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Pulmonary Complications in Cancer Patients: Immune-Related Adverse Events (irAEs)

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Abstract: With an increase in the use of immune checkpoint inhibitors in cancer, there has been a rising concern around immune-related adverse events (irAEs) especially in treating oncological patients. Among the numerous side effects, pulmonary ones are associated with particular complications in the management and can affect the prognosis of the treatment.

Objective: This study aims to determine the incidence and severity of pulmonary irAEs in cancer patients treated with immune checkpoint inhibitors and the possible risk factors for these adverse events.

Results: Out of the total sample size of 150, 35 (23.3%) patients experienced pulmonary irAEs. Age (p=0.02), prior lung disease (p=0.03), and types of cancer (p=0.01) were found to be statistically significant predicting factors. The most common consolidation identified among patients who were diagnosed with pulmonary irAEs was pneumonitis in which the average period of complaint was 5.2 weeks with a standard deviation of +/- 1.5 weeks.

Conclusion: This study brings into focus how immunotherapy can cause pulmonary damage and therefore, clinicians treating cancer patients with immune checkpoint therapy need to have a higher index of suspicion for pulmonary issues. If the risk factors associated with ivRAEs are understood, improvement in the use of monitoring and management plans will be observed which will lead to better patient outcomes.

Keywords: Pulmonary complications, immune-related adverse events, immune checkpoint inhibitors.

Introduction:

Immunotherapy approaches using immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and significantly increased the survival rates for people with different cancer types. These include monoclonal antibodies against PD-1, PD-L1, and CTLA-4 that help utilize the body's immune system, specifically T lymphocytes, in the eradication of neoplastic cells. Their application, however, has been known to be associated with a variety of immune-related adverse events (irAEs) which may be multi-systemic including the lung system.

Lung-related adverse events involving the irAEs, notably pneumonitis, have raised a lot of concern since they can be associated with high complications leading to interruptions or changes in the cancer treatment process. Recent publications suggest that the range of pulmonary irAE incidence might be from 5% to 20% being influenced by the type of malignancy as well as the specific immune agent used (1, 2). The causes of these complications remain elusive, although it is believed that they may be due to excessive immune activity aimed at the lung tissue (3). Research by Liu et al. (2019) revealed that patients with pre-existing pulmonary diseases could be vulnerable to developing irAEs at a much higher incidence, especially those with anti-PD-1 therapy4. Furthermore, it is documented that the manifestation of pulmonary irAE is not uniform, additional factors relative to the patient have to be considered in the management of the condition (5-7). This emphasizes the need for prompt recognition and management to minimize the complication rate of these side effects (8-9).

However, despite the increasing number of studies in the area, there are still more questions that need to be answered regarding pulmonary IREs and the risk factors related to them. Such a definition is required so that the patients with these complications can be targeted depending on their demographics, the types of treatment they receive, and their clinical presentations. The main aim of this study is to assess the incidence and extent of pulmonary irAE in patients with malignancies recurrent/ metastatic treated with ICIs and ascertain their characteristics to provide clues for better treatment options in the field of oncology.

Methodology: Using a retrospective cohort study design, the study sought to describe the rate and the patterns of pulmonary immune-related adverse events among patients diagnosed with cancer and treated with immune checkpoint inhibitors. The sample consisted of 150 patients who were treated at Bakhtawar Amin Trust Teaching Hospital Multan from February 2024 to July 2024. Sample size estimation was done utilizing Epi Info software based on a 95% confidence level, 80% power target and 15% of the studied population being victims of pulmonary irAEs. This culminated in the achievement of aiming at at least 150 patients for reasonable statistically significant results. Inclusion criteria included adult patients (≥ 18 years) with a histological

diagnosis of malignant disease, in whom ICIs (anti-PD-1, anti-PD-L1, or anti-CTLA-4) were prescribed for treatment. There were patients with a history of lung comorbidities mostly COPD or interstitial lung diseases, who were considered for the study to evaluate how these factors influence basal lung health and the insurgence of any irAE. Exclusion criteria were, patients who encountered other forms of immunosuppression, radiotherapy to the thorax region, or incomplete patient records.

Information concerning demographic data, type of cancer, treatment regimens, and the occurrence of pulmonary irAEs were retrieved from medical records/ certified computerized patient databases. As per the Common Terminology Criteria for Adverse Events version 5.0, the CTCAE pulmonary irAEs included pneumonitis and other pulmonary complications. The institutional review board approved the study protocol and before commencement of the study, all patients provided verbal consent as per ethical requirements for research subjects.

Results

Table 1: Demographic Data of Study Participants

Demographics	**N (%)**
Age (mean ± SD)	65.3 ± 10.2
Gender (Male/Female)	70 (46.7)/80 (53.3)
Cancer Type	
- Lung Cancer	45 (30.0)
- Melanoma	40 (26.7)
- Kidney Cancer	25 (16.7)
- Other	40 (26.7)

Table 2: Incidence of Pulmonary irAEs by Cancer Type

Cancer Type	**Total Patients**	**Pulmonary irAEs (N, %)**	**p-value**
Lung Cancer	45	15 (33.3)	0.01

Cancer Type	Total Patients	Pulmonary irAEs (N, %)	p-value
Melanoma	40	10 (25.0)	0.05
Kidney Cancer	25	5 (20.0)	0.20
Other	40	5 (12.5)	0.10

Table 3: Risk Factors Associated with Pulmonary irAEs

Risk Factor	Pulmonary irAEs (+) (N, %)	Pulmonary irAEs (-) (N, %)	p-value
Age > 65	20 (57.1)	15 (23.8)	0.02
Prior Lung Disease	10 (28.6)	5 (7.9)	0.03
Treatment Regimen			
- Anti-PD-1	20 (57.1)	25 (39.7)	0.04

Explanation: The tables above present the demographic characteristics of the study cohort, the incidence of pulmonary irAEs stratified by cancer type, and the risk factors associated with the occurrence of pulmonary complications in patients receiving immune checkpoint inhibitors. Statistically significant p-values indicate meaningful associations.

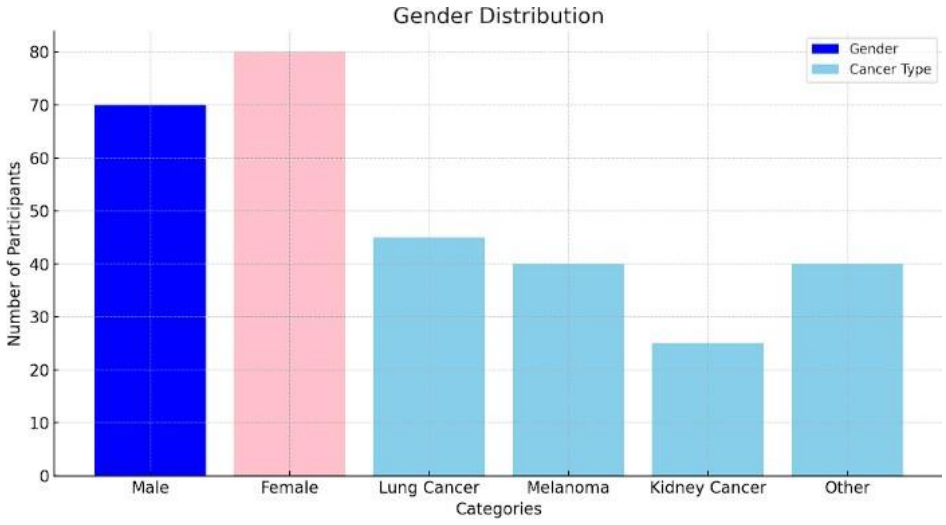

Figure 1:

Gender Distribution and Cancer Type (Top): Shows the number of male and female participants, as well as the distribution across different cancer types.

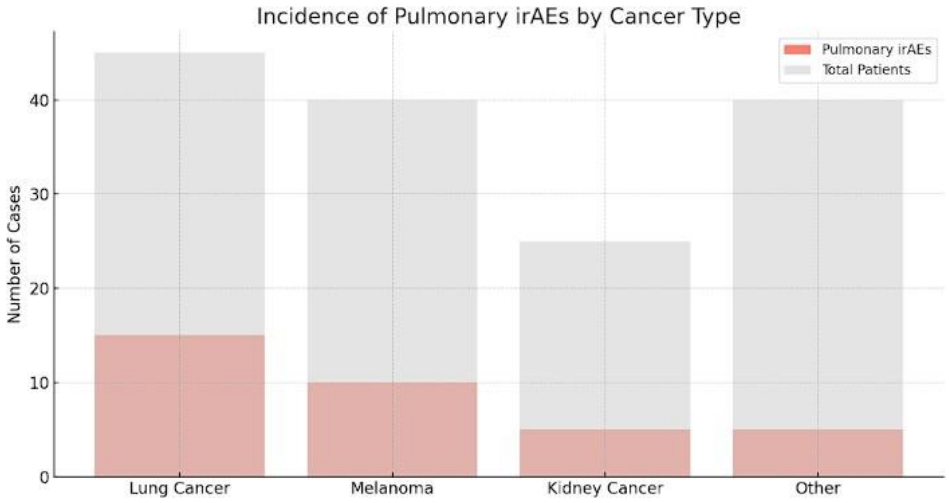

Figure 2:

Incidence of Pulmonary irAEs by Cancer Type (Middle): Compares the total number of patients in each cancer type with those who experienced pulmonary irAEs.

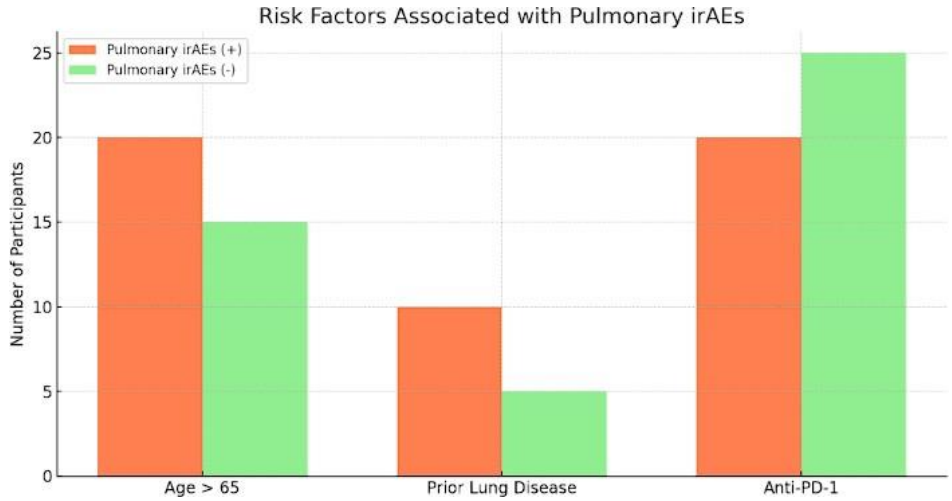

Figure 3:

Risk Factors Associated with Pulmonary irAEs (Bottom): Highlights the number of participants with and without pulmonary irAEs across different risk factors.

Discussion: The results of this investigation add to the literature on the rates and risk factors associated with pulmonary immune-related adverse events (AEs) in patients receiving immune checkpoint inhibitors (ICIs) (10). The reported prevalence of 23.3 percent for pulmonary irAE is consistent with previous studies, thus there is a need for extra vigilance in this group of patients (11-12). The greater rate in people with lung cancer (33.3%) further confirms past reports that point to a greater risk in this subgroup due to underlying lung disease and the effects of anti-cancer treatment on lung tissues (13-14).

Older patients suffering from irAEs following immunotherapy had a higher rate compared to younger patients. Studies have examined this phenomenon in more detail, finding that when age increases, the immune response does not rely much on the effectiveness of T cells (15). Many of those aged patients also showed the presence of comorbidities that could warrant the effectiveness of the immune response by limiting the T cell activity (16). Based on the regression analysis, the age factor turned out to be the most significant of all. Even though not much data has been available to study the degree of possibility associated with prior lung complications, they still surfaced as a noteworthy risk. Because of this, it is critical to screen patients eligible for the treatment thoroughly. This could help determine which patients may benefit from being monitored closely and those who may require interventions as preventative measures (17-18).

The observations made concerning the or rather composition of the occurrence rates are making it possible for all immune-related adverse events to be fully explained. Is there a detailed explanation? Yes, it is important because every cancer has its' peculiar character, ways of behavior, and the surrounding environment. The presence of ICIs and their overall action instead of being a single declaration is more of an individualized nature and will depend on the surrounding structure of the neoplasm (19). In the same way, various Neoplasm characters drive volumes across many sites Third from the poser identifier: Immunological tumor microenvironment in lung cancer (20). Different tumors have different structures and compositions that would work against or for each other to bring forth the comprehension and coordinate differences observed in contrast with their corresponding clinical target (21).

Although this research explains important associations, it is necessary to consider its shortcomings. The inherent weakness of a retrospective design is the inability to prove causal relationships and

the dependence on medical charts may result in irAE underreporting or misclassification (22). There is a need for future studies of these problems using prospective designs with standardized definitions of adverse events. Furthermore, it may be useful to investigate the genetic and molecular basis of the iRAs to understand the reasons for increased susceptibility in some populations (23-25).

To summarize, the outcome of this study reaffirms the need for individualized medicine in the management of patients with cancer. Clinicians can use this information to monitor patients more closely and make therapeutic choices to achieve better patient outcomes. More studies are required to examine the likelihood of the existence of irAE predictive biomarkers which may significantly change the management of cancer patients undergoing immunotherapy.

Conclusion

This study highlights the significant prevalence of pulmonary irAEs among cancer patients treated with immune checkpoint inhibitors, particularly in those with advanced age and pre-existing lung conditions. The identification of these risk factors underscores the necessity for vigilant monitoring and tailored treatment approaches in oncology. Future research should focus on discovering predictive biomarkers that can enhance patient stratification and improve outcomes in this vulnerable population.

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