# Rate of Hearing Loss in Platinum-Naïve Patients Receiving Immune Checkpoint Inhibitors

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## Abstract

**Objective:** Hearing loss from immune-checkpoint inhibitors (ICIs) has been documented in case reports and case series. We present the largest retrospective study investigating the rate of ICI-related ototoxicity in a monitored cohort of platinum-naïve patients.

**Study Design:** Retrospective cohort study

**Setting:** Tertiary-care center.

**Methods**: Patients treated with ICI between January 1, 2017 and December 31, 2022 with baseline and post-treatment audiograms were included. Patients with a history of platinum-based chemotherapy were excluded. Demographics, oncologic diagnosis, ICI treatment details, and temporal bone irradiation (TBRT) were recorded. Audiometric thresholds were compared before and after ICI therapy. The primary outcome measure was a change in hearing as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Secondary outcome measures included changes in hearing using the American Speech-Language-Hearing Association (ASHA) and TUNE criteria.

**Results:** Among 15,390 ICI recipients, 29 platinum-naïve patients met inclusion criteria. Six of 29 patients (20.7%) experienced a CTCAE grade 1 or higher hearing loss. The proportions of hearing loss as defined by ASHA and TUNE criteria were 44.8% and 27.6%, respectively. The interval between audiograms was statistically associated with an increased proportion of hearing loss (CTCAE: p<0.01; ASHA: p = 0.05; TUNE: p = 0.45). None of the other potential covariates believed to be confounders were significantly associated with the outcome.

**Conclusion**: A significant proportion of our monitored platinum-naïve ICI patients met hearing loss criteria. Prospective studies with standardized audiologic surveillance are needed to further quantify the true incidence of ICI ototoxicity.

## Introduction

- Immune checkpoint inhibitors (ICI) have expanding indications for cancer treatment[1,2]
- Numerous immune-related adverse events (irAEs) have been reported but are incompletely characterized[3]
- Audiovestibular dysfunction is an underexplored irAE[3-7]
  - Long-term impact on cancer survivorship quality of life[8,9]

**Objectives:**

- Estimate proportion of hearing loss (HL) in patients initiating ICI
- Explore demographic factors that may influence ICI-related HL

## Methods & Materials

**Retrospective case series (IRB# PA19-0106):**

- Adult patients who received ICI with 2 audiograms timed pre- and post-ICI initiation
- Exclusion: Platinum-based chemotherapy exposure

**Primary outcome:**

- Incidence of HL as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[10]

**Secondary outcomes:**

- Incidence of HL by American Speech-Language-Hearing Association (ASHA)[11] and TUNE scale criteria[12]
- Association between patient factors and HL with univariable logistic regression
- Two-tailed t-test comparing time interval of auditory monitoring and from ICI-initiation to follow-up auditory monitoring in non-HL and HL patients

**Statistical considerations:**

- p<0.05, 95% confidence intervals reported

## Results

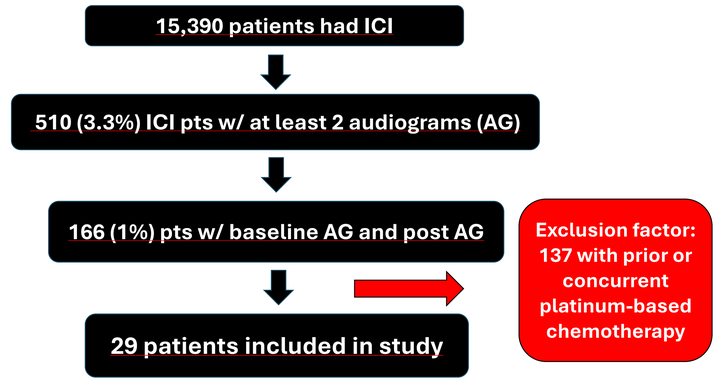


Figure 1- Identifying patient cohort and current percentage of patients receiving ICI and auditory monitoring.

| Patient Factor | N(%) or mean ± SD |
|---|---|
| Age at start of ICI, years | 65.9 ± 16.0 |
| Male sex | 18 (62%) |
| No. of ICI cycles | 6.4 ± 6.5 |
| No. of pts receiving >1 agent | 4 (14%) |
| Time from ICI to post- AG, days | 121.7 ± 114.4 |
| Otologic Surgery | |
| None/Prior | 17 (59%) |
| During | 12 (41%) |
| HN Radiation | 14 (48%) |
| Radiation dose to left cochlea, Gy | 15.2 ± 16.6 |
| Radiation dose to right cochlea, Gy | 15.4 ± 14.5 |

Table 1- Cohort characteristics.

- No demographic factors were significantly associated with HL in all 3 grading scales
- Interval between audiograms statistically associated with increased proportion of HL

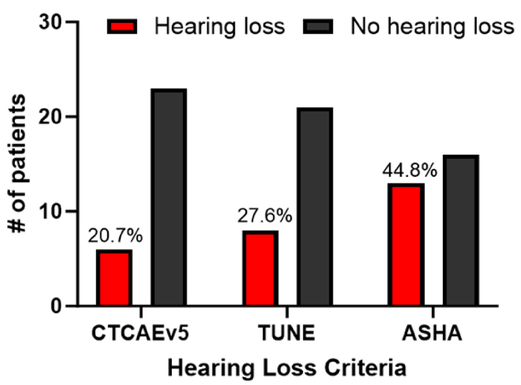


Figure 2- Incidence of hearing loss per CTCAE, TUNE, and ASHA scales.

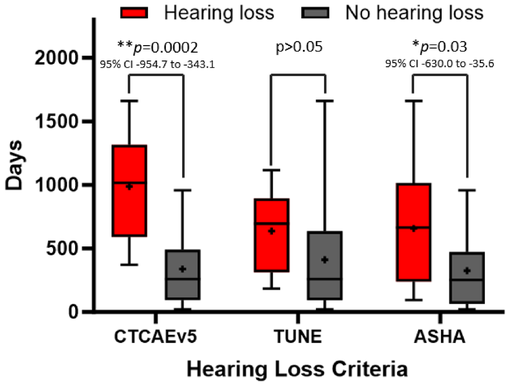


Figure 3- Time from ICI initiation to follow-up AG between HL and non-HL patients.

## Discussion & Conclusion

- Ototoxic hearing loss is a side effect of ICI treatment.
- Possible mechanisms leading to HL:
  - Damage to intra-labyrinthine melanocyte-like cells.
  - Pathophysiological response resembling autoimmune inner ear disease.
- Enrollment in auditory monitoring protocols is insufficient.[3-7]
- **Limitations:** Retrospective design, small sample size, and vestibular and tinnitus morbidity unanswered.
- **Conclusion:**
  - Hearing loss found in 20 – 45% of our ICI patient cohort.
  - Further larger retrospective and prospective studies are needed.
  - Auditory monitoring protocols are recommended for patients receiving ICI.

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