Influence of cancer on COVID-19 incidence, outcomes, and vaccine effectiveness: A Prospective Cohort Study of U.S. Veterans
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SUPPLEMENTAL APPENDIX
INDEX

Topic	**Page**
Supplemental Table 1	2
Supplemental Table 2	3-4
Supplemental Figures 1A / 1B	5-6
Supplemental Tables 3A / 3B	7-8
Supplemental Figure 2A/ 2B	9
Supplemental Figures 3A-3D	10-13
Directed acyclic graph (DAG)	14
Detailed methods and analyses	15-19

Supplemental Table 1 - Cancer Therapy Categorization

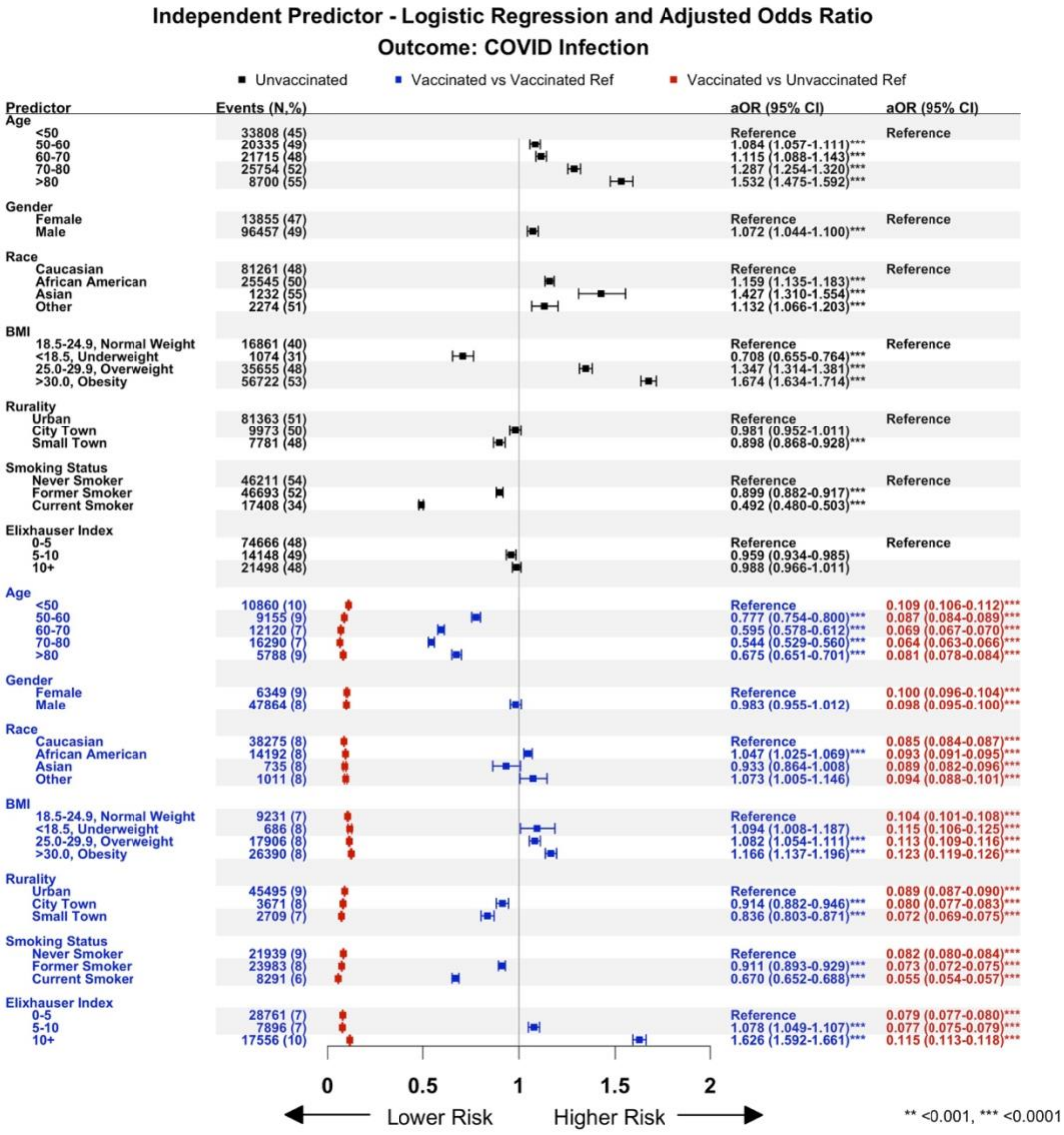
Name	Main type	Subtype	Name	Main type	Subtype
Abemaciclib	Targeted	CDK4/6(i)	Fluorouracil	Chemo	N/A
Abiraterone	Targeted	CYP17(i)	Gemcitabine	Chemo	N/A
Acalabrutinib	Targeted	BTK(i)	Goserelin	Endocrine	ADT
Anastrozole	Endocrine	N/A	Histrelin	Endocrine	ADT
Apalutamide	Targeted	AR(a)	Ibrutinib	Targeted	BTK(i)
Ara-C	Chemo	N/A	Idarubicin	Chemo	N/A
Atezolizumab	Targeted	PD-L1(ab)	Imatinib	Targeted	BCRABLTKI
Avelumab	Targeted	PD-L1(ab)	Ipilimumab	Targeted	CTLA4(ab)
Axitinib	Targeted	VEGFTKI	Irinotecan	Chemo	N/A
Azacytidine	Chemo	N/A	Ixazomib	Targeted	Proteasome(i)
Bendamustine	Chemo	N/A	Lenalidomide	Targeted	ImmuneMod
Bevacizumab	Targeted	VEGF(ab)	Lenvatinib	Targeted	MKTKI
Bleomycin	Chemo	N/A	Letrozole	Endocrine	AI
Bortezomib	Targeted	Proteasome(i)	Leucovorin	Chemo	N/A
Bosutinib	Targeted	BCRABLTKI	Leuprolide	Endocrine	ADT
Brentuximab vedotin	Targeted	CD30(ab)	Nab-paclitaxel	Chemo	N/A
Buserelin	Endocrine	ADT	Nilotinib	Targeted	BCRABLTKI
Cabazitaxel	Chemo	N/A	Niraparib	Targeted	PARP(i)
Cabozantinib	Targeted	MKTKI	Nivolumab	Targeted	PD1(ab)
Capecitabine	Chemo	N/A	Olaparib	Targeted	PARP(i)
Carboplatin	Chemo	N/A	Oxaliplatin	Chemo	N/A
Carfilzomib	Targeted	Proteasome(i)	Paclitaxel	Chemo	N/A
Cemiplimab	Targeted	PD1(ab)	Palbociclib	Targeted	CDK4/6(i)
Cetuximab	Targeted	EGFR(ab)	Panitumumab	Targeted	EGFR(ab)
Cisplatin	Chemo	N/A	Pembrolizumab	Targeted	PD1(ab)
Cyclophosphamide	Chemo	N/A	Pemetrexed	Chemo	N/A
Dacarbazine	Chemo	N/A	Pertuzumab	Targeted	HER2(ab)
Daratumumab	Targeted	CD38(ab)	Pomalidomide	Targeted	ImmuneMod
Darolutamide	Targeted	AR(a)	Ponatinib	Targeted	BCRABLTKI
Dasatinib	Targeted	BCRABLTKI	Regorafenib	Targeted	MKTKI
Daunorubicin	Chemo	N/A	Ribociclib	Targeted	CDK4/6(i)
Decitabine	Chemo	N/A	Rituximab	Targeted	CD20(ab)
Degarelix	Endocrine	ADT	Rucaparib	Targeted	PARP(i)
Docetaxel	Chemo	N/A	Talazoparib	Targeted	PARP(i)
Doxorubicin	Chemo	N/A	Tamoxifen	Endocrine	SERM
Durvalumab	Targeted	PD-L1(ab)	TDM1 (ado-trastuzumab emtansine)	Targeted	HER2(ab)
Enzalutamide	Targeted	AR(a)	Trastuzumab	Targeted	HER2(ab)
Etoposide	Chemo	N/A	Triptorelin	Endocrine	ADT
Exemestane	Endocrine	AI	Venetoclax	Targeted	BCL2
Fam-Trastuzumab Deruxtecan	Targeted	HER2(ab)	Vinblastine	Chemo	N/A
Fludarabine	Chemo	N/A	Vincristine	Chemo	N/A

Abbreviations: ab, antibody; ADT, androgen deprivation therapy; AI, aromatase inhibitor; AR(a), androgen receptor antagonists; BCL2, B-cell lymphoma 2; BCRABLTKI, breakpoint cluster region-Abelson leukemia virus tyrosine kinase inhibitor; BTK(i), Bruton tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CD38, cluster of differentiation 38; CDK4/6(i), cyclin dependent kinase 4/6 inhibitor; chemo, chemotherapy; CTLA-4(ab), anti-CTLA-4 antibody – CTLA-4 is also known as CD152, cluster of differentiation 152 [immunotherapy]; CYP17i, cytochrome P17 inhibitor; HER2ab, anti-human epidermal growth factor receptor 2 antibody; i, inhibitor; ImmuneMod, immunomodulator; MKTKI, multi-kinase tyrosine kinase inhibitor; PD1(ab), anti-programmed cell death 1 antibody [immunotherapy]; PD-L1(ab); anti-program cell death-ligand 1 antibody [immunotherapy]; SERM, selective oestrogen receptor modulator; TKI, tyrosine kinase inhibitor; PARP(i), poly adenosine diphosphate-ribose polymerase inhibitor; Proteasome(i), proteasome inhibitor; VEGF(ab), anti-vascular endothelial growth factor antibody; VEGFTKI, vascular endothelial growth factor tyrosine kinase inhibitor

Supplemental Table 2 Characteristics of the cancer cohort and matched control cohort (Total patients N = 314,144)					
	With cancer diagnosis Median follow up: 161 days		Without cancer diagnosis Median follow up: 162 days		Test Cancer vs Noncancer
	Not vaccinated (N=27,474)	Vaccinated (N=129,598)	Not vaccinated (N=27,474)	Vaccinated (N=129,598)	
Demographic at index date					
Age, years (median, IQR)	72 (64-76)	72 (67-76)	72 (64-76)	73 (68-77)	Wilcoxon, p<0.0001
Age, years, Categorical					
<50	1229 (4)	2398 (2)	1183 (4)	2370 (2)	Chi-2, p<0.0001
50-60	2750 (10)	8455 (7)	2682 (10)	8039 (6)	
60-70	7140 (26)	31976 (25)	6882 (25)	30326 (23)	
70-80	12322 (45)	67609 (52)	12325 (45)	65966 (51)	
>80	4033 (15)	19160 (15)	4402 (16)	22897 (18)	
Gender (N, %)					
Female	1748 (6)	6515 (5)	1748 (6)	6515 (5)	Chi-2, p = 1.0000
Male	25726 (94)	123083 (95)	25726 (94)	123083 (95)	
Race (N, %)					
Caucasian	21205 (77)	95738 (74)	21205 (77)	95738 (74)	Chi-2, p = 1.0000
African American	5786 (21)	31416 (24)	5786 (21)	31416 (24)	
Asian	99 (<1)	705 (<1)	99 (<1)	705 (<1)	
Other	384 (1)	1739 (1)	384 (1)	1739 (1)	
Ethnicity (N, %)					
Non-Hispanic	25805 (95)	120547 (94)	25793 (95)	120176 (94)	Chi-2, p=0.0311
Hispanic	1257 (5)	7245 (6)	1250 (5)	7521 (6)	
Unknown/Missing (N, % of total data)	412 (2)	1806 (1)	431 (2)	1901 (1)	
BMI (median, IQR)	28.19 (24.43-32.46)	28.39 (24.89-32.47)	28.21 (24.44-32.78)	28.42 (24.89-32.75)	Wilcoxon, p<0.0001
BMI, Categorical					
<18.5, Underweight	832 (3)	2682 (2)	832 (3)	2682 (2)	Chi-2, p = 1.0000
18.5-24.9, Normal weight	6967 (25)	30626 (24)	6967 (25)	30626 (24)	
25.0-29.9, Overweight	9146 (33)	45669 (35)	9146 (33)	45669 (35)	
>30.0, Obesity	10529 (38)	50621 (39)	10529 (38)	50621 (39)	
30.0-34.9 Moderate Obesity	6405 (23)	31340 (24)	5926 (22)	29145 (22)	Chi-2, p<0.0001
>35.0 Severe Obesity	4124 (15)	19281 (15)	4603 (17)	21476 (17)	
Rurality (N, %)					
Urban	19262 (79)	96170 (85)	18872 (78)	94329 (84)	Chi-2, p=0.0047
City Town	2685 (11)	9412 (8)	2734 (11)	9418 (8)	
Small Town/Rural	2470 (10)	7971 (7)	2483 (10)	8192 (7)	
Unknown/Missing (N, % of total data)	3057 (11)	16045 (12)	3385 (12)	17659 (14)	
Comorbidities (2 years prior index date)					
Smoking Status (N, %)					
Never Smoker	8744 (32)	39581 (31)	8804 (32)	39722 (31)	Chi-2, p=0.0076
Former Smoker	13134 (48)	65102 (50)	12840 (47)	64616 (50)	
Current Smoker	5596 (20)	24915 (19)	5830 (21)	25260 (19)	
Elixhauser Comorbidity index (median, IQR)	11 (7-21)	12 (7-21)	11 (6-17)	11 (6-17)	Wilcoxon, p<0.0001
Elixhauser Comorbidity index, Categorical					
0-5	3663 (13)	16069 (12)	3663 (13)	16069 (12)	Chi-2, p = 1.0000
5-10	9517 (35)	44498 (34)	9517 (35)	44498 (34)	
10+	14294 (52)	69031 (53)	14294 (52)	69031 (53)	
Comorbidities (N, %)					
Asthma	1592 (6)	7935 (6)	1988 (7)	9845 (8)	Chi-2, p<0.0001
Chronic Lung Disease	11394 (41)	58307 (45)	12457 (45)	63598 (49)	Chi-2, p<0.0001
COPD	7756 (28)	38751 (30)	8887 (32)	44190 (34)	Chi-2, p<0.0001
Acute Respiratory Failure	2478 (9)	10025 (8)	2810 (10)	12095 (9)	Chi-2, p<0.0001
Venous Thromboembolism	1295 (5)	5808 (4)	1332 (5)	6173 (5)	Chi-2, p=0.0007
Spleen Removed	97 (<1)	438 (<1)	34 (<1)	197 (<1)	Chi-2, p<0.0001

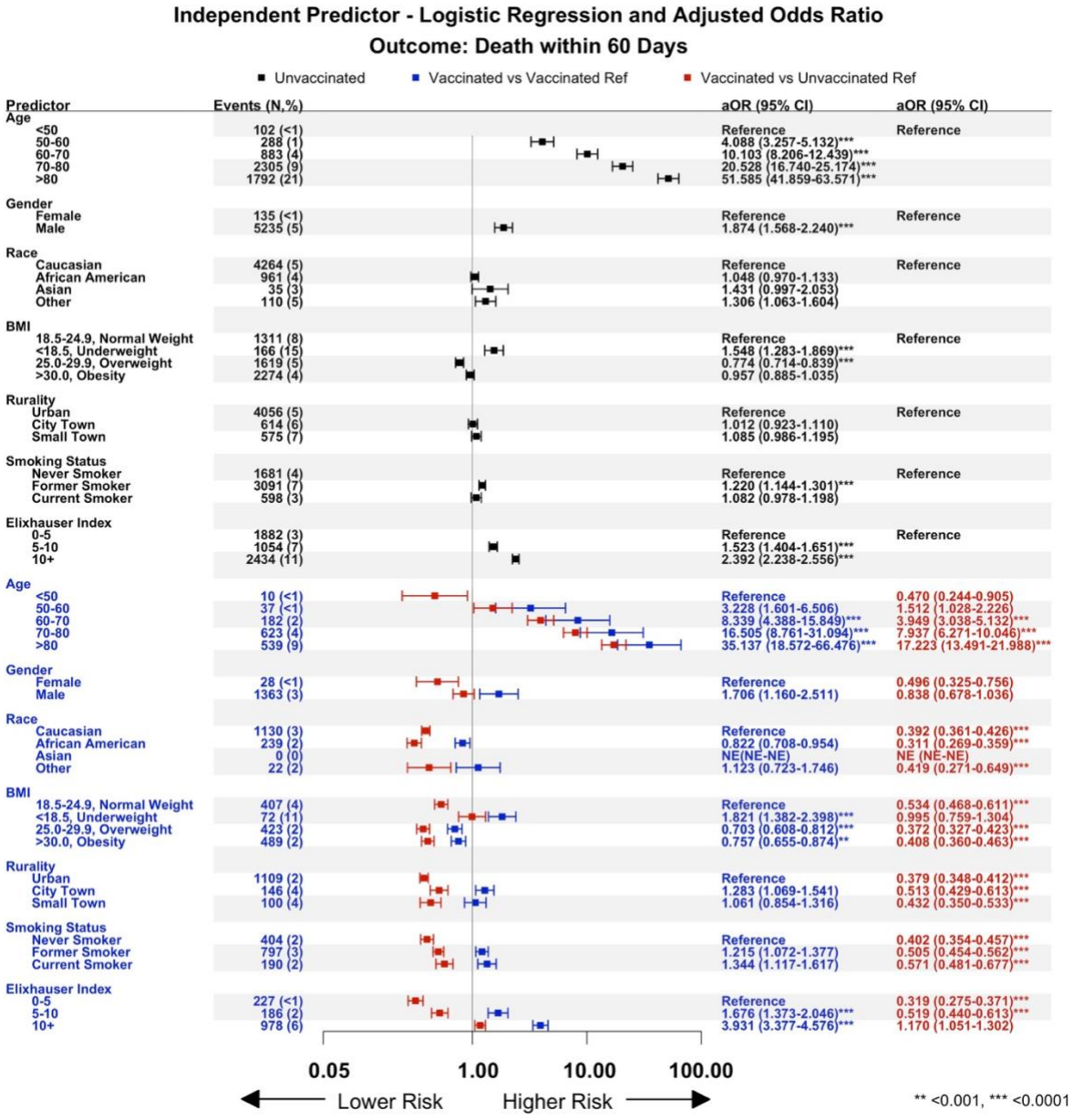
Supplemental Table 2, continued: Characteristics of the cancer cohort and matched control cohort (Total patients N = 314,144)					
	With cancer diagnosis		Without cancer diagnosis		Test Cancer vs Noncancer
	Not vaccinated (N=27,474)	Vaccinated (N=129,598)	Not vaccinated (N=27,474)	Vaccinated (N=129,598)	
Vaccination					
Primary Vaccine Brand (N, %)					
Janssen	/	5277 (3)	/	6036 (4)	Chi-2, p<0.0001
Pfizer		61079 (39)		58410 (37)	
Moderna		62936 (40)		64820 (41)	
Mixed		184 (<1)		210 (<1)	
Other		16 (<1)		10 (<1)	
Unknown		106 (<1)		112 (<1)	
Vaccine Dose (N, %)					
Janssen, Full	/	3533 (2)	/	4243 (3)	Chi-2, p<0.0001
Janssen, Booster, Janssen		702 (<1)		734 (<1)	
Janssen, Booster, Other		1042 (<1)		1059 (<1)	
Pfizer, Partial		1347 (<1)		1620 (1)	
Pfizer, Full		22476 (14)		23605 (15)	
Pfizer, Booster, Pfizer		36328 (23)		32047 (20)	
Pfizer, Booster, Other		1018 (<1)		1138 (<1)	
Moderna, Partial		1521 (<1)		1950 (1)	
Moderna, Full		25179 (16)		28388 (18)	
Moderna, Booster, Moderna		35026 (22)		33162 (21)	
Moderna, Booster, Other		1210 (<1)		1320 (<1)	
Mixed		184 (<1)		210 (<1)	
Other		16 (<1)		10 (<1)	
Unknown		106 (<1)		112 (<1)	

Supplemental Figure 1A



Supplemental Figure 1 (S1): Adjusted odds ratios for infection (**S1A**) and death within 60 days of infection (**S1B**) presented as forest plots. The vertical line at 1 represents the risk of infection or death within 60 days of infection for the respective reference cohort. The data is shown as the means with their respective confidence intervals. Movement to the right occurs when the risk is increased, while movement to the left represents a reduction in the risk. The reference cohorts are age less than 50 for the age cohorts, females for the gender cohorts, Caucasians for the race cohorts, normal weight for the BMI cohorts, urban residence for rurality, never smoker for the smoking status cohorts and Elixhauser Index of 0-5 for the Elixhauser Index cohorts. In each case results with the unvaccinated cohort are represented by **black** symbols while results for the vaccinated cohort are shown as **blue** or **red** symbols. The data in the **black** and **blue** symbols were generated using as the reference a cohort matched for vaccination status. This allows one to see the impact of the seven characteristics [predictors] and assess whether vaccination had any impact on the adjusted odds ratios (aORs). The **red** symbols describe results for the vaccinated cohort but in this case using as the reference the unvaccinated cohort allowing one to appreciate the impact of vaccination across the cohorts of each characteristic.

Supplemental Figure 1B



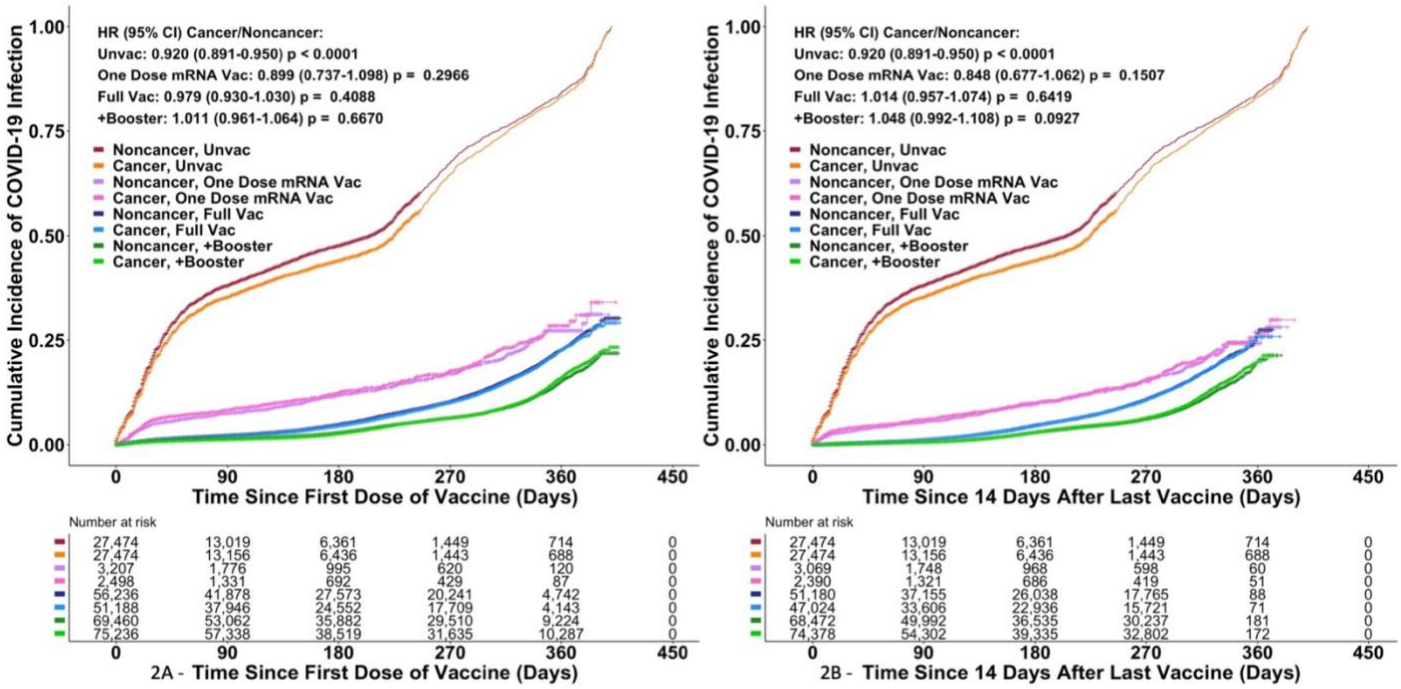
Supplemental Table 3A: Sensitivity analysis 1: Main cohort + missing data

	All patients (N=1,143,862)	COVID Infection		COVID-19 Positives (N=220,474)	Death within 60 Days	
	% Positive	aOR (95% CI)	p value	% Event	aOR (95% CI)	p value
Demographics at index date						
Age, years, Categorical (N, %)						
<50, Unvaccinated	60470 (40)	**ref**		155 (<1)	**ref**	
50-60, Unvaccinated	30271 (44)	1.078 (1.058-1.099)	<0.0001	364 (1)	4.110 (3.401-4.968)	<0.0001
60-70. Unvaccinated	27655 (44)	1.091 (1.069-1.113)	<0.0001	1057 (4)	10.954 (9.216-13.019)	<0.0001
70-80, Unvaccinated	29405 (51)	1.333 (1.303-1.363)	<0.0001	2688 (9)	23.003 (19.416-27.252)	<0.0001
>80, Unvaccinated	10477 (54)	1.676 (1.621-1.733)	<0.0001	2258 (22)	59.633 (50.146-70.914)	<0.0001
<50, Vaccinated	13295 (10)	0.095 (0.093-0.097)	<0.0001	11 (<1)	0.429 (0.231-0.796)	0.0072
50-60, Vaccinated	10594 (9)	0.077 (0.075-0.079)	<0.0001	46 (<1)	1.645 (1.169-2.316)	0.0043
60-70, Vaccinated	13629 (7)	0.061 (0.060-0.063)	<0.0001	201 (1)	3.970 (3.141-5.019)	<0.0001
70-80, Vaccinated	18065 (7)	0.059 (0.058-0.060)	<0.0001	686 (4)	8.032 (6.531-9.879)	<0.0001
>80, Vaccinated	6608 (9)	0.077 (0.074-0.079)	<0.0001	626 (9)	18.238 (14.728-22.585)	<0.0001
Gender (N, %)						
Female, Unvaccinated	35533 (39)	**ref**		187 (<1)	**ref**	
Male, Unvaccinated	122749 (46)	1.032 (1.013-1.051)	0.0011	6335 (5)	2.757 (2.353-3.232)	<0.0001
Female, Vaccinated	7494 (9)	0.090 (0.087-0.093)	<0.0001	31 (<1)	0.532 (0.358-0.792)	0.0019
Male, Vaccinated	54698 (8)	0.086 (0.084-0.089)	<0.0001	1539 (3)	0.903 (0.744-1.097)	0.3061
Race (N, %)						
Caucasian, Unvaccinated	92384 (46)	**ref**		4768 (5)	**ref**	
African American, Unvaccinated	29666 (47)	1.137 (1.115-1.158)	<0.0001	1082 (4)	1.058 (0.983-1.139)	0.1300
Asian, Unvaccinated	1616 (48)	1.331 (1.240-1.428)	<0.0001	45 (3)	1.499 (1.086-2.070)	0.0139
Other, Unvaccinated	2704 (47)	1.110 (1.052-1.172)	0.0002	125 (5)	1.317 (1.085-1.599)	0.0054
Caucasian, Vaccinated	40711 (8)	0.086 (0.085-0.088)	<0.0001	1215 (3)	0.397 (0.367-0.429)	<0.0001
African American, Vaccinated	15085 (8)	0.094 (0.092-0.096)	<0.0001	252 (2)	0.312 (0.272-0.359)	<0.0001
Asian, Vaccinated	797 (8)	0.090 (0.083-0.097)	<0.0001	1 (<1)	0.042 (0.006-0.296)	0.0015
Other, Vaccinated	1095 (8)	0.096 (0.090-0.103)	<0.0001	24 (2)	0.414 (0.273-0.630)	<0.0001
BMI, Categorical (N, %)						
18.5-24.9, Normal weight, Unvaccinated	22730 (38)	**ref**		1571 (7)	**ref**	
<18.5, Underweight, Unvaccinated	1390 (29)	0.676 (0.632-0.722)	<0.0001	211 (15)	1.599 (1.350-1.894)	<0.0001
25.0-29.9, Overweight, Unvaccinated	45125 (46)	1.352 (1.323-1.381)	<0.0001	1923 (4)	0.788 (0.732-0.848)	<0.0001
>30.0, Obesity, Unvaccinated	70011 (52)	1.711 (1.676-1.747)	<0.0001	2630 (4)	0.978 (0.910-1.051)	0.5480
30.0-34.9 Moderate Obesity	39203 (51)	1.626 (1.589-1.663)	<0.0001	1439 (4)	0.864 (0.798-0.936)	0.0003
>35.0 Severe Obesity	30808 (53)	1.837 (1.793-1.883)	<0.0001	1191 (4)	1.180 (1.082-1.286)	0.0002
18.5-24.9, Normal weight, Vaccinated	10573 (7)	0.109 (0.106-0.112)	<0.0001	457 (4)	0.521 (0.460-0.590)	<0.0001
<18.5, Underweight, Vaccinated	786 (8)	0.119 (0.110-0.128)	<0.0001	81 (10)	0.969 (0.752-1.249)	0.8073
25.0-29.9, Overweight, Vaccinated	20397 (8)	0.118 (0.115-0.121)	<0.0001	474 (2)	0.372 (0.330-0.420)	<0.0001
>30.0, Obesity, Vaccinated	29763 (9)	0.129 (0.126-0.132)	<0.0001	552 (2)	0.415 (0.369-0.466)	<0.0001
30.0-34.9 Moderate Obesity	16939 (8)	0.127 (0.124-0.130)	<0.0001	311 (2)	0.379 (0.330-0.435)	<0.0001
>35.0 Severe Obesity	12824 (9)	0.133 (0.129-0.136)	<0.0001	241 (2)	0.473 (0.406-0.552)	<0.0001
Location						
Urban, Unvaccinated	121147 (45)	**ref**		4955 (4)	**ref**	
City Town, Unvaccinated	13057 (48)	1.029 (1.002-1.056)	0.0318	742 (6)	1.033 (0.950-1.124)	0.4475
Small Town, Rural, Unvaccinated	9545 (46)	0.914 (0.887-0.941)	<0.0001	671 (7)	1.088 (0.995-1.189)	0.0631
Urban, Vaccinated	52360 (9)	0.075 (0.074-0.076)	<0.0001	1256 (2)	0.392 (0.363-0.424)	<0.0001
City Town, Vaccinated	4099 (8)	0.067 (0.065-0.069)	<0.0001	158 (4)	0.507 (0.428-0.601)	<0.0001
Small Town, Rural, Vaccinated	3010 (7)	0.060 (0.058-0.063)	<0.0001	112 (4)	0.437 (0.359-0.534)	<0.0001
Comorbidities (2 years prior index date)						
Smoking Status (N, %)						
Never Smoker, Unvaccinated	50704 (54)	**ref**		1832 (4)	**ref**	
Former Smoker, Unvaccinated	50380 (52)	0.906 (0.889-0.923)	<0.0001	3285 (7)	1.176 (1.105-1.251)	<0.0001
Current Smoker, Unvaccinated	18791 (34)	0.481 (0.470-0.492)	<0.0001	629 (3)	1.077 (0.977-1.189)	0.1362
Never Smoker, Vaccinated	23734 (9)	0.083 (0.081-0.084)	<0.0001	426 (2)	0.401 (0.354-0.454)	<0.0001
Former Smoker, Vaccinated	25695 (8)	0.074 (0.072-0.076)	<0.0001	841 (3)	0.508 (0.458-0.563)	<0.0001
Current Smoker, Vaccinated	8823 (6)	0.056 (0.054-0.057)	<0.0001	194 (2)	0.560 (0.474-0.662)	<0.0001
Elixhauser Comorbidity index, Categorical						
0-5, Unvaccinated	118462 (43)	**ref**		2588 (2)	**ref**	
5-10, Unvaccinated	15766 (49)	0.979 (0.955-1.004)	0.0982	1184 (8)	1.448 (1.343-1.561)	<0.0001
10+, Unvaccinated	24054 (48)	1.004 (0.982-1.026)	0.7370	2750 (11)	2.304 (2.167-2.450)	<0.0001
0-5, Vaccinated	34027 (7)	0.065 (0.064-0.067)	<0.0001	285 (<1)	0.338 (0.296-0.386)	<0.0001
5-10, Vaccinated	8692 (7)	0.063 (0.061-0.065)	<0.0001	205 (2)	0.518 (0.443-0.605)	<0.0001
10+, Vaccinated	19473 (10)	0.097 (0.095-0.099)	<0.0001	1080 (6)	1.170 (1.061-1.289)	0.0016

Supplemental Table 3B: Sensitivity analysis 2: Main cohort + missing data + addition of those who were excluded for infection/vaccination prior to 12/14/2020

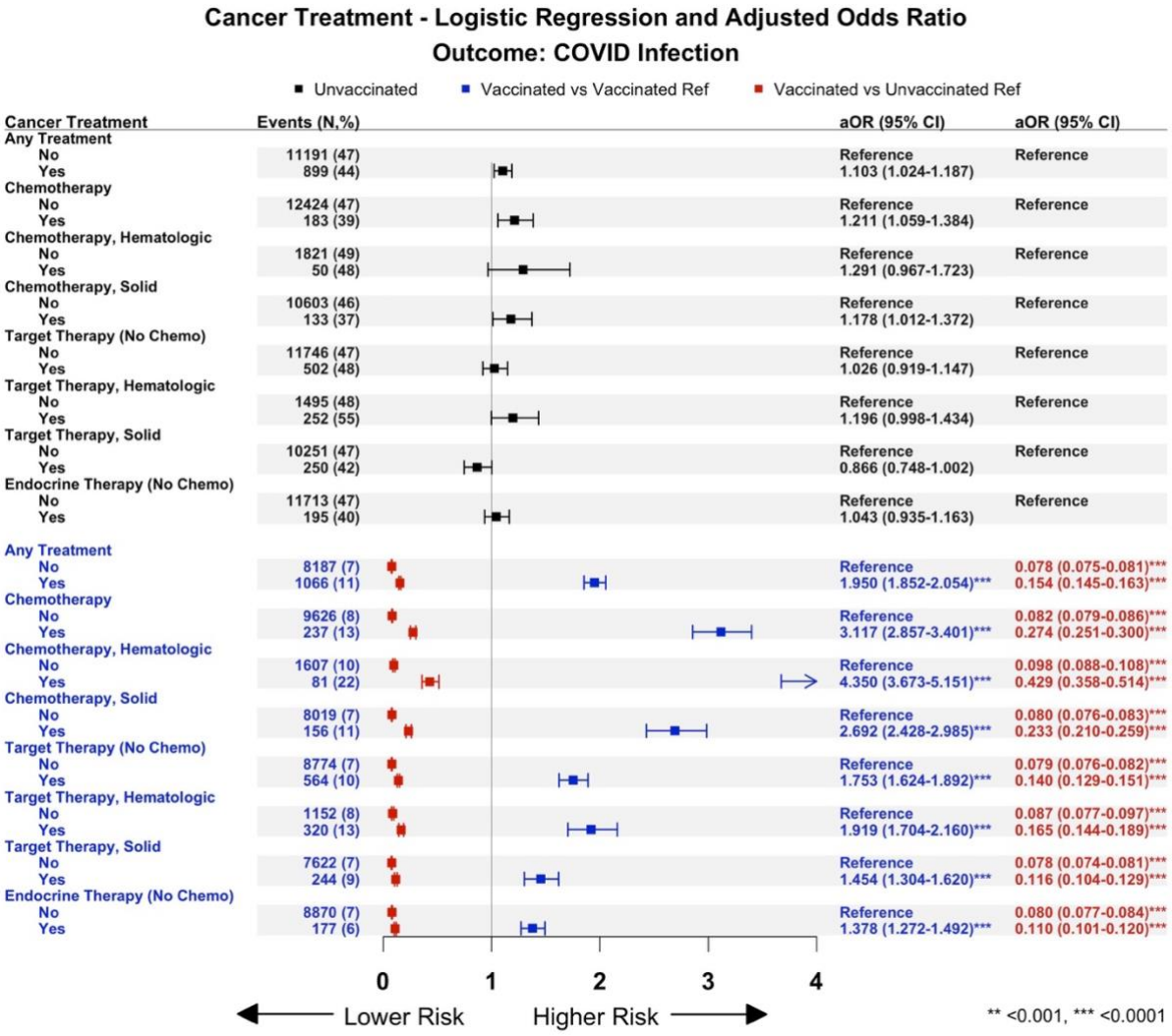
	All patients (N=1,509,831)	COVID Infection		COVID-19 Positives (N=355,839)	Death within 60 Days	
	% Positive	aOR (95% CI)	p value	% Event	aOR (95% CI)	p value
Demographics at index date						
Age, years, Categorical (N, %)						
<50, Unvaccinated	103012 (34)	**ref**		252 (<1)	**ref**	
50-60, Unvaccinated	53908 (42)	1.185 (1.168-1.202)	<0.0001	658 (1)	4.450 (3.845-5.151)	<0.0001
60-70, Unvaccinated	52184 (43)	1.225 (1.206-1.243)	<0.0001	2177 (4)	13.032 (11.408-14.886)	<0.0001
70-80, Unvaccinated	60067 (51)	1.550 (1.525-1.576)	<0.0001	5976 (10)	27.825 (24.418 -31.709)	<0.0001
>80, Unvaccinated	23992 (48)	1.693 (1.656-1.731)	<0.0001	5866 (24)	75.985 (66.588-86.708)	<0.0001
<50, Vaccinated	13438 (10)	0.083 (0.081-0.085)	<0.0001	11 (<1)	0.534 (0.289-0.988)	0.0455
50-60, Vaccinated	10692 (9)	0.068 (0.066-0.070)	<0.0001	46 (<1)	2.045 (1.461-2.861)	<0.0001
60-70, Vaccinated	13730 (7)	0.055 (0.054-0.056)	<0.0001	201 (1)	4.969 (3.972-6.217)	<0.0001
70-80, Vaccinated	18169 (7)	0.054 (0.052-0.055)	<0.0001	691 (4)	10.166 (8.381-12.330)	<0.0001
>80, Vaccinated	6631 (9)	0.071 (0.068-0.073)	<0.0001	626 (9)	23.252 (19.057-28.370)	<0.0001
Gender (N, %)						
Female, Unvaccinated	59167 (32)	**ref**		418 (<1)	**ref**	
Male, Unvaccinated	234010 (44)	1.054 (1.404-1.069)	<0.0001	14511 (6)	2.447 (2.199-2.722)	<0.0001
Female, Vaccinated	7587 (9)	0.073 (0.071-0.076)	<0.0001	31 (<1)	0.583 (0.395-0.859)	0.0063
Male, Vaccinated	55074 (8)	0.070 (0.068-0.072)	<0.0001	1544 (3)	0.957 (0.809-1.132)	0.6066
Race (N, %)						
Caucasian, Unvaccinated	173285 (43)	**ref**		10596 (6)	**ref**	
African American, Unvaccinated	58204 (47)	1.261 (1.244-1.278)	<0.0001	2704 (5)	1.066 (1.016-1.119)	0.0093
Asian, Unvaccinated	2835 (44)	1.291 (1.226-1.360)	<0.0001	85 (3)	1.368 (1.079-1.734)	0.0095
Other, Unvaccinated	5209 (41)	1.110 (1.069-1.153)	<0.0001	286 (5)	1.386 (1.216-1.580)	<0.0001
Caucasian, Vaccinated	41020 (8)	0.072 (0.071-0.074)	<0.0001	1218 (3)	0.436 (0.405-0.470)	<0.0001
African American, Vaccinated	15193 (8)	0.080 (0.078-0.082)	<0.0001	253 (2)	0.353 (0.308-0.405)	<0.0001
Asian, Vaccinated	800 (8)	0.078 (0.072-0.084)	<0.0001	1 (<1)	0.045 (0.006-0.320)	0.0019
Other, Vaccinated	1109 (9)	0.081 (0.076-0.087)	<0.0001	24 (2)	0.458 (0.301-0.695)	0.0003
BMI, Categorical (N, %)						
18.5-24.9, Normal weight, Unvaccinated	42087 (35)	**ref**		3758 (9)	**ref**	
<18.5, Underweight, Unvaccinated	2639 (25)	0.620 (0.592-0.650)	<0.0001	485 (18)	1.609 (1.434-1.805)	<0.0001
25.0-29.9, Overweight, Unvaccinated	84889 (45)	1.446 (1.424-1.469)	<0.0001	4491 (5)	0.778 (0.741-0.817)	<0.0001
>30.0, Obesity, Unvaccinated	131780 (52)	1.885 (1.857-1.914)	<0.0001	5749 (4)	0.930 (0.886-0.975)	0.0030
30.0-34.9 Moderate Obesity	73602 (51)	1.786 (1.757-1.816)	<0.0001	3181 (4)	0.828 (0.784-0.873)	<0.0001
>35.0 Severe Obesity	58178 (54)	2.031 (1.996-2.068)	<0.0001	2568 (4)	1.110 (1.047-1.177)	0.0004
18.5-24.9, Normal weight, Vaccinated	10628 (7)	0.105 (0.102-0.108)	<0.0001	458 (4)	0.543 (0.481-0.613)	<0.0001
<18.5, Underweight, Vaccinated	789 (8)	0.117 (0.109-0.127)	<0.0001	81 (10)	1.032 (0.802-1.329)	0.8040
25.0-29.9, Overweight, Vaccinated	20545 (8)	0.113 (0.111-0.116)	<0.0001	475 (2)	0.385 (0.342-0.433)	<0.0001
>30.0, Obesity, Vaccinated	30018 (9)	0.125 (0.122-0.128)	<0.0001	555 (2)	0.435 (0.389-0.487)	<0.0001
30.0-34.9 Moderate Obesity	17081 (8)	0.122 (0.119-0.125)	<0.0001	314 (2)	0.396 (0.346-0.453)	<0.0001
>35.0 Severe Obesity	12937 (9)	0.128 (0.125-0.132)	<0.0001	241 (2)	0.501 (0.431-0.581)	<0.0001
Location						
Urban, Unvaccinated	216101 (41)	**ref**		11445 (5)	**ref**	
City Town, Unvaccinated	23496 (45)	1.019 (1.000-1.039)	0.0529	1583 (7)	0.997 (0.940-1.056)	0.9129
Small Town, Rural	18078 (44)	0.931 (0.911-0.951)	<0.0001	1527 (8)	1.083 (1.020-1.150)	0.0089
Urban, Vaccinated	52743 (9)	0.064 (0.063-0.065)	<0.0001	1261 (2)	0.433 (0.402-0.465)	<0.0001
City Town, Vaccinated	4133 (8)	0.057 (0.055-0.059)	<0.0001	158 (4)	0.554 (0.468-0.656)	<0.0001
Small Town, Rural	3023 (7)	0.051 (0.049-0.053)	<0.0001	112 (4)	0.475 (0.390-0.579)	<0.0001
Comorbidities (2 years prior index date)						
Smoking Status (N, %)						
Never Smoker, Unvaccinated	95438 (54)	**ref**		4084 (4)	**ref**	
Former Smoker, Unvaccinated	98770 (51)	0.900 (0.888-0.912)	<0.0001	7435 (8)	1.134 (1.088-1.183)	<0.0001
Current Smoker, Unvaccinated	32510 (32)	0.448 (0.441-0.456)	<0.0001	1281 (4)	1.110 (1.037-1.190)	0.0028
Never Smoker, Vaccinated	23944 (9)	0.079 (0.078-0.081)	<0.0001	426 (2)	0.424 (0.375-0.478)	<0.0001
Former Smoker, Vaccinated	25873 (8)	0.071 (0.070-0.073)	<0.0001	846 (3)	0.541 (0.490-0.597)	<0.0001
Current Smoker, Vaccinated	8874 (6)	0.054 (0.053-0.055)	<0.0001	194 (2)	0.608 (0.516-0.717)	<0.0001
Elixhauser Comorbidity index, Categorical						
0-5, Unvaccinated	213539 (39)	**ref**		6046 (3)	**ref**	
5-10, Unvaccinated	30700 (50)	0.977 (0.959-0.995)	0.0114	2570 (8)	1.317 (1.251-1.386)	<0.0001
10+, Unvaccinated	48939 (44)	0.862 (0.849-0.876)	<0.0001	6313 (13)	2.092 (2.008-2.180)	<0.0001
0-5, Vaccinated	34340 (7)	0.054 (0.053-0.055)	<0.0001	285 (<1)	0.348 (0.305-0.396)	<0.0001
5-10, Vaccinated	8759 (7)	0.049 (0.048-0.050)	<0.0001	207 (2)	0.532 (0.457-0.619)	<0.0001
10+, Vaccinated	19562 (10)	0.075 (0.073-0.076)	<0.0001	1083 (6)	1.200 (1.096-1.313)	<0.0001

Supplemental Figures 2A/2B



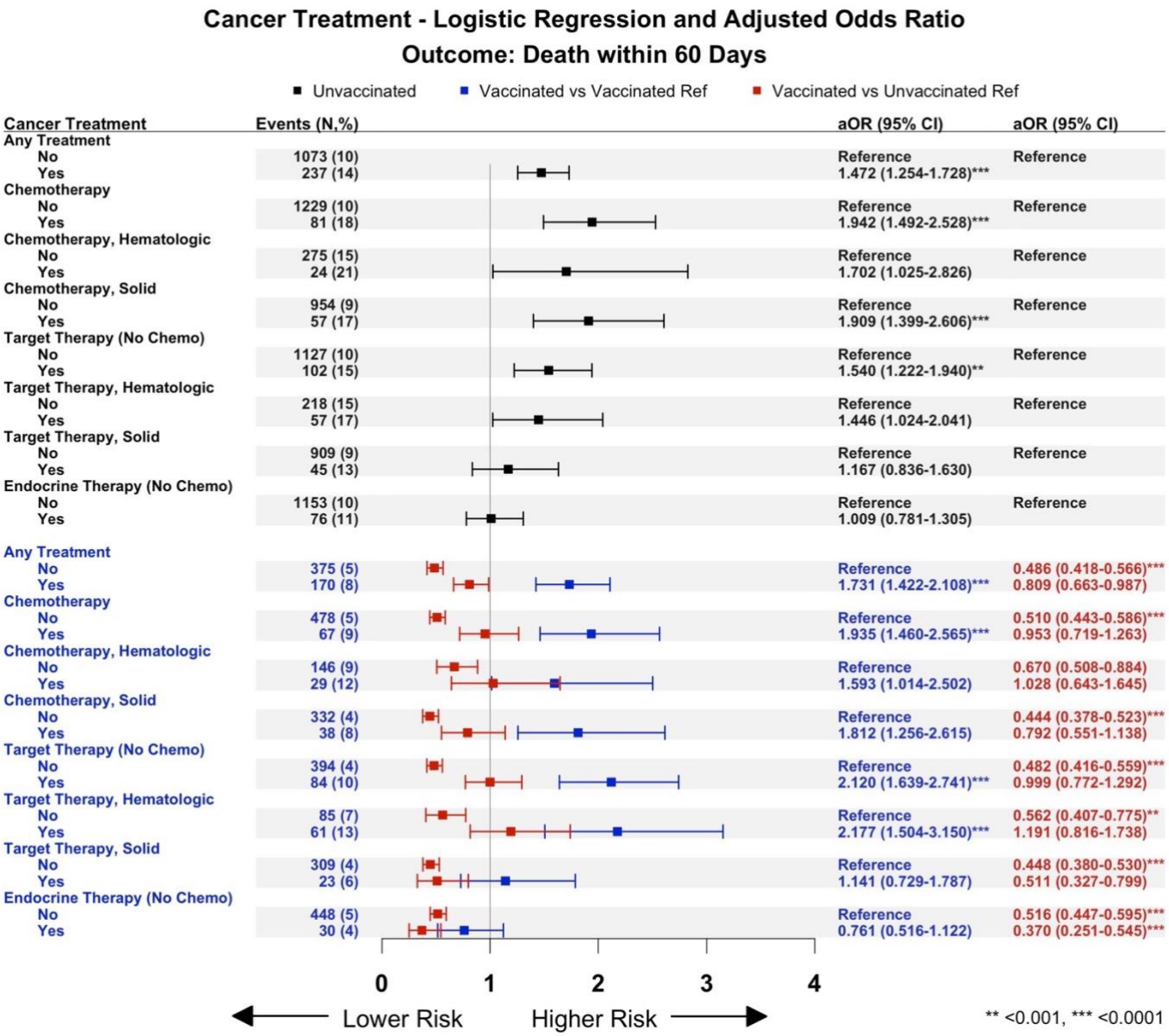
Supplemental Figure 2 (S2): Kaplan-Meier plots of COVID-19 infection over time. As in **Figure 4, Supplemental Figure 2** demonstrates a comparable impact of vaccination and of boosting in Veterans without/with a diagnosis of cancer. Surprising results with a single dose of the mRNA vaccines are observed in the group of Veterans who received only one dose. Out of a total of 312,773 Veterans who were vaccinated and included in this analysis, 262 had an infection after receiving the first vaccination and received only one dose of either the Pfizer-BioNTech or the Moderna mRNA products. These were individuals whose goal was to be completely vaccinated and not necessarily "failures" of a single dose mRNA vaccine strategy. In **Figure 4**, they were not assigned to the single dose of mRNA vaccine cohort. In **Supplemental Figure 2A,** those 262 with infection after a single dose have been assigned to the single mRNA dose cohort. In this analysis, one can still see comparable efficacy of the single-dose as evidenced by a slope of acquired infections with the single-dose that is comparable to that of the planned two doses (Full Vac). Hazard ratios: One dose versus Unvaccinated: 0.420 (0.380-0.464). Full doses versus Unvaccinated: 0.223 (0.215-0.230). Full dose + booster versus Unvaccinated: 0.146 (0.142-0.15. In **Supplemental Figure 2B** the 262 Veterans who had an infection prior to a planned second dose of their mRNA vaccine are again assigned to a cohort. The Kaplan-Meier plots depict infections starting 14 days after the last dose of the primary vaccination series. This was chosen as the method of comparison here in accordance with WHO guidelines that state *"For the primary analysis of VE studies, a conservative approach is recommended in considering a person as potentially protected from vaccination only from 14 days after the date of first dose of vaccination (the time required to achieve protection for the majority of vaccine recipients for most vaccines), and 7–14 days after second doses of vaccine".* Again, the slopes of acquired infections are comparable. Hazard ratios: One dose versus Unvaccinated: 0.243 (0.217-0.271). Full doses versus Unvaccinated: 0.119 (0.115-0.124). Full dose + booster versus Unvaccinated: 0.075 (0.073-0.078).

Supplemental Figure 3A

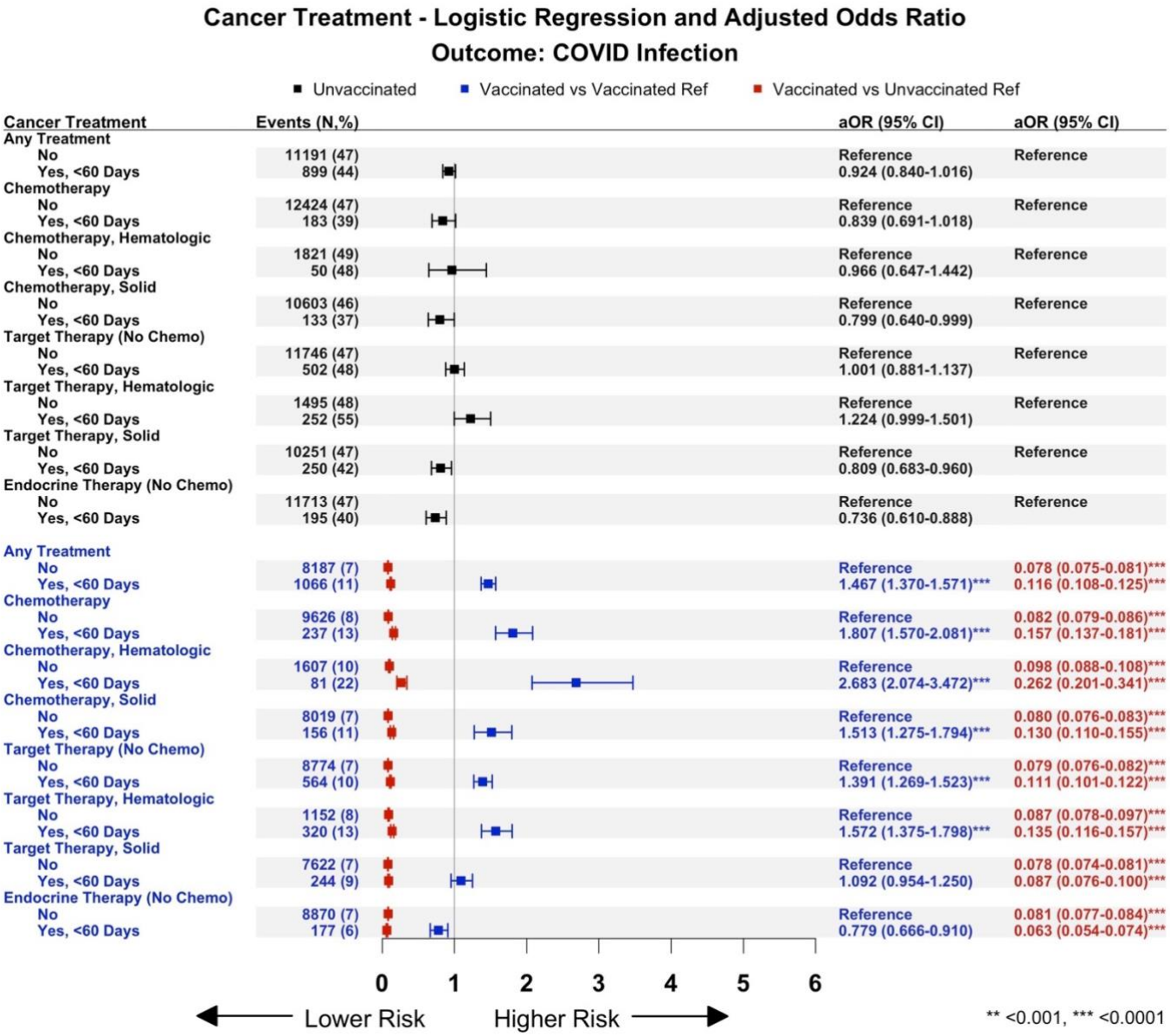


Supplemental Figure 3 (S3): Adjusted odds ratios for infection **(S3A)** and death within 60 days of infection **(S3B)** are presented as forest plots. The interval for acquiring infection after therapy was administered is not confined. As in **Figure 2** and **Supplemental Figure 1**, **black** symbols are used for the unvaccinated with **blue** and **red** symbols for the vaccinated. **S3A** shows aORs for infection that are similar in unvaccinated Veterans whether they did/did not receive treatment. Note the high baseline number of events – 47-51% in the Veterans who were not vaccinated and did not receive any therapy. However, turning to the vaccinated cohort, one can see marked reductions in the aORs for infection (**red** symbols) with vaccination in both those who did/did not receive treatment demonstrating vaccination provides robust protection from infection. However, within the vaccinated cohort, one can see that compared to those not treated, infections occurred more frequently amongst Veterans with hematologic malignancies who received either chemotherapy (aOR, 4.350, 95%CI 3.673–5.151, p<0.0001) or targeted therapies (aOR, 1.919, 95%CI, 1.704–2.160, p<0.0001) and in Veterans with solid tumors treated with chemotherapy (aOR, 2.692, 95%CI, 2.428–2.985, p<0.0001) or targeted therapies (aOR, 1.454. (5%CI, 1.304–1.620, p<0.0001). The increased risks of infection in Veterans with either hematologic malignancies or a solid tumor diagnosis treated with either chemotherapy or targeted therapies, are concordant with the KM plots in **Figure 5**. **S3B**, reports the likelihood of death within 60 days of infection, not 60 days of receipt of treatment. **S3C**, presents the aORs for survival amongst vaccinated Veterans with a diagnosis of cancer who received treatment. The interval for acquiring infection is confined to the first 60 days after therapy was administered. Worse aORs for infection can be seen in Veterans with hematologic malignancies who received either chemotherapy (aOR, 2.683, 95%CI, 2.074–3.472, p<0.0001) or targeted therapies (aOR, 1.572, 95%CI, 1.375–1.798, p<0.0001) and in Veterans with solid tumors treated with chemotherapy (aOR, 1.513, 95%CI, 1.275–1.794, p<0.0001). **S3D**, reports the likelihood of death within 60 days of infection, not 60 days of receipt of treatment

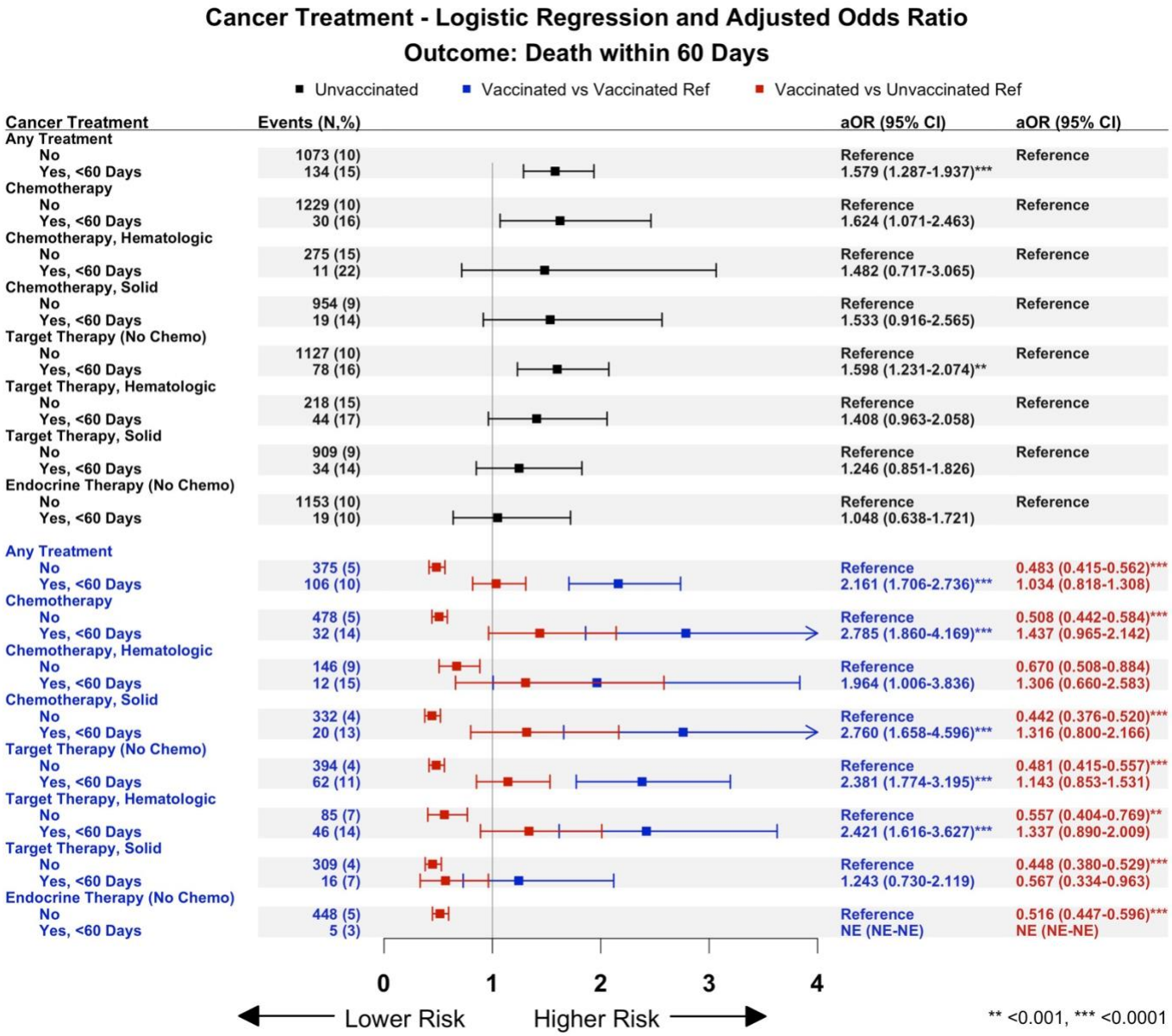
Supplemental Figure 3B



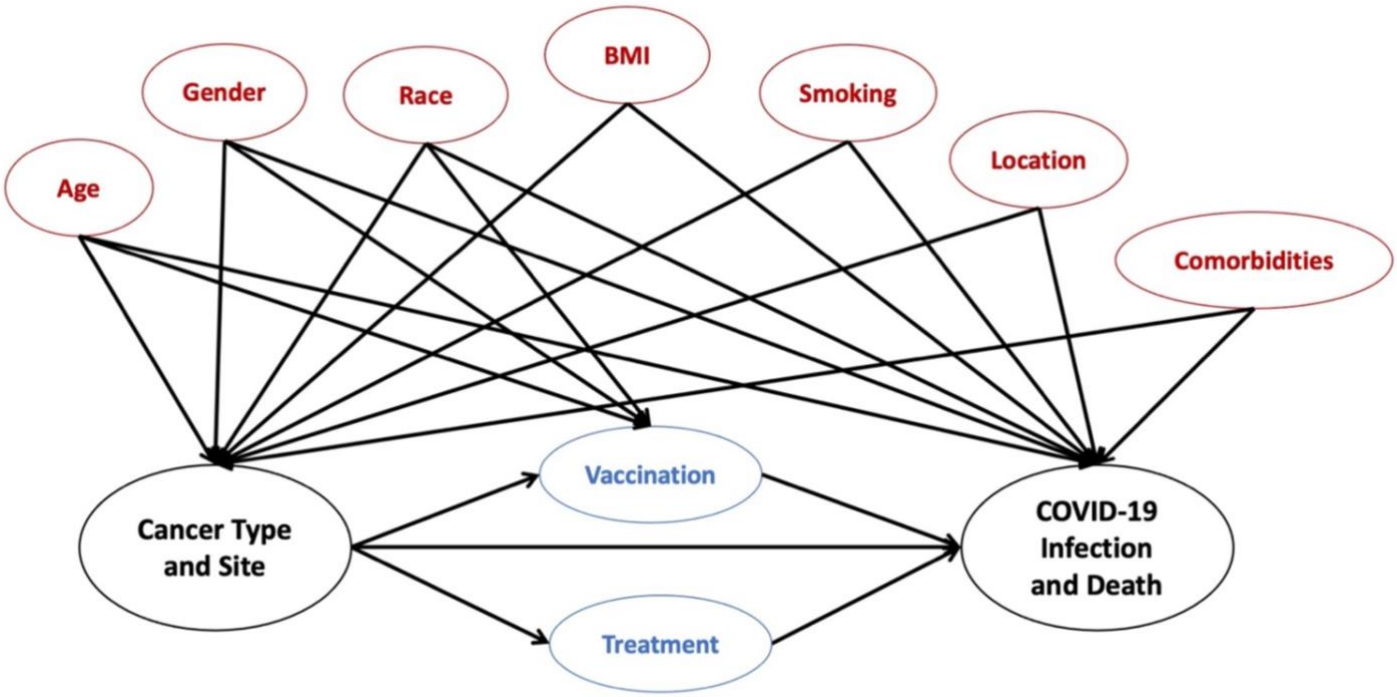
Supplemental Figure 3C



Supplemental Figure 3D



Directed acyclic graph (DAG)



METHODS

Patient population

We conducted a cohort study of US Veterans by mining data from VA corporate data warehouse (CDW) using the VA Informatics and Computing Infrastructure (VINCI). This study was approved by the Institutional Review Board (IRB) of the James J Peters VA Medical Centre, Bronx, New York

The VA National Surveillance Tool (VA-NST) is the authoritative data source of all positive or negative COVID-19 data. Data is made available through the VA COVID-19 Shared Data Resource (CSDR) and is updated/refreshed hourly. CSDR contains information on all Veterans who received a COVID-19 nucleic acid real-time polymerase chain reaction (RT-PCR) test either positive or negative within the VA system and uses natural language processing (NLP) to extract data from clinical notes if a Veteran had a positive test outside the VA system. Our observation period covers dates from 12/14/2020, the start date of vaccination at VA facilities, to 1/25/2022 and Veterans aged 18 years or older. The CSDR is a dynamic dataset allowing us to do this analysis in a prospective manner with data extraction date being 1/25/2022.

Definitions

Index date is the date when a Veteran had a first positive/first negative COVID test in that hierarchical order, or the inpatient admission date closest to the first positive/first negative test in the 15 days prior. There is only one index date; if the patient never had a positive test, then the date of the first negative test is considered the index date. If a patient had a positive test and had multiple negative and/or positive tests before and after, the date of first positive test is considered the index date. All Veterans were included, regardless of the reason for testing – screening, symptoms, travel, pre-procedure. RT-PCR test was the standard test done at VA centres.

We Identified Veterans with an active cancer diagnosis either new or established within two years preceding the index date in the CSDR, which was provided as a structured variable. We then cross-referenced the data with the Oncology registry and the Observational Medical Outcome Partnership (OMOP) common data modeling infrastructure available in VINCI which standardizes all ICD-9/ICD 10 codes to one Systemized Nomenclature of Medicine (SNOMED) code to improve the accuracy of cancer diagnosis. Any diagnosis of leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome, and myelofibrosis was considered a hematologic malignancy with the rest as a solid malignancy. We harvested data regarding 82 anti-cancer drugs that Veterans were receiving at the time of or preceding the index date within the observation period. We categorized drugs into chemotherapy, endocrine therapy, and targeted therapy. (**Supplemental Table 1**)

Covariates

Vaccine type and dates of administration were collected. Additionally, age, gender, location, race, ethnicity, BMI, and smoking status at index, and history of chronic lung disease, COPD, asthma, and deep vein thrombosis in the two years preceding the index date were collected. The Elixhauser comorbidity index was calculated using all diagnoses in the two years preceding the index date and was provided directly by the CSDR.

Outcomes
Hospitalization, ICU admissions, duration of stay in both settings, ventilator requirement, and all-cause mortality within 60 days after testing positive for COVID-19 were collected. Veterans who were still alive on 1/25/2022 were censored on that day.

Statistical analysis
Summary of patient characteristics and descriptive statistics
Patients were classified based on their race: Caucasian, African American, Asian, and other, which includes American Indians, Alaska natives, native Hawaiians, and other Pacific islanders. A categorical version of the three continuous variables was also created. For age in years at index date: <50, 50-60, 60-70, 70-80, and >80. For BMI at index date: <18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and >30.0 kg/$m^{2.}$ For Elixhauser Comorbidity Index within 2 years before index date: <5, 5-10, and >10. Location was classified based on rurality: Urban, small town, city. Using descriptive analysis, the absolute and relative frequencies of the categorical demographic and comorbidity characteristics were presented separately in the unvaccinated and the vaccinated cohort. A Chi-Square test was used to compare the difference between the two cohorts. Additionally, the medians and interquartile ranges (IQRs) for continuous variables were also presented and compared using the Mann-Whitney Wilcoxon test.

Matching process to generate the control cohort
Matching between the cancer cohort and noncancer control was performed using a 1:1 ratio and the following criteria: age $\pm$5 years, same gender, race, BMI category, Elixhauser index category, and vaccine status. A Chi-square test was used to compare the categorical variables between the cancer cohort and the matched cohort. Veterans with a diagnosis of cancer for whom a matched control could not be found were excluded from the analysis.

Risk of COVID Infection and death outcomes, logistic regression, and forest plots
The two primary outcomes in this study were COVID infection and death within 60 days, which were coded as binary variables. Modelling of these two outcomes was performed separately in the unvaccinated and vaccinated populations. Individuals who were vaccinated by January 25, 2022 but had an infection event before their first dose of vaccination, were included in logistic regression models as unvaccinated infected patients. One patient is only counted once, if an *unvaccinated* patient was infected, and then received the vaccine during the observation periods they were not included in the *vaccinated* cohort. To account for the difference in time during the pandemic, a covariate was included in the model and calculated as the time in days of infection or recent negative test since the start of the study period (i.e., December 14, 2020).

Using data from the entire study population, we identified seven potential independent predictors of COVID infection and death within 60 days. For each of the predictors, a univariate logistic regression model was tested first to compare the risk among other groups to that of the selected reference group. A final multivariate model including all variables with significant association with the outcomes, along with the covariate of

time, was also built to obtain the adjusted odds ratios. The selected reference groups are as follows: <50 years old for age, female for gender, Caucasian for race, 18.5-24.9 kg/m^2 for BMI, urban area for rurality, never smoker for smoking status, and 0-5 for Elixhauser index.

Using data from the cancer cohort and its corresponding matched control, we further studied the risk of COVID infection and death within 60 days among patients with different cancer characteristics and taking different medications/treatments. Two cancer types (hematologic and solid), eleven cancer sites (leukemia, lymphoma, MDS, myeloma, breast, colon, lung, prostate, skin, other, and multiple), and five cancer treatments (any, chemotherapy, endocrine therapy, target therapy and ADT therapy among prostate cancer) were studied. In each of the cancer subgroups, logistic regression was used to compare the risk among both the overall cancer cohort and its subgroups to that of the matched noncancer cohort (reference), adjusting for age, gender, race, BMI, smoking, rurality, Elixhauser index and time during the pandemic. To explore the relationship between the cancer subgroups and the outcomes, we compared the unvaccinated groups to the unvaccinated reference and vaccinated groups to the vaccinated reference. To demonstrate the protective effects of the vaccine, we also compared vaccinated groups to the unvaccinated reference group. The treatment analysis was performed only in the cancer cohort. In each of the treatment groups, similar logistic regression was used to compare the risk among treated cancer patients against the reference untreated cancer patients, adjusting for the same set of covariates. The overall effects of treatment were tested by modelling the treated group without limiting the time of receiving the treatment. We also tested the effects of recent treatments by further breaking down the treated group into receiving the therapy more than or less than 60 days prior to index date.

The adjusted odds ratios and the 95% confidence intervals were extracted from the logistic regression models and presented in forest plots. The corresponding p values for the model parameters were annotated in the figures using asterisks, with ** <0.001, and *** <0.0001. Bonferroni correction was done to adjust for multiple comparisons and only tests with p values of less than 0.001 were considered significant. No logistic regression was performed in any subgroup with frequencies of less than 10 Veterans. Their odd ratios and 95% CIs were marked as not evaluable (NE).

Vaccine effectiveness, binary outcome, stacked bar graph

For binary outcomes of COVID infection and death within 60 days, the vaccine effectiveness was studied using logistic regression models comparing the risk in the vaccinated cohort to that in the unvaccinated cohort, adjusting for age, gender, race, BMI, smoking, rurality, Elixhauser index and time during the pandemic. Vaccine effectiveness was defined as (1-OR)•100%. We additionally referred to the WHO calculator for the evaluation of COVID-19 vaccine effectiveness (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement_tool-2021.1). Using a predicted VE of 90%, a precision of 10%, and an attack rate of 45%, it estimated we would need N = 373 to conduct the VE analysis. Our sample size is 314,444 patients. For VE against death, we changed from VE among

only those who were infected to VE among the overall population, so all our analyses satisfied this minimum sample size. As noted, logistic regression was not performed in any subgroup with frequencies of less than 10 Veterans. Their odd ratios and vaccine effectiveness were marked as not evaluable (NE).

Vaccine effectiveness, time-to-event outcome, and stacked bar graph

The risk of COVID infection was also studied using time-to-event analysis. We included Veterans who had received one dose of mRNA vaccine (Moderna or Pfizer-BioNTech), had been fully vaccinated (i.e., at least 2 doses for Moderna, Pfizer-BioNTech, and at least 1 dose for Janssen) or received the additional booster shot and patients who remained unvaccinated. Those who were infected prior to the first dose of vaccination were assigned to the unvaccinated group. The start date of follow-up was defined as the date of the first dose for vaccinated patients, or the date of the first negative test result for unvaccinated patients. For unvaccinated patients with only positive results, the start date of follow-up was set to 12/14/20. The probability of COVID infection was estimated using the Kaplan-Meier method. For patients who had COVID infection, the first date of a positive result was used to calculate the time to infection. Patients who had no infection, were censored on the date of their most recent negative test. In **Figure 4A**, for patients who had received only one dose of vaccine, we excluded those who died or infected before their schedule second dose. We also provided another two versions of the figure in the Supplemental Appendix, first where we only excluded those who died but not infected before second dose (**Supplemental Figure 2A**) and second where we use time starting 14 days after the last dose of primary vaccination series as the x-axis without excluding anyone (**Supplemental Figure 2B**). This was chosen as the method of comparison here in accordance with WHO guidelines that state *"For the primary analysis of VE studies, a conservative approach is recommended in considering a person as potentially protected from vaccination only from 14 days after the date of first dose of vaccination (the time required to achieve protection for the majority of vaccine recipients for most vaccines), and 7–14 days after second doses of vaccine".*

The curves were presented and compared between the overall unvaccinated and vaccinated population, between cancer and noncancer cohort and among the three major vaccine types (Moderna, Pfizer-BioNTech and Janssen) for the cancer subgroup analysis. In the treatment analysis, we compared the curves between treated and untreated cancer patients, and specifically between those who received chemotherapy and target therapy. Hazard ratios comparing different groups were obtained using the Cox proportional hazard model, adjusting for age, gender, race, BMI, smoking, rurality and Elixhauser index.

	Outcome: COVID Infection	Time to Infection
Vaccinated	Yes, event	First positive – First dose
	No, censored	Recent negative – First dose
Unvaccinated	Yes, event	First positive – First negative
	No, censored	Recent negative – First negative

Time of infection since treatment and time of death since infection, and histograms

For patients who received therapies, we looked at the distribution of their time of infection since the end of their most recent treatments, using histograms showing relative frequencies and the density curves. The distribution their time of death since infection was also presented and compared to that among the untreated population. A Mann-Whitney Wilcoxon test was used to compare the differences.

Software

All analyses were conducted using SAS, version 9.4, and R, version 3.6.1.