Predictors of Hepatotoxicity in Patients Receiving Immune Checkpoint Inhibitors: A large Population-based Study

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Introduction and Aim

Immune checkpoint inhibitors (ICPI) are monoclonal antibodies that interrupt co-inhibitory signaling pathways (e.g cytotoxic T-lymphocyte antigen-4, programmed cell death protein-1, and its ligand PD-L1) and promote immune-mediated eradication of cell tumors. The use of ICPI has emerged in recent years as an efficacious treatment for advanced malignancies. Immune medicated hepatotoxicity is an established adverse event associated with ICPI utilization. The aim of this study is to determine the predictors of hepatotoxicity in patients receiving ICPI.

Methods

We reviewed data from a large commercial database (Explorys IBM) that aggregates electronic health records from 26 large nationwide healthcare systems. Using systemized nomenclature of clinical medical terms (SNOMED CT) we identified adults who received ICPI from 2011 to 2021. We excluded patients with diagnosis of alcoholism, viral hepatitis, other drug induced liver injury (DILI), and biliary disease. Of this cohort, we collected data on hepatocellular injury after the initiation of ICPI. Demographic information was collected. Data on potential risk factors were collected including malnutrition, chronic kidney disease (CKD), metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), smoking, concomitant use of cytochrome P450- CYP2E1 enhancing medications and the use of ICPI combination. Univariable and multivariable logistic regression analyses were performed. IBM SPSS® Statistics version 28.0.1 is used for statistical analysis.

Results

Out of 69 million adults in the database, 21060 received ICPI (0.03%) of whom 1780 had ICPI-induced hepatotoxicity (8.4%). Men received more ICPI than women (57.4% vs 42.5%). The majority who received ICPI were > 65 years old (63.7%). Table 1 summarizes the characteristics of patients received ICPI. In multivariable model, NAFLD & the use of ICPI combination were most associated with hepatotoxicity (OR 4.29 [95% CI: 4.15-4.43)] & (OR 4.30 [95% CI: 4.18-4.43]), respectively. These factors were closely followed by metabolic syndrome & malnutrition (OR 3.16 [95% CI: 3.10-3.22]) & (OR 3.07 [95% CI: 2.97-3.16]), respectively. Moreover, ICPI-induced hepatotoxicity was significantly associated with CKD (OR 2.46 [95% CI: 2.39-2.52]), smoking (OR 2.33 [95% CI: 2.28-2.38]), concomitant CYP2E1 inducers (OR 2.85 [95% CI: 2.77-2.93]), and to a lesser extent, with age >65 (OR 1.39 [95% CI: 1.33-1.44]). No significant association with gender was noted (OR 1.00 [95% CI: 0.93-1.07]), Figure 1.

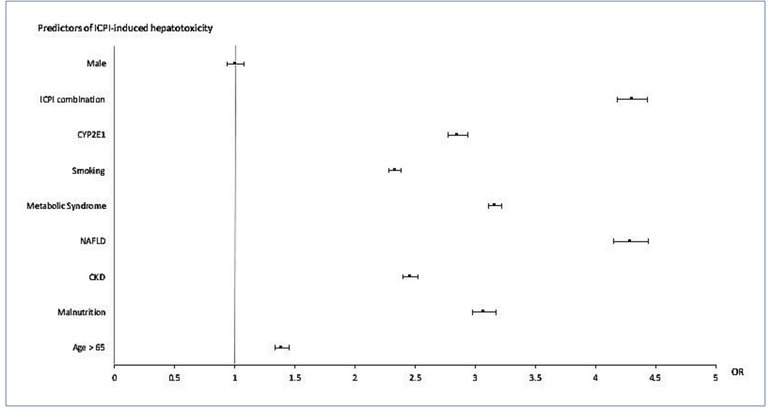

Table 1: Characteristics of patients in cohort

	ICPI		ICPI + Hepatoxicity	
Total patients	21060		1780	
	Number	**Percentage**	**Number**	**Percentage**
Age				
18-65	7630	36.3%	630	35.4%
>65	13430	63.7%	1150	64.6%
Gender				
Female	8960	42.5%	760	42.7%
Male	12100	57.4%	1020	57.3%
NAFLD	1530	7.2%	270	15.1%
Malnutrition	6080	28.8%	770	43.2%
Metabolic Syndrome	230	1.09%	50	2.8%
CKD	5140	24.4%	550	30.8%
Smoking	6400	30.3%	640	35.9%
CYP2E1 inducers	2140	10.1%	330	18.5%

ICPI: Immune checkpoint inhibitor; NAFLD: Non-alcoholic fatty liver disease; CKD: Chronic Kidney disease

Supplementary table 1: Medications addressed in cohort

ICPI	Pembrolizumab, Ipilimumab, Nivolumab, Atezolizumab, Durvalumab
CYP2E1 inducers	Carbamazepine, Barbiturates, Phenytoin, Rifampicin, Isoniazid, Ritonavir

Conclusion

This large retrospective study shows that the highest predictors of ICPI-induced hepatoxicity were underlying NAFLD and the use of combination ICPIs. Other significant factors were age >65, metabolic syndrome, malnutrition, CKD, smoking, and concomitant use of cytochrome P450- CYP2E1 inducers. Further studies are needed to evaluate the pathophysiology and molecular aspects of these relationships.

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