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Original Contribution

Cardiometabolic biomarkers are predictors of readmission and death in patients hospitalized for acute dyspnea

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ABSTRACT

Background: Acute dyspnea affects a large heterogeneous patient group with high mortality and readmission rates.
Purpose: To investigate if cardiometabolic biomarkers and clinical characteristics predict readmission and death in patients hospitalized for acute dyspnea.
Methods: 65 dyspnea patients at a general internal medicine ward were followed for six months. The combined endpoint was readmission or death.
Measurements and results: Cardiometabolic biomarkers at admission were related to the endpoint in Cox proportional hazard models (adjusted for sex, age, oxygen saturation, respiratory rate and C-reactive protein (CRP)). The biomarkers tissue-type plasminogen activator (tPA), prolactin (PRL), tumor necrosis factor receptor superfamily member 6 (FAS) and C-C motif chemokine 3 (CCL3) were independently and significantly related to the endpoint and combined into a biomarker risk score (BRS). Each SD increment of the BRS conferred a hazard ratio (HR) of 2.13 (1.39–3.27) $P = 0.001$. The top vs bottom tertile of the BRS conferred a HR of 4.75 (1.93–11.68) $P = 0.001$. Dyspnea severity was also associated with worse outcome, HR = 3.43 (1.28–9.20) $P = 0.014$. However, when mutually adjusted the BRS remained significant ($P = 0.004$) whereas dyspnea severity was not. The BRS was related to the endpoint among patients with mild to moderate dyspnea ($P = 0.016$) but not among those with severe dyspnea.
Conclusion: A score of tPA, PRL, FAS and CCL3 predicts 6-month death and readmission in patients hospitalized for acute dyspnea and may prove useful to optimize length of stay and follow-up. Although the BRS outweighs dyspnea severity in prediction of the endpoint, its prognostic role is strongest in mild-moderate dyspnea.

1. Introduction

Patients with acute dyspnea are a large and heterogeneous patient group with high mortality and readmission rates [1-6]. Dyspnea is a common manifestation of diseases in the cardiovascular and respiratory system such as congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease and pulmonary thromboembolism [3, 6]. Due to the diversity, diagnostics is often challenging and delayed. Early risk assessment is crucial for patient outcome but individual risk assessment is difficult and reliable predictive tools are missing [7,8].

Today, medical history, physical examination and clinical characteristics are often combined with blood chemistry for diagnostic and prognostic evaluation in patients with acute dyspnea. This approach has its limitations and the need for further methods has been addressed to optimize medical care [8]. There are few studies investigating the long-term outcome for patients with acute dyspnea [6,9]. Improvement of early prognostic judgments in patients admitted for acute dyspnea has the potential of both shortening the length of stay and to stratify patients for intensified treatment or direct for thorough search for the underlying condition if the patient is at high risk of adverse outcome. Importantly, any prognostic role of biomarkers has to yield additional clinical information on top of currently used risk stratification tools. Not at least, a structured classification of the severity of dyspnea needs to be taken into account [8]. In this context, a standardized classification of dyspnea severity is necessary. The NYHA functional classification is a widely used prognostic tool for patients with congestive heart failure [6, 10] but to our knowledge it has not been evaluated for prognosis in unselected patients hospitalized for dyspnea. So far no one has investigated the link between a broad panel of inflammation, immune response, metabolism and cardiovascular stress biomarkers with outcome for patients hospitalized for acute dyspnea. However, with novel multimarker panels recently developed, such broad biomarker characterization has now become feasible.

The purpose of this study is to investigate if circulating cardiometabolic biomarkers can be used to predict outcome of patients hospitalized due to

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acute dyspnea on top of clinical characteristics used for risk stratification today.

2. Materials and methods

We studied in-patients hospitalized due to acute dyspnea during 2012 and 2013 at a general internal medicine ward at the University Hospital of Skåne in Malmö, Sweden. The inclusion criterion was acute dyspnea on arrival, defined as either "dyspnea" as the preliminary diagnosis on admission to the emergency department or as the presence of dyspnea on arrival to the internal medicine department. A written form of consent was obtained from all study participants. Patients with cognitive dysfunction, defined as a mini mental state examination performance of <13, were excluded [11]. The study was approved by the regional board of ethics in Lund, Sweden.

Data collection was performed by review of medical records, blood sample analysis and interviews. Variables recorded were patient baseline characteristics, medical history, social status, functional and physical examinations, vital signs, physical findings, severity of dyspnea, cardiometabolic biomarkers and routine blood chemistry. The variables included are shown in Table 1. We measured circulating cardiometabolic plasma biomarkers using the multiplex immunoassay Proseek Multiplex CVD I biomarker panel (Olink Bioscience, Uppsala, Sweden), (http://www.olink.com/proseek-multiplex/cvd/). More information of the biomarkers in the biomarker panel can be found in the supplementary data. In total, 80 patients were enrolled. Due to missing data on respiratory rate for 14 patients and blood biomarkers for 1 patient, 15 patients were excluded. This yielded 65 study participants.

The severity of dyspnea was defined as the impact of dyspnea and measured as a single rating of disability on day 0. The severity was graded into a four-level score with the following values: no dyspnea, mild dyspnea, moderate dyspnea and severe dyspnea. The classification was based on the NYHA functional classification [10] and named dyspnea severity score (DSS). The combined study endpoint was readmission or death within six months. Readmission was considered as a following hospital stay, with the date of readmission as the endpoint date. The date of death was derived from the Swedish national civil registry. Statistical analysis was performed with IBM SPSS statistics 22 (SPSS) (SPSS Inc., Chicago, IL, USA).

Venous blood samples were obtained on admission day 0. Routine blood chemistry was analyzed using a Radiometer ABL800 Flex machine or Afinion AS100 Analyzer System [12] (http://www.alere.com/en/home/product-details/afinion-as100-analyzer-us.html). Three 7 mL EDTA blood samples and three 5 mL serum blood samples were drawn from each study participant for cardiometabolic biomarker analysis with Proseek. The samples were transferred into immunoassay plates with 24 plasma aliquots and 12 serum aliquots. The immunoassays were centrifuged 3000 turns per minute in 10 min and stored in −80 °C for later analysis made by Proseek in Uppsala, Sweden. Detailed instructions of the methods in this analysis is found at the homepage of the manufacturer (http://www.olink.com/proseek-multiplex/cvd/)

For biomarkers with skewed data distribution natural logarithms were used to transform data to standardized scales and express the results per one standard deviation increment. All parameters were related to the endpoint by using Cox proportional hazard ratios adjusted for sex, age, peripheral oxygen saturation (SpO2), respiratory rate and C-reactive protein (CRP). A P value of <0.05 (95% CI) was considered significant. Biomarkers independently related to outcome were analyzed using Cox regression with stepwise backward elimination. Significant biomarkers were combined into a biomarker risk score (BRS). The standardized values of significant biomarkers were weighted by their respective beta-coefficients and summed up to comprise the BRS. The BRS was also ranked and patients were categorized into tertiles according to the BRS, with the bottom tertile (lowest risk) used as the reference group.

Table 1
Patient baseline characteristics, $n = 65$.

Age (years), mean (±SD)	81.9 (±9.3)
Sex (males), n (%)	36 (55.4)
Smoking, n (%)	
Current-smoker	7 (10.8)
Former-smoker	39 (60.0)
Never-smoker	19 (29.2)
C-reactive protein (mg/L), median (range)	17 (209.4)
NT-proBNP (ng/L), median (range)	3754 (34950)
Medications, n (%)	
ASA or TRC-inhibitors	34 (52.3)
Warfarin or DOACs	18 (27.7)
Beta-antagonists	44 (67.7)
ACE-inhibitors	25 (38.5)
Angiotensin II receptor antagonists	15 (23.1)
Calcium channel antagonists	23 (35.4)
Diuretics	44 (67.7)
Inhalations (SABA, LABA, LAMA, ICS)	22 (33.8)
Nitroglycerin	18 (27.7)
Anxiolytics	7 (10.8)
Anti-diabetics	10 (15.4)
Medical history, n (%)	
Congestive heart failure	46 (70.8)
Anemia	45 (69.2)
Ischemic heart disease	43 (66.2)
Hypertension	42 (64.6)
Atrial fibrillation	35 (53.8)
Chronic obstructive pulmonary disease	23 (35.4)
Pneumonia or sepsis	22 (33.8)
Diabetes	19 (29.2)
Chronic kidney disease	14 (21.5)
Pulmonary thromboembolism	8 (12.3)
Asthma	5 (7.7)
Vital parameters, mean (±SD)	
Oxygen saturation (%)	95 (±3.6)
Respiratory rate (min^{-1})	22 (±4.5)
Heart rate (min^{-1})	80 (±15.9)
Systolic blood pressure (mm Hg)	132 (±18.6)
Diastolic blood pressure (mm Hg)	75 (±11.4)
Body temperature (°C)	36.9 (±0.7)
Severity of dyspnea, n (%)	
Dyspnea severity score, DSS 1 - no dyspnea	0 (0)
Dyspnea severity score, DSS 2 - mild	15 (23.1)
Dyspnea severity score, DSS 3 - moderate	30 (46.2)
Dyspnea severity score, DSS 4 - severe	20 (30.8)

3. Results

The mean age of in-patients with acute dyspnea was 81.9 (±9.3) years. The proportion of men was 36 (55.4%). A medical history of earlier chronic diseases was common (Table 1). During the six months of follow up, 27 (41.5%) of the patients experienced a first readmission and 17 (26.2%) deceased. Main diagnosis at discharge is shown in Table 2.

Oxygen saturation level was marginally lowered (95%) and respiratory rate elevated (22 ± 4.5), (Table 1). Most of the patients had moderate dyspnea 30 (46.2%) (DSS 3) but a substantial number suffered from severe dyspnea 20 (30.8%) (DSS 4). No patient had DSS 1.

The biomarkers tissue-type plasminogen activator (tPA), prolactin (PRL), tumor necrosis factor receptor superfamily member 6 (FAS)

Table 2
Main diagnoses at discharge, n (%).

Heart failure	29 (44.6)
COPD/asthma	13 (20.0)
Pneumonia/sepsis	8 (12.3)
Acute coronary syndrome	2 (3.1)
Pulmonary thromboembolism	2 (3.1)
Malignancy	1 (1.5)
Others	10 (15.4)