# Immune Checkpoint Inhibitors and Venous Thromboembolism in Patients with Head and Neck Cancer Undergoing Surgery

Febronia M. Mansour BS[1], Komal Akhtar MD[2], Kiranya E. Arnold MD[3]

1: SUNY Upstate Alan & Marlene Norton College of Medicine
2: SUNY Upstate, Division of Hematology and Oncology
3: SUNY Upstate, Department of Otolaryngology

## Introduction

- Patients with cancer have an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) due to factors like tumor biology, oncologic surgery, and use of chemotherapeutic agents.[1]
- Recent evidence suggests that immune checkpoint inhibitors (ICIs) may also increase venous thromboembolism (VTE) risk by means of triggering an inflammatory response.[2]
- Despite the success of clinical trials like KEYNOTE-689, these trials were not designed to evaluate differences in VTE events among patients receiving ICI treatment.[3,4]
- Therefore, with the rapid growth of ICIs in head and neck cancer treatment, understanding the risk of VTE as a consequence is particularly relevant.

**Table 1: Patient characteristics after propensity score matching***

**Characteristics After Propensity Score Matching**
**Cohort 1 (N = 1,471) and Cohort 2 (N = 1,471)**

**Demographics**

| Cohort | | | Mean ± SD | Patients | % of Cohort | P-Value | Std diff. |
|---|---|---|---|---|---|---|---|
| 1<br>2 | AI | Age at Index | 63.9 +/- 13.3<br>64.1 +/- 13.1 | 1,471<br>1,471 | 100%<br>100% | 0.566 | 0.021 |
| 1<br>2 | 2106-3 | White | | 1,195<br>1,219 | 81.2%<br>82.9% | 0.249 | 0.043 |
| 1<br>2 | UNK | Unknown Race | | 86<br>84 | 5.8%<br>5.7% | 0.874 | 0.006 |
| 1<br>2 | F | Female | | 371<br>370 | 25.2%<br>25.2% | 0.966 | 0.002 |
| 1<br>2 | 2054-5 | Black or African American | | 79<br>77 | 5.4%<br>5.2% | 0.869 | 0.006 |
| 1<br>2 | M | Male | | 1,044<br>1,049 | 71.0%<br>71.3% | 0.839 | 0.008 |
| 1<br>2 | 2028-9 | Asian | | 50<br>36 | 3.4%<br>2.4% | 0.125 | 0.057 |

**Diagnosis**

| Cohort | | | Mean ± SD | Patients | % of Cohort | P-Value | Std diff. |
|---|---|---|---|---|---|---|---|
| 1<br>2 | J40-J4A | Chronic lower respiratory diseases | | 165<br>178 | 11.2%<br>12.1% | 0.455 | 0.028 |
| 1<br>2 | K50-K52 | Noninfective enteritis and colitis | | 19<br>23 | 1.3%<br>1.6% | 0.534 | 0.023 |
| 1<br>2 | I26 | Pulmonary embolism | | 32<br>33 | 2.2%<br>2.2% | 0.900 | 0.005 |
| 1<br>2 | I82 | Other venous embolism and thrombosis | | 55<br>52 | 3.7%<br>3.5% | 0.768 | 0.011 |
| 1<br>2 | I83 | Varicose veins of lower extremities | | 10<br>10 | 0.7%<br>0.7% | 1 | <0.001 |
| 1<br>2 | I21 | Acute myocardial infarction | | 21<br>20 | 1.4%<br>1.4% | 0.875 | 0.006 |
| 1<br>2 | D68.51 | Activated protein C resistance | | 0<br>0 | 0%<br>0% | -- | -- |

*Patients were also matched according to history of anticoagulant or antiplatelet use, radiation and/or chemotherapeutic history, TNM stage, and BMI.

## Materials & Methods

- This study was approved by the SUNY Upstate IRB.
- We performed a propensity score-matched cohort study using the TriNetX Global Collaborative Network Database.
- Patients were identified with ICD-10 and CPT codes and were included according to the following criteria:
  - Adults 18 – 90 years with head and neck cancer (excl. thyroid)
  - Underwent ablative and/or reconstructive surgery
  - Received ICI therapy with Nivolumab, Pembrolizumab, and/or Cemiplimab within 12 months before and up to 3 months after surgery
    - The control cohort did not receive ICIs during this time period
- The index event was defined as the day a patient satisfied criteria for relevant CPT and ICD-10 codes, with or without related ICIs.
- **Study Outcomes**
  - *Primary Outcome:* 3-month composite rate of VTE
  - *Secondary Outcomes:* 3-month rates of DVT and PE
- **Statistical Analysis**
  - Cohorts were propensity score matched in a 1:1 ratio through a logistic regression
  - Baseline characteristics were compared with standardized mean differences using Chi-squared (categorical variables) and independent t-tests (continuous variables)
  - A propensity score was generated for each patient according to previously defined methods with a standardized mean difference (SMD) <1.0 suggesting balanced covariates.[5]

## Results

- Mean ages for the experimental and control cohorts were 63.9 ± 13.3 and 64.1 ± 13.1 years, respectively (**Table 1**)
- Both cohorts had higher percentages of male (71.0% vs 71.3%, SMD = 0.008) and Caucasian patients (81.2% vs 82.9%, SMD = 0.04) (**Table 1**)

**Table 2: Primary and secondary Study Outcomes**

**Study Outcomes**

| | Experimental cohort | | | Control Cohort | | | Odds ratio | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Patients in cohort | Patients with outcome | Risk | Patients in cohort | Patients with outcome | Risk | | |
| **Composite VTE Rate** | 1,297 | 60 | 4.6% | 1,350 | 39 | 2.9% | 1.6 | 1.1, 2.5 |
| **PE** | 1,397 | 24 | 1.7% | 1,420 | 10 | 0.7% | 2.5 | 1.2, 5.2 |
| **DVT** | 1,339 | 50 | 3.7% | 1,372 | 29 | 2.1% | 1.8 | 1.1, 2.9 |

- The risk of PE in the ICI cohort was 1.7% as compared to 0.7% in the control group (OR, 2.5; 95% CI, 1.2, 5.2) (**Table 2**)
- The risk of DVT was higher in the ICI cohort (3.7% versus 2.1%; OR, 1.8; 95% CI, 1.1, 2.9) (**Table 2**)

## Discussion & Conclusions

- ICIs were associated with increased risk of composite VTE when administered within 12-months prior to and/or up to 3-months after surgery for HNC.
- The overall increase in composite VTE risk was predominantly driven by a **higher rate of DVT in the ICI-treated group**.
- The statistically significant increase in PE events is clinically relevant because they are associated with **higher rates of mortality.**

Questions? Contact MansourF@Upstate.edu

### References

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