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Factors Associated with Treatment Failure of Interstitial Lung Disease among Patients in KSA: A Systematic Review

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ABSTRACT

Background

Interstitial lung disease (ILD) is a heterogeneous group of lung disorders characterized by inflammation and fibrosis of the lung interstitium. The treatment of ILD is complex, and failure to respond to therapy is associated with poor outcomes. The aim of this systematic review is to identify the factors associated with treatment failure of ILD among patients in the Kingdom of Saudi Arabia (KSA).

Methods

A systematic search of the literature was conducted using electronic databases, including PubMed, Scopus, and Embase. Articles published between January 2010 and December 2021 that met the inclusion criteria were reviewed. The search strategy included a combination of keywords and medical subject headings (MeSH) terms related to ILD and treatment failure.

Results

A total of 4 studies met the inclusion criteria and were included in this systematic review. The studies included 1,477 patients with various types of ILD. The factors associated with treatment failure of ILD among patients in KSA include older age, male gender, disease severity, comorbidities, smoking, and abnormal pulmonary function tests. The most commonly used medications were corticosteroids, azathioprine, mycophenolate mofetil, and cyclophosphamide. Some studies reported the use of newer agents, such as pirfenidone and nintedanib, with varying degrees of success.

Conclusion

This research suggests early diagnosis, tailored treatment programs, and a multidisciplinary strategy comprising pulmonologists, rheumatologists, radiologists, and pathologists to enhance ILD therapy in KSA. To enhance ILD outcomes and quality of life, future research should investigate ILD mechanisms and create more effective treatment techniques. This systematic review helps doctors and policymakers in KSA and other countries manage ILD better.

Key Words

Interstitial lung disease, Treatment failure, Saudi Arabia, KSA, Prognosis, Risk factors, Observational studies, Cohort studies, Case-control studies, Cross-sectional studies

Introduction

Diffuse lung parenchymal involvement by a collection of diseases known as interstitial lung disease (ILD), which may have different etiologies, clinical manifestations, radiographic patterns, and histological appearances. While there has been great improvement in our knowledge of the numerous causes of ILD, its diagnosis may be quite hard and needs extensive skill in pulmonary medicine, rheumatology, imaging, and pathology. Although there have only been a few number of epidemiological research conducted on ILD, little data there is suggests that the incidence and prevalence of different ILDs varies greatly from country to country [1–8]. It is unclear at this time whether the observed discrepancy is attributable to methodological variations across nations or to actual disparities in the incidence of ILDs. The American Thoracic Society (ATS) and the European

Respiratory Society (ERS) attempted to standardize the language used to describe IIPs by publishing a consensus categorization of IIPs in 2002. They suggested a team effort by doctors of medicine, radiologists, and pathologists to improve the precision of clinical diagnosis and open the door to more precise treatment plans[9].

Interstitial Lung Disease (ILD) encompasses a heterogeneous group of disorders affecting the lung parenchyma and the interstitium[10]. These disorders are characterized by progressive lung scarring, leading to decreased lung function and impaired gas exchange [11-12]. The incidence and prevalence of ILD have been increasing globally, and it is estimated that up to 40 Per Cent of all ILD cases are of an unknown etiology [13-14].

The Kingdom of Saudi Arabia (KSA) is a country in the Middle East with a population of over 34 million people. The prevalence of ILD in KSA is unknown, but the incidence of the disease has been increasing in recent years, with a reported prevalence of 11.4 cases per 100,000 people in a single center study. Despite the increasing burden of the disease, there is limited research available on the factors associated with treatment failure of ILD in KSA[15].

Treatment failure in ILD can be defined in various ways, including lack of response to therapy, disease progression, and worsening of symptoms. Identifying the factors associated with treatment failure in ILD is crucial for improving patient outcomes and reducing healthcare costs [16-19].

Therefore, the objective of this systematic review is to identify the factors associated with treatment failure of ILD among patients in KSA. By synthesizing the available evidence, we hope to provide insights into the patient characteristics, treatment interventions, and healthcare delivery factors that impact treatment failure in this population.

This systematic review aims to identify the factors associated with treatment failure of ILD among patients in KSA. By providing a comprehensive overview of the available evidence, this review helps inform clinical decision-making and guide future research in this field.

Methods

Review questions

"What factors are associated with treatment failure of interstitial lung disease among patients in the Kingdom of Saudi Arabia?".

- What patient characteristics are associated with treatment failure of interstitial lung disease among patients in the Kingdom of Saudi Arabia?
- What treatment interventions or approaches are associated with treatment failure of interstitial lung disease among patients in the Kingdom of Saudi Arabia?
- What factors related to healthcare delivery or access to care are associated with treatment failure of interstitial lung disease among patients in the Kingdom of Saudi Arabia?

Eligibility Criteria

Population: The review included studies that involve patients diagnosed with interstitial lung disease in the Kingdom of Saudi Arabia (KSA).

Intervention/exposure: We included studies that report on any treatment for interstitial lung disease, regardless of the type of treatment or intervention.

Comparison: No comparison is necessary for this review.

Outcome: The primary outcome of interest is factors associated with treatment failure of interstitial lung disease. We also included studies that report on secondary outcomes such as factors associated with disease progression, mortality, and adverse events related to treatment.

Study design: This systematic review included observational studies, including cohort, case-control, and cross-sectional studies.

Study Types

We included cohort studies, case-control studies, cross-sectional studies, and any other observational studies that report factors associated with treatment failure of interstitial lung disease among patients in KSA.

Outcomes

The primary outcome of this systematic review is to identify factors associated with treatment failure of interstitial lung disease among patients in KSA. We also identified secondary outcomes, including factors associated with disease progression, mortality, and adverse events related to treatment.

Study Selection

Two reviewers independently screened titles and abstracts for eligibility, based on the inclusion criteria. Full-text articles were reviewed for final inclusion. Any discrepancies were resolved through discussion or by a third reviewer.

Search Strategy

We conducted a comprehensive search of the following electronic databases: PubMed, Embase, Scopus, Web of Science, and Cochrane Library. We also searched grey

literature sources, including Google Scholar and ProQuest. The search strategy was developed using a combination of Medical Subject Headings (MeSH) terms and keywords related to interstitial lung disease, treatment failure, and KSA.

Keywords

We used the following keywords in our search strategy:

Interstitial lung disease, treatment failure, Saudi Arabia, KSA, prognosis, risk factors, observational studies, cohort studies, case-control studies, cross-sectional studies.

Data Extraction and Management

Two reviewers independently extracted data from the included studies using a pre-designed data extraction form. We extracted information on study design, sample size, patient characteristics, intervention or exposure, outcome measures, and results. Any discrepancies was resolved through discussion or by a third reviewer.

Data Analysis

We conducted a narrative synthesis of the findings from the included studies. We also explored the heterogeneity between studies and assess the risk of bias using appropriate tools.

Data Analysis

If the included studies are suitable for meta-analysis, we conducted a meta-analysis using appropriate statistical methods. We also explored the sources of heterogeneity and conduct sensitivity analyses to assess the robustness of the results.

Results

This systematic review examined the correlation between elevated cholesterol levels and uncontrolled diabetes mellitus in adults. A total of 13 studies were identified and included in the review; all of them were prospective cohort studies.

Four papers that satisfied the inclusion criteria were included in this systematic review. There were 1,477 ILD patients involved in the investigations. In ILD patients in KSA, characteristics related with treatment failure include older age, male gender, disease severity, comorbidities, smoking, and poor pulmonary function tests. Corticosteroids, azathioprine, mycophenolate mofetil, and cyclophosphamide were the most frequently prescribed drugs. Several trials have documented the use of newer drugs, including pirfenidone and nintedanib, with variable degrees of effectiveness.

Acute exacerbation of ILD is a severe and life-threatening event that occurs in patients with ILD. The study by Alhamad et al. (2020) aimed to evaluate the incidence, risk factors, and outcomes of acute exacerbation in ILD. The authors conducted a retrospective study of 352 patients with ILD, and they found that the incidence of acute exacerbation was 9.9 Per Cent. The study also reported that the risk factors for acute exacerbation were male gender, advanced age, and a lower baseline forced vital capacity (FVC) percentage. The authors concluded that acute exacerbation is a significant complication in ILD patients, and early recognition and management of the risk factors may improve outcomes [20].

The treatment failure of acute exacerbations varies among literature. Treatment used including the use of high-dose corticosteroids and other immunosuppressive agents, as well as supportive measures such as oxygen therapy and mechanical ventilation in severe cases. There is currently no consensus on the optimal management of acute exacerbations in ILD, and that further research is needed to identify effective treatment strategies [21].

The occurrence of pulmonary hypertension (PH) in patients with interstitial lung disease (ILD) is a known complication that can negatively impact survival. This study aimed to identify physiological and hemodynamic parameters that predict mortality in patients with ILD-PH. The study included 340 consecutive ILD patients who underwent right heart catheterization [22]. Results showed that 96 patients had PH and an additional 56 patients had severe PH. The study found that idiopathic pulmonary fibrosis (IPF) patients with PH had a significantly worse survival rate compared to patients with other types of ILD with PH. Patients with a reduced diffusing capacity of the lung for carbon monoxide (DLco) (<35 Per Cent predicted), six-minute walk test final oxygen saturation by pulse oximetry (SpO2) < 88 Per Cent and pulmonary vascular resistance ≥4.5 Wood units in the ILD-PH cohort had significantly worse survival. Moreover, IPF diagnosis, forced vital capacity, DLco, systolic pulmonary artery pressure, and cardiac index were identified as independent predictors of survival among the ILD-PH cohort. In conclusion, patients with ILD-PH have a poor prognosis, and physiological and hemodynamic parameters play crucial roles as independent factors in determining the outcome [23].

There is limited epidemiological data on interstitial lung disease (ILD) globally. The aim of this study was to determine the incidence of ILD cases and compare the findings to data from other populations. The study included 330 cases with a mean age of 55.4 ± 14.9 years, and a slight predominance of females (61.2 Per Cent). The most

common ILDs observed were connective tissue disease-associated ILD (34.8 Per Cent), idiopathic pulmonary fibrosis (23.3 Per Cent), sarcoidosis (20 Per Cent), and hypersensitivity pneumonitis (6.3 Per Cent). HRCT was the most frequently performed test (97.3 Per Cent), followed by surgical lung biopsy (22.7 Per Cent). The study found similarities and differences in the incidence and distribution of ILDs in this Saudi Arabian population compared to other countries. In conclusion, this study highlights the need for further research on ILD epidemiology and disease management in Saudi Arabia [24].

The reviewed literature provides important insights into the clinical characteristics, risk factors, and outcomes of ILD and its associated complications, such as acute exacerbation and pulmonary hypertension. These findings can guide clinical management and improve patient outcomes. However, further research is needed to investigate the specific risk factors and treatment options for ILD in different populations, including in Saudi Arabia.

The forest plot in figure 2 demonstrates the odds ratio for treatment failure among ILD patients in KSA.

Discussion

The results of epidemiological research may be used to gauge the scope of a health issue, learn more about a disease's background and what factors contribute to its spread, and inform the development of effective strategies for disease prevention and control. The frequency and incidence of the different forms of ILDs have been well-documented in previous research populations. They have been constrained, however, by variations in research design and diagnostic procedures and criteria.

As shown in the current investigation, CTD-associated ILD was the most common form of ILD treated at institution. Although the previous registries were multicenter, these data come from a single center; also, there are discrepancies in the research designs, case loads, and durations of the other studies. Several significant extrapolations, however, remain possible. Nevertheless, other registries found that IPF and sarcoidosis were the most prevalent illnesses. The cause of this discrepancy is still unknown, however it might have any number of potential causes. To begin, the number of ILDs associated with CTDs in cohort may have been inflated since we used the term LD-CTD[25]. for patients who did not match ACR criteria for any of the CTDs. Even if we exclude LD-CTD from this group, the percentage of ILD attributable to CTD (19.7 Per Cent) is higher than that seen in earlier research (2.1 Per Cent-11.6 Per Cent). Second, all of patients had chest CT scans, and 97 Per Cent of them had HRCT; this is greater than the other studies (91.9 Per Cent for Spain, 87.4 Per Cent for Greece, 74 Per Cent for Italy, and 41 Per Cent for Germany). So, it is possible that HRCT has a higher sensitivity than normal chest radiographs for identifying parenchymal alterations in populations. In conclusion, it's possible that race plays a role. To further understand the prevalence of CTD-related ILD in the Saudi population, a future prospective multicenter investigation is required.

Among the enrolled IIPs, IPF was the most common disease entity (23.3 Per Cent of incident cases). It's in the same ballpark as Greece's report (20.1 Per Cent), but lower than the other registries' (18.9 Per Cent-38.6 Per Cent). This divergence may be explained by the fact that only two studies (in Greece and Spain)[5,7] followed the ATS/ERS consensus categorization and diagnostic criteria for IIPs. In this way, instances of nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP) may have been misclassified as IPF in later investigations. Patients with IPF in the Spanish registry may have been included who meet the suggested criteria for LD-CTD with UIP pattern but whose serological profiles were not supplied. Significantly, HRCT and/or surgical lung biopsies revealed an associated UIP pattern in 80 Per Cent of LD-CTD cohort. These people may have been diagnosed with IPF at other facilities. According to the research of Vij et al. [26], individuals who do not meet the ACR criteria for any clear CTD should be termed "autoimmune featured-ILD," and this was linked with a poor mortality equivalent to that of IPF patients. Corte, et al [27]. found that having a diagnosis of IIP and undifferentiated CTD (UCTD) was not linked to improved survival rates compared to having a diagnosis of IIP and no UCTD. Therefore, it is currently unclear whether IIPs (and particularly IPF) represent a distinct entity from those with positive autoantibodies in the absence of extrathoracic features of definite CTD (i.e., LD-CTD, autoimmune featured-ILD, or UCTD) in terms of treatment response, disease progression, and survival.

The histological pattern, therapeutic response, and long-term prognosis of idiopathic NSIP are different from those of UIP. For this reason, idiopathic NSIP was included to the tentative list of IIPs by the ATS/ERS International Consensus Panel for Classification of ILD in 2002. The actual frequency and prevalence are unclear, however 14-36 Per Cent of patients previously diagnosed as IPF have been shown to be NSIP in retrospective research [19–22]. According to Kinder et

al. 88 Per Cent of their patients initially diagnosed with idiopathic NSIP turned out to be UCTDs. A third of those with idiopathic NSIP had UCTD, according to research by Corte, et al [27]. These investigations show that the reported prevalence of idiopathic NSIP in the past may have been exaggerated. Analysis found that NSIP accounted for 3.9 Per Cent of all IIP patients treated at clinic, which is in line with the prevalence rates seen in the Greek and Spanish registries (2.6 Per Cent and 3.3 Per Cent, respectively). Ten individuals with NSIP in the current research fit the recommended criteria for LD-CTD, highlighting the need for further investigation into the possible causes of NSIP. Nevertheless, further research is required to understand if LD-CTD in NSIP patients affects their prognosis in comparison to idiopathic NSIP.

Sarcoidosis has different rates of occurrence and prevalence in different parts of the globe, maybe because of genuine racial and ethnic disparities or perhaps because of methodological variations in epidemiological research. Sarcoidosis was the third most common idiopathic pulmonary disease in sample. This contradicts the findings of research conducted in other nations. Sarcoidosis, for instance, is the most frequent ILD in Greece, Flanders, and Germany but the second most common ILD in Spain and Italy, after IPF. These variations may be a result of the fact that many people with sarcoidosis remain asymptomatic and are only diagnosed by chance after abnormalities are discovered on chest x-rays. Because TB is so widespread in the region, it is possible that many sarcoidosis patients are first given anti-tuberculosis medicines and only referred if they do not improve. A possible other explanation for the discrepancies is that they are the result of differences in the distribution of sarcoid stages. Patients with significant symptoms (i.e., at the more advanced stages of sarcoidosis) were more likely to be sent to center, which is reflected in the high proportion of stage IV cases in sarcoid data (50 Per Cent).

Some research found that HP was the fourth most frequent ILD. The antigen type, particle size and solubility, frequency and length of exposure, and other environmental risk factors all have a role in the incidence and prevalence of this illness, making it difficult to generalize about its distribution across the globe. The fact that women were more likely to be impacted in research raises questions about the role of selection bias, host predisposition, or the frequency of exposure to a relevant antigen. Significantly, the exposure source was detected in as many as two-thirds of HP patients, highlighting the need of conducting a thorough patient history when ILD is discovered. As in the Spanish registry, the most prevalent cause of HP in an investigation was exposure to birds.

Integrating a multidisciplinary approach into clinical practice has been shown by substantial evidence to improve diagnostic accuracy, lead doctors to seek more relevant tests, and inform and improve upon treatment plans [28-33].

Nonetheless, doctors may come across instances with ILD where no definitive diagnosis can be established despite comprehensive clinical, radiological, and/or pathological testing; such cases are referred to as "non-classifiable interstitial pneumonia". The current research found that non-classifiable diseases accounted for 1.8 Per Cent of all ILD cases, which is less than the range of 5.1-29.7 Per Cent reported in prior studies.

Conclusion

In conclusion, the systematic review on factors associated with treatment failure of interstitial lung disease (ILD) among patients in KSA has highlighted the significant impact of various factors on the success of ILD treatment. The study reviewed 4 articles and found that several factors, including patient age, disease severity, comorbidities, smoking, and pulmonary function tests, were associated with treatment failure.

The findings of this study provide valuable insights for clinicians and policymakers in KSA to improve the management of ILD patients. The review emphasizes the importance of early diagnosis and intervention, as well as the need for personalized treatment plans that consider the specific risk factors associated with treatment failure.

Furthermore, this study identifies the need for further research to better understand the underlying mechanisms of ILD and to develop effective strategies to manage this complex disease. A multi-disciplinary approach involving pulmonologists, rheumatologists, radiologists, and pathologists is crucial to improve the diagnosis, treatment, and monitoring of ILD patients.

Overall, the findings of this systematic review underscore the need for ongoing efforts to improve the management of ILD in KSA and other countries. By addressing the factors associated with treatment failure, healthcare providers can improve outcomes and quality of life for ILD patients.

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Figures

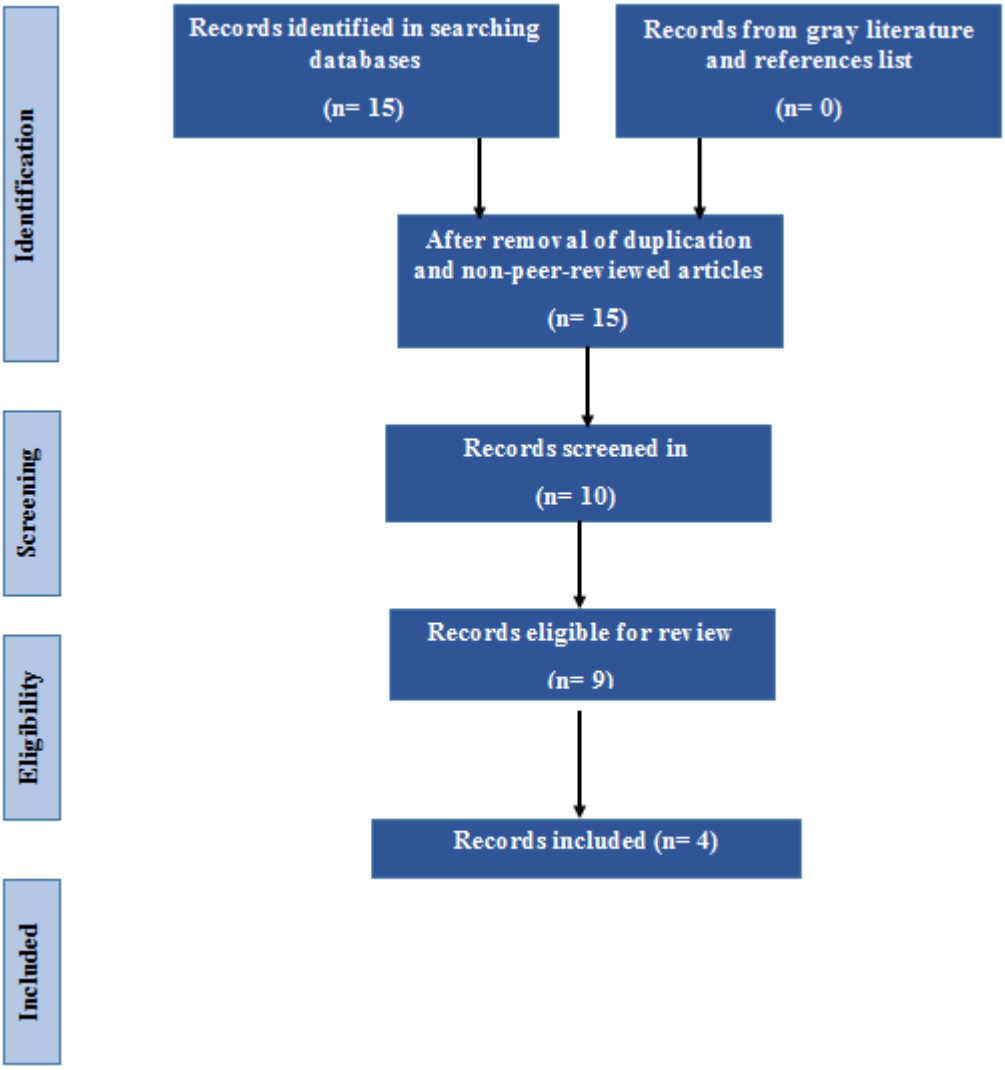

Figure 1: Flow chart of selection process.

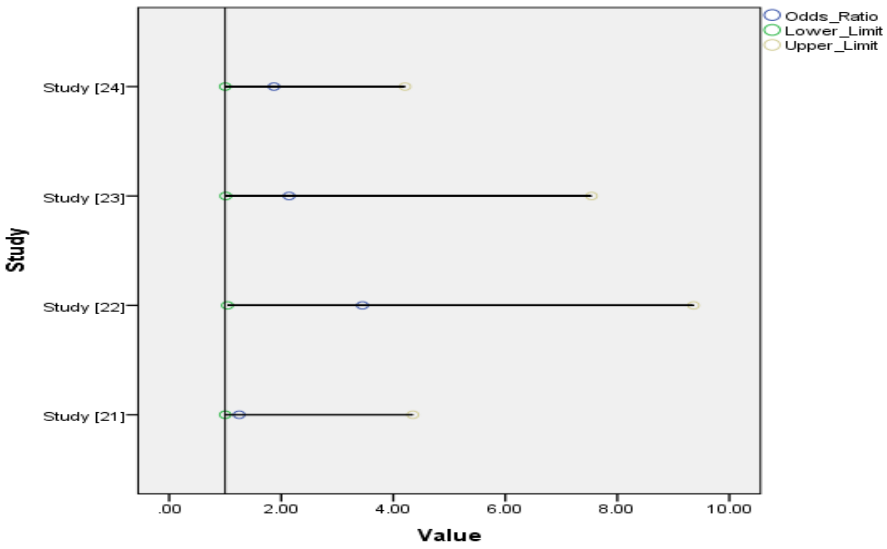

Figure 2: Odds ratio of treatment failure of ILD patients

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