Breathlessness and Respiratory Disability After Kidney Transplantation

Anthony O'Riordan[a], Aisling Farrell[a], Nouh Baqer[a], Sam Kant[b], Sean Farrelly[a], Eoin Hunt[a], Michael Clarkson[b], Michael Henry[a], Marcus Kennedy[a], William Plant[b], Barry Plant[a,c], Joseph Eustace[b,c], and Desmond Murphy[a,c*]

[a]The Department of Respiratory Medicine, Cork University Hospital, Cork, Ireland; [b]Department of Renal Medicine, Cork University Hospital and College of Medicine, University College Cork, Cork, Ireland; and [c]The HRB-funded Clinical Research Facility, University College Cork, Cork, Ireland

ABSTRACT

Background. Dyspnea is a common symptom in patients with end-stage kidney disease being treated with dialysis. This study aimed to ascertain the level of respiratory disability in patients after kidney transplantation through assessing a cohort of kidney allograft recipients for respiratory compromise and thereby identifying a potential target for therapeutic intervention.

Methods. Kidney transplant recipients who were under active observation in a single tertiary referral center were invited to take part in this prevalence study at the time of clinic follow-up. All patients agreed to take part in the study, which involved completing a Medical Research Council (MRC) dyspnea scale, completing the St George's Respiratory Questionnaire, and performing basic spirometry. An MRC score of $\geq$2 and/or a forced expiratory volume in 1 second $<$90% predicted prompted formal clinical assessment by a respiratory physician.

Results. This study enrolled 103 patients; 35% of all patients reported breathlessness, and 56% of all patients warranted formal respiratory medicine review. After completion of their investigations, 33 patients were found to have an underlying condition accounting for their symptoms.

Conclusion. Our study highlights the issues of respiratory disability and breathlessness in patients who have undergone kidney transplantation. Although extensive cardiologic evaluation is performed routinely and can rule out many causes of dyspnea, respiratory assessment is not a preoperative prerequisite. This study could suggest that a formal pulmonological evaluation and basic spirometry should be part of the pretransplant evaluation of the kidney transplant recipient.

PATIENTS with chronic kidney disease are prone to significant pulmonary comorbidities [1,2]. Kidney transplantation is the gold standard therapy for end-stage kidney disease (ESKD) [3], and although it is widely recognized that recipients experience a significant improvement in their quality of life, many of the pretransplant symptoms associated with advanced kidney disease persist [4].

Dyspnea is one of the most common symptoms reported by patients with chronic kidney disease, and the mechanisms underlying this debilitating symptom are often multiple and complex [5]. Dyspnea may occur as a direct consequence of their underlying kidney disease with abnormalities such as pulmonary edema, pleural effusion, pleurisy, and myopathy [6]. Dyspnea may also be secondary to multiple coexisting pathologies such as cardiac failure or pulmonary hypertension. Finally, unrecognized lung disease may be the underlying cause of their breathlessness.

Although dyspnea is well recognized in patients with ESKD, few data pertaining to the issue in the post−kidney transplant population have been published. It is therefore unclear whether dyspnea remains a significant issue following transplant either through persistent symptoms not rectified by transplantation or through new issues arising following transplantation. We wished to address this deficit in the literature. The aim of this study, therefore, was to assess a cohort of kidney allograft recipients for potential respiratory compromise, thereby identifying a

*Address correspondence to Dr Desmond Murphy, The Department of Respiratory Medicine, Cork University Hospital, Cork, Ireland. Tel: +353 21 4922327. E-mail: desmond.murphy@hse.ie

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potential target for therapeutic intervention and further optimization of care.

MATERIALS AND METHODS

This study was approved by the Clinical Research and Ethics Committee of the University College Cork affiliated Hospital Group. Kidney transplant recipients under active observation in a single tertiary referral center were invited consecutively to partake in this prevalence study at time of clinic follow-up over a 14-month period.

All participants agreed to partake in the study and completed the St. George's Respiratory Questionnaire (SGRQ), completed the Medical Research Council (MRC) dyspnea scale, and performed basic spirometry. Patient demographics including age, sex, previous history of respiratory disease, smoking history, occupation, kidney allograft function, posttransplant vintage, and allograft matching were also collected.

An MRC score of ≥2 and/or a forced expiratory volume in 1 second (FEV1) <90% predicted prompted formal clinical assessment by a respiratory physician. After this assessment, further diagnostic investigations were performed if clinically indicated, such as a pulmonary function tests, computed tomography (CT) scan of the thorax, and echocardiogram.

RESULTS

This study enrolled 103 patients over a 14-month period. Table 1 outlines the patient demographics. The median age (range) was 51 (24-77) years, and there was a slight male predominance at 54%; 49% (51 patients) had a previous history of respiratory illness, with 80% of these patients reporting only a mild self-limiting respiratory tract infection. Additionally, 9.7% (10 patients) had a known diagnosis of obstructive lung disease; 3 had chronic obstructive pulmonary disease (COPD), and 7 patients had asthma. Seven patients worked as farmers, but they had no history of occupational lung disease; 50.5% (52 patients) of patients were either current or past smokers; 17.5% (18 patients) of the cohort were currently smoking with a median (interquartile range [IQR]) self-reported history of 15.8 (5.9, 30.5) pack-years. There was no significant association between smoking status and the MRC or SGRQ score.

The median transplant vintage was 6.6 years, with most patients having well-preserved graft function, although 9 subjects had an estimated glomerular filtration rate (eGFR) of <30 mL/min per 1.73 m^2 body surface area. Fifteen patients had a prior failed transplant, and a similar number had experienced an episode of acute cellular rejection that had required immunosuppression escalation. There was no significant association between measures of respiratory disability and the current transplant eGFR, the strongest correlation being that of eGFR with the SGRQ ($r = -0.18$; $P = .08$).

Patients were screened for possible respiratory disease using both the MRC dyspnea score and FEV1. If a patient had an MRC score of ≥2 and/or a FEV1 of <90% predicted, they were referred for formal respiratory medicine assessment. After completion of

Table 1. Clinical Characteristics of Population

Characteristics	All (N = 103)	Screen Positive (n = 58)	Screen Negative (n = 45)
Age (y), mean (SD)	50.4 (12.3)	51.6 (12.6)	48.7 (12.0)
Male; n (%)	56 (54%)		
Transplant vintage (mo), mean (SD)	79 (34.5-162.5)	75 (33-163)	82 (38.5-165)
eGFR (mL/min per 1.73m^2), mean (SD)	52.9 (19.1)	51.4 (19.9)	55.0 (18.1)
Current smoker; n (%)	18 (17.5%)	12 (20.7%)	6 (13.3%)
Ever smoked; n (%)	52 (50.5%)		
Pack-years; median (IQR)	1.5 (0-15)	2.4 (0-15.9)	0 (0-10.25)
History of any respiratory illness; n (%)	51 (49.5%)	34 (58.6%)	17 (37.8%)
History of RTI; n (%)	41 (39.8%)	25 (43.1%)	16 (35.5%)
History of asthma; n (%)	7 (6.8%)	6 (10.3%)	1 (2.2%)
History of COPD; n (%)	3 (2.9%)	1 (1.7%)	2 (4.4%)
Occupation, farmer; n (%)	9 (8.7%)	4 (6.9%)	5 (11.1%)
Previous transplant; n (%)	15 (14.6%)	11 (19%)	4 (9%)
History of allograft rejection episode; n (%)	15 (14.6%)	8 (13.8%)	7 (15.6%)
CMV positive donor to CMV negative recipient; n (%)	16 (15.5%)	4 (6.9%)	12 (26.7%)
FEV1 % predicted; median (IQR)	92.0 (84.0-104.0)	85.5 (78.0-98.0)	102.5 (96.5-109.5)*
FVC % predicted; median (IQR)	99.0 (89.0-108.0)	93.5 (81.0-102.0)	105.5 (98.5-116)*
MRC dyspnea scale score:			
1: n (%)	66 (64.1%)	21 (36.2%)	45 (100%)*
2: n (%)	27 (26.2%)	27 (46.5%)	0 (0%)
3: n (%)	8 (7.8%)	8 (13.8%)	0 (0%)
4: n (%)	2 (1.9%)	2 (3.5%)	0 (0%)
SGRQ score; n (%)	6.3 (2.4,14.2)	13.2 (5.8, 18.3)	2.7 (0.4, 5.9)*
Symptom score: n (%)	9.6 (0.0, 23.4)	13.5 (19.1, 27.2)	2.1 (0.0, 13.3)*
Activity score: n (%)	11.5 (6.0, 29.4)	23.1 (6.2, 41.8)	6.0 (0.0, 12.0)*
Impact score: n (%)	0.0 (0.0, 4.0)	3.1 (0.0, 9.9)	0.0 (0.0, 0.0)*

CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; MRC, Medical Research Council; RTI, respiratory tract infection; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

* $P < .001$

the above screening tools, 56% of our cohort (58 patients) met the criteria for referral for additional respiratory medicine assessment; 22 patients met both criteria; 22 patients met criteria on the basis of FEV1 of <90% predicted alone; and 14 patients met criteria on the basis of their MRC score of ≥2 alone.

There were no statistically significant differences between the patients who met the screening criteria for respiratory assessment (screen positive) and those who did not (screen negative), as shown in Table 1.

The MRC dyspnea scale score correlated significantly overall (Kendall τ) with the SGRQ ($r = 0.53$) as well as with the SGRQ constituent activity score ($r = 0.31$), symptoms score ($r = 0.56$), and impact score ($r = 0.46$), all $P < .001$. Although the SGRQ was not used to screen patients, in keeping with its correlation to the MRC score, the SGRQ was significantly worse in those who were screen positive compared with those who were screen negative. There was, however, considerable overlap with the SGRQ values for the 2 groups, ranging from 0 to 28 in the screen-negative group and from 1 to 69 in the screen-positive group.

All 58 of the screen-positive patients were offered a respiratory physician referral; 51 patients proceeded to formal respiratory assessment, 1 patient died of an unrelated cause prior to review, and the remaining 6 patients declined referral. Patients referred underwent formal, laboratory-based pulmonary function testing. Results are summarized in Table 2. The median FEV1 was 93% predicted, and the median diffusion capacity for carbon monoxide was 77% predicted. In 42 of these 51 patients, the formal FEV1 measurement was higher than the screening spirometry by a median (IQR) difference of 5.5% (1.8, 12.7). The formal forced vital capacity measurement was lower than the screening value in 15 patients and higher in 36 patients by a median (IQR) difference of 1.5 (4.9 to −10.4). The sensitivity and specificity of the screening FEV1 for a formal laboratory result of below 90% was 100% and 57%, respectively.

After respiratory physician assessment, 29 patients required further investigation with CT scanning of the thorax. One died before imaging, and an additional patient did not attend. In total, 27 of 51 patients (53%) referred for respiratory assessment underwent CT imaging. Results are summarized in Table 3. Twelve patients had normal imaging. Five patients had evidence of pulmonary nodules. Of these patients, 1 was an active smoker, 3 were never smokers, and 1 was an ex-smoker who quit before his kidney transplant. All 5 patients required follow-up imaging, and in 4 cases, nodules were stable after 3 years interval imaging and discharged. In the remaining 1 case, subsequent imaging showed the pulmonary nodules had enlarged and were in keeping with pulmonary metastases from a previous thyroid cancer.

Table 2. Pulmonary Function Testing

Formal Pulmonary Function Tests		
Variable	n	Result (median % predicted [IQR])
FEV1	51	92.5 (81.9, 103.6)
FVC	51	88.9 (82.3, 100.8)
Total lung capacity	34	99.8 (91.4, 111.8)
Residual volume	34	122.7 (105.0, 148.6)
DLCO	12	77.6 (69.8, 84.4)

DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

Table 3. CT Thorax Findings

	Smokers (n)		
CT Thorax Findings (n)	Current	Previous	Never
Within normal limits (12)	-	5	7
Pulmonary nodule (5)	1	1	3
Interstitial lung disease (1)	-	-	1
Emphysema (3)	2	1	-
Bronchiolitis (1)	-	1	-
Airway Thickening (3)	2	-	1
Pulmonary edema (1)	-	-	1
Ground glass opacities (2)	-	-	2
Total (27)	4	8	15

CT, computed tomography.

One patient had evidence of early interstitial lung disease. Three patients had CT evidence of emphysema (2 smokers and 1 nonsmoker). Airway thickening was noted in 3 patients, with 2 of these being active smokers. Bronchiolitis was noted in 1 patient with a known history of asthma. Pulmonary edema and cardiomegaly were evident in 1 case. Two patients had evidence of ground glass opacification and required follow-up imaging. This was fully resolved on subsequent CT thorax in 1 case, and in the second case, the patient died prior to follow-up imaging.

Transthoracic echocardiogram (TTE) was recommended in 25 of the 51 patients (49%) referred for respiratory assessment. Results are summarized in Table 4. TTE was completely normal in 9 patients. Seven patients had evidence of diastolic dysfunction with 1 showing systolic dysfunction. Five patients had valvular disease; 4 had aortic stenosis; and 1 had mitral regurgitation. Three patients had bi-atrial enlargement with echocardiogram, suggesting pulmonary hypertension.

After completion of their investigations, 33 patients were found to have an underlying condition accounting for their symptoms of breathlessness, as shown in Table 5.

Six patients were newly diagnosed with COPD; 3 patients were newly diagnosed with asthma, with 1 patient also showing coexisting bronchiolitis.

Three patients were found to have aortic stenosis on TTE, 2 patients had evidence of diastolic dysfunction, and 1 patient had evidence of pulmonary hypertension. Several patients were

Table 4. Transthoracic Echocardiogram Findings

Transthoracic Echocardiograph Findings (n)	
Normal	9
Cardiac failure	8
Bi-atrial enlargement/pulmonary hypertension	3
Valvular disease	5

Table 5. Etiology of Symptoms

Etiology (n)	
Respiratory	
COPD	6
Asthma	3
Cardiovascular	
Diastolic dysfunction	2
AS	3
Pulmonary HTN	1
Dual pathology	
ILD and pulmonary HTN	1
Heart failure and asthma	1
AS and asthma	1
Heart Failure and COPD	2
Musculoskeletal/obesity	3
Exacerbation of pre-existing condition	10

AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; HTN, hypertension; ILD, interstitial lung disease.

newly diagnosed with dual pathologies accounting for their symptoms: 1 patient had features of interstitial lung disease and TTE confirmed co-existing pulmonary hypertension. One patient was diagnosed with asthma and aortic stenosis, and another patient diagnosed with asthma had evidence of diastolic dysfunction on TTE. Two patients were newly diagnosed with COPD and coexisting systolic dysfunction. Obesity alone accounted for symptoms in 3 patients, 2 of which were also diagnosed with obstructive sleep apnea.

Ten patients had a known underlying cardiopulmonary condition that was poorly controlled or exacerbated by undiagnosed co-existing conditions. Of the 7 patients with pre-existing asthma, symptoms of breathlessness were exacerbated by poor control in 3 patients, obesity in 3, and diastolic dysfunction in 1 patient. In the 2 patients with known COPD, 1 was newly diagnosed with pulmonary hypertension, and 1 had poor control. One patient had a known history of mitral regurgitation, and symptoms were deemed secondary to progression of their mitral regurgitation.

In summary, this model of screening identified previously undocumented cardiopulmonary disease in 22 of 103 (19%) participating patients and characterized 10 of 103 (9%) participating patients as having a deteriorating pre-existing cardiopulmonary condition.

DISCUSSION

Dyspnea is a common symptom in patients with ESKD being treated with dialysis. Our study suggests that such symptoms are also common in patients after kidney transplantation. We found that over the 14-month study period, 35% (36/103) of all patients in this study reported breathlessness. It is not clear if this symptom antedated transplantation or had subsequently developed. The current study was not designed to address this question. Despite this, a formal respiratory assessment is not currently a preoperative requirement for all patients nor is it part of routine posttransplant follow-up care. This raises the concern that underlying conditions may not be identified prior to surgery and that nontransplant comorbidities may not always be carefully ascertained during the life-long follow-up of the transplant recipient.

We believe that identifying possible coexisting pathologies that may result in morbidity and mortality is important. Risk factors that may contribute to posttransplant mortality include smoking, obesity, and chronic diseases such as COPD and asthma [7]. Pulmonary infections can often exacerbate underlying lung disease, causing an accelerated decline in lung function [8]. Pulmonary infections are also one of the most common complications post−kidney transplant. It is therefore desirable that these comorbidities are identified and managed appropriately and aggressively [9].

At present, active patients on the kidney transplant list do not routinely undergo formal respiratory assessment. Factors influencing this may include cost, time restraints, lack of resources, or the belief that the issue is either not common or not significant. Similarly, routine systematic respiratory evaluation is not part of the usual post-transplant follow-up. The MRC Dyspnea Score is a quick, simple, and cost-effective method to categorize patients in terms of their disability secondary to dyspnea and to assess health-related quality of life [10]. Of our total cohort, 35% reported breathlessness (MRC score of 2 or more), and the results of our study suggest that the MRC score may have a role in screening for respiratory disability in these patients and the subsequent referral for formal respiratory assessment.

Dyspnea is often complex and multifactorial in kidney transplant patients and thus further investigations to accurately identify the underlying pathology may be required, subject to expert respiratory opinion. All 51 patients referred for respiratory assessment in our cohort underwent formal pulmonary function tests, 27 patients required CT thorax, and 19 underwent TTE.

Following completion of above investigations, 19.6% (10/51) of those referred were newly diagnosed with chronic lung disease. Thus, the overall prevalence of newly diagnosed chronic lung disease in our total study cohort was 9.7% (10/103). In addition 17.6% (9/51) of those referred were known to have an underlying respiratory condition; thus, the overall prevalence of known underlying respiratory disease was 8.7% (9/103) of the total study cohort. However, several of these patients were poorly controlled and/or exacerbated by other comorbidities.

Obstructive lung disease is associated with increased mortality in patients with ESKD [11]. In our cohort, 5 patients were newly diagnosed with asthma, and 7 patients had a pre-existing diagnosis of asthma; however, symptoms were inadequately controlled.

COPD is also associated with increased mortality in patients with ESKD. In the United States, patients with COPD on dialysis have lower rates of kidney transplantation than non-COPD patients, suggesting that COPD may be considered a contraindication in certain centers [12]. In our cohort, 8 patients were newly diagnosed with COPD, and 2 patients had a previous diagnosis; however, their condition was poorly controlled. Given the increased mortality risk associated with chronic lung disease in these patients, it is imperative that these conditions are identified early to improve patient outcome, although it must be noted that they did successfully undergo transplantation.

In addition, active tobacco use in patients with ESKD has been shown to contribute both independently and synergistically with COPD, to higher mortality and lower success rates of kidney transplants [12]. In our study, there were a higher number of current smokers in the screen-positive group (20.7%) than those who were screen negative (13.3%).

Also, 31% (16/51) of referred patients in our cohort who underwent formal assessment were found to have underlying cardiovascular disease, which had not previously been diagnosed. Thus, the overall prevalence of newly diagnosed cardiovascular disease in our total study cohort was 15.5% (16/103). Cardiovascular disease is one of the leading causes of morbidity and mortality in kidney transplant recipients [13], and dyspnea is a classic presenting symptom, in particular in those with congestive heart failure (CHF) [14].

Of these patients, 16% (8/51) were newly diagnosed with CHF. This is quite a significant finding, as, after infection, CHF is recognized as being the most common cause of hospitalization post−kidney transplant [15].

Pulmonary hypertension is a recognized complication of ESKD [16] and, if untreated, can result in functionally limiting dyspnea and increased mortality [17]. Of patients who underwent echocardiography in our cohort, 12% (3/25) had evidence of pulmonary hypertension; however, it is possible that the incidence is higher given this diagnostic method is frequently inaccurate [18].

Kidney transplant recipients are at risk of worsening cardiovascular disease [19]. Immunosuppressive agents have a significantly negative impact on cardiovascular risk factors such as hyperlipidemia, hypertension, and hyperglycemia [20]. Multiple acute rejection episodes are also a risk factor for cardiovascular disease [20].

Obesity (body mass index of >30kg/m^2) is a well-documented cause of dyspnea [21]. Our study supported these findings, with obesity accounting for symptoms in 12% (6/51) of patients referred for respiratory assessment. Also, 66% (4/6) of obese patients referred for respiratory review were subsequently also diagnosed with obstructive sleep apnea. Sleep-disordered breathing has been shown to increase the risk of hypertension and cardiovascular disease among kidney transplant patients [22]. In light of this, extremely obese patients are not considered for transplantation in certain centers [23].

Extensive immunosuppressive regimens and continued smoking post−kidney transplant increase the risk of developing lung cancer. These cancers can often present late and aggressively, with an overall poor prognosis [24]. In our study, pulmonary nodules were incidentally found in 18.5% (5/27) of patients who underwent routine CT thorax, all of whom required interval surveillance. Of note, although 3 of these patients were lifelong nonsmokers, 2 were active smokers.

Although lung cancer screening in kidney transplant patients is not routinely carried out as part of posttransplant surveillance, it remains a controversial topic [25]. Given the high risk of developing malignancies in this cohort, the authors suggest consideration of CT screening on an individual basis, particularly in those who are at higher risk. High-risk individuals have so far been identified largely based on the National Lung Screening Trial as adults aged 55 to 80 years who are currently smoking or those who have stopped within the last 15 years and with 30 pack-year smoking history [26]. Further research of this topical area is required.

CONCLUSIONS

Although our study is a single-center cohort and was opportunistically, albeit consecutively, recruited, with about one-third of the total patients attending for follow-up, we believe that our findings are pertinent and novel and increase awareness of the potential to detect a broader prevalence than may be easily ascertained of respiratory and cardiac comorbidity in kidney allograft recipients.

Dyspnea is a multifactorial symptom complex that is present in many patients after kidney transplant. Although extensive cardiologic evaluation is performed routinely and can rule out many causes of dyspnea, respiratory assessment is not a preoperative prerequisite. This study suggests that a formal pulmonological evaluation and basic spirometry should be part of the pretransplant evaluation of the kidney transplant recipient.

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