Supplemental Material

Associations of Influenza Vaccination with Severity of Immune-Related Adverse Events in Patients with Advanced Thoracic Cancers on Immune Checkpoint Inhibitors

Appendix

I. **Types of Comorbidity**

II. **Precision Analysis (eTable 1-2)**

III. **Sensitivity Analysis I (eTable 3-6; eFigure 1)**

IV. **Sensitivity Analysis II (eTable 7-10; eFigure 2)**

V. **Survival curves (eFigure 3)**

Types of Comorbidity

Cardiovascular comorbidities were defined as any of the following: coronary artery disease, congestive heart failure, atrial fibrillation, cardiac arrhythmias not otherwise specified [NOS], conduction block, aortic aneurysm, valvular heart disease, pulmonary embolism, and peripheral vascular disease. Pulmonary comorbidities were defined as any of the following: COPD, asthma, pulmonary fibrosis, obstructive sleep apnea. Metabolic comorbidities were defined as any of the following: diabetes mellitus, dyslipidemia, metabolic syndrome, steatocystoma multiplex, and osteoporosis. Autoimmune comorbidities were defined as any of the following: rheumatoid arthritis, lupus, Sjogren syndrome, Crohn's disease, ulcerative colitis, autoimmue thyroiditis, and antiphospholipid syndrome. Renal comorbidities were defined as any of the following: chronic kidney disease, renal artery stenosis, and renal stones. Cerebrovascular comorbidities were defined as any of the following: stroke, brain aneurysm, and transient ischemic attack. Neurological comorbidities were defined as any of the following: Parkinson's disease, multiple sclerosis, torticollis, meningitis NOS, migraine and dementia. Neuromuscular IRAE were defined as any of the following: encephalitis NOS, acute encephalopathy, peripheral neuropathy, Bell's palsy, restless leg syndrome, myalgia, progression of multiple sclerosis, and polymyositis.

Precision Analysis

The precision analysis was performed using simulation studies with 5,000 runs to estimate the odds ratio (OR) and half-width of 90% confidence interval (CI) based on univariate ordinal logistic regression model with outcome IRAE (grade 3-5, grade 1-2, No) and exposure variable FV-Positive vs. FV-Negative. Simulation dataset was generated using parameters on the left hand side of the table, taking eTable 1 as an example, 142 FV-Positive samples were generated with 29% grade 3-5 IRAE, 38% grade 1-2 IRAE and 75% no IRAE; and 105 FV-Negative samples were generated with 39% grade 3-5 IRAE, 16% grade 1-2 IRAE and 50% no IRAE. Then, the ordinal logistic regression model was used to estimate OR of FV-Positive vs. FV-Negative. Replicating the above process for 5,000 times, we obtained 5,000 ORs, the average of the ORs and the 95% confidence interval consisting of 0.025 and 0.975 percentiles of the ORs. The half-width of the 95% confidence interval of the estimated odds ratio is less than 0.28.

eTable 1. Original dataset – summary statistics of IRAE stratified by FV-Positive vs. FV-Negative; estimated OR with its 90% CI as well as the half-width of 90% CI of the estimated OR.

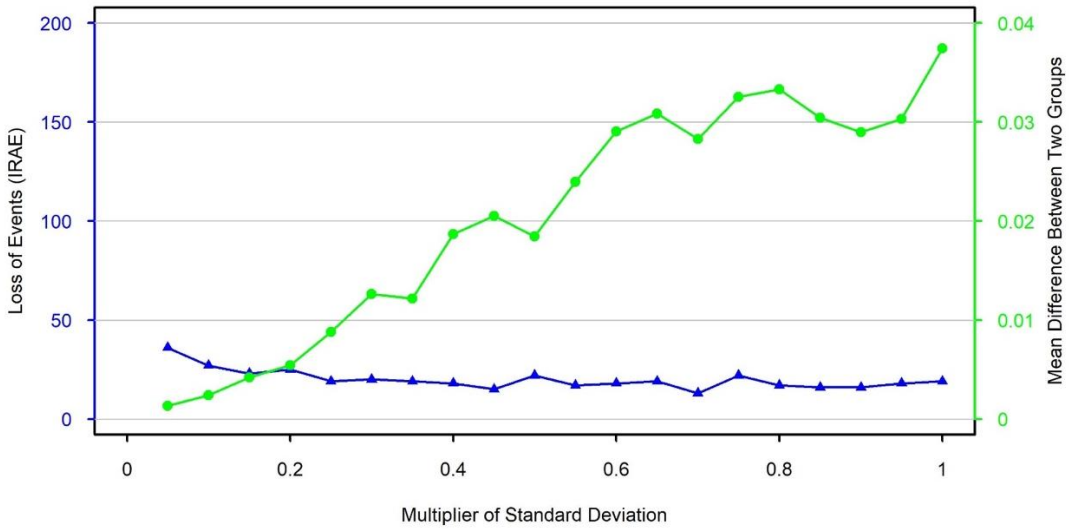
	FV-Positive (N=142)	FV-Negative (N=105)	Combined (N=247)	Estimated OR (90% CI)	Half-width of 95% CI of the estimated OR
Grade 3-5 IRAE	29 (20%)	39 (37%)	68 (28%)	0.67 (0.43 to 0.98)	0.28
Grade 1-2 IRAE	38 (27%)	16 (15%)	54 (22%)		
No IRAE	75 (53%)	50 (48%)	125 (50%)		

eTable 2. Imputation data set 1 (after PSM) – summary statistics of IRAE stratified by FV-Positive vs. FV-Negative; estimated OR with its 90% CI as well as the half-width of 90% CI of the estimated OR.

	FV-Positive (N=105)	FV-Negative (N=105)	Combined (N=210)	Estimated OR (95% CI)	Half-width of 95% CI of the estimated OR
Grade 3-5 IRAE	20 (19%)	39 (37%)	59 (28%)	0.66 (0.42 to 0.96)	0.27
Grade 1-2 IRAE	30 (29%)	16 (15%)	46 (22%)		
No IRAE	55 (52%)	50 (48%)	105 (50%)		

Sensitivity Analysis I

Propensity-score nearest neighbor matching without replacement was performed based on logistic regression model, generating 1:1 matched cohort of FV-negative to FV-positive with caliper 0.2 of standard deviation of propensity score. The caliper was selected according to eFigure 1. The optimal value of 0.2 was selected to have mean difference of propensity score between FV-positive and FV-negative groups as small as possible as well as number of loss of events. The following potential confounders were included in PSM model: race (white vs non-white), gender (male vs female), age (<60 vs ≥60 years), smoking status (ever smoker vs never smoker), trial patients (yes vs no), ICI received (PD-L1, PD1 vs CTLA-4/CTLA-4 combinations), cardiovascular (yes vs no), pulmonary (yes vs no), second primary cancers (yes vs no), metabolic (yes vs no), autoimmune (yes vs no), other comorbidities (yes vs no; other comorbidities defined as renal, cerebrovascular or neurological comorbidities).



eFigure 1. Number of loss of events and mean difference of propensity score between FV-positive and FV-negative groups at each multiplier of standard deviation.

eTable 3. Sensitivity analysis I - Associations between clinical features and immune-related adverse events using ordinal logistic regression analysis

	Grade 3-5 IRAE vs Grade 1-2 IRAE vs No IRAE		
	OR	**90% CI**	**P-value**
FV - Positive vs. Negative (ref)	0.65	(0.39 to 1.07)	0.077
Race - White vs. Non-White (ref)	2.86	(0.97 to 8.38)	0.054
Gender - Male vs. Female (ref)	0.93	(0.58 to 1.49)	0.393
Smoking Status - Ever vs. Never (ref)	3.63	(0.97 to 13.65)	0.054
Age - < 60 vs. ≥ 60 (ref)	0.90	(0.53 to 1.53)	0.369
Trial - Yes vs. No (ref)	1.14	(0.65 to 2.01)	0.350
ICI received -			
PD-L1 vs. PD-1 (ref)	2.13	(0.95 to 4.77)	0.062
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	2.13	(0.95 to 4.77)	0.061

Harrell's c-statistics = 0.638

eTable 4. Sensitivity analysis I - Associations between clinical features and severe immune-related adverse events using logistic regression analysis

	Grade 3-5 IRAE vs Grade 1-2 IRAE plus No IRAE		
	OR	**90% CI**	**P-value**
FV - Positive vs. Negative (ref) †	0.44	(0.23 to 0.83)	0.017
Race - White vs. Non-White (ref)	1.84	(0.54 to 6.26)	0.205
Gender - Male vs. Female (ref)	0.86	(0.48 to 1.51)	0.327
Smoking Status - Ever vs. Never (ref)	5.24	(0.89 to 30.95)	0.063
Age - < 60 vs. ≥ 60 (ref)	1.04	(0.56 to 1.94)	0.458
Trial - Yes vs. No (ref)	0.78	(0.37 to 1.62)	0.286
ICI received -			
PD-L1 vs. PD-1 (ref)	2.23	(0.93 to 5.36)	0.066
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	3.19	(1.30 to 7.86)	0.017

*Comparisons made between patients with grade 3-5 IRAE and patients with no IRAE plus patients with grade 1-2 IRAE.

Harrell's c-statistics = 0.693

† OR=0.45 by Elastic-net logistic regression with α=0.5; OR=0.70 by Bayesian logistic regression with horseshoe prior

eTable 5. Sensitivity analysis I - Subset analysis for the associations between clinical features and IRAE

	Grade 3-5 IRAE vs No IRAE		
	OR	**90% CI**	**P-value**
FV - Positive vs. Negative (ref)	0.48	(0.25 to 0.92)	0.032
Race - White vs. Non-White (ref)	2.50	(0.72 to 8.61)	0.112
Gender - Male vs. Female (ref)	0.85	(0.45 to 1.57)	0.328
Smoking Status - Ever vs. Never (ref)	6.09	(0.98 to 37.66)	0.052
Age - < 60 vs. ≥ 60 (ref)	0.89	(0.45 to 1.74)	0.387
Trial - Yes vs. No (ref)	0.91	(0.42 to 1.97)	0.418
ICI received			
PD-L1 vs. PD-1 (ref)	2.59	(0.98 to 6.84)	0.054
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	3.12	(1.15 to 8.44)	0.030

Harrell's c-statistics = 0.691

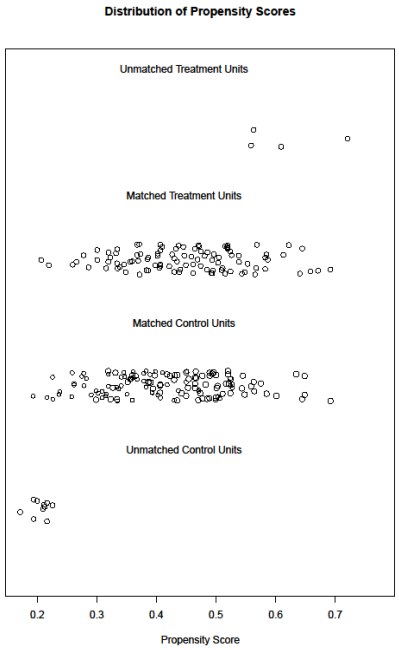
eTable 6. Sensitivity analysis I - Associations between clinical features and survival (PFS and OS)

	PFS			OS		
	HR	**90% CI**	**P-value**	**HR**	**90% CI**	**P-value**
FV - Positive vs. Negative (ref)	0.94	(0.72 to 1.24)	0.359	1.11	(0.81 to 1.54)	0.290
Race - White vs. Non-White (ref)	0.71	(0.41 to 1.24)	0.155	1.03	(0.54 to 1.97)	0.467
Gender - Male vs. Female (ref)	0.81	(0.60 to 1.08)	0.115	1.00	(0.73 to 1.38)	0.499
Smoking Status - Ever vs. Never (ref)	0.77	(0.44 to 1.35)	0.225	1.07	(0.56 to 2.04)	0.432
Age - < 60 vs. ≥ 60 (ref)	1.13	(0.84 to 1.53)	0.247	0.97	(0.67 to 1.40)	0.449
Trial - Yes vs. No (ref)	0.74	(0.52 to 1.04)	0.071	0.66	(0.44 to 0.97)	0.039
ICI received						
PD-L1 vs. PD-1 (ref)	0.65	(0.37 to 1.13)	0.099	0.63	(0.34 to 1.18)	0.114
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	1.13	(0.71 to 1.81)	0.328	1.14	(0.67 to 1.95)	0.344

Harrell's c-statistics for PFS = 0.533 and for OS = 0.523

Sensitivity Analysis II

Propensity-score nearest neighbor matching without replacement was performed based on logistic regression model, generating 1:2 matched cohort of FV-negative to FV-positive with caliper 0.25 of standard deviation of propensity score. The caliper was selected according to eFigure 2. The optimal value of 0.25 was selected to keep as many cases as possible in the study cohort. The following potential confounders were included in PSM model: race (white vs non-white), gender (male vs female), age (<60 vs ≥60 years), smoking status (ever smoker vs never smoker), trial patients (yes vs no), ICI received (PD-L1, PD1 vs CTLA-4/CTLA-4 combinations), cardiovascular (yes vs no), pulmonary (yes vs no), second primary cancers (yes vs no), metabolic (yes vs no), autoimmune (yes vs no), other comorbidities (yes vs no; other comorbidities defined as renal, cerebrovascular or neurological comorbidities).



eFigure 2. Distribution of propensity score

eTable 7. Sensitivity analysis II - Associations between clinical features and immune-related adverse events using ordinal logistic regression analysis

	Grade 3-5 IRAE vs Grade 1-2 IRAE vs No IRAE		
	OR	**90% CI**	**P-value**
FV - Positive vs. Negative (ref)	0.67	(0.43 to 1.03)	0.064
Race - White vs. Non-White (ref)	2.32	(0.98 to 5.49)	0.054
Gender - Male vs. Female (ref)	0.81	(0.52 to 1.26)	0.216
Smoking Status - Ever vs. Never (ref)	3.60	(1.24 to 10.41)	0.024
Age - < 60 vs. ≥ 60 (ref)	0.81	(0.50 to 1.30)	0.232
Trial - Yes vs. No (ref)	1.13	(0.70 to 1.83)	0.333
ICI received -			
PD-L1 vs. PD-1 (ref)	2.05	(1.02 to 4.15)	0.046
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	2.35	(1.09 to 5.05)	0.033

Harrell's c-statistics = 0.635

eTable 8. Sensitivity analysis II - Associations between clinical features and severe immune-related adverse events using logistic regression analysis

	Grade 3-5 IRAE vs Grade 1-2 IRAE plus No IRAE		
	OR	**90% CI**	**P-value**
FV - Positive vs. Negative (ref) †	0.45	(0.27 to 0.75)	0.005
Race - White vs. Non-White (ref)	1.61	(0.60 to 4.36)	0.215
Gender - Male vs. Female (ref)	0.79	(0.46 to 1.35)	0.231
Smoking Status - Ever vs. Never (ref)	4.84	(0.74 to 31.75)	0.084
Age - < 60 vs. ≥ 60 (ref)	0.93	(0.52 to 1.65)	0.414
Trial - Yes vs. No (ref)	0.69	(0.37 to 1.29)	0.164
ICI received -			
PD-L1 vs. PD-1 (ref)	2.18	(1.00 to 4.74)	0.050
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	3.74	(1.61 to 8.68)	0.005

*Comparisons made between patients with grade 3-5 IRAE and patients with no IRAE plus patients with grade 1-2 IRAE.

Harrell's c-statistics = 0.698

† OR=0.45 by Elastic-net logistic regression with α=0.5; OR=0.65 by Bayesian logistic regression with horseshoe prior

eTable 9. Sensitivity analysis II - Subset analysis for the associations between clinical features and IRAE

	Grade 3-5 IRAE vs No IRAE		
	OR	**90% CI**	**P-value**
FV - Positive vs. Negative (ref)	0.50	(0.29 to 0.88)	0.022
Race - White vs. Non-White (ref)	2.10	(0.76 to 5.83)	0.116
Gender - Male vs. Female (ref)	0.73	(0.41 to 1.3)	0.184
Smoking Status - Ever vs. Never (ref)	6.02	(0.93 to 38.97)	0.057
Age - < 60 vs. ≥ 60 (ref)	0.78	(0.42 to 1.45)	0.257
Trial - Yes vs. No (ref)	0.86	(0.43 to 1.71)	0.360
ICI received			
PD-L1 vs. PD-1 (ref)	2.50	(1.07 to 5.85)	0.038
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	3.52	(1.35 to 9.15)	0.015

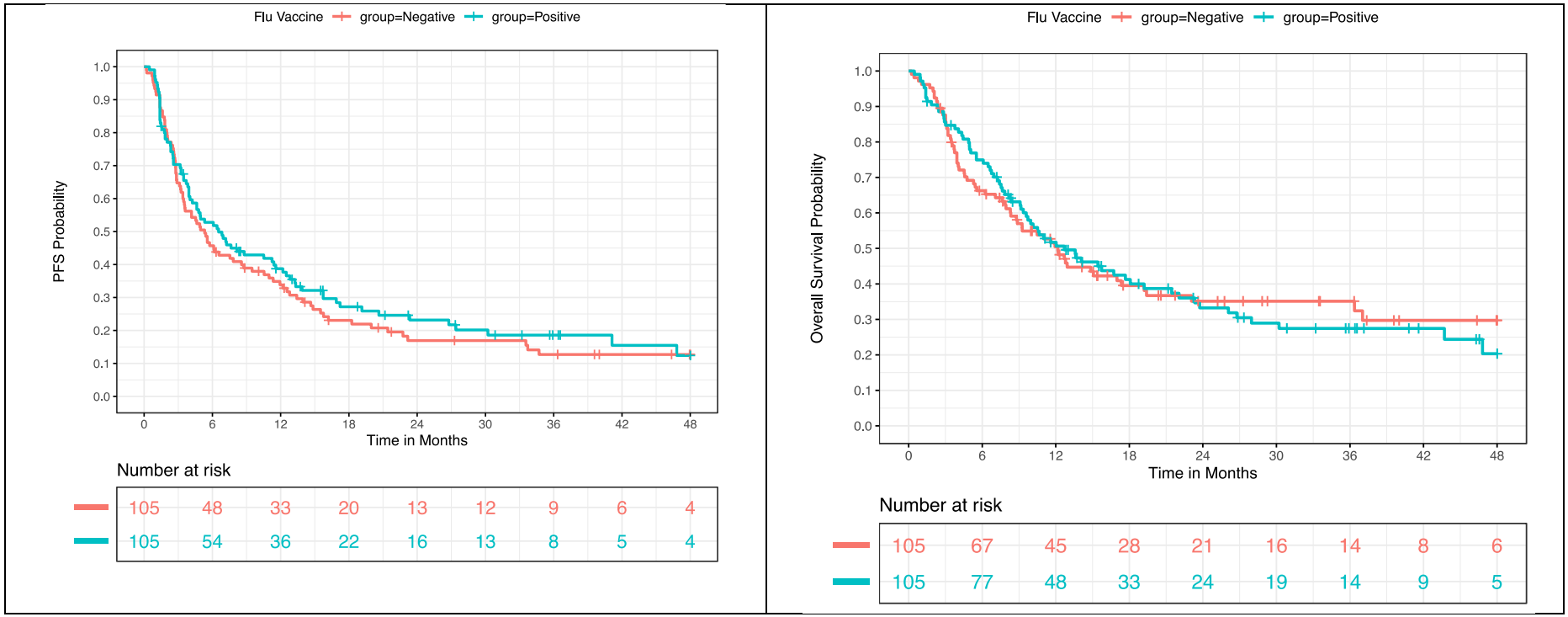
Harrell's c-statistics = 0.690

eTable 10. Sensitivity analysis II - Associations between clinical features and survival (PFS and OS)

	PFS			OS		
	HR	**90% CI**	**P-value**	**HR**	**90% CI**	**P-value**
FV - Positive vs. Negative (ref)	0.90	(0.70 to 1.16)	0.254	1.04	(0.79 to 1.38)	0.404
Race - White vs. Non-White (ref)	0.78	(0.51 to 1.19)	0.165	1.09	(0.66 to 1.82)	0.387
Gender - Male vs. Female (ref)	0.80	(0.62 to 1.03)	0.077	0.95	(0.71 to 1.26)	0.383
Smoking Status - Ever vs. Never (ref)	0.70	(0.43 to 1.14)	0.114	1.01	(0.57 to 1.81)	0.487
Age - < 60 vs. ≥ 60 (ref)	1.15	(0.88 to 1.52)	0.195	0.99	(0.72 to 1.35)	0.477
Trial - Yes vs. No (ref)	0.71	(0.54 to 0.93)	0.020	0.59	(0.43 to 0.80)	0.003
ICI received						
PD-L1 vs. PD-1 (ref)	0.70	(0.44 to 1.13)	0.110	0.71	(0.41 to 1.21)	0.145
CTLA-4/CTLA-4 combinations vs. PD-1 (ref)	1.22	(0.80 to 1.87)	0.214	1.32	(0.84 to 2.09)	0.159

Harrell's c-statistics for PFS = 0.547 and for OS = 0.537

Survival curves



eFigure 3. (A) KM plot of PFS in thoracic cancer patients. (B) KM plot of OS in thoracic cancer patients.