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Quality of Life in Lung Transplantation

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Abstract

Improving health-related quality of life is an important goal of lung transplantation. In this review, we describe background concepts including definitions, measurement and interpretation of health-related quality of life (HRQL) and other patient-reported outcomes. Lung transplantation is associated with dramatic and sustained improvements in health-related quality of life, particularly in measures of physical health and functioning. Physical rehabilitation may augment the early improvements in HRQL, while bronchiolitis obliterans syndrome and psychological conditions have a negative impact. More research is needed, particularly longitudinal, multicenter studies, to better understand the trajectory and determinants of HRQL after lung transplantation, and the impact of targeted interventions to improve HRQL.

Keywords

Lung transplantation; health-related quality of life; utility; disability; patient reported outcomes

Introduction

For many illnesses, technological advances over the last century have driven an evolution in the conceptualization of health. Initially defined in terms of survival alone, concepts of health next focused on freedom from disease. Towards the end of the 20th century, concepts of health evolved further to focus on the ability to perform activities of daily living and finally to emphasizing themes of well-being and quality of life. Today, the World Health Organization defines health as “physical, mental, and social well-being, and not merely the absence of disease and infirmity.”[1] In the field of lung transplantation, however, this evolution has been compressed into just three decades. Indeed, prior to 1984, physicians struggled with surgical and medical approaches that would allow for lung transplant recipient survival beyond the immediate perioperative period. With remarkable and rapid advances, the primary clinical aims of lung transplantation quickly evolved to emphasize both improved survival and improved quality of life (QOL).[2]

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Patients, clinicians, and investigators alike recognize that a primary clinical aim of lung transplantation is to improve QOL. Indeed, many patients consider lung transplantation for palliation of symptoms and improvement of QOL even when extended survival is not assured. Despite its clinical primacy, however, translating the existing biomedical literature evaluating QOL in lung transplantation into clinical practice remains challenging.[3] This review aims to define QOL, demystify quantitative instruments used to measure QOL, and highlight key studies from the biomedical literature with important clinical implications.

Background: Patient Reported Outcomes and Health Related Quality of Life

The Importance of Assessing Patient-Reported Outcomes

Pulmonologists well appreciate that measures of lung function, such as FEV_1, correlate poorly with exercise capacity.[4] Further, for some respiratory diseases such as chronic obstructive pulmonary disease (COPD) or asthma, even relatively small decrements in FEV_1 may be associated with significant symptomatic impairment[5]. Recognizing the dissociation, at times, between measures of lung function and patients' perception of the impact of their disease on their lives, clinicians also assess patients' perceived disease burden at each clinic visit. This assessment includes pulmonary specific questions such as breathlessness, wheezing, and cough, as well as potentially related extra-pulmonary questions such as mobility and functioning, sleep-quality, and mood. Akin to the taking of a comprehensive clinical history, quantitative measures employed in research to assess the patient's perspective of their own health status are collectively referred to as Patient Reported Outcome (PRO) instruments. By definition, a PRO is a measure of a subject's health status directly elicited from that subject.[6] PROs range from unidimensional symptom scales such as the Baseline Dyspnea Index[7] (BDI), the Medical Research Council Dyspnea Scale[8] (MMRC), and the UCSD Shortness of Breath Questionnaire[9] to multidimensional health-related quality of life (HRQL) instruments.

Health Related Quality of Life: A Conceptual Framework

Quality of life instruments are among the most well-known PROs. *Health-related* QOL can be conceptualized as the aggregate effects of health, illness and illness' consequent medical therapy on QOL.[10] Indeed, HRQL is just one domain of the larger multi-dimensional conceptual construct of QOL which, itself, has multiple domains including factors such as access to basic needs such as food, water, housing; financial status; social support; spirituality; physical environment; and health.[10] The World Health Organization (WHO) defines QOL as an "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."[1] Within this WHO definition of QOL, the word "perception" is important. It underscores that in order to measure QOL and its subdomains like HRQL, subject perceptions must be elicited. Typically, the elicitation of subject or patient perceptions is accomplished through structured questionnaires referred to as instruments. Like QOL, HRQL is also multi-dimensional by definition and encompasses domains including symptoms, physical functioning, cognitive performance, psychosocial conditions, emotional status, and adaptation to disease, among others.[11]

Measuring Health-Related Quality of Life

The theoretical constructs underpinning HRQL drive the development of instruments used to measure it.[10] Further, since HRQL is, by definition, multidimensional, questions in HRQL instruments are explicitly included to test the impact of health and illness on each dimension. For example, the Medical Outcomes Survey Short Form-36 (SF-36)[12] is a generic HRQL instrument designed to be applicable to all subjects whether healthy or ill from any disease. Thus, SF-36 questions (referred to as items) are designed to test all areas of life (domains) that may be impacted by illness. These domains include physical functioning, emotional status, pain, energy/fatigue, and others. Given the multidimensional nature of HRQL, instruments used to measure it are designed to be administered whole.

Instruments for measuring HRQL may be categorized broadly as either generic or specific for a particular disease.[10] Both generic and disease-specific instruments have advantages and limitations. Notably, the advantages of one category typically offset the limitations of the other. Therefore, it is common for studies to utilize both generic and disease-specific instruments in HRQL assessment. Indeed, generic instruments are explicitly designed to be applicable across diseases as well as healthy (normative) populations. One advantage of this broad applicability is that the impact on HRQL of one disease can be compared to other diseases. Further, since disease treatments may cause systemic side effects, generic HRQL instruments may better detect the impact of these side effects than HRQL instruments focused on a specific organ system. Some generic instruments have established normative values allowing the impact of a disease on HRQL to be quantified against healthy populations. Despite these advantages, generic instruments have inherent limitations. Their very breadth may decrease their sensitivity for detecting changes in HRQL in diseases that affect HRQL domains unevenly. For example, lung transplant recipients with advanced chronic allograft dysfunction suffer from profound dyspnea. Very few items in generic instruments, however, focus on respiratory symptoms. Therefore, while generic instruments will likely detect differences in subjects with advanced allograft dysfunction compared to those with perfect allograft function, they may fail to discriminate smaller but clinically significant differences in respiratory specific symptoms.

In contrast, disease-specific HRQL instruments are designed to focus on QOL as it is impacted by a specific disease and its treatments.[10] Although specific for a disease, these measures are also multidimensional. Disease-specific instruments complement the advantages and disadvantages of generic instruments. Since all the items in disease-specific instruments are directly related to the disease of interest, they have better ability to discriminate among individuals with differing degrees of disease-specific impairment. They may also be more responsive to treatments resulting in organ-specific physiologic changes. Disease-specific instruments, however, have clear disadvantages; data from these instruments cannot be compared to other diseases and they may be less sensitive to impact of medical therapies causing systemic side effects.

Interpreting HRQL instruments

When interpreting HRQL outcomes, several important concepts should be considered. First, studies may demonstrate statistically significant differences in HRQL that are not actually

clinically relevant. To determine clinical relevance, some instruments have a defined Minimum Important Difference (MID), which is the smallest change in score that is considered meaningful to a patient and/or is associated with objective measures of disease severity. For studies employing instruments that lack a MID, the studies should provided estimates of what HRQL scores might be considered clinically relevant. This guidance may be provided by anchoring scores to results from other diseases. Second, studies frequently include HRQL measures as secondary outcomes. Especially common in clinical trials, it is common for these studies to identify clinically relevant changes in HRQL scores that fail to achieve statistical significance. Before discounting these results as "negative" for lack of statistical significance, it should be considered that the study may not have been powered to detect differences in secondary outcomes. Third, HRQL data is frequently presented as a single number or "summary score". This is common in clinical trials. Since HRQL is, by definition, multidimensional, interpreting these summary scores beyond making an assessment of "better" or worse" is difficult. In addition to summary scores, some HRQL instruments have profile or dimension scores that isolate specific health domains. For example, the SF-36 has profile scores for each of the eight health domains evaluated: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. It also has physical and mental summary scores that cluster the health domains relating to either physical or mental HRQL.[12] Therefore, the decision to present HRQL results in the form of summary scores or profile scores is frequently driven by the study aims. Proponents of summary score scores argue that evaluating the impact of a clinical intervention on multiple domains creates confusion. By comparing single summary scores, a clearer picture of the efficacy of one therapeutic approach versus another is established. Thus, clinical trials evaluating medical technologies commonly use summary scores. Proponents of profile scores argue that profile scores better reflect the multi-dimensional nature of HRQL. For clinicians profile scores may identify specific domains especially affected by a disease (e.g., pain or emotional health) that may aid in developing therapeutic strategies. Fourth, it is not unusual for interventional studies to demonstrate significant changes in physiologic parameters without demonstrating changes in HRQL and vice versa. While these results may appear discordant, it is important to recall that HRQL is multidimensional. For example, inherent to their design, respiratory-specific instruments should detect changes from interventions that effect positive changes in dyspnea, cough, exercise capacity, or depression/anxiety, even if measures of lung function remain unchanged. Thus, HRQL endpoints complement physiological endpoints, and they allow for the assessment of outcomes that matter most to patients.

Related to multidimensional HRQL instruments, health utility measures are a specific type of summary score which provide a measure of overall patient preference. Utility measures are typically scaled from 0 to 1, where 0 denotes death and 1 denotes "perfect health" as this is understood by the study subject. Some utility instruments allow scores of less than 0, indicating a health state worse than death. Although utilities are frequently estimated using a visual analog scale where the respondent simply marks a point on a line between 0 and 1, the underlying theoretical construct dictates than some sort of trade-off or gamble exercise be used to ensure that the value obtained is meaningfully anchored by death and perfect health. This trade-off exercise captures patients' willingness to undergo risk to reduce

existing impairment from disease. While utilities can provide a useful summary measure of HRQL, they can also be multiplied by survival to derive "quality-adjusted survival".[13] For example, two years of life lived with a utility of 0.5 would correspond to one quality-adjusted life year (QALY), equivalent to one year lived in perfect health. Health utilities are conceptually related to HRQL but are not wholly interchangeable. While utility measures are used as HRQL measures, their item content rarely reflects the multidimensional nature of HRQL.

A major limitation of studies of HRQL in lung transplant is the failure to formally account for subjects who die or otherwise drop out.[14] HRQL estimates will be biased towards more favorable results if those who die or drop out had worse HRQL than those who remained in the study. There are a variety of modeling techniques to account for this bias but research studies should be explicit on the handling of this important "missing" data.[15] Reporting of quality-adjusted survival is another way to integrate the two important outcomes of survival and HRQL.[13]

Health Related Quality of Life and Lung Transplantation

The impact of lung transplantation on HRQL

Overall, lung transplantation confers clinically meaningful and statistically significant improvements in HRQL. Indeed, this HRQL improvement is substantial and consistently observed regardless of whether HRQL is measured by generic[16–24] or respiratory-specific HRQL instruments[25–30] or by utility measures[20,25,31–35]. When pre-transplant HRQL is compared to normative populations, impairments tend to be greatest in the conceptual domains related to physical functioning and less so in those related to mental health. In most studies, however, all domains are affected to at least some degree.[36] After transplant, the greatest HRQL improvements cluster in the domains related to physical functioning.[30,36–38]

Despite the systemic effects of immunosuppressants and development of often serious comorbidities, lung transplantation results in large improvements in generic HRQL. The most commonly used generic HRQL instrument in lung transplantation is the SF-36. An updated version of the SF-36 has a theoretical range of 0–100 and population normative scores of 50 with a standard deviation of 10.[12] In addition to scores for each of the 8 health domains tested, the SF-36 version 2 also features physical and mental summary scores (PCS and MCS) also featuring normative scores of 50 with 10 point standard deviations. A 4-point change in the SF-36 is generally considered clinically significant.[39] Studies have employed the SF-36 in both Europe and the United States. Kugler et al. performed a longitudinal, repeated measures design study in Germany. In that study, generic HRQL was measured in 61 subjects with the SF-36 before and at 8 weeks, 6 months, and 12 months following lung transplantation.[29] By six months after transplant, subjects experienced improvements of ≥20 points in the physical functioning, role physical, and general health domains. Between 6 and 12 months, little additional improvement was observed. This early improvement in HRQL within the first 6 months following transplant were supported by a U.S. based study conducted between 1999 and 2003.[40] In this study, 106 lung transplant recipients who survived the first two months after surgery completed the SF-36 at 2, 7, and 12 months after transplant. Lung transplant recipients exhibited substantial and significant improvements in

most SF-36 health domains (except for mental health) between 2 and 7 months after transplant. Little to no change, however, was observed between 7 and 12 months. The authors employed a mixed-effects statistical approach that explicitly accounted for missing data. Further, their results were robust across sensitivity analyses accounting for subjects who had died. Most recently, the first multicenter study testing impact of lung transplant on HRQL as a secondary outcome confirmed previous findings. In a U.S. multi-center, prospective, randomized controlled trial of cytomegalovirus prevention, 131 adult subjects were asked to complete the SF-36 before and repeatedly at 3, 6, 9, and 12 months after transplant.[41] Finlen-Copeland *et. al* employed a mixed effects modeling approach that accounted for multiple measures over time and could accommodate missing data. Instead of highlighting domain specific results, the authors presented SF-36 physical and mental summary data (PCS, MCS) to facilitate interpretation. They identified that lung transplant conferred a large (10.9 points) and significant improvement in SF-36 PCS HRQL. The rate of improvement was greatest within the first 3 post-operative months but continued throughout the first year. Notably, transplant did not impact SF-36 MCS scores, which remained below population norms. When analyzed by individual domains, the lack of improvement was largely explained by the mental health and vitality domains. This lack of change in mental HRQL domains is consistent with prior studies.[22,25,37,42] Contrary to these recent findings, however, prior studies identified mental HRQL is frequently comparable with normative population values suggesting there is little room for improvement after transplant.[16,38,43–45] Other studies utilizing a variety of generic HRQL instruments have also demonstrated clinically and statistically significant improvements.[17,18,21,23,25,27,32–35,44,46–50] Lastly, following transplant, pain may be worsened[19,30,43] but tends to improve over time[29,47].

As observed in generic HRQL measures, lung transplantation improves respiratory-specific HRQL. The most frequently employed respiratory-specific HRQL instrument is the St. George's Respiratory Questionnaire (SGRQ).[26–30,44,51–53] The SGRQ was originally designed for use in COPD. It has a theoretical range of 0–100; higher scores denote worse HRQL. The instrument affords a summary score and scores for three domains: symptoms, activity, and impacts (including social functioning and psychological disturbances caused by COPD). A change of 4 points is considered clinically significant.[54] In a recently published report from the University of Toronto, 55 subjects with COPD completed internet-based HRQL questionnaires before and at least once in the first year after lung transplant.[51] The authors divided patients into groups based on severity of BODE Scores[55] (5–6 versus 7–10). Before transplant, subjects reported markedly impaired respiratory-specific HRQL (SGRQ total score 62.5 ±13.0 for those with BODE Scores 5–6 and SGRQ total score 72.6 ± 9.7 for those with BODE Scores 7–10). At a mean of 4 months (range 2–12) after transplant, SGRQ scores improved dramatically with both groups reporting a statistically significant improvement of 33 points (8 times the MID). Similar findings were observed for each of the three domain scores and persisted when the worst possible scores were assigned to patients who died after transplantation. In addition to the SF-36, Kugler, et al. also administered the SGRQ to 61 subjects before and repeatedly after transplant.[29] HRQL was severely impaired before transplant in the total score (range 68–88) and in each domain score and improved throughout the first year after transplant (range 15–26 points 1-year after transplant).

Beyond the first post-operative year, the trajectory of HRQL becomes less predictable. Some studies report HRQL remains stable following the first year after transplant[21,49], whereas other report it worsens.[56,57].To date, limitations in the existing literature make it difficult to provide reliable estimates past one year. Survivorship bias, loss to follow-up, a preponderance of cross-sectional study designs, and a very limited number of cumulative subjects assessed beyond the first transplant year conspire to preclude robust estimates. With these caveats in mind, however, a limited number of studies evaluated HRQL in subjects surviving more than three years after transplant. In a prospective cohort study of heart and lung transplant recipients, Kugler and colleagues measured generic HRQL (SF-36) at the time of regularly scheduled clinic visits in 170 patients before and repeatedly after cardiothoracic transplantation.[29] Of note, subjects were only included if they survived the first-year after transplant. HRQL data were collected on 72 lung transplant recipients surviving to three-years after transplant and, of these, 48 provided data five-years after transplant. At three-years after transplant, HRQL was nearly equivalent to population normative scores in psychosocial, vitality, pain, and general health domains. Scores were approximately 8 points lower than population normative scores in physical functioning and role physical domains. Notably, statistical tests for differences were not performed. At five years after transplant, HRQL scores in psychosocial and vitality domains remained nearly equivalent to population norms. HRQL impairments increased in physical domains including physical functioning, role physical, pain, and general health. Of clinical relevance, impairments in HRQL never came close to the levels of HRQL impairments reported before transplant. The authors identified that bronchiolitis obliterans syndrome (BOS), lack of family support, and a failure to return to work were all negative predictors of poorer HRQL. Rutherford and colleagues evaluated HRQL (SF-36) in 21 of 22 lung transplant recipients surviving at least 10 years after transplant (median 12.1; range 10.4–16.0).[56] Of the cohort, 5 (24%) had BOS grade 2 or 3. HRQL scores were compared to both published population normative scores as well as scores of those living with other chronic illnesses. Compared to health populations and those living with chronic illnesses, these long term survivors reported poorer HRQL in all physical domains and the role emotional psychosocial domain. Despite their poorer HRQL relative to other chronically ill populations, their scores remained better than those of wait listed candidates from other studies. Although subject to numerous sources of bias, these data support that for years after surgery, for those patients capable of returning to transplant clinic, the HRQL benefit from lung transplant is durable.

A notable limitation in applying the existing literature to contemporary U.S. populations is that in 2005, the system of organ allocation (Lung Allocation Score [LAS]) was overhauled.[58] This overhaul dramatically increased the medical acuity of patients undergoing lung transplant and contributed to the trend of providing lung transplantation to an increasingly older population.[59] This shift in recipient characteristics raises the possibility that estimates of the effect of lung transplant on HRQL may no longer valid. Published abstracts of LAS-era U.S. populations, however, continue to demonstrate that lung transplant results in substantial and significant improvements in both generic and respiratory-specific HRQL.[48,60]

The studies examining whether transplant type affects HRQL outcomes are mixed. Only seven published studies examined this important topic. On the whole, it appears that HRQL

may be better amongst recipients of bilateral and heart-lung transplant compared to single-lung transplant. A European multicenter study administered the EuroQOL 5D and Visual Analog Scale health-utility instruments to a cross-section of 255 lung transplant recipients.[31] Recipients of bilateral- (n=79) and heart-lung (n=70) transplants reported better EQ5D and VAS scores than recipients of single-lung transplants (n=106) (p=.001). These differences in scores were large enough to be considered clinically important. A lack of adjustment for potential confounders, however, such as age and diagnostic indication for transplant as well as the sampling technique of surveying only clinic attendees limits these data. A separate cross-sectional study utilized the Standard Gamble (SG) utility measurement administered to 90 lung transplant recipients also at the time of regularly scheduled clinic appointments.[34] Recipients of bilateral- and heart-lung transplants reported significantly better SG scores than recipients of single-lung transplants. At this center, the indication for transplant primarily drove transplant type raising the potential for confounding by both diagnostic indication and age. Not all studies, however, support improved HRQL in recipients of bilateral- versus single-lung transplantation. Indeed, Vasiliadis and colleagues showed recipients of bilateral-lung transplant reported poorer HRQL in the SF-36 domains of general health, vitality, and social functioning compared to recipients of single-lung transplant.[22] Recently, Finlen-Copeland and colleagues reported that transplant type did not impact the HRQL benefit from lung transplantation.[41] Unique in the literature, their modeling approach to assess the impact of transplant type on HRQL outcomes accounted for covariates including age, gender, and indication for transplant (transplant indication excluded cystic fibrosis since these patients uniformly received bilateral transplants). Recipients of both single-and bilateral-lung transplants experienced large improvements in generic HRQL (SF-36 PCS). Between these two groups, there was no statistical difference HRQL scores (p=0.30). Notably, while not statistically significant, the SF-36 PCS scores in recipients of bilateral-lung transplant were approximately 6+ points higher than recipients of single-lung transplants. It remains to be determined whether HRQL differences by transplant type will be observed with larger sample sizes or respiratory-specific HRQL instruments that may be more sensitive to differences in lung function.

Albeit limited to only 6 studies, the evidence supports that patients undergoing lung transplantation for cystic fibrosis experience greater improvement in HRQL compared to other disease indications for transplant.[20,22,41,50,53,61] These findings do not detract from the clear evidence that patients undergoing lung transplant for all disease indications experience large and early improvements in generic and respiratory-specific HRQL. Data remains too limited to draw conclusions on whether HRQL outcomes differ by age or gender.

Determinants of HRQL after lung transplantation

Perhaps not surprisingly, chronic allograft dysfunction and/or BOS is strongly associated with poorer HRQL.[23,26,34,44,53,62–65] In a combined cross-sectional and longitudinal study of the impact of BOS on HRQL, van den Berg, *et al.* identified that BOS was associated with poorer generic HRQL.[64] The authors used the Nottingham Health Profile instrument. They defined BOS as either a decrease in FEV_1 to <80% of the best value obtained after transplant or obliterative bronchiolitis identified in lung biopsies regardless of spirometric performance. In the cross-sectional analysis, subjects with BOS (n=52) generally reported

poorer mobility and energy dimension scores than subjects without BOS (n=64). Within this larger cohort, 22 subjects had completed HRQL surveys before and at at least two time points following the development of BOS. A longitudinal analysis of these 22 subjects demonstrated mobility and energy domains worsened after the development of BOS. The authors did not provide data on other NHP domains. In a separate report from the same transplant center, Vermeulen, *et al.* studied 29 subjects before and at 6-month intervals after BOS developed for 18 months.[23] The authors employed the same definition for BOS as the van den Berg study and also used the NHP. Impairments in energy and mobility domains were identified after BOS developed whereas no negative impact on other health domains including emotional, sleep, pain, or social isolation was observed . BOS was also associated with significantly lower Standard Gamble utility scores in a cross-sectional study of 90 lung transplant recipients.[34] Respiratory-specific HRQL is also worse in patients with BOS compared to those without. Smeritschnig and colleagues conducted a single center mail-based HRQL survey of all living lung transplant recipients.[53] BOS was defined as Grade ≥1 by ISHLT criteria[66]; respiratory specific HRQL was quantified by the SGRQ (higher scores denote poorer HRQL; 4 points is considered a clinically significant difference). Of 108 living recipients, 94 returned the survey (87% response). Twenty percent of the subjects met BOS criteria. Subjects with BOS reported poorer total SGRQ scores (22±17) than those without BOS (33±21) ($p = 0.02$) although adjustment for potential confounders was not performed.

Given the high prevalence of medication-related side effects and comorbidities after transplantation, it is perhaps surprising that few data exist on the association between extra-pulmonary medical factors and HRQL. Singer and colleagues examined the effects of select extra-pulmonary factors on SG utility in a cross-sectional study of 90 lung transplant recipients. Poorer renal function was associated with poorer utility scores; each 25 mL/min decrement in creatinine clearance was associated with a modest but clinically significant 0.1 reduction in utility. Other factors including diabetes mellitus, body mass index, and number of medications, however, were not associated with utility.[34] It is clear, however, that larger longitudinal studies are needed to better elucidate the effects of extra-pulmonary medical factors on HRQL after transplantation. At least one such study is ongoing but results have been published in abstract form only at this point.[60]

Psychosocial factors also impact HRQL in lung transplant recipients. A substantial proportion of lung transplant recipients report anxiety, depression, concerns with body image, and impairments in HRQL emotional health and role limitations domains.[17,47,67–69] In a cross-sectional study, Limbos and colleagues mailed surveys to both waitlisted transplant candidates and lung transplant recipients.[17] Among other instruments, the survey included measures of anxiety and depression (Hospital Anxiety and Depression [HAD] questionnaire) and HRQL (RAND-36 generic HRQL instrument). Sixty-one percent of eligible subjects completed the survey. Fully 44% of wait listed candidates and 28% of lung transplant recipients reported borderline or clinical anxiety. These data are similar to a longitudinal study of 43 subjects surveyed before and at 3- and 6-months following lung transplantation.[47] Subjects completed a questionnaire that included a health-utility measure (HUI Mark 3), and the HAD instrument. Although subjects reported improvements in

anxiety and depression, 29% met criteria for borderline or clinical anxiety six-months after transplant. In a longitudinal study of 106 lung transplant recipients, Myaskofsky and colleagues studied the impact of psychosocial factors on HRQL.[40] Subjects surviving 2 months after transplant were approached and ultimately included in the analysis if they survived one year after transplant. Patients were interviewed at the time of regularly scheduled clinic visits at 2, 7, and 12 months after transplant; home visits or phone interviews were conducted when clinic-based interviews were not possible. Factors tested included optimism (Life Orientation Test; measures positive versus negative expectations about the future), caregiver support (quality of the caregiver-patient relationship), friend support, religiosity, and coping strategies (Brief COPE Scale); HRQL was measured with the SF-36. The predictive impact of these psychosocial factors measured at 2-months on HRQL at 12-months after transplant was tested using multivariate regression analyses controlling for demographic variables and all psychosocial factors. A higher sense of optimism and greater friend support predicted better 1-year HRQL in certain domains whereas avoidant coping (a negative coping strategy) predicted poorer 1-year HRQL in the physical functioning domain. In sum, these data demonstrate that anxiety, depression, and other psychosocial morbidities are prevalent in lung transplant recipients and that these morbidities negatively impact HRQL.

Interventions to Improve HRQL

To date, very few studies have examined the impact of interventions on HRQL in lung transplant recipients. Interventions aimed at improving exercise capacity are a logical approach. As discussed above, impairments in HRQL after transplant tend to cluster in the domains related to physical functioning and mobility. Further, not only are the beneficial effects of pulmonary rehabilitation on HRQL in patients with a variety of lung diseases well established[70–72] but both calcineurin inhibitors and corticosteroids used to as maintenance immunosuppressive therapy negatively affect skeletal muscle metabolism and function.[73,74] As a result of medications, debilitation, and likely other factors, exercise capacity after transplant typically is limited to approximately 50–60% of predicted values.[75] To address this potential target, two randomized controlled trials evaluated the impact of structured exercise programs on outcomes that included HRQL assessments. In one, Langer *et. al* performed a randomized, controlled trial of a 3-month supervised exercise training program.[76] Patients aged 40–65 who experienced no major perioperative complications were recruited. The intervention included thrice-weekly 90-minute sessions comprised of cycling, walking, stair climbing and lower-extremity resistance exercises, and education. The primary study outcome was daily walking time measured immediately following and 9 months after completion of the exercise intervention. Secondary outcomes included generic HRQL (SF-36; a 4-point difference is considered clinically significant). Forty subjects were randomized; 34 were analyzed (18 in the intervention group and 16 in the control group). The intervention group reported better HRQL in physical functioning and role physical domains. After adjusting for baseline values, 1-year after transplant, the intervention group reported physical functioning domain scores 10 points better than the control group (95% Confidence Interval [CI]: 1–20; p=0.04) and role physical domain scores 29 points better than the control group (95% CI: 7–51; p=0.01). HRQL was not different in other health domains between the two groups. In the other trial, Ihle and colleagues investigated whether

an inpatient exercise program would improve exercise capacity and HRQL for patients who were free from BOS and had survived ≥1-year after transplant.[28] HRQL was quantified by the SF-36. Sixty subjects (mean time after transplant: 4.5 ± 3.2 years) were randomized equally to either the inpatient exercise program intervention or a standard outpatient physiotherapy program. At the end of the intervention, no changes in HRQL were observed in either group. Notably, baseline SF-36 domain scores were all >80% of the best possible creating a potential ceiling affect. Further, the sampling strategy of this study could have been subject to selection bias. In sum, these two trials suggest that a focus on physical rehabilitation soon after lung transplantation results in large improvements in HRQL; later after transplant the impact of physical rehabilitation programs HRQL in ambulatory patients without BOS is less clear.

Given the prevalence of psychosocial morbidities after transplant including anxiety and depression, most other interventional studies examined behavioral interventions.[33,77–79] Limitations in these interventional studies aimed at psychological factors preclude making robust estimates of the impact on HRQL. Clinicians should be aware, however, of the prevalence of these conditions and consider standard medication and behavioral interventions aimed at treating them. Until proven otherwise, it stands to reason that lung transplant recipients should derive similar HRQL benefits from treatment of psychological morbidities as any other patient group. Importantly, drug-drug interactions with immunosuppressants (in particular, calcineurin inhibitors) must be considered when selecting any new medication, including anxiolytics and anti-depressants.

Finally, transplant program protocols for immunosuppression, infection prophylaxis and treatment of comorbidities vary substantially. The effects of different routine management protocols on HRQL are largely unknown. Finlen-Copeland's analysis did not find any effect of prolonged valganciclovir on the SF-36 trajectory in the first post-transplant year.[41]

Caregivers of Lung Transplant Patients

Given the medical and psychosocial complexities patients face before and after lung transplantation, most transplant programs consider a robust social support system obligatory to transplant candidacy. Unique to organ transplantation, the caregiver burden changes dramatically as transplant recipients experience improvements in health, functioning, energy and re-engages with activities sacrificed before transplant or, alternatively, experience new morbidities due to complications after transplant. Further, the impact of transplant on financial stability may also be profound and impact the caregiver-lung transplant dyad. The demands placed upon caregivers of patients awaiting transplant are substantial and may impact multiple aspects of caregiver quality of life. Since the impact on caregiver QOL may extend to domains beyond health (e.g., financial, relationships, work, recreation, etc…), instruments used to measure caregiver QOL are not always restricted to *health-related* QOL.

Over a one-year period, Rodrigue *et. al.* administered surveys to spouses of patients waitlisted for lung transplantation.[80] QOL was measured with the QOL Inventory, HRQL was measured with the SF-36; other instruments measured mood, caregiver strain, caregiver benefit, and social intimacy. Of the 73 spouses surveyed, 36% reported poor QOL and life

satisfaction and 56% reported clinically significant levels of caregiver strain. The areas of caregiver strain most severely impacted were physical strain, inconvenience, feeling confined, and being upset that their spouse had changed from their former self. Further, higher caregiver strain was associated with more emotional distress and less intimacy. Compared to population norms, caregivers reported both poorer QOL and HRQL. A majority of caregivers, however, realized caregiving benefits through discovering inner strength and support from others. Lefaiver and colleagues surveyed 29 dyads of waitlisted lung transplant candidates and their primary caregivers.[81] Each candidate and their respective caregiver independently completed structured surveys. QOL was quantified by the Quality of Life Index. This instrument provides an overall QOL score and subscale domain scores for health and functioning, psychological/spiritual, socioeconomic, and family. HRQL was quantified by the SF-12, a generic instrument adapted from the SF-36.[82] It yields PCS and MCS scores but not domain scores. Other instruments included a caregiver burden measure (Caregiver Reaction Assesment [CRA]) and a measure of mood (Profile of Mood States-Short Form [POMS-SF]). Emphysema and pulmonary fibrosis were the dominant listing diagnoses (41% each); caregivers were generally white (79%) females (66%). In general, caregivers reported good QOL. The best scores clustered in the socioeconomic subscales whereas QOL was poorest in the health and functioning subscales. Employing a stepwise multiple regression approach, depression (POMS-SF), general health (SF-12 single health item), impact of finances (on caregiver burden, CRA), and lack of family support (CRA) explained 79% of the QOL variance, however the statistical significance of these predictors was not presented. Notably, although caregivers reported physical HRQL similar to population normative values, they reported poorer mental HRQL. Further, instrument subscales demonstrated caregivers suffer from fatigue, depressive symptoms, and concern for the impact of transplant on financial well-being. Only one study has examined QOL or HRQL in caregivers of lung transplant recipients. This is particularly important since primary caregiver support and QOL impacts clinical and HRQL outcomes in other organ transplant populations.[83–86] In a sister-study to their investigation of the impact of psychosocial factors on HRQL[40], Myaskofsky and colleagues interviewed 134 caregivers of lung transplant recipients longitudinally at 2, 7, and 12 months after their respective patients' transplant. Of note, the overall study focused on caregivers of cardiothoracic transplant recipients and so it also included 108 caregivers of heart transplant recipients. The study aimed to investigate the trajectory of caregiver HRQL over the first post-transplant year, whether caregiver psychosocial factors impacted their HRQL, and whether caregiver HRQL at 1-year post-transplant impacted recipient survival up to 7.5 years after transplant. Caregiver HRQL was measured with the SF-36; psychosocial resources were measured with the Life Orientation Test (LOT), the Sense of Mastery Scale, Brief COPE scale (coping strategies), and two measures of social support. Four measures of caregiver burden were also administered. Since the trajectory of HRQL over the first post-transplant year was not different between caregivers of heart or lung transplant recipients, data were combined. Overall, over the first post-transplant year, caregiver HRQL was generally good and remained stable. Some key areas, however, demonstrated change. Vitality improved whereas physical functioning and pain worsened. At one-year after transplant, compared to population norms, caregivers had better HRQL in several mental subscales and similar scores in general health, vitality, and role-physical subscales. Further, younger caregivers

reported better HRQL when compared to older caregivers. Baseline psychosocial and caregiver burden factors predicted HRQL at one-year. Interestingly, caregiver HRQL predicted cardiothoracic transplant recipient survival after controlling for transplant recipients' health status and type of caregiver relationship (spouse vs. other family member). Indeed, for every 5 point decrement in caregiver SF-36 PCS, mortality rates increased by 10%.

Limitations to the Existing Literature and Future Directions

Only one systematic review of HRQL in lung transplantation has been performed.[14] This review identified several methodologic limitations in the existing literature that could result in biased estimates of HRQL. These limitations include incomplete/no multivariate adjustment, studies of HRQL determinants that focused on single risk factors (*e.g.*, pain), survivor bias, and modest sample sizes. In addition, the existing literature is dominated by cross-sectional studies. Only two studies followed patients from before transplant to beyond the first post-transplant year, hindering the ability to identify high yield targets for interventions aimed at improving HRQL. Further, a broad array of HRQL instruments have been employed limiting cross-study comparisons. Within the U.S., no study of HRQL has been reported since the Lung Allocation Score was implemented, potentially limiting the generalizability of the existing literature to contemporary U.S. patients.

This review identified the need for consensus definitions of HRQL in lung transplantation to guide instrument selection and reduce study heterogeneity. Beyond study-specific advantages, once the pulmonary community identifies those instruments that best measure HRQL in lung transplant recipients, these instruments could be used to incorporate HRQL data into existing registries. Doing so could help to address sample size limitations, improve efforts to quantify the impact of lung transplant on HRQL, and to identify areas for intervention. Internet-based HRQL measurement protocols have the potential to greatly facilitate multicenter data collection[87]. Further, while the clinical aim of lung transplant is to improve both survival *and* HRQL, "transplant success" in research is currently defined by patient or allograft survival alone. Future research and organ allocation policy may seek to incorporate HRQL to more comprehensively capture the "net-benefit" of lung transplant. Indeed, as was shown in lung volume reduction surgery for emphysema, by accounting for HRQL, a substantial net-benefit could arguably be achieved from lung transplant even when extended survival may not be clear.[88]

Conclusion

For most patients suffering from end-stage lung disease, lung transplantation provides dramatic, clinically meaningful improvements in health-related quality of life. These improvements are demonstrable regardless of the instrument used, including generic, respiratory specific, or preference-based utility measures. HRQL is, by definition, a multi-dimensional construct and the gains in HRQL afforded by lung transplantation manifest most in the domains related to physical health and functioning. The largest magnitude improvements in HRQL occur early, within the first six-months after transplant. Improvements continue up to one year, after which the emergence of co-morbidities and

BOS make the trajectory of HRQL less predictable. Several factors impair HRQL domains related to physical functioning including BOS, medical co-morbidities, debilitation and psychosocial factors such as anxiety, and depression. HRQL domains related to mental health are negatively affected by anxiety and depression and personality traits such as avoidant coping behaviors. Despite these impairments, HRQL scores compare favorably to levels observed before transplant, even in long-term survivors afflicted with medical co-morbidities.

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