Lipid Profile and Statin Use: The Paradox of Survival After Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract: *Background:* A paradoxical association between cholesterol level and clinical outcome has been suggested, yet never previously established, in patients with chronic obstructive pulmonary disease (COPD). *Objectives:* The authors sought to investigate the interaction between long-term survival, lipid profile and statin use in patients after acute exacerbation of COPD (AECOPD). *Methods:* A retrospective study evaluating demographic, clinical and laboratory data of 615 consecutive patients admitted for AECOPD over a mean follow-up period of 24.8 months. Kaplan–Meier survival curves and multivariate analysis were used to identify independent prognostic predictors for all-cause mortality. *Results:* Mean ± standard deviation (SD) age of the study population was 71.8 ± 11.4 years. Unexpectedly, mean serum cholesterol ± SD levels were significantly higher in survivors (N = 340) versus nonsurvivors (N = 275): 181.5 ± 43.6 versus 171.6 ± 57.2 mg/dL, respectively, (P = 0.0043). Median survival for patients with cholesterol levels <150 and >200 mg/dL were 16.0 and 64.4 months, respectively (P = 0.0173). On multivariate analysis, cholesterol level <150 mg/dL was an independent predictor of mortality, irrespective of cardiovascular risk factors (hazard ratio [HR] = 1.8430, 95% confidence interval [CI] = 1.2547–2.7072, P = 0.0019). Statin use had an independent protective effect, regardless of cholesterol level (HR = 0.4924, 95% CI = 0.2924–0.8292, P = 0.0080). *Conclusions:* Low cholesterol levels are significantly associated with increased mortality after AECOPD. Nonetheless, as statin treatment was associated with reduced mortality over the entire range of cholesterol levels, its use should be considered in all COPD patients.

Key Indexing Terms: Chronic obstructive pulmonary disease; Cholesterol; Prognosis; Statins. **[Am J Med Sci 2015;349(4):338–343.]**

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a major public health issue and a major cause of mortality worldwide.[1,2] The natural course of COPD is characterized by a progressive decline in pulmonary function and recurrent exacerbations requiring hospitalizations. Acute exacerbation of COPD (AECOPD) is associated with both substantial in-hospital mortality and may impact long-term prognosis after hospital discharge with adverse affect on the natural course of the disease.[3,4] It has been suggested that cardiovascular mortality accounts for roughly 50% of deaths in COPD patients.[5–7] Paradoxical associations between traditional cardiovascular risk factors and clinical outcome, referred to as "reverse epidemiology," have been observed in various chronic disease states.[8] Counterintuitive epidemiological trends regarding cholesterol levels and body weight have been observed in dialysis patients, patients with congestive heart failure (CHF), rheumatoid arthritis and acquired immune deficiency syndrome.[8] The inverse relationship between body mass index (BMI) and COPD-related mortality has been previously described.[9] Data on the association between cholesterol level and COPD-related mortality is sparse. One large epidemiological study documented a nonsignificant decreased risk of COPD-related hospitalization, in the setting of high cholesterol in men, but not in women, and an inverse relationship between cholesterol level and COPD-related deaths.[10] To the best of our knowledge, no previous study has investigated the association of serum cholesterol with the risk of mortality after AECOPD.

Accumulating data suggest that lipid lowering agents, namely statins, may decrease mortality in COPD patients.[11–13] Statins may also produce additional beneficial pleiotropic effects, including increased nitric oxide and prostacyclin, antithrombosis and decreased inflammation, perhaps indicating their therapeutic utility for COPD.[14,15] However, interpretation of these results is controversial, some claim that these studies cannot provide definitive proof of cause and effect and may have selection bias because none of them discuss baseline cholesterol.[16,17] Consequently, by revealing an association between low cholesterol levels and increased mortality after AECOPD would have major clinical implications for evaluating whether the beneficial effects of statins are relevant to patients with a wide spectrum of serum cholesterol levels.

The purpose of the current report was to investigate the relationship between all-cause mortality after admission for AECOPD and lipid profile and use of lipid lowering agents.

METHODS

Study Population

Approval for this study was obtained from the Rambam Medical Center Review Board. No personally identifiable information was used. A retrospective study of all consecutive patients admitted to the General Medicine Wards at the Rambam University Hospital, Haifa, Israel, over an 8-year period between January 1, 2001, and December 31, 2008, with a primary diagnosis of acute exacerbation COPD. All patient admissions during the study period with a primary *ICD-10* (International Statistical Classification of Diseases and Related Health Problems, 10th revision) discharge-coded diagnosis of chronic obstructive pulmonary disease, chronic obstructive pulmonary disease with acute exacerbation or chronic obstructive pulmonary disease with acute lower respiratory tract infection were included. COPD was further identified from the patient's premorbid pulmonary function testing results. Patients were included if the following criteria were met: diagnosis of COPD, according to the criteria set by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (ie, all patients had FEV_1/FVC <70% and symptoms indicating an acute

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exacerbation of COPD).[18] AECOPD was defined by the presence of an increase in at least 2 of the 3 symptoms, dyspnea, cough and sputum purulence, severe enough to warrant hospital admission without concomitant evidence of pneumonia. Patients with pneumonia, pulmonary edema, pulmonary embolism and pneumothorax were excluded from the study. Patients who were initially admitted to an intensive care unit or subsequently transferred to such unit were excluded. Patients who required either invasive or noninvasive ventilatory support during hospitalization were excluded. Only patients who survived to discharge were included in the study, and patients who died during index hospitalization were excluded.

Epidemiological and Baseline Laboratory Data

Data were collected retrospectively. The age, gender and smoking status of the patients were documented. Active smoking status was defined as having smoked within the last 6 months. For all patients included in the study, the following data were assessed and recorded on standardized forms from patient charts: medical history and comorbid conditions (diabetes mellitus, ischemic heart disease [IHD], CHF and chronic renal failure).

Results of laboratory analyses performed within 24 hours of hospital admission were retrieved from the hospital's laboratory database. If multiple results were available, average levels were used. Lipid profile was evaluated at the fasting state on the first morning after admission.

Outcome and Follow-up

Hospital discharge date was used as the starting point, regarding the follow-up period. End of follow-up was December 31, 2010. Patients were followed up for 6 years after admission, by review of the clinical note sent through the death registration record in event of out-of-hospital death.

Statistical Analysis

Descriptive data are presented as mean ± standard deviation (SD) or median (range). Comparisons between groups were made by using the Mann–Whitney's *U* test (for continuous variables) or Fisher's exact test (for categorical variables), where appropriate. Receiver operating characteristic curve analysis was used to determine the optimal cutoff level for cholesterol that predicted mortality. Survival curves were estimated by the Kaplan–Meier product–limit method and compared using the log-rank test. Univariate Cox regression analysis was completed to identify significant variables predicting survival status. Variables, which were significant by univariate Cox regression analysis, were taken as potential predictors of survival and were used as covariates in multivariable Cox proportional hazards model analysis, to identify independent predictors of survival. Two-sided P value of <0.05 was considered to be statistically significant. All of the statistical analyses were performed using a statistical software package (version 9.3.0.0; MedCalc, MedCalc Software, Ostend, Belgium).

RESULTS

Between January 1, 2001, and December 31, 2008, 615 eligible patients were admitted to the General Medicine Wards with a primary admission diagnosis of AECOPD and survived to discharge. A total of 83 patients were excluded from the study of which 44 patients died during index hospitalization. The recruitment of patients for the study and the exclusion process is described in Figure 1. The study population's baseline characteristics are listed in Table 1. The mean ± SD age of the study population was 71.8 ± 11.4 years (range: 35–100 years). The majority of patients (68.4%) were male. Nearly half (48.9%) were still actively smoking. Twenty percent had IHD, and 26% had diabetes mellitus. Over a mean follow-up period of 24.8 months (range: 6–96 months), 275 (44.7%) patients had died. The differences in main parameters between survivors and nonsurvivors during follow-up are listed in Table 1. Patients who died were older, more likely to have IHD, CHF and were active smokers. Compared with survivors, patients who died were significantly more hypercapnic (mean $PaCO_2$ ± SD in mm Hg, 46.5 ± 13.0 versus 50.6 ± 17.0, respectively). Total cholesterol levels of nonsurvivors were unexpectedly lower than survivors (mean ± SD, 171.6 ± 57.2 versus 181.5 ± 43.6 mg/dL, $P = 0.0403$). Compared with nonsurvivors, patients who survived were more likely taking statins 16% versus 30.5% ($P = 0.0001$).

The overall median survival was 41.7 months. Overall survival rates at 1, 2 and 3 years were 68.9%, 59.6% and 52.7%, respectively. When patients were stratified to 3 quintiles according to their cholesterol levels, Kaplan–Meier plot of survival probability demonstrated a significant survival disadvantage for patients with low cholesterol levels (Figure 1). Median survival for patients with cholesterol levels <150 mg/dL, between 150 and 200 mg/dL and >200 mg/dL were 16.0, 40.3 and 64.4 months, respectively; $P = 0.0173$ by log-rank test. As shown in Figure 2, median survival for patients who

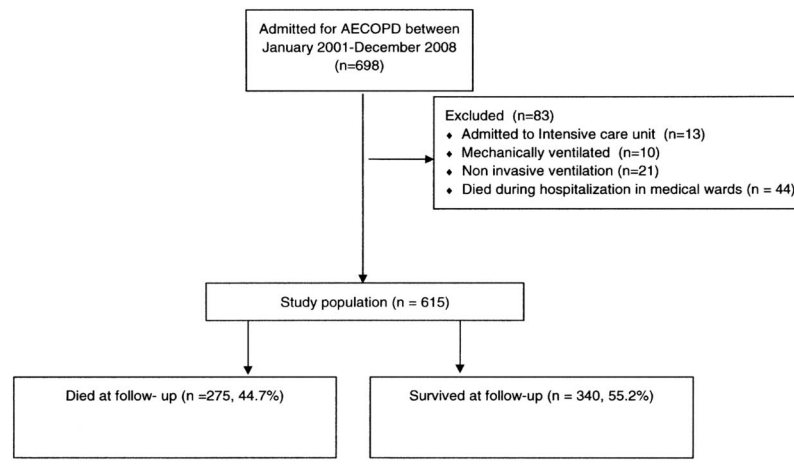

FIGURE 1. Flowchart of study patients recruitment and follow-up.