Associations of influenza vaccination with severity of immune-related adverse events in patients with advanced thoracic cancers on immune checkpoint inhibitors

Emily Pei-Ying Lin 1,2,3,4,5, Li-Ching Huang1,2, Jennifer Whisenant6, Sally York6,7, Travis Osterman6,7,8, Jennifer Lewis6,7, Wade Iams6,7, Emily Skotte6, Amanda Cass 6, Chih-Yuan Hsu1,2, Yu Shyr1,2,7,9 and Leora Horn6,7,9

1Dept of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA. 2Center for Quantitative Sciences, Vanderbilt University Medical Center, Nashville, TN, USA. 3Dept of Medical Research, Taipei Medical University Hospital, Taipei, Taiwan. 4Division of Pulmonary Medicine, Dept of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan. 5Dept of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. 6Division of Hemato-oncology, Dept of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. 7Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA. 8Dept of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA. 9These authors contributed equally.

Corresponding author: Emily Pei-Ying Lin (emilypylin@tmu.edu.tw)

Shareable abstract (@ERSpublications)
Influenza vaccination does not increase toxicity for thoracic cancer patients on immune checkpoint inhibitors, but is associated with a decreased risk of severe immune-related adverse events and could be encouraged, especially in the #COVID19 pandemic https://bit.ly/3bw1z7u

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Abstract

Background Whether influenza vaccination (FV) is associated with the severity of immune-related adverse events (IRAEs) in patients with advanced thoracic cancer on immune checkpoint inhibitors (ICIs) is not fully understood.

Methods Patients enrolled in this retrospective cohort study were identified from the Vanderbilt BioVU database and their medical records were reviewed. Patients with advanced thoracic cancer who received FV within 3 months prior to or during their ICI treatment period were enrolled in the FV-positive cohort and those who did not were enrolled in the FV-negative cohort. The primary objective was to detect whether FV is associated with decreased IRAE severity. The secondary objectives were to evaluate whether FV is associated with a decreased risk for grade 3–5 IRAEs and better survival times. Multivariable ordinal logistic regression was used for the primary analysis.

Results A total of 142 and 105 patients were enrolled in the FV-positive and FV-negative cohorts, respectively. There was no statistically significant difference in patient demographics or cumulative incidences of IRAEs between the two cohorts. In the primary analysis, FV was inversely associated with the severity of IRAEs (OR 0.63; p=0.046). In the secondary analysis, FV was associated with a decreased risk for grade 3–5 IRAEs (OR 0.42; p=0.005). Multivariable Cox regression showed that FV was not associated with survival times.

Conclusions Our study showed that FV does not increase toxicity for patients with advanced thoracic cancer on ICIs and is associated with a decreased risk for grade 3–5 IRAEs. No statistically significant survival differences were found between patients with and without FV.

Introduction

Patients with advanced thoracic cancer are at high risk of developing complications from infectious diseases, especially those frequently affecting the respiratory system, such as influenza and coronavirus disease 2019 (COVID-19) [1]. Influenza and COVID-19 share common symptoms, such as fever, muscle ache, dyspnea, pneumonia and acute respiratory distress syndrome [2]. These two diseases can hardly be differentiated without molecular testing and their co-infections were reported [3].
Prior studies suggested a high risk of influenza-related complications in cancer patients receiving cytotoxic chemotherapy and that vaccination is the primary protective strategy against influenza [1, 4–6]. Accordingly, annual influenza vaccination (FV) for cancer patients is suggested by the guidelines of the National Comprehensive Cancer Network, Infectious Diseases Society of America and Advisory Committee on Immunization Practices [7–9]. Consensus on FV for cancer patients receiving immune checkpoint inhibitors (ICIs), however, has not been reached. This is partially attributed to the unpredictability of the occurrence and severity of immune-related adverse events (IRAEs) relevant to ICI treatment. A recently published multicentre prospective observational study (INVIDIa-2) showed significantly less influenza-like illness in cancer patients on ICIs with FV. The INVIDIa-2 study results, therefore, supported the recommendation for FV in patients with advanced cancers on ICIs based on the overall reduction of influenza-relevant complications [10]. This study, however, did not discuss the association of FV with IRAEs. While three prior studies and a systemic review showed no evidence of increased IRAE incidence among cancer patients receiving FV when they were on ICIs, one study showed the opposite results [11–15]. In addition, data on the associations of FV with IRAE severity in thoracic cancer patients are lacking.

In the COVID-19 pandemic, FV is more important than ever. As immune checkpoint inhibition is taking an increasingly central role in thoracic oncology, it is of particular importance to get a better insight into this issue to decipher whether FV should be encouraged in this patient population. The primary objective of this study was to detect whether FV is associated with decreased IRAE severity. The secondary objectives were to evaluate whether FV is associated with a decreased risk for grade 3–5 IRAEs and better survival times.

Methods

Data source, study population and objectives

Patients enrolled in this retrospective cohort study were identified from the Vanderbilt BioVU database (www.vumc.org/dbmi/biovu) through programmer data pull followed by manual review of the electronic medical records (EMRs). Vanderbilt BioVU is a de-identified EMR-based biorepository that enables longitudinal EMR study and paired genetic data assessment. All data collected were de-identified and the study was approved by the Vanderbilt University Medical Center (Nashville, TN, USA) Institutional Review Board (190712) according to the principles of the Declaration of Helsinki.

Patients who fulfilled the diagnostic codes of the International Classification of Diseases, 9th or 10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) for lung cancer, malignant mesothelioma or thymic cancer (ICD-9-CM 162.0–163.9; ICD-10-CM C33–C34 and C37–C38) and received at least one dose of ICIs between July 2012 and December 2018 were identified. The cut-off date of the data pull was 25 October 2019. The EMRs of the identified subjects were manually reviewed. Only those who fulfilled the inclusion criteria confirmed by the manual review were enrolled. Patients who received FV during or within 3 months prior to their ICI treatment period were subgrouped to the FV-positive cohort and those who did not were subgrouped to the FV-negative cohort.

The primary objective of this study was to detect whether FV is associated with decreased IRAE severity. The secondary objectives were to evaluate whether FV is associated with a decreased risk for grade 3–5 IRAEs and better survival times, i.e. progression-free survival (PFS) and overall survival (OS).

Definitions

The ICIs used in the study population included programmed cell death 1 (PD-1) inhibitors (nivolumab or pembrolizumab), PD-1 ligand 1 (PD-L1) inhibitors (atezolizumab or durvalumab) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors (ipilimumab or tremelimumab). If a therapeutic regimen included a single ICI, it is categorised based on the ICI given. For example, when the regimen is pembrolizumab plus chemotherapy, then it is categorised into the pembrolizumab group. If a regimen included two ICIs, e.g. ipilimumab plus nivolumab or tremelimumab plus durvalumab, it is categorised into the CTLA-4 combination group. Two types of influenza vaccines were used in the study cohort: 1) standard-dose quadrivalent influenza vaccine and 2) high-dose quadrivalent influenza vaccine.

The ICI treatment responses were defined as stable disease, partial response, complete response or progressive disease based on RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria [16]. Severity of IRAE was defined per CTCAE (Common Terminology Criteria for Adverse Events) version 5.0 [17]. PFS was defined as the number of months between the date of first ICI administration and the date of first disease progression following ICI treatment or the date of death, whichever came first. OS was defined as the number of months between the date of first ICI administration...
and the date of death. Patients with no event observed were censored at the last follow-up date. Types of comorbidity among the study subjects are listed in the supplementary material.

**Exposures and outcome measurement**

The treatment exposure was recorded as binary for FV (positive versus negative). The severity of IRAEs was recorded as no IRAEs or grade 1–5 IRAEs per CTCAE version 5.0 [17]. The primary outcome was the severity of IRAEs. The secondary outcomes included grade 3–5 IRAEs (yes (i.e. grade 3–5 IRAEs) versus no (i.e. grade 1–2 IRAEs and no IRAEs)), PFS and OS. Patients were separated into subgroups for additional analysis for IRAEs (grade 3–5 IRAEs versus no IRAEs).

**Statistical analysis**

The primary objective of this study was to evaluate whether FV is associated with decreased IRAE severity. The null hypothesis for the primary outcome is that FV will increase or has no impact on the severity of IRAEs and the alternative hypothesis is that FV will decrease the severity of IRAEs. The secondary objectives were to evaluate whether FV is associated with decreased IRAE severity and better PFS and OS. The null hypotheses for the secondary outcomes were that FV is associated with an increased risk for grade 3–5 IRAEs and poorer PFS and OS, or has no impact on the severity of IRAEs and survival times. The alternative hypotheses were that FV is associated with a decreased risk for grade 3–5 IRAEs and better PFS and OS.

The study sample size was determined using precision analysis (described in the supplementary material). With a proposed sample size of 247 (FV-positive n=142 and FV-negative n=105), the half-width of the 90% confidence interval of the estimated odds ratio is <0.28. Therefore, it is reassured that our study has excellent precision of the reported results.

Multiple imputations for missing values using chained equations were first carried out. To improve the balance of covariate distribution between the FV-positive and FV-negative cohorts, propensity score matching (PSM) using the nearest-neighbour method with a 1:1 ratio without caliper was then applied and the following factors were adjusted: age, race, gender, smoking status, trial patients or not, ICI type received, cardiovascular comorbidities, pulmonary comorbidities, second primary cancers, metabolic comorbidities, autoimmune comorbidities and other comorbidities (defined as renal, cerebrovascular or neurological comorbidities).

The primary analysis was done with ordinal logistic regression and included seven pre-determined variables: FV status, race, gender, smoking status, age, trial patients or not and types of ICI received. Goodness of fit was assessed by Harrell’s C-statistic [18]. Logistic regression was used for the secondary analysis and seven pre-determined covariates were adjusted: FV status, race, gender, smoking status, age, trial patients or not and types of ICI received. The survival curves were estimated by the Kaplan–Meier method and the differences were compared by Cox regression for the time-to-event outcomes. The subgroup analysis was done with logistic regression and adjusted for FV status, race, gender, smoking status, age, trial patients or not and types of ICI received. Adjusted odds ratios (ORs) or hazard ratios (HRs) with 90% confidence intervals were reported. Methods for sensitivity analyses are shown in the supplementary material.

Descriptive statistics were used to display the demographic information of the participants. Differences between the cohorts were compared with the Chi-squared-test for categorical variables and with the Wilcoxon rank sum test for continuous variables. Elastic-net and horseshoe regression analysis were used to validate the consistency and robustness of the estimated FV effect. Statistical significance was present as one-sided α=0.05. All data analyses were performed using base R 4.0 (R Foundation, Vienna, Austria), and the R packages rms, MatchIt, Hmisc, survival, survminer, MASS, glmnet and bayesreg [19–23].

**Results**

**Patient characteristics**

A total of 247 patients were included in the analysis. There were 142 patients in the FV-positive cohort and 105 patients in the FV-negative cohort. For the patients in the FV-positive cohort, 91% (n=129) were White, 51% (n=72) were male, 89% (n=126) were ever-smokers and 67% (n=95) had the cancer diagnosed at age ≥60 years. For the patients in the FV-negative cohort, 90% (n=95) were White, 56% (n=59) were male, 93% (n=98) were ever-smokers and 70% (n=74) had the cancer diagnosed at age ≥60 years. One percent (n=2) or 3% (n=3) of the patients had influenza prodromes (fever, rigour or myalgia) in the FV-positive or FV-negative cohort, respectively, and 1% (n=1) of the patients in each group were admitted due to influenza-related complications.
| TABLE 1 Demographic features of the study cohorts |
|--------------------------------------------------|
| Before propensity score matching | After propensity score matching* |
| n | FV-positive | FV-negative | Combined | p-value | n | FV-positive | FV-negative | Combined | p-value |
|---|-------------|-------------|----------|---------|---|-------------|-------------|----------|---------|
| Race | 247 | 0.921 | 210 | 0.448 |
| White | 129 (91) | 95 (90) | 224 (91) | 98 (93) | 95 (90) | 193 (92) |
| Non-White | 13 (9) | 10 (10) | 23 (9) | 7 (7) | 10 (10) | 17 (8) |
| Gender | 247 | 0.393 | 210 | 0.889 |
| Male | 72 (51) | 59 (56) | 131 (53) | 60 (57) | 59 (56) | 119 (57) |
| Female | 70 (49) | 46 (44) | 116 (47) | 45 (43) | 46 (44) | 91 (43) |
| Age, years | 247 | 0.550 | 210 | 0.537 |
| <60 | 47 (33) | 31 (30) | 78 (32) | 27 (26) | 31 (30) | 58 (28) |
| ⩾60 | 95 (67) | 74 (70) | 169 (68) | 78 (74) | 74 (70) | 152 (72) |
| Smoking status | 247 | 0.219 | 210 | 1 |
| Ever-smoker | 126 (89) | 98 (93) | 224 (91) | 98 (93) | 98 (93) | 196 (93) |
| Never-smoker | 16 (11) | 7 (7) | 23 (9) | 7 (7) | 7 (7) | 14 (7) |
| Cancer type | 247 | 0.126 | 210 | 0.260 |
| NSCLC | 124 (87) | 86 (82) | 210 (85) | 89 (85) | 86 (82) | 175 (83) |
| SCLC | 10 (7) | 16 (15) | 26 (11) | 9 (9) | 16 (15) | 25 (12) |
| Mixed NSCLC/ SCLC | 3 (2) | 2 (2) | 5 (2) | 3 (3) | 2 (2) | 5 (2) |
| Others | 5 (4) | 1 (1) | 6 (2) | 4 (4) | 1 (1) | 5 (2) |
| Malignant mesothelioma | 4 (3) | 0 (0) | 4 (2) | 4 (4) | 0 (0) | 4 (2) |
| Thymic cancer | 1 (1) | 1 (1) | 2 (1) | 0 (0) | 1 (1) | 1 (0) |
| Stage | 247 | 0.479 | 210 | 1 |
| III | 13 (9) | 7 (7) | 20 (8) | 7 (7) | 7 (7) | 14 (7) |
| IV | 129 (91) | 98 (93) | 227 (92) | 98 (93) | 98 (93) | 196 (93) |
| Trial patient | 247 | 0.326 | 210 | 0.471 |
| Yes | 56 (39) | 35 (33) | 91 (37) | 40 (38) | 35 (33) | 75 (36) |
| No | 86 (61) | 70 (67) | 156 (63) | 65 (62) | 70 (67) | 135 (64) |
| ICI received* | 247 | 0.163 | 210 | 0.284 |
| PD-1 inhibitor | 111 (78) | 81 (77) | 192 (78) | 83 (79) | 81 (77) | 164 (78) |
| PD-L1 inhibitor | 19 (13) | 11 (10) | 30 (12) | 10 (10) | 11 (10) | 21 (10) |
| CTLA-4 inhibitor | 3 (2) | 0 (0) | 3 (1) | 3 (3) | 0 (0) | 3 (1) |
| CTLA-4 combination | 9 (6) | 13 (12) | 22 (9) | 9 (9) | 13 (12) | 22 (10) |
| Best ICI response | 247 | 0.396 | 210 | 0.474 |
| PD | 48 (34) | 41 (39) | 89 (36) | 36 (34) | 41 (39) | 77 (37) |
| Responses other than PD | 94 (66) | 64 (61) | 158 (64) | 69 (66) | 64 (61) | 133 (63) |
| Comorbidities, n | 234 | 0.905 | 210 | 0.719 |
| 0 | 2 (2) | 1 (1) | 3 (1) | 3 (3) | 1 (1) | 4 (2) |
| 1 | 39 (30) | 29 (28) | 68 (29) | 33 (31) | 30 (29) | 63 (30) |
| 2 | 33 (25) | 30 (29) | 63 (27) | 28 (27) | 31 (30) | 59 (28) |
| ≥3 | 57 (44) | 43 (42) | 100 (43) | 41 (39) | 43 (41) | 84 (40) |
| Comorbidity | 234 | 85 (65) | 68 (66) | 153 (65) | 0.856 | 210 | 68 (65) | 69 (66) | 137 (65) | 0.685 |
| Cardiovascular | 234 | 53 (40) | 50 (49) | 103 (44) | 0.216 | 210 | 50 (48) | 50 (48) | 100 (48) | 1 |
| Pulmonary | 234 | 53 (40) | 47 (46) | 100 (43) | 0.427 | 210 | 43 (41) | 47 (45) | 90 (43) | 0.577 |
| Metabolic | 234 | 34 (26) | 17 (17) | 51 (22) | 0.082 | 210 | 18 (17) | 17 (16) | 35 (17) | 0.853 |
| Second primary cancers | 234 | 25 (19) | 27 (26) | 52 (22) | 0.193 | 210 | 23 (22) | 28 (27) | 51 (24) | 0.421 |
| Autoimmune | 234 | 16 (12) | 15 (15) | 31 (13) | 0.599 | 204 | 11 (11) | 15 (15) | 26 (13) | 0.432 |
| Nephrology/ urology | 234 | 13 (10) | 11 (11) | 24 (10) | 0.850 | 204 | 8 (8) | 11 (11) | 19 (9) | 0.498 |
| Cerebrovascular | 234 | 6 (5) | 8 (8) | 14 (6) | 0.308 | 204 | 4 (4) | 8 (8) | 12 (6) | 0.248 |
| Neurological | 247 | 0.830 | 210 | 0.313 |
| Influenza prodromes | Yes | 2 (1) | 3 (3) | 5 (2) | 1 (1) | 3 (3) | 4 (2) |
| No | 140 (99) | 102 (97) | 242 (98) | 104 (99) | 102 (97) | 206 (98) |
| Continued | 4 |
All patients had locally advanced or metastatic thoracic cancer. The most common cancer type in both cohorts was nonsmall cell lung cancer (NSCLC). For patients in the FV-positive cohort, 87% (n=124) had NSCLC, 7% (n=10) had small cell lung cancer (SCLC), 2% (n=3) had mixed NSCLC/SCLC and 4% (n=5) had malignant mesothelioma (n=4) or thymic cancer (n=1). For patients in the FV-negative cohort, 82% (n=86) had NSCLC, 15% (n=16) had SCLC, 2% (n=2) had mixed NSCLC/SCLC and 1% (n=1) had thymic cancer.

In the FV-positive cohort, 78% (n=111) of the patients received a PD-1 inhibitor (nivolumab or pembrolizumab), 13% (n=19) received a PD-L1 inhibitor (atezolizumab or durvalumab), 2% (n=3) had ipilimumab monotherapy and 6% (n=9) had CTLA-4 combination therapy (ipilimumab plus nivolumab). In the FV-negative cohort, 77% (n=81) of the patients received a PD-1 inhibitor (nivolumab or pembrolizumab), 10% (n=11) received a PD-L1 inhibitor (atezolizumab or durvalumab) and 12% (n=13) had CTLA-4 combination therapy (ipilimumab plus nivolumab or tremelimumab plus durvalumab). There was no statistically significant difference in cumulative incidences among the basic demographic features, types and numbers of comorbidities, disease stages or cell types, and types or routes of ICI received between the two cohorts both before and after PSM (all p>0.05) (table 1).

The median (IQR) time interval between the first dose of ICI and the occurrence of IRAEs was 5.2 (3.0–7.0) months in the FV-positive cohort and 2.9 (1.4–6.8) months in the FV-negative cohort. The cumulative incidences of IRAEs were not of statistically significant difference between the two cohorts: FV-positive cohort 47% (n=67) versus FV-negative cohort 52% (n=55); p=0.42. However, among all the IRAEs, there was a trend towards a higher likelihood of pneumonitis (17% versus 12%), myocarditis (4% versus 1%) and neuromuscular complications (10% versus 3%) in the FV-negative cohort compared with the FV-positive cohort. The cumulative incidence of grade 3–5 IRAEs was lower in the FV-positive cohort than in the FV-negative cohort (20% (n=29) and 37% (n=39), respectively; p=0.004). 23% (n=32) or 39% (n=41) of the patients required immunosuppressive agents for the control of IRAEs in the FV-positive and FV-negative cohort, respectively (p=0.005). ICIs were permanently discontinued due to IRAEs among 18% (n=25) of the patients in the FV-positive cohort and 30% (n=32) of the patients in the FV-negative cohort (p=0.018). As shown in table 2, the trends were similar before and after PSM. Moreover, despite statistically nonsignificant, there was a higher likelihood of IRAE development during the influenza season (fall and winter) than outside the influenza season (spring and summer) in the FV-negative cohort (55% versus 45%) (table 3).

**FV is associated with a decreased severity of IRAEs but not OS**

We first investigated whether FV is associated with decreased severity of IRAEs. In the primary analysis, a PSM matching ratio of 1:1 without caliper was applied (n=105 in each cohort). Ordinal logistic regression showed an inverse association between FV and the severity of IRAEs (OR 63; p=0.046) (table 4). In the secondary analysis, logistic regression showed that FV was associated with a decreased risk for grade 3–5 IRAEs (OR 0.42; p=0.005) (table 5). In the subgroup analysis, when only subjects with no IRAEs and grade 3–5 IRAEs were included, the results revealed that FV was associated with a decreased risk for
We next investigated whether FV is associated with better survival times. The median PFS times were 6.55 or 5.32 months and the median OS times were 12.7 or 12.2 months for the FV-positive or FV-negative cohort, respectively. Multivariable Cox regression showed that FV was not associated with PFS (HR 0.96; p=0.395) or OS (HR 1.06; p=0.371) (table 7 and supplementary figure E3). Similar results were revealed in the additional analyses (sensitivity analysis I and II in supplementary tables E6 and E10, respectively).

### Table 2: Immune-related adverse events (IRAEs) in the study cohorts

| IRAEs                  | Before propensity score matching | p-value | After propensity score matching | p-value |
|------------------------|---------------------------------|---------|---------------------------------|---------|
|                        | n  | FV-positive (n=142) | FV-negative (n=105) | Combined (n=247) | p-value | n  | FV-positive (n=105) | FV-negative (n=105) | Combined (n=210) | p-value |
| IRAEs                  | 247 | 0.419 | 210 | 0.49 |
| Yes                    | 67 (47) | 55 (52) | 122 (49) | 50 (48) | 55 (52) | 105 (50) |
| No                     | 75 (53) | 50 (48) | 125 (51) | 55 (52) | 50 (48) | 105 (50) |
| IRAE severity grading  | 247 | 0.004* | 210 | 0.004* |
| Grade 5                | 1 (1) | 0 (0) | 1 (0) | 1 (1) | 0 (0) | 1 (0) |
| Grade 4                | 2 (1) | 1 (1) | 3 (1) | 1 (1) | 1 (1) | 2 (1) |
| Grade 3                | 26 (18) | 38 (36) | 64 (26) | 18 (17) | 38 (36) | 56 (27) |
| Grade 2                | 27 (19) | 16 (15) | 43 (17) | 22 (21) | 16 (15) | 38 (18) |
| Grade 1                | 11 (8) | 0 (0) | 11 (4) | 8 (8) | 0 (0) | 8 (4) |
| No IRAEs               | 75 (53) | 50 (48) | 125 (51) | 55 (52) | 50 (48) | 105 (50) |
| IRAE severity group    | 247 | 0.006* | 210 | 0.005* |
| Grade 3–5              | 29 (20) | 39 (37) | 68 (28) | 20 (19) | 39 (37) | 59 (28) |
| Grade 1–2              | 38 (27) | 16 (15) | 54 (22) | 30 (29) | 16 (15) | 46 (22) |
| No IRAEs               | 75 (53) | 50 (48) | 125 (50) | 55 (52) | 50 (48) | 105 (50) |
| IRAE type              | 247 | 0.440 | 210 | 0.282 |
| Endocrinopathy         | 27 (19) | 16 (15) | 43 (17) | 17 (16) | 12 (11) | 29 (12) |
| Hypothyroidism         | 21 (15) | 12 (11) | 33 (13) | 5 (5) | 6 (6) | 11 (5) |
| Adrenal insufficiency  | 8 (6) | 4 (4) | 12 (5) | 6 (6) | 4 (4) | 10 (10) |
| Hypophysitis           | 1 (1) | 1 (1) | 2 (1) | 1 (1) | 1 (1) | 2 (2) |
| Pneumonitis            | 247 | 0.250 | 210 | 0.237 |
| 12 (17) | 35 (14) | 42 (20) | 12 (11) | 18 (17) | 30 (14) |
| Dermatological         | 247 | 0.160 | 210 | 0.107 |
| 7 (7) | 24 (10) | 31 (15) | 14 (13) | 7 (7) | 21 (10) |
| Hepatitis/collitis     | 247 | 0.340 | 210 | 0.16 |
| 16 (11) | 8 (8) | 24 (10) | 8 (8) | 16 (8) |
| Hepatitis              | 9 (6) | 6 (6) | 15 (6) | 5 (5) | 6 (6) | 11 (5) |
| Colitis                | 7 (5) | 2 (2) | 9 (4) | 3 (3) | 2 (2) | 5 (2) |
| Neuromuscular          | 247 | 0.051 | 210 | 0.097 |
| 5 (3) | 10 (10) | 15 (6) | 4 (4) | 10 (10) | 14 (7) |
| Severe fatigue         | 247 | 0.660 | 210 | 0.701 |
| 4 (4) | 8 (3) | 3 (3) | 4 (4) | 7 (3) |
| Myocarditis            | 247 | 0.087 | 210 | 0.174 |
| 1 (1) | 4 (4) | 5 (2) | 4 (4) | 5 (2) |
| Haematological         | 247 | 0.390 | 210 | 0.155 |
| 0 (0) | 2 (2) | 1 (0) | 2 (2) | 2 (2) |
| Nephritis              | 247 | 0.390 | 210 | 0.316 |
| 1 (1) | 1 (0) | 0 (0) | 1 (0) | 0 (0) |
| **Immunosuppressive agents for IRAEs** | 247 | 0.005* | 210 | 0.004* |
| Yes                    | 32 (23) | 41 (39) | 73 (30) | 22 (21) | 41 (39) | 63 (30) |
| No                     | 110 (77) | 64 (61) | 174 (70) | 83 (79) | 64 (61) | 147 (70) |
| **ICI discontinuation due to IRAEs** | 247 | 0.018* | 210 | 0.014* |
| Yes                    | 25 (18) | 32 (30) | 57 (23) | 17 (16) | 32 (30) | 49 (23) |
| No                     | 117 (82) | 73 (70) | 190 (77) | 88 (84) | 73 (70) | 161 (77) |
| **Grade 3–5 IRAEs**    | 247 | 0.004* | 210 | 0.004* |
| Yes                    | 29 (20) | 39 (37) | 68 (28) | 20 (19) | 39 (37) | 59 (28) |
| No                     | 113 (80) | 66 (63) | 179 (72) | 85 (81) | 66 (63) | 151 (72) |

Data are presented as n (%), unless otherwise stated. FV: influenza vaccination; ICI: immune checkpoint inhibitor. *: one of the five propensity score matching models run after multiple imputations (the numbers varied very slightly among the five runs); ‡: three patients had both hypothyroidism and adrenal insufficiency; †: one patient had both hypothyroidism and adrenal insufficiency; †: two patients had both hypothyroidism and adrenal insufficiency; ‡: one patient had both hypothyroidism and adrenal insufficiency; ‡: denominator: cases with positive IRAE (annotated as IRAE=Yes in the table). *: p<0.05.

grade 3–5 IRAEs (OR 0.46; p=0.016) (table 6). Similar results were shown by the additional analyses (sensitivity analysis I and II in supplementary tables E3–E5 and E7–E9, respectively).

We next investigated whether FV is associated with better survival times. The median PFS times were 6.55 or 5.32 months and the median OS times were 12.7 or 12.2 months for the FV-positive or FV-negative cohort, respectively. Multivariable Cox regression showed that FV was not associated with PFS (HR 0.96; p=0.395) or OS (HR 1.06; p=0.371) (table 7 and supplementary figure E3). Similar results were revealed in the additional analyses (sensitivity analysis I and II in supplementary tables E6 and E10, respectively).
Discussion
This study investigated associations between FV and the risks of IRAEs among thoracic cancer patients on ICIs. The treatment regimens were not restricted to a single PD-1 inhibitor, but included PD-1, PD-L1 or CTLA-4 inhibitors, and their combinations, reflecting real practice. There was no statistically significant difference in the IRAE cumulative incidence between the FV-positive and FV-negative cohorts. In the primary analysis, we showed an inverse association between FV and severity of IRAEs. In the secondary analyses, the data further indicated a statistically significant inverse association between FV and development of grade 3–5 IRAEs, while no association between FV and survival times was revealed. The subgroup analysis also suggested a decreased risk for grade 3–5 IRAEs in the FV-positive cohort. The results imply potential benefits of FV for patients with advanced-stage thoracic cancer on ICI therapy.

The cumulative incidence of overall IRAEs (49%) observed in our study was higher than those reported in the prior studies [24–28]. This could be partly explained by the fact that ICIs included in our study were not restricted to a single PD-1/PD-L1 axis inhibitor. Consistent with the data from the prior studies, the most frequently observed IRAE in our study population was endocrinopathy (17%); dermatological adverse events (10%) as well as hepatitis/colitis (10%) were also ranked in the top five. A distinct feature observed here is the high cumulative incidence of pneumonitis (14%). Nevertheless, although the incidence of pneumonitis observed is higher than those reported in clinical trial settings (3–5%) [25, 26], it is close to the numbers reported in real-world datasets, including a cohort with 205 ICI-treated NSCLC patients (19%) [29] and a cohort with 91 PD-1/PD-L1 inhibitor-treated NSCLC patients (10%) [24].

Table 3: Seasonal distribution of immune-related adverse event (IRAE) occurrence

| Season of IRAEs | Before propensity score matching | After propensity score matchinga |
|-----------------|---------------------------------|---------------------------------|
|                 | n FV-positive (n=67) | FV-negative (n=55) | Combined (n=122) | p-value | n FV-positive (n=50) | FV-negative (n=55) | Combined (n=105) | p-value |
| Spring          | 122 | 15 (22) | 9 (16) | 24 (20) | 0.620 | 12 (24) | 9 (16) | 21 (20) | 0.464 |
| Summer          | 15 (25) | 16 (29) | 33 (27) | | | 15 (30) | 16 (29) | 31 (30) | |
| Fall            | 12 (18) | 14 (25) | 26 (21) | | | 7 (14) | 14 (25) | 21 (20) | |
| Winter          | 23 (35) | 16 (30) | 39 (32) | | | 16 (32) | 16 (30) | 32 (30) | |
| Influenza season of IRAEs | 122 | | | | | 0.799 | | 0.382 |
| Fall/winter     | 35 (52) | 30 (55) | 65 (53) | | | 23 (46) | 30 (55) | 53 (50) | |
| Spring/summer   | 32 (48) | 25 (45) | 57 (47) | | | 27 (54) | 25 (45) | 52 (50) | |

Data are presented as n (%), unless otherwise stated. FV: influenza vaccination. a: one of the five propensity score matching models run after multiple imputations (the numbers varied very slightly among the five runs).

Table 4: Associations between clinical features and immune-related adverse events (IRAEs) using ordinal logistic regression analysis: grade 3–5 IRAEs versus grade 1–2 IRAEs versus no IRAEs

| OR (90% CI) | p-value |
|-------------|---------|
| FV: positive versus negative (reference) | 0.63 (0.40–0.99) | 0.046* |
| Race: White versus non-White (reference) | 3.27 (1.13–9.47) | 0.034* |
| Gender: male versus female (reference) | 0.93 (0.57–1.53) | 0.406 |
| Smoking status: ever versus never (reference) | 2.86 (0.97–8.42) | 0.055 |
| Age: <60 versus ≥60 years (reference) | 0.86 (0.49–1.52) | 0.335 |
| Trial: yes versus no (reference) | 1.23 (0.73–2.07) | 0.254 |
| ICI received: | | |
| PD-L1 versus PD-1 (reference) | 2.36 (0.94–5.90) | 0.062 |
| CTLA-4/CTLA-4 combinations versus PD-1 (reference) | 2.06 (0.97–4.38) | 0.057 |

FV: influenza vaccination; ICI: immune checkpoint inhibitor; PD-L1: PD-1 ligand 1; PD-1: programmed cell death 1; CTLA-4: cytotoxic T-lymphocyte antigen 4. Harrell’s C-statistic=0.642. *: p<0.05.
Of note, the incidence of pneumonitis was higher in the FV-negative cohort than in the FV-positive cohort. The same trend was also observed with neuromuscular complications and myocarditis. Pneumonitis, severe neuromuscular complications and myocarditis are potential lethal IRAEs that deserve special attention. In our primary and secondary analyses, we showed inverse associations between FV and the severity of IRAEs. In the subgroup analysis, a significant increased risk for severe IRAEs was revealed in the FV-negative cohort. These results suggested a potential protective effect of FV for severe IRAEs. In line with our findings, a recent study also reported reduced risks for major adverse cardiac events among patients on ICIs and FV who developed myocarditis [30].

Remarkably, despite without statistical significance, there was a trend towards a higher IRAE incidence during the influenza season (fall and winter) than outside the influenza season (spring and summer) in the FV-negative cohort. Importantly, pulmonary complications are not uncommon upon influenza infection, and influenza-related neuronal and cardiac complications can be fatal [31, 32]. With the retrospective nature of the current study, incidence of influenza might be underestimated, especially in the FV-negative cohort, and so also the influenza-relevant complications. According to the INVIDIa-2 study, FV significantly reduced influenza-like illness in patients with advanced cancer on ICIs [10]. The results of the INVIDIa-2 study suggested favourable outcomes with FV for patients on ICIs. The phenomenon observed was not quite the same as it was among cancer patients on chemotherapy, for which suppressed host immunity might impede the generation of satisfactory antibody levels in response to FV. Despite this fact, FV is still recommended for cancer patients on chemotherapy as it stands as the most practical way for influenza prevention. It is plausible that among cancer patients on ICIs, FV reduces severe inflammatory complications.

### Table 5

| Clinical Feature                  | OR (90% CI)      | p-value |
|----------------------------------|------------------|---------|
| FV: positive versus negative     | 0.42 (0.24–0.73) | 0.005*  |
| Race: White versus non-White     | 1.94 (0.60–6.25) | 0.175   |
| Gender: male versus female       | 0.90 (0.51–1.58) | 0.378   |
| Smoking status: ever versus never| 4.34 (0.73–25.76)| 0.088   |
| Age: <60 versus ≥60 years        | 0.99 (0.53–1.85) | 0.489   |
| Clinical Feature                 | OR (90% CI)      | p-value |
| FV: positive versus negative     | 0.46 (0.26–0.84) | 0.016*  |
| Race: White versus non-White     | 2.70 (0.79–9.25) | 0.092   |
| Gender: male versus female       | 0.89 (0.48–1.67) | 0.382   |
| Smoking status: ever versus never| 4.97 (0.82–30.18)| 0.072   |
| Age: <60 versus ≥60 years        | 0.86 (0.43–1.72) | 0.357   |
| Clinical Feature                 | OR (90% CI)      | p-value |
| FV: positive versus negative     | 2.80 (0.91–8.61) | 0.065   |
| Smoking status: ever versus never| 2.95 (1.13–7.72)| 0.032*  |

**Legend:** FV: influenza vaccination; ICI: immune checkpoint inhibitor; PD-L1: PD-1 ligand 1; PD-1: programmed cell death 1; CTLA-4: cytotoxic T-lymphocyte antigen 4. Harrell’s C-statistic=0.695. *: p<0.05.
complications on major organs, both due to the infection itself or the interaction between infection and drug-induced inflammatory responses. Taken together, the benefit of FV may outweigh its risk for patients with advanced thoracic cancer on ICIs both from the IRAEs and influenza-related complication points of view.

This study is limited by the lack of randomisation and missing variables are inevitable due to its retrospective nature. While adjustments and varying methodological techniques were applied, residual confounding may affect the results. Nevertheless, this is the largest cohort study investigating the safety of FV in patients with advanced thoracic cancer on ICIs. Furthermore, all the study subjects were enrolled from a single institute with high-quality de-identified EMR and low loss-to-follow-up rate. These advantages facilitated comprehensive data collection.

In summary, our study suggests that FV does not increase toxicity for patients with advanced thoracic cancer on ICIs and FV is associated with a decreased risk for severe IRAEs. Taken together, FV may be recommended for this patient population.

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**TABLE 7. Associations between clinical features and survival (progression-free survival (PFS) and overall survival (OS))**

|                      | PFS                      | OS                      |
|----------------------|--------------------------|-------------------------|
|                      | HR (90% CI) | p-value | HR (90% CI) | p-value |
| FV: positive versus negative (reference) | 0.96 (0.73–1.26) | 0.395 | 1.06 (0.79–1.43) | 0.371 |
| Race: White versus non-White (reference) | 0.70 (0.45–1.11) | 0.100 | 1.03 (0.59–1.80) | 0.465 |
| Gender: male versus female (reference) | 0.81 (0.62–1.05) | 0.091 | 0.97 (0.72–1.30) | 0.427 |
| Smoking status: ever versus never (reference) | 0.80 (0.48–1.33) | 0.235 | 1.14 (0.61–2.15) | 0.363 |
| Age: <60 versus ≥60 years (reference) | 1.19 (0.88–1.60) | 0.176 | 0.96 (0.68–1.37) | 0.428 |
| Trial: yes versus no (reference) | 0.71 (0.53–0.95) | 0.026* | 0.60 (0.43–0.83) | 0.005* |
| ICI received: | | | | |
| PD-L1 versus PD-1 (reference) | 0.60 (0.34–1.07) | 0.074 | 0.56 (0.28–1.12) | 0.083 |
| CTLA-4/CTLA-4 combinations versus PD-1 (reference) | 1.17 (0.77–1.78) | 0.264 | 1.26 (0.80–1.99) | 0.202 |

FV: influenza vaccination; ICI: immune checkpoint inhibitor; PD-L1: PD-1 ligand 1; PD-1: programmed cell death 1; CTLA-4: cytotoxic T-lymphocyte antigen 4. Harrell’s C-statistic for PFS=0.541 and for OS=0.542.

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