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Incidence, mortality, and risk factors of immunotherapy-associated hepatotoxicity: A nationwide hospitalization analysis☆

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Abstract

Background and aims: Anti-neoplastic immunotherapy has revolutionized cancer management; however. its safety profile with respect to liver-related injury remains largely unexplored. Herein, we analyzed a United States national database to determine the incidence, mortality, and predictors of hepatotoxicity in the setting of anti-neoplastic immunotherapy.

Methods: This was a nationwide retrospective study of hospital encounters from 2011 to 2014 using the National Inpatient Sample (NIS) database. We utilized the International Classification of Diseases, Ninth Revision (ICD-9) coding system to identify all adult patients who underwent anti-neoplastic immunotherapy during hospitalization. The primary outcome was the incidence of

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Authors' contributions

S. Weissman, S. Saleem, M. Krupka, F. Inayat, and M. Aziz assisted with data acquisition, analyses, and manuscript preparation. S. Weissman, S. Saleem, S. Sharma drafted and critically revised the manuscript. J. H. Tabibian critically revised the manuscript and provided input regarding methodology. J. H. Tabibian provided direct supervision and guidance. S. Weissman is the article guarantor. All authors agree to the final version of this manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

hepatotoxicity during the same hospitalization. Secondary outcomes included in-hospital mortality as well as socioeconomic and ethno-racial predictors of hepatotoxicity. Analyses were performed using IBM SPSS Statistics 23.0.

Results: The sample included 3002 patients who underwent inpatient anti-neoplastic immunotherapy. The incidence of hepatotoxicity was 10.1%, which was significantly higher as compared to a matched inpatient population (adjusted odds ratio (aOR) 4.93, 95% confidence interval (CI): 3.80–6.40. $P = 0.001$). No significant mortality difference was seen in those that developed hepatotoxicity compared to those who did not (aOR 0.47. 95% CI: 0.03–8.03, $P = 0.612$). Age under 60 (aOR 1.56. 95% CI: 123–1.78, $P = 0.050$) and white race (aOR 1.85. 95% CI: 1.35–2.04, $P<0.010$) were independent risk factors for developing immunotherapy-associated hepatotoxicity.

Conclusions: In this large, nationwide database analysis, we found that anti-neoplastic immunotherapy was associated with a nearly five-fold risk of in-hospital hepatotoxicity as compared to a matched inpatient population, though without an associated mortality difference. Additionally, younger age and white race were identified as predictors of immunotherapy-associated hepatotoxicity. Heightened vigilance and prospective investigation of the risk factors and liver-related adverse effects of anti-neoplastic immunotherapy are warranted.

Keywords

Hepatotoxicity; Tumor immunotherapy; Liver enzymes; Outcomes; Risk factors; Mortality

1. Introduction

Anti-neoplastic immunotherapy consists of monoclonal antibodies that target immune checkpoints inhibitors thus stimulating the natural T-cell mediated immune response.[1] Acting as cellular checkpoint inhibitors, they augment the body's response against cancer.[2] Taken together, they have revolutionized the treatment of cancer owing to their ability to improve overall survival in a wide variety of cancers, even after treatment failure with conventional cytotoxic chemotherapy.[2–4] As anti-neoplastic immunotherapy is relatively new, the available literature regarding its safety profile, particularly the potential for causing hepatotoxicity, is scant.[5,6]

Given novel anti-neoplastic immunotherapies are expected to be enlisted amongst the growing armamentarium of cancer treatments, the need to understand their toxicity and adverse effects is paramount.[5–7] Herein, we analyzed a United States (US) national database to determine: (i) the real-world incidence of hepatotoxicity in the setting of anti-neoplastic immunotherapy, (ii) mortality associated with hepatotoxicity, and (iii) potential ethno-racial and socioeconomic predictors of hepatotoxicity in this population.

2. Methods

2.1. Data source

In this retrospective study patients were identified using the National Inpatient Sample (NIS) database from 2011 to 2014. The NIS is the largest publicly available all-payer inpatient

database in the US containing more than seven million hospital admission per annum, as a part of the Healthcare Cost and Utilization Project (HCUP). The HCUP database contains de-identified data on nationwide hospital admissions including demographic and clinical data, comorbidities, discharge diagnoses, procedures, outcomes, and hospitalization costs.

2.2. Ethical approval

Institutional review board approval was not needed as only de-identified, publically-available data were obtained.

2.3. Study population and variables

We identified hospital encounters for patients without a history of cirrhosis who underwent anti-neoplastic immunotherapy from 2011 to 2014 using the International Classification of Diseases. Ninth Revision (ICD-9) diagnostic code (V58.12) (Fig. 1). We then identified the presence/diagnosis of jaundice (ICD-9 code-782.4), abnormal liver enzymes (ICD-9 codes-790.4 and 790.5), abnormal coagulation profile (ICD-9 code-790.92), and/or drug-induced hepatitis (ICD-9 code-573.3) amongst these patients. The study variables, including age, sex, race/ethnicity and median household income (by quartile) were recorded.

2.4. Study outcomes

The primary outcome was the incidence of hepatotoxicity as defined by: jaundice, liver enzyme abnormalities, abnormal coagulation profile, and/or the presence of drug-induced hepatitis, amongst patients who underwent anti-neoplastic. Secondary outcomes were mortality among patients who developed hepatotoxicity and socioeconomic and/or ethno-racial predictors of hepatotoxicity in this population.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS statistics 23.0 (Armonk, NY, USA). This software facilitates analysis to produce nationally-representative unbiased results, variance estimates, and *P*-values. Weights for patient-level observations was implemented. We used Chi-square test and student's *t*-test for categorical and continuous variables, respectively, to assess the patient demographics and hospital diagnosis between two cohorts (patients with an encounter for anti-neoplastic immunotherapy vs. those without) in hospitalized patients. Univariate analysis was initially performed to calculate adjusted odds ratio (aOR) and determine potential confounders significantly associated with the outcomes. Multivariate regression models were built adjusting for age, sex, race/ethnicity and median household income to evaluate the risk of hepatotoxicity in patients receiving anti-neoplastic immunotherapy. Logistic regression was used for binary outcomes, and linear regression was used for continuous outcomes. All *P*-values were two sided, with 0.05 as threshold for statistical significance.

3. Results

3.1 Patient characteristics

Three thousand and two adult patients with a hospital encounter for anti-neoplastic immunotherapy were included in the study. The mean age was 54.33 years, the majority of patients were male (62.8%), white (83.1%), and from higher median household incomes (32.5%) (top quartile–76–100th percentile, of median household income).

3.2 Liver enzyme abnormalities

The incidence of liver enzyme (aspartate aminotransferase and alanine aminotransferase) abnormalities in patients who underwent anti-neoplastic immunotherapy was 3.9% (116/3002). Upon multivariate analysis, there was a significantly increased likelihood of developing liver enzyme abnormalities in patients who underwent anti-neoplastic immunotherapy compared to a matched inpatient population (aOR 2.87, 95% confidence interval (CI): 1.94–4.23, $P < 0.001$).

3.3. Jaundice

The incidence of developing jaundice in patients who underwent anti-neoplastic immunotherapy was 6.4% (193/3002). Upon multivariate analysis there was a significantly increased likelihood of developing jaundice in patients who underwent anti-neoplastic immunotherapy compared to a matched inpatient population (aOR 37.04. 95% CI: 15.15–90.00, $P < 0.001$).

3.4. Abnormal coagulation profile

The incidence of developing an abnormal coagulation profile in patients who underwent anti-neoplastic immunotherapy was 0.5% (16/3002). Although, there were higher odds of developing an abnormal coagulation profile in univariate analysis, after adjusting confounders upon multivariate analysis, it was not statistically significant compared to a matched inpatient population (aOR 0.62, 95% CI: 0.34–1.15, $P < 0.001$).

3.5. Drug-induced hepatitis

The incidence of developing drug-induced hepatitis in patients who underwent anti-neoplastic immunotherapy was 0.3% (10/3002). Although, there were higher odds of drug-induced hepatitis in univariate analysis, after adjusting for confounders upon multi-variate analysis, it was not statistically significant (aOR 4.60, 95% CI: 0.98–21.27, $P = 0.050$).

3.6. Composite primary outcome

The composite outcome of hepatotoxicity, as defined a *priori.* amongst patients who underwent anti-neoplastic immunotherapy was 10.1%(304/3002). Upon multivariate analysis, the likelihood of developing hepatotoxicity in patients who underwent anti-neoplastic immunotherapy was significantly increased as compared to a matched inpatient population (aOR 4.93, 95% CI: 3.80–6.40, $P = 0.001$). See Table 1 for additional data on the incidence of developing hepatotoxicity in patients who underwent anti-neoplastic immunotherapy.

3.7. Mortality

Of the 304 patients that developed hepatotoxicity after undergoing anti-neoplastic immunotherapy, 9 (3.0%) died in the inpatient setting. However, upon multivariate analysis, this was not statistically significant compared to those who did not develop anti-neoplastic immunotherapy-associated hepatotoxicity (aOR 0.47, 95% CI: 0.03–8.03. $P = 0.612$).

3.8. Ethno-racial and socioeconomic predictors of immunotherapy-associated hepatotoxicity

Of the 304 patients that developed hepatotoxicity, 192 (63.2%) were male, 252 (88.1%) were white, and 99 (33.4%) were from the top quartile—76–100th percentile group of median household income. There was a significantly increased risk of developing hepatotoxicity after undergoing anti-neoplastic immunotherapy if one was younger than 60 years of age (aOR 1.56, 95% CI: 1.23–1.78, $P = 0.050$) or white (aOR 1.85, 95% CI: 1.35–2.04, $P < 0.010$). Male gender (aOR 2.24, 95% CI: 0.82–6.13, $P = 0.110$) and median household income >$66,000 (the top quartile—76–100th percentile) (aOR 1.83, 95% CI: 0.62–5.45, $P = 0.270$) were not associated with an increased risk of developing hepatotoxicity. See Table 2 for more details regarding predictors of developing hepatotoxicity in this setting.

4. Discussion

By way of this large, nationally representative cohort study, we identified a significant association between anti-neoplastic immunotherapy and the development of hepatotoxicity —as 1 in 10 patients who received anti-neoplastic immunotherapy developed hepatotoxicity. Compared to a matched inpatient population, this represents a nearly five-fold increased risk. In particular, anti-neoplastic immunotherapy conveyed a significantly increased risk of developing jaundice and liver enzyme abnormalities.

Awareness as to the array and frequency of adverse effects of anti-neoplastic immunotherapy is important for both physicians and patients. Physicians must understand the risks involved in specific treatment options and be able to communicate this information to patients to allow for informed and shared medical decision making. Additionally, the recognition of these potential adverse effects is an important step towards further investigating and conducting additional prospective studies to gain better insight regarding this class of drugs and their side effect profiles.[8,9]

Our findings of no mortality difference amongst these patients appears to be consistent with the current literature.[10,11] Additionally, previous studies have suggested that anti-neoplastic immunotherapy may have significant hepatotoxic effects.[10–12] Being that prior studies examined small, homogenous populations, our findings confirm this association on a larger, more nationally representative scale.

Our finding of age (younger than 60 years) being a significant predictor for the development of hepatotoxicity in patients receiving anti-neoplastic immunotherapy has not been reported in literature to date. This result may be particularly important for clinicians treating malignancies that tend to manifest in younger peoples. A study by Wang *et al.*[12] found a number of additional risk factors for the development of hepatotoxicity in patients being

treated with anti-neoplastic immunotherapy. Specifically, the type and dose of immune checkpoint Inhibitor used, as well as the presence of a pre-existing autoimmune/inflammatory conditions or chronic infection, have been shown to be culprits.[12–14] These risk factors, as well as the other risk factors elucidated by our study should be considered when determining a specific medication regimen for cancer patients.[8,9]

Several study limitations should be recognized. Firstly, as this study was entirely ICD code-based, laboratory values and physical examination could not be analyzed. As such, a certain degree of granularity is missing. Also, as with any other national database, miscoding can occur and lead to bias. In addition, our finding of white race being a risk factor for the development of hepatotoxicity should be interpreted with caution as the majority of patients (83.1%) in the dataset were, indeed, white race. Moreover, this study was conducted solely in the inpatient setting, thus the ability to draw conclusions pertaining to patients in other settings, *e.g.* infusion centers, remains uncertain. Finally, this study was retrospective in nature, and the results should be confirmed in a prospective fashion. Despite these, this study also has numerous strengths. Primarily, the large sample size accrued limits bias and adds value to our findings. Additionally, we provided nationally representative data, evenly distribution among the whole US. As such, we believe that, overall, our study was successful in identifying a significantly increased risk of hepatotoxicity associated with immunotherapy.

In conclusion, anti-neoplastic immunotherapy is associated with a nearly five-fold risk for developing hepatotoxicity as compared to the general inpatient population, and younger age and white ethno-racial background appear to be independent predictors of immunotherapy-associated hepatotoxicity. These findings are insightful and important, given the relative novelty and growing use of these drugs. Based on these findings, heightened clinical vigilance pertaining to risk factors for and liver-related adverse effects of anti-neoplastic immunotherapy would seem warranted. Nevertheless, prospective studies are needed to confirm these findings for further clinical application.

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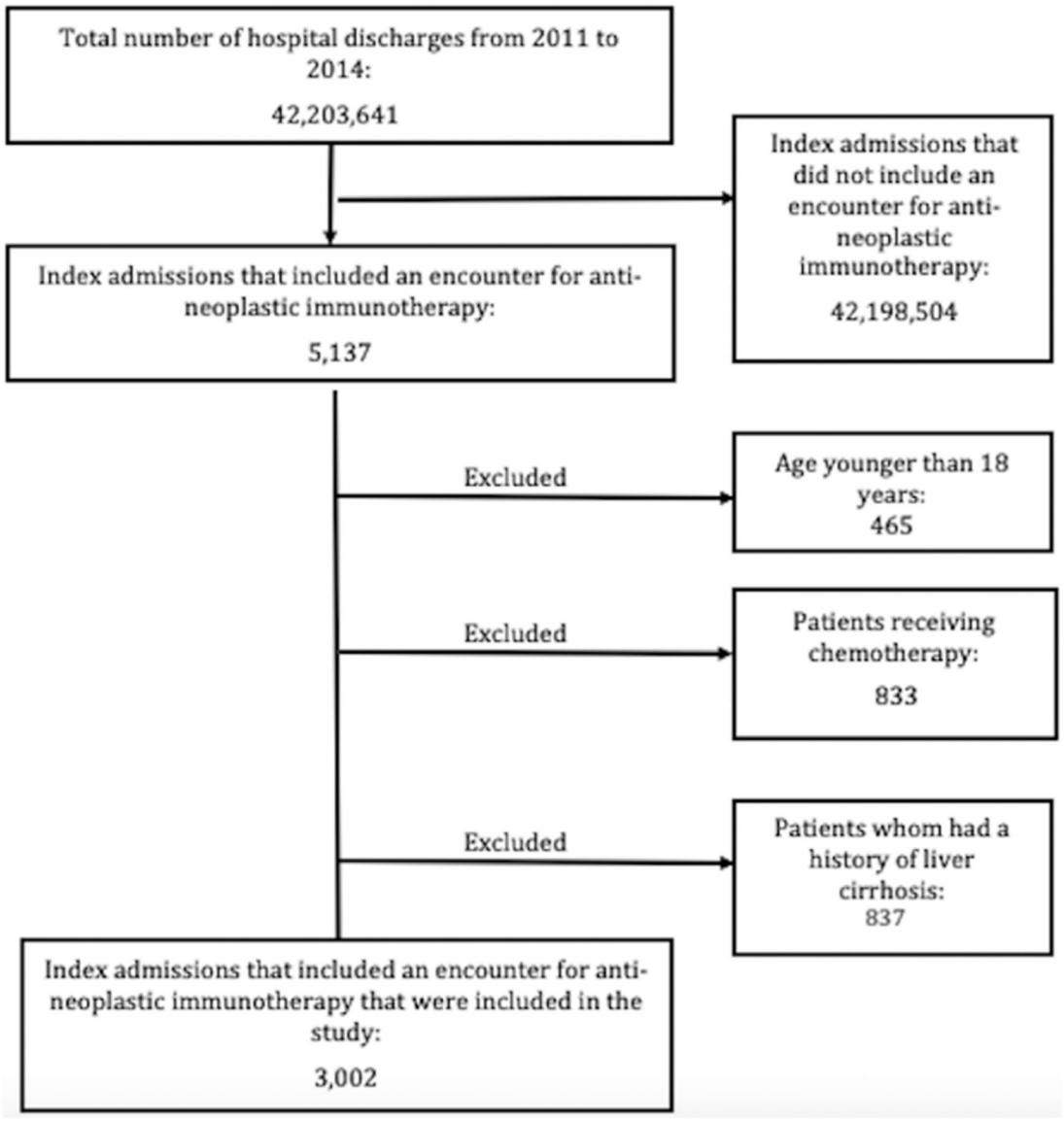

Fig. 1.

Patient inclusion and exclusion flow diagram based upon United States hospital discharges using the Nationwide Inpatient Sample (NIS) database.

Table 1

Hepatotoxicity in those who underwent anti-neoplastic immunotherapy.

Factors	Encounters for immunotherapy (*n* = 3002)	No encounter for immunotherapy (*n* = 42.198.504)	aOR (95%CI)	*P*-value
Abnormal liver enzymes	116 (3.9)	506,382 (12)	2.87 (1.94–423)	<0.001
Jaundice	193 (6.4)	84,397 (0.2)	37.04 (15.15–90.00)	<0.001
Abnormal coagulation profile	16 (0.5)	379,786 (0.9)	0.62 (0.34–1.15)	<0.001
Drug induced hepatitis	10 (0.3)	42,199 (0.1)	5.46 (0.98–21.27)	0.050

Data are shown as *n* (%).

Abbreviation: aOR, adjusted odds ratio.

Table 2

The ethno-racial and socioeconomic predictors for the development of hepatotoxicity in patients who underwent anti-neoplastic immunotherapy.

Variable	Hepatotoxicity (*n* = 304)	No hepatotoxicity (*n* = 2698)	*P*-value
Male	192 (63.2)	1694 (62.8)	0.899
Age			0.020
18–39 years	52 (17.1)	355 (13.2)	
40–59 years	183 (60.2)	1276 (47.3)	
60–79 years	66 (21.7)	998 (37.0)	
≥80 years	3 (1.0)	69 (2.6)	
Median household income			0.160
$1–$39,999	48 (15.9)	510 (18.9)	
$40,000–$50,999	83 (27.4)	607 (22.5)	
$51.000–$65,999	71 (23.3)	699 (25.9)	
$66,000	102 (33.4)	882 (32.7)	
Race/ethnicity			0.010
White	268 (88.1)	2228 (82.6)	
Black	4 (1.4)	156 (5.8)	
Hispanic	20 (6.6)	175 (6.5)	
Asian or Pacific Islander	2 (0.7)	67 (2.5)	
Native American	1 (0.3)	8 (0.3)	
Other	9 (2.8)	64 (2.4)	

Data are shown as *n* (%). Percentages may not total 100 because of rounding.