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

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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, dyspnoea, 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 (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
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										
Cardiovascular	234	85 (65)	68 (66)	153 (65)	0.856	210	68 (65)	69 (66)	137 (65)	0.885
Pulmonary	234	53 (40)	50 (49)	103 (44)	0.216	210	50 (48)	50 (48)	100 (48)	1
Metabolic	234	53 (40)	47 (46)	100 (43)	0.427	210	43 (41)	47 (45)	90 (43)	0.577
Second primary cancers	234	34 (26)	17 (17)	51 (22)	0.082	210	18 (17)	17 (16)	35 (17)	0.853
Autoimmune	234	25 (19)	27 (26)	52 (22)	0.193	210	23 (22)	28 (27)	51 (24)	0.421
Nephrology/ urology	234	16 (12)	15 (15)	31 (13)	0.599	204	11 (11)	15 (15)	26 (13)	0.432
Cerebrovascular	234	13 (10)	11 (11)	24 (10)	0.850	204	8 (8)	11 (11)	19 (9)	0.498
Neurological	234	6 (5)	8 (8)	14 (6)	0.308	204	4 (4)	8 (8)	12 (6)	0.248
Influenza prodromes	247				0.830	210				0.313
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

TABLE 1 Continued

	Before propensity score matching					After propensity score matching[#]				
	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
Influenza-related hospitalisation	247				0.419	210				0.316
Yes		1 (1)	1 (1)	2 (1)			0 (0)	1 (1)	1 (0)	
No		141 (99)	104 (99)	245 (99)			105 (100)	104 (99)	209 (100)	

Data are presented as n (%), unless otherwise stated. FV: influenza vaccination; NSCLC: nonsmall cell lung cancer; SCLC: small cell lung cancer; ICI: immune checkpoint inhibitor; PD-1: programmed cell death 1; PD-L1: PD-1 ligand 1; CTLA-4: cytotoxic T-lymphocyte antigen 4; PD: progressive disease. [#]: one of the five propensity score matching model runs after multiple imputations (numbers change very slightly among five runs); [¶]: PD-1 inhibitors include nivolumab and pembrolizumab; PD-L1 inhibitors include atezolizumab and durvalumab; CTLA-4 inhibitor here indicates ipilimumab; CTLA-4 combinations include ipilimumab plus nivolumab and tremelimumab plus durvalumab.

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 or 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

TABLE 2 Immune-related adverse events (IRAEs) in the study cohorts

	Before propensity score matching					After propensity score matching[#]				
	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										
Endocrinopathy	247	27[¶] (19)	16[+] (15)	43 (17)	0.440	210	22[§] (21)	16[f] (15)	38 (18)	0.282
Hypothyroidism		21 (15)	12 (11)	33 (13)			17 (16)	12 (11)	29 (28)	
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	17 (12)	18 (17)	35 (14)	0.250	210	12 (11)	18 (17)	30 (14)	0.237
Dermatological	247	17 (12)	7 (7)	24 (10)	0.160	210	14 (13)	7 (7)	21 (10)	0.107
Hepatitis/colitis	247	16 (11)	8 (8)	24 (10)	0.340	210	8 (8)	8 (8)	16 (8)	1
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	5 (3)	10 (10)	15 (6)	0.051	210	4 (4)	10 (10)	14 (7)	0.097
Severe fatigue	247	4 (3)	4 (4)	8 (3)	0.660	210	3 (3)	4 (4)	7 (3)	0.701
Myocarditis	247	1 (1)	4 (4)	5 (2)	0.087	210	1 (1)	4 (4)	5 (2)	0.174
Haematological	247	0 (0)	2 (2)	2 (2)	1	210	0 (0)	2 (2)	2 (1)	0.155
Nephritis	247	1 (1)	0 (0)	1 (0)	0.390	210	1 (1)	0 (0)	1 (0)	0.316
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; [f]: 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).

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

	Before propensity score matching					After propensity score matching[#]				
	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
Season of IRAEs	122				0.620	105				0.464
Spring		15 (22)	9 (16)	24 (20)			12 (24)	9 (16)	21 (20)	
Summer		17 (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	105				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. [#]: one of the five propensity score matching models run after multiple imputations (the numbers varied very slightly among the five runs).

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 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.

TABLE 5 Associations between clinical features and severe immune-related adverse events (IRAEs) using logistic regression analysis: grade 3–5 IRAEs *versus* grade 1–2 IRAEs plus no IRAEs[#]

	OR (90% CI)	p-value
FV: positive *versus* negative (reference)[¶]	0.42 (0.24–0.73)	0.005*
Race: White *versus* non-White (reference)	1.94 (0.60–6.25)	0.175
Gender: male *versus* female (reference)	0.90 (0.51–1.58)	0.378
Smoking status: ever *versus* never (reference)	4.34 (0.73–25.76)	0.088
Age: <60 *versus* ⩾60 years (reference)	0.99 (0.53–1.85)	0.489
Trial: yes *versus* no (reference)	0.78 (0.41–1.46)	0.257
ICI received:		
PD-L1 *versus* PD-1 (reference)	2.24 (0.87–5.79)	0.081
CTLA-4/CTLA-4 combinations *versus* PD-1 (reference)	2.89 (1.22–6.87)	0.022*

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. [#]: comparisons made between patients with grade 3–5 IRAEs and patients with no IRAEs plus patients with grade 1–2 IRAEs; [¶]: OR 0.45 by elastic-net logistic regression with α=0.5 and OR 0.61 by Bayesian logistic regression with horseshoe prior. Harrell's C-statistic=0.695. *: 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

TABLE 6 Subset analysis for the associations between clinical features and immune-related adverse events (IRAEs): grade 3–5 IRAEs *versus* no IRAEs

	OR (90% CI)	p-value
FV: positive *versus* negative (reference)	0.46 (0.26–0.84)	0.016*
Race: White *versus* non-White (reference)	2.70 (0.79–9.25)	0.092
Gender: male *versus* female (reference)	0.89 (0.48–1.67)	0.382
Smoking status: ever *versus* never (reference)	4.97 (0.82–30.18)	0.072
Age: <60 *versus* ⩾60 years (reference)	0.86 (0.43–1.72)	0.357
Trial: yes *versus* no (reference)	0.94 (0.48–1.85)	0.439
ICI received:		
PD-L1 *versus* PD-1 (reference)	2.80 (0.91–8.61)	0.065
CTLA-4/CTLA-4 combinations *versus* PD-1 (reference)	2.95 (1.13–7.72)	0.032*

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=0.691. *: p<0.05.

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.

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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