMID: 14585388](#).

A cross-sectional sample of 50 patients (36 lung, 14 heart–lung) between 2 and 17 months post-transplant were interviewed to assess physical symptoms, current physical impairment and psychosocial well-being in the areas of mental health, sense of mastery and coping. Medical record reviews established the presence of medical complications and secondary illnesses concurrent with the interviews. 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. When the impact of concurrent medical complications was controlled, recipients with elevated psychologic distress remained significantly more likely to report more physical symptoms and higher physical impairment levels. Patients' physical health status may be influenced by many factors. To the extent that psychologic distress increases the likelihood of perceived physical limitations, timely identification and treatment of distress may help to maximize quality of life after lung and heart–lung transplantation.

- 7) Parekh, P.I., et al., *Psychiatric disorder and quality of life in patients awaiting lung transplantation*. *Chest*, 2003. **124**(5): p. 1682-8. [PMID: 14605035](#).

This cross-sectional study of 100 lung transplant candidates aimed to examine the relationship between diagnosed psychiatric disorders and HRQL (general and disease-specific), psychological status, psychosocial aspects and shortness of breath. Psychiatric diagnoses were made through the DSM-IV. HRQL was measured using the SF-36 and Pulmonary-Specific Quality of Life Scale (PQLS). Psychological status was measured using the Beck Depression Inventory II (BDI-II), State-Trait Anxiety Inventory (STAI), General Health Questionnaire (GHQ), Perceived Stress Scale, Life Orientation Test-Revised (LOT-R), Perceived Social Support Scale, and the Health Practices Index. Dyspnea was measured with the UCSD Shortness of Breath (SOB) Questionnaire. The authors adjusted for age, gender, ethnicity, FEV1 and lung disease diagnosis. They found that 25% of subjects had a diagnosis of at least one mood or anxiety disorder, most commonly panic and anxiety disorder. This group of subjects had greater physical and emotional role limitations, less vitality, poorer mental health, poorer patient-reported physical functioning on the SF-36. The group also reported decreased ability to perform activities of daily living and overall worse quality of life on the PQLS compared to subjects without a psychiatric diagnosis. On psychological measures, subjects having at least one psychiatric diagnosis reported more symptoms of distress, depression and anxiety, higher stress levels, lower optimism, fewer positive health habits and lower social support. On the SOB questionnaire, they reported greater shortness of breath.



- 8) Archonti, C., et al., *[Physical quality of life and social support in subjects on the waiting list and after a lung transplantation]*. *Psychother Psychosom Med Psychol*, 2004. **54**(1): p. 17-22. [PMID: 14722835](#). [English abstract only, full text German only.]

This cross-sectional study aimed to assess HRQL, psychological status and social support before and after lung transplantation. Transplant candidates (n=19) and recipients (n=20) completed a survey battery that included the SF-36, Beck Depression Inventory (BDI) and questionnaire for perceived social support (F-SOZU). SF-36 subscales for physical functioning, role physical, vitality, health perception and social functioning were significantly better from before to after transplant. Depression and number of perceived support persons were comparable before and after transplant. Better perceived support was inversely correlated with depression on the BDI and directly correlated with better HRQL on the SF-36.

- 9) Claar, R.L., et al., *Emotional distress and quality of life in caregivers of patients awaiting lung transplant*. *J Psychosom Res*, 2005. **59**(1): p. 1-6. [PMID: 16126089](#).

This was a cross-sectional study of multiple psychosocial measures of anxiety, depression, coping and caregiver burden and HRQL measured by SF-36 in 82 caregivers of lung transplant candidates. 12/82 caregivers had clinically significant levels of depression and 2 had significant levels of anxiety; coping styles were associated with emotional distress. Caregivers had lower than predicted SF-36 social functioning domain scores, but otherwise their SF-36 scores were not significantly different from normative values.

- 10) Rodrigue, J.R. and M.A. Baz, *Waiting for lung transplantation: quality of life, mood, caregiving strain and benefit, and social intimacy of spouses*. *Clin Transplant*, 2007. **21**(6): p. 722-7. [PMID: 17988265](#).

This single center cross-sectional cohort study assessed the quality-of-life (QOL), mood, caregiving strain and benefits, and social intimacy in 73 of 98 approached lung transplant candidate spouse caregivers. About one-third of spouses reported clinically low QOL, and they had significantly lower physical and emotional QOL in comparison to a normative sample. Over half of the spouses had clinically elevated caregiving strain. Heightened physical strain, inconvenience, feeling confined, and feeling upset that patient has changed so much contributed most to caregiver strain. Higher caregiving strain showed an association with more mood disturbance, lower emotional QOL, lower social intimacy, and longer disease duration. Caregivers benefited from discovering inner strength, support from others, and realizing what is important in life.

- 11) Goetzmann, L., et al., *Psychological response and quality of life after transplantation: a comparison between heart, lung, liver and kidney recipients*. *Swiss Med Wkly*, 2008. **138**(33-34): p. 477-83. [PMID: 18726733](#).

The authors aimed to study and compare HRQL and psychological response to transplant among heart, lung, liver and kidney recipients. This cross-sectional study evaluated 370 transplant recipients (n=41 heart, 66 liver, 76 lung and 187 kidney) using the SF-36 and the Transplant Effects Questionnaire (TxEQ-D). Overall, all groups scored worse on the SF-36 general health perceptions, physical functioning, physical role functioning, social functioning and emotional role functioning subscales compared to normative population scores. Lung recipients scored higher than other groups in the SF-36 role emotional and mental component summary (MCS) scales. Overall, subjects in all groups reported an increased feeling of responsibility for the received organ and towards their

family, friends, medical staff and donor. Very few reported feelings of guilt, issues with disclosure of transplant status, or difficulties with compliance. Heart and lung transplant subjects worried less about their organ than liver and kidney subjects, and lung transplant subjects reported higher adherence to medical treatment than other organ transplant groups.

- 12) Nilsson, M., et al., *The perceived threat of the risk for graft rejection and health-related quality of life among organ transplant recipients*. J Clin Nurs, 2011. **20**(1-2): p. 274-82. [PMID: 20964748](#).

This cross-sectional study tested the validity of the Perceived Threat of the Risk for Graft Rejection (PTGR) questionnaire, a new patient-reported measure of threat of risk of rejection, in solid organ transplant recipients. PTGR associations with clinical characteristics and HRQL were also evaluated. Subjects included kidney (n=117), liver (n=39), heart and/or lung (n=29) transplant recipients.. Clinical characteristics included organ type, time since transplant, presence and number of acute graft rejection episodes, age, sex, marital status and current occupational status. HRQL was measured by the Medical Outcomes Short Form-36 (SF-36). Three PTGR domains of intrusive anxiety, graft-related threat and lack of control demonstrated convergent and discriminatory validity. The graft-related threat domain demonstrated moderate correlations with all SF-36 subscales. Kidney transplant recipients were significantly more likely to perceive graft-related threat than liver, heart or lung recipients. There were no associations between PTGR and time after transplant, whether or not subject had experienced acute rejection, or number of acute rejection episodes. Compared to men, women reported poorer scores in the intrusive anxiety domain but better scores in the lack of control domain.

- 13) DeVito Dabbs, A., et al., *Quality of recipient-caregiver relationship and psychological distress are correlates of self-care agency after lung transplantation*. Clin Transplant, 2013. **27**(1): p. 113-20. [PMID: 23004565](#).

This study examined levels of self-care agency (defined as the capability and willingness to engage in self-care behaviors), and its correlates to identify characteristics of lung recipients who may be at risk for lower self-care agency and thus difficulty performing self-care behaviors after transplantation. Levels of self-care agency and recipient characteristics (socio-demographics, psychological distress, quality of relationship with primary lay caregiver, and health locus of control) were assessed in 111 recipients. Mean (S.D.) score for Perceptions of Self-Care Agency (scale range 53-265) was 223.02 (22.46). Recipients were assigned to either the low (n =30) or high (n=81) self-care agency comparison group at the 25<sup>th</sup> percentile (lowest scores). Recipients with the lowest self-care agency scores reported significantly poorer quality of caregiver relationships ( $p < .001$ ) and greater psychological distress ( $p < .001$ ). After controlling for the presence of psychological distress, the quality of the recipient-caregiver relationship was the characteristic most associated with lower levels of self-care agency. Most recipients reported high levels of self-care agency; recipients with poorer caregiver relationships and greater psychological distress may need additional support to perform the self-care behaviors expected after lung transplantation.

- 14) Seiler, A., et al., *Post-transplant outcome-clusters of psychological distress and health-related quality of life in lung transplant recipients*. Swiss Med Wkly, 2015. [PMID: 26710349](#).

This study assessed psychological distress and health-related quality of life during the first 6 month post-transplant, how to identify patients with poor psychosocial outcomes, and determine potential predictors of psychological distress and HRQL. Investigators administered the Symptom Checklist

short version-9 and EuroQOL 5D to 40 lung transplant recipients during their first 6 months post-transplant. Analyses were summarized according to three clusters: (1) optimal (high EQ5D and low SCL-K-9 pre- and post-tx), (2) good (increase in EQ5D and decrease in SCL-K-9 from pre- to post-tx), and (3) poor outcome-clusters (low EQ5D and high SCL-K-9 or no significant change to either pre- and post-tx). The poor-outcome cluster tended to be older, suffered from more severe disease, more co-morbidities, prolonged ICU or hospital stay, more hospital admissions, and more frequent treatment with anti-depressants post-transplant.

- 15) Lundmark, M., et al., *Health transition after lung transplantation – a grounded theory study*. J Clin Nurs, 2016. **25**(15-16): p. 2285-2294. [PMID 27230156](#).

Authors used a qualitative inductive approach using Grounded Theory (GT) to understand the transitional health process of lung transplant recipients, specifically what their main concerns are and how they dealt with them. They interviewed 15 post-lung transplant recipients one year after transplantation using open-ended interviews and analyzed using the Charmaz constructivistic approach of GT. Results indicated that there was a strong relationship between reconstructing daily occupations (specifically the outcome of whether adjustments to routines have been successful in adapting to changing medical or social needs) and experiencing good health. Health trajectories of transition were non-linear, going from illness to feeling relatively healthy and back depending on the course of their illness, recuperation, complications, and changes to medical treatment.. Other results indicated other commonalities such as denying the seriousness of their illness, experiencing a later acceptance of their disease and limitations it would pose on their daily lives, and a focus on adjusting their daily activities because of their health. Most subjects emphasized the importance of scheduling to ensure they could complete their tasks and the stress of preparing for death and having no expectations of the transplant even when actively listed. After transplant, goal setting, exercising, and coping were important for recovery and experiencing good health. Subjects also reported adherence, changing habits, asking for help, accepting support, and self-monitoring as important in experiencing good health after the transplant. The authors emphasize that the key approach for subjects experiencing good health was their ability to adjust to physical demands, complications, and changes in everyday life.

### **Theme III. Comparisons of HRQL before and after lung transplantation**

- 1) O'Brien, B.J., et al., *The Nottingham Health Profile as a measure of quality of life following combined heart and lung transplantation*. J Epidemiol Community Health, 1988. **42**(3): p. 232-4. [PMID: 3150765](#).

This longitudinal study evaluated the impact of heart-lung transplant on HRQL. Subjects were evaluated using the Nottingham Health Profile (NHP) before transplant and at 3, 6 and 12 months after transplant (n=48, 28, 24 and 13 respectively). The NHP is composed of two parts: the first assesses health status across 6 dimensions including energy, pain, emotional reactions, sleep, social isolation and physical mobility, and the second assesses health impact on 7 areas including occupation, home tasks, social life, sexual life, home life, hobbies and holidays. NHP scores in all 6 dimensions showed significant improvements from before transplant to and 3 months after. From there, no further changes were observed at 6 and 12 months. In the 13 subjects with data at 12 months after transplant, subjects reported fewer health impacts on all 7 areas than before transplant.

- 2) Caine, N., et al., *Survival and quality of life of cystic fibrosis subjects before and after heart-lung transplantation*. *Transplant Proc*, 1991. **23**(1 Pt 2): p. 1203-4. [PMID: 1989186](#).

This longitudinal study the impact of heart-lung transplantation on survival and HRQL in subjects with cystic fibrosis (CF). Subjects completed assessments at the time of listing (n = 54). Assessments were repeated every 3 months before transplant and at 3, 6, and 12 months after transplantation. HRQL was assessed using the Nottingham Health Profile (NHP) which includes physical, social, emotional health dimensions as well as health impact on seven areas of daily living. Of the 54 listed subjects, 24 underwent heart-lung transplantation but only 13 completed surveys after transplantation. The authors found that heart-lung transplantation conferred a substantial survival and HRQL benefit. Compared to those on the waiting list, heart-lung transplant recipients experienced significant HRQL benefit in physical mobility, energy, looking after the home, social life, sex life, hobbies, and holiday domains.

- 3) Busschbach, J.J., et al., *Measuring the quality of life before and after bilateral lung transplantation in subjects with cystic fibrosis*. *Chest*, 1994. **105**(3): p. 911-7. [PMID: 8131563](#).

This small cross-sectional study of six subjects aimed to evaluate health utilities and HRQL in subjects with cystic fibrosis (CF) before transplant, during the transplant window, and after transplant. The transplant window was loosely defined as the interval of time in a subject's prognosis between being at greater risk of dying as a result of transplant and being at greater risk of dying as a result of their preexisting condition. Survey batteries were administered to three subjects listed for transplant and three subjects who were 12-16 months out from transplant. The transplant recipients were also asked to recall what their survey responses *might* have been during the transplant window. Measures of utility included standard gamble, time trade-off, Karnofsky performance status, and EuroQol visual analog scale. HRQL was measured using the Nottingham Health Profile (NHP). All utilities worsened from before transplant to the transplant window but increased after transplantation to levels higher than before transplant. NHP scores in energy and physical mobility domains were significantly worse in the transplant window compared to either pre- or post-transplant timepoints. Interestingly, problems reported on the NHP both before and after transplant were less than those reported in the normative population.

- 4) MacNaughton, K.L., et al., *Health-related quality of life and symptom frequency before and after lung transplantation*. *Clin Transplant*, 1998. **12**(4): p. 320-3. [PMID: 9686326](#).

Health-related quality of life (HRQOL) and symptom frequency and severity were assessed in 17 patients pre and post-lung transplantation. Physical functioning, general health, vitality and social functioning significantly improved post-transplantation. Compared to the normative sample, recipients had significantly lower scores on all health-related quality of life indices pre and post lung transplant. Perhaps as a consequence of immunosuppression medication, recipients reported increased frequency of symptomatology following the procedure; however, considered together the symptoms were not reported as significantly more problematic following transplantation. These findings document improved HRQOL for lung transplant recipients and provide useful information for patients considering this potentially life-saving treatment option.

- 5) TenVergert, E.M., et al., *The effect of lung transplantation on health-related quality of life: a longitudinal study*. *Chest*, 1998. **113**(2): p. 358-64. [PMID: 9498952](#).

This Dutch single-center prospective cohort study used self-administered questionnaires to assess

health-related quality of life (HRQL) before and after lung transplantation, and the study reported results in 24 of 69 transplanted patients who had complete data. Before transplantation, patients reported major restrictions on the dimensions mobility and energy, a low level of experienced well-being, depressive symptoms, difficulties in performing activities of daily living (ADL), and a low ability to take care of themselves. Surviving recipients showed improvements in mobility, energy, sleep, ADL dependency, level, and dyspnea from 4 through 15 months after transplantation.

- 6) Lanuza, D.M., et al., *Prospective study of functional status and quality of life before and after lung transplantation*. Chest, 2000. **118**(1): p. 115-22. [PMID: 10893368](#).

The authors conducted a longitudinal cohort study to evaluate the impact of lung transplantation on respiratory function, patient perceptions of functional status and psychological status, and HRQL. 10 subjects were evaluated prior to lung transplant and again at 1 and 3 months after transplant. Measures included the Sickness Impact Profile (SIP) for functional status, Brief Symptom Inventory (BSI) for psychological status, and General Health/ QOL Rating Scale for satisfaction with health, HRQL and transplant. Lung function measures included FEV1, FVC and FEF. The authors found that functional status improved most significantly at 3 months after transplant. Functional status improvement was associated with increased satisfaction with physical strength, health and quality of life. Respiratory function significantly improved for all three pulmonary measures from before to after transplant, but only FEV1 continued to improve between 1 and 3 months. Psychological status and the number of psychological symptoms did not change significantly between any point of assessment, although symptom intensity and distress did decrease over time.

- 7) Shih, F.J., et al., *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*. Transplant Proc, 2002. **34**(7): p. 2801-6. [PMID: 12431617](#).

This study assessed HRQL of 8 female lung transplant patients before and longitudinally up to 12 months after transplant. Both quantitative and qualitative methods were used. The Visual Analog Scale (VAS) was used to measure subjects' perception of HRQL and work competence (WC), while semi-structured qualitative interviews were conducted and analyzed for themes framing the context of HRQL changes. Compared to baseline, HRQL was improved throughout the first post-transplant year. Notably, HRQL worsened from 6 to 12 months post-transplant. WC changed from pre-transplant to post-transplant stages, but did not improve overall. HRQL and WC improved the most between 1 and 3 months post-transplant. Semi-structured interviews identified themes of intense pain, discomfort and insecurity from hospitalization; frustration from physical impairment post-transplant; and conflict between being dependent on transplant care providers and learning independent self-care.

- 8) Rodrigue, J.R., et al., *Does lung transplantation improve health-related quality of life? The University of Florida experience*. J Heart Lung Transplant, 2005. **24**(6): p. 755-63. [PMID: 15949737](#).

This was a cross-sectional study of 84 lung transplant recipients (9 with BOS) who had also completed HRQL assessments before transplantation, so that pre- and post-transplant HRQL could be compared. Instruments included SF-36 and Transplant Symptom Frequency Questionnaire (TSFQ). Pre-transplant scores were lower than normative values for most SF-36 domains. Post-transplant SF-36 scores were higher than COPD normative values but lower than general population normative values for most domains. SF-36 scores increased in all domains after transplant except

mental health, which was not impaired pre-transplant. Total TSFQ scores did not change after transplant but sub-scale scores varied with some improving and others worsening. BOS was associated with lower SF-36 role functioning-physical and vitality scores. Female gender, obesity and time since transplant were associated with HRQL differences.

- 9) Ortega, T., et al., *Health-related Quality of Life before and after a solid organ transplantation (kidney, liver, and lung) of four Catalonia hospitals*. *Transplant Proc*, 2009. **41**(6): p. 2265-7. [PMID: 19715893](#).

The purpose of this study was to compare HRQoL using the SF-36 between pre and 3 and 12 months after solid organ transplantation comparing results among various transplantations and the general population. The sample included 162 renal, 159 liver, and 58 lung candidates and 126 renal, 108 liver, and 22 lung recipients. The median age of all transplant recipients was 53 years with 68% men. All subjects showed clear improvements after transplantation. Lung recipients showed the worst HRQoL, followed by the liver, and then renal. HRQoL at 3 months post-transplantation showed significant improvements from pre-transplant. At 12 versus 3 months, mental health was somewhat better for renal, and almost all dimensions showed significant improvement for liver and lung patients. All patients showed clear improvements after transplantation when mental health was compared with the general population, particularly lung transplant recipients who expressed the greatest improvement. However, they still showed deficits in physical health.

- 10) Eskander, A., et al., *BODE index and quality of life in advanced chronic obstructive pulmonary disease before and after lung transplantation*. *J Heart Lung Transplant*, 2011. [PMID: 21782467](#).

This article describes a prospective cohort study patients with COPD and FEV1<50%. Multiple health-related quality of life measures (SGRQ, SF-36, visual analog scale, standard gamble and EQ-5D) were administered repeatedly over time to 112 patients, of whom 66 were transplanted during the study period. The BODE index was significantly associated with all HRQL measures. Large improvements in HRQL occurred after transplantation, and the magnitude of these improvements was similar in patients with pre-transplant BODE of 5-6 and 7-10.

- 11) Singer, L. G., et al., *Effects of Recipient Age and Diagnosis on Health-related Quality of Life Benefit in Lung Transplantation*. *Am J Respir Crit Care Med*, 2015. **192**(8): p. 965-973. [PMID: 26131729](#).

This was a prospective cohort study that administered HRQL measurements in 845 adults with advanced lung disease who eventually underwent lung transplantation. The instruments used were the St. George's Respiratory Questionnaire (SRGQ), Medical Outcomes Short Form Health Survey 36 (SF-36), and the Euroqol 5D (EQ-5D), Standard Gamble (using a scale of 0-1), and the visual Analog Scale (VAS); scale 0-100). The instruments were administered pre-transplant and every 3-12 months depending on when the subject had a routine clinic visit scheduled. The HRQL measures were used to determine whether QOL benefits differ by recipient age and diagnosis. In 326 subjects, transplantation improved HRQL in all measures: St. George's change of -47 units (95% confidence interval, -48 to -44), 36-Item Short-Form Health Survey physical component summary score of 17.7 (16.5-18.9), EQ-5D of 0.27 (0.24-0.30), Standard Gamble of 0.48 (0.44-0.51), and Visual Analog of 44 (42-47). Age was not associated with differences in HRQL and interstitial lung disease patients experienced a lower HRQL benefit than cystic fibrosis patients. Overall, observed mean changes in HRQL were exceeded the minimally important difference for all measures and changes were far

great than seen with other treatments for advanced lung disease. This study demonstrated the large impact of lung transplantation on HRQL.

- 12) Fatigati, A., et al., *Patterns and Predictors of Sleep Quality Within the First Year After Lung Transplantation*. *Prog Transplant*, 2016. **26**(1): p. 62-69. [PMID 27136251](#).

This study determined patterns and predictors of poor sleep quality and its effects on health-related quality of life in lung transplant recipients one year after transplantation. In 75 lung transplant recipients, the Pittsburgh Sleep Quality Index (PSQI) was administered at baseline, 2, 6, and 12 months post-transplant and self-management and HRQL were measured at 12 months using the Medical Outcomes Short-Form Health Survey 36 (SF-36). Results indicated that sleep quality was relatively stable during the first year post-transplant, that female gender was a predictor of poor sleep (odds ratio = 3.421; P = .026). Poor sleep was only associated with mental health domain in the SF-36. (r = -.348; P < .01).

- 13) Singer, J. P., et al., *Effect of Lung Transplantation on Health-Related Quality of Life in the Era of the Lung Allocation Score: A U. S. Prospective Cohort Study*. *Am J Transplant*, 2016. [PMID 27743488](#).

This prospective cohort study examined changes in health-related quality of life in lung transplant patients from 2010 to 2016 at the University of California, San Francisco. HRQL was assessed pre-transplant and repeatedly up to three years post-transplant in 211 subjects using the SF-12 Physical and Mental Health, Airway Questionnaire-20 Revised, and the Euroqol 5D/Visual Analog Scale utility measures by multivariate linear mixed models jointly modeled with death. The authors also tested changes in LT-Valued Life Activities disability, BMI, allograft function, and 6-min walk test exercise capacity as predictors of HRQL change. HRQL improved for all 5 measures and SF-12 improved Three times the minimally clinically important difference and were durable for up to 3 years after transplant. The authors also identified that the majority of the changes in HRQL were mediated through improvements in physical disability.. Older participants and diagnoses other than CF experienced a lower HRQL benefit than younger participants or those with a diagnosis of CF.

- 14) Smith, P. J., et al., *Depressive symptoms and early mortality following lung transplantation: a pilot study*. *Clin Transplant*, 2017. **31**(2). [PMID 27859626](#).

This study examined the association between depression, quality of life, and short-term mortality in lung transplant recipients. In 66 patients, depression (Patient Health Questionnaire-9; Hospital Anxiety and Depression Scale; Centers for Epidemiologic Studies Depression Scale) and quality of life (UCSD Shortness of Breath Questionnaire; Pulmonary Quality of Life Scale) were assessed prior to transplantation (median 0.9 months [IQR=1.6]) and again approximately 2 weeks following transplantation (median=0.5 months [IQR=0.5]). Greater depressive symptoms assessed shortly after transplant were associated with subsequent mortality (HR=2.17 [1.01, 4.67], P=.048), and this relationship persisted after controlling for primary graft dysfunction, duration of transplant hospitalization, and gender. Pre-transplant depression, history of depression, or pre-transplant quality of life was not associated with subsequent mortality.

#### **Theme IV. Long-term longitudinal studies of HRQL in lung transplant recipients**

- 1) Vermeulen, K.M., et al., *Long-term quality of life in subjects surviving at least 55 months after lung transplantation*. *Gen Hosp Psychiatry*, 2003. **25**(2): p. 95-102. [PMID: 12676422](#).

This study aimed to assess changes in HRQL and psychological status after lung transplantation. The study had a cross-sectional and a longitudinal study design component. In the cross-sectional study, assessment timepoints included subjects who were yet to be transplanted, four and seven months after transplant, and approximately every six months thereafter. Exact numbers of subjects participating in the cross-sectional arm differed at different measurement timepoints and ranged between 37 and 113; 28 subjects were included in the longitudinal arm and were assessed at the same timepoints listed above. Measures included the Nottingham Health Profile (NHP), dyspnea questions, the Karnofsky performance index, questions on activities of daily life (ADLs), the Index of Well-Being (IWB), the State-Trait Anxiety Inventory (STAI) and the Self-rating Depression Scale (ZUNG). Comorbid conditions including BOS, diabetes, hypertension, poor renal function, and hyperlipidemia were collected. Prior to transplant, subjects reported poor HRQL in mobility, energy and sleep domains on the NHP, significant dyspnea, low ability to care for themselves, low ability to perform ADLs, and low well-being IWB). Anxiety and depression scores (STAI and ZUNG, respectively) were similar to or higher than normative population scores. Four months after transplant, significant improvements were identified in mobility, energy, sleep, social isolation and emotional reaction domains of the NHP, dyspnea, ability for self-care, ADL performance, and psychological status. In the longitudinal cohort, NHP scores on all domains remained stable from four through 43 months after transplant. Between 43 and 55 months after transplant, scores in all NHP domains except pain declined, and greater dyspnea, lower well-being, greater anxiety, and greater depression were reported. All comorbid conditions except hypertension increased through time; these comorbidities were associated with worse scores in the NHP energy domain.

- 2) Rutherford, R.M., et al., *Functional status and quality of life in patients surviving 10 years after lung transplantation*. *Am J Transplant*, 2005. **5**(5): p. 1099-104. [PMID: 15816892](#).

This study evaluated quality of life (SF-36) in 10-year survivors after lung transplantation (n=96) and compared their QoL to population normative and chronic illness cohorts. Scores for physical function, role-physical/emotional and general health, but not mental health and bodily pain subscales were significantly lower compared to normative and chronic illness cohorts. Energy and social-function subscale scores were significantly lower than normative cohorts. Long-term survival after lung transplantation is characterized by an absence or delayed development of BOS, low iatrogenic morbidity and preserved mental, but reduced physical health status.

- 3) Myaskovsky, L., et al., *Trajectories of Change in Quality of Life in 12-Month Survivors of Lung or Heart Transplant*. *American Journal of Transplantation*, 2006. **6**(8): p. 1939-1947. [PMID: 16889548](#).

This single center cross-sectional cohort study assessed quality-of-life (QOL) at 1 year after transplant in 199 of 219 surviving adult lung and heart transplant recipients. In comparison to lung recipients, heart recipients showed higher QOL across several domains shortly after transplant, though the groups had similar 1 year post-transplant outcomes. Greater optimism and support from friends predicted better QOL in physical, psychological and social domains. Conversely, avoidant coping strategies predicted poorer physical functioning.



## **Theme V. The effect of therapies and interventions on HRQL**

- 1) Silvertooth, E.J., et al., *Citalopram and quality of life in lung transplant recipients*. *Psychosomatics*, 2004. **45**(3): p. 271-2. [PMID: 15123855](#).

This study evaluated whether citalopram improved depression, anxiety, and HRQL in subjects with depressive symptoms. This was a 12-week randomized, double-blinded clinical trial of citalopram compared to placebo in 27 27 patients with a Beck Depression Index score of  $\geq 15$ . It is not clear whether patients were lung transplant recipients and/ or had chronic obstructive pulmonary disease. The Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale and physical functioning subscale of the Seattle Obstructive Lung Disease Questionnaire were used to assess the treatment at baseline, 6 and 12 weeks. 19 patients completed the trial. Citalopram was more effective than placebo only among patients who had baseline mild to moderate levels of impairment (measured by all three instruments), and was comparable to placebo among patients with more severe impairment.

- 2) Irani, S., et al., *Lung transplant recipients holding companion animals: impact on physical health and quality of life*. *Am J Transplant*, 2006. **6**(2): p. 404-11. [PMID: 16426328](#).

In this cross sectional study, the authors compared overall and health related quality of life, psychological status and physical health between lung transplant recipients who owned pets (n= 46) and those who did not (n= 43). Quality of life was measured with Questions on Life Satisfaction (FLZM), which included general, health-related and summarized life satisfaction modules. Psychological status measures included the Life Orientation Test (LOT), Hospital Anxiety Depression Scale (HAD), and Social Support Questionnaire (F-SozU). Clinical measures included pulmonary function testing, levels of exhaled nitric oxide, need for antibiotic therapy and hospitalizations, creatinine clearance, and body mass index. Pet owners reported higher general and summarized life satisfaction. Psychological status scores in all three measures were also significantly higher for pet owners, except for the subgroup of pet owners less than one year after transplant. That subgroup reported lower HAD scores. No differences were identified in clinical measures between pet owners and non-pet owners.

- 3) Rodrigue, J.R., M.R. Widows, and M.A. Baz, *Caregivers of lung transplant candidates: do they benefit when the patient is receiving psychological services?* *Prog Transplant*, 2006. **16**(4): p. 336-42. [PMID: 17183941](#).

This randomized clinical trial investigated the impact of telephone-based psychological interventions for lung transplant candidates on their caregivers' HRQL. The intervention was 2-3 months of telephone-based QOL or support therapy for lung transplant recipients. Quality of life, mood disturbance and social intimacy outcomes in both patients and caregivers were measured by Quality of Life Inventory (QOLI), Profile of Mood States Short Form (POMS-SF), and Miller Social Intimacy Scale (MSIS), prior to the intervention and at 1 month and 3 months after start of the intervention. The study found that caregivers had higher QOL, lower mood disturbances, and comparable social intimacy to their respective patient-partner; QOL therapy improved QOL vicariously for caregivers in all three outcomes; and patient changes in all three outcomes in response to QOL therapy predicted for caregiver functioning in all three outcomes at 3 months.

- 4) DeVito Dabbs, A., et al., *Evaluation of a hand-held, computer-based intervention to promote early self-care behaviors after lung transplant*. Clin Transplant, 2009. **23**(4): p. 537-45. [PMID: 19473201](#).

This trial evaluated the effect of Pocket PATH<sup>®</sup> (Personal Assistant for Tracking Health) a smartphone intervention developed for patients to record health data, review data trends, and report condition changes on self-care agency, self-care behaviors, and health-related quality of life (HRQOL) between recipients randomized to use Pocket PATH (n=15) versus standard care (n=15) for the first two months following hospital discharge after lung transplantation. Patients in the Pocket PATH group showed significantly higher ratings of self-care agency, performed self-care behaviors at significantly higher rates, and reported significantly better HRQOL than standard care controls. Pocket PATH is more efficacious than standard care in promoting early self-care agency, self-care behaviors and HRQOL in lung recipients. A large-scale randomized controlled trial is needed to test the impact of Pocket PATH on long-term self-care behaviors.

- 5) Santana, M.-J., et al., *Assessing the use of health-related quality of life measures in the routine clinical care of lung-transplant patients*. Quality of Life Research, 2010. **19**(3): p. 371-379. [PMID: 20146009](#).

This randomized controlled trial tested whether including HRQL assessments in routine clinical care of pre- and post-lung transplant outpatients would improve patient-clinician communication, clinical management, and patient health status and HRQL. 108 subjects were randomized to receive the Health Utilities Index self-assessment 2 and 3 (HUI2, HUI3) before each clinic visit and the EQ-5D after and 105 were randomized to standard care. Baseline assessments included the HUI2, HUI3, Hospital Depression and Anxiety Scale (HADS), adherence to medication and exercise, Consumer Assessment of Healthcare Providers and Systems Clinician and Group Survey (CAHPS) and EuroQol (EQ-5D). Outcomes included assessments of tape-recordings of each clinical visit, medical chart review and EQ-5D. It was found that the implementation of this intervention had small effects on patient communication and management and no effect on HRQL outcomes.

- 6) Ihle, F., et al., *Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: a prospective, randomized study*. J Heart Lung Transplant, 2011. **30**(8): p. 912-9. [PMID: 21489819](#).

This was a randomized trial of an inpatient rehabilitation program vs. outpatient physiotherapy in 60 stable lung transplant recipients (30 in each group) more than 1 year post transplant. HRQL measurements including SF-36, SGRQ and Quality of Life Profile for Chronic Diseases were performed before and after the study intervention. Both groups had improvements in exercise capacity. HRQL scores were quite good at baseline and did not significantly improve after the study interventions. Correlations were observed between exercise capacity and all HRQL measures.

- 7) Vivodtzev, I., et al., *Benefits of home-based endurance training in lung transplant recipients*. Respir Physiol Neurobiol, 2011. **177**(2): p. 189-98. [PMID: 21333761](#). The authors tested the hypothesis that a 3-month, thrice weekly, home-based exercise training on cycloergometer would improve exercise tolerance, muscle function and quality of life in lung transplant recipients. Peak aerobic capacity (VO<sub>2</sub> peak), endurance time, minute ventilation (VE), quadriceps strength, percentage of type 1 fiber, fiber diameter, and HRQL (assessed by the Chronic Respiratory Questionnaire) were collected before and after the exercise training in 12 lung transplant recipients and 7 healthy age-matched subjects. Results showed that lung transplant recipients who began the training with only moderate

muscle dysfunction and a shorter time after-transplant were able to significantly improve endurance time, VO<sub>2</sub> peak, VE and fiber diameter, though only endurance time was comparable to that of baseline healthy subjects. Meanwhile, HRQL measures in LT recipients showed that only dyspnea significantly improved, while fatigue showed a trend to improvement.

- 8) Langer, D., et al., *Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial*. Am J Transplant, 2012. **12**(6): p. 1584-92. [PMID: 22390625](#).

This study investigated whether 3 months of supervised exercise training improved functional recovery and cardiovascular morbidity of patients up to 1 year after lung transplantation (n=21) compared to a control intervention (n=19). Minutes of daily walking time (primary outcome), physical fitness, quality of life and cardiovascular morbidity were compared between groups adjusting for baseline assessments. Year daily walking time group (p = 0.006), quadriceps force (p = 0.001), 6-minute walking distance (p = 0.002) and self-reported physical functioning (p = 0.039) were significantly higher in the intervention group. Average 24 h ambulatory blood pressures were significantly lower in the treated patients (p ≤ 0.01). Based on these results patients should be strongly encouraged to participate in an exercise training intervention after lung transplantation.

- 9) Robertson, A.G., et al., *Anti-reflux surgery in lung transplant recipients: outcomes and effects on quality of life*. Eur Respir J, 2012. **39**(3): p. 691-7. [PMID: 21778169](#).

The authors assessed the safety and effects on quality of life of laparoscopic Nissen fundoplication, an anti-reflux surgery, on 16 lung transplant recipients diagnosed with gastro-oesophageal reflux disease (GORD). There have been no previous studies of GORD symptoms and only one study of quality of life pertaining to the impact of fundoplication on the lung transplant population. Measures used include morbidity, presence of serious complications, patient-reported overall satisfaction, DeMeester Reflux Questionnaire, Reflux Symptom Index (RSI), Gastrointestinal Quality of Life index (GIQLI), body mass index (BMI) and lung function (BOS grade, FEV<sub>1</sub>). After 6 months post-operation, RSI, GIQLI and DeMeester scores improved significantly and BMI decreased significantly. This study demonstrated that this intervention is not only safe for selected lung transplant recipients, but also effective in reducing GORD symptoms and improving HRQL.

- 10) Brunner, S., et al., *Feasibility of whole-body vibration as an early inpatient rehabilitation tool after lung transplantation – a pilot study*. Clin Transplant, 2016. **30**(2): p. 93-98. [PMID: 26589261](#).

This study examined the effect of whole-body vibration (WBV) on 6 minute walk distance, pulmonary function, maximal workload, and health-related quality of life on lung transplant recipients. Of 26 lung transplant post-operative lung transplant recipients, 10 participated in and completed the study. All 10 subjects improved in 6MWD, pulmonary function, and maximal workload (measured in Watt). The SF-36 was used to measure changes in HRQL. Subjects only showed an improvement in the general medical health scale of the SF-36. Other aspects of the SF-36 showed improvement, but did not reach statistical significance.

## **Theme VI. Instrument validation and methodology**

- 1) Stavem, K., et al., *Health-related quality of life in lung transplant candidates and recipients*. Respiration, 2000. **67**(2): p. 159-65. [PMID: 10773787](#).

The purpose of this cross-sectional postal survey was to compare the health-related quality of life of lung transplant recipients (n=31) with lung transplant candidates (n= 15) using lung-specific and general instruments, and to assess the reliability and validity of the St. George's Respiratory Questionnaire (SGRQ), a lung-specific health status instrument; the Short Form 36 (SF-36), a general measure, and the Hospital Anxiety and Depression scale (HAD). The SGRQ scores were significantly higher ( $p < 0.05$ ) for transplant recipients in the impacts and activity dimensions and the total score than for candidates. SF-36 scores showed a similar improvement in all subscales of the SF-36 except bodily pain. Internal consistency for all dimensions of the SGRQ, SF-36, and HAD were acceptable with Cronbach's alpha ranging from 0.77-0.95. Patients surviving lung transplantations can expect considerable improvement in most dimensions of health-related quality of life using both lung-specific and general measures.

- 2) Matthees, B.J., et al., *Use of complementary therapies, adherence, and quality of life in lung transplant recipients*. *Heart Lung*, 2001. 30(4): p. 258-68. [PMID: 11449212](#).

This single center cross-sectional study used a mailed survey to study the use of complementary and alternative medicine (CAM), quality-of-life (QOL), and adherence information. This study included 99 respondents from the 145 surviving recipients that had lung transplant during a 13-year period. The majority (88%) of recipients used at least 1 form of CAM (median, 2; range, 0-17) which typically consisted of prayer (68%), support groups (43%), and relaxation techniques (31%). Only 44% of users reported discussing CAM with their providers. The study did not detect many differences between the small non-CAM group and the larger CAM group. Various types of CAM use showed an association with education, high symptom burden, female sex, and depression symptoms.

- 3) Singer, L.G., J. Theodore, and M.K. Gould, *Validity of standard gamble utilities as measured by transplant readiness in lung transplant candidates*. *Med Decis Making*, 2003. 23(5): p. 435-40. [PMID: 14570301](#).

This was a cross-sectional study of standard gamble (SG) utility for current health in 57 patients referred for lung transplantation. The aim was to validate the SG by correlating SG scores with self-reported readiness for transplant listing (ie. acceptance of the real-life gamble of transplantation). Utility scores were significantly higher in patients who were not ready for listing than in those who were ready or listed. All transplant-ready patients had utilities  $\leq 0.85$  for current health which was less than the maximum expected utility of transplantation, supporting the validity of SG measurement.

- 4) Lobo, F.S., C.R. Gross, and B.J. Matthees, *Estimation and comparison of derived preference scores from the SF-36 in lung transplant patients*. *Qual Life Res*, 2004. 13(2): p. 377-88. [PMID: 15085910](#).

The purpose of this study was to estimate and compare preference scores derived from MOS Short Form-36 (SF-36) data for a sample of lung transplant patients using three methodologies: Fryback, Nichol and Brazier. Data were gathered from 99 lung transplant recipients using a mail survey, which included the SF-36 and other health-related quality of life (HRQL) measures. The mean preference score for the sample was 0.643 (range 0.43–0.83), 0.765 (range 0.36–1.0), and 0.697 (range 0.33–1.00) for Fryback, Nichol and Brazier methods, respectively. Correlations between the derived scores and visual analogue ratings of health (0.58–0.68) and pulmonary symptoms (–0.59 to –0.62) were moderate to good and in the expected directions. The mean preferences of patients grouped by

levels of dyspnea, depression symptoms, illness burden, and self-rated general health differed significantly with all methods and supported the construct validity of the derived scores as measures of preference. The Nichol and Brazier scores, both derived with standard gamble utilities, were generally higher than Fryback scores, which are not utility-based. Given the popularity of the SF-36, these three methods could be useful where direct elicitation of preferences is not feasible. Researchers must be cognizant of the derivation method used, as absolute preference levels, hence quality adjusted life years (QALYs), will differ by method.

- 5) Vasiliadis, H.M., et al., *A cost-effectiveness and cost-utility study of lung transplantation*. *J Heart Lung Transplant*, 2005. **24**(9): p. 1275-83. [PMID: 16143245](#).

This paper described a cost-effectiveness and cost-utility analysis of lung transplantation in the province of Quebec, Canada. Standard gamble utilities for current health were measured in a cross-sectional cohort of 34 waiting list patients and 71 lung transplant recipients. Survival for each disease group was measured in a longitudinal cohort of Quebec patients. The economic base case analysis used a health care system perspective. The mean QALYs gained from transplant was 2.19, with costs/QALY of US \$46,631, and significant variation across diagnostic groups. Patients in the CF and bronchiectasis group gained most from transplant. Results were sensitive to variations in clinical factors, utility and costs.

- 6) Santana, M.J., et al., *The construct validity of the health utilities index mark 3 in assessing health status in lung transplantation*. *Health Qual Life Outcomes*, 2010. **8**: p. 110. [PMID: 20920198](#).

The authors tested the construct validity of the Health Utilities Index Mark 3 (HUI3) cross-sectionally in 103 pre- and 110 post-lung transplant recipients. The HUI3, EQ-5D, Hospital Anxiety and Depression Scale (HADS), 6 minute walk, and FEV1 were assessed at baseline. Investigators made a consensus set of 90 *a priori* hypotheses of expected direction and degree of association between HUI3 and all other measures. After data analysis, 43 hypotheses were found to be correct, 31 were slightly lower than predicted and 7 were significantly higher. These results support the cross-sectional construct validity of HUI3 in a lung transplant population.

- 7) Singer, J.P., et al. *Development and validation of a lung transplant-specific disability questionnaire*. *Thorax*, 2014. **69**(5):437-42 [PMID: 24355825](#).

The purpose of this study was to shorten and validate the 32-item Valued Life Activities (VLA) disability questionnaire for use specifically in lung transplantation. In this prospective cohort study of 140 lung transplant candidates, subjects completed a survey and physical assessment battery before and repeatedly after lung transplantation. The authors evaluated construct validity by assessing the correlation between VLA disability and functioning assessed by the six-minute walk test and FVC% predicted as well as between VLA disability and HRQL assessed by the SF-12 Physical Function subscale. Responsiveness was assessed through percent change and effect size calculations in 84 subjects who completed evaluations before and three months after transplant. The authors reduced the 32-item VLA scale to a 15-item Lung Transplant Valued Life Activities (LT-VLA) scale. The LT-VLA demonstrated internal consistency, construct validity, excellent correlation with the 32-item VLA, and responsiveness to change in clinical condition. This is the only instrument developed specifically for use in lung transplant recipients.

- 8) Hoffman, B. M., et al., *Development and psychometric properties of the Pulmonary-specific Quality-of-Life Scale in lung transplant patients*. J Heart Lung Transplant, 2015. **34**(8): p. 1058-1065. [PMID 25980570](#).

This study demonstrated the reliability, validity, and ability of the Pulmonary-specific Quality-of-Life Scale (PQLS) to detect changes in HRQL in patients with advanced lung disease. Data was taken from a dual-site randomized controlled trial of coping skills training in 389 lung transplant candidates. The PQLS was internally consistent (Cronbach's alpha for the total scale and three subscales, > 0.8). Convergent validity was established through strong correlations between PQLS Total Score and SF-36 and disease-specific SOBQ. Factor analyses identified three sub-scales of the PQLS that were labeled Physical, Psychological, and Task Interference and all of which were observed to be internally reliable and demonstrated convergent validity with regard to measures of mood and anxiety. All sub-scales were shown to be sensitive to change in quality of life after lung transplantation.

### **Theme VII. HRQL as a predictor of clinical outcomes**

- 1) Vermeulen, K.M., et al., *Pre-transplant Quality of Life Does Not Predict Survival After Lung Transplantation*. The Journal of Heart and Lung Transplantation, 2008. **27**(6): p. 623-627. [PMID: 18503961](#).

This study examined whether HRQL and psychological measures in transplant candidates predicted survival after lung transplantation. In this study, 200 subjects were evaluated before transplant and at 1, 4, and 7 months after transplant and every 6 months thereafter. Instruments included the Nottingham Health Profile (NHP), the State-Trait Anxiety Inventory (STAI), the Self-Rating Depression Scale (SDS), the Karnofsky Performance Scale and the Index of Well-being (IWB). Analyses were adjusted for age, gender, waiting time for transplant, and underlying diagnoses. Pre-transplant health-related quality of life scores were worse compared to normative population scores, particularly lower energy and mobility (measured by NHP), greater depression and lower general health status (measured by the Karnofsky Performance Scale). Notably, neither pre-operative quality of life scores nor baseline characteristics predicted survival after transplant.

### **Theme VIII. Reviews and Editorials**

- 1) Yusen, R.D. *Lung transplantation outcomes: the importance and inadequacies of assessing survival*. Am J Transplant, 2009. 9(7): p. 1493-4. [PMID: 19656141](#).

This editorial argues that measuring survival alone fails to fully quantify the efficacy of lung transplantation. In addition, the editorial highlights the risk of survivor bias with resultant inflated estimates of HRQL benefit if only those subjects well enough to complete HRQL surveys are included in studies. The author also notes that systematic assessment of HRQL within national and international transplant systems is a complicated endeavor that will require significant resources.

- 2) Yusen, R.D., *Technology and outcomes assessment in lung transplantation*. Proc Am Thorac Soc, 2009. 6(1): p. 128-36. [PMID: 19131538](#).

This publication reviews important studies in lung transplantation that address survival and HRQL outcomes. The author points out the limited evidence base and conflicting information regarding survival and HRQL outcomes in lung transplantation. The review identifies limitations in the existing

literature and identifies important areas for future investigation. The author suggests that studies of lung transplantation and its related technologies should assess transplant efficacy with tools that integrate both survival and HRQL data.

- 3) Yusen, R.D. *Survival and quality of life of patients undergoing lung transplant*. Clin Chest Med, 2011. 32(2): p. 253-64. [PMID: 21511088](#).

This publication reviews important studies in lung transplantation that address survival and HRQL outcomes. In addition to highlighting key studies, the review identifies limitations in the existing literature and identifies important areas for future investigation. The author suggests that studies of lung transplantation and its related technologies should assess transplant efficacy with tools that integrate both survival and HRQL data.

- 4) Singer, J.P., et al., *A thematic analysis of quality of life in lung transplant: the existing evidence and implications for future directions*. Am J Transplant, 2013. 13(4): p. 839-50. [PMID: 23432992](#).

The authors conducted a systematic literature review of publications (1983 - 2011) of HRQL in lung transplantation. A literature review identified 73 publications. The authors then performed comparative consensus-based thematic analysis out of which 7 core themes emerged: (1) Determinants of HRQL; (2) Psychosocial factors in HRQL; (3) Pre- and post-transplant HRQL comparisons; (4) Long-term longitudinal HRQL studies; (5) HRQL effects of therapies and interventions; (6) HRQL instrument validation and methodology; (7) HRQL prediction of clinical outcomes. The publications showed substantial heterogeneity in methodology and approach, and relatively few studies assessed HRQL longitudinally within the same persons. The authors concluded that lung transplantation significantly and substantially improves HRQL, predominantly in domains related to physical health and functioning.

- 5) Singer, J.P., et al. *Quality of life in lung transplantation*. Semin Respir Crit Care Med, 2013. 34(3): p. 421-30. [PMID: 23821515](#)

This review offers the reader a brief primer on patient-reported outcomes as well as defining, measuring, and interpreting HRQL measures. The review also evaluates key contemporary studies in lung transplantation including studies focused on the caregivers of lung transplant recipients. The review identifies limitations in the existing literature and provides recommendations on future investigation.

- 6) Seiler, A., et al., *A systematic review of health-related quality of life and psychological outcomes after lung transplantation*. J Heart Lung Transplant, 2016. 35(2): p. 195-202. [PMID 26403492](#).

A systematic review was conducted to boost evidence regarding measures of HRQL and psychological outcomes after lung transplant and to summarize HRQL and psychological outcomes after lung transplant. A literature review was performed to identify validated and standardized instruments used for assessing HRQL and psychological outcomes after lung transplant. Abstracts and publications were also reviewed for investigation of HRQL and lung transplant. Based on 371 records, 112 were excluded following title and abstract screening. Screening for additional references generated 20 more possible articles. Of the resulting 279, a total of 63 met all inclusion criteria. From these eligible studies, the authors identified HRQL as being widely accepted as an

important outcome measure in lung transplant. Additionally, the authors concluded that lung transplant does confer an improvement in HRQL and mental health post-transplant.