Therapeutic Burden in Interstitial Lung Disease: Lessons to learn

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SUMMARY AT A GLANCE:

This is the first study providing insights into the significance of therapeutic complexity and polypharmacy in patients with ILD. Patients receiving systemic corticosteroids are at high risk of drug-disease interactions. Additional studies are needed to evaluate the impacts of therapeutic burden on clinical outcomes in patients with ILD.

ABSTRACT

Background and objective: Patients with interstitial lung disease (ILD) are often prescribed disease targeted and symptomatic therapies, both of which can cause significant treatment burden due to polypharmacy and drug-disease interactions. This study aimed to evaluate medication regimen complexity before and after introduction of ILD-specific therapies.

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Potential drug-disease interactions were evaluated for patients who were prescribed prednisolone.

Methods: In this study, 214 patients with ILD were assessed for demographic information, comorbidities and medication use. Medication lists were reviewed prior to and after the introduction of ILD-specific therapies. Complexity of treatment regimen was examined using the validated Medication Regimen Complexity Index (MRCI).

Results: Of the 214 patients, 75 had idiopathic pulmonary fibrosis (IPF) while the rest had inflammatory ILD (chronic hypersensitivity pneumonitis:45; connective tissue disease-related ILD:41). Polypharmacy was common at baseline (IPF:51%, inflammatory ILD:63%). Following introduction of ILD-specific therapies, median total MRCI scores significantly increased from 8(IQR=8,15) to 22.5(17.5,27.5) and 14.5(8.5,21) to 21.5(16,30) for IPF and inflammatory ILD groups, respectively ($p<0.0001$ for both). Complex dosing instructions contributed the most to total MRCI scores for ILD-specific therapies. Among patients receiving prednisolone (n=113), 88% had ≥1 comorbidity which may be impacted. Common comorbidities included gastrointestinal diseases(56%), obesity(37%), osteoporosis(24%) and diabetes mellitus(18%).

Conclusion: Polypharmacy and complex medication regimen are common in patients with ILD of different aetiologies. There is a high frequency of potential drug-disease interactions among patients who are prescribed systemic corticosteroids. These findings highlight the need for careful evaluation of the impact of therapeutic complexity and burden in patients with ILD.

Short title:
Therapeutic Burden in ILD

Keywords:
* Interstitial lung disease

* Idiopathic pulmonary fibrosis
* Medication regimen complexity
* Anti-fibrotics
* Immunosuppressants

List of abbreviations:
ILD: Interstitial lung disease
IPF: Idiopathic pulmonary fibrosis
IQR: Interquartile range
MRCI: Medication Regimen Complexity Index

INTRODUCTION

Interstitial lung diseases (ILD) belong to a heterogeneous group of chronic lung diseases characterised by parenchymal inflammation and fibrosis. In recent years, treatment approaches for ILD have evolved with improved understanding of the pathophysiology and natural history of these conditions. Anti-fibrotic agents, nintedanib and pirfenidone, now play a central role in the management of IPF.[1,2] Immunosuppressive agents are often used for treating patients with other ILD, including connective tissue disease-related ILD, chronic hypersensitivity pneumonitis and sarcoidosis.[3-6] In addition, patients with ILD not uncommonly require symptomatic management with supplemental oxygen therapy and pharmacotherapy such as opiate-based agents.

Many ILD affect the elderly, in particular idiopathic pulmonary fibrosis (IPF), the most common form of clinically encountered ILD. Patients with ILD typically present for assessment between the age of 45 and 72 years.[7,8] Comorbidities increase with advancement in age and the frequency of comorbidities has been associated with impaired health-related quality of life and disease outcomes.[9,10] Importantly, comorbid conditions and their management can complicate clinical care and increase treatment burden for patients with ILD. Previous data show that 43% of adults aged ≥ 50 years and 66% of adults aged ≥ 75 years take 5 or more medicines.[11] Pharmacotherapy complexity is a significant contributor of non-adherence, drug-related side effects and drug interactions,[12-14] leading to substantial cost of illness and increased healthcare utilisation.[15,16] Hence, therapeutic complexity is potentially a pervasive problem among patients with ILD. Better understanding of the significance of

medication complexity and multimorbidity is an important initial step to improve delivery of holistic care in the ILD population.

This study aimed to evaluate therapeutic complexity before and after commencement of ILD-specific therapies in patients with different types of ILD. In addition, we examined the prevalence of clinically important drug-disease interactions in patients who were prescribed long-term prednisolone for management of ILD.

METHODS

This cross-sectional study was conducted using the prospective ILD registries of two tertiary hospitals in Victoria, Australia: Alfred Health (between October 2010 and February 2018) and Austin Health (between February 2015 and February 2018). All consenting patients at the specialised ILD clinics at both hospitals are included in the registries. For this study, consecutive patients with a diagnosis of ILD based on multidisciplinary team discussions who were initiated on therapies for ILD were included. Data collected included baseline demographics, smoking history, comorbidities, medication use (including domiciliary oxygen therapy), lung function tests, and dyspnoea scores (measured using the Modified Medical Research Council Dyspnoea Scale). Information regarding medication use prior to and after commencement of ILD-specific therapies was collected from the electronic medical record system for both hospitals. In patients with inflammatory ILD, potential drug-disease interactions with prednisolone use were evaluated by using documented co-morbidities prior to treatment commencement. Ethics approval was granted by the Alfred Hospital Ethics Committee and the Austin Health Human Research Ethics Committee.

Medication assessment

Complexity of medication regimens was assessed using a validated tool, the Medication Regimen Complexity Index (MRCI)[17]. This tool consists of 65 items which are divided into three components: dosage form (Section A), dosing frequency (Section B) and additional dosing instructions (Section C). Each patient's total MRCI score was calculated by summing

scores for each section. The MRCI is an open-ended scale with no upper limit, and higher scores indicate greater medication regimen complexity.[17] The number of medications which patients were taking, total medication count, was also assessed as a continuous variable. Polypharmacy was defined as the use of five or more drugs, including prescribed, over-the-counter, and complementary medicines.[18,19]

Statistical analysis

Statistical analyses were performed using Graphpad Prism (v5, Graphpad Software, San Diego, California, USA). Categorical variables were expressed as absolute number (frequencies). The Fisher's Exact test was used to compare frequencies between groups. Data distributions were tested for normality using the Kolmogorov-Smirnov test. Parametric distributions were analysed with t-tests for comparisons of two groups. For non-parametric data, the Mann-Whitney test was used for two-group comparisons. Statistical significance was accepted at $p < 0.05$.

RESULTS

Two hundred and fourteen patients were included in this study. The study population was divided into two major groups: IPF group (n = 75) and inflammatory ILD group (n = 139). Baseline characteristics of both study groups are shown in Tables 1 and 2. Patients with IPF were predominantly male and significantly older than those with inflammatory ILD ($p < 0.001$). The most common diagnoses for inflammatory ILD included chronic hypersensitivity pneumonitis and connective tissue disease related ILD. Prednisolone was prescribed widely for treatment of various inflammatory ILD, while mycophenolate was the most frequently used non-steroid immunosuppressive agents.

Medication regimen complexity in IPF

Median total medication count for IPF group was 5 (IQR: 2, 7) at baseline and increased significantly to 7 (IQR: 4, 10) with commencement of therapies for IPF. The frequency of polypharmacy significantly increased, with 75% of patients taking 5 or more medications and 29% taking 10 or more. Sub-score for MRCI section C (additional dosing instructions) contributed most significantly to the total MRCI scores of IPF therapies, compared to

baseline medications (Figure 1, Table 3).

Medication regimen complexity in inflammatory ILD

For patients with inflammatory ILD, median total medication count increased from 6 (IQR: 3, 9) to 8 (5, 10) after commencement of ILD-specific therapies ($p < 0.0001$). In this group, 81% of patients were taking 5 or more medications, and 30% were taking 10 or more, after receiving ILD-specific therapies. The major contributor to total MRCI scores of ILD therapies was once again the MRCI section C sub-score (additional dosing instructions), accounting for 70% of the total score ($p = 0.019$; Figure 2, Table 4).

Comparison of medication regimen complexity between IPF and inflammatory ILD

Patients with inflammatory ILD had higher number of median total medication count at baseline compared to those with IPF ($p = 0.007$), although there was no significant difference after initiation of ILD-specific therapies ($p = 0.22$). With regards to ILD-specific therapies, patients with IPF had significantly higher total MRCI scores compared to those with inflammatory ILD ($p < 0.001$). Sub-scores for both MRCI section A (dosage form) and B (dosing frequency) for IPF therapies were significantly higher than those for inflammatory ILD ($p < 0.001$ for both). MRCI section C sub-scores (additional dosing instructions) for ILD-specific therapies were similar between both groups.

Drug-Disease interactions for prednisolone in inflammatory ILD

A median dose of 20mg daily (IQR: 10, 32.5) was prescribed for patients with inflammatory ILD. Figure 3 shows the prevalence of significant comorbidities among patients who were prescribed prednisolone for inflammatory ILD. Of the 113 patients, 88% had at least one disease interaction with prednisolone use, while 47% and 26% had at least two and three disease interactions, respectively.

DISCUSSION

We systematically evaluated therapeutic complexity in the ILD population using the validated MRCI. Polypharmacy and high MRCI scores were common in patients with ILD. Across treatment regimens for different types of ILD, additional medication administration instructions were the major contributor for MRCI scores. Among patients with inflammatory ILD receiving systemic corticosteroids, the frequency of potential drug-disease interactions with significant comorbidities was high. Together, our data raise concerns of substantial therapeutic burden in patients with ILD which needs to be addressed timely as part of the comprehensive disease management approach.

To the best of our knowledge, this study is the first to describe the noteworthy issues of therapeutic burden in patients with ILD. More than two-thirds of our study population were taking five or more medications, with a median total MRCI scores of 21.5-22.5. While it is expected that initiation of ILD-specific therapies would increase therapeutic burden with additional medications, the total MRCI scores for ILD populations were comparable to those with other chronic diseases. Previous cohort studies reported total MRCI scores of 17.62 to 32.1 for patients with various chronic diseases, such as heart failure, HIV, chronic kidney disease and diabetes mellitus.[20-3] Patients with chronic obstructive pulmonary disease are reported to have median total MRCI score of 24.[24] Although MRCI is an open-ended index, Ferreira et al suggested total MRCI scores of 15.5 to 25.1 were indicative of high complexity for patients aged 65 years or over.[25] Hence, patients with ILD are in the high risk category for polypharmacy and therapeutic burden. In addition, there is a need for regular blood test monitoring for patients receiving either anti-fibrotic agents or immunosuppressive agents for safety surveillance. Data on blood test monitoring were not captured in our study, which may potentially underestimate the overall therapeutic burden in this population.

Compared to medication count and pill burden, the use of MRCI provides more comprehensive evaluation to identify factors contributing to treatment complexity. This allows targeting sections of the medication regimen to reduce complexity and improve medication administration practices. Additional dosing instructions contributed the most to total MRCI scores for both patients with IPF and inflammatory ILD. Most disease-targeted therapies for ILD have specific administration instructions with dose-titration and food-dosing requirement. Previous study in patients with HIV found that medication regimens with more complex administration instructions were associated with higher rates of non-

adherence.[26] As shown in patients with osteoporosis, poor adherence to dosing instructions for bisphosphonates is common despite good compliance to the treatment.[27] Non-adherence to medication administration instructions can affect treatment outcomes and increase risks of drug-related adverse effects. In order to ensure adherence to treatment regimens and dosing instructions, initiatives are needed to facilitate patient education at treatment initiation and on an ongoing basis. The involvement of ILD specialist nurses and pharmacists in patient care can provide additional support to enhance patients' adherence to treatment.

With regards to ILD-specific therapies, treatment regimens were more complex for IPF than those for inflammatory ILD. In addition to higher number of therapies, medication regimens for patients with IPF had more frequent dosing. Although new tablet formulation of pirfenidone with higher dosage is now available to reduce the pill burden by one third, a significant proportion of patients, 22.5 to 30%, require dose reduction due to drug-related adverse effects.[28,29] Additional therapies for prevention and management of drug-related adverse effects are likely contributing to the complexity of IPF treatment regimens. Both anti-fibrotic agents for treatment of IPF, nintedanib and pirfenidone, can be associated with significant adverse effects. Skin-related problems (rash and photosensitivity) occur in approximately one third of patients taking pirfenidone,[30,31] while over 60% of patients receiving nintedanib experience diarrhoea.[32] Patients taking pirfenidone are instructed to apply sunscreen regularly. On the other hand, patients who are initiated on nintedanib are typically prescribed anti-diarrhoeal medications. Other medications may be required to address nausea and dyspepsia associated with the use of anti-fibrotic agents. It is important to acknowledge this added complexity for managing drug-related adverse effects in this group of patients.

Not surprising, prednisolone was the most commonly prescribed immunosuppressive agent for patients with inflammatory ILD. We found that the occurrence of potential drug-disease interactions in patients receiving prednisolone was high, with more than 80% presenting with at least one potential interaction. This is particularly alarming as we only evaluated a restricted list of conditions which were considered clinically important. Professional awareness of potential drug-disease interactions and ensuing attentive care should be encompassed. The lowest effective dose of systemic corticosteroids for the minimum duration required to achieve treatment goal is recommended. Whenever possible, steroid-sparing agents should be considered. Collaboration between prescribing respiratory

physicians and patients' general practitioners and other physicians is needed to optimally manage co-existing chronic conditions.

There are limitations with this study. This study was conducted in specialised ILD centres, which may limit its generalisability to other clinical settings. However, both centres take referrals from primary care physicians, other hospitals and private practices across the state. Patients with various forms of ILD and treatment regimens were included in this study. Due to the retrospective design of the study, medication adherence could not be assessed. Although the use of MRCI allows comprehensive evaluation of medication-related factors for therapeutic burden, patients' perceptions and patient-related factors, such as cognition, health literacy and beliefs, were not considered. Prospective longitudinal studies will be required to evaluate the relationship between therapeutic complexity and patient outcomes and healthcare utilisation, including their health-related quality of life and impacts on management of comorbidities.

In conclusion, this study demonstrated patients with ILD face substantial therapeutic burden with high medication regimen complexity, in particularly complicated medication administration instructions for treatment of ILD. In addition, ILD patients receiving systemic corticosteroids are at high risk of drug-disease interactions in the setting of multimorbidity. Awareness of therapeutic complexity and burden in ILD should be raised. Opportunities exist for clinicians to rationalise treatment regimens and address potential drug-disease interactions in the management of patients with ILD. Studies to evaluate the impact of therapeutic complexity on quality of life and clinical outcomes in patients with ILD are needed.

Disclosure statement

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Table 1: Baseline characteristics of IPF group

Characteristics	**Study cohort (n = 75)**
Age (years)	69.6 ± 8.1
Male (%)	80
BMI (kg/m^2)	29.3 ± 3.8
FVC (% predicted)	72.5 ± 15.0
DLCO (% predicted)	50.7 ± 14.4
6MWD (m)	455 ± 120
MMRC Dyspnoea Scale*	1 (1, 2)
Antifibrotic agents, n (%)	
• Nintedanib	30 (40)
• Pirfenidone	45 (60)

Data expressed as: mean ± standard deviation; * median (interquartile range)

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index; DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; MMRC, Modified Medical Research Council

Table 2: Baseline characteristics of inflammatory ILD group

Characteristics	**Study cohort (n = 139)**
Age (years)	61.5 ± 12.7
Male (%)	51
BMI (kg/m^2)	28.5 ± 5.9
FVC (% predicted)	62.6 ± 17.9
DLCO (% predicted)	47.8 ± 17.0
6MWD (m)	413 ± 125
MMRC Dyspnoea Scale*	2 (1, 3)
Diagnosis, n (%)	
• Chronic hypersensitivity pneumonitis	45 (32)
• Connective tissue disease related ILD	41 (30)
• Interstitial pneumonia with autoimmune features	18 (13)
• Non-specific interstitial pneumonia	11 (8)
• Sarcoidosis	10 (7)
• Other	14 (10)
Immunosuppressive agent, n (%)	
• Azathioprine	10 (7)
• Cyclophosphamide	12 (9)
• Hydroxychloroquine	11 (8)
• Methotrexate	8 (6)
• Mycophenolate	36 (26)
• Prednisolone	113 (81)
• Sulfasalazine	4 (3)

Data expressed as: mean ± standard deviation; * median (interquartile range)

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index; DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; MMRC, Modified Medical Research Council

Table 3. Medication counts and MRCI scores for patients with IPF

a) Medication counts and MRCI scores for all medications prior to and after commencement of ILD-specific therapies

	IPF (n = 75)		
	Baseline	**Commencement of ILD therapies**	**p-value**
Total medication count	5 (2, 7)	7 (4, 10)	< 0.0001
Using ≥ 5 medications (%)	51	75	0.004
Total MRCI scores	8 (8, 15)	22.5 (17.5, 27.5)	< 0.0001
MRCI section A score (dosage form)	1 (1, 4)	4 (3, 7)	< 0.0001
MRCI section B score (dosing frequency)	5 (3, 7.5)	9.5 (7.5, 13)	< 0.0001
MRCI section C score (additional dosing instructions)	1 (0, 3)	6 (5, 8)	< 0.0001

b) MRCI scores for non-ILD and ILD-specific therapies

	Non-ILD therapies	**ILD therapies**	**p-value**
MRCI section A score (dosage form)	1 (1, 4)	3 (1, 4)	0.99
MRCI section B score (dosing frequency)	5 (3, 7.5)	4.5 (2.5, 6)	0.68
MRCI section C score (additional dosing instructions)	1 (0, 3)	5 (3, 6)	< 0.0001

Data expressed as: median (interquartile range)

Abbreviations: ILD, interstitial lung disease; MRCI, Medication Regimen Complexity Index

Table 4. Medication counts and MRCI scores for patients with inflammatory ILD

a) Medication counts and MRCI scores for all medications at the initial clinical assessment and after commencement of ILD-specific therapies

	Inflammatory ILD (n =139)		
	Baseline	**Commencement of ILD therapies**	**p-value**
Total medication count	6 (3, 9)	8 (5, 10)	< 0.0001
Using ≥ 5 medications (%)	63	81	0.002
Total MRCI scores	14.5 (8.5, 21)	21.5 (16, 30)	< 0.0001
MRCI section A score (dosage form)	4 (1, 6)	4 (1, 8)	< 0.0001
MRCI section B score (dosing frequency)	7 (4, 10.5)	10 (6, 13.5)	< 0.0001
MRCI section C score (additional dosing instructions)	3 (2, 6)	8 (6, 10)	< 0.0001

b) MRCI scores for non-ILD and ILD-specific therapies

	Non-ILD therapies	**ILD therapies**	**p-value**
MRCI section A score (dosage form)	4 (1, 6)	1 (1, 1)	< 0.0001
MRCI section B score (dosing frequency)	7 (4, 10.5)	2 (1, 3)	< 0.0001
MRCI section C score (additional dosing instructions)	3 (2, 6)	7 (6, 11)	0.019

Data expressed as: median (interquartile range)

Abbreviations: ILD, interstitial lung disease; MRCI, Medication Regimen Complexity Index

Figure 1. Percentage contributions of MRCI sub-sections to the total MRCI scores for (a) non-ILD therapies and (b) ILD-specific therapies in patients with IPF

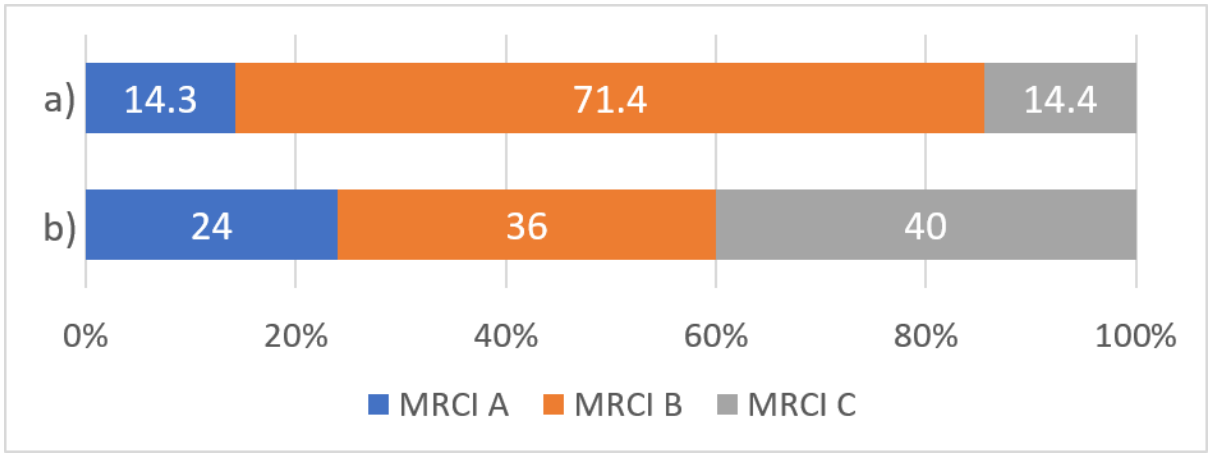
MRCI A: Dosage form; MRCI B: Dosing frequency; MRCI C: Additional dosing instructions
Abbreviation: MRCI, Medication Regimen Complexity Index

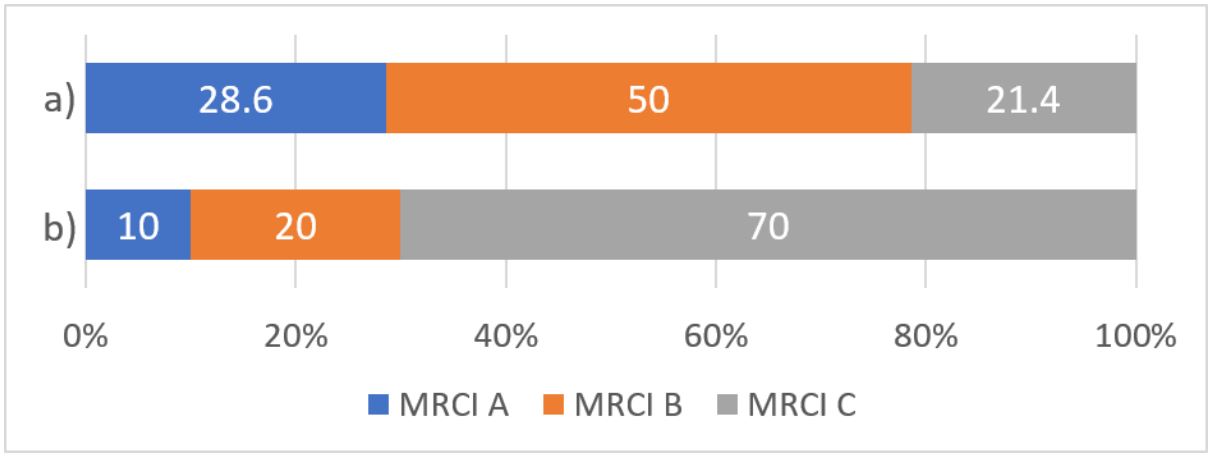
Figure 2. Percentage contributions of MRCI sub-sections to the total MRCI scores for (a) non-ILD therapies and (b) ILD-specific therapies in patients with inflammatory ILD

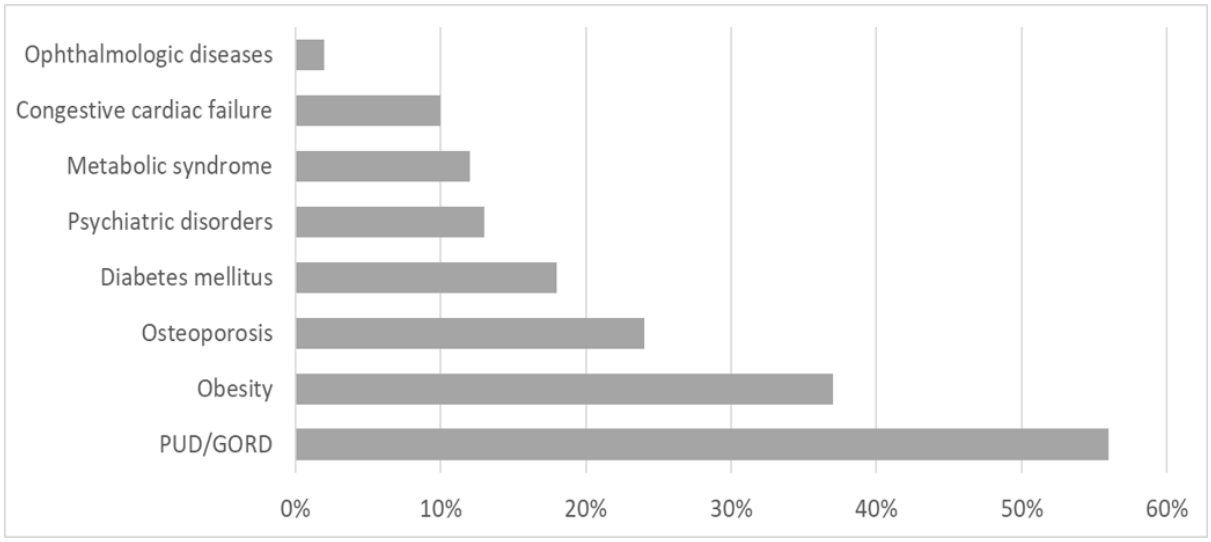
MRCI A: Dosage form; MRCI B: Dosing frequency; MRCI C: Additional dosing instructions
Abbreviation: MRCI, Medication Regimen Complexity Index

Figure 3. Prevalence of drug-disease interactions of prednisolone in patients with inflammatory ILD

Abbreviations: GORD, gastroesophageal reflux disease; PUD, peptic ulcer disease







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