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Diagnostic and prognostic properties of procalcitonin in patients with acute dyspnea: Data from the ACE 2 Study

Kristian Berge[a,b], Magnus Nakrem Lyngbakken[a,b], Gunnar Einvik[a,b], Jacob A. Winther[a], Jon Brynildsen[a,b], Ragnhild Røysland[a,b], Heidi Strand[c], Geir Christensen[b,d], Arne Didrik Høiseth[a,b], Torbjørn Omland[a,b], Helge Røsjø[a,b,*]

[a] Division of Medicine, Akershus University Hospital, Lørenskog, Norway
[b] Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Multidiciplinary Laboratory Medicine and Medical Biochemistry, Akershus University Hospital, Lørenskog, Norway
[d] Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway

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ABSTRACT

Background: Procalcitonin (PCT) concentrations increase during bacterial infections and could improve diagnosis of pneumonia and risk stratification in patients with acute dyspnea.
Methods: PCT concentrations were measured < 24 h of admission in 310 patients with acute dyspnea and compared to C-reactive protein (CRP) and white blood cells (WBC) in the total cohort and the subset of patients with concomitant acute heart failure (HF).
Results: We diagnosed pneumonia in 16 out of 140 patients with acute HF (11%) and in 45 out of 170 patients with non-HF-related dyspnea (27%). PCT concentrations were higher in patients with pneumonia vs. patients without pneumonia, both among acute HF patients (median 2.79 [Q1–3 0.18–5.80] vs. 0.10 [0.07–0.14]) ng/mL, $p < .001$) and non-HF patients (0.22 [Q1–3 0.13–0.77] vs. 0.07 [0.05–0.10] ng/mL, $p < .001$). CRP and WBC were also higher in patients with pneumonia in both groups, but among acute HF patients, only PCT concentrations were associated with pneumonia in multivariate analysis. In patients with acute HF, receiver-operating statistics area under the curve (ROC-AUC) to diagnose pneumonia was 0.90 (95% CI 0.81–0.98) for PCT, 0.84 (0.73–0.94) for CRP, and 0.72 (0.57–0.87) for WBC. The corresponding ROC-AUCs among patients with non-HF-related dyspnea were 0.88 (0.82–0.93), 0.94 (0.90–0.98), and 0.79 (0.72–0.87), respectively. During a median follow-up of 823 days (Q1–3 471–998) 114 patients died, and PCT and CRP, but not WBC concentrations were associated with all-cause mortality.
Conclusion: In acute HF patients, PCT concentrations were superior to CRP and WBC to diagnose concurrent pneumonia.

1. Introduction

Dyspnea is a common problem in Emergency Departments (EDs) worldwide. A prevalent etiology in patients with acute dyspnea is bacterial pneumonia [1, 2], which causes substantial morbidity and mortality [3]. Early initiation of appropriate antibiotic therapy reduces mortality [4, 5], but diagnosing pneumonia can be difficult due to lack of a definitive diagnostic test and overlapping symptoms with other conditions such as acute heart failure (HF) and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [6]. Accordingly, a biomarker that is able to diagnose pneumonia at hospital admission would be clinically useful.

The combination of fever, new or increasing cough, sputum production, dyspnea, and/or pleuritic chest pain is normally required to diagnose pneumonia. Chest x-ray is also easily available in the ED, but can be normal during the initial phase of lower respiratory tract infections. Microbiological culture is the gold standard to diagnose bacterial infections, but due to slow growth rate the result of the test is available later in the course of the hospitalization [7]. Other laboratory tests routinely used in Europe to help separate infectious from non-infectious diseases include C-reactive protein (CRP), white blood cells (WBC), and erythrocyte sedimentation rate (ESR) [7]. Still, as these tests have suboptimal sensitivity and specificity for bacterial infections [8] there is a need for additional tests to diagnose pneumonia and to

* Corresponding author at: Division of Medicine, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway.
E-mail address: helge.rosjo@medisin.uio.no (H. Røsjø).

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improve risk assessment in patients with acute dyspnea.

One leading biomarker candidate is procalcitonin (PCT) [9], the peptide precursor of the hormone calcitonin which is involved in calcium homeostasis. In healthy subjects serum concentrations of PCT are below 0.1 ng/mL [10] and rarely increased during viral infections and nonspecific inflammatory diseases [11]. During bacterial infections, PCT increases rapidly due to increased synthesis of PCT by several cell types and many organs in response to pro-inflammatory stimuli, in particular by bacterial products [8, 11, 12]. Circulating PCT concentrations correlate with disease severity in critically ill patients [13, 14] and could therefore provide important prognostic information in patients with acute dyspnea. Accordingly, in this study we hypothesized that PCT measurements provide additional diagnostic and prognostic information to clinical variables and other biomarkers in patients with acute dyspnea, and especially in patients with concurrent acute conditions that may increase other and more unspecific inflammatory biomarkers.

2. Methods

2.1. Akershus Cardiac Examination (ACE) 2 Study

The ACE 2 Study was a prospective, single-center study that included patients presenting to the ED of Akershus University Hospital with dyspnea from June 2009 to November 2010. Akershus University Hospital is a teaching hospital and the catchment area was approximately 360.000 during the period of patient inclusion. We have previously reported the methods of the study in detail [15]. We screened for eligible patients during the daily morning briefings at the ED and collected blood samples for PCT measurements as soon as possible, but only during daytime (8 a.m.–2 p.m.). Hence, although all included patients were identified and assessed by a physician in the ED, patients may have been transferred to the inpatient wards before study blood samples were collected. In short, patients had to be ≥18 years of age and able to provide informed consent before study inclusion. Exclusion criteria were recent major surgery, acute myocardial infarction or coronary intervention; or disseminated malignant disease or other conditions with short life expectancy. In total, we examined 468 patients with dyspnea, of which 314 patients were included into the study (Fig. 1). We performed the study in accordance with the Declaration of Helsinki and after approval from the Regional Ethics Committee. All study participants provided written consent before study inclusion.

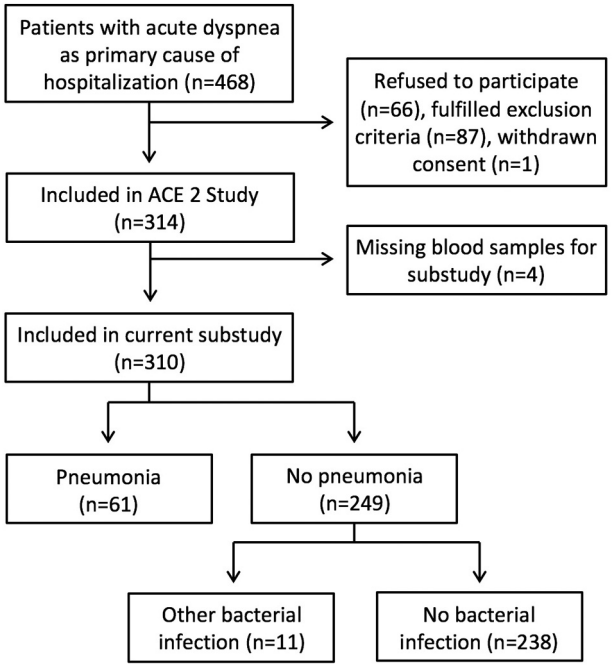

Fig. 1. Flow chart of the study.

2.2. Data collection

We collected relevant information of eligible patients through a standardized questionnaire, as previously described [15], and gathered additional patient information using the hospital's electronic records. The first set of blood samples used for PCT determination were collected from 310 patients as early as possible, and at least within 24 h of hospital admission. Notably, standard blood samples according to hospital routines, including CRP and WBC, were collected while the patients were still in the ED, and in many cases repeated shortly after hospitalization. We used the CRP and WBC samples measured the closest to the time point of PCT sampling for biomarker comparison (median difference 4.7 [Q1-Q3 2.2–15.8] h). Antibiotic therapy was based on the treating physician's evaluation of the patient, and initiated independently of time of blood sampling. Blood for PCT determination were also collected after 24 h from 229 patients and at hospital discharge from 96 patients. CRP and WBC follow-up analyses were performed at the discretion of the treating physician and included if sampled on the second day of hospital admission (as close as possible to 24 h after admission) and/or on the day of hospital discharge. We calculated body mass index (BMI) as body weight / [height × height] (kg/m^2), and left ventricular ejection fraction (LVEF) was determined based on clinical routine transthoracic echocardiography.

2.3. Adjudication and follow-up data

Two independent senior physicians reviewed all relevant patient data, including follow-up medical records and supplementary examinations, with a median of 2590 [quartile 1–3 2423–2752] days before adjudication, to determine whether patients had pneumonia at hospital admission. Diagnosis was made according to the *Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia* [7] and required a constellation of symptoms suggestive of pneumonia; e.g. fever, cough, dyspnea, sputum production, pleuritic chest pain, and preferably supported by either chest X-ray-verified pneumonia or crackles on physical examination. Other bacterial infections, including urinary tract infections, erysipelas, sinusitis and abscesses, were determined according to appropriate guidelines. When pneumonia or other bacterial infections could not be ascertained based on symptoms, results from clinical examination, and chest X-ray alone, the adjudicators accessed laboratory data, including CRP, WBC and D-dimer but not PCT. In situations of disagreement between the two adjudicators, discrepancies were resolved by consensus. To determine consistency among the adjudicators we performed interrater reliability analysis using the Kappa statistic. HF was defined as symptoms and clinical signs of HF and evidence of myocardial structural or functional impairment or injury [16], and AECOPD was defined as worsening of the patient's symptoms (dyspnea, cough and/or sputum production) beyond day-to-day variation leading to a change in medication, similar to previous studies of the ACE2 cohort [15]. We obtained survival data from the hospital's electronic records, which are synchronized with Statistics Norway on a monthly basis.

2.4. Biochemical measurements

Blood sampling was performed by venipuncture according to hospital guidelines. After centrifugation, serum was immediately frozen and stored at −80 °C. Prior to biomarker analyses serum was thawed at room temperature. PCT concentrations were determined from samples collected into standard serum-gel tubes, with the automated B·R·A·H·M·S Kryptor PCT Sensitive immunoassay (Thermo Fisher