Original Paper

Lung Dysfunction and Mortality in Patients with Chronic Kidney Disease

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Key Words

GFR categories • pulmonary function • mortality

Abstract

Background/Aims: Lung dysfunction associates with increased mortality but the impact of chronic kidney disease (CKD) is less clear. We evaluated lung function and its association with mortality among individuals with normal to severely reduced glomerular filtration rate (GFR). **Methods:** 404 individuals representing GFR category G1 (n=31; GFR >90 mL/min/1.73 m²), G2 (n=46), G3 (n=33), G4 (n=49) and G5 (n=245; GFR < 15 mL/min/1.73 m²) underwent spirometry yielding lung function indices forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁) and peak expiratory flow (PEF). Associations of lung function indices expressed as percentages of predicted values (%FEV₁, %FVC and %PEF) with 5-year mortality were analyzed by competing-risk regression models. **Results:** The prevalence of obstructive (6% in G1 and 11% in G5) and especially restrictive (9% in G1 to 36% in G5) lung dysfunction increased with declining GFR and with higher comorbidity burden. In patients (n=22) with protein-energy wasting, inflammation and cardiovascular disease, the prevalence of restrictive lung function was 64%. The highest tertiles of % FEV₁ and %FVC associated with lower sub-hazard ratios (sHR) for all-cause mortality, 0.49 (95% CI, 0.27-0.88) and 0.56 (95% CI, 0.32-0.98), and that of %FEV₁ also with lower cardiovascular mortality risk (sHR 0.16; 95%CI 0.04-0.69) after adjusting for multiple confounders. Restrictive lung dysfunction (FEV₁/FVC ≥ 0.70, and %FVC < 80) associated with increased mortality risk (sHR 1.80, 95%CI, 1.04-3.13) while the association with obstructive lung impairment was not statistically significant. **Conclusion:** Lung dysfunction and in particular restrictive lung dysfunction associates with degree of renal function impairment and presence of comorbidities, and is an independent predictor of increased mortality in CKD patients.

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Introduction

Chronic lower respiratory disease is the third leading cause of death in the United States [1] where in the general population 7% were reported to have restrictive and 14% obstructive lung dysfunction [2]. The lungs may be severely affected by advanced chronic kidney disease (CKD) [3]; however, the prevalence of lung dysfunction is increased even in patients with CKD stage 1-4, to 10% for restrictive and 16% for obstructive lung function according to the National Health and Nutrition Examination Survey (NHANES) 2007-2012 [4]. As glomerular filtration rate (GFR) falls, pulmonary edema and respiratory muscle dysfunction become more common due to fluid retention and metabolic, endocrine and cardiovascular alterations [5, 6]. Not only GFR but also urinary protein excretion may be linked to worsening lung function [7]. However, lung function assessment is not a routine clinical practice in the management of patients with CKD and the prevalence, characteristics and clinical implications of restrictive and obstructive pulmonary dysfunction in individuals with different degree of renal function impairment are not well characterized.

In the general population, impaired lung function is known to increase the risk of cardiovascular morbidity and mortality [8, 9]. In contrast, there are few reports on links between pulmonary dysfunction and mortality in CKD patients [10, 11]. In one study, reduced forced vital capacity (FVC) was independently associated with increased mortality risk in non-dialyzed CKD 5 patients [10] while in another study low forced expiratory volume in the first second (FEV₁) was not an independent risk factor for mortality in patients undergoing dialysis [11]. The association between pulmonary dysfunction and mortality across different GFR categories remains a largely unexplored area.

In the present study, we analyzed pulmonary function in relation to specified GFR categories in carefully phenotyped individuals with normal to reduced renal function and assessed associations of lung dysfunction with all-cause and cardiovascular disease (CVD) related mortality. To the best of our knowledge, this is the first comprehensive study of the association of impaired pulmonary function with mortality in individuals with normal to severely reduced renal function, GFR categories 1-5.

Materials and Methods

Patients and study design

Pulmonary function was investigated by spirometry in 404 clinically stable patients with G-1 (n=31; GFR >90mL/min/1.73 m²), G-2 (n=46), G-3 (n=33), G-4 (n=49), and G-5 (n=245; GFR <15mL/min/1.73 m²). Exclusion criteria were age <18 years, acute renal failure, signs of overt clinical infection and unwillingness to participate. Informed consent was obtained from each individual. The Ethics Committee of the Karolinska Institute (EPN) at the Karolinska University Hospital Huddinge, Stockholm, Sweden, approved study protocols. The studies were conducted in adherence to the Declaration of Helsinki.

The GFR categories were defined according to current guidelines based on estimated GFR (eGFR) calculated according to the CKD-EPI (CKD Epidemiology Collaboration) equation [12]. Patients were classified into GFR categories 1-5 according to the National Kidney Foundation's K/DOQI guidelines [13]. The clinical and laboratory characteristics of the patients in the different GFR categories are shown in Table 1. The cohorts and the underlying causes of CKD are briefly described below:

G-1 individuals (n=31) and G-2 individuals (n=46) were recruited from a population-based sample of individuals from the Stockholm region, randomly selected by Statistics Sweden (a government agency), who served as control subjects for a study on malnutrition, inflammation and atherosclerosis in patients with CKD 3-4, the PRIMA study [14].

G-3 individuals (n=33) were recruited from PRIMA study (n=31) and control subjects in the PRIMA study (n=2). The causes of CKD were chronic glomerulonephritis (n=6), diabetic nephropathy (n=4), others (n=21) and unknown (n=2).

G-4 individuals (n=49) were recruited from an ongoing study of associations between malnutrition, inflammation and atherosclerosis in CKD patients initiating dialysis therapy, the MIA study [15] (n=6), and from the PRIMA study (n=43). The causes of CKD were chronic glomerulonephritis (n=12), hypertension and reno-vascular disease (n=2), diabetic nephropathy (n=8) and others (n=27).

G-5 individuals (n=245) were recruited from the MIA study [15] (n=224), and from the PRIMA study [14] (n=21). The causes of renal failure included: chronic glomerulonephritis (n=54), hypertension and reno-vascular disease (n=55), diabetic nephropathy (n=74) and others (n=62). At the time of baseline investigation, 65 patients had been on hemodialysis (n=44) or peritoneal dialysis (n=21) dialysis for a median time of 11 (2-36) days.

All anthropometric, biochemical and clinical measurements were performed on the same day as – or close to – the investigation of lung function. Lung function assessments among the G-5 (n= 245) patients were repeated after one year (n=130) and after two years (n=65) in some of the patients. At baseline, all patients including G-5 patients, were treated conservatively, while subsequently almost all G-5 patients initiated dialysis treatment (n=237) and many of them underwent renal transplantation (n=112) during the follow up period of five years. In hemodialysis patients, investigations were performed on dialysis-free day. Peritoneal dialysis patients were investigated with peritoneal dialysis fluid in the peritoneum cavity.

Table 1. Clinical and biochemical characteristics and lung function data in 404 patients with GFR categories G1 - 5. Continuous variables are presented as median (10 – 90 percentile). Categorical variables are presented as number (n)/percentage (%). Abbreviations: Mean BP, mean blood pressure; GFR, glomerular filtration rate; Total BMD, Total bone mineral density; SGA, Subjective global nutritional assessment; HDL, high-density lipoprotein; intact-PTH, intact parathyroid hormone; hsCRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; TNF, tumor necrosis factor; ACEi, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; PEF, peak expiratory flow. ^aLow physical activity or bed or wheelchair bound (according to questionnaire where patient reported one of four domains: 1) exercise frequently, 2) normal activity, 3) low activity, or 4) bedridden or wheelchair bound); ^b % HGS, Handgrip strength as percentage of values for CKD 1 and 2. Obstructive lung function: FEV₁/FVC <0.70. Restrictive lung function: FEV₁/FVC ≥0.70 and %FVC <80

Demography and clinical characteristics	G 1 (n=31)	G 2 (n=46)	G 3 (n=33)	G 4 (n=49)	G 5 (n=245)	P value
Age (years)	59 (38-69)	64 (49-77)	61 (30-74)	60 (37-75)	56(34-69)	<0.001
Males, n (%)	22 (71)	32 (70)	26 (79)	33 (67)	149 (61)	0.21
Diabetes mellitus, n (%)	2 (6.5)	1 (2.2)	8 (24.2)	20 (40.8)	83 (33.9)	<0.001
Cardiovascular disease, n (%)	3 (9.7)	2 (4.4)	9 (27.3)	13 (26.5)	84 (34.3)	<0.001
Smoker, n (%) (n=28/44/29/42/200)	18 (64.3)	26 (59.1)	16 (55.2)	21 (50)	47 (23.5)	<0.001
Mean BP (mmHg, n=31/46/33/49/244)	100 (87-117)	104 (89-123)	113 (87-133)	109 (93-123)	110 (92-130)	<0.001
eGFR (ml/min/1.73 m ²)	102 (93-150)	75 (64-89)	37 (31-55)	23 (15-29)	6.4 (3.7-11.1)	<0.001
Total BMD (g/cm ² , n=31/46/33/47/211)	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.2 (1.0-1.3)	1.1 (1.0-1.3)	0.02
Low physical activity ^a , n (%) (n=31/45/29/45/225)	1 (3)	1 (2)	0 (0)	7 (15)	35 (15)	<0.001
Nutritional status						
PEW (SGA>1), n (%) (n=30/44/33/49/243)	1 (3.3)	1 (2.3)	0 (0)	8 (16)	53 (22)	<0.001
Body mass index (kg/m ²)	24.8 (20.3-31.1)	25.4 (20.4-31.2)	27.0 (22.2-31.7)	25.5 (21.0-33.1)	24.6 (19.7-30.8)	0.11
Lean body mass index (kg/m ² , n=31/44/31/47/237)	17.7 (14.4-20.3)	17.6 (14.7-21.3)	18.1 (14.9-21.3)	17.9 (14.8-21.0)	17.0 (13.6-19.9)	0.01
Fat body mass index (kg/m ² , n=31/44/31/47/237)	7.8 (4.5-12.3)	7.5 (4.6-10.7)	8.2 (4.7-12.5)	7.4 (4.8-12.3)	7.7 (4.2-11.9)	0.90
%HGS ^b , n=31/46/33/48/241	100	100	97 (70-124)	100 (51-128)	88 (58-122)	<0.001
Markers of metabolism						
Creatinine (μmol/L)	70 (56-81)	90 (68-101)	155 (121-205)	250 (182-341)	691 (430-1060)	<0.001
Triglyceride (mmol/L, n=30/46/32/48/244)	1.1 (0.7-3.1)	1.0 (0.7-2.5)	1.6 (0.8-3.9)	1.9 (0.9-2.9)	1.8 (0.9-3.5)	<0.001
Total Cholesterol (mmol/L, n=30/46/32/49/245)	4.8 (3.6-6.5)	5.1 (4.1-6.6)	4.8 (3.9-6.0)	5.1 (3.7-7.0)	4.7 (3.2-6.7)	0.18
HDL Cholesterol (mmol/L, n=31/46/17/25/243)	1.5 (0.9-2.4)	1.4 (1.1-2.1)	1.1 (0.9-1.8)	1.2 (0.8-1.8)	1.2 (0.8-1.9)	<0.001
Calcium (mmol/L, n=30/46/33/49/241)	2.4 (2.1-2.4)	2.3 (2.2-2.4)	2.4 (2.3-2.6)	2.4 (2.2-2.6)	2.5 (2.1-2.8)	<0.001
Phosphate (mmol/L, n=30/46/33/49/240)	1.0 (0.7-1.2)	1.0 (0.8-1.2)	1.1 (0.7-1.5)	1.3 (1.0-1.6)	1.9 (1.3-2.7)	<0.001
Intact-PTH (ng/L, n=30/45/33/48/244)	34 (22-64)	37 (27-62)	84 (31-142)	105 (47-156)	211 (47-527)	<0.001
Circulating biomarkers						
Albumin (g/L)	39 (37-42)	39 (35-43)	38 (32-43)	37 (29-41)	34 (27-40)	<0.001
Hemoglobin (g/L)	142 (125-158)	146 (131-155)	132 (112-149)	124 (104-147)	107 (90-127)	<0.001
hsCRP (mg/L)	0.9 (0.4-8.1)	1.4 (0.4-5.5)	2.8 (0.5-10.0)	2.8 (0.6-12.3)	4.9 (0.7-28.4)	<0.001
IGF-1 (μg/mL, n=20/34/23/42/200)	132 (39-248)	111 (70-159)	148 (61-233)	136 (65-233)	186 (95-333)	<0.001
IL-6 (pg/mL, n=28/40/13/34/241)	1.7 (0.4-7.7)	2.1 (0.8-8.5)	3.3 (2.0-6.1)	2.5 (1.6-13.8)	6.1 (2.3-16.8)	<0.001
Fibrinogen (g/L, n=30/46/31/49/240)	3.1 (2.4-3.9)	2.8 (2.3-3.7)	3.2 (2.4-4.3)	3.9 (2.9-5.9)	4.7 (3.4-6.9)	<0.001
TNF (pg/mL, n=15/25/22/35/228)	3.9 (2.5-6.2)	3.7 (1.5-9.1)	6.6 (4.6-14.2)	8.3 (5.4-16.6)	11.4 (6.3-21.4)	<0.001
Leucocytes count (10 ⁹ /L)	5.7 (4.0-8.0)	6.0 (4.4-8.7)	6.1 (4.5-8.2)	7.5 (5.1-10.1)	7.6 (5.3-11.5)	<0.001
Medications						
β-blockers, n (%) (n=31/46/31/49/234)	6 (19)	9 (20)	15 (48)	30 (61)	153 (65)	<0.001
Ca-blocker, n (%) (n=31/46/31/49/234)	2 (6)	2 (4)	11 (35)	24 (49)	95 (41)	<0.001
ACEi/ARB, n (%) (n=31/46/31/49/245)	3 (10)	8 (17)	22 (71)	39 (80)	153 (62)	<0.001
Statins, n (%) (n=31/46/31/49/245)	7 (23)	4 (9)	9 (29)	13 (27)	70 (29)	0.04
Diuretics, n (%) (n=31/46/31/49/242)	0 (0)	5 (11)	18 (58)	37 (76)	205 (85)	<0.001
Pulmonary function						
FVC (% predicted)	88 (69-113)	97 (78-114)	103 (75-117)	90 (58-109)	83 (59-105)	<0.001
FEV ₁ (% predicted)	94 (78-117)	104 (81-123)	103 (69-118)	96 (49-113)	84 (57-106)	<0.001
PEF (% predicted)	87 (49-119)	87 (56-126)	85 (52-122)	75 (40-118)	69 (37-100)	<0.001
FEV ₁ /FVC (%)	86 (70-96)	85 (74-97)	84 (68-93)	84 (69-97)	85 (68-95)	0.52
Pulse oximetry (% saturation, n=30/45/31/46/224)	97 (94-99)	97 (95-99)	97 (95-99)	98 (96-99)	98 (95-99)	0.007
Normal lung function, n (%)	21 (68)	38 (83)	27 (82)	36 (74)	130 (53)	
Obstructive lung function, n (%)	3 (10)	3 (6)	3 (9)	5 (10)	28 (11)	<0.001
Restrictive lung function, n (%)	7 (22)	5 (11)	3 (9)	8 (16)	87 (36)	
Albuminuria (mg/24 hours) (n=26/44/26/40/145)	0 (0-7)	0 (0-51)	308 (4-1469)	188 (12-1389)	1458 (92-6196)	<0.001
Framingham CVD score (%)	14.1 (2.3-47.8)	20.2 (7.2-52.2)	24.4 (2.8-75.3)	20.2 (5.9-86.1)	21.8 (4.4-55.6)	0.12

Pulmonary function

The spirometry assessments of forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁) and peak expiratory flow (PEF) were obtained using Spirolab (Medical International Research, Rome, Italy) with flow accuracy $\pm 5\%$ and volume accuracy $\pm 3\%$ at the Department of Clinical Physiology, Karolinska University Hospital, Karolinska Institutet, Campus Flemingsberg, Stockholm. Predicted normal values were calculated using the formulas by Crapo et al. [16] and expressed as %FEV₁, %FVC and %PEF. At least three reproducible tests were carried out for each measurement and the highest was recorded. Pulse oximetry yielding oxygen saturation (SpO₂) was performed with a Datex-Engström Finger Sensor (Datex-Engström Division, Instrumentarium Division, Finland) measuring red and infrared light absorption with accuracy $\pm 2\%$ in the SpO₂ interval 80-100%. Obstructive impairment was defined as FEV₁/FVC < 0.70, and restrictive impairment as the FEV₁/FVC $\geq$ 0.70, and %FVC < 80 [17].

Relatively few (n=24) of the patients had pre-existing pulmonary disease diagnoses at baseline. Based on ICD-10 codes (10th revision of the International Statistical Classification of Diseases and Related Health Problems) previously recorded diagnoses included: upper respiratory infection (J069-J101; n=3); pneumonia (J180-J189; n=5); bronchitis (J209; n=2); chronic obstructive pulmonary disease, COPD (J441-J449; n=10); asthma (J459; n=2); interstitial pulmonary disease (J841; n=1); and pneumothorax (J939; n=1). None of these patients had signs of overt clinical infection at the time of investigation.

Biochemical analysis

Blood samples were collected at baseline evaluation after overnight fasting. The plasma was separated within 30 minutes, and samples were kept frozen at -70°C if not analyzed immediately. Analyses of plasma high-sensitivity C-reactive protein (hsCRP; coefficient of variation, CV, 5%), cholesterol, triglycerides, HDL-cholesterol, calcium, phosphate, hemoglobin, creatinine, and albumin (CV 3-4%) were performed at the Clinical Laboratory of Karolinska University Hospital, Campus Flemingsberg, Stockholm. Interleukin-6, IL-6 (CV 4%), insulin-like growth factor-1, IGF-1 (CV 4.3%) and tumor necrosis factor (TNF) were measured on an Immulite 1000 Automatic Analyzer (Siemens Healthcare, Diagnostics Products Ltd, Los Angeles, CA, USA) at the laboratory of Department of Renal Medicine using assays manufactured for this analyzer and according to the manufacturer's instructions. Presence of CVD was defined as a clinical history or signs of ischemic cardiac disease, and/or presence of peripheral vascular disease, cerebrovascular disease/presence of heart failure, and arrhythmia. Blood pressure is presented as mean blood pressure defined as [diastolic pressure + (systolic pressure – diastolic pressure) / 3].

Nutritional assessment

According to the subjective global assessment (SGA) score, patients were classified as well nourished (SGA score=1) or as having mild (SGA=2), moderate (SGA=3) or severe (SGA=4) malnutrition (i.e., protein-energy wasting, PEW) [18]. For simplicity, the patients were combined in two groups; malnourished (SGA $\geq$ 2) and well nourished (SGA=1). Handgrip strength (HGS) was evaluated in the non-dominant arm using the Harpenden dynamometer (Yamar, Jackson, MI, USA) and repeated three times, and the greatest value was recorded. The individual values for HGS were expressed as percentage of healthy individuals (%HGS), adjusting for the gender, when included in the statistical analyses. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Lean body mass and fat mass were calculated by anthropometry with measurements of biceps, triceps, subscapular and supra-iliac skinfold thickness using the Durnin and Womersley caliper method [19], and by equations proposed by Siri [20]. Lean body mass index (LBMI) and fat body mass index (FBMI) were calculated according to the method of Kyle et al. [21] and expressed as kg/m². Physical activity was reported by each individual in a questionnaire allowing choices between four domains: 1) exercise frequently, 2) normal activity, 3) low activity, and 4) bedridden or wheelchair bound.

Statistical analysis

Data are expressed as median (10th to 90th percentile) or percentage or sub hazard ratios, as appropriate. Statistical significance was set at the level of $P < 0.05$. Comparisons between two groups were assessed with the non-parametric Wilcoxon test for continuous variables and Fischer's exact test for

nominal variables. Differences between more than two groups were analyzed using the non-parametric ANOVA Kruskal-Wallis test followed by the Dunn's test.

The patients were followed from the inclusion date until renal transplantation, death, completion of 60 months of follow-up, or until Dec 31, 2015. The cause of death was established through death certificate issued by the attending physician. We applied Framingham CVD risk score [22] in order to consider the following traditional risk factors: age, gender, diabetes, systolic blood pressure, anti-hypertensive medication, total cholesterol, HDL-cholesterol and smoking. Survival during follow-up was analyzed by the competing-risk regression model and the cumulative incidence curve [23]. We used Fine & Gray models and these were adjusted for confounders [24]. The sub-hazard ratios (sHR) for one standard deviation (1-SD) higher level of %FEV₁ and %FVC and sHR for high tertile of %FEV₁ and %FVC were calculated with competing-risk regression models with transplantation as a competing risk. Framingham CVD risk score, BMI, history of CVD, albumin, PEW, hsCRP and albuminuria were considered as confounding factors. Albuminuria was investigated by 24 hours urine collection. We used cutoff of urinary albumin excretion $\geq 30\text{mg/day}$ as a clinically meaningful definition of albuminuria. Goodness of fit of the models was also evaluated with particular attention to the underlying proportionality assumption; no violations of the assumption were found in our analyses. We used logistic regression analysis to examine factors associated with the prevalence of CVD. In addition to gender, diabetes, and smoking, one standard deviation (1-SD) increments of age, albumin, hsCRP, eGFR, %FEV₁ and %FVC were considered in the multivariable logistic model. All statistical analyses were performed using statistical software SAS version 9.4 (SAS Campus Drive, Cary, NC, USA).

Results

Clinical characteristics

Clinical and biochemical characteristics of all individuals (n=404; GFR categories 1-5), divided according to whether they had normal (n=252; 63%), obstructive (n=42; 10%) or restrictive (n=110; 27%) lung function at baseline, are presented in Table 2. While age and sex were similar among the three groups, patients with restrictive lung function had more often comorbidities (diabetes mellitus, DM, CVD, and PEW), higher levels of inflammation biomarkers (hsCRP and IL-6), lower physical activity, lower HGS, and more frequent usage of β -blockers and statins.

Patients with restrictive lung function had low %FVC (median 69%) and %FEV₁ (median 73%); however, the decline in %FVC was more pronounced than that of %FEV₁, resulting in a high ratio of FEV₁/FVC (median 88%). In those with obstructive lung function, %FEV₁ was reduced to median 63% while %FVC was less altered (median 82%), and consequently the FEV₁/FVC ratio was markedly reduced to median 65%.

Patients with more advanced GFR categories had more often comorbidities (DM, CVD and PEW), lower HGS and were more inflamed than those in other GFR categories, and they had lower %FEV₁, %FVC and %PEF while FEV₁/FVC was similar across GFR categories (Table 1). Obstructive and especially restrictive lung dysfunction was more common among those with advanced CKD (GFR category 4 and 5). Univariate associations between lung function indices and other parameters are given in Table 3. DM patients (n=114) had lower %FVC and %FEV₁, and more often comorbid conditions than non-DM patients. Patients with CVD (n=111) had lower %FVC and %FEV₁, and were older, and had more often comorbid conditions, inflammation and PEW than patients without CVD (n=293). CVD was predicted in multivariate logistic regression by 1-SD increments of %FVC OR, 95% CI(0.59 (0.41-0.84) p=0.003) and %FEV₁ OR, 95% CI(0.70 (0.51-0.96) p=0.03) respectively, after adjusting for age, gender, DM and smoking and 1-SD increments of albumin, hsCRP, and eGFR. Patients with PEW (SGA>1; n=63) had lower %FVC and %FEV₁, and had more often comorbid conditions and inflammation than well-nourished patients (n=336) (data not shown).

Table 2. Clinical and biochemical characteristics of 404 individuals divided according to lung function. Continuous variables are presented as median (10 – 90 percentile). Categorical variables are presented as number (n)/percentage (%). Abbreviations: Mean BP, mean blood pressure; GFR, glomerular filtration rate; Total BMD, Total bone mineral density; PEW, protein-energy wasting; SGA, Subjective global nutritional assessment; HDL, high-density lipoprotein; intact-PTH, intact parathyroid hormone; hsCRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; TNF, tumor necrosis factor; ACEi, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; PEF, peak expiratory flow. ^aLow physical activity or bed or wheelchair bound (according to questionnaire where patient reported one of four domains: 1) exercise frequently, 2) normal activity, 3) low activity, or 4) bedridden or wheelchair bound); ^b % HGS, Handgrip strength as percentage of values for CKD 1 and 2. Obstructive impairment: FEV₁/FVC <0.70. Restrictive impairment: FEV₁/FVC ≥0.70 and %FVC <80

Demography and clinical characteristics	Normal (n=252)	Obstructive (n=42)	Restrictive (n=110)	P value
Age (years)	57 (36-71)	63 (32-72)	59 (37-71)	0.14
Males, n (%)	159 (63)	28 (67)	75 (68)	0.62
Diabetes mellitus, n (%)	52 (21%)	11 (26%)	51 (46%)	<0.001
Cardiovascular disease, n (%)	45 (18%)	13 (31%)	53 (48%)	<0.001
Smoker, n (%) (n=219/37/87)	85 (39)	11 (30)	32 (37)	0.56
Mean BP (mmHg, n=252/41/110)	109 (91-125)	106 (90-137)	107 (90-130)	0.99
Low physical activity ^a , n (%) (n=234/36/105)	14 (6)	6 (17)	24 (23)	<0.001
Framingham CVD risk score (%) (n=252/42/110)	17.8 (3.8-56.3)	31.3 (4.5-58.3)	24.9 (5.3-61.0)	0.01
Urine albumin ≥ 30mg/day, n (%) (n=190/26/65)	121 (64)	19 (73)	54 (69)	0.009
eGFR (ml/min/1.73 m ²)	13.5 (4.6-88.9)	9.8 (4.4-76.4)	6.9 (3.8-68.1)	<0.001
Nutritional status				
PEW (SGA>1), n (%) (n=250/40/109)	17 (7%)	12 (30%)	34 (31%)	<0.001
Body mass index, (kg/m ²)	25.2 (20.2-30.8)	22.9 (18-28.6)	24.7 (20.3-32.4)	0.004
Lean body mass index, (kg/m ² , n=249/40/101)	17.4 (14.6-20.5)	16.3 (13.2-19.7)	17.3 (13.6-20.6)	0.03
Fat body mass index, (kg/m ² , n=249/40/101)	7.9 (4.6-11.7)	6.8 (3.9-10.8)	7.5 (4.1-12.6)	0.06
% HGS ^b (%), n=251/41/107)	100 (70-122)	80 (50-106)	85 (55-122)	<0.001
Total BMD (g/cm ² , n=238/37/93)	1.17 (1.02-1.31)	1.14 (0.98-1.29)	1.15 (1.03-1.33)	0.30
Markers of metabolism and nutrition				
Hemoglobin (g/L)	123 (94-148)	116 (86-146)	109 (93-138)	<0.001
Albumin (g/L)	37 (30-42)	35 (27-41)	34 (24-40)	<0.001
IGF-1 (μg /mL, n=204/29/86)	155 (81-307)	170 (53-234)	158 (65-289)	0.62
Triglyceride (mmol/L, n=249/42/109)	1.6 (0.7-3.3)	1.7 (0.9-3.3)	1.7 (0.9-3.3)	0.57
Total cholesterol (mmol/L, n=251/42/109)	5.0 (3.6-6.6)	5.1 (3.7-7.0)	4.4 (3.1-6.6)	<0.001
HDL cholesterol (mmol/L, n=216/39/107)	1.3 (0.9-2.1)	1.2 (0.7-2.1)	1.2 (0.8-2.0)	0.22
Calcium (mmol/L, n=251/40/108)	2.4 (2.2-2.8)	2.5 (2.1-2.7)	2.4 (2.1-2.7)	0.22
Phosphate (mmol/L, n=250/40/108)	1.4 (0.9-2.5)	1.5 (0.9-2.6)	1.8 (0.9-2.7)	<0.001
Intact-PTH (ng/L, n=248/42/110)	103 (30-398)	93 (30-482)	197 (33-469)	<0.001
Biomarkers of inflammation				
hsCRP (mg/L)	2.5 (0.5-14.0)	4.3 (0.8-52.3)	7.7 (1.1-30.8)	<0.001
IL-6 (pg/mL, n=214/37/105)	3.3 (1.2-10.1)	8.1 (2.2-18.7)	6.3 (2.3-21.7)	<0.001
Fibrinogen (g/L, n=247/41/108)	3.7 (2.6-5.9)	4.1 (2.8-6.4)	5.0 (3.1-6.9)	<0.001
TNF (pg/mL, n=194/35/96)	8.9 (4.1-16.7)	10.3 (3.9-27.4)	12.8 (6.5-21.4)	<0.001
Leucocytes count (10 ⁹ /L)	6.8 (4.7-9.6)	7.4 (5.4-11.3)	8.3 (5.1-12.4)	<0.001
Medications				
β-blocker, n (%) (n=244/40/107)	122 (50)	22 (55)	69 (64)	0.04
Ca-blocker, n (%) (n=244/40/107)	80 (33)	11 (28)	43 (40)	0.26
ACEi/ARB, n (%) (n=251/41/110)	149 (59)	18 (44)	58 (53)	0.13
Statins therapy, n (%) (n=251/41/110)	56 (22)	5 (12)	42 (38)	<0.001
Diuretics, n (%) (n=249/41/109)	148 (59)	29 (71)	88 (81)	<0.001
Pulmonary function				
FVC (% predicted)	94 (83-112)	82 (59-118)	69 (51-78)	<0.001
FEV ₁ (% predicted)	98 (83-118)	63 (46-96)	73 (54-86)	<0.001
PEF (% predicted)	81 (49-118)	39 (23-85)	68 (40-97)	<0.001
FEV ₁ /FVC (%)	85 (75-95)	65 (52-69)	88 (76-96)	<0.001
Pulse oxymetry (% saturation, n=239/35/102)	98 (95-99)	98 (95-99)	98 (94-99)	0.45

Table 3. Univariate associations expressed as rho correlations of %FEV₁ and %FVC with other variables at baseline in 404 GFR categories G1 - 5 individuals. Abbreviations: %FEV₁, percentage of predicted forced expiratory volume in 1 second value; %FVC, percentage of predicted forced vital capacity value; eGFR, estimated glomerular filtration rate; PEW, protein-energy wasting; SGA, Subjective global nutritional assessment score; %HGS, Handgrip strength as percentage of values for CKD 1 and 2; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6

Characteristics	%FEV ₁		%FVC	
	rho	p value	rho	p value
Age (years)	-0.04	0.48	-0.08	0.096
Males (%)	0.01	0.78	-0.06	0.23
Diabetes mellitus (present)	-0.22	<0.001	-0.25	<0.001
Cardiovascular disease (present)	-0.29	<0.001	-0.34	<0.001
Smoking	0.04	0.50	0.01	0.79
Mean blood pressure (mmHg)	-0.08	0.12	-0.02	0.66
eGFR (ml/min/1.73 m ²)	0.34	<0.001	0.28	<0.001
PEW (SGA>1) (%)	-0.31	<0.001	-0.31	<0.001
Body mass index (kg/m ²)	0.07	0.15	0.01	0.79
Lean body mass index (kg/m ²)	0.14	0.007	0.07	0.19
Fat body mass index (kg/m ²)	-0.004	0.94	-0.02	0.64
%HGS (%)	0.31	<0.001	0.32	<0.001
Calcium (mmol/L)	-0.06	0.23	-0.02	0.72
Phosphate (mmol/L)	-0.30	<0.001	-0.28	<0.001
hsCRP (mg/L)	-0.41	<0.001	-0.36	<0.001
IL-6 (pg/mL)	-0.45	<0.001	-0.40	<0.001
Albuminuria (mg/24 hours)	-0.34	<0.001	-0.27	<0.001
Framingham CVD score (%)	-0.13	0.008	-0.18	<0.001

The proportion of individuals with obstructive and especially restrictive lung function increased with increasing number of comorbid conditions (CVD, inflammation and PEW (Fig. 1). The prevalence of restrictive lung function increased from 13% in patients with none of these factors to 64% when three of them were present.

Fig. 2 shows %FEV₁ and %FVC at baseline and follow-up in patients who had normal lung function, or obstructive or restrictive lung function at baseline in total 404 patients. As expected patients with restrictive lung impairment at baseline had lower %FVC and %FEV₁ than patients with normal lung function.

Among the G-5 patients (n=245) who were re-assessed after 1 year (n=130) and 2 years (n=65), both %FEV₁ and %FVC remained essentially unchanged over time, independent of whether they had obstructive or restrictive lung function at baseline (data not shown). Renal replacement treatment did not appear to impact on lung function indices during follow up in G-5 patients; thus %FEV₁ and %FVC levels were essentially similar independent of whether patients underwent conservative, hemodialysis (HD) or peritoneal dialysis (PD) treatment (data not shown).

Association between lung function and mortality

During follow-up over 5 years, the overall mortality rate was 24% (n=95) among the 404 individuals. As almost half of the G-5 individuals underwent renal transplantation (n=112) during the follow-up period, competing-risk regression models with transplantation as a competing risk were used for survival analyses.

Among all 404 GFR categories 1-5 individuals, 1-SD higher %FEV₁ and 1-SD higher %FVC associated with lower mortality risk with crude sHR = 0.49 (95%CI 0.27 to 0.88) and crude sHR = 0.56 (95%CI 0.32 to 0.98) respectively. After adjusting for tertiles of Framingham CVD score (representing age, gender, DM, systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL-cholesterol and smoking), the survival benefits associated with 1-SD higher %FEV and 1-SD higher %FVC remained significant, sHR 0.62 (95% CI 0.48 to 0.79; p=0.001) and sHR 0.63 (95% CI 0.47 to 0.85; p=0.003) respectively.

The highest tertiles (as compared to the other tertiles) of %FEV₁ and %FVC respectively associated with lower all-cause mortality after adjustments for tertiles of Framingham CVD score (representing age, gender, DM, systolic blood pressure, use of anti-hypertensive

Fig. 1. Prevalence of restrictive and obstructive lung dysfunction and normal lung function among 404 individuals with GFR categories G-1 to G-5 in relation to number of concomitantly present comorbid conditions, PEW, inflammation and CVD. Abbreviations: Obstructive, Obstructive lung function; Restrictive, Restrictive lung function.

Fig. 2. Lung function indices, %FEV₁ and %FVC, in 404 patients with GFR categories G-1 to G-5 who had normal, obstructive or restrictive lung function at baseline (n=404), and results at follow up after 1 year (n=192) and 2 years (n=118) respectively. Abbreviations: %FEV₁, Forced expiratory volume in the first second expressed as percentage of predicted normal values; %FVC, Forced vital capacity expressed as percentage of predicted normal values; Base, baseline; 1Y, 1 year; 2Y, 2 years.

medication, total cholesterol, HDL-cholesterol and smoking), presence of CVD and PEW, and albumin, BMI, hsCRP, and albuminuria, sHR of 0.49 (95% CI, 0.27 to 0.88, $p = 0.01$) and sHR of 0.56 (95% CI, 0.32 to 0.98, $p=0.04$) respectively (Fig. 3A and 3B).

After applying the same adjustments, the highest tertile (as compared to the other tertiles) of %FEV₁ associated with lower CVD mortality with sHR of 0.16 (95% CI, 0.04 to 0.69, $p = 0.01$) (Fig. 3C). The association of the highest tertile of %FVC with CVD mortality was not significant; data not shown).

Restrictive lung dysfunction associated with increased mortality risk (sHR of 1.80, 95%CI, 1.04 to 3.13, $p = 0.03$) while the association with obstructive lung impairment was not significant after adjusting for Framingham CVD risk score (representing age, gender, DM, smoking, total cholesterol, HDL-cholesterol and anti-hypertensive treatment); presence of CVD, PEW and albuminuria; and levels of BMI, plasma albumin and hsCRP, as well as %HGS, (Fig. 3D).

Fig. 3. Cumulative incidence curves of 5-year survival in 404 patients with GFR categories G-1 to G-5 in relation to baseline values of %FEV1, %FVC, %FEV1, and baseline presence of normal vs obstructive or restrictive lung function. Associations were expressed as SHR(95%CI) following adjustments for: Framingham CVD risk score (representing age, gender, DM, smoking, total cholesterol, HDL-cholesterol, and anti-hypertensive treatment), presence of CVD, PEW and albuminuria, and BMI and plasma albumin and hsCRP levels. **A:** The highest tertile (n=140) as compared to low + middle tertiles (n=264) of %FEV1 associated with lower all-cause mortality with sHR of 0.49 (95% CI, 0.27 to 0.88). **B:** The highest tertile (n=139) as compared to low + middle tertiles (n=265) of %FVC associated with lower all-cause mortality with sHR of 0.56 (95% CI, 0.32 to 0.98). **C:** The highest tertile (n=140) as compared to low + middle tertiles (n=264) of %FEV1 associated with lower CVD mortality with sHR of 0.16 (95% CI, 0.04 to 0.69). **D:** Restrictive lung function associated with higher all-cause mortality risk with sHR of 1.80 (95% CI 1.04 to 3.13, p=0.03). The association of obstructive lung impairment with mortality was not significant.

Discussion

Although lung dysfunction is a known complication in CKD, its prevalence, characteristics and clinical implications in relation to GFR are largely unexplored. In this cohort study of 404 clinically stable individuals, representing all GFR categories, and few (6%) had pre-existing pulmonary disease diagnoses, lung dysfunction was a strong independent predictor of worse 5-year survival. The present study is the first longitudinal study exploring associations between pulmonary function and mortality over the spectrum of all GFR categories.

The negative impact of lung dysfunction on clinical outcome appeared to be mainly due to restrictive lung dysfunction that was a common complication among those with advanced CKD, especially in those with comorbidities. In the Swedish population, the prevalence of chronic obstructive pulmonary disease (COPD) was reported to range between 10% and 16% among selected-middle aged participants; however, the role of impaired GFR was not investigated [25, 26]. In the present study, while the prevalence of *obstructive lung function*

increased slightly across GFR categories 1-5, from 6% in G-2 to 11% in G-5, these figures are lower than in the general Swedish population. Whether this discrepancy reflects selection bias for example due to putative survival benefit of CKD patients with normal lung function (who lived long enough to be included in our study), or differences in methodology and criteria for lung dysfunction is unclear. On the other hand, the prevalence of *restrictive lung function* was markedly higher as GFR declined in our individuals, from 9% in G-3 to 36 % in G-5 individuals, and it was as high as 64% in individuals (n=22) with concomitant presence of PEW, inflammation and CVD (Fig. 1). The prevalence of restrictive lung function in our patients is higher than values reported in a Swedish general population sample, aged 21-86 years, where the prevalence of a restrictive spirometric pattern was 9-11% when based on pre-bronchodilator values and 7% when based on post-bronchodilator values; however, the role of GFR was not investigated [27].

In the general population, reduced %FEV₁ and %FVC are associated with presence of CVD and increased all-cause mortality risk [8, 9] and, in middle-aged individuals as well as in patients with COPD, lung dysfunction associates with CVD and increased CVD-related mortality [28, 29]. However, there are few previous studies on associations between pulmonary function and all-cause and CVD-mortality across the entire spectrum of GFR categories. In the present study, using competing-risks regression analysis, and adjusting for Framingham CVD score (representing age, gender, DM, systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL-cholesterol, and smoking), presence of CVD, PEW, and albuminuria, and levels of BMI, albumin, hsCRP and albuminuria, the highest tertiles of %FEV₁ and %FVC associated with lower all-cause mortality and the highest tertile of %FEV₁ associated also with lower CVD mortality. In accordance, a previous study reported that a low %FVC was associated with high mortality in CKD 5 patients [10] while another study failed to show that low %FEV₁ was associated with mortality in dialysis patients [11].

Although it is well recognized that smoking impairs lung function and associates with cardiovascular events [30-33], impaired lung function associates with all-cause and cardiovascular mortality, independent of smoking [8, 34, 35]. The present study confirms that impaired lung function in CKD is associated with all-cause and CVD mortality, independent of smoking. Among possible explanations, the loss of renal function in CKD results in fluid overload and metabolic and endocrine abnormalities that may promote restrictive lung impairment in CKD [6]. Our finding that lower muscle strength (%HGS) associates with impaired lung function is in line with previous observations that decreased respiratory muscle strength may lead to decreased vital capacity in CKD patients [36].

Previous studies reported an inverse association between inflammation and lung function indices FVC and FEV₁ [37-39]. In the present study, lung function indices were inversely associated with inflammation (data not shown). Since a longitudinal association between lower lung function and inflammation has been reported [40], it is possible that a reduced lung volume in our individuals may be linked to increased systemic inflammation. A previous study reported associations of inflammation with obstructive and restrictive lung disease [41]. Impaired lung function associates with inflammation and increased cardiovascular risk [42]. Inflammation is a strong predictor of atherosclerosis and cardiovascular events in the general population [43-47]. The mechanisms for pathogenesis of COPD, which may lead to CVD, are thought to involve inflammation, neurohumoral activation, cachexia, and skeletal muscle dysfunction [48-51]. In the present study, presence of CVD was independently associated with %FEV₁ or %FVC even after adjusting for age, gender, inflammation, albumin, smoking, diabetes and eGFR (data not shown).

Protein-energy wasting (PEW) and inflammation are common (30-50%) interlinked conditions in patients with advanced CKD, and presence of chronic low-grade inflammation is thought to play a central role in the pathophysiology of a range of complications in uremia [15, 52]. In the present study, lung function indices, %FVC and %FEV₁, were significantly lower in individuals presenting with PEW and inflammation. Concomitant presence of more comorbid factors (PEW, inflammation and CVD) associated with progressively higher

prevalence of restrictive lung function (Fig. 1). On the other hand, measurements repeated in G5 patients after 1 year and 2 years showed that %FEV₁ and %FVC remained essentially unchanged during follow up, independent of uremia treatment (conservative, hemodialysis or peritoneal dialysis). Thus it is likely that abnormalities of uremia including inflammation rather than the type of uremia treatment may contribute to impaired lung function in CKD. Our findings of strong associations of lung function with inflammation, PEW, and CVD and with clinical outcomes across GFR categories suggest that also lung status, a previously often overlooked factor, should be considered in risk assessments in these individuals. Furthermore, in the Atherosclerosis Risk in Communities (ARIC) Study, reduced lung function, particularly lower percent-predicted FVC, was found to be independently associated with CKD progression [53].

When interpreting these results one should consider some limitations and strengths of the present study. First, this was an observational study so no conclusions can be made about causality. Second, we included only clinically stable individuals few of whom had pre-existing lung disease, and due to this selection bias, our findings may not necessarily be valid for the CKD population as a whole. Third, we did not investigate confounders such as volume overload, subclinical pulmonary edema and interstitial fibrosis, which are common in patients with advanced CKD [3, 5, 6]. On the other hand, to the best of our knowledge, this is the first study exploring association of pulmonary dysfunction with mortality in extensively phenotyped individuals over a broad range of GFR categories.

Conclusion

Impaired lung function, especially restrictive lung dysfunction, is a common feature of advanced CKD that associates with severity of renal failure, presence of PEW, inflammation and CVD, and with 5-year all-cause and CVD-related mortality. The prevalence of restrictive lung function increased in proportion to the number of comorbid conditions, PEW, inflammation and CVD, being present concomitantly, from 13% in patients with none of these conditions to 64% when three of them were present. Further studies in larger cohorts of CKD patients on causes and consequences of lung dysfunction, especially restrictive lung function, are warranted to confirm these findings.

Disclosure Statement

Bengt Lindholm is employed by Baxter Healthcare Corporation. None of the other authors declare any conflict of interest.

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