

Determinants of quality of life after lung transplant: an Italian collaborative study

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ABSTRACT: *Determinants of quality of life after lung transplant: an Italian collaborative study. S. Ricotti, P. Vitulo, L. Petrucci, T. Oggionni, C. Klersy for the Italian Group on QoL in Lung Transplant.*

Background. With the improvement in survival rates after lung transplantation, concern has arisen about evaluating quality of life (QoL). This multicenter cross-sectional study aimed at describing QoL and identifying factors associated with it.

Methods. We assessed QoL in 129 lung transplant recipients from 5 centres in Italy, during scheduled follow-up visits, using the SF-36, GHQ and St George's respiratory questionnaires (SGRQ).

Results. The SF-36 elicited impaired QoL in the physical, but not in the mental domains (PCS=44; MCS=53). The GHQ identified 29 patients (23%) with psychological

discomfort and the SGRQ scores were significantly better than those of patients with chronic respiratory disease. On multivariate analysis, exertional dyspnea was an independent predictor of the PCS (adjusted Δ -6.3 ($p<0.001$), while osteoporosis (Δ =-3.1), BOS (Δ =-4.3), acute rejection (Δ =-3.9) and heart and lung transplant (Δ =+6.4) were only marginally associated. Dyspnea was also related to a GHQ score >5 .

Conclusions. The study identified exertional dyspnea as the main determinant of QoL as measured both by SF36 (PCS) and GHQ. Other objective measures contributed only to the PCS. Thus, the SF-36 (PCS) and GHQ were useful in identifying patients who needed treatment not only for complications but also psychological support and continued physical rehabilitation.

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Keywords: *Quality of life; lung transplant; SF-36 Health Survey; GHQ, St George's Respiratory Questionnaire.*

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Introduction

Lung transplantation is a treatment option for patients with end-stage lung disease. Between 1991 and 2002, 591 single and double lung transplantations were performed in Italy. One- and 5-year survival is reported to be 61% and 41% respectively for single or double lung and heart and lung transplantation in the Italian Lung Transplant Registry. With the improvement in survival rates, concern has arisen about how to assess quality of life (QoL) in these patients. Over the last few years the assessment of health-related QoL after lung

transplantation has been included as a measure of patient outcomes, together with survival and rates of complications [1, 2]. QoL after lung transplantation has been measured by various questionnaires and dramatic improvements have been observed [3-5]. Several factors and their association with QoL have been evaluated in turn and include age, gender, education, length of time since transplant, presence of bronchiolitis obliterans syndrome (BOS), pulmonary diagnosis and psychic conditions [6-10].

The aim of the study was to describe health-related QoL measured by generic and disease-spe-

cific questionnaires in a large population of lung transplant recipients from different Italian centres. It also aimed to identify factors associated with an impaired QoL by assessing several aspects of patients' characteristics, in order to highlight areas requiring medical/psychological intervention. In particular, we assessed the relationship between QoL and disease-specific symptoms or treatment-related side effects, as well as other demographic and functional characteristics of the patients.

Material and methods

Study Design

This was a multicentre cross-sectional observational study.

Patients

129 lung transplant recipients, from five centres in Italy, participated in the project. They attended scheduled follow-up visits between February 2001 and February 2002 at the pneumologic outpatient clinics of the participating centres, three or more months after transplant. More than 60% of the patients were enrolled in one centre, while 83% were enrolled in 2 centres. The project was approved by the Ethical Review Board of the reference centre.

Clinical assessments

During these visits each patient underwent a complete clinical assessment by both a pneumologist and a psychiatrist. This included a personal interview in which patients were asked whether they had returned to work or resumed sporting activities, as well as questions about their level of autonomy, the presence of symptoms and signs, as listed in table 1. A physical examination was also carried out and respiratory function was measured. Pre-transplant data was retrieved from clinical charts or directly from the patient. Respiratory function was evaluated by the 6-minute walking test (6MWT) [11, 12]. The degree of dyspnea was measured both on a visual analogic scale (VAS) and on the Borg scale before and after the 6MWT [12]. Forced expiratory volume in 1 second (FEV_1) and oxygen arterial pressure (PaO_2) were measured according to standard procedures [13]. The occurrence of severe infection, acute rejection and the presence of bronchiolitis obliterans syndrome (BOS) and of osteoporosis in the previous month was also assessed. Infection and acute and chronic rejection were diagnosed according to current international guidelines [14-16]. Osteoporosis was diagnosed clinically and/or by means of bone mineral density measurements [17, 18]. Questionnaires to investigate the patients' health-related QoL were handed out for self-completion and were collected at the end of the visit. No time limit or specific order was set for the completion of the questionnaire.

Health-related quality of life

Three different instruments were used to investigate generic (SF-36 and GHQ) and disease-specific (SGRQ) aspects of QoL. All of them were translated and validated for use in the Italian population [19-21].

The MOS 36-Item Short-Form Health Survey (SF-36) is an internationally-validated instrument for generic health surveys. Eight domains are explored: physical functioning (PF); role limitations due to physical problems (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role limitations due to emotional problems (RE), and mental health (MH). The SF-36 also measures changes in health status over time. The questionnaires were scored in accordance with the SF-36 Manual [22]. Finally, we computed norm-based physical (PCS) and mental (MCS) component summaries that aggregate information regarding the mental and physical components from the 8 domains [23]. Norm-based scores were calculated for the eight domains and the aggregate measures, based on the 1998 healthy Italian population [19] to allow a direct comparison between the 8 domains and the normal reference population. All scores above or below 50 are above or below the average, respectively, compared to the healthy Italian Reference Population. Higher scores correspond to a better QoL.

The General Health Questionnaire (GHQ-30 items) is a recognised instrument for detecting current non-psychotic disorders and has been widely used to detect minor psychiatric disorders [24]. For each item, the respondent is asked to compare his recent health status with his usual status and an item is scored as being present only if it is being experienced 'more (less) than usual'. Scores range from 0 to 30; the lower the score, the better the QoL. A threshold of between 5 and 6 was used in the present study to identify patients with psychiatric disorders, in order to reach a higher specificity than that obtained with the usual cut-off between 4 and 5 [25].

The St. George's Respiratory Questionnaire (SGRQ) is a standardised self-administered airways disease-specific questionnaire divided into 3 subscales [26]: symptoms (8 items), activity (16 items) and impact (26 items). These questionnaires were scored according to the Manual for the Italian Version [21]. Scores range from 0 (no impairment) to 100 (maximum impairment). No healthy group-based norms are available for the general Italian population.

Statistical Analysis

Descriptive statistics were reported as mean and standard deviation (SD), or median and interquartile range (IQR), for continuous variables, and as absolute and relative (%) frequencies for categorical variables. Mean and 95% confidence intervals (95% CI) were also computed for the SF-36 and SGRQ scores. The SF-36 norm-based scores were also compared against the average value of the Italian population, and the SGRQ scores

Table 1. - Socio-demographic, clinical and functional characteristics (For abbreviations, see text)

Characteristic	Description
Age-years (mean (SD))	47.9 (13.0)
	≤ 50 years
	58 (45%)
Male	84 (65%)
BMI	Pre Tx (mean (SD))
	22.7 (4.1)
	Post Tx (mean (SD))
	22.6 (4.4)
Diagnosis	Emphysema
	32 (25%)
	Pulm. Fibrosis
	42 (33%)
	Cystic Fibrosis
	29 (23%)
	Pulm. hypertension
	16 (12%)
	Other
	9 (7%)
Transplant	Single Lung
	63 (49%)
	Double lung
	59 (45%)
	Heart & Lung
	8 (6%)
Months since transplant (median (IQR))	27 (9-51)
Return to work	34 (26%)
	After occupation suspended due to lung disease
	26 (30%)
Return to sport	28 (22%)
	After sport suspended due to lung disease
	17 (39%)
Independence	Going out alone
	104 (81%)
	Going out accompanied
	15 (12%)
	Going upstairs
	116 (90%)
	Driving
	88 (68%)
	Cycling
	42 (33%)
Symptoms	Tremors
	55 (43%)
	Paresthesias
	36 (28%)
	Tiredness
	29 (22%)
	Exertional Dyspnea
	50 (39%)
	Cough
	29 (22%)
	Secretions (mucus)
	19 (15%)
	Pain (joints/muscles)
	48 (37%)
	Osteoporosis
	32 (25%)
FEV ₁ l (mean (SD))	2.23 (1.02)
PaO ₂ mm Hg (mean (SD))	84 (12)
6MWT meters (median (IQR))	560 (400-630)
VAS	Pre-6MWT (median (IQR))
	0.5 (0.0-2.0)
	Post-6MWT (median (IQR))
	2.7 (1.1-5.0)
Borg scale	Pre-6MWT
	0.5 (0.0-1.5)
	Post-6MWT
	3.0 (1.0-4.0)
Major infections (current or in the previous months)	26 (20%)
Acute rejection (current or in the previous months)	13 (10%)
BOS	18 (14%)
	Grade I-II
	11 (61%)

were compared against the average values of the validating population with chronic respiratory disease, by means of one-sample *t*-test. The Kruskal Wallis test was used to compare scores from QoL questionnaires (SF-36 and SGRQ) across risk groups, as defined below. The Fisher exact test was used to compare GHQ categories. Risk groups were defined according to age, gender, pneumologic diagnosis, type of transplant, time from transplant, concomitant or recent major infection, acute and chronic rejection, osteoporosis, presence of pain and respiratory function. For study purposes, the 6MWT, FEV₁ and time from transplant were categorised according to the tertiles of their distribution and age according to its median distribution. A multivariate general linear regression model was fitted to identify independent determinants of the physical component summary (PCS) of SF-36. After assessing for collinearity, variables with a *p*-value <0.2 on univariate analysis were considered.

Stata 8 (StataCorp, College Station, TX) was used for computation. A 2-sided *p*-value <0.05 was considered statistically significant. The results of tests on QoL are reported without correction for multiple tests.

Results

Patients' sociodemographic, clinical and functional characteristics are summarised in table 1. Half of the patients were assessed between 9 and 51 months after the transplant. The majority were male; half of them were aged 50 or under. Body mass index (BMI) was within normal ranges. Emphysema, pulmonary fibrosis and cystic fibrosis percentages were similar and accounted for 81% of all native lung diagnoses, overall. Single and bilateral lung grafts were evenly distributed. Only a quarter of the entire study population was employed and/or practised a sport when QoL was assessed. However, 30% of those patients who had previously been employed had returned to work and 40% had resumed sport. The vast majority had achieved a satisfactory level of autonomy. A wide percentage of patients (15 to 44%) reported symptoms and signs. Most of these were related to side effects of treatment and included tremors, paresthesias, muscle and joint pain and osteoporosis. Respiratory function was fair. Most patients (84%) were able to perform the 6MWT, with only 25% of them walking less than 400 metres, with a minor increase in the degree of dyspnea, as measured by the VAS and Borg scales. Mean FEV₁ was good and PaO₂ was within normal ranges. A minority of patients suffered from recent episodes of severe infection, acute rejection and BOS (mainly grade I and II).

Health-related QoL. Patient co-operation was high: all patients completed at least one questionnaire and 95% completed all three. Most norm-based SF-36 scores were very close to 50, the average for the normal population. Compared to the reference population, QoL could be considered normal regarding BP and SF, and better than normal with respect to VT and MH (*p*=0.003 and *p*<0.001,

respectively), but worse than average PF, RP and GH (*p*<0.001 in all cases) (figure 1a). In the RP dimension, in particular, 25% of the patients had norm-based scores below 28. Overall, a moderate deterioration in QoL was elicited in the summary measure for physical well-being, with a mean PCS of 44.3 (95%CI 42.5-46.0), *p*<0.001, while mental well-being was even above the average for the normal population, with a mean MCS of 52.6 (95%CI 51.0-54.2), *p*<0.001. Health was rated as better or much better compared to one year earlier by 62% of patients and worse by only 10%. The GHQ questionnaire highlighted good results in the psychic dimensions, with a low median score of 2 (IQR 0-5), although 29 patients (23%) were identified as having signs of psychological discomfort (score >5) and 35 (28%) had a score >4. Scores calculated from the SGRQ are illustrated in figure 1b; they were well below values measured in the Italian validation cohort of patients with chronic respiratory disease, reported to be 54.4 (SD 19.2), 43.3 (SD 24.3), 71.1 (SD 19.0) and 48.6 (SD 22.0) overall, for symptoms, activity and impact, respectively (*p*<0.001 in all cases) [21].

The association between QoL and clinical characteristics for subjective and objective measures (SF-36 and GHQ) is reported in table 2. The PCS measure of QoL was significantly worse in patients over 50, in those with osteoporosis, exertional dyspnea and in patients who had experienced acute rejection in the last few months. It was marginally worse in patients who had undergone single lung transplantation and in patients with joint or muscle pain. On multivariate analysis (model *p*<0.0001, R²=0.28), exertional dyspnea was the only independent determinant of PCS, with an adjusted decrease in the QoL score of -6.3 (95%CI -9.8 to -2.9, *p*<0.001). Osteoporosis, BOS and acute rejection were marginally associated with a decreased QoL and heart and lung transplant with an increased QoL (compared to double lung transplant): adjusted differences and confidence intervals pointed to an association of these characteristics and patients' well-being and were -3.1 (95%CI -6.8 to 0.6, *p*=0.102) for osteoporosis, -4.3 (95%CI -8.9 to 0.4, *p*=0.072) for BOS, -3.9 (95%CI -9.2 to 1.5, *p*=0.154) for acute rejection and 6.4 (95%CI -0.4 to 13.2, *p*=0.063) for heart and lung vs. double lung transplant. Interestingly, no time effect was apparent.

On the contrary, the MCS score did not differ between the categories of risk groups, although, surprisingly, patients with BOS tended to perform better.

Only exertional dyspnea was associated with psychological discomfort with a GHQ score >5 and was more frequent in patients with an impaired GHQ. A marginal association was observed for osteoporosis. Also here the length of time since transplant did not influence the level of QoL.

Similarly, when considering SGRQ scores, no group appeared to perform worse, although we did observe some variability between the categories of patients.

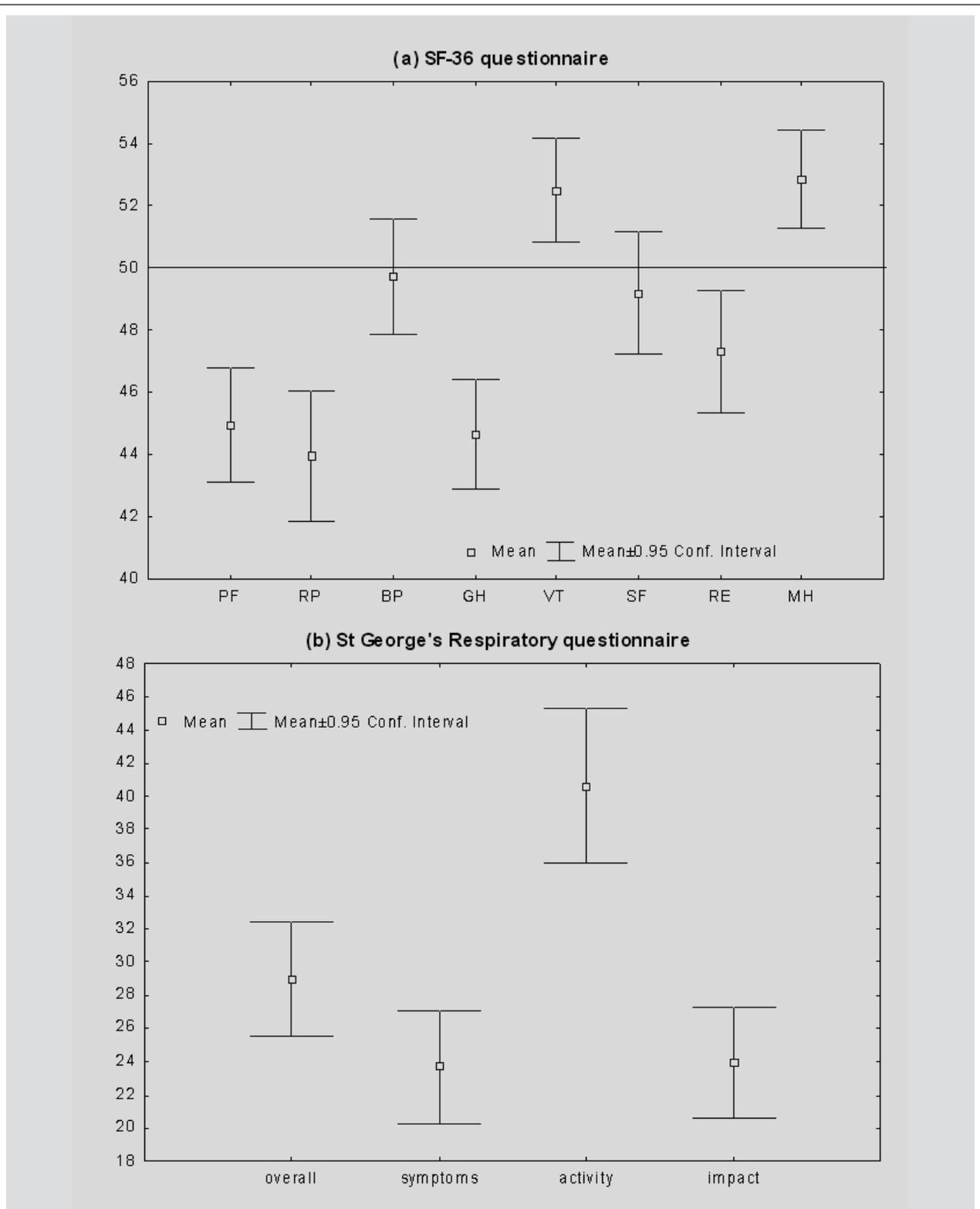


Fig. 1. - Health related QoL evaluated by the SF-36 (panel a) and SGRQ (panel b). Mean (squares) and 95% CI (segments) are reported for each domain in the two questionnaires. The horizontal line in panel "a" corresponds to the norm for the Italian population. (For abbreviations see text).

No centre effect was elicited in any of the dimensions explored by the three questionnaires.

Discussion

An assessment of the general health of 129 lung or heart and lung transplant recipients at a median of 27 months after surgery highlighted an

overall fair quality of life, as measured by the three questionnaires, as well as good levels of autonomy and normalization of functional indices (FEV₁, paO₂ and distance covered during the 6MWT). Our patients were evaluated during scheduled follow-up visits, three or more months after the transplant, and thus were clinically stable. Major infections and acute rejection were observed in a mi-

Table 2. - Association of clinical characteristics and QoL: Generic questionnaires (SF-36 & GHQ)

Characteristic		SF-36		GHQ		p-value	
		PCS ¹	p-value	MCS ¹	Impaired (GHQ>5)		
Age	≤50 yrs	48 (42-54)	0.015	54 (45-59)	0.332	11 (19%)	0.396
	>50 yrs	41 (35-51)		54 (48-60)		18 (24%)	
Gender	F	46 (36-54)	0.508	54 (49-58)	0.939	10 (24%)	1.000
	M	45 (37-51)		54 (47-60)		19 (23%)	
Diagnosis	emphysema	47 (38-54)	0.335	53 (49-58)	0.766	8 (26%)	0.703
	pulm fibrosis	42 (35-52)		52 (46-60)		10 (24%)	
	cystic fibrosis	49 (42-52)		54 (47-59)		6 (21%)	
	pulm hypert	45 (38-49)		58 (45-60)		2 (12%)	
	other	40 (25-57)		58 (54-62)		2 (25%)	
Type of TX	single lung	44 (35-50)	0.052	53 (47-60)	0.707	14 (23%)	0.892
	double lung	47 (40-53)		54 (47-60)		12 (21%)	
	heart & lung	51 (45-56)		58 (51-60)		2 (25%)	
Time since TX	≤18 months	45 (37-50)	0.316	51 (46-57)	0.116	9 (22%)	1.000
	18-41 months	47 (40-54)		54 (46-60)		9 (21%)	
	>41 months	46 (35-52)		56 (49-61)		10 (23%)	
6MWT	≤490 m	46 (37-51)	0.521	53 (47-59)	0.468	11 (23%)	0.092
	491-629 m	52 (47-59)		53 (48-58)		7 (32%)	
	≥630 m	53 (48-61)		57 (51-60)		3 (9%)	
Exertional dyspnea	no	49 (41-54)	<0.001	54 (49-60)	0.949	34 (36%)	0.030
	yes	40 (31-47)		54 (45-60)		17 (61%)	
Osteoporosis	no	47 (39-53)	0.008	55 (48-57)	0.317	18 (19%)	0.089
	yes	40 (31-49)		52 (43-60)		11 (34%)	
BOS	no	46 (38-52)	0.119	53 (47-59)	0.082	26 (54%)	0.762
	yes	40 (29-49)		58 (55-62)		3 (17%)	
Acute rejection	no	46 (37-53)	0.030	54 (47-60)	0.522	24 (21%)	0.171
	yes	41 (29-45)		50 (47-60)		5 (38%)	
Severe infection	no	46 (38-53)	0.137	53 (47-59)	0.357	21 (21%)	0.301
	yes	43 (36-49)		57 (45-61)		8 (31%)	
FEV ₁	≤2.14	46 (31-52)	0.116	56 (49-60)	0.354	11 (27%)	0.628
	2.15-3.05	45 (35-49)		51 (45-59)		7 (18%)	
	>3.05	50 (40-54)		54 (48-60)		9 (24%)	
Pain (joints, muscles)	no	47 (40-53)	0.053	53 (47-59)	0.295	17 (21%)	0.668
	yes	42 (35-49)		56 (48-60)		12 (25%)	
Centre	Pavia	43 (36-52)	0.151	52 (47-60)	0.847	19 (23%)	1.000
	Others	46 (40-53)		53 (47-60)		10 (22%)	

¹ Median (IQR); abbreviations: see text.

nority of patients (10-20%). Only 18 patients had signs of BOS; 61% of them being BOS grade I-II.

The SF-36 questionnaire elicited some impairment in the physical domain while the mental domain, showed an increase compared to the normal Italian population, as expected after a successful transplant. This coincides with the findings of Pinson *et al* [1] who report a PCS of 36 and an MCS of 53 and those of Stavem *et al* (PCS=41 and MCS=57) [3]. However, scores for the single dimensions calculated in our study were lower than those reported by Limbos [7], as regards PF, RP and GH in particular. This author did not find substantial differences between the physical and mental dimensions after transplantation. The clinical characteristics of his transplant recipients were similar to those of our patients, except for a higher prevalence (48%) of patients with an original diagnosis of emphysema. On the contrary, our scores were higher than those recorded by Hummel [5], although he did not provide any information on functional assessment in these patients for a meaningful comparison. In accordance with the MCS evaluation in our population, the GHQ questionnaire gave good results in the psychic dimension. In addition, it allowed us to identify a minority of patients with signs of psychological discomfort who required further investigation: 23% of our patients scored >5 and 28% >4. To our knowledge, no studies have been carried out in lung transplant patients using the GHQ. Triffaux reported higher figures after heart transplantation; 37% of his patients evaluated between 1 to 41 months after transplant had a GHQ score >4 [27]. The SGRQ scores in our population were significantly better than those in the Italian validating series with chronic respiratory disease [21]. An informal comparison with published scores measured in the healthy Spanish population showed values close to the upper limit (95th percentile) [28]. Scores in the activity and impact areas were comparable with those published by Stavem [3] in a population with lower mean FEV₁ (1.6 l), although our patients showed better scores in the symptoms area (24 vs. 43).

Age (>50 years), exertional dyspnea, osteoporosis and acute rejection in the previous month were definitely associated with an impaired QoL in the PCS of the SF-36 on univariate analysis, although single lung transplant and joint or muscle pain were also marginally involved in determining a lower score. On multivariate analysis, the presence of exertional dyspnea was the major determinant of PCS, although the role of osteoporosis, BOS, acute rejection and type of transplant (heart and lung particularly) should not be ignored. On the contrary, time since transplant and underlying diagnosis were not found to be associated with QoL in our sample. Exertional dyspnea in our case series also allowed us to identify patients with psychological discomfort (GHQ>5); similarly, osteoporosis was more frequent in these patients, although not significantly. No determinants of QoL as measured by the MCS of the SF-36 and SGRQ were elicited in our case series.

Others have also explored some of these risk factors and our results are in line with the existing

literature, although the use of different instruments makes it difficult to draw comparisons. The various authors have identified (with formal statistical comparisons or informally) BOS, age, type of transplant, comorbidities and complications as being associated with QoL impairment in the physical dimension [2, 4, 6, 10], while no relationship has generally been reported with the length of time since transplant during a follow-up comparable to ours [3, 4], with the exception of McNaughton [8] who reported an association of time since transplant and the mental but not the physical dimension of SF-36. Our data is also consistent with a case series of heart transplant patients who were followed-up at the same co-ordinating centre for at least 10 years [29].

This evaluation of mid-longterm transplant patients from different centres gives a picture of the situation in Italy 10 years after the lung transplantation program started. We assessed QoL using standardised instruments validated in Italy. Compared to other case series [1, 3, 6, 7], it covered a large population, over a wide time span, with 50% of our patients having undergone a transplant operation over two years earlier, and 25% more than four years earlier. The evaluation of QoL was well accepted, with a compliance of 95% for the three questionnaires. QoL was also correlated, by means of a multivariate analysis, to symptoms and signs, including those related to treatment side effects, respiratory function and levels of autonomy in a comprehensive assessment of patients' characteristics, while most of the published literature has considered only a few of them at a time [6, 8-10]. The study identified exertional dyspnea as the main determinant of QoL as measured by both SF36 (PCS) and GHQ. Other objective measures contributed only to the PCS.

The main limit of the study was its cross-sectional design, which did not allow us to gauge the actual improvement in QoL after lung transplantation, nor how it changed over time in each patient. In this case series, time since transplant did not elicit different values of QoL scores between the groups of patients. However, the study was able to answer the stated aims of identifying risk factors for a deteriorated QoL.

Lung and lung and heart transplant recipients evaluated at midterm after transplantation showed a fair to good health-related QoL as measured by three standardised instruments, more in the mental than in the physical dimension. The disease-specific questionnaire (SGRQ) we used was not able to discriminate between patients. This was not unexpected, given that it was developed for chronic respiratory disease, whereas few patients in our case series showed signs of BOS. On the other hand, the generic SF-36 and GHQ questionnaires, were sensitive towards patients' symptoms and functioning and easy to administer, and so may be useful in identifying subgroups of patients who need treatment not only for complications such as infections, acute rejection or BOS, but who should also receive psychological support and continued physical rehabilitation.

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