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Article

Elevated levels of IL-8, TGF-β, and TNF-α associated with pneumoconiosis: A meta-analysis

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SUMMARY

There have been multiple studies over the years looking into the role of cytokines, which are regulators of inflammation in the development of pneumoconiosis. The aim of this study to determine whether serum levels of certain cytokines can be useful as biomarkers for pneumoconiosis. To date, the most investigated cytokines have been Interleukin 8 (IL-8), transforming growth factor beta 1 (TGF-β1), and tumor necrosis factor alpha (TNF-α). Results from previous studies generally show that the serum levels of these cytokines are altered in pneumoconiosis, however not all of these deviations are statistically significant. Here we attempt to determine whether levels of IL-8, TGF-β1, and TNF-α are significantly related to pneumoconiosis, by conducting a meta-analysis of 11 studies on the serum levels of three cytokines: IL-8, TGF-β1, and TNF-α. The meta-analysis concluded that pneumoconiosis patients display significantly elevated levels of IL-8 and TNF-α. The meta-analysis for serum TGF-β1 in pneumoconiosis patients failed to reach statistical significance. The results of the meta-analysis suggest that serum levels of IL-8 and TNF-α could be utilized in the diagnosis of pneumoconiosis, and further studies should be conducted to investigate the correlation strength of these two cytokines with pneumoconiosis.

INTRODUCTION

Pneumoconiosis is an occupational lung disease caused by dust inhalation. Those who are at risk of pneumoconiosis are people who work in an environment where they are often exposed to a high level of dust particles (1). Coal workers, construction workers, glass manufacturers, and stone cutters are just a few occupations that have a high risk of contracting pneumoconiosis as they are often exposed to dust irritants. Inhaled dust causes the activation of pulmonary alveolar macrophages to attack the foreign particles, which damages lung tissues and eventually results in fibrosis (2). Depending on the degree of scarring in the lungs, patients may face symptoms like shortness of breath, fatigue, chest pain, and coughs that produce phlegm (1). Currently, treatments for the disease focus on management of symptoms, and no cure for pneumoconiosis exists.

Pneumoconiosis can be divided into three subcategories: silicosis, asbestosis, and coal workers' pneumoconiosis. Silicosis is caused by silica dust inhalation and is usually prevalent in stone cutters as stones contain the harmful silica particles (3). Asbestosis is caused by the inhalation of asbestos fibers and is usually apparent in construction workers, as their jobs often involve using asbestos fibers (3). Coal workers' pneumoconiosis (CWP) is caused by coal dust inhalation (4). CWP can take the form of simple pneumoconiosis where the patient only has a small amount of scarring in the lungs and shows few to no symptoms, or CWP can take the form of complicated pneumoconiosis, often referred to as progressive massive fibrosis, which is when a patient has large amounts of scarring in their lung tissues, cough up bloody sputum, and face breathing difficulties (4).

Increasing safety precautions are being implemented across various industries where workers are at risk of pneumoconiosis resulting in a reduced number of cases. Pneumoconiosis is nevertheless a global issue with roughly 527,500 cases reported in 2017, of which 60,000 were new cases (5).

The diagnosis of pneumoconiosis currently consists of X-rays and CT scans to identify tissue scarring in the lungs (6). Symptoms of patients are also considered during diagnosis. Since pneumoconiosis is incurable, an early diagnosis is critical for slowing disease progression and avoiding possible death. Pneumoconiosis takes years to develop and show symptoms, so workers who have the disease may continue to work in an environment with high levels of dust, unknowingly worsening their condition (6). Only when diagnosed will workers begin to take precautions and medicine to help slow down progression of the disease. These precautions involve performing lung exercises to utilize undamaged areas of the lungs more efficiently and avoiding areas with high levels of dust particles. There are also medications available to help alleviate pain and open up airways for more oxygen intake (1). Thus, an early diagnosis can be the crucial step in saving a patient's life.

Cytokines are a group of proteins secreted by the immune system that serve as chemical messengers (7). When the body detects a pathogen, cytokines are released by cells in the body, mainly by macrophages and lymphocytes, to regulate an immune response (7). In pneumoconiosis, dust particles that reach the lungs are identified by interferons as a foreign substance, and they signal the immune system. Chemokines then induce chemotaxis in immune cells towards the area of infection where the rest of the cytokines will then be secreted to regulate the inflammatory response (8). The cytokines that are secreted can serve as biomarkers for pneumoconiosis, and therefore, by measuring the cytokine levels in the serum of high-risk workers, doctors may be able to diagnose them at an earlier stage before symptoms begin.

Various studies on the relationship of specific cytokines

and pneumoconiosis have yielded inconsistent results, some studies reporting that the levels of certain cytokines are significantly altered in patients with pneumoconiosis, while failing to reach significance in other studies (9-13). Although results vary between studies on the degree of correlation between the change in cytokine levels and pneumoconiosis, they all acknowledge that the rise or decline in cytokine levels are related to pneumoconiosis (9-13).

The purpose of this study was to analyze the data from multiple studies and identify the specific cytokines that may be used as biomarkers for pneumoconiosis. Could cytokines be potential biomarkers for the diagnosis of pneumoconiosis? We hypothesize that cytokines may have varying roles in the progression of pneumoconiosis and that a combination of multiple cytokine levels could be implemented into the diagnosis of pneumoconiosis for a more accurate and early diagnosis. Upon collecting data from various studies, we focused on three specific cytokines that had enough data for us to conduct a meta-analysis on: Interleukin 8 (IL-8), transforming growth factor beta 1 (TGF-β1), and tumor necrosis factor alpha (TNF-α).

RESULTS

In order for a study to be included in our meta-analysis, it must have analyzed patients with pneumoconiosis, compared cytokine levels between pneumoconiosis patients and controls, and recorded cytokine levels for both patients and controls. A review of the literature found that there were three cytokines for which three or more studies that met the inclusion criteria had gathered data, namely: IL-8 (3 studies), TGF-β1 (4 studies), and TNF-α (7 studies). A meta-analysis for each of the three cytokines was performed. The publication dates for the studies used in the meta-analysis ranged from 1994 to 2021 (9-20). In total, the 11 studies combined were comprised of 547 control (healthy) participants and 938 patients with pneumoconiosis.

Meta-analysis for IL-8

The meta-analysis for IL-8 comprised of 3 studies published between 2010 and 2021, comprising of a total of 79 control participants and 445 pneumoconiosis patients (9,12,13). All three studies individually showed a significant increase of serum IL-8 levels in pneumoconiosis patients compared to that of the controls, which was confirmed by the overall finding of the meta-analysis (Z = 2.79, P = 0.005). However, significant between-study heterogeneity was also detected (I^2 = 94%, p < 0.00001) (**Figure 1**).

Meta-analysis for TGF-β1

The meta-analysis for TGF-β1 comprised of four studies published between 1994 to 2021, consisting of a total of 494 pneumoconiosis patients and 283 control participants (9,15,18,19). Three of the four studies individually showed a significant increase in serum TGF-β1 levels compared to that of controls. However, the combined effect of the four studies failed to show that TGF-β1 levels were significantly higher in pneumoconiosis patients than controls (Z = 1.70, p = 0.09) (**Figure 2**). Once again, significant between-study heterogeneity was observed in the meta-analysis (I^2 = 99%, p < 0.00001) (**Figure 2**).

Meta-analysis for TNF-α

The meta-analysis for TNF-α was composed of the most studies with seven studies that were published from 1995 to 2021, with a total of 643 controls and 267 patients with pneumoconiosis included in the meta-analysis (9,10,12,14,16,17,20). Three of the studies reported significantly increased TNF-α levels in patients with pneumoconiosis compared to controls, while the other four reported nonsignificant results. Combining the seven studies in a meta-analysis found that TNF-α levels in pneumoconiosis patients were significantly increased compared to controls (Z = 2.83, p = 0.005) (**Figure 3**). However, the meta-analysis also showed significant between-study heterogeneity, but it was relatively less when compared to the other meta-analyses (I^2 = 84%, p < 0.00001) (**Figure 3**).

DISCUSSION

As of now, there is no known cure for pneumoconiosis and only treatments or medications exist to alleviate some of the symptoms. Therefore, an early diagnosis of pneumoconiosis is crucial in preventing further harm and enabling patients to start rehabilitation exercises early to better cope with the difficulties caused by the disease. Unfortunately, it is difficult to diagnose pneumoconiosis early as it takes years for the symptoms to appear; however, if we can identify biomarkers that precede symptoms, then an early diagnosis may be possible. In this study, our aim was to identify some of the cytokines that may serve as biomarkers for pneumoconiosis. Our results from the meta-analysis suggest IL-8 and TNF-α as possible biomarkers, as these were found to be significantly upregulated in pneumoconiosis patients across many studies. The meta-analysis of TGF-β1, however, failed to reach significance. More studies regarding the relationship between TGF-β1 and pneumoconiosis could help clarify the potential of TGF-β1 as a biomarker for pneumoconiosis.

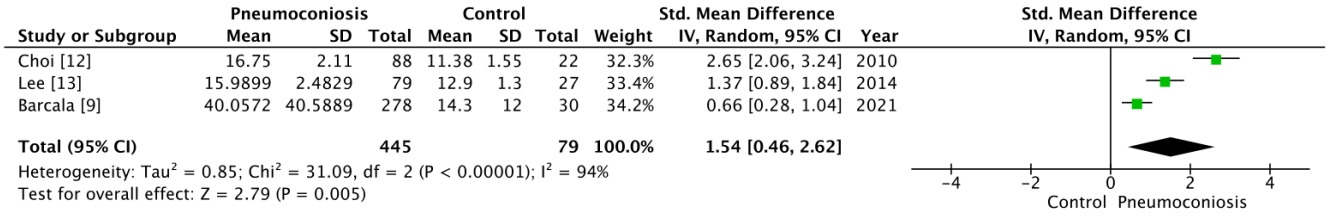

Figure 1: Overall comparison of blood IL-8 levels between pneumoconiosis patients and controls. The green boxes show the standardized mean difference between the two groups and the lines to either side represent the 95% confidence intervals. The black diamond shows the combined effect size for the studies included in the meta-analysis. IV = Inverse variance, SD = Standard deviation.

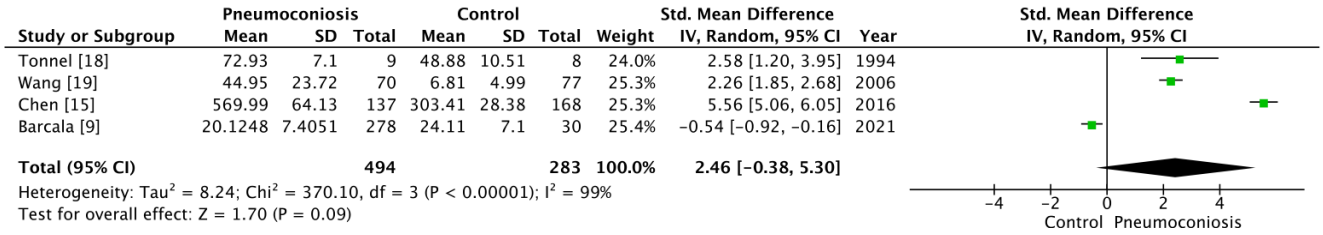

Figure 2: Overall comparison of blood TGF-β1 levels between pneumoconiosis patients and controls. The green boxes show the standardized mean difference between the two groups and the lines to either side represent the 95% confidence intervals. The black diamond shows the combined effect size for the studies included in the meta-analysis. Abbreviations, IV: Inverse variance, SD = Standard deviation

We observed significant heterogeneity in all our meta-analyses, which is not surprising since the number of studies included in the meta-analyses was not very large, and each study contained data from diverse patient populations with varying disease progression over multiple time periods.

The results of this study suggest that cytokines IL-8 and TNF-α have potential as biomarkers of pneumoconiosis could be considered in the diagnosis of the condition. In other words, during the diagnosis of pneumoconiosis, clinicians may have patients tested for both IL-8 and TNF-α levels; this may be especially critical for early diagnosis of individuals at risk of developing pneumoconiosis (such as coal workers). The meta-analysis for TGF-β1 failed to reach significance, however this result is based on only four studies and may yet prove to be a useful indicator of pneumoconiosis. As of now, more studies need to be conducted before discarding TGF-β1 as a potential biomarker for pneumoconiosis.

A major limitation in our meta-analysis was the generalization of the data for certain studies. Multiple studies reported their data for pneumoconiosis patients in subgroups of different levels of pneumoconiosis severity and subtypes. Therefore, when inputting their data into the forest plots, an average of the data from the subgroups was calculated and used. The generalization of the subgroups may not be the most accurate representation of the data, and therefore, the results of the meta-analysis may not be the most reliable. It is possible that cytokine levels were connected to the severity of the disease, as one study showed that TNF-α levels increased with severity, but another showed that it decreased with severity (9,17). This study also only performed a meta-analysis for three cytokines, a decision made based on the available data. However, it is possible that other cytokines such as IL-6 could also be potential targets for future studies. Another major limitation is the level of connection between the three cytokines we evaluated and pneumoconiosis. The upregulation and downregulation of cytokines can be a response to many outside factors and not just from excessive dust inhalation causing inflammation in the lungs. TNF-α and IL-8 levels have been found to increase in patients who have experienced trauma or burns (21). The studies from which we collected our data did not address this concern, and therefore, it is unclear how much impact outside factors like trauma could have on elevated cytokine levels. Additionally, TGF-β1 has been found to be related to cancer and connective tissue disorders, which could interfere with the accuracy of TGF-β1 as a biomarker for pneumoconiosis (22).

In summary, we found a significant increase in serum levels of both IL-8 and TNF-α in pneumoconiosis patients when compared to controls. We believe this difference could be used in the diagnosis of pneumoconiosis. However, more studies and research are needed regarding both cytokines before any conclusive argument can be made. Nevertheless, we hope that this meta-analysis can highlight some of the cytokines that may serve as biomarkers of pneumoconiosis, encouraging further studies such that one day these blood tests could be incorporated into pneumoconiosis diagnostics.

MATERIALS AND METHODS

In order to perform the meta-analysis, the PubMed database was searched using the following keywords: Pneumoconiosis OR Silicosis OR Asbestosis OR CWP and Cytokines. Reference lists in review papers were manually searched to gather additional data.

Study Selection Criteria

The criteria for the inclusion of studies were as

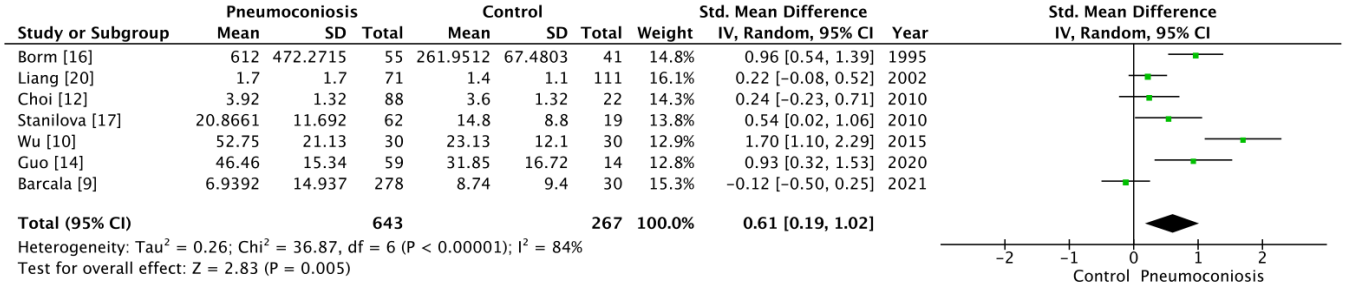

Figure 3: Overall comparison of blood TNF-α levels between pneumoconiosis patients and control. The green boxes show the standardized mean difference between the two groups and the lines to either side represent the 95% confidence intervals. The black diamond shows the combined effect size for the studies included in the meta-analysis. Abbreviations, IV: Inverse variance, SD = Standard deviation

follows: (a) the study analyzed patients with pneumoconiosis, (b) the study compared cytokine levels between patients with pneumoconiosis and controls, and (c) the study determined cytokine levels of patients from serum extracts.

The criteria for the exclusion of studies were as follows: (a) the study lacked data regarding cytokine levels of controls, (b) the study failed to disclose the method of measuring cytokine levels, (c) the study did not include data for at least one of the three selected cytokines mentioned above, and (d) the study was a review study. No language restriction was applied.

Variable Extraction

The following variables were manually extracted from the selected studies: (a) author, (b) year of publication, (c) cytokine measurement methodology, (d) patient cytokine levels (mean, SD, sample size), (e) control cytokine levels (mean, SD, sample size), and (j) title of study.

Meta-analysis

The meta-analysis was performed using Review Manager (Revman) version 5.4.1 using a random effects model. The effect size was the standardized mean difference, and the studies were combined using the inverse variance weighted method. For each meta-analysis, the combined effect size, p-value, and heterogeneity were reported. Any p-values below 0.05 and I^2 values greater than 75% were considered significant.

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