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ORIGINAL RESEARCH

Nine-Year Follow-Up of Interleukin 6 in Chronic Obstructive Pulmonary Disease – Complementary Results from Previous Studies

Robson Prudente[1]
Renata Ferrari[2]
Carolina Mesquita[2]
Luiz Machado[2]
Estefânia Franco[1]
Irma Godoy[2]
Suzana Tanni[2]

[1]Clinical Hospital of Botucatu Medical School, Department of Internal Medicine, Pneumology Area, Botucatu School of Medicine, São Paulo State University (UNESP), Botucatu, São Paulo, Brazil; [2]Department of Internal Medicine, Pneumology Area, Botucatu School of Medicine, São Paulo State University (UNESP), Botucatu, São Paulo, Brazil

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Background: Systemic manifestations of chronic obstructive pulmonary disease (COPD) are related to increased systemic inflammatory process; however, it is not entirely clear how much they are related and how the systemic inflammation, in particular interleukin-6 (IL-6), is associated with exacerbation and mortality risk.

Objective: To evaluate the role of IL-6 in COPD patients over nine years.

Study Design and Methods: A total of 133 COPD patients were assessed at baseline between 2004 and 2006 and reassessed after three and nine years through clinical evaluation, comorbidities, hematological blood count and IL-6 analysis.

Results: After nine years, 19 patients lost the follow-up and were not possible to identify the date of death of four patients; 12 refused to participate and 1 could not be involved due to recurrent exacerbations. Therefore, 33 patients were included in the reassessment after nine years of follow-up and 92 patients were included in the Cox mortality analysis with IL-6 as a time-dependent covariate. Regarding the inflammatory profile, in patients who survived after nine years, there was a significant increase in IL-6 [0.4 (0.2–0.8) vs 5.7 (3.4–11) pg/mL; $p < 0.001$] and reduction in lymphocyte count [2.1 (1.6–2.4) vs 1.4 (1.2–2.1)10^9/L; $p < 0.01$] with an increase in the neutrophil/lymphocyte ratio (2.0 ± 0.7 vs 2.7 ± 1.2; $p = 0.003$). The Cox mortality model did not show a statistical significance influence of IL-6 assessed during the follow-up.

Conclusion: There was a progressive increase in IL-6 during the follow-up, however, without influence on mortality.

Keywords: chronic obstructive pulmonary disease, inflammation, interleukin-6, severity of illness index, mortality

Background

Chronic obstructive pulmonary disease (COPD) is defined as a frequent, preventable, and treatable condition characterized by persistent respiratory symptoms and progressive, not fully reversible airflow obstruction. The etiology is multifactorial and involves genetic aspects, exposure to risk factors and abnormal lungs inflammatory response.[3] Local manifestations are characterized by reduction in forced expiratory volume in the first second (FEV_1), pulmonary hyperinflation, a decrease in respiratory muscle strength and resistance, together these factors are associated with ventilation decrease and dyspnea increase. These changes are associated with the restriction of activities of daily living (ADLs) and, consequently, worsening quality of life.[3–5] Moreover, studies have shown that the condition does not only affect the lungs and respiratory muscles but there is also significant systemic

Correspondence: Robson Prudente
Clinical Hospital of Botucatu Medical School, Department of Internal Medicine, Pneumology Area, Botucatu School of Medicine, São Paulo State University (UNESP), Botucatu, São Paulo, Brazil
Email robsonapp@gmail.com

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impairment such as protein-energy malnutrition, reduced peripheral muscle strength and endurance, and decreased exercise tolerance, which also have a great impact on the severity of the disease and quality of life.[3,5,6]

It is known that the systemic manifestations of COPD are related to increase systemic inflammatory process[7] despite, it is not fully understood or how much they are related in this process.[8] In addition, the most recent studies show that systemic inflammation, especially the activation of interleukin-6 (IL-6), is associated with higher risk of exacerbation, symptom burden and mortality.[9–12]

IL-6 corresponds to a cytokine that acts on both the innate and adaptive immune responses; it is synthesized by monocytes, endothelial cells, fibroblasts, and other cells in response to microorganisms and stimulation by other cytokines, mainly interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α).[13] During the differentiation of CD4 T cells, IL-6 promotes the production of IL-17 and IL-21 and suppresses the regulatory function of T cells. The effect generated is precisely the deposition of matrix, antibody complexes and proteases in the target tissue and, consequently, lung parenchyma destruction.[14,15] Especially during the period of exacerbation, macrophages are unable to ingest apoptotic cells and bacteria, causing more activation of inflammatory cells and the release of several mediators, including IL-6.

In that regard, there are few studies which evaluated the influence of IL-6 in a long time of follow-up and its association with mortality in COPD patients.[2,16] Furthermore, we did not find many data from nearly a decade of follow-up related to IL-6 in Brazilian COPD patient.[10,17–24] In this sense, better understanding the role of IL-6 over time, helps in a more effective search for inflammation control and, consequently, minimizes its related outcomes, such as reduced physical capacity, greater occurrence of exacerbations and increased mortality.[9–12] Thus, our hypothesis is that IL-6 is associated to COPD mortality over nine years of follow-up and the objective of our study was to assess the association of IL-6 in mortality risk in patients with COPD over nine years, as well as verify the variation of IL-6 in survivals over nine years.

Study Design and Methods

Settings

This is the third of three studies that evaluated patients with COPD over nine years, approved by Botucatu School of Medicine Research Ethics Committee (approval number: 1.527.377) and was conducted in accordance with the principles of the Declaration of Helsinki. All subjects involved in the research agreed to participate signing the informed consent form after objectives and methods of the research have been clarified. The applied methodology was the same used in this previous study, where further details can be found.[22,24]

Participants

In general, between 2004 and 2006, 133 COPD patients from the Pulmonology outpatient clinic of Botucatu Medical School were invited to participate in this study. Inclusion criteria were patients diagnosed with COPD, clinical stability, and optimized drug therapy. Exclusion criteria were patients with diagnoses of other respiratory diseases, noncompliance with treatment, myocardial infarction four months before the beginning of the study, unstable angina, and congestive heart failure class III and IV.

Outcomes Measurements

The regular follow-up of these patients was performed by medical appointments at least every six months and by telephone contact with the survivors who had stopped outpatient medical follow-up. A protocol of telephone contact was also used to confirm the cause of death from family members and to confirm clinical condition, frequency of exacerbations, hospitalizations and use of non-programed health-care attendance. For data collection in clinical reassessment, we considered the following periods: baseline, after three and nine years of follow-up.[18,19,22]

At baseline, all recruited patients were assessed by pulse oximetry, pulmonary function, nutritional evaluation, exercise tolerance, sensation of dyspnea, and presence of comorbidities. Clinical assessment, arterial blood sample, pulse oximetry and spirometry (pre- and post-bronchodilator) were performed on the first day, and venous blood sample, nutritional status, six-minute walking distance (6MWD), quality of life and dyspnea perception were assessed on another day. These assessments were reapplied to survivors after three and nine years and more details are available in previous studies.[18,19,22,24]

Laboratory Assessments

Laboratory evaluation included complete hematological blood count and biochemical examinations. And the analysis was performed according to the criteria and methods

routinely used by the Technical Section of Botucatu School of Medicine Laboratory and Clinical Analysis.

To IL-6 analysis, blood was collected in a 10mL vacutainer tube with heparin and was centrifuged in a refrigerated centrifuge (Eppendorf 5403®) at 1000rpm for 5 minutes. The plasma from the top of the tubes was removed and centrifuged again to obtain clear plasma. The samples were stored in 1.5 mL eppendorf tubes in a refrigerator at −80°C until analysis.

The IL-6 cytokine assays were performed in duplicates by means of commercially available immunoenzymatic assays (ELISA) (Biosource International, Inc, CA, USA). For serum measurements, 0.16 to 10.0pg/mL ultrasensitive ELISA were used for IL-6 (Human IL-6 US – Cytoscreen). The sequence of cytokines dosing followed the recommendations from the kits supplier company.

Statistical Analysis

Descriptive statistics were used to describe the features of all participants. Means, ± standard deviation or medians and interquartile range (25–75%) were used depending on the data distribution. Categorical variables were expressed as percentages. The Chi-square test was used to compare the values of categorical variables.

The comparison between two independent groups was performed by means of the Student's *t*-test for variables with normal distribution and Mann–Whitney test for variables with non-normal distribution. The tool to compare two dependent groups, was paired Student's *t*-test for variables with normal distribution and Wilcoxon test for non-normal distribution. Chi-square tests were used to compare qualitative variables with a frequency higher than five and Fisher's exact test for frequency less than five.

IL-6 cutoff points were determined by 90th and 95th percentile of sample distribution. These cutoff points were used to assess associations with mortality over nine years. The Kaplan–Meier curve followed by the Log rank test was used to evaluate mortality rate related to categorization of IL-6 cut-off points.

IL-6 as a time dependent covariate was used in the Cox regression analysis to analyze the association of variation of IL-6 over time and the risk of mortality including all subjects evaluated at baseline, adjusted by baseline data of age, male gender, BODE index, Charlson Comorbidities index, number of exacerbations in the first three years of follow-up and SpO_2.

The significance level was set at $p < 0.05$. All data were analyzed using SPSS version 17.0 (IBM Software, Dallas, TX, USA) and SAS (USA).

Results

Among the 133 patients initially evaluated (69% male, 65 ±9.5 years old, and FEV_1: 59.7±24.9%) nineteen lost the follow-up, four did not have their cause of death identified, twelve refused to participate in the last follow-up, and one could not be included due to recurrent exacerbations. Therefore, 33 patients who survived (54.5% male, 61 ±8.6 years old, and FEV_1: 64.2±26.6%) completed nine years follow-up assessment and 110 patients [67% male, 65±9 years old, and FEV_1: 52.5 (40–73%)] were included in the mortality analysis. However, only 92 were included in Cox regression due to missing data.

Regarding the causes of death, 41 were attributed to respiratory failure, 9 to cancer, 5 to cardiovascular disease, and 9 to other causes. Four patients were excluded from the analyses due to a lack of information concerning date and cause of death. Demographic and clinical characteristics of the involved patients in the survival analysis, and the evolution of other markers at baseline, after three and nine years can be consulted in a previous publication and in Supplemental Material.[22,24]

In relation to the IL-6 of survival patients (n = 33), after nine years there was a significant increase in IL-6 values [0.4 (0.2–0.8) vs 5.7 (3.4–11) pg/mL; $p < 0.001$], reduction in lymphocyte count [2.1 (1.6–2.4) vs 1.4 (1.2–2.1)10^9/L; $p < 0.001$] and increased neutrophil/lymphocyte (N/L) ratio (2.0 ±0.7 vs 2.7±1.2; $p = 0.003$). The other peripheral blood cells showed no variation at baseline and after nine years. In addition, when analyzed those who had a reduction in $FEV_1 >$ 40mL after nine years (n = 14) was observed an increase in IL-6 after nine years when compared to baseline [0.4 (0.23–0.88) vs 5.73 (3.67–10.47) pg/mL; $p < 0.001$], and a reduction in lymphocyte count (1.8±0.41 vs 1.6±0.6 10^9/L; $p = 0.01$) at the final moment.

The comparison of IL-6 at baseline between patients who survived or not after nine years showed that the survivors had statistically significant lower IL-6 values at baseline [0.49 (0.2–0.8) vs 1.29 (0.6–1.9) pg/mL; $p < 0.001$]. The comparison of the lymphocyte count of these groups did not show statistically significant differences ($p = 0.20$), whereas the N/L ratio was higher in patients who died [2.0 (1.5–2.3) vs 2.4 (1.9–3.5); $p = 0.006$]. The evolution of inflammatory profile at baseline, after three and nine years can be seen in Table 1.

Table 1 Evolution of Inflammatory Profile at Baseline, After Three and Nine Years

Variables	Baseline (n = 33)	After Three Years (n = 33)	After Nine Years (n = 33)	p value
IL-6 (pg/mL)	0.5 (0.2–0.9)	2.3 (0.9–4.5)	5.2 (3.3–8.5)	<0.001
Lymphocytes (10^9/L)	2.1 (1.6–2.4)	1.9 (1.5–2.1)	1.4 (1.2–2.2)	0.10
Neutrophils (1000/mm^3)	4.1 (3.4–4.7)	4.2 (3.4–6.2)	3.8 (3–5)	0.25
Leukocytes (1000/mm^3)	6.5 (6.1–8.4)	7.1 (5.4–9.2)	6.5 (5.2–7.9)	0.32
N/L ratio	2.0 (1.5–2.3)	2.4 (1.8–2.9)	2.5 (1.5–3.3)	0.14

Notes: Values presented as mean ± standard deviation or median (quartiles 25–75). Mixed model; $p < 0.05$.
Abbreviations: IL-6, interleukin-6; N/L, neutrophils/lymphocytes.

The IL-6 distribution of the population at baseline can be seen in Figure 1 and, to evaluate the association of the 90th (≥2.3pg/mL) and 95th (≥3.1pg/mL) percentiles of IL-6 baseline with the mortality of all patients, the Kaplan–Meier curve followed by the Log Rank test showed a statistically significant difference between the groups when categorized as <3.1pg/mL or ≥3.1pg/mL. Patients with higher values of IL-6 at baseline showed higher death risk during nine years. However, it is noteworthy that the sample ≥3.1pg/mL consisted only of five individuals (Figure 2). A similar result was observed using the cutoff point of 90th of the sample, with seven being the number of individuals categorized with IL-6 ≥2.3pg/mL (Figure 3).

Cox's regression analysis showed no association between the IL-6 variation over time and the mortality rate over nine years (n = 92) (Table 2). When imputing the missing data by using multiple imputation of covariates and IL-6 as a time dependent covariate, of IL-6 influence could not be assessed, and only BODE index was a predictor of mortality [Hazard ratio (HR): 1.4 (95% HR Confidential interval: 1.1–1.7); p = 0.003].

Discussion

The present study aimed to evaluate the role of IL-6 in patients with COPD over nine years. Previous studies have already shown that patients with stable COPD have higher serum IL-6 concentrations compared to healthy controls, however, our findings indicate that the increase in IL-6 is gradual over time, according to the evolution of the disease itself.[25,26] The increase in inflammation, even in patients with less FEV_1 variation, draws attention to the fact that the systemic inflammation is a persistent and progressive process, even in those who maintain pulmonary function unchanged or with small loss, suggesting that an isolated analysis of COPD prognostic markers requires some caution.

FEV_1 has already been shown to be closely related to chronic respiratory symptoms in the general population.[27]

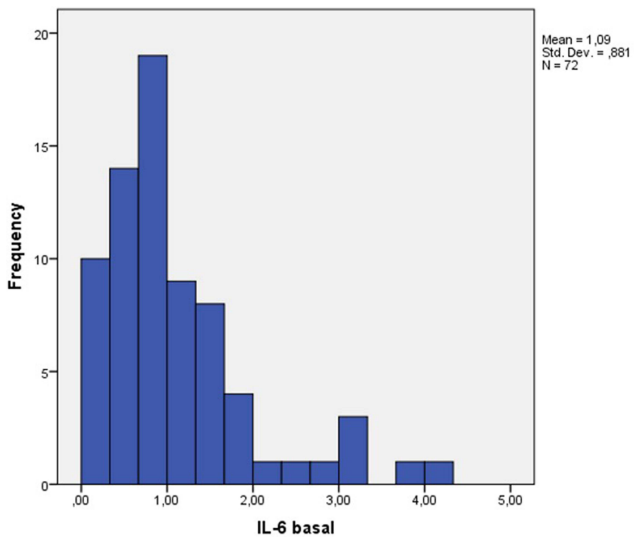

Figure 1 IL-6 distribution of the population studied at baseline.

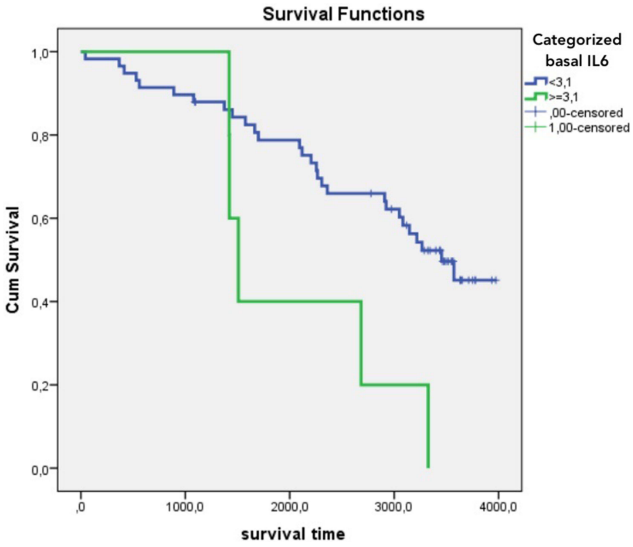

Figure 2 Kaplan–Meier mortality curve in relation to patients with IL-6 ≥ or < 3.1pg/mL.

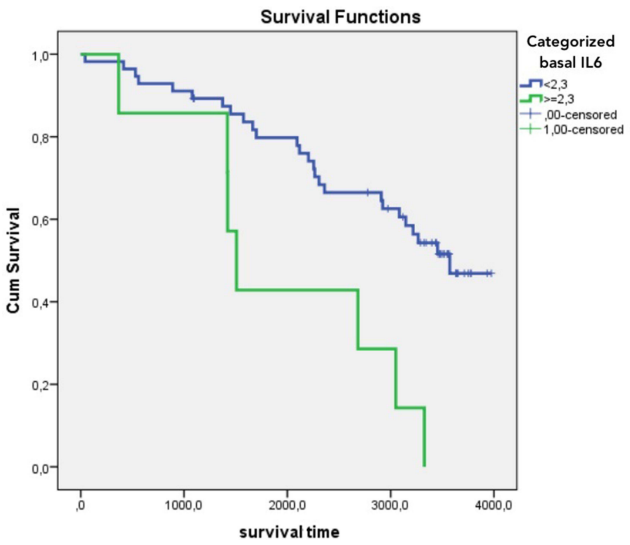

Figure 3 Kaplan–Meier mortality curve in relation to patients with IL-6 ≥ or < 2.3pg/m.

Tantucci and Modina[28] have also warned that would be more logical to undertake efforts for early detection of COPD based on risk factors, rather than just symptoms. Thus, based on this assumption and our findings, we can infer that the association of evaluation of the disease markers, such as prognostic and inflammatory markers, may be more appropriate in the assessment of these patients over long periods.

In addition, we also found that the IL-6 analysis showed that patients who survived after nine years of follow-up had less inflammation at baseline compared to those who were known to have died, showing a better prognosis for those with lower cytokine values. We also found that when considering the individuals with highest IL-6 values (90th and 95th percentiles of the sample) there was a higher risk of death, nevertheless, in the latter case, we should consider the small number of subjects categorized in these groups. Similar findings were observed in the study conducted by Mehrotra et al[29] where IL-6 was a significant predictor of mortality in 268 individuals with obstructive airway disease, however, for some years now, prospective studies have shown that elevated IL-6 has been a useful marker for predicting worse outcomes in COPD.[9,10,30,31] The population of this study has already demonstrated in the three-year follow-up, that a significant increase in IL-6 was associated with higher mortality.[10]

On the other hand, other studies have found no major link between IL-6 and worse outcomes in COPD. The ECLIPSE study,[16] for example, found no association between IL-6 with a greater number of exacerbations in three years and, similarly, the Fermont et al[32] meta-analysis showed associations between high levels of IL-6 with the hospitalization rate of patients with COPD, it also did not indicate associations with the number of exacerbations and mortality of these patients. Likewise, our model with serial analysis of IL-6 in three moments also did not show influence of IL-6 on the mortality rate of these individuals during the follow-up period. However, we cannot affirm that our results show a true relationship between IL-6 and mortality, since we have no power in relation to the sample size. There is no consensus in the literature about the influence of IL-6 on mortality of patients COPD and, in this sense, although some authors such as Celli et al[30] have shown that IL-6, by itself, improves the ability to predict mortality in COPD, the authors themselves claim that the association of biomarkers further improves this ability, which corroborates with the idea that the combination of inflammatory markers assessment and other COPD markers (such as FEV_1, for example) may be more accurate.

Therefore, it can be said that the systemic impairment caused by COPD, not directly related to the inflammatory

Table 2 Assessment of IL-6 as a Time Dependent Covariate in Cox Regression Analysis

Parameter	Parameter Estimate	Standard Error	Chi-Square	P value	Hazard Ratio
Age, year	−0.07069	0.04440	2.5352	0.1113	0.932
Male gender	−0.16364	0.56907	0.0827	0.7737	0.849
BODE Index, class	0.12288	0.14311	0.7373	0.3905	1.131
Comorbidities, score	0.84229	0.31803	7.0144	0.0081	2.322
Exacerbations, n	0.29959	0.22177	1.8248	0.1767	1.349
SpO2, %	0.03991	0.07682	0.2699	0.6034	1.041
IL-6, pg/mL	0.02757	0.07842	0.1236	0.7252	1.028

Note: $p < 0.05$.

Abbreviations: BODE, body mass index, airflow obstruction, dyspnea and exercise capacity; Exacerbations, number of exacerbations in three first years; SpO2, pulse oximeter; IL-6, interleukin-6.

aspect, is also capable of influencing the mortality of these individuals, given that the patients who are known to have died, both at baseline and after three years of follow-up, still had low IL-6 values. In a previous study carried out with these individuals, we observed that were predictive of mortality in nine years the number of exacerbations in the first three years of follow-up, greater severity by the BODE index, higher scores on the Charlson index and lower BMI.[22] We observed that in the imputation of the missing data in Cox's regression analysis, the BODE index predicted the mortality of this population in nine years, considering IL-6 as a time-dependent covariate. However, the limitations related to the imputation of data require that these results should be analyzed with greater caution to prevent wrong conclusions.[33] Specifically, in relation to the BODE index and IL-6, Khan et al[34] demonstrated that serum IL-6 concentrations exhibited significant correlation with BODE index, thus, future studies with these variables can be considered to assess these patients.

Regarding the reduction in the number of lymphocytes, we observed a decrease in the cell count with a significant increase in N/L ratio. It is known that low lymphocyte count is associated with poor prognosis in acute and chronic conditions, and factors such as age and deficient nutritional status[35] and with agreement of that, Acanfora et al[36] in a three-year prospective study with 218 patients with COPD and age around 75 years, observed that the relative reduction in cell count was associated with higher mortality. Besides that, Xiong et al[37] found that neutrophils and lymphocytes independently correlate with mortality, but with less relevance compared to the N/L ratio. A study conducted by Lee et al[38] demonstrated a correlation of FEV_1 in COPD patients only with N/L ratio and not with the cells count alone, in accordance with our findings which demonstrated that only the lymphocyte count in patients who died was no different at baseline from those who survived, whereas the N/L ratio was significantly higher in those who died over the nine years of follow-up. However, further analysis should be performed despite these findings for better conclusions.

The present study has limitations that need to be clarified. During the follow-up, we had about 17% of loss, which may have interfered in our findings. Nevertheless, longitudinal population studies show that the loss of follow-up is greater in longer periods and the percentage presented in the literature is like our findings.[20] In addition, we emphasize that the present study does not aim to identify cause and effect, so we can only affirm the possible associations between IL-6 and the mortality of patients with COPD in nine years, thus, more robust studies are encouraged for confirm these findings.

Conclusion

When outlining the role of IL-6 in COPD patients over nine years, it was seen that there was a progressive increase in cytokine during the follow-up period, even though, without influence on mortality. It is suggested, therefore, that in longitudinal segments with longer periods, for prognostic evaluation and mortality of this population, both inflammatory markers and other COPD markers should be analyzed together.

Acknowledgment

The manuscript is part of a PhD thesis of São Paulo State University. After the thesis defense, the full thesis is temporarily made available on-line.[1] Besides that, the abstract of this paper has been presented at the ERS International Congress 2018 as a poster presentation. The poster's abstract was published in the European Respiratory Journal 2020 56: 2471; DOI: 10.1183/13993003.congress-2020.2471.[2]

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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