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Underdiagnosis of myocardial infarction in COPD — Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation

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Summary
Background: Patients with chronic obstructive pulmonary disease (COPD) are usually former or current smokers, and are at increased risk of ischemic heart disease. We used Cardiac Infarction Injury Score (CIIS) to assess the prevalence of prior myocardical infarction (MI) in COPD patients and compared this to clinicians' previous diagnosis of MI.
Methods: From the hospital database, 897 patients (mean age 70.9 years, 50.8% female) discharged after treatment for COPD exacerbation in the years 2000–2003 were identified. Disease history was established from medical records and the hospital patient database. Electrocardiograms from the day of admission were available in 827 patients, and were coded according to the CIIS algorithm by an investigator blinded to clinical and outcome data. The CIIS score was validated using follow-up data for the first year after discharge.
Results: Two hundred and twenty-nine patients had CIIS ≥ 20, out of whom only 30% (95% confidence interval: 24–36%, $n = 68$) had a recognised history of MI. Female patients had a lower probability of diagnosis despite ECG evidence. Validation of CIIS using multivariate Cox regression analysis showed that a score ≥ 20 had independent prognostic value for the first year after discharge, with an adjusted HR of 1.52 (1.14–2.03).
Conclusion: Unrecognised MI is common in patients hospitalised with COPD exacerbation. Less than one-third of patients with ECG evidence of previous MI by the CIIS system actually have the diagnosis in their medical records.

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Background

Chronic obstructive pulmonary disease (COPD) is a common and debilitating disease, the pathophysiological hallmark of which is airflow limitation, caused by airway inflammation.[1] COPD is one of the very few diseases that still has a rising mortality rate worldwide.[2]

At least since 1976, when Friedman and coworkers showed an association between lung function and risk of myocardial infarction (MI),[3] it has been known to physicians that cardiac comorbidity in COPD patients is common. In recent years, there has been increasing awareness among clinicians and researchers that cardiovascular disease is a significant contributor to morbidity and mortality in COPD patients.[4–6]

The clinical diagnosis of cardiovascular disease in COPD patients may be elusive. Exercise capacity may be limited by impaired lung function, concealing coronary symptoms, and while symptoms such as chest pain and dyspnea are common during COPD exacerbations, they may be interpreted as COPD related even when their origin is cardiac. Based on death certificates and adjudication of medical records, estimates of ischemic heart disease prevalence vary in the range of 10–40%.[7–9] There is reason to believe that cardiac comorbidity in COPD patients is underdiagnosed.

In their review of the relationship between reduced lung function and cardiovascular mortality,[5] Sin and coworkers found an intriguing association between Forced Expiratory Volume in 1 s (FEV_1) and changes in the electrocardiogram (ECG) as measured with a scoring system called Cardiac Infarction Injury Score (CIIS) in COPD outpatients. CIIS is an epidemiological tool designed to discriminate between the presence and absence of MI based on a standard 12-lead ECG, and has been reported to have a specificity of 98% for detecting MI at a score of 20 points or higher.[10] The prognostic value of CIIS has been validated in healthy populations,[11] hypertensive patients,[12] and in the post-MI setting.[13]

There are, however, no published papers on CIIS and COPD exacerbations. The primary objective of the present study was to determine the prevalence of MI, as assessed by CIIS, in patients hospitalised for COPD exacerbation, and to compare this with the diagnosis of MI from patients' medical records. A secondary objective was to validate the prognostic value of CIIS in COPD patients.

Methods

The study population consisted of patients discharged from Akershus University Hospital, a 700-bed teaching hospital, after treatment for COPD exacerbation. Patients aged 40 years or older who were admitted during the four-year period from 1 January 2000 to 31 December 2003, and who were discharged with a primary diagnosis of COPD exacerbation, ICD 10 (International Classification of Diseases, 10th revision) code J44.0 or J44.1, or COPD (J44.x) as an underlying diagnosis combined with pneumonia (J13-J18.9) as the main diagnosis, were studied. Patients with previous diagnoses of sarcoidosis, interstitial lung disease, or neuromuscular disease, or who received a secondary diagnosis of acute MI during the index admission, were excluded. For patients with more than one admission during the inclusion period, the latest admission date was used. A total of 1087 admissions satisfied inclusion and exclusion criteria. Forty-one patient records were not available for manual review. Fifty cases of erroneous ICD coding (5%) were discovered during manual record review. Data for the 897 patients discharged alive were used in this study. For the purpose of validating the prognostic value of CIIS, we used follow-up data until death or 30 June 2005, whichever occurred first.

ECGs recorded on admission were retrieved from patients' records. Seventeen discrete features of the ECG were manually measured and tabulated, and later converted to a score according to a CIIS algorithm. Several versions of the CIIS algorithm exist — the present study used the version modified for visual coding published by Dekker.[14] Right ventricular hypertrophy was defined according to NOVACODE criteria.[15] Heart rate and rhythm were gathered from the ECG. ECG coding was performed by physicians blinded to the outcome of interest. Seventy patients with irretrievable or illegible ECGs were excluded from further analyses.

Intra- and inter-rater agreement of the CIIS scoring was performed by randomly selecting 70 ECGs for re-measurement by the primary rater (PHB) and by a medical student blinded to the study hypothesis and the CIIS algorithm (ALS).

The patients' medical record were manually searched for a history of MI. Additionally, each patient's discharge ICD codes since 1987, until but not including the date of admission, were obtained from the hospital database, and MIs thus identified were added. A history of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) and atrial fibrillation was gathered in the same manner. History of cancer, diabetes, hypertension and congestive heart failure was compiled from 1987 to 2003 discharge ICD codes.

Spirometry data, if performed in a stable state at least one week before or four weeks after hospital discharge, were gathered from patient records. Forced vital capacity (FVC), Expiratory Volume in 1 s (FEV_1), height and weight were recorded, and body mass index (BMI), defined as weight in kilograms divided by the square of height in meters, was calculated. FVC and FEV_1 values are expressed as percent of predicted using the European Community for Steel and Coal equations.[16] FEV_1% of predicted and BMI were dichotomised at the 25th/75th percentile.

All statistical analyses were performed using Stata/SE version 8.2 software (StataCorp LP, Texas, USA). Ninety-five percentage confidence intervals (CI) are given in parentheses. All-cause mortality data, gathered from the Central National Register, was used as the outcome measure in the validation analysis. Multivariate analysis was performed using Cox proportional hazards regression. The proportional hazard assumption was visually tested using log–log plots. Results are reported as hazard ratio (HR) for Cox analyses.

The study was approved by the Data Inspectorate and the Regional Committee for Research Ethics.

Results

Mean age at discharge was 70.9 years, and 50.8% were female. Baseline data are presented in Table 1. After discharge, cumulative survival was 75.6% and 65.2% at one and two years, respectively. Only 55 patients (6%) had never

Table 1 Baseline characteristics of 827 patients by CIIS score

	CIIS < 20 ($n = 598$)	CIIS ≥ 20 ($n = 229$)
Clinical data, mean (SD)		
Age (years)	69.9 (10.8)	74.6 (9.8)
Female, *n* (%)	328 (55)	93 (41)
FEV_1%	47.3 (20.0)	46.4 (18.3)
FVC%	72.0 (22.6)	71.1 (23.1)
Heart rate (beats/min)	96.3 (20.0)	98.0 (19.8)
BMI	24.4 (5.5)	23.9 (5.3)
Atrial fibrillation, *n* (%)	49 (8)	42 (18)
Medical history, *n* (%)		
Previous infarction	61 (10)	68 (30)
CAGB	12 (2)	13 (6)
PCI	13 (2)	5 (2)
Heart failure	36 (6)	45 (20)
Hypertension	122 (20)	50 (22)
Diabetes	63 (11)	36 (16)
Thromboembolism	16 (3)	3 (1)
Cancer	78 (13)	30 (13)
Ex-smoker	51 (9)	27 (12)
Never smoker	35 (6)	13 (6)
Medication use at discharge, *n* (%)		
Beta-blockers	76 (13)	25 (11)
ACEI or ARB	107 (19)	63 (29)
Statins	75 (13)	35 (16)
Warfarin	43 (8)	32 (15)
Acetylsalicylate	147 (26)	64 (29)

CIIS — Cardiac Infarction Injury Score; FEV_1% — Forced Expiratory Volume in 1 s in percent of predicted; FVC% — forced vital capacity in percent of predicted; BMI — body mass index; CABG — coronary artery bypass graft surgery; PCI — percutaneous coronary intervention; ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers.

smoked. Spirometry data was available for 696 patients, and among these, 604 (87%) had FEV_1/FVC-ratio ≤ 0.7.

Incomplete or complete right bundle branch block (RBBB) was observed in 50 patients. Ninety-one patients had atrial fibrillation (acute or chronic), and 30 had signs of right ventricular hypertrophy according to NOVACODE criteria.

The CIIS score was very nearly normally distributed, with a mean score of 13.4 points (standard deviation (SD): 11.6). Men had slightly higher mean scores at 14.9 (SD: 11.9) vs females at 12.0 (SD: 11.3). The prevalence of heart disease in general, and specifically a history of previous myocardial infarction, increased with CIIS score.

When using a CIIS cut-off value of 20 points, 27.7% of patients in this study had had an MI according to the ECG. On the other hand, the prevalence of MI *diagnosis* according to ICD codes and medical records was 15.6%.

Of the 229 patients with ECG signs of previous infarction, 30% (CI: 24—36%, $n = 68$) had a recognised history of MI, compared to 10% (CI: 8—13%, $n = 61$) of 598 patients with a CIIS below the cut-off. When using a cut-off CIIS value of 30 points, the proportions changed to 36% (CI: 25—47%, $n = 29$) and 13% (CI: 11—16%, $n = 100$), respectively. Female patients and younger age groups were less likely to have an established MI diagnosis despite ECG evidence of a previous infarction, whereas patients with known hypertension had a higher likelihood of diagnosis. Separate percentages for subgroups of patients at a CIIS cut-off of 20 points are shown in Table 2.

For CIIS dichotomised at 20 points, the intra-rater kappa was 0.84, and the inter-rater kappa was 0.88. Average difference in discrete measured ECG features was less than 0.2 mm (0.02 mV on the amplitude scale or 4 ms on the time scale), average difference in scores between raters was 0.7 ($p = 0.3$). Disagreement was most common in ECGs with a noisy baseline.

Because CIIS may be influenced by the presence of other conditions, we performed analyses on further restricted datasets, first excluding patients with right ventricular hypertrophy, then patients with disease history or signs associated with an elevated probability of pulmonary embolism (history of thromboembolic disease, atrial arrythmia, RBBB) were excluded. Results of these restricted analyses are presented in Table 3.

Finally, as CIIS has not been validated in COPD patients, we investigated the prognostic value of elevated CIIS in the first year after discharge. The unadjusted HR for CIIS ≥ 20 was 1.98 (1.50—2.61). Fig. 1 shows a Kaplan—Meier survival curve for patients with CIIS ≥ 20 vs patients with CIIS < 20. Adjusting for age, gender, spirometry values, history of heart failure, diabetes and cancer, elevated CIIS remained a highly significant independent predictor of mortality, with an adjusted HR of 1.52 (1.14—2.03). The model did not violate the proportional hazards assumption.

Discussion

We have found that a large proportion of COPD patients has electrocardiographic evidence of previous MI, but has never been diagnosed with one. In this study, 15.6% of patients had a recognised history of MI, whereas ECG evidence suggests a prevalence of nearly twice that. Of patients with MI according to CIIS, less than one-third (30%) actually had an established MI diagnosis. Among female patients, the proportion of recognised MIs was only 17%.

Table 2 Percentage of patients (95% confidence interval) with previously recognised myocardial infarction, by characteristic

Characteristic	CIIS ≥ 20
Gender	
Male (%)	38 (30—47)
Female (%)	17 (10—26)
Age group	
<60 (%)	20 (6—44)
60—69 (%)	21 (9—36)
70—79 (%)	34 (25—45)
>80 (%)	31 (21—43)
Medical history	
Diabetes (%)	25 (12—42)
Hypertension (%)	44 (30—59)

Table 3 Percentage of patients (95% confidence interval) with previously recognised myocardial infarction after progressive restriction of the cohort

Excluded patients	In analysis (*n*)	CIIS $\geq$ 20 (%)
Right ventricular hypertrophy	797	31 (25–37)
+Atrial fibrillation	710	31 (25–39)
+Right bundle branch block	682	32 (25–39)
+History of thromboembolic disease	668	32 (25–39)

Among the strengths of this study are the number of patients involved, the large proportion of available ECG recordings, and the magnitude of the findings. Furthermore, the fact that a high CIIS score has independent prognostic value in this population adds credibility to the score's ability to discriminate between patients with and without significant comorbidity.

In the study on the association between CIIS and lung function by Sin and coworkers,[5] they found a mean score of 10 points in COPD outpatients with ''moderate'' (FEV_1 50–80% of predicted) and 11.2 in patients with ''severe'' ($FEV_1 < 50\%$ of predicted) airways obstruction. The higher mean score of 13.4 in our group of hospitalised patients corresponds well with their more advanced disease and generally more pronounced airways obstruction. We were not, however, able to confirm the same association between COPD severity and CIIS score as Sin and Man – this may be explained by a greater variability in the timing of spirometry measurements relative to the ECG date in our patient group.

Hemodynamic changes related to COPD, such as increased pulmonary vascular resistance and increased right ventricular workload, cause changes in the ECG. Patients with obvious acute ECG changes would probably receive a heart disease related primary diagnosis, and thus not be included in our cohort in the first place, but more subtle changes may also influence the score. While the CIIS does not include ST-segment changes in the algorithm, we have accounted for the possibility of such effects on the scoring system by restricting analyses to a group without known confounders, and also by raising the cut-off value at which we counted the ECG changes as a possible infarction to 30 points, without significantly affecting our findings.

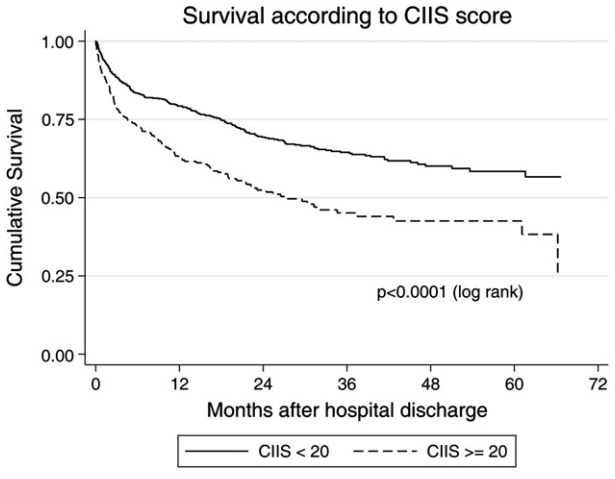

Figure 1 Kaplan–Meier survival curve for CIIS $\geq$ 20 vs CIIS $<$ 20.

The ECG evaluation in this study was performed visually, whereas other investigators have used computer algorithms to evaluate electronic ECGs. Since the investigator was blinded to clinical data, the visual coding should not introduce a bias in the data, but it may have resulted in less precision than an automated procedure. Any such non-differential misclassification would, however, cause an under-estimation of the effect of CIIS.

We used ICD codes and manual searching of medical records to establish whether a patient had a previous diagnosis of MI. The database of diagnoses goes back to 1987. It is possible that patients may have had an MI at another hospital, and that the diagnostic code has not been included in our system at later visits. We believe, however, that the MI diagnosis has a fairly high ''impact'', and that by the combination of database and manual searching for the mention of MI in the patient records, we have been able to register most of the established MI diagnoses.

Several previous studies have shown that patients with COPD have an increased risk of cardiovascular disease.[4,17,18] Few papers report on MI or IHD prevalence in COPD patients. Using the Saskatchewan Health database, Curkendall et al. reported a period prevalence for MI of 2.3% for a one-year observation time.[18] This corresponds quite well with the cumulative prevalence of diagnoses in our cohort (16%), which is based on a longer observation period. A study by van Manen and coworkers found that 15.6% of persons with an $FEV_1 < 70\%$ of predicted had self-reported heart disease.[19] While Antonelli-Incalzi and coworkers[20] report a perhaps surprisingly low 10% prevalence of IHD diagnosis in their study of patients with severe COPD (mean FEV_1 34%) hospitalised for exacerbation, they also found that 21% of patients had ECG evidence of IHD, supporting the hypothesis that heart disease in this patient population remains unrecognised.

Epidemiological studies have shown that unrecognised MI is prevalent in general populations; Kannel and Abbott reported that 25% of a Framingham population had unrecognised MI,[21] and de Torbal et al. found that one-third to one-half of MIs in a general population in Rotterdam remained clinically unrecognised.[22] To the best of our knowledge, the present study is the first to address underdiagnosis of MIs in a population of COPD patients.

The diagnosis of COPD in this study was made at discharge, based on all available clinical data. A physician specialised in internal medicine or pulmonary medicine verified the diagnoses. While the diagnosis was not based on specific criteria such as suggested by the Global initiative for chronic Obstructive Lung Disease (GOLD), we consider the study population to be well defined, and representative of COPD patients seen in pulmonary care units in Western countries.[1] Norway is one of the very few countries where smoking is more prevalent among females than males,[23] which explains the high percentage of female patients in our study.

In conclusion, our study suggests that MI is frequently unrecognised in patients hospitalised for COPD exacerbation. Less than one-third of patients with evidence of

previous MI by the CIIS ECG system actually have the diagnosis in their medical records. Furthermore, CIIS has prognostic value in the first year after discharge. The relationship between COPD and ischemic heart disease highlights the need for further studies to illuminate pathophysiological mechanisms and assess the effect of therapy.

Conflicts of interest

The authors have no conflicts of interest.

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