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Hormonal harmony disrupted: hypothyroidism and diabetes mellitus in interstitial lung disease. An observational study

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Abstract

Interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) are chronic respiratory diseases that affect the lungs and airways. ILD encompasses approximately 200 different conditions with known and unknown causes. Various comorbidities, such as cardiovascular, psychological, obstructive sleep apnea, and gastrointestinal disorders, are often associated with them. However, little is known about the relationship and prevalence of hypothyroidism and diabetes mellitus (DM) in ILD and COPD. Therefore, understanding these connections is crucial for proper treatment. This cross-sectional, prospective observational study was conducted at a tertiary care hospital in North India. After obtaining informed consent, we consecutively enrolled 100 patients with ILD and 100 patients with COPD who reported to the Respiratory Medicine Outpatient Department. We collected demographic, clinical, and medical data from the patients and conducted appropriate statistical analysis to determine the prevalence of hypothyroidism and DM in patients with ILD. ILD patients exhibit a significantly higher prevalence of hypothyroidism (24% *versus* 4%) and DM (24% *versus* 4%) compared to those with COPD ($p<0.05$). Additionally, the study showed that ILD patients also had a significantly higher prevalence of self-reported gastroesophageal reflux disease (30%), had a higher body mass index, and consulted a pulmonologist earlier than COPD patients after the onset of symptoms ($p<0.05$). Therefore, it is important to screen for hypothyroidism and DM in ILD patients due to their high prevalence and potential impact on disease progression and management. Additionally, evidence suggests a bidirectional relationship between these conditions, making it essential to screen patients with hypothyroidism and DM for ILD if there is any suspicion. These screening measures could contribute to the early detection and management of these comorbidities, thereby improving the overall outcome for ILD patients.

Key words: ILD, COPD, hypothyroidism, diabetes mellitus, GERD.

Introduction

Chronic Respiratory Disease (CRD) is a group of lung and airway conditions that includes Chronic Obstructive Pulmonary Disease (COPD), Asthma, Allergic Bronchopulmonary Aspergillosis (ABPA), Interstitial Lung Disease (ILD), Occupational Lung Diseases, and more. It is the third leading cause of death worldwide in 2019 and is associated with a significant burden and cost [1,2]. A proper understanding of CRD and its associated co-morbidities is essential for their management and treatment. COPD and ILD are complex respiratory conditions with overlapping and distinct characteristics that various comorbidities can worsen. COPD is a progressive lung disease primarily characterized by chronic bronchitis and emphysema, leading to airflow limitation and respiratory symptoms [3]. Interstitial Lung Disease refers to a group of diverse lung conditions that cause gradual scarring and fibrosis of the lung's parenchyma [4]. Over 200 entities fall under this category, leading to dyspnoea, reduced life expectancy, and a gradual decline in the ability to exercise [5]. The availability of high-resolution computed tomography (HRCT) scans of the thorax has increased the recognition of ILD [6]. Interstitial lung diseases can be caused by exposure to some substances, radiation, medication side effects, and connective tissue diseases (CTD). Idiopathic pulmonary fibrosis (IPF), pulmonary sarcoidosis, cryptogenic organizing pneumonia, and eosinophilic pneumonia are examples of ILD cases with unknown causes. Connective tissue diseases associated with ILD, which include rheumatoid-associated ILD (RA-ILD) and systemic sclerosis-associated ILD (Ssc-ILD), is a group of disorders characterized by inflammation and scarring of the lungs that occur alongside CTD. The treatment involves managing the underlying CTD and addressing ILD symptoms, often requiring immunosuppressive therapy. However, ILD and COPD patients often suffer from concurrent diseases such as pulmonary hypertension (PH), systemic hypertension (HTN), diabetes mellitus (DM), hypothyroidism, gastroesophageal reflux disease (GERD), coronary artery disease (CAD), obstructive sleep apnea (OSA), osteoporosis, and mental health comorbidities. It's crucial to manage comorbidities to enhance the well-being and prognosis of patients as they have a significant impact on clinical outcomes. Therefore, understanding the complex interplay of these comorbidities in ILD and COPD is vital for providing comprehensive patient care. The bidirectional relationship between ILD and various comorbidities necessitates a multidisciplinary approach that includes pulmonologists, cardiologists, rheumatologists, endocrinologists, and other health professionals. However, literature is scarce on the possible

association of ILD with hypothyroidism and DM. To address this unmet need, we investigated the relationship between ILD with hypothyroidism and DM.

Materials and Methods

Study design and sample size

This cross-sectional, prospective observational study was conducted over one year at a tertiary care hospital in North India with the approval of the institutional review board. After obtaining informed consent, 100 patients with ILD and 100 patients with COPD, both newly diagnosed and under treatment, were consecutively enrolled in the study from respiratory medicine outpatient department. ILD was diagnosed using a multidisciplinary approach, including clinical, radiological, and pathological features [7,8]. COPD was diagnosed based on the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease [3].

Exclusion criteria: The study excluded patients who were under 18 years of age, refused to provide their informed consent, were not competent enough to complete the questionnaires, had a psychiatric illness before being diagnosed with ILD/COPD, showed apparent memory deficits on clinical assessment, had organicity (like delirium or dementia) or malignancy, or were critically ill.

Methodology

Then all the patients with ILD and COPD underwent a thorough clinical evaluation, including arterial blood gas (ABG) analysis, complete blood count, renal function tests, liver function tests, thyroid function tests (TSH, fT3, fT4), fasting blood glucose, postprandial blood glucose, Six-minute walk test (6-MWT), spirometry and dual-energy x-ray absorptiometry (DEXA) scan. The diagnosis of hypothyroidism and DM was made as per the established guidelines [9,10]. The diagnosis of self-reported GERD was made by using the symptoms-based (heartburn, regurgitation, epigastric pain, nausea, disturbed sleep, and need for additional medications for these symptoms) six-item GERDQ questionnaire [11]. Anemia was diagnosed with hemoglobin levels less than 13 grams per deciliter (< 13gm/dL) in adult males and less than 12 gm/dL in adult females (non-pregnant and non-lactating) as per the established criteria by the World Health Organization [12]. The cardiologist diagnosed pulmonary hypertension (PH) using a transthoracic echocardiogram (TTE). This diagnosis of PH was based on a combination of factors, including tricuspid regurgitant velocity, right ventricular size, interventricular septal function, fluctuations in the diameter of the inferior vena cava during the respiratory cycle,

systolic right atrial area, the pattern of systolic flow velocity, early diastolic pulmonary regurgitant velocity, and the diameter of the pulmonary artery [13]. The diagnosis of osteoporosis was made according to the World Health Organization guidelines, where a T-score greater than 2.5 is used to diagnose osteoporosis [14]. Psychological illness was diagnosed based on the score of the self-administered hospital anxiety and depression scale (HADS) [15]. All the patients were given all the necessary information before conducting the tests.

Statistical analysis

The statistical analysis was done using the computer-based Statistical Package for Social Sciences, version 22.0 (SPSS 22.0). Quantitative variables were summarized as mean ± SD or median (interquartile range) and qualitative variables as frequency/percentage. Unpaired student *t*-test and Chi-square test were used, as appropriate, to compare continuous and nominal variables between ILD and COPD patients. A *p-value* of <0.05, was considered statistically significant with a confidence interval of 95%.

Results

The mean age of the ILD cohort (n=100) was 56.22 (SD 9.05) years (range 36-76 years) with a predominance of males (*n* = 56, 56%), and the mean duration of ILD symptoms was 12.72 (SD 10.16) months (range 2- 48 months). However, at presentation, COPD patients (n=100) were older than patients with ILD (63.48 vs 56.22 years; p = 0.009) and had more duration of symptoms before consultation with a pulmonologist as compared to ILD (30.26 vs 12.72 months; p < 0.001) respectively. Patients with ILD also had lesser exposure to noxious matters, higher BMI, a higher percentage (%) predicted FEV1 and a lower %predicted FVC as compared to COPD patients (Table 1). In the ILD cohort, only 22 (22%) patients were above 65 years of age, and 18 (82%) patients of this subgroup were diagnosed with IPF.

The study cohort had various comorbidities as depicted in Table 2. Fifty-eight (58%) patients of ILD and 52 (52%) patients of COPD had at least one comorbidity. The most common comorbidities observed in ILD patients were GERD- 30% (n= 30, male- 16, female- 14), HTN- 28% (n= 28, male- 16, female- 12), type 2 DM- 24% (n= 24, male- 14, female- 10), and hypothyroidism- 24% (n= 24, male- 18, female- 6). Among the 24 patients who were diagnosed with hypothyroidism in the ILD cohort, six patients (25%) exhibited the presence of thyroid peroxidase antibody (anti-TPO). Out of these six, three patients were found to have CTD-ILD, two patients were diagnosed with sarcoidosis, and the remaining one was found to have UIP

pattern on the HRCT of the chest. Other comorbidities observed in patients with ILD were osteoporosis- 22% (n= 22, male- 9, female- 13), followed by psychological illness- 18% (n= 18, male- 10, female- 8), pulmonary hypertension- 16% (n= 16, male- 9, female- 7), dyslipidemia- 14% (n= 14, male- 8, female- 6), CAD (8%), anemia (6%) and polycythemia (4%). Out of 100 (70 newly diagnosed and 30 under treatment) patients with ILD, only seven (7%) patients were on oral steroids, and one of these seven patients was diagnosed with type 2 DM.

In patients with COPD, the most common comorbidities were HTN- 20% (n= 20, male-12, female- 8), followed by osteoporosis- 16% (n= 16, male- 6, female- 10), psychological illness- 14% (n= 14, male- 7, female- 7), GERD- 12% (n= 12, male- 7, female- 5), pulmonary hypertension- 10% (n= 10, male- 6, female- 4), dyslipidemia- 10% (n= 10, male- 6, female- 4) polycythemia- 8% (n= 8, male-5, female- 3), type 2 DM- 4% (n= 4, male- 1, female- 3), hypothyroidism (4%, n= 4, male- 1, female- 3), CAD (4%), and anemia (3%). The prevalence of hypothyroidism, type 2 DM, and GERD was significantly higher in patients with ILD than in patients with COPD (Table 2).

In Figure 1, a comparison of different comorbidities in patients with ILD and COPD is presented. The distribution of sub-categories of ILD is shown in Figure 2, where the highest proportion is made up of IPF- 26% (n= 26, male- 22, female- 4) and sarcoidosis- 26% (n=26, male- 12, female- 14), followed by RA-ILD- 22% (n= 22, male- 10, female 12), hypersensitivity pneumonitis- 18% (n=18, male- 11, female- 7), Ssc-ILD- 4% (n= 4, female-4) and NSIP- 4% (n= 4, male- 1, female- 3). Figure 3 illustrates the distribution of hypothyroidism, type 2 DM, and GERD in the sub-categories of ILD. About 46% (n= 12) of patients with CTD-ILD had hypothyroidism followed by sarcoidosis (n= 6, 23%) and IPF (n= 6, 23%) (Figure 3). Almost 90% of diabetic patients in the ILD cohort belong to sarcoidosis (n= 8), CTD-ILD (n= 8), and IPF (n= 6) (Figure 3). Similarly, about 80% (n=24) of GERD patients in the ILD cohort belong to sarcoidosis (n=7), IPF (n=8), and CTD-ILD (n=9) groups (Figure 3).

Discussion

The present study revealed that the average age of the ILD patients was significantly lower (56.22 vs 63.48; $p = 0.009$) than COPD patients (Table 1). This could be because 70% of the ILD patients in the study cohort had non-IPF ILD (Figure 2), which generally affects middle-aged adults, and this finding is consistent with the previous studies [8,16]. The Patients with ILD consulted a pulmonologist earlier than patients with COPD after the onset of symptoms (12.72 vs 30.26; $p < 0.001$, Table 1). This may be due to the more severe symptoms experienced by

ILD patients, such as intractable coughing, which is difficult to manage by a general physician. Patients with ILD had a significantly higher Body Mass Index (BMI) of 25.11 compared to COPD patients with a BMI of 23.28 (p=0.006). The higher weight of ILD patients could be attributed to the presence of hypothyroidism and type 2 diabetes mellitus [17,18]. Patients with ILD also had a higher %FEV1 but a lower %FVC than COPD patients (Table 1). This difference in %FEV1 and %FVC could be because COPD patients tend to have preserved or higher FVC and experience more decline in FEV1. Interstitial lung disease and COPD are both chronic respiratory disorders that can lead to various comorbidities, resulting in significant morbidity and mortality in affected patients [19,20]. The present study showed a significantly higher prevalence of hypothyroidism, type 2 DM, and self-reported GERD in ILD patients as compared to COPD patients ($p < 0.05$, Table 2). However, data are scarce on the possible association of ILD with hypothyroidism and DM [21,22].

In our study, hypothyroidism was found in 24% of ILD patients, which was significantly higher than the hypothyroidism in COPD patients 4% (p= 0.004). Although, it is not clear how ILD may cause hypothyroidism. However, it is possible that chronic inflammation in ILD can influence the function of the thyroid gland, through its impact on the hypothalamic-pituitary-thyroid axis leading to hypothyroidism. This hypothesis is supported by a case series of two patients who suggested a link between hypothyroidism and radiological ILD, which improved with thyroxine replacement therapy for hypothyroidism and returned to a euthyroid state [23]. Conversely, in a few studies, the induction of a hypothyroid state in mice appears to prevent pulmonary fibrosis associated with systemic sclerosis and accelerate the recovery of liver fibrosis, raising doubt that hypothyroidism itself could contribute to IPF onset or progression [24,25]. Another possible link between hypothyroidism and ILD may be immune dysregulation in ILD, this is supported by the expression of several genes including *CTLA-4*, *ICOS*, and *CD28* in patients with ILD [26]. Additionally, the relationship between ILD and hypothyroidism is complex and multi-faceted. Hypothyroidism weakens respiratory muscles, reduces lung function, and affects the immune system, leading to the progression of lung damage. Therefore, it is important to regularly check the thyroid functions in all patients with ILD, and patients with hypothyroidism should be screened for ILD if there is any suspicion.

In the present study, patients with ILD had a significantly higher prevalence of type 2 DM compared to those with COPD (24% vs 4%, p= 0.004, as shown in Table 2). This finding corroborates previous studies that have also reported a higher incidence of DM in patients with ILD [22,27]. The etiology of such a correlation might be attributed to the impact of ILD on

glucose processing and blood sugar regulation. The chronic inflammation and fibrotic alterations in the lung tissue may lead to systemic inflammation, insulin resistance, and disruption of glucose homeostasis. Furthermore, the hypoxia associated with ILD can exacerbate insulin resistance, in patients with coexisting DM. Studies from around the globe have reported a 20% to 32% prevalence of ILD in DM patients due to diabetic-related pneumopathy, also highlighting a bidirectional relationship between these two conditions [28,29]. However, it is important to note that international guidelines on ILD and DM, do not mention either DM as a risk factor for ILD, or ILD as a risk factor for DM. These are two separate medical conditions, but they can occur together and affect each other's progression and management. Thus, it is crucial to comprehend the connection between ILD and DM to provide comprehensive care to patients affected by these conditions. While the underlying mechanisms of this association are not completely understood, chronic inflammation and alterations in the blood vessels associated with DM may contribute to the development or aggravation of pulmonary fibrosis [28,29]. Therefore, managing DM in patients with ILD requires coordination among medical professionals, including pulmonologists, endocrinologists, and other healthcare providers, with regular monitoring of blood glucose levels, and adjusting diabetes medication to avoid interactions with ILD therapies.

In the present study, the prevalence of self-reported gastroesophageal reflux disease (GERD) was also significantly higher in ILD patients compared to those with COPD (30% vs 12%, p=0.027, Table 2). It may be due to secondary progressive pulmonary fibrosis, which can cause negative pressure in the chest, distorting the mediastinal structures and weakening the lower esophageal sphincter. Alternatively, it could be due to more frequent involvement of the esophagus in CTD-ILD [30]. GERD and ILD share a relationship based on the microaspiration of gastric contents into the lungs. This process triggers inflammation and fibrotic responses. It is important to note that chronic microaspiration can worsen ILD and lead to a more rapid decline in lung function. Thus, healthcare providers need to recognize and manage GERD in ILD patients to improve their quality of life and reduce the burden on healthcare systems. Early diagnosis and customized treatment strategies can prevent further complications and improve overall health outcomes.

According to the present study, ILD patients were more likely to have several other health issues also, such as cardiovascular disorders, psychological disorders, osteoporosis, dyslipidemia, and anemia as compared to COPD patients (Table 2); however, this difference is not statistically significant. These comorbidities can worsen the prognosis and outcomes of ILD patients,

especially cardiovascular diseases such as pulmonary hypertension (PH), ischemic heart disease, and heart failure. The impaired gas exchange associated with ILD can exacerbate cardiac conditions, making it difficult to manage both systems. A coordinated approach between cardiologists and pulmonologists is essential for managing these conditions simultaneously. The chronic nature of ILD and COPD, combined with the daily functioning challenges, can significantly impact mental health. Consequently, incorporating psychosocial support into the overall management of ILD and COPD is essential to address the holistic well-being of patients. Additionally, ILD and COPD patients have an increased risk of developing osteoporosis due to common factors such as aging, chronic inflammation, and glucocorticoid use [31]. Therefore, managing bone health in these patients requires a careful balance between therapies for these diseases and strategies to prevent and treat osteoporosis. Dyslipidemia is closely associated with both ILD and COPD, although the exact nature of this relationship remains unclear. Managing lipids in this population requires a nuanced approach that considers the potential impact of medications on lung function. Hematological disorders such as anemia and polycythemia are also encountered in these patients. Chronic inflammation and hypoxia contribute to anemia, while chronic lung disease can lead to polycythemia as a compensatory response [32]. Addressing these hematological abnormalities necessitates a tailored approach that considers the underlying mechanisms in each case. Therefore, it is crucial to identify and manage these comorbidities in ILD and COPD patients to improve their overall well-being, and potentially slow lung function decline.

Conclusions

The co-occurrence of different comorbidities with ILD creates a challenging scenario. Therefore, whenever dealing with ILD patients, it's crucial to screen for these comorbidities, including hypothyroidism and DM as they have a significant impact on disease progression and management. It is also important that patients with hypothyroidism and DM should be screened for ILD if there is any suspicion, as there is evidence of a two-way relationship between these conditions. Ensuring that these screening measures are implemented could contribute to the early detection and management of these comorbidities, thereby improving the overall outcome for patients with ILD. However, it should be noted that neither the international guidelines on ILD nor diabetes/hypothyroidism mention diabetes/hypothyroidism as a risk factor for ILD, or vice versa, due to insufficient data. Therefore, further studies with larger sample sizes are needed to establish a clearer understanding of ILD with hypothyroidism and DM.

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Table 1. Association of baseline characteristics of ILD and COPD patients.

Characteristics		ILD (n= 100)	COPD (n= 100)	P-value
Age (years)	Mean	56.22	63.48	0.009*
	Median	58.60	64.16	
	SD	9.05	6.82	
Gender, Male (n/%)		56 (56%)	66 (66%)	0.305
Duration of Symptoms (Months)	Mean	12.72	30.26	0.0001*
	Median	6.10	12.80	
	SD	10.16	23.80	
Cough present (n/%)		76 (76%)	68 (68%)	0.373
Dyspnea (mMRC grade)	Mean	2.26	2.18	0.061
	Median	2.10	2.20	
	SD	1.20	1.12	
Exposure/Ever smokers (n/%)		70 (70%)	100 (100%)	0.0001*
Chullah (n/%)		34 (34%)	46 (46%)	0.221
Old PTB (n/%)		12 (12%)	04 (04%)	0.140
LTOT (n/%)		06 (06%)	18 (18%)	0.065
Systemic Steroid use		07 (07%)	03 (3%)	0.097
SaO2 (%)	Mean	94.72	93.16	0.093
	Median	96.0	94.40	
	SD	3.70	5.35	
BMI (kg/m^2)	Mean	25.11	23.28	0.006*
	Median	25.13	23.37	
	SD	3.40	3.14	
% predicted FEV1	Mean	69.34	60.98	0.003*
	Median	67.50	61.20	
	SD	15.20	12.20	
% predicted FVC	Mean	62.94	78.34	0.0001*
	Median	61.50	79.80	
	SD	15.11	12.46	
6-MWD (meters)	Mean	299.38	288.42	0.499
	Median	313.20	294.60	
	SD	100.11	54.84	

ILD, interstitial lung disease; COPD, chronic obstructive lung disease; n, cumber; %, percentage; M, male; F, female; mMRC, modified medical research scale; PTB, pulmonary tuberculosis; LTOT, long-term oxygen therapy; SaO2, arterial oxygen saturation; BMI, body mass index; kg/m^2, kilograms per square meter; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; 6-MWD, six-minute walk distance; *significant p value at a confidence interval of 95.

Table 2. Association of various comorbidities between ILD and COPD.

Comorbidities		ILD (n-100)	COPD (n-100)	P-value
Comorbidity (n/%)		58 (58%)	52 (52%)	0.546
Hypertension		28 (28%)	20 (20%)	0.349
Type 2 Diabetes mellitus		24 (24%)	04 (04%)	0.004*
Hypothyroidism (n= 24)	anti-TPO positive (n= 6)	24 (24%)	04 (04%)	0.004*
	anti-TPO negative (n= 18)			
CAD		08 (08%)	04 (04%)	0.401
GERD		30 (30%)	12 (12%)	0.027*
Pulmonary hypertension		16 (16%)	10 (10%)	0.372
Psychological illness		18 (18%)	14 (14%)	0.338
Osteoporosis		22 (22%)	16 (16%)	0.345
Dyslipidemia		14 (14%)	10 (10%)	0.349
Anemia		06 (06%)	03 (03%)	0.307
Polycythemia		04 (04%)	08 (08%)	0.169

ILD, interstitial lung disease; COPD, chronic obstructive lung disease; n, number; %, percentage; TPO, thyroid peroxidase antibody; CAD, coronary artery disease; GERD, gastro-esophageal regurgitation disease; *significant p value at a confidence interval of 95.

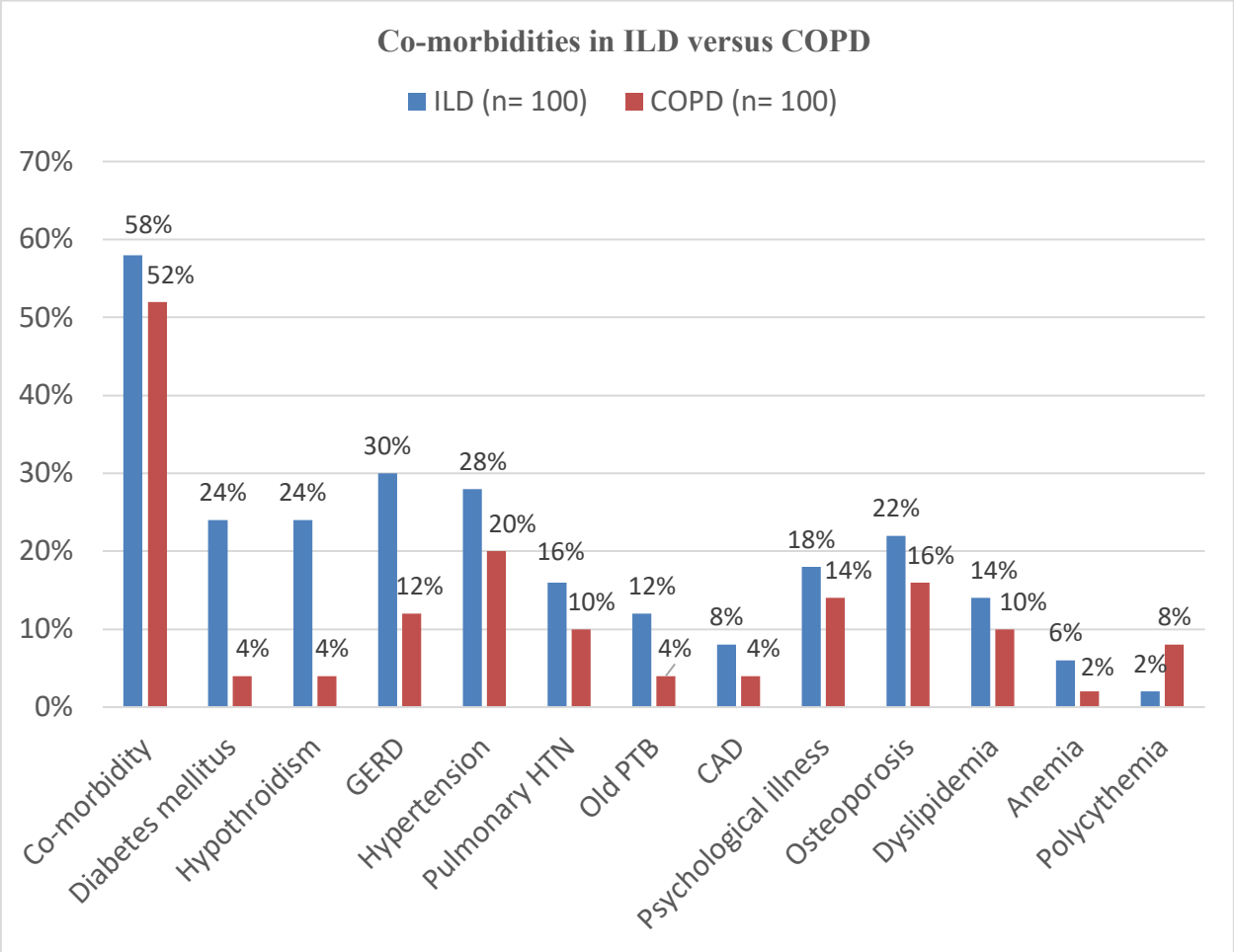

Figure 1. Bar diagram showing percentage (%) of different comorbidities in ILD and COPD patients.

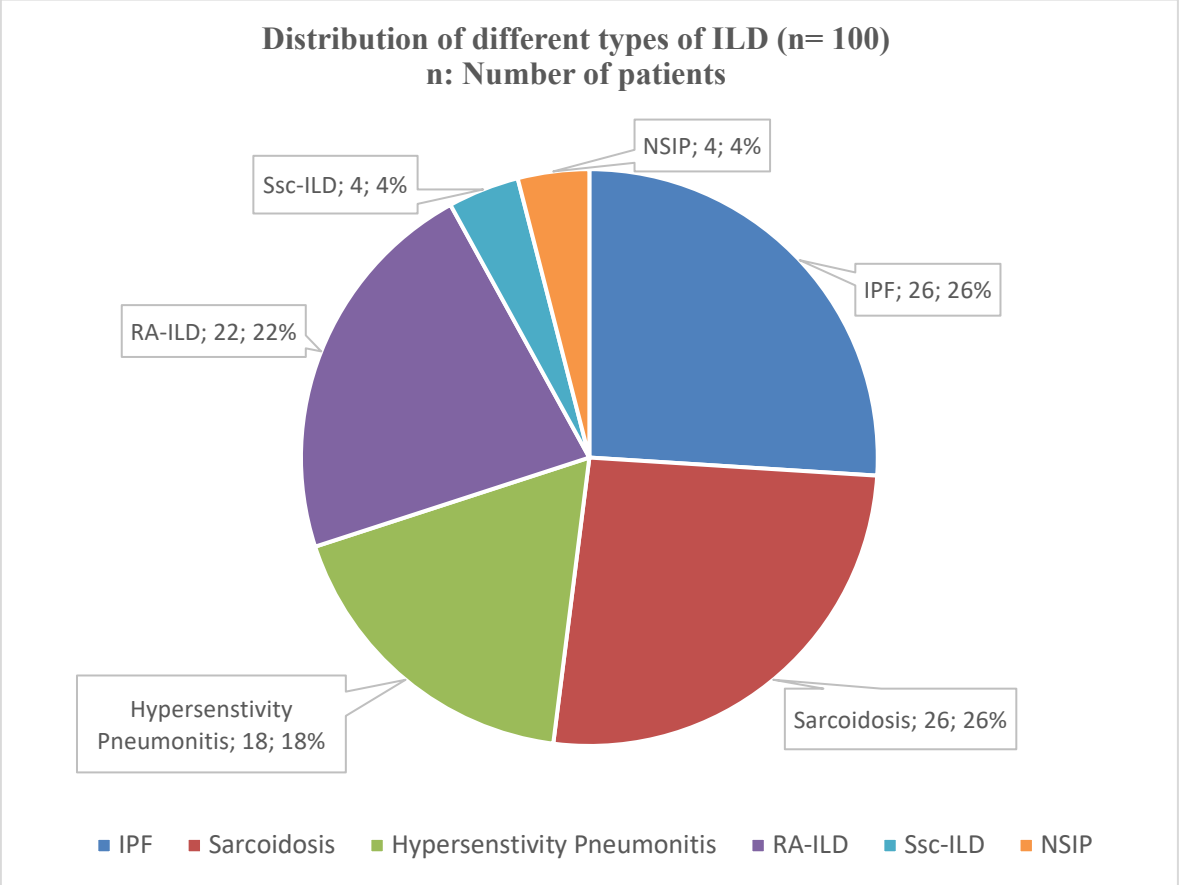

Figure 2. Pie chart showing the distribution of different types of ILDs

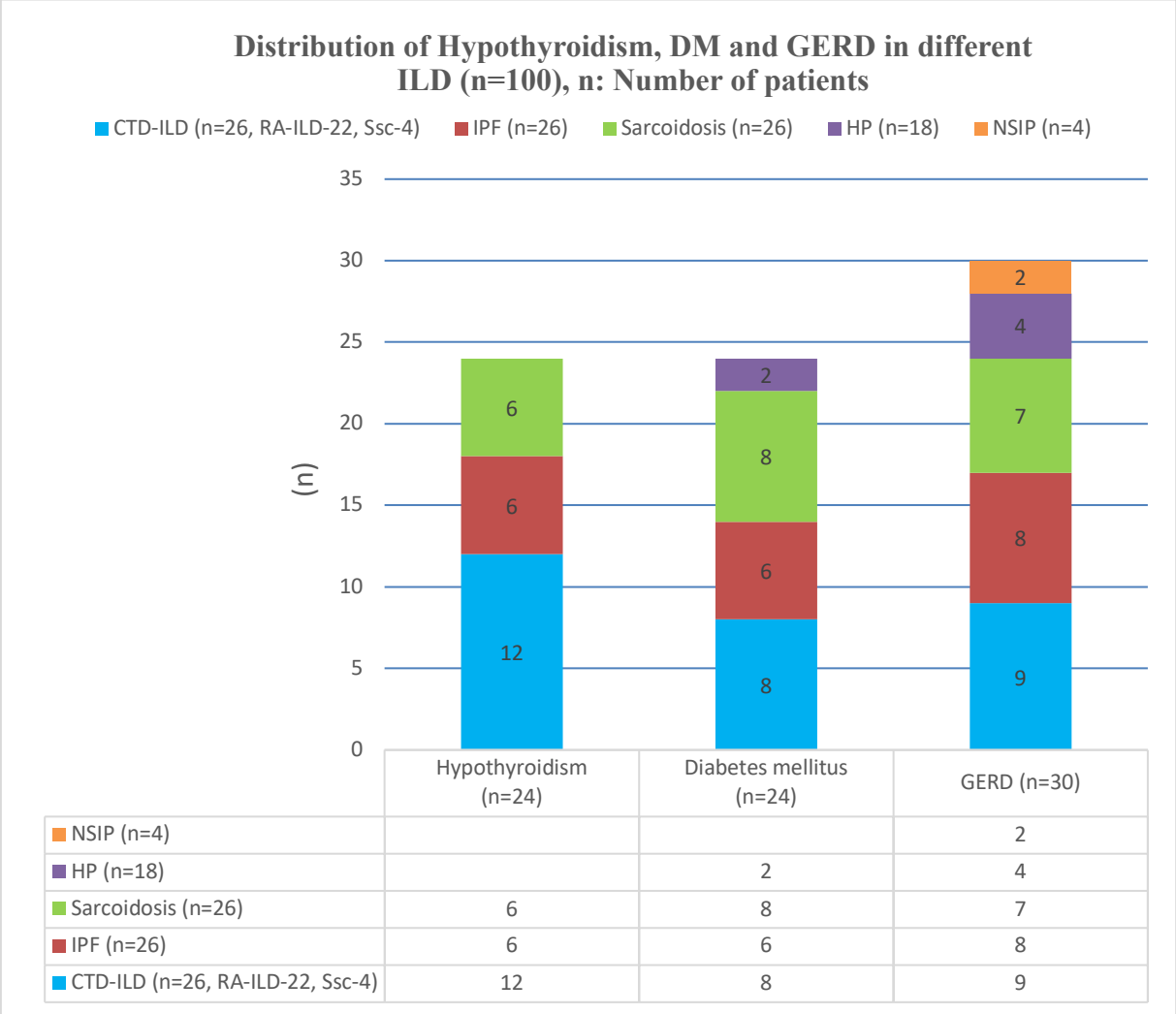

Figure 3. Bar diagram showing the distribution of hypothyroidism, DM, and GERD in different ILDs (CTD-ILD, IPF, Sarcoidosis, HP, NSIP).