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Chronic Renal Failure : A Neglected Comorbidity of COPD

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CHEST

Original Research

COPD

Chronic Renal Failure

A Neglected Comorbidity of COPD

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Background: **To the best of our knowledge, the association between COPD and chronic renal failure (CRF) has never been assessed. Lean mass is frequently reduced in COPD, and the glomerular filtration rate (GFR) might be depressed in spite of normal serum creatinine (concealed CRF). We investigated the prevalence and correlates of both concealed and overt CRF in elderly patients with COPD.**

Methods: **We evaluated 356 consecutive elderly outpatients with COPD enrolled in the Extrapulmonary Consequences of COPD in the Elderly Study and 290 age-matched outpatients free from COPD. The GFR was estimated using the Modification of Diet in Renal Disease Study Group equation. Patients were categorized as having normal renal function (GFR ≥ 60 mL/min/1.73 m²), concealed CRF (normal serum creatinine and reduced GFR), or overt CRF (increased serum creatinine and reduced GFR). Independent correlates of CRF were investigated by logistic regression analysis.**

Results: **The prevalence of concealed and overt CRF in patients with COPD was 20.8% and 22.2%, respectively. Corresponding figures in controls were 10.0% and 13.4%, respectively. COPD and age were significantly associated with both concealed CRF (COPD: odds ratio [OR] = 2.19, 95% CI = 1.17-4.12; age: OR = 1.06, 95% CI = 1.04-1.09) and overt CRF (COPD: OR = 1.94, 95% CI = 1.01-4.66; age: OR = 1.06, 95% CI = 1.04-1.10). Diabetes (OR = 1.96, 95% CI = 1.02-3.76), hypoalbuminemia (OR = 2.83, 95% CI = 1.70-4.73), and muscle-skeletal diseases (OR = 1.78, 95% CI = 1.01-3.16) were significant correlates of concealed CRF. BMI (OR = 1.05, 95% CI = 1.01-1.10) and diabetes (OR = 2.25, 95% CI = 1.26-4.03) were significantly associated with overt CRF.**

Conclusions: **CRF is highly prevalent in patients with COPD, even with normal serum creatinine, and might contribute to explaining selected conditions such as anemia that are frequent complications of COPD.** ***CHEST 2010; 137(4):831–837***

Abbreviations: CRF = chronic renal failure; GFR = glomerular filtration rate; OR = odds ratio

Chronic renal failure (CRF) rises in prevalence with age[1] and is frequently associated with chronic diseases such as congestive heart failure and diabetes mellitus.[2,3] When present as a comorbidity, CRF carries negative prognostic implications[2,4,5] and impacts the therapeutic strategy. In frail elderly patients, who are the majority of those suffering from chronic disabling conditions, CRF is often associated with normal serum creatinine concentration, a condition known as unrecognized or concealed CRF.[6]

COPD is the seventh most frequent chronic disease and is expected to rank fourth by 2020.[7] It is associated

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*A complete list of study participants is located in the Appendix.

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with several comorbidities,[8] but it is unknown to which extent it is associated with CRF. Coronary artery disease, which is highly prevalent in patients with COPD,[9] is associated with vascular kidney disease.[10] Furthermore, both nicotine and selected heavy metals, which are components of smoke, are risk factors for kidney disease.[11] Thus, COPD is expected to be significantly associated with CRF. Nonetheless, most studies reporting about comorbidity in COPD refer to selected populations (eg, patients having a serum creatinine lower than 2 mg/dL),[12] do not specify how a diagnosis of CRF was made,[13] or do not include kidney diseases among self-reported comorbid diseases.[14] A diagnosis of kidney disease was self reported by a surprisingly low 0.2% of patients with COPD studied by van Manen et al[15] and by 11.3% of participants in a large multinational telephone survey.[16] Other studies used an index of overall comorbidity, but not a list of individual comorbid diseases.[17] The only study systematically assessing CRF in an unselected population with COPD showed that CRF has a 6% prevalence and predicted long-term mortality independently from well-recognized risk factors; however, CRF was diagnosed based on serum creatinine, and its prevalence likely was underestimated.[18] In fact, a variable, yet consistent, proportion of patients with COPD has a reduced muscular mass,[19] and thus, serum creatinine might be falsely low as the result of decreased creatine release.

The present study proposes to assess the prevalence of CRF, defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, in a population with COPD aged 65 years and older and to verify whether concealed CRF[6,20] (ie, a reduced GFR despite normal serum creatinine) is associated with a distinctive clinical profile of patients with COPD.

Materials and Methods

Design Overview

We used data coming from the Extrapulmonary Consequences of COPD in the Elderly study, a population-based observational study of white patients with COPD aged 65 years and older aimed at exploring extrapulmonary consequences of COPD. The diagnosis of COPD conformed to American Thoracic Society/European Respiratory Society guidelines.[21] To be included in the study, patients had to be in a stable condition and with no physical findings or symptoms suggestive of acute exacerbation or therapy modifications in the 30 days before enrollment. People with a diagnosis of cancer were excluded, regardless of disease activity. The study protocol was approved by the ethical committee at the coordinating center (University of Palermo, Italy). In order to verify whether and to what extent COPD is distinctively associated with CRF, the prevalence of CRF in the study population was compared with that obtained in a population of geriatric outpatients free from COPD (control population).

Settings and Participants

Participants were consecutively recruited among those attending the pulmonary medicine outpatient facilities of 15 participating centers located throughout Italy (see list of participating centers in the Appendix). At first visit, patients gave written consent to participate in the study and underwent spirometry and a multidimensional assessment as described in Table 1.[22-26]

Twenty-seven of 516 screened patients were excluded because the diagnosis of COPD was not confirmed at the diagnostic work-up, and five because of low-quality spirometry results. The final population consisted of 484 patients with COPD. Given that one or more of the measures needed to compute the GFR (creatinine, blood urea nitrogen, albumin) were lacking for 128 patients, the final sample included 356 patients. The control population consisted of 290 age- and gender-matched outpatients attending the geriatric ambulatory facility of the Campus Bio-Medico University for the evaluation and treatment of chronic conditions other than respiratory diseases.

Outcomes

The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study Group equation:[27]

$$170 \times [\text{serum creatinine}]^{-0.999} \times [\text{age}]^{-0.176} \times [\text{blood urea}]^{-0.170} \times [\text{serum albumin}]^{0.318} \times (0.762 \text{ for women}) \times (1.180 \text{ for African-American subjects})$$

The MDRD formula was preferred over other formulas, such as the Cockroft-Gault, because it seems to be more accurate in older people.[28] Patients were categorized according to their renal function as having normal renal function (GFR ≥ 60 mL/min/1.73 m^2), concealed CRF (normal serum creatinine and GFR <60 mL/min/1.73 m^2), or overt CRF (increased serum creatinine and GFR <60 mL/min/1.73 m^2). GFR <60 mL/min/1.73 m^2 marks the threshold for moderate renal dysfunction in the Kidney Disease Outcomes Quality Initiative guidelines classification.[29] Serum creatinine was measured by the standardized Jaffe method in all laboratories of the participating centers. The cutoff used for serum creatinine was 1.26 mg/dL in men and 1.04 mg/dL in women.[30]

Table 1—*Multidimensional Assessment*

Assessment Categories
Clinical history: smoking, long-term oxygen therapy use, number of active diseases, respiratory and nonrespiratory drugs, frequency of exacerbations, and dysphagia were recorded.
Anthropometric measurement: height, weight, BMI, waist and hip circumference; percent of the ideal weight was calculated using the equation by Robinson et al.[22]
Nutritional status: Mini Nutritional Assessment[23]
Rating of dyspnea: MRC scale[24]
Personal independence: Barthel Index scores[25]
Exercise capacity: 6-min walking test[26]
Arterial hemoglobin oxygenation: pulse oxymeter
12-leads electrocardiography
Laboratory analyses: blood cell count, total protein and albumin concentration, C-reactive protein concentration, ESR, creatinine, blood urea nitrogen, uric acid, total cholesterol, and sodium, potassium, and chlorine concentration
Arterial blood gases were measured while the patient was breathing room air for at least 1 h

ESR = erythrocyte sedimentation rate; MRC = Medical Research Council.

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Statistical Analysis

First, we investigated the prevalence of concealed and overt CRF in both the study and control populations. Afterward, we compared socio-demographic, clinical, and laboratory characteristics of patients with COPD grouped according to whether they had normal renal function, concealed CRF, or overt CRF. Plasma albumin and hemoglobin were also considered in the analyses because low serum albumin (< 3.5 g/dL) might reflect protein malnutrition and, therefore, might be associated with depressed serum creatinine, while anemia (Hb < 13 g/dL for men and < 12 g/dL for women)[31] is expected to increase in prevalence for decreasing GFR values.

We used contingency tables with a χ^2 test for categorical variables. A one-way ANOVA with the Scheffè *post hoc* test was used for multiple comparisons for continuous variables.

To verify whether COPD was independently associated with concealed or overt CRF, we used a backward stepwise logistic regression model, including as independent variables the ones expected to increase the risk of renal impairment and, among these, also cardiovascular and cerebrovascular diseases because both are frequently associated with renal atherosclerosis. The BMI also was considered among potential correlates of CRF based upon the epidemiologic evidence.[32] As potential independent correlates of CRF, we also tested hypoalbuminemia and muscle-skeletal diseases because proteic malnutrition and decreased mobility might be associated with reduced muscle mass and, thus, decreased creatine release, a condition likely to characterize concealed CRF.

Finally, we built a model including only COPD patients. In this second analysis, we also considered smoking exposure (pack-years) and, as an index of COPD severity, FEV_1 % predicted. Statistical analysis was performed using the SPSS for WIN statistical software package, v 10.0 (SPSS Inc; Chicago, IL).

Results

The mean age of enrolled patients was 75.4 years (SD 6.1, range 61-92), 19.7% of them were women. The mean serum creatinine concentration was 1.06 mg/dL (SD 0.40), and the mean estimated GFR was 64.2 mL/min/1.73 m^2 (SD 19.2). The control group had a similar mean age (73.9 years, SD 7.9, range 59-89), and 21.0% of them were women. The mean serum creatinine in the control group was 1.05 (SD 0.55), and the mean estimated GFR was 75.4 mL/min/1.73 m^2 (SD 22.4). The most common main diseases in the control group were hypertension (n = 179, 61.7%), muscle-skeletal disease (n = 78, 26.9%), cardiovascular disease (n = 69, 23.8%), diabetes (n = 66, 22.8%), cerebrovascular disease (n = 34, 11.7%), and dementia (n = 33, 11.4%), and the mean number of chronic conditions was 3.7 ± 2.5 vs 4.0 ± 2.7 in the study group ($P = .147$).

The prevalence of normal renal function, concealed CRF, and overt CRF in COPD was 57.0%, 20.8%, and 22.2%, respectively. The corresponding figures in the control group were 76.6%, 10.0%, and 13.4, respectively (case vs control group: χ^2 27.6, $P < .001$). However, GFR values were 66.7 ± 18.9, 60.7 ± 18.3, 61.2 ± 19.0, and 59.1 ± 18.6 mL/min/1.73 m^2 in patients with COPD and an $FEV_1 > 80\%$, 50% to 80%, 30% to 50%, and < 30%, respectively ($F = 2.917$, $P = .034$), which indicates only a small difference among participants with different degrees of COPD severity.

The overall prevalence of CRF (ie, of GFR < 60 mL/min/1.73 m^2) was 43.0% in the study group and 23.4% in the control group ($\chi^2 = 27.1$, $P < .001$). Normal serum creatinine was observed in 52.5% of patients with COPD who had a GFR between 30 and 59.9 mL/min/1.73 m^2 and in 53.2% of control patients ($\chi^2 = 0.01$, $P = .923$), while all patients with COPD who had a GFR less than 30 mL/min/1.73 m^2 had increased serum creatinine.

Clinical and laboratory characteristics of patients with COPD grouped according to whether they had normal renal function, concealed CRF, or overt CRF are reported in Table 2. Patients with concealed CRF were more frequently women, had lower $PaCO_2$, and were more frequently affected by muscle-skeletal diseases. Patients with overt CRF had higher overall comorbidity and prevalence of diabetes when compared with those who had normal renal function (Table 1). The prevalence of hypoxemia (ie, $PaO_2 \leq$ 56 mm Hg) was 5.4%, 2.7%, and 3.8% in patients with normal renal function, concealed CRF, and overt CRF, respectively ($P = .716$).

Data pertaining to the nutritional status of patients with COPD are summarized in Table 3. BMI and waist circumference were increased in patients with overt renal dysfunction, but only BMI was still significantly higher in patients with overt CRF with respect to the group with normal renal function after adjusting for multiple comparisons. Hypoalbuminemia was present in 25.2% of controls and in 21.3% of patients with COPD ($P = .261$), but it was more prevalent among patients with COPD and concealed CRF. Neither hemoglobin levels (13.1 ± 2.2 vs13.3 ± 2.0, $P = .232$) nor the prevalence of anemia (27.9% vs 24.4%, $P = .323$) distinguished cases from controls. Among patients with COPD, the prevalence of anemia increased from 19.2% in participants without CRF to 23.0% in those with concealed CRF and to 39.2% in those with overt CRF. This linear relationship was also present after stratification for age and gender (data not shown).

Independent correlates of concealed or overt CRF in the general sample (ie, pooled cases and controls) are reported in Table 4. COPD and age were significantly associated with both concealed and overt CRF. Diabetes, hypoalbuminemia, and muscle-skeletal diseases were significantly associated with concealed CRF. BMI and diabetes qualified as independent correlates of overt CRF.

Logistic regression analysis limited to patients with COPD identified age (odds ratio [OR] 1.11, 95% CI, 1.03-1.19), muscle-skeletal disease (OR 2.73; 95% CI,

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Table 2—*Demographic and Clinical Characteristics of Patients Divided According to Renal Function*

Characteristics	Normal Renal Function, n = 203	Concealed Renal Dysfunction, n = 74	Overt Renal Dysfunction, n = 79	*P* Value
Age, y	74.3 ± 6.2	76.3 ± 5.8	75.8 ± 6.0	.026
Gender, males	170 (83.7)	54 (73.0)[a]	62 (78.5)	.122
FEV_1, %	54.9 ± 18.1	57.3 ± 17.2	56.5 ± 17.2	.565
Pack-years	47.0 ± 40.0	40.7 ± 44.4	50.7 ± 36.5	.330
Barthel score, self-care	47.4 ± 6.4	48.0 ± 4.8	46.2 ± 7.8	.219
Barthel score, mobility	42.2 ± 8.2	42.9 ± 7.1	41.8 ± 7.7	.668
Barthel score, total	89.4 ± 13.6	90.9 ± 10.5	87.9 ± 14.1	.381
6WD, m	330 ± 143	303 ± 118	291 ± 123	.090
6WD, %	76.2 ± 31.6	73.9 ± 24.1	70.5 ± 26.3	.453
pH	7.42 ± 0.04	7.42 ± 0.03	7.41 ± 0.04	.051
$nPaCO_2$, mm Hg	43.0 ± 9.4	39.1 ± 5.2[a]	41.2 ± 6.2	.011
PaO_2, mm Hg	72.4 ± 12.7	76.8 ± 14.8	76.3 ± 11.7	.037
SaO_2, %	94.1 ± 2.9	94.8 ± 2.4	94.1 ± 2.8	.215
Respiratory drugs, n	1.7 ± 1.2	1.4 ± 0.9	1.7 ± 1.6	.150
Comorbidities, n	3.5 ± 2.4	4.2 ± 2.7	5.2 ± 3.2[b]	.001
Hypertension	111 (54.7)	47 (63.5)	53 (67.1)	.115
Cardiovascular diseases	51 (25.1)	19 (25.7)	19 (24.1)	.972
Muscle-skeletal diseases	52 (25.6)	29 (39.2)[a]	20 (25.3)	.068
Gastrointestinal diseases	59 (29.1)	20 (27.0)	24 (30.4)	.899
Diabetes	34 (16.7)	19 (25.7)	28 (35.4)[c]	.003
Cerebrovascular diseases	14 (6.9)	6 (8.1)	10 (12.7)	.292

Data are number of cases (percentage) or mean ± SD. Cardiovascular diseases: heart failure, coronary heart disease, history of pulmonary embolism, venous thrombosis, arrhythmias, valvular diseases, peripheral vascular disease. Muscle-skeletal diseases: osteoporosis, arthritis, kyphosis, scoliosis, fractures, myastenia. Gastrointestinal diseases: gastroesophageal reflux disease, peptic ulcer, liver diseases, inflammatory and/or vascular bowel diseases, chronic pancreatitis. Cerebrovascular diseases: transient ischemic attack, stroke, chronic cerebrovascular disease. 6WD = 6-min walk distance; SaO_2 = arterial oxygen saturation.

[a]$P < .05$ vs normal renal function.

[b]$P < .01$.

[c]$P < .001$.

1.26-5.92), hypoalbuminemia (OR 2.98; 95% CI, 1.22-7.30), and $PaCO_2$ (OR 0.92; 95% CI, 0.87-0.98) as significant correlates of concealed CRF; and identified diabetes (OR 3.42; 95% CI, 1.77-6.60), cardiovascular disease (OR 2.12; 95% CI, 1.11-4.03), and hypertension (OR 1.85; 95% CI, 1.0-3.46) as independent correlates of overt CRF.

Discussion

This study shows that CRF is highly prevalent in an elderly population with COPD and associates with selected nonrespiratory comorbidities. While serum creatinine greater than 1.26 mg/dL for men and 1.04 mg/mL for women[30] is a reliable marker of CRF, the GFR is frequently depressed despite normal serum creatinine, mainly in women and older patients.

The estimated prevalence of CRF in the population with COPD was greater than that observed in the control population with a comparable burden of polipathology but free from COPD, and in about half of the cases, CRF could not be recognized on the basis of serum creatinine. Interestingly, one of four patients with COPD older than 64 years with normal serum creatinine values actually has CRF. Potential clues to recognize these patients are low serum albumin, older age, muscle-skeletal diseases, and diabetes. Indeed, low serum albumin, beyond reflecting depressed hepatic synthesis, is commonly associated

Table 3—*Nutritional Parameters and Prevalence of Anemia in Patients Divided According to Renal Function*

Parameters	Normal Renal Function, n = 203	Concealed Renal Dysfunction, n = 71	Overt Renal Dysfunction, n = 82	*P* Value
BMI, kg/m^2	27.0 ± 5.3	26.5 ± 4.4	29.2 ± 5.6[a]	.002
Waist circumference, cm	101 ± 15	100 ± 15	106 ± 15	.021
Serum albumin < 3.5 g/dL	38 (18.7)	23 (31.1)[b]	15 (19.0)	.072
Anemia	39 (19.2)	17 (23.0)	32 (39.2)[c]	.002

Data are number of cases (percentage) or mean ± SD.

[a]$P < .01$.

[b]$P < .05$ vs normal renal function.

[c]$P < .001$.

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Table 4—*Backward Stepwise Logistic Regression Models of Selected Variables to Concealed or Overt Renal Dysfunction vs Normal Renal Function*

Variables	OR	95% CI
Concealed renal dysfunction[a]		
Age, y (for each 1-y increase)	1.06	1.04-1.09
COPD	2.19	1.17-4.12
Serum albumin < 3.5 g/dL	2.83	1.70-4.73
Muscle-skeletal disease	1.78	1.01-3.16
Diabetes	1.96	1.02-3.76
Overt renal dysfunction[b]		
Age, y (for each 1-y increase)	1.06	1.04-1.10
BMI	1.05	1.01-1.10
COPD	1.94	1.01-4.66
Diabetes	2.25	1.26-4.03

OR = odds ratio.

[a]Cardiovascular disease and gender were removed on step 2, hypertension and BMI were removed on step 3, and cerebrovascular disease was removed on step 4.

[b]Hypoalbuminemia and muscle-skeletal disease were removed on step 2, cardiovascular disease was removed on step 3, and gender was removed on step 4; hypertension and cerebrovascular disease were removed on step 5.

with decreased muscle mass, a common condition in COPD,[33] and therefore, muscle release of creatine. Furthermore, muscle mass decreases with age.[34] Finally, the limitation of physical activity and the ensuing loss of muscle mass likely mediates the link between muscle-skeletal diseases and concealed CRF. Interestingly, COPD qualified as an independent correlate of both concealed and overt CRF, which testifies to the strength of the association between COPD and renal dysfunction. However, COPD *per se*, and not COPD severity, at least as reflected by the FEV_1 percent predicted, was associated with CRF.

The negative association between concealed CRF and $PaCO_2$ is hard to interpret. Indeed, CO_2 might depress GFR by increasing renal peripheral vascular resistance,[35] provided that the experimental evidence applies to a chronic *in vivo* model of CO_2 renal exposure. Furthermore, in the presence of depressed GFR, total blood CO_2 is inversely related to the daily protein intake.[36] Accordingly, in our population higher $PaCO_2$ might reflect lower protein intake more than ventilatory dysfunction. Unfortunately, we had no formal estimate of protein intake to test this hypothesis.

The high prevalence of CRF in patients with COPD might have important clinical implications. First, CRF is associated with increased serum levels of inflammatory biomarkers and prothrombotic molecules.[37] Thus, CRF might partly mediate the association between COPD and cardiovascular diseases. Indeed, CRF *per se* is a major cardiovascular risk factor: the age-standardized risk of cardiovascular event for 100 person-years rises from 3.65 in subjects having a GFR from 45 to 69 mL/min/kg to 21.8 and 36.6 in those with a GFR from 15 to 29 mL/min/kg and a GFR less than 15 mL/min/kg, respectively.[5] As far as we know, the COPD-related systemic proinflammatory status has been considered to reflect bronchial inflammation, and neither the association between FEV_1 and polymerase chain reaction nor the inverse association between FEV_1 and flow-mediated dilation has been adjusted for GFR.[38,39]

Second, CRF might help understand the link between COPD and anemia. The prevalence of anemia in COPD ranges from 10% to 23%, depending upon the diagnostic criteria and the COPD severity,[39] and chronic inflammation has been considered its main causal factor, with iron and folate deficits playing a minor role.[40] However, CRF likely explains some proportion of the cases through impaired production of erythropoietin.[41] which in patients with diabetes frequently precedes the decline of GFR.[42] This latter finding is of special concern for patients with diabetes, given that diabetes is an important comorbidity of COPD and the renal secretion of erythropoietin promotes polycythemia compensating for hypoxemia.[43]

Third, CRF, whether overt or concealed, is a well-known risk factor for adverse drug reactions to hydrosoluble drugs.[20] Indeed, most of the antibiotics commonly used for exacerbated COPD are cleared by the kidney, as also are drugs frequently used to treat comorbid conditions (eg, thiazides for hypertension or digoxin for atrial fibrillation).[20]

Finally, renal α1-hydroxylase activity decline parallels GFR decline. In the Third National Health and Nutrition Examination Survey, adjusted mean serum 25-hydroxyvitamin D was significantly lower in subjects with a GFR from 15 to 29 mL/min/1.73 m^2 compared with those with normal kidney function (61.6 vs 73.3 nmol/L, $P = .0063$).[44] However, the K/DOQI states that renal α1-hydroxylase activity starts to decline even for cases of GFR <60 mL/min/1.73 m.[2,45] Depressed renal α1-hydroxylase activity might add to the list of the factors considered to underlie the association between COPD and osteoporosis/fractures. This list presently includes malnutrition, inactivity, low sun exposure, smoke, topic and systemic steroids, and proinflammatory/procatabolic status.[46]

This study has some limitations. First, the GFR was estimated and not directly measured. However, MDRD equation-based GFR is a reliable surrogate for measured GFR in both healthy elderly and diseased populations.[28] Second, the present conclusions apply to an elderly population with a low prevalence of hypoxemia. It is likely that the prevalence of concealed CRF increases when chronic hypoxemia supervenes, and therefore, fat-free mass declines faster.[47] On the other hand, younger age is expected

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to be associated with higher fat-free mass. Finally, reflecting the epidemiologic characteristics of COPD in the Italian population aged 65 years and older,[48] women were underrepresented in our population. This might have weakened the association between concealed CRF and the female gender, which is biologically plausible because of the greater age-related loss of fat-free mass in women.[49] Thus, the present results might not be generalized to the overall population with COPD.

In conclusion, CRF should be considered a common comorbidity of COPD, and it should be screened for because its recognition might either directly affect clinical practice (eg, drug prescribing and dosing)[20] or have prognostic implications.[4,5] Within the context of the rising interest in systemic features of COPD and related comorbidities, CRF should not be ignored or underestimated simply because it frequently cannot be recognized on the basis of serum creatinine.

Appendix

The Extrapulmonary Consequences of COPD in the Elderly Study participating centers and study investigators are as follows:

- DIMPEFINU, Università di Palermo (Resp: Prof Bellia V.; Refer: Dott Battaglia S., Dott Paglino G.).
- Università Campus Biomedico, Rome (Resp: Prof Antonelli Incalzi R.; Refer: Dott Scarlata S., Dott.ssa Conte E.).
- Università Cattolica, Rome (Resp: Prof Pistelli R.; Refer: Dott.ssa Andreani M., Dott.ssa Baldari F.).
- Medicina Respiratoria, Spedali Civili, Brescia (Resp: Prof Grassi V.; Refer: Prof Tantucci, Dott.ssa Ghibelli S., Dott.ssa Casella).
- Università degli Studi Federico II, Napoli (Resp: Prof Rengo F.; Refer: Dott.ssa Visconti C.).
- Azienda ULSS13, Mirano (VE) (Resp: Dott Cester A.; Refer: Dott Vitale E.).
- Policlinico Ospedale D'Avanzo, Foggia (Resp: Prof.ssa Foschino M. P.; Refer: Dott.ssa Ventura I., Dott.ssa Cagnazzo M. G.).
- Università S.Cuore-CEMI, Rome, Italy (Resp: Prof Bernabei R.; Refer: Dott Cerullo F., Dott.ssa Palmacci C.).
- Pio Albergo Trivulzio, Milano (Resp: Dott Berardinelli P.; Refer: Dott Carotenuto E.).
- Policlinico di Bari (Resp: Prof Onofrio Resta; Refer: Dott Di Gioia G., Dott.ssa Scoditti C.).
- Università di Perugia (Resp: Prof Lucio Casali; Refer: Dott Gradoli C.).
- Fondazione San Raffaele, Cittadella della Carità, Taranto (Resp: Dott Guadalupi G.).
- Università degli Studi di Firenze (Resp: Prof Masotti G.; Refer: Prof Di Bari M.).
- I.N.R.C.A. Istituto di Ricovero e Cura a Carattere Scientifico, Cosenza (Resp: Dott Mazzei B.; Refer: Dott Zottola C.).
- Ospedale San Giuseppe Moscati, Taranto (Resp: Dott Giusti A.; Refer: Dott Spada C.).

Acknowledgments

Author contributions: *Dr Antonelli Incalzi:* participated in the study design, data analysis and interpretation, and manuscript preparation.
Dr Corsonello: participated in data collection, data analysis, and manuscript preparation, and can vouch for the data.
Dr Pedone: participated in data collection, data analysis, and manuscript preparation.
Dr Battaglia: participated in data collection, data analysis, and manuscript preparation, and can vouch for the data.
Dr Paglino: participated in data collection, data analysis, and manuscript preparation.
Dr Bellia: participated in the study design, data analysis and interpretation, and manuscript preparation.
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References

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.
2. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation*. 2004;109(8):1004-1009.
3. Joseph J, Koka M, Aronow WS. Prevalence of moderate and severe renal insufficiency in older persons with hypertension, diabetes mellitus, coronary artery disease, peripheral arterial disease, ischemic stroke, or congestive heart failure in an academic nursing home. *J Am Med Dir Assoc*. 2008;9(4):257-259.
4. Mahon NG, Blackstone EH, Francis GS, Starling RC III, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol*. 2002;40(6):1106-1113.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.
6. Middleton RJ, Foley RN, Hegarty J, et al. The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant*. 2006;21(1):88-92.
7. Rabe KF, Hurd S, Anzueto A, et al; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-555.
8. Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J*. 2008;31(1):204-212.
9. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest*. 2005;128(4):2099-2107.
10. Preston RA, Epstein M. Ischemic renal disease: an emerging cause of chronic renal failure and end-stage renal disease. *J Hypertens*. 1997;15(12 Pt 1):1365-1377.
11. Cooper RG. Effect of tobacco smoking on renal function. *Indian J Med Res*. 2006;124(3):261-268.
12. Bellia V, Pistelli R, Catalano F, et al. Quality control of spirometry in the elderly. The SA.R.A. study. SAlute Respiration nell'Anziano=Respiratory Health in the Elderly. *Am J Respir Crit Care Med*. 2000;161(4 Pt 1):1094-1100.
13. Almagro P, Calbo E, Ochoa de Echagüen A, et al. Mortality after hospitalization for COPD. *Chest*. 2002;121(5):1441-1448.
14. Ferrer M, Alonso J, Morera J, et al; The Quality of Life of Chronic Obstructive Pulmonary Disease Study Group. Chronic obstructive pulmonary disease stage and health-related quality of life. *Ann Intern Med*. 1997;127(12):1072-1079.
15. van Manen JG, Bindels PJ, IJzermans CJ, van der Zee JS, Bottema BJ, Schadé E. Prevalence of comorbidity in patients

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with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol*. 2001;54(3):287-293.
16. Rennard S, Decramer M, Calverley PM, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J*. 2002;20(4):799-805.
17. Fan VS, Ramsey SD, Giardino ND, et al; National Emphysema Treatment Trial (NETT) Research Group. Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med*. 2007;167(21):2345-2353.
18. Antonelli Incalzi R, Fuso L, De Rosa M, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J*. 1997;10(12):2794-2800.
19. Ischaki E, Papatheodorou G, Gaki E, Papa I, Koulouris N, Loukides S. Body mass and fat-free mass indices in COPD: relation with variables expressing disease severity. *Chest*. 2007;132(1):164-169.
20. Corsonello A, Pedone C, Corica F, Mussi C, Carbonin P, Antonelli Incalzi R; Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA) Investigators. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med*. 2005;165(7):790-795.
21. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932-946.
22. Robinson JD, Lupkiewicz SM, Palenik L, Lopez LM, Ariet M. Determination of ideal body weight for drug dosage calculations. *Am J Hosp Pharm*. 1983;40(6):1016-1019.
23. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. 1999;15(2):116-122.
24. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ*. 1959;2(5147):257-266.
25. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.
26. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed)*. 1982;284(6329):1607-1608.
27. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470.
28. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;354(23):2473-2483.
29. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 suppl 1):S1-S266.
30. Jones CA, McQuillan GM, Kusek JW, et al. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 1998;32(6):992-999.
31. World Health Organization. *Nutritional Anaemias. Report of a WHO Scientific Group*. Technical report series no. 405. Geneva, Switzerland: World Health Organization; 1968.
32. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA*. 2004;291(7):844-850.
33. Sergi G, Coin A, Enzi G, et al. Role of visceral proteins in detecting malnutrition in the elderly. *Eur J Clin Nutr*. 2006;60(2):203-209.
34. Thompson LV. Age-related muscle dysfunction. *Exp Gerontol*. 2009;44(1-2):106-111.
35. Sharkey RA, Mulloy EM, O'Neill SJ. The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. *Chest*. 1999;115(6):1588-1592.
36. Gennari FJ, Hood VL, Greene T, Wang X, Levey AS. Effect of dietary protein intake on serum total CO_2 concentration in chronic kidney disease: Modification of Diet in Renal Disease study findings. *Clin J Am Soc Nephrol*. 2006;1(1):52-57.
37. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation*. 2003;107(1):87-92.
38. Aronson D, Roterman I, Yigla M, et al. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. *Am J Respir Crit Care Med*. 2006;174(6):626-632.
39. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Eur Respir J*. 2007;29(5):923-929.
40. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and inflammation in COPD. *Chest*. 2005;127(3):825-829.
41. Ble A, Fink JC, Woodman RC, et al. Renal function, erythropoietin, and anemia of older persons: the InCHIANTI study. *Arch Intern Med*. 2005;165(19):2222-2227.
42. Bosman DR, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care*. 2001;24(3):495-499.
43. Tsantes A, Bonovas S, Tassiopoulos S, et al. A comparative study of the role of erythropoietin in the pathogenesis of deficient erythropoiesis in idiopathic pulmonary fibrosis as opposed to chronic obstructive pulmonary disease. *Med Sci Monit*. 2005;11(4):CR177-CR181.
44. Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int*. 2007;71(2):134-139.
45. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 suppl 3):S1-S201.
46. Jørgensen NR, Schwarz P. Osteoporosis in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med*. 2008;14(2):122-127.
47. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis*. 1993;147(5):1151-1156.
48. Istat. Annuario Statistico 2008. http://www.istat.it/dati/catalogo/20081112_00/PDF/cap3.pdf. Accessed June 24, 2009.
49. Kyle UG, Melzer K, Kayser B, Picard-Kossovsky M, Gremion G, Pichard C. Eight-year longitudinal changes in body composition in healthy Swiss adults. *J Am Coll Nutr*. 2006;25(6):493-501.

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