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# The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway

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**Summary**
Patients with COPD are at risk for other comorbid diseases, like heart failure, coronary heart disease, and depression. However, little is known about COPD phenotypes and prevalence of sub-clinical renal failure.

433 COPD patients and 233 subjects without COPD, from Western Norway, age 40–75, GOLD stage II–IV, were examined in 2006/07 upon entry to the Bergen COPD Cohort Study. Plasma creatinine was measured in 422 of the COPD patients. The Glomerular Flow Rate (GFR) was determined with the Cockcroft Gault formula, and having a GFR $< 60$ was defined as renal failure. Examined explanatory factors were sex, age, smoking habits, GOLD stage, hypoxemia, exacerbation history, cachexia, use of daily inhaled steroids, Charlson comorbidity score, use of ACE inhibitors and/or ARBs, and the inflammatory plasma markers C-reactive protein (CRP), soluble tumor necrosis factor receptor 1 (sTNF-R1) and neutrophil gelatinase associated lipocalin (NGAL). Associations between explanatory variables and renal failure were examined by a logistic regression analysis.

The prevalence of having GFR $< 60$ was 9.6% in female COPD patients and 5.1% in male COPD patients ($p = 0.08$). In multivariable analysis, female sex, higher age, cachexia, and the inflammatory markers sTNF-R1 and NGAL were all independently associated with a higher risk for renal failure, whereas use of inhaled steroids, Charlson score, GOLD stage, respiratory failure, and exacerbation frequency were not.

Undiagnosed renal failure is a concern particularly in elderly COPD patients and COPD patients with cachexia.


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Chronic Obstructive Pulmonary Disease (COPD) is a multifactorial inflammatory disease. COPD affects the airways and lung parenchyma where it causes progressive and irreversible airflow limitation. COPD is caused mainly by inhalation of toxic particles and gases like in tobacco smoke,[1] but inherited factors may also contribute to the development.[2]

COPD affects 9–10% of adults over the age of 40 years,[3] and the prevalence increases with age. In 2004, COPD was the fifth leading cause of death, and the mortality rate is rising.[4] Patients with COPD have a high frequency of comorbidities.[5] The most frequent comorbid diseases are hypertension and heart failure, depression and anxiety, diabetes, osteoporosis, lung cancer and cachexia.[6] The inflammatory component and frequent comorbidities has led to a common view that COPD is a systemic inflammatory disease affecting many organs or biological mechanisms. Especially heart- and coronary diseases, depression and cachexia are known to have an inflammatory component.[7–9]

Renal failure is usually defined using one of several different formulas, most of which includes measured blood creatinine.[10] As most patients developing renal failure will have an asymptomatic rise in creatinine over time, many COPD patients may have an undiagnosed renal failure well before being discovered. Renal failure is a significant risk factor for cardiovascular diseases; conditions which COPD patients are at risk for, particularly with increasing severity of COPD.[11] Polypharmacy is frequent in COPD patients, and undiagnosed renal failure could increase the risk of adverse reactions. Finally, both COPD and renal failure are associated with an increase in systemic inflammation,[12–14] which potentially could add to the complications of either disease.

However, the relationship between renal failure and COPD is largely undescribed. To date, only one Italian study has examined the prevalence of renal failure in COPD patients.[15] The Italian study of 356 elderly COPD patients, found a high prevalence of renal failure, 43%, of which half had known renal failure and half undiagnosed renal failure.

Such a high prevalence of undiagnosed renal failure as this is likely to have important consequences for our treatment of COPD, but needs to be confirmed in other studies. In particular, the relationship between COPD severity and undiagnosed renal failure needs to be assessed.

The purpose of the current study was to estimate the frequency of undiagnosed renal failure in a population of COPD patients, and to examine if there was an association between important COPD characteristics, including inflammatory markers, and renal failure.

## Materials and methods

### Study population

The baseline survey of the Bergen COPD Cohort Study (BCCS) was conducted between February 2006 and September 2007, and a total of 433 COPD patients and 233 subjects without COPD, aged 40–76 years, were examined.[12] Most of the patients were recruited from health institutions in Hordaland County in Western Norway, whereas the subjects without COPD were recruited among former participants from a general population survey from Hordaland County.[16] The sampling and data collection in the BCCS have previously been published in detail.[12]

Briefly, a study physician examined all subjects, and reported a full medical history based on patient interview and hospital journals. Exacerbations history, comorbidities, smoking habits and use of medications were recorded. Causes for exclusion were known renal failure requiring treatment, rheumatoid arthritis, systemic lupus erythematosus or other connective tissue disorders, inflammatory bowel disease or active cancer during the last five years. Participants with other diseases like heart failure, coronary heart disease, hypertension or diabetes were not excluded.

All COPD patients were required to meet the following spirometry criteria: Having a post-bronchodilator FEV1/FVC ratio $< 0.7$, and an FEV1 $< 80\%$ predicted based on Norwegian pre-bronchodilation reference values.[17] Furthermore, COPD patients had to have a smoking history of 10 pack-years to be included. Patients were not admitted into the study while having an active exacerbation defined as having received oral steroids or antibiotics the last 4 weeks.

All participants received written information, and a consent signature was required before acceptance into the study. All participation was voluntary. The regional ethical committee approved the study.

### Data sampling

Spirometry was performed using a Viasys Masterscope, before and 15 min after inhalation of 0.4 mg salbutamol. Weight and height were recorded for every subject. The fat free mass index (FFMI, kg/m2) was estimated with bioelectrical impedance measurements, using a Bodystat 1500 (Bodystat Ltd, Isle of Man, UK) after an overnight fasting period. Cachexia was defined as having an FFMI below 17 kg/m2 for men and below 14 kg/m2 for women.[18] Arterial oxygen tension (Pa02) was estimated with a Radiometer ABL 520 blood gas analyzer.

The plasma samples were centrifugated within 30 min at 2150 *g* for 15 min at 4 °C. The samples were stored at −80 °C and thawed $< 3$ times. The inflammatory markers C-reactive protein (CRP), soluble tumor necrosis factor receptor 1 (sTNF-R1), and neutrophil gelatinase associated lipocalin (NGAL) were analyzed by enzyme immunoassays (EIAs), as described in a former study.[12] Plasma creatinine levels were measured by routine laboratory methods (Modular PP, Roche Diagnostics, Basel, Switzerland).

### Definition of renal failure

The Glomerular Filtration Rate (GFR) was determined with the Cockcroft Gault formula, which takes into account sex, age, weight and creatinine.[19] A GFR $< 60$ was defined as renal failure, according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines classifications.[20]

## Statistical analyses

Bivariate associations were tested with chi-square tests for categorical variables and independent-sample *t*-test or non-parametric Mann Whitney test for continuous variables, depending on distribution. Odds ratios (OR) with 95% confidence Intervals (CI) for having a GFR $< 60$ were estimated using logistic regression analysis. Examined explanatory factors were sex, age, smoking habits, GOLD stage, Charlson score, estimated from Charlson's comorbidity index,[21,22] exacerbation history, hypoxemia, cachexia, use of inhaled steroids, use of angiotensin converting enzyme-inhibitors (ACE inhibitors) or angiotensin II receptors blockers (ARBs), and the inflammatory plasma markers CRP, sTNF-R1 and NGAL. *P*-values $< 0.05$ were considered statistically significant. All statistical analyses were carried out using Stata version 11.

## Results

The baseline characteristics of the COPD patients are shown in Table 1. The men had more severe COPD judged by GOLD stage, but were less likely to use inhaled steroids daily, compared with women. Male patients were more likely to have a larger burden of comorbidities (Charlson score) and were less likely than female patients to be daily smokers (Table 1).

The baseline characteristics of the 233 subjects without COPD have been previously published.[12] Among the 231 subjects without COPD for which we had valid plasma creatinine measurements, only 2 subjects had undiagnosed renal failure (defined as having a GFR $< 60$), a prevalence of 0.8%. In contrast, the prevalence of undiagnosed renal failure in the COPD patients was 6.9%, significantly higher than among the subjects without COPD ($p < 0.001$, Fishers exact test).

Stratified by sex, the prevalence of undiagnosed renal failure was 9.6% in female COPD patients and 5.1% in male COPD patients (Table 2). Undiagnosed renal failure was not present in COPD patients under 55 years of age, but reached a prevalence of 12.7% in COPD patients over 65 years of age. Although there was a trend that undiagnosed renal failure was more common in COPD patients in GOLD stage IV, among those who had frequent exacerbations, and in COPD patients with more comorbidities, none of these trends were statistically significant. However, in COPD patients with cachexia, the prevalence of undiagnosed renal failure was 16.3% compared to 3.0% in COPD patients without cachexia ($p < 0.01$, Table 2).

The plasma levels of the three inflammatory markers CRP, sTNF-R1, and NGAL, in COPD patients with and without undiagnosed renal failure are shown in Table 3. Both sTNF-R1 and NGAL was significantly elevated in patients with undiagnosed renal failure, whereas CRP was not.

The multivariable logistic regression analysis is shown in Table 4. Generally, the multivariable analysis confirmed the results from the bivariate analyses. Female sex, higher age, and cachexia were strong clinical predictors of having undiagnosed renal failure. A higher GOLD stage and having frequent exacerbations trended toward higher risk for undiagnosed renal failure, but failed to reach statistical significance. Plasma levels of CRP were insignificant, but for both sTNF-R1 and NGAL did higher systemic levels predict higher risk for undiagnosed renal failure, also after adjustment (Table 4).

**Table 1** The baseline characteristics of 433 patients in the Bergen COPD cohort study.[a]

| | Women, $n = 175$ | Men, $n = 258$ | *p*-value[b] |
|---|---|---|---|
| Age, *n*(%) | | | 0.80 |
| 40–49 | 7(4.0) | 11(4.3) | |
| 50–59 | 48(27.4) | 54(20.9) | |
| 60–69 | 94(53.7) | 130(50.4) | |
| >69 | 26(14.9) | 63(24.4) | |
| Smoking habits, *n*(%) | | | 0.41 |
| ex | 94(53.7) | 149(57.8) | |
| current | 81(46.3) | 109(42.2) | |
| GOLD stage, *n*(%) | | | 0.04 |
| II | 91(52.0) | 113(43.8) | |
| III | 72(41.1) | 108(41.9) | |
| IV | 12(6.9) | 37(14.3) | |
| Hypoxemia (Pa02 $< 8.0$ kPa), *n*(%) | | | 0.25 |
| No | 128(84.8) | 214(88.8) | |
| Yes | 23(15.2) | 27(11.2) | |
| Exacerbations the last year | | | 0.08 |
| <2 | 138(78.9) | 220(85.3) | |
| 2 or more | 37(21.1) | 38 (14.7) | |
| Cachexia | | | 0.64 |
| No | 120(69.4) | 183(71.5) | |
| Yes | 53(30.6) | 73(28.5) | |
| Daily use of inhaled steroids, *n*(%) | | | 0.04 |
| No | 45(27.7) | 90(34.9) | |
| Yes | 130(74.3) | 168(65.1) | |
| Charlson comorbidity index, *n*(%) | | | 0.01 |
| 1 | 113(64.6) | 137(53.5) | |
| 2 | 42(24.0) | 60(23.4) | |
| 3 or more | 20(11.4) | 59(23.0) | |
| Used ACE inhibitors and/or ARBs, *n*(%) | | | 0.07 |
| No | 140(80.0) | 187(72.5) | |
| Yes | 35(20.0) | 71(27.5) | |

[a] Plasma creatinine measured on 422 of the patients.
[b] Chi-square test.

## Discussion

Among COPD patients, female sex, higher age, and cachexia were strong predictors of risk for undiagnosed renal failure. In contrast, important COPD disease characteristics like GOLD stage, exacerbation frequency, hypoxemia, and use of inhaled steroids failed to show a significant relationship with risk for renal failure in our COPD patients. Systemic inflammation measured by CRP did not predict risk for undiagnosed renal failure in this population, but the more specific inflammatory markers sTNF-R1 and NGAL did.

There are some methodological issues to discuss. Firstly, the study sample was not randomly selected, and the

**Table 2** The prevalence (%) of renal failure according to disease characteristics in a cohort of 422 COPD patients.

| | *n* | GFR < 60 | *p*[a] |
|---|---|---|---|
| Overall | 422 | 6.9% | |
| Sex | | | 0.08 |
| Women | 167 | 9.6% | |
| Men | 255 | 5.1% | |
| Age | | | <0.001 |
| 40–49 | 18 | 0.0% | |
| 50–59 | 99 | 1.0% | |
| 60–69 | 220 | 5.9% | |
| >69 | 85 | 17.7% | |
| Smoking habits | | | 0.62 |
| ex | 237 | 6.3% | |
| current | 185 | 7.6% | |
| GOLD stage | | | 0.49 |
| II | 197 | 5.6% | |
| III | 176 | 7.4% | |
| IV | 49 | 10.2% | |
| Hypoxemia (PaO2<8.0 kPa) | | | 0.93 |
| No | 333 | 6.6% | |
| Yes | 48 | 6.3% | |
| Exacerbations the last year | | | 0.29 |
| <2 | 350 | 6.3% | |
| 2 or more | 72 | 9.7% | |
| Cachexia | | | <0.001 |
| No | 299 | 3.0% | |
| Yes | 123 | 16.3% | |
| Daily use of inhaled steroids | | | 0.66 |
| No | 130 | 7.7% | |
| Yes | 292 | 6.5% | |
| Charlson Comorbidity Index | | | 0.17 |
| 1 | 243 | 5.4% | |
| 2 | 101 | 6.9% | |
| 3 or more | 78 | 11.5% | |
| Used ACE inhibitors and/or ARBs | | | 0.22 |
| No | 366 | 6.3% | |
| Yes | 56 | 10.7% | |

[a] Chi-square test.

results reflect the population from which our participants were recruited. The subjects without COPD were recruited from a previous randomly sampled general population survey. However, for the present study, which was the baseline phase of a three-year cohort study, subjects were voluntarily included and did therefore not represent a random population sample. It is likely that our control population sample may be a little healthier than the source population, and that our prevalence of undiagnosed renal failure is lower than that seen in the general population aged 40–76 years. This is supported by findings from a large general population survey from Nord-Trondelag County (the HUNT survey) in Norway.[23] In that sample of over 60 000 subjects, GFR was estimated based on sampled serum creatinine and the MDRD formula. In the HUNT survey, the prevalence of renal failure was found to be 2.0% in subjects 50–59 years old, 6.5% in subjects 60–69 years old, and 13.7% in subjects 70–79 years old.[23] Importantly however, whether the subjects in the HUNT survey knew they had renal failure or not was unknown. Our study only assessed undiagnosed renal failure, and subjects with known renal failure were prevented from inclusion.

**Table 3** The levels of three inflammatory markers in COPD patients with and without renal failure.

| | GFR < 60 | GFR > 60 | *p*[a] |
|---|---|---|---|
| CRP, ug/mL | | | 0.43 |
| median (IQR) | 3.19 (1.23–9.01) | 4.24 (1.94–10.44) | |
| sTNF-R1, ng/mL | | | <0.01 |
| median (IQR) | 7.88 (6.90–12.80) | 6.85 (5.69–8.24) | |
| NGAL, pg/mL | | | <0.001 |
| median (IQR) | 103.6 (72.3–129.2) | 66.0 (50.7–92.7) | |

[a] Kruskal Wallis test.

The COPD patients were recruited from several sources including a previous COPD study from the Hordaland County in Western Norway conducted at the Haukeland University Hospital ('GenKOLS', $n = 270$),[24] the outpatient clinic at Haukeland University Hospital ($n = 107$), outpatient clinics from other hospitals in Western Norway ($n = 22$), and from the clinics of private lung specialists practicing in Hordaland County ($n = 34$). The Department of Thoracic Medicine, Haukeland University Hospital, has both a local function and serves as the referral center for pulmonary disorders in Western Norway. Thus, the range of patients seen at the outpatient clinic is quite large. However, selection of patients from the outpatient clinic of a hospital usually means selecting the most severe cases among patients, with more polypharmacy, and more comorbidities. Thus, if our patients differ from the COPD patient population as a whole, including patients seen only by general practitioners, it is likely that our study population include patients with more severe disease. Regardless, we did not establish a relationship between disease severity and undiagnosed renal failure except for cachexia, and believe it unlikely that the COPD population as a whole would have a higher prevalence of undiagnosed renal failure than the one measured in this study.

Secondly, for Charlson score the ORs from the adjusted multivariable analysis were opposite what was found in the bivariate analyses. This was due to the adjustment for the inflammatory markers. In a model not including the three markers, Charlson score had ORs (95% CI) of 1.2 (0.4–3.8) for a score of two, and 2.1 (0.7–6.8) for a score of three or more. There was no significant interaction between any of the markers and Charlons score ($p > 0.05$ for all three, data not shown). Although the ORs for Charlson score in the model not including the three inflammatory markers were not statistically significant, the trend was that more comorbidities implied higher risk for undiagnosed renal failure.

Thirdly, we have previously shown that plasma levels of CRP, sTNF-R1, and NGAL was higher in COPD patients than in subjects without COPD.[12,25] The current study shows that undiagnosed renal failure in patients with COPD may be associated with systemic inflammation. NGAL is an antimicrobial peptide actively secreted from neutrophils, epithelial cells, endothelial cells and tubuli cells in the

**Table 4** The associations between COPD disease characteristics and undiagnosed renal failure.

| | n | OR | (95% CI) | p |
|---|---|---|---|---|
| *Sex* | | | | 0.02 |
| Women | 140 | 1 | | |
| Men | 228 | 0.25 | (0.08—0.77) | |
| *Age* | | | | <0.01 |
| per 10 years increase | 368 | 6.25 | (1.83—21.32) | |
| *Smoking habits* | | | | 0.35 |
| ex | 205 | 1 | | |
| current | 163 | 1.77 | (0.53—5.92) | |
| *GOLD stage* | | | | 0.58 |
| II | 177 | 1 | | |
| III | 151 | 1.38 | (0.42—4.55) | |
| IV | 40 | 2.92 | (0.41—6.24) | |
| *Hypoxemia (PaO2 < 8.0 kPa)* | | | | 0.69 |
| No | 322 | 1 | | |
| Yes | 46 | 0.42 | (0.08—2.27) | |
| *Exacerbations the last year* | | | | 0.69 |
| <2 | 313 | 1 | | |
| 2 or more | 55 | 1.36 | (0.30—6.24) | |
| *Cachexia* | | | | 0.03 |
| No | 262 | 1 | | |
| Yes | 106 | 4.03 | (1.15—14.07) | |
| *Daily use of inhaled steroids* | | | | 0.75 |
| No | 114 | 1 | | |
| Yes | 254 | 0.83 | (0.26—2.67) | |
| *Charlson Comorbidity Index* | | | | 0.74 |
| 1 | 219 | 1 | | |
| 2 | 87 | 0.67 | (0.17—2.68) | |
| 3 or more | 62 | 0.55 | (0.10—2.90) | |
| *Used ACE inhibitors and/or ARBs* | | | | 0.32 |
| No | 327 | 1 | | |
| Yes | 41 | 2.28 | (0.45—11.51) | |
| *CRP* | | | | |
| per 1 ug/mL increase | 368 | 0.95 | (0.88—1.03) | 0.19 |
| *sTNF-R1* | | | | |
| per 100 ng/mL increase | 368 | 1.26 | (1.00—1.58) | <0.01 |
| *NGAL* | | | | |
| per 10 ng/mL increase | 368 | 1.32 | (1.10—1.58) | 0.048 |

kidneys.[26] Whether the increased plasma levels of sTNF-R1 and NGAL are a cause or effect of undiagnosed renal failure cannot be inferred from this cross-sectional study.

Finally, we chose the Cockcroft Gault formula for defining renal failure. This formula takes into account sex, age, creatinine, and the weight of the subject. Creatinine varies with muscle mass and thus weight, and formulas not taking weight into account tend to underestimate GFR in subjects with large muscle mass, and overestimate GFR in subjects with smaller muscle mass.[27] The Cockcroft Gault formula does not take race into account. In our study sample, the study subjects had Caucasian background save one subject, who was of South American origin. Thus, we believe lack of adjustment for race was unimportant, whereas adjustment for weight was important for our cohort of COPD patients.

Compared with the Italian study of 356 COPD patients, we found a much lower prevalence of undiagnosed renal failure, 6.9%—21%. There are several possible explanations for this. Firstly, the Italian study subjects were older, all participants more than 65 years. Age was found in both studies to be an independent risk factor for undiagnosed renal failure. In our study sample the prevalence of undiagnosed renal failure in subjects above 65 years of age was 12.7%. Secondly, the Italian study used the Modification of Diet in Renal Disease (MDRD) formula, which does not take weight into account. The mean body mass index (BMI) in the patients with undiagnosed renal failure in the Italian study was 29.2 kg/m2, which is rather high. Thus, it is possible that their use of the MDRD formula led to an overestimation of renal failure. Thirdly, their patients were recruited from outpatient clinics in several hospitals in Italy, and the difference in prevalence could be explained by differences in study populations. Finally, the difference might reflect that the prevalence of undiagnosed renal failure actually is higher in Italian COPD patients than in Norwegian COPD patients.

This study underscores the importance of being vigilant about comorbidities in COPD patients. Undiagnosed renal failure is arguably a poorly recognized comorbidity in COPD, however it is not trivial, and COPD patients often use several medications that are metabolized through the kidneys. We urge physicians to be vigilant for this potential comorbidity.

The finding that COPD patients with cachexia were at increased risk for undiagnosed renal failure is a novel finding. It is well known that advanced renal failure leads to cachexia,[28] however that does not apply to the patients in this study. On the contrary, this finding could imply that COPD patients who are in a catabolic state may be at increased risk for developing renal failure. However, this theory would also need to be confirmed in longitudinal studies.

In conclusion, in this study the prevalence of undiagnosed renal failure was found to be about 7% among patients with COPD. Female sex, higher age, cachexia, and the systemic inflammatory markers sTNF-R1 and NGAL predicted a higher risk for having undiagnosed renal failure in our COPD patients.

## Conflict of interest statement

"The prevalence of undiagnosed renal failure in a cohort of COPD patients in Western Norway".

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BG, PB and TU report no known conflict of interest.

Within the past 5 years, Dr Eagan received sponsorship for travel and accommodations to seminars (American Thoracic Society) from GlaxoSmithKline and received grant monies from AstraZeneca (not related to this study).

Within the past 5 years, Dr Hardie received sponsorship for travel and accommodations to seminars (American

Thoracic Society) from GlaxoSmithKline and received grant monies, lecture honoraries, and honoraries for consultation on print material (only BI) from AstraZeneca, GlaxoSmithKline, and Boehringer-Ingelheim (not related to this study).

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