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Original Research Article

Correlation of serum TNF alpha level with severity of chronic obstructive pulmonary disease

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ABSTRACT

Background: Tumor necrosis factor alpha (TNF α) is the most widely studied cytokine of TNF super family. TNF α plays a significant role in many inflammatory diseases affecting the lung, such as chronic bronchitis (CB), chronic obstructive pulmonary disease (COPD), asthma, acute lung injury (ALI) and acute respiratory distress syndrome. Elevated levels of TNF-alpha are seen in COPD patients. An increased level of TNF-α has been found in induced sputum or lung biopsy of COPD patients. 14-16 This study includes correlation of level of TNF α with severity and characterization of individuals with COPD. There are only limited numbers of studies being conducted regarding this topic in the world, including India. Objectives of present study were to measure the TNF-α level in patients with chronic obstructive pulmonary disease and to correlate TNF α level with severity of chronic obstructive pulmonary disease.

Methods: The study was conducted on one hundred and eight (108) patient's COPD patients attending the Pulmonary medicine department of Sri Manakula Vinayagar Medical College and Hospital Puducherry, who are aged above forty years, with a duration of 18 months, starting from the date of getting approval from the Ethics Committee. The subjects were analysed on their TLC, DLC was done to rule out any co-existing infections. Spirometry was done to confirm the diagnosis of COPD. Blood was taken from the confirmed COPD patients after getting their approval, for the estimation of serum TNF α level.

Results: The Serum TNF alpha levels increases according to the COPD severity. The mean serum TNF alpha level in patients with mild obstruction, moderate obstruction, severe and very severe obstruction were 9.91+2.9, 21.25+4.8, 32.4+8.2 and 39.2+3.1pg/dl respectively. Mean TNF alpha value was 26.7pg/dl. The values of TNF α increases with the stages of COPD which is statistically significant with p value of 0.0001.

Conclusions: The present study showed that serum TNF alpha level correlates with severity of airway obstruction in spirometry among the COPD patients. It also correlates with the disease severity as per the different stages of COPD patients (GOLD COPD staging 2016). Thus, serum TNF alpha is a useful marker to monitor the disease severity in addition to spirometric parameters like FVC, FEV_1 and FEV_1/FVC. However, further studies are needed with larger sample size.

Keywords: TNF Alpha, COPD, Exacerbations, Spiromertry

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality across the globe. It is a disease of increasing public health importance around the world. COPD is the sixth leading cause of death worldwide[1], according to the 1990 Report of the Global Initiative Chronic Obstructive Lung Disease

(GOLD) and will become the fourth leading cause of worldwide death by the year 2030.[1-3]. Rather than a respiratory disease, COPD is now considered to be a systemic disease. The definition for COPD that GOLD lays down in its 2015 Report is that, COPD is defined as a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co morbidities contribute to the overall severity in individual patients.[4]

Crude estimates suggest there are 30 million COPD patients in India.[5] COPD is a common problem in patients hospitalized in respiratory medical wards. COPD is associated with significant economic burden. COPD is a major cause of morbidity and mortality throughout the world. COPD will have a negative impact on workplace and home productivity. Every year half a million people die in India due to COPD.[6]

GOLD defines an exacerbation of COPD as, an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication.[7-9]

On a pathological basis, COPD consists of

- Emphysema, where there is destruction of the gas-exchanging surfaces of the lung (alveoli) causing irreversible enlargement of airspaces and loss of lung elasticity, and
- Chronic Bronchitis, where there is presence of cough and sputum production for at least three months in each of the two consecutive years

For diagnosis of COPD, GOLD recommends the use of spirometry, where the presence of a post bronchodilator FEV_1/FVC (Forced Expiration Volume in 1st second/Forced Vital Capacity) is less than 0.70. This criterion is simple, independent of reference values. Along with this, GOLD also recommends some criteria for diagnosis of COPD. These includes- age of the individual should be more than 40yrs, dyspnea that is characteristically worse with exercise and which is persistent. Chronic cough that is intermittent and which may be non – productive is another indicator and Chronic sputum production. These indicators are not diagnostic themselves, but the presence of such key indicators increases the probability of COPD.[10]

A detailed medical history is needed regarding; Patient's exposure to risk factors, Past medical history, Family history of COPD or other chronic respiratory disease, History of exacerbations or previous hospitalizations for respiratory disorder.[11] Differential diagnosis for COPD includes asthma, congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, diffuse panbronchiolitis and pulmonary fibrosis. COPD is associated with many co-morbidities, like cardiovascular disease, osteoporosis depression, infections.

Tumor necrosis factor alpha (TNF α) is the most widely studied cytokine of TNF superfamily. TNF α plays asignificant role in many inflammatory diseases affecting the lung, such as chronic bronchitis (CB), chronic obstructive pulmonary disease (COPD), asthma, acute lung injury (ALI) and acute respiratory distress syndrome.[12] TNF-α is one of the most extensively studied cytokines in COPD. Elevated levels of TNF-alpha is seen in COPD patients. TNF-α was originally described as afactor produced by the endo-toxin stimulated macrophages that causes hemorrhagic necrosis of tumors.[13] An increased level of TNF- α has been found in induced sputum or lung biopsy of COPD patients.[14-16] This study includes correlation of level of TNF α with severity and characterization of individuals with COPD. There are only limited numbers of studies being conducted regarding this topic in the world, including India.

The aim of the study was to measure the TNF α level in patients with chronic obstructive pulmonary disease and to correlate TNF α level with severity of chronic obstructive pulmonary disease.

METHODS

This study was carried out in Chest OPD on all COPD patients attending the Pulmonary medicine department of Sri Manakula Vinayagar Medical College and Hospital, Puducherry who are aged above forty years were included in the study. The study duration was 18 months (November 2014 to May 2016). The study was initiated after getting approval from the Ethics Committee. It is a hospital based cross sectional Study. This study was conducted on one hundred and eight (108) patients (with mean as 31.3 and standard deviation as 26pg/ml) with an allowed error of 5% and confidence interval of 95%.[17] Sample size was calculated using open Epi info software version 3.4.3.

Inclusion criteria

All patients who are diagnosed as COPD, using spirometry are included in this study. Patients who are having typical symptoms of chronic cough with or without expectoration with shortness of breath on exertion are included in the study after confirming the diagnosis by FEV_1/FVC <70% and post bronchodilator FEV_1<80% on spirometry as per the GOLD guidelines. Severity of COPD is diagnosed according to GOLD 2015 guidelines. CAT scoring is also done to assess the severity of symptoms patient have.

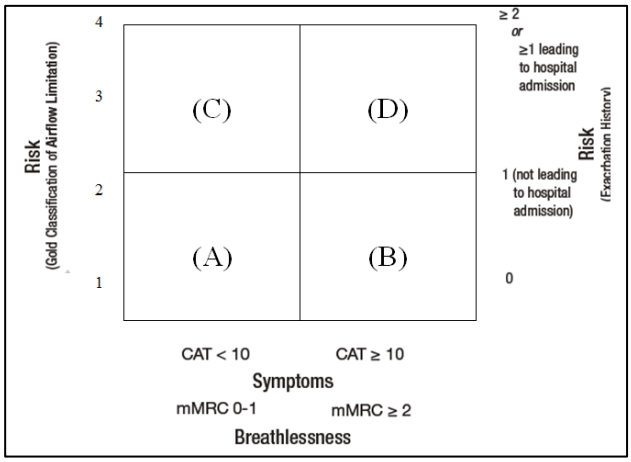
Exclusion criteria

Patients on Oral steroids, patients with sputum positive pulmonary tuberculosis, asthma patients, and patients

with bronchiectasis and with acute exacerbations are excluded from the study.

Clinical examination of patients

The patients were assessed based on Modified Medical Research Council (mMRC) Questionnaire for Assessing the Severity of Breathlessness (shown in Figure 1), Gold Spirometric Criteria for COPD severity, spirometry.[18]



mMRC Grade 0:I only get breathless with strenuous exercise, mMRC Grade 1:I get short of breath when hurrying on the level or walking up a slight hill, mMRC Grade 2.I walk slower than people of the same age on the level because of breathlessness or I have to stop for breath when walking on my own pace on the level, mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level, mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.

Figure 1: Modified Medical Research Council (mMRC) questionnaire for assessing the severity of breathlessness

GOLD pyrometric criteria for COPD severity

In patients with $FEV_1/FVC<0.70$

GOLD 1 Mild COPD; $FEV_1 \geq 80\%$ predicted

GOLD 2 Moderate COPD; $50\% \leq FEV_1 < 80\%$ predicted

GOLD 3 Severe COPD; $30\% \leq FEV_1 < 50\%$ predicted

GOLD 4 Very severe COPD; $FEV_1 < 30\%$ predicted

The study was carried out after approval from the institutional ethical committee and with fully informed written consent from the subjects. A fully informed written consent was taken from the patient in his native language. Detailed clinical history was taken and clinical examination was done. Inclusion and exclusion criteria were carried out. The subjects who satisfied the above-mentioned criteria, a thorough analysis on their TLC, DLC was done to rule out any co-existing infections. A chest X-ray PA view was done to further support the evidence of COPD (like hyper-inflated lung fields). Sputum AFB and Grams stain was done to rule out any active Tuberculosis and other Lung infections. Spirometry was done to confirm the diagnosis of COPD. Blood was taken from the confirmed COPD patients after getting their approval, for the estimation of serum TNF α level.

Spirometry

Spirometry including reversibility test was performed as per the ATS recommendation on WinspiroPRO 5.8 pneumotach. All tests were carried out in a fixed hour of day (10.00-14.00 hrs) to minimize diurnal variation.

The following instructions were given to the patients prior doing spirometry

- Abstain smoking at least one hour prior to test.
- Abstain from alcohol at least four hours prior to the test.
- Avoid any sort of vigorous exercise at least 30 minutes prior to the test.
- Avoid wearing clothing that can substantially restrict full chest and abdominal expansion
- Avoid a heavy meal at least two hours prior to the test.[19]

The standardization methods of performing spirometry as mentioned in the ATS guidelines19 by the ATS/ERS task force for standardization on lung function testing was adopted for the present study.

Acceptability criteria for a spirometry test results, according to ATS guidelines.

a. Effort with good start, with no hesitation.
b. Good peak expiratory flow.
c. Extrapolated volume should be less than 5% of FVC or 0.15 litres, whichever is greater.
d. Duration of 6 seconds (3 seconds for children) or a plateau in the volume-time curve or if the subject cannot or should not continue to exhale.
e. Should be free from artifacts like
    - Cough during the first second of exhalation.
    - Glottis closure that influences the measurement.
    - Early termination or cut-off.
    - Effort that is not maximal throughout.
    - Leak.
    - Obstructed mouthpiece.

After three acceptable spirograms have been obtained, apply the following tests

- The two largest values of FVC must be within 0.150 litres of each other.
- The two largest values of FEV_1 must be within 0.150 litres of each other.

- If both these criteria are met, the test session may be concluded.
- If both of these criteria are not met, continue testing until both of the criteria are met with analysis of additional acceptable spirograms. or
- A total of eight tests have been performed (optional) or
- The patient/subject cannot or should not continue
- Save, as a minimum, the three satisfactory maneuvers.
- The above criteria had been maintained in the study undertaken for measuring the FEV_1.

Spirometry technique

Preparing the patient

Indications for postponing the test included:

- A recent viral infection (within two or three weeks) or other acute illness.
- Cigarettes or heavy meal within an hour of testing

The patient was put at ease by briefly explaining the test, how it is done, and the importance of the test.

Positioning the patient

- Any tight clothing (ties, belts) were loosened.
- Patient's dentures were removed (if present).
- Patient is advised to sit. Sitting provided the benefit of support in event of loss of balance. During sitting patient's legs are kept uncrossed and feet on the floor.
- The chin was slightly elevated and the neck slightly extended. Some bending was acceptable but excessive bending of the chin or back was discouraged

Explaining the procedure

The procedure was explained thoroughly to the patient while demonstrating the correct technique using the pneumotach.

- How to use the pneumotach and nose clips was explained.
- It was made certain that patient had a tight seal with his/her lips around pneumotach.
- The tongue didn't extend into the tube.
- The patient's hand did not cover the end of the pneumotach.
- A disposable nose clip was placed securely on the patient's nose.
- Again, the proper head and neck position was demonstrated.
- An explanation in the simplest terms on how test should be performed was provided.

Later the correct maneuver was demonstrated reminding the patient of importance of correct position, blasting the air out, and continuing to blow until told to stop.

Reversibility testing

For reversibility testing, a dose of inhaled beta-agonist (400 microgram of salbutamol) was administered after the initial test and spirometry was repeated 20 minutes later. Absence of improvement of 12% or more and 200ml or more in Post Bronchodilator FEV_1 or FVC was taken as absence of reversibility. Post Bronchodilator FEV_1 was recorded in all COPD cases to assess severity of airway obstruction.

Serum TNF α estimation

Serum TNF α level was determined using Ray Bio Human TNF-alpha kit. It is an in vitro enzyme –linked immunosorbent assay for the quantitative measurement of human TNF-alpha in serum, plasma and cell culture supernatants. This assay employs an antibody specific for Human TNF- alpha, which is coated on a well plate. Standards and samples are pipette into the wells. TNF-alpha present in the sample binds to the well by immobilized antibody. Wells are later washed and anti-human TNF alpha antibody is added. After washing the unbound antibody, HRP-conjugated streptavidin is added to the wells. Wells are again washed and TMB substrate solution is added to the wells and color develops in proportion to amount of TNF alpha bounded. Stop solution is added, it changes colour from blue to yellow. Color intensity is measured at 450nm.

Statistical analysis

The data were entered using Epi info software version 3.5.4 and analyzed using SPSS version 24. Proportions were calculated for all variables and Chi-square test and paired T test were used to find the association and statistical significance. The results were mentioned in mean±standard deviation. A p value of <0.05 was considered to be statistically significant. Microsoft MS Excel was used to generate graphs and chart

RESULTS

In this study, total of 108 patients with COPD were included from Chest OPD, Tertiary care Hospital, Puducherry. In this study, 33% (n=37) of COPD cases were in the age group of 61-70 years. 29% (n=31) of COPD cases belonged to ages between 51 and 60, 18.7% (n=20) COPD patients were between 40 and 50 years of age, 17.8% (n=19) COPD patients were between 71 and 80 years of age), 0.9% (n=1) COPD patient between 81-90 years of age. Mean age in the study was 60.7 years. Age distribution of COPD cases are shown in Table 1.

Table 1: Distribution of patient based on severity of obstruction.

Age group(years)	Mild	Moderate	Severe	Very severe	Total
40-50	0 (0)	13 (72.2)	7 (38.9)	1 (5.6)	21 (16.7)
51-60	2 (6.5)	9 (29.0)	15 (48.4)	5 (16.1)	31 (28.7)
61-70	5 (13.9)	14 (38.9)	14 (38.9)	3 (8.3)	36 (33.3)
71-80	0 (0)	12 (63.2)	7 (36.8)	0 (0)	19 (17.6)
81-90	1 (100.0)	0 (0)	0 (0)	0 (0)	1 (0.9)
Total	8	45	19	26	108

Table 4: Body mass index distribution among the respondents.

BMI Group	Frequency	%
Under weight (<18)	39	36.1
Normal (18-25)	59	54.6
Over weight (25-30)	10	9.3
Obese (>30)	0	0
Total	108	100.0

Distribution of patient based on severity of obstruction. Out of 108 COPD patients included in our study, 105 (97.2%) were males, and 3 (2.8%) of them were females.

Table 5: BMI with COPD.

BMI	Mild	Moderate	Severe	Very severe	Total
<18	2 (5.1)	15 (38.5)	20 (51.3)	2 (5.1)	39 (36.1)
18-25	6 (10.2)	27 (45.8)	21 (35.6)	5 (8.5)	59 (54.6)
>25	0 (0)	6 (60.0)	2 (20.0)	2 (20.0)	10 (9.3)

Table 6: Correlation of BMI and TNF alpha levels.

BMI	TNF-alpha (mean±SD)	p-value
<18	22.9±3.4	0.0005
18-25	20.3±3.4	
>25	19.4±3.9	

Out of 108 COPD patients, 59 (54.6%) patients had normal weight according to their BMI. 39 (36.1%) patients were classified as underweight. 10 (9.3%) of them are classified as overweight. Mean BMI in the study is 19.8. body mass index distribution among the respondents is shown in Table 4. Table 5 shows distribution of BMI based on the severity of airway obstruction and Table 6 shows Correlation of BMI and TNF alpha levels.

In our study, the most common symptom reported by the patients was Cough and breathlessness was seen in all patients (100%) followed by wheeze (42.6%) and fever (42.6%). Chest tightness was seen in 26.9% of COPD patients. 10.2% patient's complaints of other symptoms like body pain, fatigue etc. All patients had symptoms of cough and breathlessness. 46 patients had fever and wheeze. 29 patients had chest tightness.

Among 108 COPD patients in our study, 59 (54.6%) patients were farmers followed by 25 (23.1%) patients were daily wages workers. 14 (13%) patients were drivers, 8 (7.4%) patients were with other jobs (e.g. government staff, teacher, business) and 2 (1.9%) patients were house wifes.

In our study, the mean Post FEV_1/FVC was found to be 57.25 and FEV_1 was 52.23 which comes under moderate level of obstruction in COPD patients according to the GOLD guidelines.

In our study, spirometry was done in all 108 patients out of whom 48 (44.4%) patients had moderate obstruction, 43 (39.8%) patients had severe obstruction, 8 (7.4%) patients had mild obstruction, and 9 (8.3%) patients had very severe obstruction. It was found that most of the cases had moderate airway obstruction.

The levels of TNF alpha show a steady increase with increasing severity of airway obstruction. Serum TNF alpha levels according to the COPD severity. The mean serum TNF alpha level in patients with mild obstruction, moderate obstruction, severe and very severe obstruction were 9.91+2.9, 21.25+4.8, 32.4+8.2 and 39.2+3.1pg/dl respectively. Thus, the TNF alpha level raises with severity of airway obstruction which is statistically significant (p value 0.0001).

DISCUSSION

COPD patients were identified based on the history and spirometry.Spirometric values showing the diagnosis by Post bronchodilator FEV_1/FVC <70% and FEV_1<80% on spirometry as per the GOLD guideline.[21]

Patients were divided into 4 groups according to the stages of COPD as per the GOLD guidelines.[22]

In our study 108 COPD patients were included. Most of the COPD cases were in the age group of 61-70 years, with mean age of 60.7years. The prevalence shows the occurrence of the disease in higher age groups.

Majority of the COPD cases 105(97.2%) were males in our study. This is due to increase in the prevalence of diseases among male's due to well known risk factors like cigarette smoking. 3 of them (2.8%) were females with history of exposure to smoke from cooking in a closed room using hay stick and cow dung cakes for fire (Bio mass fuel).

Chapman et al studied the prevalence of COPD in North American population and showed increased prevalence of the disease in males than females.[23] Mahesh et al based on their study on validation of structured questionnaire for COPD in rural area of Mysore,which was a pilot study, found that the prevalence of disease to be more common in males (11.1%) when compared to females (4.5%).[24]

In present study, the most common symptoms reported by the patients were Cough and breathlessness in all patients (100%) followed by wheeze (42.6%) and fever (42.6%). Chest tightness was seen in 26.9% of COPD patients. 10.2 % patients complained of other symptoms like body pain, fatigue etc.

In current study, spirometry was done in all 108 patients out of whom 48 (44.4%) patients had moderate airway obstruction, 43 (39.8%) patients severe obstruction, 8 (7.4%) patients mild obstruction, and 9 (8.3%) patients very severe obstruction. It was found that most of the cases had moderate airway obstruction.

Bednarek et al studied the prevalence, severity, underdiagnosis of COPD in primary care settings in which COPD was diagnosed in 183 patients (9.3%). Of these patients the degree of post-bronchodilator airflow limitation was mild in 30.6%, moderate in 51.4%, severe in 15.3% and very severe in 2.7%.[25] This could be due to the fact of increased awareness of the disease in the Western population which in turn increases the chance of diagnosing the disease at early stage. But, in our study, majority of the COPD cases were found to have moderate (44.4%) and severe (39.8%) airflow obstruction. This could be due to lack of symptoms and awareness about the disease among the developing countries like India, so the patients present late in course of the disease to the tertiary care hospital.

Vigg A et al studied the prevalence of COPD in a tertiary care hospital in South India and noted that out of 946 patients studied, 284 had mild COPD (30%), 286 moderate disease (30%) and the remaining 376 patients (40%) severe COPD.[26] The overall prevalence of COPD was 6.85% with prevalence of disease in males being 7.4% and in females 4.64%.

Out of 108 COPD patients, 59 (54.6%) patients had normal weight according to their BMI. 39 (36.1%) patients were classified as underweight. 10 (9.3%) of them were classified as overweight.

De et al studied body mass index in COPD patients found that 38% COPD patients in their study were underweight (BMI <18.5 kg/m2).[27] The mean BMI also reduced significantly with progression of COPD severity. In our study, most of the patients were of normal weight (54.6%) and underweight (36.1%) category.

Mario Montes deocaet al in their study of COPD and body mass index in 5 Latin American cities (PLATINO STUDY) noted that when compared with non COPD group.[28] There was a higher proportion of COPD subjects in the underweight and normal weight categories, and a lower proportion in the obese category. Factors associated with lower BMI in males with COPD were aging, current smoking and Global initiative for chronic obstructive lung disease (GOLD) stages III- IV. Thus, the findings of Mario Montes deoca and coworkers correlates with our study that most of the COPD patients were in normal and underweight category.

Francia and colleagues studied TNF alpha levels and weight loss in COPD patients, found that TNF alpha level and BMI have an inverse relationship which correlates with present study. As the BMI decreases, the TNF alpha level increases.[29]

Study done by Gupta et al, found COPD in general was associated with malnutrition. (83% patients being BMI < $20kg/m^2$.[30]

In present study, the mean BMI in COPD patients was 19.8. The serum TNF alpha levels increases as the BMI decreases, which is statistically significant with p value of 0.0005.

Shin et al in their study on effects of TNF-α and leptin on weight loss in patients with stable chronic obstructive pulmonary disease suggested that, the activity of the TNF-α system may not involve with weight-loss in patients with stable COPD.[31] In present study, the mean level of TNF alpha in patients with very severe obstruction was 39.2pg/dl whereas the patients with severe obstruction had a mean value of 32.4pg/dl. The mean values of serum TNF alpha in patients with mild and moderate obstruction were 9.91pg/dl and 21.25pg/dl respectively. Thus, the serum TNF alpha levels increase with increase in the severity of airflow obstruction which is statistically significant with p value of 0.0001.

Haehling V et al in their paper "Elevated TNF alpha production in whole blood in patients with severe COPD: the potential link to disease severity" have demonstrated that Serum TNFα was significantly elevated in patients versus controls (2.1±0.3 vs. 1.1±0.1 pg/ml, mean±SEM, *P*=0.007). Spontaneous TNFα production in severe COPD was 5.0 times higher compared to mild-to-moderate COPD (*P*=0.02). The above findings are similar to present study i.e, the levels of TNF alpha increase with the increase in severity of airway obstruction. In the above study, BMI of COPD patients was lower than

healthy control subjects. This also correlates with our study almost of the COPD patients were in normal and underweight category.

Takabatake et al studied levels of the TNF- alpha in COPD patients, found correlations between PaO_2 level and TNF alpha level in COPD patients compared to healthy controls.[32] An inverse relationship was noted between COPD severity and PaO_2 level. TNF alpha level were found to be elevated with severity of COPD, i.e., the higher the COPD severity, the higher the TNF alpha levels and lower the PaO_2 level. This data suggested that, systemic hypoxemia noted in COPD patients is associated with activation of TNF alpha system.The above findings are similar to our study, i.e., the levels of TNF alpha increases with the increase in severity of airway obstruction. But in our study PaO_2 was not measured to correlate the hypoxemia and the level of TNF alpha level.

Pitsiou et al also demonstrated that, TNF alpha levels were increased in patients with hypoxemia and this may be a factor contributing to the weight loss of these patients.[18]

Tanni et al, studied the correlation of smoking status and TNF alpha levels in COPD current smoker, COPD ex-smoker, current smoker control and ex-smoker control, found that TNF alpha level was higher in current smoker control and COPD current smokers.[33] This correlates with our study. 97.2% patients in our study were smokers. Thus, the results suggest that smoking may be associated with higher TNF alpha mediated systemic inflammation in COPD patients.

Verooy et al, compared local and systemic inflammation in a small sample of COPD patient and did not find influence of smoking on plasma concentration of TNF alpha.[34] In present study it was also found that, the values of TNF α increases with the stages of COPD which is statistically significant with p value of 0.0001.

However, further large-scale investigations with respect to age, sex, ethnic groups, genetic factors, patient characterization etc. are required to assess and confirm the validity of TNF α as a biomarker in COPD.

CONCLUSION

In conclusion, present study showed that serum TNF alpha level correlates with severity of airway obstruction in spirometry among the COPD patients. It also correlates with the disease severity as per the different stages of COPD patients (GOLD COPD staging 2016). Thus, serum TNF alpha is a useful marker to monitor the disease severity in addition to spirometric parameters like FVC, FEV1 and FEV1/FVC. However, further studies are needed with larger sample size.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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