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Elevated C-reactive protein and mortality risk among COPD patients

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a progressive disease associated with autoimmune systemic inflammation. The evidence on the role of C-reactive protein (-CRP) in predicting mortality among people with COPD remains mixed.

Methods Data from the National Health and Nutrition Examination Survey (1999–2010) were linked with mortality files up to December 31st, 2019, from the National Death Index. Adults ages 20 years or older were included in the analytic sample to assess the relationship between physician-diagnosed self-reported COPD and mortality based on blood CRP levels. Multivariate complex samples Cox regression analyses were conducted to determine the hazards ratios (with 95% CI).

Results A total of 30,669 individuals comprised of the final sample with 2215 deaths observed upon follow-up for an average of 10.2 years. Compared to individuals without COPD or elevated CRP, individuals with COPD but without elevated CRP (HR = 1.25, 95% CI = 0.97–1.61) did not have a significantly higher risk of mortality. However, those with both COPD and elevated CRP had a significantly higher risk of mortality (HR = 2.70, 95% CI = 1.08–6.81). Age, health insurance status, and a history of comorbidities modified these relationships.

Conclusions Biomarkers such as CRP continue to show promise for long-term COPD-related outcomes. Additional prospective assessments of individuals with airway obstruction are warranted to understand if CRP levels predict the occurrence or worsening of COPD and if those relate to long-term health outcomes.

Keywords Inflammation, COPD, Mortality, Biomarker, Pulmonology

Introduction

Globally, chronic obstructive pulmonary diseases (COPD) are now among the top 3 leading causes of death with more than 3 million deaths per year and more than 50 million living with the disease [1–3]. While it is well established that COPD is a progressive disease resulting from persistent and abnormal inflammatory processes damaging the lung tissue, the search for definitive and distinct biomarkers for the disease continues [2–5]. A plethora of studies in recent times have shared genetic and biochemical data for individuals with COPD. Among the biomarkers, inflammatory markers are probably the most highly researched and assessed. For example, multiple studies indicate that levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF—α), fibrinogen, and Interleukins (e.g., 6 and 8) are elevated among patients with COPD [4–7].

One particular biomarker (i.e., CRP) has been apprised extensively in a wide variety of studies of individuals with COPD [5–8]. Many of these studies suggest that elevated CRP is a marker for COPD-related exacerbations and worsening while some report that CRP is elevated even among stable COPD patients [1, 6–9]. In contrast, some studies have found no significant elevation of CRP in

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stable COPD patients [6, 10]. The ECLIPSE cohort study found CRP to be the most variable marker upon follow-up after 3 months in more than 200 patients and one with the least repeatability among the 34 biomarkers assessed [3]. Similarly, the evidence on mortality prediction by CRP levels among COPD patients remains scattered; ranging from no relationship to a significant positive association [6]. A major weakness of these studies has been the limited accounting for sociodemographic or health-related variables while assessing the relationship between COPD, CRP, and mortality [6, 9, 11]. Thus, the purpose of this study was to prospectively assess the impact of elevated CRP on mortality risk among individuals with COPD after adjusting for numerous sociodemographic characteristics, lifestyle behaviors, and history of chronic diseases.

Methods

Data from the National Health and Nutrition Examination Survey (NHANES) cycles 1999–2010 were analyzed by linking them with mortality data up to December 2019 from the National Death Index (NDI) [12–14]. The participants in our analysis comprised a national random sample of American NHANES participants 20 years of age and older. Data collection for NHANES consists of an in-home interview and a physical exam component at a mobile health examination center. The survey interview includes questions about sociodemographic details and health-related questions. The physical exam component includes medical, physiological, and laboratory measurements (e.g., CRP). For the processing of CRP from blood samples, latex-enhanced nephelometry with particle-enhanced assays was used for quantification. Assays were performed on a Behring Nephelometer to determine CRP levels. The primary standard used for processing was organized by Behring Diagnostics and standardized against WHO reference material. A cutoff level of ≥ 2 mg/dL was considered as elevated CRP in study participants who gave blood samples.

Participant characteristics such as age, sex, education, race/ethnicity, and health insurance status were assessed for this analysis. For income, FIPR (family income to poverty ratio) was considered for analysis. Obesity prevalence was determined based on participants' height and weight. Prevalence of diabetes and smoking were determined by participant self-reports. Also, cardiovascular disease history was determined by the self-reported diagnosis of coronary heart disease, hypertension, stroke, or myocardial infarction. For chronic kidney disease (CKD), the glomerular filtration rate was derived from the Cockcroft-Gault equation. COPD was assessed by combining self-reported doctor-diagnosed emphysema or chronic bronchitis. Additional details about the NHANES data analysis and procedures have been published extensively in studies using this data and on the CDC website. NCHS Research Ethics Review Board approved all study protocols and procedures before data collection [12–14].

Study variables were first analyzed using descriptive statistics for sociodemographic and health-related characteristics (e.g., frequencies and percentages). Next, a series of bivariate tests were used to assess differences between those with and without COPD. Multivariate analysis was performed using complex samples Cox regressions to determine the relationship between COPD and mortality. Multiple Cox regression models were constructed to examine differences in mortality among people with COPD (based on whether or not they had elevated CRP) after adjusting for health-related (e.g., comorbidities) and sociodemographic characteristics. Four groups were utilized in this analysis: those with COPD only, elevated CRP only, both COPD and elevated CRP, or neither COPD nor elevated CRP (this last group serves as the reference group for mortality assessment). Statistical significance was assumed a priori at an alpha level of $p < 0.05$.

Results

A total of 30,669 NHANES participants were included in the final analysis where the majority were males (52%), Whites (70.5%), or with some college education (55.2%) (Table 1). COPD prevalence was found to be 7.3% and elevated CRP levels were found in 2.8% of participants. For COPD, a significantly higher prevalence was noted among older participants, males, smokers, those with lower education or income, or those with diabetes, CVD, and CKD. Individuals with COPD had a statistically significantly higher proportion of participants with elevated CRP (Table 1). There was a mean follow-up of 10.2 years from data collection to mortality for all groups.

Among the study participants, in adjusted analysis, the risk of mortality among those with COPD was 1.30 times (95% CI = 1.02–1.66) higher compared to those who did not have COPD (Table 2). When stratified by CRP levels, individuals with COPD but without elevated CRP (HR = 1.25, 95% CI = 0.97–1.61) did not have a significantly higher risk of mortality than those without COPD or elevated CRP (reference group). In contrast, those with elevated CRP and no COPD had a significantly higher risk of mortality (HR = 1.69, 95% CI = 1.23–2.32). The highest risk of mortality was observed among those with both COPD and elevated CRP levels (HR = 2.70, 95% CI = 1.08–6.81) with age serving as a significant moderator of this relationship. Except for the group with both COPD and elevated CRP, in all of the other comparison groups, the relationship with mortality among study participants was moderated by CVD, CKD, smoking,

Table 1 Characteristics of study participants stratified by COPD diagnosis

Characteristics	Total population *(n = 30,669)*	COPD (+) *(n = 2219)*	COPD (−) *(n = 28,450)*
Age (years, mean)**	46.5 (46.1–47.0)	53.2 (52.4–54.0)	45.9 (45.5–46.4)
Male (%)**	52.0 (51.5–52.5)	64.5 (61.9–67.1)	51.0 (50.6–51.5)
Education level (%)**			
Less than high school	19.9 (18.6–21.1)	25.6 (22.3–28.8)	19.4 (18.3–20.6)
High school graduate	25.0 923.9–26.9)	27.5 (24.8–30.1)	24.8 (23.6–25.9)
Some college or above	55.2 (53.4–57.0)	47.0 (43.8–50.1)	55.8 (54.1–57.6)
Race/ethnicity (%)**			
Non-Hispanic White	70.5 (67.9–73.0)	79.8 (77.0–82.7)	69.7 (67.2–72.3)
Non-Hispanic Black	11.2 (9.8–12.5)	9.1 (7.50–11.0)	11.3 (9.9–12.7)
Hispanic	12.9 (10.9–14.9)	6.5 (4.8–8.8)	13.4 (11.4–15.4)
Other	5.5 (4.8–6.2)	4.54 (3.6–5.8)	5.5 (4.9–6.3)
Family Poverty Income Ratio** (%) (PIR < 1)**	13.6 (12.7–14.5)	19.1 (16.3–21.8)	13.1 (12.3–14.)
No insurance	18.7 (17.7–19.7)	16.0 (13.8–18.1)	18.9 (17.9–19.9)
Obesity*	33.1 (3.2–34.9)	29.7 (27.5–31.8)	33.4 (32.4–34.4)
Diabetes**	7.8 (7.3–8.3)	13.0 (11.2–14.9)	7.4 (6,9–7.8)
Smoking**	23.5 (22.6–24.4)	34.7 (32.6–36.9)	22.6 (21.7–23.5)
Cardiovascular disease**	8.7 (8.1–9.2)	22.7 (20.5–24.8)	7.6 (7.1–8.1)
Chronic kidney disea**e****	7.1 (6.7–7.6)	12.1 (10.4–13.9)	6.7 (6.3–7.2
CRP (≥ 2 mg/dL)**	2.8 (2.6–3.1)	5.4 (4.4–6.5)	2.6 (2.4–2.9)
All deaths (*N*)**	2215	907	1308

Numbers with 95CI indicate 95% confidence intervals for proportions

*$p < .05$, **$p < .01$

diabetes, and health insurance providing indications for the major avenues of adequate COPD management.

Discussion

This analysis of NHANES and NDI data suggests that while having COPD increases the risk of mortality, elevated CRP levels may further increase the risk of mortality among those with COPD. Previous studies have suggested the role of inflammation in the pathogenesis, progression, and exacerbation of COPD by assessing CRP [4–6, 15]. Some studies have also found CRP to have a high predictive value in diagnosing exacerbations of COPD [1, 12]. A recent meta-analysis of 61 biomarkers from 29 studies also found a moderate association between CRP and the presence of bacterial pathogens in the sputum of patients with acute exacerbation of COPD [16]. Progression and worsening of COPD are also associated with complications ranging from infections, metabolic abnormalities, psychiatric disorders, and cardiovascular diseases to acute or chronic respiratory failure [8, 11, 17]. All of these outcomes have the potential to increase the risk of mortality and could be the mechanisms underlying our findings.

Further research is needed on the relationship between COPD, CRP, and mortality [4, 6, 12, 17, 18]. First, the mortality profiles need exploration in patients with COPD and elevated CRP (e.g., cardiovascular vs. other types of mortality). Second, prospective assessments of individuals with airway obstruction are needed to understand if CRP levels predict the occurrence of COPD. Third, as many experts argue that CRP is a non-specific marker, additional studies are needed to identify a biomarker profile or composite indices (along with CRP) that can predict outcomes among those with COPD. Also, the causes and roles of comorbidities among those with COPD need to be explored in light of CRP levels. Finally, there are several phenotypes of COPD patients and to establish a definitive role of CRP, the integration of proteomic and metabolomics networks along with genetic studies is recommended to understand the pathways for COPD-related outcomes [17, 18].

This study utilized a large random sample of American adults with high representativeness and complex sample survey analysis procedures to reduce bias and produce precise estimates. Also, we accounted for several variables in our analysis, making this a unique contribution to the literature on COPD-related outcomes and the factors influencing these outcomes. Despite that, the study has potential limitations that warrant attention. Many health-related measures were based on self-reported

Table 2 Risk of mortality based on COPD and elevated CRP

	Total population [HR (95% CI)]; *N* = 30,669	**COPD − and CRP −[(ref) *N* = 27,703]**	**COPD + and CRP +; HR (95% CI); *N* = 128**	**COPD + and CRP −; HR (95% CI); *N* = 1965**	**COPD- and CRP +; HR (95% CI); *N* = 873**
COPD	1.30 (1.02–1.66)*	R	2.70 (1.08–6.81)*	1.25 (0.97–1.61)	1.69 (1.23–2.32)*
Cardiovascular disease	1.56 (1.37–1.77)**	E	1.83 (0.87–3.85)	1.54 (1.36–1.75)**	1.59 (1.36–1.86)**
Chronic kidney disease	1.64 (1.44–1.87)**	F	1.71 (0.93–3.14)	1.62 (1.40–1.87)**	1.72 (1.50–1.98)**
Smoking	1.64 (1.44–1.87)**	E	0.96 (0.45–2.08)	1.66 (1.46–1.89)**	1.60 (1.41–1.80)**
Diabetes	1.75 (1.51–2.01)**	R	0.75 (0.36–1.53)	1.80 (1.56–2.08)**	1.84 (1.58–2.14)**
Obesity	1.05 (0.92–1.20)	E	1.64 (0.94–2.85)	1.05 (0.91–1.20)	1.00 (0.86–1.17)
No insurance	1.38 (1.10–1.74)*	N	0.77 (0.30–1.94)	1.44 (1.15–1.81)*	1.44 (1.17–1.76)*
Ethnicity		C			
Non-Hispanic White	Ref	E	Ref	Ref	Ref
Non-Hispanic Black	1.14 (1.00–1.30)		1.20 (0.72–1.99)	1.11 (0.96–1.28)	1.15 (0.99–1.35)
Hispanic	0.62 (0.46–0.85)*	G	1.25 (0.37–4.21)	0.59 (0.46–0.76)*	0.61 (0.48–0.79)*
Other	0.51 (0.28–0.95)*	R	0.99 (0.96–1.01)	0.54 (0.29–1.01)	0.52 (0.28–0.98)*
Age	1.08 (1.07–1.09)**	O	1.06 (1.04–1.08)**	1.09 (1.08–1.09)**	1.09 (1.08–1.09)**
Gender (Ref: Male)	0.76 (0.66–0.86)**	U	0.89 (0.53–1.49)	0.75 (0.65–0.85)**	0.76 (0.67–0.87)**
Family Poverty-Income-Ratio (Ref: PIR ≥ 1)	1.38 (1.14–1.68)*	P	2.09 (0.65–6.77)	1.33 (1.09–1.62)*	1.28 (1.04–1.56)*
Education level					
Some college and beyond	Ref		Ref	Ref	Ref
Less than high school	0.90 (0.73–1.10)		1.13 (0.49–2.59)	0.90 (0.74–1.11)	0.87 (0.69–1.10)
High school graduate	0.70 (0.61–0.81)**		0.99 (0.38–2.58)	0.70 (0.61–0.81)**	0.68 (0.59–0.78)**

HR (95CI) indicates hazard ratios with 95% confidence intervals for the outcome (i.e., mortality), *Ref* indicates the reference group among each variable for comparison with other groups

*$p < .05$, **$p < .01$

data which could lead to bias. The cross-sectional nature of the data from NHANES may limit the validity of the findings. Also, while this analysis was limited by data in the NHANES and NDI files, a longer duration of follow-up could have allowed better exploration of the specific impact of CRP levels on mortality. Survival probability can be influenced by a variety of factors that we may not have accounted for due to the limitations of existing data. Finally, while we accounted for major comorbidities (e.g., diabetes, CVD, and CKD), the NHANES data does not have details on the duration or severity of these comorbidities. More details about these comorbidities could have further enhanced our understanding of the relationship between COPD, CRP, and mortality.

Conclusions

In this study using NHANES data collected from a multiyear national random sample of community-dwelling American adults, elevated CRP was associated with a more than two times higher risk of mortality among those with a history of COPD. In contrast, individuals with COPD along with those without elevated CRP did not have a significantly higher risk for mortality. The assessment and monitoring of CRP could be of value among people with COPD as a part of diagnosis and management given the association of CRP with risk of mortality among COPD patients. Biomarkers such as CRP continue to show promise for long-term COPD-related outcomes. Additional prospective assessments of individuals with airway obstruction are warranted to understand if CRP levels predict the occurrence or worsening of COPD and if those relate to long-term health outcomes.

Abbreviations

COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
IL	Interleukin
NHANES	National Health and Nutrition Examination Survey
NDI	National Death Index
CKD	Chronic kidney disease
CVD	Cardiovascular diseases
HR	Hazard ratios

Authors' contributions

All authors read and approved the final manuscript.

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Availability of data and materials
All of the study data are publicly available at the U.S. Centers for Disease Control and Prevention NHANES website- https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Competing interests
The authors declare that they have no conflicts of interest.

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