**Adverse reaction signal mining of off-label use of immune checkpoint inhibitors based on** **the FAERS database**

**Objective:** Off-label use of immune checkpoint inhibitors (ICIs) is prevalent in clinical treatment. However, the safety of off-label use of ICIs remains unclear.

**Methods:** Adverse Event Reports on the FDA Adverse Event Reporting System (FAERS) database including demographic, drug, adverse reaction and outcome records from April 2011 to December 2023 were collected. Patients with off-label use were identified using the MedDra Dictionary. We performed a disproportionality analysis using reporting odds ratios (ROR) and proportional reporting ratios (PRR) to detect adverse reaction signals of off-label use of ICIs. Logistic regression analysis was used to evaluate the association between off-label use and the risk of serious outcomes in patients with ICI use after adjusting for confounders, including sex, age, and targets of ICIs. The definition of serious outcomes included life-threatening events or hospitalization, disability, and death.

**Results:** 142,679 cases were reported using ICIs, of whom 9044 cases had off-label use (52.7% male). The average age of patients with off-label use of ICIs was 61.79±14.67 years. Lung cancer was the most common indication for off-label use of ICIs, followed by skin and kidney cancer. The joint positive signals aggregated in endocrine disorders (ROR: 8.04, 95% CI 7.38-8.75; PRR: 7.56) and hepatobiliary disorders (ROR: 2.77, 95% CI 2.56-3.01; PRR: 3.15). Logistic regression analysis showed that off-label use of ICIs was associated with a decrease in the reported frequency of serious outcomes (adjusted OR=0.55, 95%CI: 0.52-0.58).

**Conclusion:** This study suggests that adverse reactions related to endocrine and liver disorders should be generally considered for off-label use of ICIs in clinical practice regardless of cancer types. The risk of serious adverse outcomes from off-label use of ICIs may be lower than for on-label use, but further evidence is needed to demonstrate the safety of different situations of off-label use.

**Keywords:** Pharmacovigilance; Adverse reactions; Signal mining; Off-label use