

# Relationship of serum levels of interleukin 6, interleukin 8, and C-reactive protein with forced expiratory volume in first second in patients with mustard lung and chronic obstructive pulmonary diseases: systematic review and meta-analysis

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## Abstract

**Introduction:** The chronic systemic inflammation is a result of releasing inflammatory cytokines from the cells relating to the body immunity system and chronic activation of the innate immunity system.

**Aim:** To evaluate the relationship among serum levels of interleukin 6 (IL-6), interleukin 8 (IL-8), C-reactive protein (CRP) with forced expiratory volume in 1<sup>st</sup> s (FEV<sub>1</sub>) in patients with mustard lung (ML) and chronic obstructive pulmonary diseases (COPD).

**Material and methods:** A published literature search was performed through SID, web of science, ISI, Science Direct, Scopus, Medline, and PubMed databases for articles published in English. The correlation coefficient (*r*) and 95% confidence intervals (95% CIs) were calculated using random or fixed effects models. Heterogeneity was assessed using  $\chi^2$  and *I*<sup>2</sup> statistics.

**Results:** In total, 4 published studies were included in the final analysis. Using the random-effect model, meta-analysis showed that the *r* was  $-0.052$  (95% CI:  $-0.14-0.049$ , *p* = 0.28) at serum level of IL-8, serum levels of CRP and FEV<sub>1</sub> in these results were *r* =  $-0.13$ , *p* = 0.012, serum levels of tumor necrosis factor (TNF) and FEV<sub>1</sub> levels were *r* =  $-0.39$ , *p* = 0.03 in the conducted studies on mustard lung patients. The IL-6 serum level was explored in COPD patients. The results of the given studies in these patients are *r* =  $-0.006$ , 95% CI:  $-0.37-0.15$ , and *p* = 0.44.

**Conclusions:** In this meta-analysis, there was evidence that serum levels of CRP and TNF have been significantly increased in chronic obstructive pulmonary diseases compared to the healthy control group, which signifies the presence of systemic inflammation in ML and COPD patients.

**Key words:** mustard lung, chronic obstructive pulmonary diseases, interleukin 8, interleukin 6, C-reactive protein, forced expiratory volume in 1<sup>st</sup> s.

## Introduction

The chronic systemic inflammation is a result of releasing inflammatory cytokines from the cells relating to the body immunity system and chronic activation of the innate immunity system [1]. Propagation of inflammatory cytokines and activation of the innate immunity system may be a result of external factors (biologic or chemical) and/or internal ones (genetic mutations/variations).

Sulfur mustard (SM) or bis (2-chloroethyl) sulfide is one of these factors, which is assumed a strong alkylate vesicant warfare chemical and used in several wars such as the Iraqi army against Iran [2, 3]. It causes various short-term and long-term side effects in the lungs, skin, stomach and intestine, central nervous system and immunity system, and bone marrow [4, 5]. Respiratory impairments are the most prevalent long-term disorders among chemically injured veterans who were poisoned with SM or, in

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other words, the patients suffer from mustard lung (ML) [6]. The studies indicate that there is some possibility for involvement of immunity and inflammatory mechanisms during the long-term side effects resulting from SM, of which the systemic inflammation may devote the major part of the existing mechanisms in patients with ML [7, 8]. Similarly, systemic inflammation is one of the key processes in pathogenesis of chronic obstructive pulmonary diseases (COPD) in which some of inflammatory mediators in bronchoalveolar lavage fluid (BALF), chest and lung sputa may be some symptoms of this disease [9]. Whereas the clinical table in these patients is very similar to ML [10–12], the present study is intended to compare the mechanism of inflammatory cytokines in these two diseases. Nonetheless, the results of epidemiologic studies are unstable in analysis of systemic inflammation in patients with ML and COPD and a positive, negative, or no relationship has been reported.

## Aim

Therefore, a study including meta-analysis, systematic review was carried out in order to explore the status of the relationship among serum levels of interleukin 6 (IL-6), interleukin 8 (IL-8), C-reactive protein (CRP), and forced expiratory volume in 1<sup>st</sup> s (FEV<sub>1</sub>) in patients with ML and COPD.

## Material and methods

### Literature of research

In order to extract given data from the published papers, the reliable data banks were used. These sources include SID, web of science, ISI, Science Direct, Scopus, Medline, and PubMed. To achieve further sources, a list of references of selected papers was examined to find further studies.

In order to interpret the search strategy, a composition of the following key words was utilized: Mustard gas, sulfur mustard, [bis-(2-chloroethyl) sulfide], 2,2'-dichloroethyl sulfide; HD; SM, TNF- $\alpha$ , CRP, C-reactive protein, tumor necrosis factor-alpha, chemically injured veterans, cardiovascular complications, chronic pulmonary effects, chronic obstructive pulmonary disease, COPD, interleukin (IL)-8 and IL-6, markers of pulmonary inflammation, systemic inflammation, extra pulmonary complications, mustard lung.

### Inclusion and exclusion criteria

The observational studies were adapted to examine systemic inflammation in patients with ML and compare with COPD patients. The studies in the abstract form only were excluded from this survey. Among the studies, which have been published several times, only a relatively new study was selected and, if necessary, the classic

publications were only used to analyze methodology or main specifications of population in studies.

The study design and original purpose, year, author, COPD patients, controls, inflammatory marker and laboratory measurement were extracted from the studies.

### Data synthesis and analysis

The correlation coefficient ( $r$ ) was utilized to determine the relationship among systemic inflammation and FEV<sub>1</sub> in patients with ML and to compare them with COPD patients. All of results were estimated and reported at 95% level of confidence. Data synthesis and analysis were conducted using Revman and R software.  $\chi^2$  was used to identify heterogeneity of data at a 10% confidence level ( $p < 0.10$ ). Similarly,  $I^2$  [13] statistical test was adapted to examine heterogeneity quantitatively between results. If  $I^2$  is greater than 50%, intensity reflection of heterogeneity is at a high level. Tau-squared statistical method was used for estimation of variances between studies. Statistical models including a fixed effect or Mantel Haenszel and Random Effect (REM) or DerSimonian-Laird were utilized. The REM was calculated to identify heterogeneity between studies.

## Results

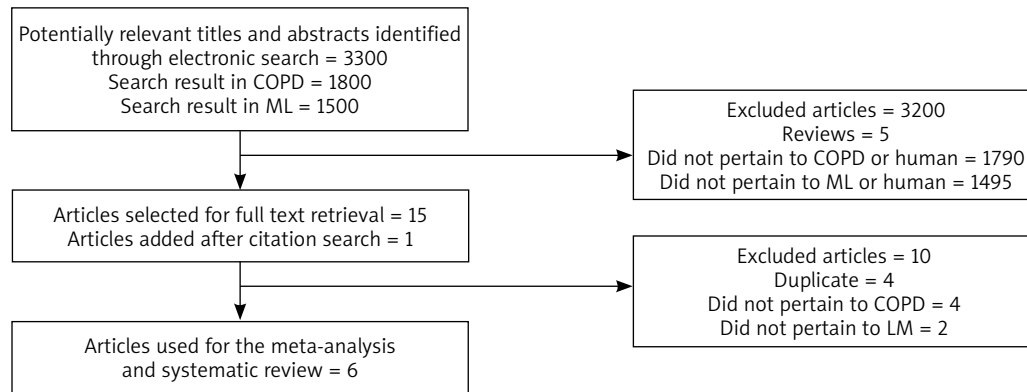
The results of search strategy are given in Figure 1. Out of 330 identified studies, 3284 articles were not qualified at the beginning because some of studies have been explored on non-human subjects and they included a review and/or systemic inflammation had not been examined in patients with ML and COPD. Fifteen papers were selected in the full-text format and with a review of references in these studies it seemed that one of them was appropriate so it was added to this group. Ten papers were rejected after evaluation of details in 16 articles since they were either redundant or not suitable for studying systemic inflammation in patients with ML and COPD.

Two papers for IL-6, 2 for IL-8, one for CRP, 1 for fibrinogen and tumor necrosis factor (TNF) in SM-poisoned pulmonary patients as well as 3 articles for IL-6, 2 for IL-8 and one paper for CRP and TNF, and fibrinogen were studied and analyzed.

### The main characteristics of the given studies

The main specifications of cohort studies in which systemic inflammation was explored in patients with ML, are shown in Table 1. These studies were published from 2009 through 2013. Three studies were analyzed in Iran. Data extraction was done in ML patients in 3 studies by means of a questionnaire.

Likewise, main specifications of control and cross-sectional case studies in which systemic inflammation was examined in COPD patients are shown in Table 2. These studies were published from 2009 through 2012. One study was done in Iran and two studies were examined



**Figure 1.** Search results

in China and Japan; data extraction was conducted in patients with COPD within 3 studies using medical files.

### Outcome

The  $r$  was  $-0.052$  (95% CI:  $-0.14-0.049$ ,  $p = 0.28$ , Figure 2) at a serum level of IL-8 in the conducted studies on ML patients and no statistical significant relationship was observed among serum levels of IL-8 and FEV<sub>1</sub>.

Similarly, no statistically significant relationship was seen among the IL-6 serum level with FEV<sub>1</sub> in the conducted studies on them ( $r = -0.005$ , 95% CI:  $-0.14-0.049$ ,  $p = 0.28$ , Figure 3). The results showed that there was no statistically significant relationship between inflammatory cytokines IL-1 $\beta$ , IL-1 $\alpha$ , IL-1Ra, and IL1Ra/IL1 $\beta$ , and IL-6 serum level. The existing heterogeneity among results of studies may be due to the difference in intensity of the disease and the method by which the control group

members have been chosen in any study (test for heterogeneity,  $p = 0.002$ ).

Only in one study on the CRP level in the studied ML patients, no statistically significant relationship was seen among serum levels of IL-6 and CRP in these patients while a negative significant relationship was observed between serum levels of CRP and FEV<sub>1</sub> in these results ( $r = -0.13$ ,  $p = 0.012$ ).

In another study on the TNF level analyzed in ML patients, the results showed that except for IL-1 $\alpha$ , there was a strong significant relationship among serum levels of IL-8, IL-1 $\beta$ , and IL-1 $\alpha$ . At the same time, a reverse significant relationship was seen between TNF and FEV<sub>1</sub> levels ( $r = -0.39$ ,  $p = 0.03$ ).

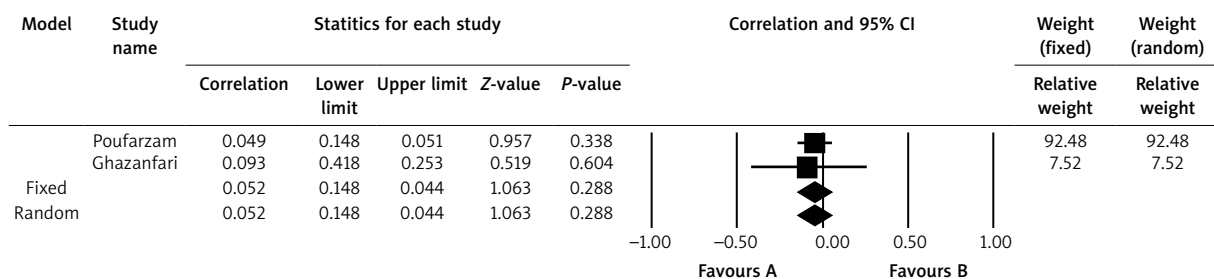
In three studies, the IL-6 serum level was explored in COPD patients. The results of the given studies in these patients included  $r = -0.006$ , 95% CI:  $-0.37-0.15$ ,

**Table 1.** Main characteristics of the studies on chemically injured veterans exposed to sulfur mustard

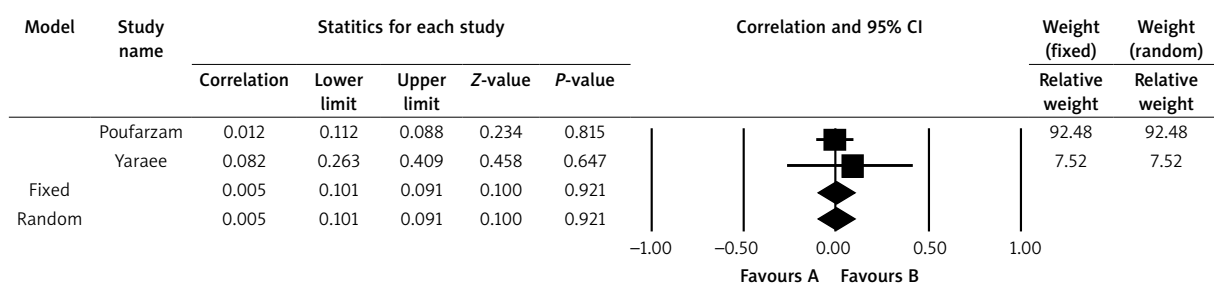
Author	Year	Country	COPD patients and controls	Inflammatory marker and laboratory measurement
Pourfarzam	2009	Iran	Final sample size, with all necessary data was 348. SM exposed and 120 unexposed controls. The exposed subjects were male individuals from Sardasht categorized into two major subgroups hospitalized ( $n = 159$ ) and not hospitalized ( $n = 189$ ) based on severity of problems at the time of exposure. This study was approved by the Ministry of Health of Iran, Shahed University and the Board of Research Ethics of Janbazan Medical and Engineering Research Center	Human IL-6 and IL-8 DuoSet® ELISA Development Kits (R&D Systems) were used to measure IL-6 and IL-8 levels in the sera
Yaraee	2013	Iran	The participants in this study were a subgroup of 40 male SM-exposed individuals in the Sardasht-Iran Cohort Study (SICS). Based on the documents in the medical records verified by the Medical Committee of the Foundation of Martyr and Veterans Affairs, the participants were exposed to SM in June 1987. The mean age was $44.2 \pm 9.9$ , and about 12% were smokers and 88% were non-smokers	Human TNF, IL-1 $\alpha$ and IL-1 $\beta$ , IL-1Ra and IL-6 DuoSet® ELISA Development Kit (R&D Systems) and fibrinogen (AssayPro ELISA Kit) were used to measure the level of the mediators in the sera and sputum
Ghazanfari	2009	Iran	500 participants including 372 exposed individuals and 128 control subjects were studied. This study was approved by the Ministry of Health of Iran and the Board of Research Ethics of the Janbazan Medical and Engineering Research Center	ELISA kits were used to measure the chemokine MCP-1/CCL2, RANTES/CCL5, IL-8/CXCL8, Fractalkine/CX3CL1 levels

**Table 2.** Main characteristics of the studies on patients with chronic obstructive pulmonary disease

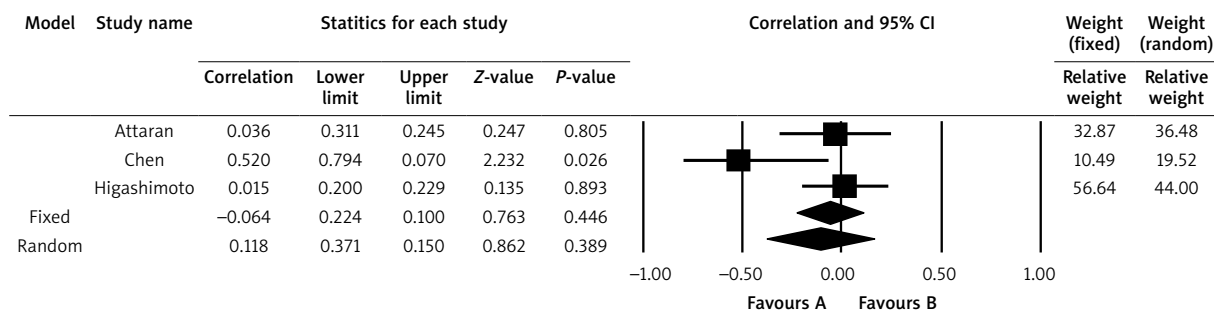
Author	Year	Country	COPD patient and Controls	Inflammatory marker and laboratory measurement
Higashimoto	2009	Japan	COPD was diagnosed when the post-bronchodilator FEV <sub>1</sub> /forced vital capacity (FVC) ratio was less than 70% (GOLD stages IeIV). A total of 96 patients with COPD were recruited from patients seen in the Department of Internal Medicine of the Wakayama Medical University Kihoku Hospital	Serum CRP was measured by immune nephelometry using the TBA-200FR NEO system, with a lower detection limit of < 0.030 mg/dl. Serum $\alpha$ 1-antitrypsin ( $\alpha$ 1-AT) was also determined using immune nephelometry. Tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-8, IL-6, TGF- $\beta$ 1, neutrophil elastase, matrix metalloproteinase (MMP)-9 and TIMP-1 concentrations were measured by ELISA
Chen	2012	China	12 patients with COPD were recruited in the study, where 6 were in the clinical stable condition and 6 in the acute exacerbation stage. Six healthy people were also enrolled as normal controls. Three smokers and three non-smokers were included in each group. COPD was diagnosed on the basis of clinical evaluation and pulmonary function tests showing airflow obstruction, according to the GOLD criteria (FEV <sub>1</sub> < 80% predicted, FEV <sub>1</sub> /FVC < 70% and bronchodilation effect < 12%)	Serum IL-1 F6, IL-17B R, IL-17D, IL-19, Lymphotoxin beta, MMP-10 measuring inflammatory factors: A Custom Raybio® Human Inflammation Antibody Array kit
Attaran	2010	Iran	Between April and September 2008, 50 patients with COPD were recruited in the study who attended the pulmonary clinic of Ghaem hospital, Mashhad, Iran, were entered into that cross-sectional study	Serum IL-6 was measured by the Bender MedSystem Human IL-6 (BMS 213/2; Medical System Diagnostic GmbH, Austria, test sensitivity 1.4 pg/ml)



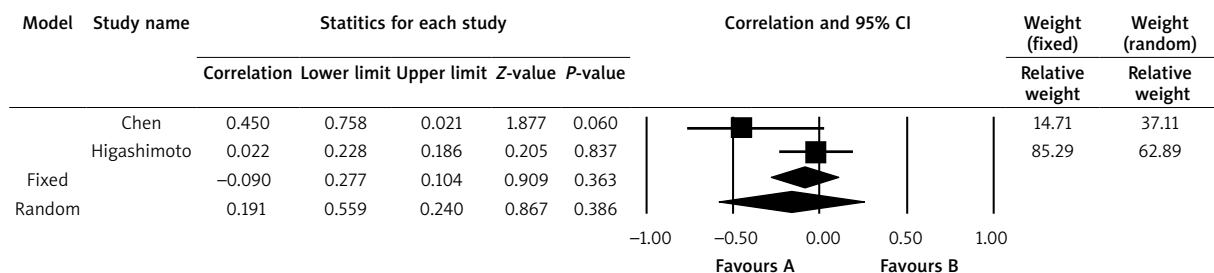
**Figure 2.** The relationship between, interleukin 8 (IL-8) and mustard lung. Based on the regression coefficient between mean forced expiratory volume in 1<sup>st</sup> s (25–75<sup>th</sup> percentile) and IL-8



**Figure 3.** The relationship between, interleukin 6 (IL-6) and mustard lung. Based on the regression coefficient between mean forced expiratory volume in 1<sup>st</sup> s (25–75<sup>th</sup> percentile) and IL-6



**Figure 4.** The relationship between, interleukin 6 (IL-6) and chronic obstructive pulmonary disease. Based on the regression coefficient between mean forced expiratory volume in 1<sup>st</sup> s (25–75<sup>th</sup> percentile) and IL-6



**Figure 5.** The relationship between, interleukin 8 (IL-8) and chronic obstructive pulmonary disease. Based on the regression coefficient between mean forced expiratory volume in 1<sup>st</sup> s (25–75<sup>th</sup> percentile) and IL-8

$p = 0.44$ , while no reverse significant relationship with  $FEV_1$  was observed (Figure 4). In two studies, IL-8 levels in COPD patients were explored and the results of these studies indicated that this serum level in COPD patients had no statistically significant relationship with  $FEV_1$  ( $r = -0.19$ , 95% CI:  $-0.55-0.24$ ,  $p = 0.38$ , test for heterogeneity,  $p = 0.003$ , Figure 5). The conducted studies on COPD patients were significant in terms of heterogeneity.

Only in one study on serum levels of CRP and TNF in the given COPD patients, it has been reported that there was a reverse significant relationship among serum levels of CRP and  $FEV_1$  in patients who suffered from this disease ( $r = -0.35$ ,  $p = 0.002$ ). However, no statistical significant relationship was seen among serum levels of TNF and  $FEV_1$  ( $r = -0.14$ ,  $p < 0.001$ ).

**Discussion**

The study proved that there is some evidence showing that systemic inflammation has been identified as a risk factor in several side effects including atherosclerosis, cachexia, anorexia, and osteoporosis that have been noticeably observed in COPD patients. We concluded in this meta-analysis that serum levels of CRP and TNF have been significantly increased in chronic obstructive pulmonary diseases compared to the healthy control group,

which shows the presence of systemic inflammation in ML and COPD patients.

A review study was carried out by Ghanei *et al.* regarding long-term effects of mustard gas on the respiratory system in ML patients. It was characterized in this study that there have been numerous respiratory symptoms in the long run including coughing, bloody sputum, and chest pain and these effects have been remarkably related to chronic pulmonary disease, chronic bronchitis, asthma, and COPD [8, 14, 15].

The results of previous studies showed that serum levels of CRP as types of inflammatory markers have been increased in ML patients and they were inversely related to  $FEV_1$  [16]. Gan *et al.* were the first ones who examined the importance of the CRP high level in COPD patients. The results of this study showed that the CRP serum level is high in smokers and/or COPD patients and the pulmonary function is at a low level. These levels are affected by various factors including cardiovascular diseases [17, 18], physical function intensity, diabetes, nephral disease, hypertension, metabolic syndrome, smoking, and dosage of some drugs such as astatine where these factors may tarnish the results of the study about the CRP level as a predictor in the diagnosis of COPD [19]. There is less evidence of the presence of systemic inflammation among smokers and in pulmonary patients such as COPD patients and this indicates that cessation of

smoking may lead to a reduction of the related inflammatory processes to this subject.

It was examined in a study that IL-6 and IL-8 have a primary role in chronic diseases such as COPD and asthma and they act as biomarkers for diagnosis and function of this disease. The results of the study conducted in the Sardasht zone in Iran showed that in comparison with control group members, serum levels of IL-6 and IL-8 were lower in patients who were exposed to SM. No significant relationship has been seen between serum levels of IL-8 and IL-6, and pulmonary symptoms (chronic coughing, sputum, and rhonchus) [20–23].

The studies conducted by Emad and Emad on local inflammation indicated that there was a significant increase in serum levels of IL-8 and IL-6 in BALF in patients with ML who also suffered from pulmonary fibrosis as compared to the control group [24, 25]. In addition, it has been implied in other studies that the systemic inflammation might result in exacerbation of asthma attacks [26]. Several studies showed that there is a rising rate of the serum level of IL-8 in sputum or BALF in COPD patients and asthmatic patients, especially in exacerbated and symptomless cases [26–29]. Similarly, in another investigation, an increase in the serum level of IL-8 is observed in patients exposed to SM [29]. The IL-8 level observed in BALF of patients with bronchiolitis obliterans (BO) has been remarkably increased after transplantation and pulmonary infections [30–32].

The results of studies conducted by Purfarzam showed that CRP serum levels have been dramatically increased in COPD patients. This is the best parameter for systemic inflammation and pulmonary function deficiency in these patients [33, 34]. This study indicated that there was no relationship between IL-8 serum levels and spirometry parameters. Likewise, other studies indicated that a negative significant relationship was seen between serum levels of CRP and FEV<sub>1</sub> in ML patients and in comparison with the control group, the patients with this disease had a higher CRP serum level [35, 36]. It was identified in this study that there was no symptom of systemic inflammation processes in patients with ML while there was some evidence about the presence of these symptoms in patients with this disease in the studies by Ghanei *et al.* [8, 37].

Donaldson *et al.* examined the relationship between systemic and airway inflammation. This study showed that there was no relationship between sputum IL-6 and fibrinogen and also there was no direct relationship between systemic and airway inflammation [38]. Vernooy *et al.* reported that there is no direct relationship between sputum IL-6 and TNF plasma receptors in patients with COPD [39].

The results of a study by Attaran *et al.* indicated that in comparison with the control group, IL-6 serum levels have been significantly higher in chemically injured veterans with SM and this statistical significant relationship exists

between IL-6 levels and FEV<sub>1</sub> predicted percentage. It was identified in this study that serum levels of TNF and IL-8 in habitual smokers have been higher compared to non-smokers and smoking was considered as a risk factor for reducing FEV<sub>1</sub> predicted percentage and it is independently deemed as a factor for systemic inflammation [16].

There were some constraints and potential bias in this meta-analysis. We intended in this study to evaluate effects of other tarnishing variables such as cardiovascular diseases, physical function intensity, diabetes, nephral disease, hypertension, metabolic syndrome, and smoking. But in fact these variables have not been reported in many studies and this may increase the possibility of information bias. Despite this constraint, this meta-analysis can present remarkable evidence about systemic inflammation in ML and COPD.

Furthermore, some new information was acquired about systemic inflammation in ML and COPD in this meta-analysis including:

- acquisition of summarized data from estimations of the *r* with respect to the effect of systemic inflammation on ML and COPD;
- lack of a statistically significant relationship regarding inflammatory cytokines IL-8, IL-6, and FEV<sub>1</sub> in ML and COPD;
- the existing reverse statistically significant relationship in inflammatory cytokines CRP, TNF, and FEV<sub>1</sub> in ML; and
- presence of a reverse statistically significant relationship in inflammatory cytokine CRP and FEV<sub>1</sub> in COPD and lack of a statistical relationship with TNF.

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## Conflict of interest

The authors declare no conflict of interest.

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