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*Original Research*

# Gynecomastia and Risk of Non-Specific Lung Disease: Biochemical and Radiological Relevance

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## Abstract

Lung diseases with increased numbers of cases are reported worldwide with multiple factors including, smoking, lifestyle, and particularly people associated with petrochemical industries. Employees of petrochemical products industries, always at high risk. A single case control 56 years old long-term study from 2014 to final disposal of the case was undertaken, employed in industrial division, exposed to organic fumes, with low albumin, creatinine, elevated serum proteins (91.6 g/L), globulin, $CO_2$ (39 to 41 mmol/L). His radioallergosorbent test (RAST) positive for dog dander, English plantain, Parientaria officinalis and Dermatophagoides pteronyssinus, cat epithelium and Bermuda grass, Timothy grass, Penicillium notatum and Alternaria tenuis, birch and Japanese cedar with high IgE was positive at 547 without eosinophilia. Bilateral gynecomastia, enlarged right paratracheal lymph node (1.2 cm), subcarinal lymph node (1.1 cm), scattered peripheral fine reticular opacities, bilateral traction bronchiectasis with mild patchy ground glass opacity and micronodules. Nonspecific Interstitial lung diseases (NSILD) diagnosed with fall in lung volume (54.6%). 19.3% for upper, 23.9% mid, and 11.4% lower lung zone. Elevated INR (1.2), PT (5.5) and low PTT (30.9) and 7.92 neutrophil, made it classical case of lung transplantation in 2022. Bilateral gynecomastia was over looked that might occurred due exposure of organic fumes of benzene and other chemicals engine oil, smoke of the burning fuel, and hobbies of hunting birds in desert could have cause this disturbance. Hence it might be concluded that in such cases gynecomastia must be the defining factor in diagnosis and treatment before initiating respiratory therapy.

**Keywords**: gynecomastia, lung disease, environment toxins, smoke fumes, benzene fumes

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## Introduction

Non-specific interstitial lung disease (NSILD) is a progressive disease with multiple options for etiology with multiple ambiguous prevalence [1, 2]. The incidence of NSILD is low in Middle East compared to European and American countries [3, 4], and diagnosis of NSILD is the function of radiological pattern of usual interstitial pneumonia comprising of patchy interstitial fibrosis with alternating normal lung tissue, influenced by heterogenic fibrosis characterized by scattered fibroblastic foci in circumstantial dense acellular collagen with or without chronic architectural changes in lung tissues also referred as honeycombing [5] with median survival range of 2-5 years from the time of diagnosis [6]. Multiple genes and pathways are associated with NSILD [7] and presents varied clinical state of disease.

Gynecomastia benign proliferation of male breast glandular tissue, usually, caused by increased estrogen and decreased testosterone, more common in boys and older men [8], with known reasons including obesity [9], new born babies [10], estrogen passes through placenta from mother to baby, puberty, adverse effects of anti-ulcer drugs, cannabis or anabolic steroids, misuse of alcohol [11, 12], kidney failure or liver disease [13] and Klinefelter syndrome [14]. Presently tamoxifen and surgery are the best treatment options available for gynecomastia, individual treatment regimens can be considered on clinical features of patients with higher risk of recurrence [15]. As of date, nothing is known about the association incidence and presentation of NSILD and gynecomastia. The present case report illustrates a typical presentation of a patient finally diagnosed with NSILD.

## Material and Methods

### Case Presentation

The present work is a descriptive study of patient 55 -year old already diagnosed with ILD (specific or non-specific?). Standard clinical information, including symptoms, smoking history, medication use, environmental history, occupational history, family history, and physical findings. HRCT, pulmonary function tests, serological tests, bronchoalveolar lavage (BAL), transbronchial lung biopsy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or surgical lung biopsy were the part of suspicion of ILD. A multidisciplinary approach involving pulmonologists, radiologists and pathologists was implemented. The follow up was made for six years involving Chest X Ray, High-resolution computed tomography (HRCT), Multiaxial high-resolution CT, Surgical biopsy with General Lab test, Pulmonary function laboratory and NM Perfusion Quantitative Lung Scan to assess the prognosis of disease. Basic feature of this study was that the patient was working in the industrial division with exposure to organic fumes from the combustion of gasoline. Petrochemical industry is one of the largest industries of Saudi Arabia with a major economy driving from these sources of energy [16]. In the present study the patient was exposed to organic fumes of benzene and other chemicals, engine oil, smoke of the burn fuel, and his hobbies were hunting birds in the desert. His radioallergosorbent test (RAST) inhalation panel was positive for dog dander, English plantain, Parientaria officinalis and Dermatophagoides pteronyssinus, cat epithelium and Bermuda grass, Timothy grass, Penicillium notatum and Alternaria tenuis, birch and Japanese cedar with high IgE was positive at 547 with no eosinophilia and stable complete blood count (CBC) and LFT. The regular pulmonary function test (PFT) and CT scan of the chest showed regular progression of lung disease at lower lobe without any specific interpretation (Figs 1-3).

## Results

Initial diagnosis of 2014 represents the bilateral gynecomastia, with normal lungs volume, enlarged right paratracheal lymph node measuring about 1.2 cm and subcarinal lymph node measuring about 1.1 cm in short axis. No hilar or axillary lymph nodes. Scattered peripheral fine reticular opacities associated with bilateral traction bronchiectasis with mild patchy ground glass opacity and micro nodules more appreciated at the upper lung. No honeycombing. No cystic changes. No pleural effusion or pericardial effusion (Figs 1 and 4).

November 2016, HRCT demonstrated the presence of subpleural reticulations associated with traction bronchiectasis and tiny subpleural cysts. No frank honeycombing. There was extension to the central lung and the lower lobes (Fig. 2). The lungs were involved predominantly at the lower lobes with progression of the disease in the lower lungs posteriorly. Sub centimetric and mildly enlarged mediastinal lymph nodes likely reactive, with fissural nodularity on the left lung. The main pulmonary artery measures 2.7 cm in maximum dimension. No pleural or pericardial effusion. Decrease lung volume was noted in 2018 and 2019, with disease with patchy opacities and reticulations in both lungs (Figs 3 and 4). The general lab results of biochemical parameters indicated increase in WBC, Monocytes, Neutrophils and Globulin ($13.3 \times 10^9$/L), ($1.10 \times 10^9$/L), ($7.90\times 10^9$/L) and (41 g/dL.) respectively with high Hb (16.2 g/dl). NM Perfusion Quantitative Lung Scan results demonstrate. Both lungs show heterogeneous tracer distribution with no segmental or subsegmental perfusion defects in perfusion study. The left lung contributes 54.6% of the total lung volume distributed as 19.3% for upper lung zone, 23.9% for mid lung zone, and 11.4% for the lower lung zone. The right lung contributes 45.3% of the total lung perfusion distributed as 12% for

upper lung zone, 25.4% for mid lung zone, and 7.9 % for the lower lung zone. The lab results indicate low albumin, $Cl^-$, Creatinine and high $CO_2$, Globulin and total protein with high INR, prothrombin time test (PT) and low partial thromboplastin time (PTT) at 1.2. 15.5 and 31.1 respectively in June 2022.

## Discussion

NSILD are heterogenous group of disorder with no specific etiology, clinical presentation, with or without biochemical alteration in the patient's serum parameters [17]. Epidemiological studies on prevalence of lung diseases in middle east [18] especially in Saudi Arabia a 5th major cause of death in kingdom according to Centre for disease control and prevention [19] is reported. NSILD, is distinguished from specific lung diseases in terms of treatment pattern , better diagnosis and favorable response [20]. Among all lung disease NSILD range from 14-36% of these cases [21, 22].

The present study is an attempt to use the modern techniques along with associated parameters with NSILD in a single case control study that took a long

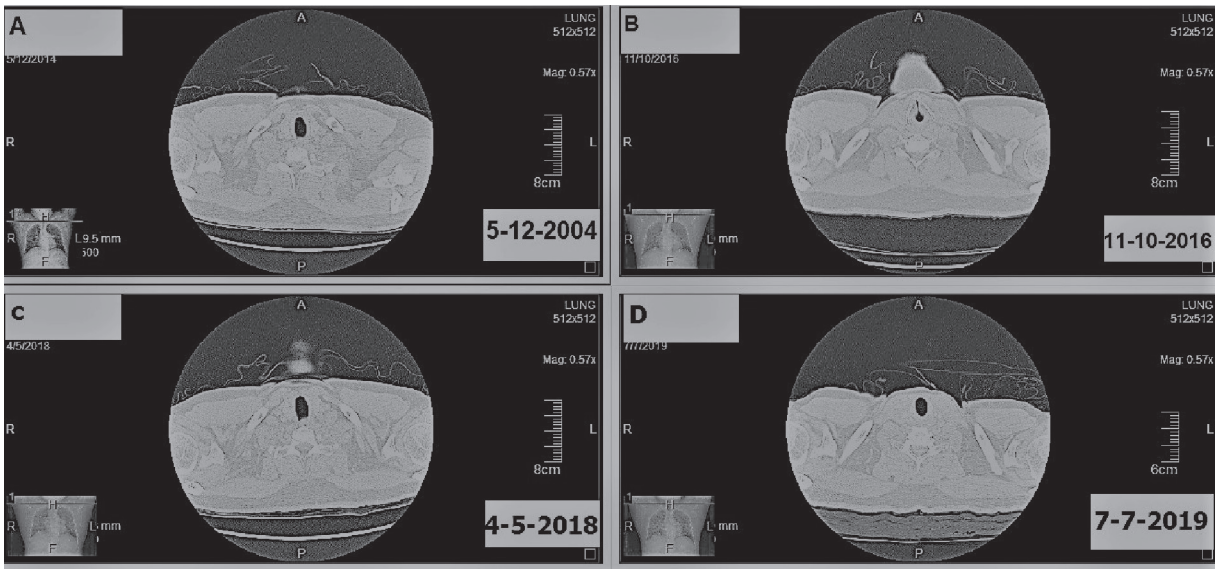


Fig. 1. Upper Section of Lungs- Comparative Evaluation of radiological pattern over time, demonstrating various changes presence of subpleural reticulations associated with traction bronchiectasis and tiny subpleural cysts from various position of lungs through HRCT over years of disease presentation (A-2014) (B-2016) (C-2018) (D-2019).

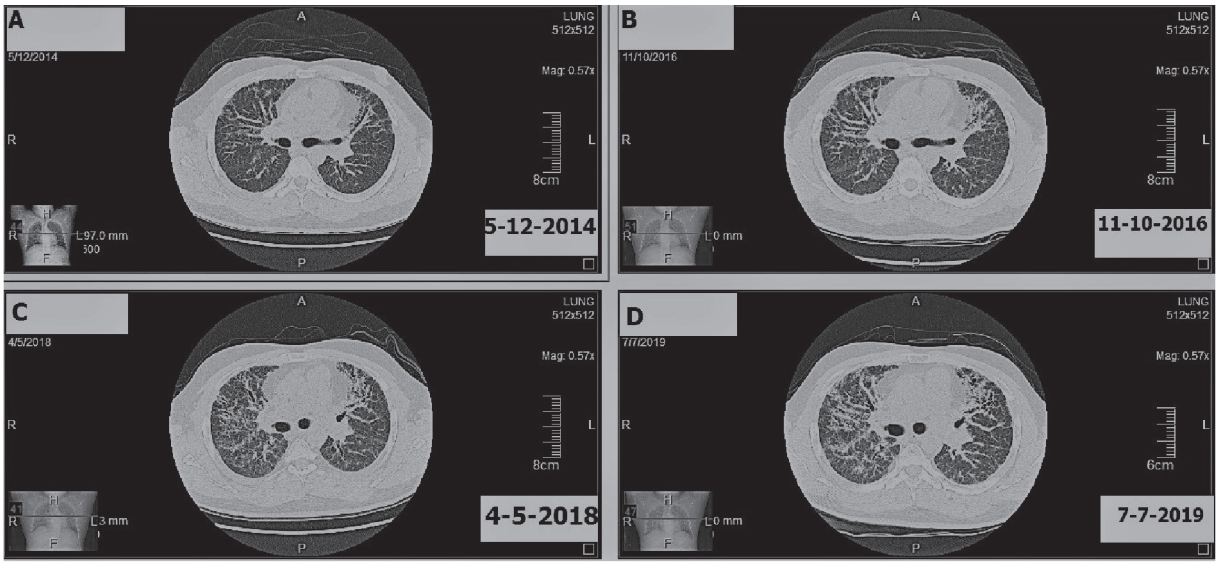


Fig. 2. Middle Section of Lungs- Comparative Evaluation of radiological pattern over time, demonstrating various changes presence of subpleural reticulations associated with traction bronchiectasis and tiny subpleural cysts from various position of lungs through HRCT over years of disease presentation (A-2014) (B-2016) (C-2018) (D-2019).

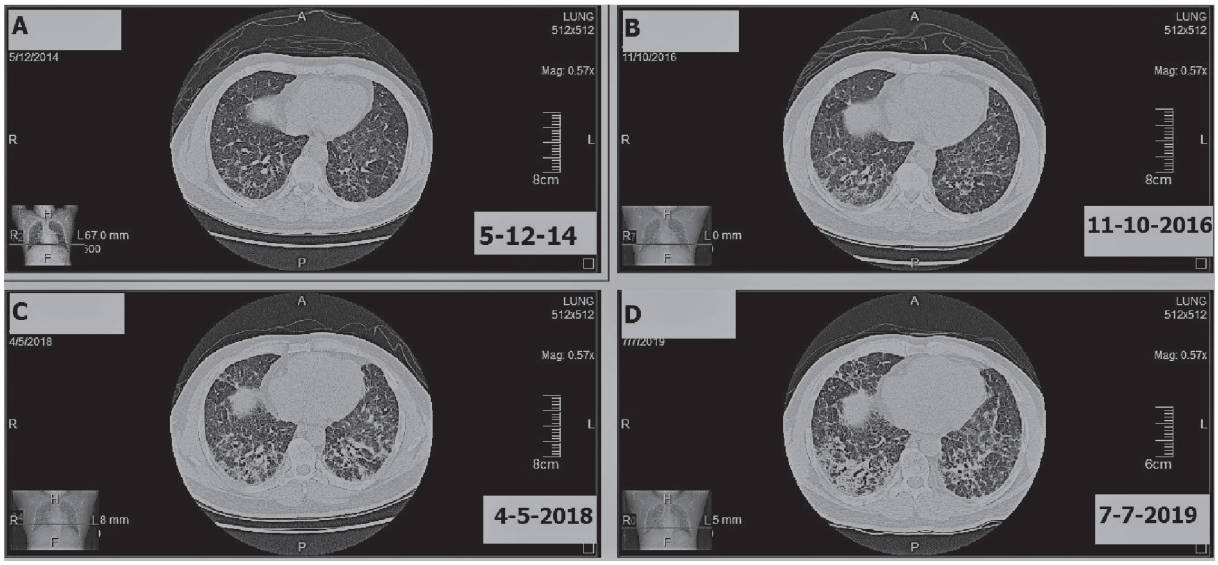


Fig. 3. Lower Section of Lungs- Comparative Evaluation of radiological pattern over time, demonstrating various changes presence of subpleural reticulations associated with traction bronchiectasis and tiny subpleural cysts from various position of lungs through HRCT over years of disease presentation (A-2014) (B-2016) (C-2018) (D-2019).

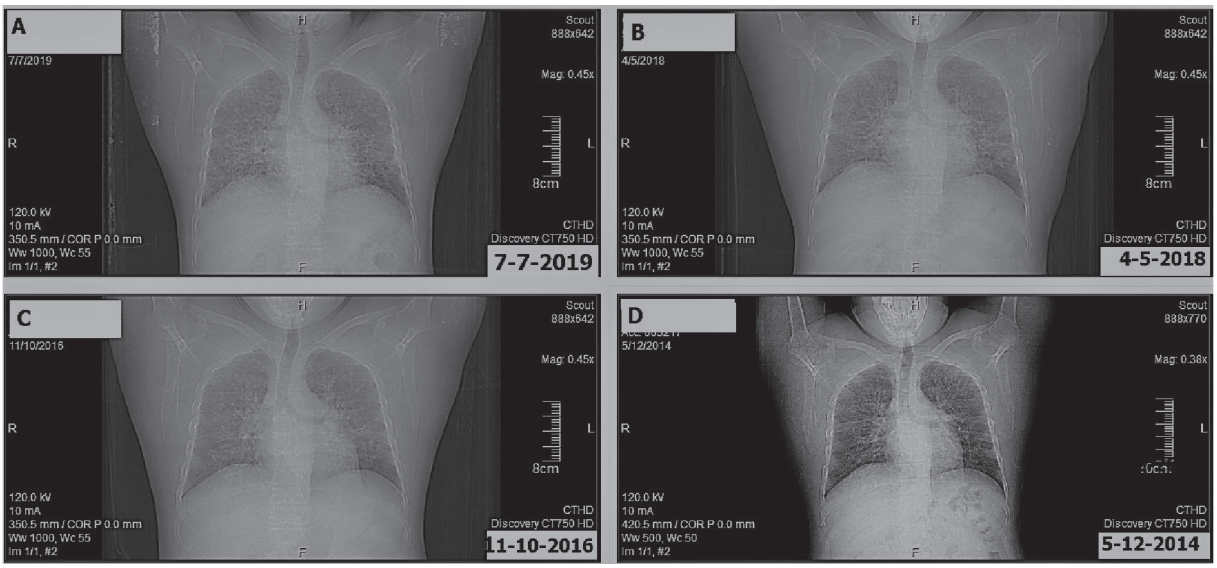


Fig. 4. Comparative Evaluation of Scout radiological pattern over time, demonstrating multiple ground glass opacity and consolidation in various lobes over the time. (A-2019) (B-2018) (C-2016) (D-2014).

time to reach to a conclusion. Petrochemical is one of the largest industry of Saudi Arabia with major economy driving from these sources of energy [23], where a case is presented for this study. The risk of exposure to such chemicals are always high in a recent study benzene exposure have demonstrated significant negative health outcome on people working on gas station in Makkah region of Saudi Arabia through determining by blood biochemical parameters, stating that exposure of benzene to such workers have decreases the albumin, glucose, total proteins and hemoglobin level ($p<0.0001$), with increase in cholesterol ($p<0.01$). when compared to normal individuals [16], with no significant lowering of glucose, total proteins and hemoglobin level. The adverse effects are results of benzene metabolites generated in liver via lung inhalation from phenolic category affecting bone marrow [24-26]. The presence of benzene and its metabolites may be associated with the high level of cholesterol, but due to deficiencies in circulating angiogenic cells [27].

Existing studies reported elevated creatinine levels in such cases however our results totally counter it [28, 29]. The low blood creatinine continuously for 5 months, may be attributed to changes in the muscle mass causing muscle atrophy [30, 31] along, with duration of exposure, chemical concentration of the fumes and other working

conditions may have played an important role in low creatinine in the given patient.

Studies have demonstrated that fall or low hemoglobin level is observed in the population ($p>0.0001$) working in exposed environment of gasoline as compared to normal individual [32, 33], resulting shorter life span of red blood cell with reduction in production heme by benzene metabolites or other free radicals including aliphatic hydrocarbon elements. Present study does not support this hypothesis, the Hb level was above 14.9 to 16.2 g/dl throughout the disease, low level of oxygen in blood over a long period of time cause bone marrow cell to increase the production RBC in order maintain the normal supply of oxygen to essential body organs [34, 35]. Exposure to benzene is associated with alteration in blood glucose leading reduction in liver and muscle glycogen [36]. These reports totally contraindicated with our results, with no alteration in blood glucose level in entire period of disease due to normal hemoglobin level during the entire course of treatment.

Serum total protein represents the amount of albumin, globulin and other associated proteins in the blood, representing the health and growth condition and are important markers for various metabolic disorders that might have leaked from various tissues as a result of tissue or organ damage [37]. Earlier studies have demonstrated the decrease in total serum protein in workers exposed to benzene approximately to 20% from normal value making it highly significant factor ($p>0.0001$) among such workers [38]. Our results do not support previous results. Elevated levels of serum proteins were observed in the patient reaching a maximum of 91.6 g/L, indicating a severe damage to the internal organ may be the lungs. Such alteration set new pathway for onset of disease associated with genetic variants in a particular population [39]. Further it is observed that blood serum proteins have changed throughout human lifespan [40], particularly in the old age. Our results can state that there is cross talk between the exposure of organic solvent, genetic variants and serum proteins.

The elevated level of globulin indicates alteration in the immune system [41]. Our results are in accordance with study by Drew et al [42], demonstrating a significant alteration of immune response due to smoke or air pollution . The smoke or the fumes generated or person exposed may have generated high number of free radicals stimulated the cells through variety of signals including Toll like receptors, reactive oxygen species, sensing pathway and poly aromatic hydrocarbon sensing pathways, activating proinflammatory intracellular signaling cascade such as Nuclear factor kappa B (NFκB) and MAPK pathway.

Alteration in the concentration of $CO_2$ in blood is a biomarker for health problems associated with change in acid base balance leading to lung or kidney disorders ranging from lung disease, Cushing syndrome, kidney failure and metabolic alkalosis [43]. In the present case the $CO_2$ was constantly high indicating lung disease complications range almost double (39 to 41 mmol/L) the normal range (22-31 mmol/L). Elevated $CO_2$ concentration (hypercapnia), decreases $O_2$ consumption and ATP production [44] and can impair cell proliferation in fibroblast and alveolar epithelial cells , interfering with expression of isocitrate dehydrogenase and α ketoglutarate, in the patient [45].

Multiple radiological diagnostic examination pattern especially HRCT have key role in diagnosis and follow up of NSILD [46], represented by alteration in lung parenchyma and its particular characteristics in distribution within lung tissues [47] with honeycombing, reticular opacity, emphysema, ground glass opacity, consolidation and normal lungs are considered as few radiological pattern to define the regional disease state [48, 49].

Fibrotic and non-fibrotic tissue is a function and source of antigen exposure and multidisciplinary integration of radiological and pathological findings can evaluate the NSILD triggered by environment antigens including organic (fungi, bacteria, proteins and animal enzymes) and non-organic (chemicals and metals) antigens [50]. Evaluation of antigen exposure is associated with patient occupation, hobbies, geographical location and regional cultural hobbits [51].

Subpleural reticulations suggested by HRCT associated with traction bronchiectasis [52] and tiny subpleural cysts [53] were observed, extending to the central lung and the lower lobes, with progression of the disease in the lower lungs posteriorly with fissural nodularity [54] on the left lung, indication the stability of disease till 2016. The surgical pathology(July 2017) after biopsy stated the development of NISP with focal lung swelling along with bilateral reticulonodular shadowing and ground glass densities [55] with fall in lung volume with further constant fall in lung volume till December 2021 and in December left lung volume fall to 54.6% of the total lung volume distributed as 19.3% for upper lung zone, 23.9% for mid lung zone, and 11.4% for the lower lung zone. The right lung contributes 45.3% of the total lung perfusion distributed as 12% for upper lung zone, 25.4% for mid lung zone, and 7.9 % for the lower lung zone with high INR OF 1.2, PT 15.5, PTT low as 30.1 and 7.92 neutrophil, making it classical case of lung transplantation in 2022.

However, in this classical case bilateral gynecomastia a benign enlargement of the male breast (usually bilateral but sometimes unilateral) resulting from a proliferation of the glandular component of the breast [11] was over looked. Not much has been written about the correlation of gynecomastia and lung disease, but reports are available that suggest its correlation with multiple cancers including lung [56], bladder [57] and pelvis cancer [58]. There were signs of any tumour or cancer in the given case but alteration neutrophil, lung architecture, high IgE, with elevated $CO_2$ level, altered total protein content, low creatinine level and low chloride ions. The disturbance in hormones like

estrogen and testosterone can cause gynecomastia from increased ratio of estrogen and testosterone [59]. The patient exposed to organic fumes of benzene and other chemicals, engine oil, smoke of the burn fuel [60], and hobbies of hunting birds in the desert could have caused this disturbance.

The disturbance of hormones can be linked NSILD [61]. Altered level of estrogen is associated with lung disease [62] and low level of testosterone is associated with increased COVID-19 infection [63] and same factor responsible for patient condition where altered level of hormones have created a condition of gynecomastia was responsible for NSILD. Hence it might be concluded that in such cases gynecomastia must be the defining and treatment factor before initiating respiratory therapy. Sex hormones regulates lung development, physiology, and pathology [64], idiopathic pulmonary fibrosis more prevalent in males than in females [65], making it more controversial, lymphangioleiomyomatosis and collagen vascular disease associated interstitial lung disease affect young to middle age women, supporting the role of estrogen and its signaling mechanism in both in disease development and progression [66], underlining the importance to sex hormones in prevention and treatment chronic lung disease [67] associated with similar cases of gynecomastia.

## Conclusion

Gynecomastia and lung disease were never corelated but reports are available that suggest gynecomastia is associated with multiple cancer including lung, bladder and pelvis cancer. No signs of tumour but altered alteration in neutrophil, lung architect, high IgE, with elevated $CO_2$ level, altered total protein content, low creatinine level and low chloride ions indicated alteration may be due to disturbance of hormones like estrogen and testosterone causing gynecomastia from increase ration of estrogen and testosterone from the exposure of organic fumes of benzene and other chemicals engine oil, smoke of the burn fuel, and hobbies of hunting birds in desert could have cause this disturbance. Hence it might be concluded that in such cases gynecomastia must be the defining and treatment factor before initiating other respiratory therapy.

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## Conflict of Interests

The authors declare no conflicts of interest.

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