Supplementary Online Content

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eMethods. Cohort Criteria and Propensity Score Matching

eAppendix. Post Hoc Analysis

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Cohort Criteria and Propensity Score Matching

Cohort Criteria:

First Dose COVID-19 cohort:

Persons in this cohort had appearances of at least one of any the following ICD-10 codes specifying receipt of the first dose of mRNA COVID-19 vaccination:

1. 91300: "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted, for intramuscular use"
2. 91301: "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage, for intramuscular use"
3. 0001A: "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30mcg/0.3mL dosage, diluent reconstituted; first dose"
5. 0011A: "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage; first dose"
7. 2468231: "SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein"

Second Dose COVID-19 cohort:

Persons in this cohort had appearances of the one or both of the following ICD-10 codes specifying receipt of the second dose of mRNA COVID-19 vaccination:

1. 0002A: "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted; second dose"
2. 6. 0012A: "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL; second dose"

Influenza cohort:
Persons in this cohort had appearances of at least one of any the following ICD-10 codes specifying receipt of the influenza vaccination:

1. 90686: “Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for intramuscular use”
2. 90658: “Influenza virus vaccine, trivalent (IIV3), split virus, 0.5 mL dosage, for intramuscular use”
3. 90662: “Influenza virus vaccine (IIV), split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use”
4. 90688: “Influenza virus vaccine, quadrivalent (IIV4), split virus, 0.5 mL dosage, for intramuscular use”
5. 90656: “Influenza virus vaccine, trivalent (IIV3), split virus, preservative free, 0.5 mL dosage, for intramuscular use”
6. 90685: “Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.25 mL dosage, for intramuscular use”

Tdap cohort:
Persons in this cohort had appearances of at least one of any the following ICD-10 codes specifying receipt of the influenza vaccination:

1. 90715: “Tetanus, diphtheria toxoids and acellular pertussis vaccine (Tdap)”
2. 90714: “Tetanus and diphtheria toxoids (Td) older than age 7”

Retinal vascular occlusion diagnostic criteria:
Retinal vascular occlusion was qualified by the presence of at least one of any of the following ICD-10 codes appearing in the patient chart within 21 days of the respective vaccination:

H34 Retinal vascular occlusions

H34.0 Transient retinal artery occlusion

H34.00 Transient retinal artery occlusion, unspecified eye

H34.01 Transient retinal artery occlusion, right eye

H34.02 Transient retinal artery occlusion, left eye

H34.03 Transient retinal artery occlusion, bilateral

H34.1 Central retinal artery occlusion

H34.10 Central retinal artery occlusion, unspecified eye

H34.11 Central retinal artery occlusion, right eye

H34.12 Central retinal artery occlusion, left eye

H34.13 Central retinal artery occlusion, bilateral

H34.2 Other retinal artery occlusions

H34.21 Partial retinal artery occlusion

H34.211 Partial retinal artery occlusion, right eye

H34.212 Partial retinal artery occlusion, left eye

H34.213 Partial retinal artery occlusion, bilateral

H34.219 Partial retinal artery occlusion, unspecified eye

H34.23 Retinal artery branch occlusion

H34.231 Retinal artery branch occlusion, right eye

H34.232 Retinal artery branch occlusion, left eye

H34.233 Retinal artery branch occlusion, bilateral

H34.239 Retinal artery branch occlusion, unspecified eye

H34.8 Other retinal vascular occlusions

H34.81 Central retinal vein occlusion

H34.811 Central retinal vein occlusion, right eye

H34.812 Central retinal vein occlusion, left eye

H34.813 Central retinal vein occlusion, bilateral

H34.819 Central retinal vein occlusion, unspecified eye

H34.82 Venous engorgement

H34.821 Venous engorgement, right eye

H34.822 Venous engorgement, left eye

H34.823 Venous engorgement, bilateral

H34.829 Venous engorgement, unspecified eye

H34.83 Tributary (branch) retinal vein occlusion

H34.831 Tributary (branch) retinal vein occlusion, right eye

H34.832 Tributary (branch) retinal vein occlusion, left eye

H34.833 Tributary (branch) retinal vein occlusion, bilateral

H34.839 Tributary (branch) retinal vein occlusion, unspecified eye

H34.9 Unspecified retinal vascular occlusion

Propensity Score Matching:
Groups were matched using a 1:1 logistic regression model to balance the proportion of compared groups with respect to the following covariates:

1. AI: “Age at index” (Continuous)
2. F: “Female” (Present/Absent)
3. M: “Male” (Present/Absent)
4. UN: “Unknown Gender” (Present/Absent)
5. 2186-5: “Not Hispanic or Latino” (Present/Absent)
6. UN: “Unknown Ethnicity” (Present/Absent)
7. 2135-2: “Hispanic or Latino” (Present/Absent)
8. 2106-3: “White” (Present/Absent)
9. 2131-1: “Unknown Race” (Present/Absent)
10. 2054-5: “Black or African American” (Present/Absent)
11. 2028-9: “Asian” (Present/Absent)
12: 1002-5: “American Indian or Alaska Native” (Present/Absent)
13. 2076-8: “Native Hawaiian or Other Pacific Islander” (Present/Absent)
14. E08-E13: “Diabetes Mellitus” (Present/Absent)
15. I10-I16: “Hypertensive diseases” (Present/Absent)
16. E78.5: “Hyperlipidemia, unspecified” (Present/Absent)

All queries and analyses were performed on October 20th, 2022.

eAppendix **Post Hoc Analysis**
RVO Diagnoses 21 Days after COVID-19 Infection vs. mRNA COVID Vaccine

Post Hoc Methods

Using the COVID-19 Research Network of the TriNetX Analytics federated health database, a post hoc analysis comparing RVO diagnoses after diagnosed COVID-19 infection compared with the mRNA COVID-19 vaccine was performed. The comparison was performed to provide a frame of reference for diagnosed RVO risk after the mRNA vaccine compared to COVID-19 infection itself. The two groups compared in this post hoc analysis are defined below (exact diagnostic codes detailed in the Post Hoc Supplementary section):

1. COVID-19 infection diagnosed between 12/15/2020-9/1/2021 (Group 1)
2. Received first dose mRNA COVID-19 vaccine from 12/15/2020-9/1/2021 (Group 2)

Individuals in the COVID-19 infected group (Group 1) were defined as having diagnosed COVID-19 within the specified timeframe without any instance of mRNA COVID-19 vaccination within the timeframe. Individuals with mRNA vaccination were excluded from this group in order to eliminate the possibility of vaccination related RVO within this group. The same procedure for propensity matching was utilized for this post hoc analysis as was utilized in the main text of the manuscript. However, due to limitations of the TriNetX Analytics Network in handling large sample sizes in its multivariate propensity score matching procedures, one change was made from the procedure followed in the main body of the manuscript. The date timeframes were changed from 12/15/2020-6/1/2022 in the original manuscript to 12/15/2020-9/1/2021 in this analysis because sample sizes were too large for the capabilities of the TriNetX

database to perform appropriate propensity matching when the original dates were utilized. While this change may introduce bias and limit a comparison between these results and the comparisons performed in the main body of the manuscript, the results reported here provide valuable additional information. Propensity score matching was performed with a 1:1 logistic regression model using TriNetX built-in analysis software. Patients were matched demographically based on age at vaccination, sex, race, and ethnicity and matched medically by the proportion of patients with a diagnosis of diabetes, hypertension, and hyperlipidemia (ICD-10 codes provided in Supplementary Information document included with the main text).

Post Hoc Results

After propensity matching, there were 2,423,095 patients included in each of the two groups: COVID-19 infection (Group 1) and the first dose mRNA COVID-19 vaccination (Group 2). The risk for newly diagnosed RVO within 21 days was 4.25 (95% CI: 3.24 - 5.56) times higher after COVID-19 infection than after mRNA COVID-19 vaccination. In the COVID-19 infection group, there were 276 cases of diagnosed RVO within 21 days of COVID-19 infection diagnosis indicating a 0.011% (95% CI: 0.010% – 0.013%) incidence. In the mRNA COVID-19 vaccination group, there were 65 cases of diagnosed RVO within 21 days indicating a 0.003% (95% CI: 0.002%-0.003%) incidence. The results of propensity score matching with standardized mean differences for each ICD-10 covariate before and after matching are provided in the Post Hoc Table.

Post Hoc Discussion

The risk for newly diagnosed RVO was found to be higher acutely after COVID-19 infection than after the first dose of the mRNA COVID-19 vaccination. This post hoc analysis provides valuable data showing a lower risk for RVO after mRNA COVID-19 vaccination than after the infection that is aimed to be prevented by the vaccination. While the risk for newly diagnosed RVO was higher after COVID-19 infection than mRNA COVID-19 vaccination, the risk for RVO remained very low after infection at 0.011%. The results of this analysis put the main results of the manuscript into perspective by providing a comparison group that did not undergo a vaccination but was diagnosed with an infection. The results support the main conclusion of the manuscript which is that the risk for new-onset diagnosed RVO acutely after mRNA COVID-19 vaccination is low. Limitations of this analysis include the change in dates that was required as compared to the main manuscript, possible uncontrolled confounders that are inherent to large dataset designs, and differences in coding practices between vaccination events and infections.

Post Hoc Supplementary

Cohort Criteria:

First Dose COVID-19 cohort:

Persons in this cohort had appearances of at least one of any the following ICD-10 codes specifying receipt of the first dose of mRNA COVID-19 vaccination:

1. 91300: “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted, for intramuscular use”
2. 91301: “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage, for intramuscular use”
3. 0001A: “Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30mcg/0.3mL dosage, diluent reconstituted; first dose”
5. 0011A: “Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage; first dose”
7. 2468231: “SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein”

COVID-19 Infection cohort:

Persons in this cohort had appearances of the one or both of the following ICD-10 codes specifying diagnosis of COVID-19 infection:

1. 94500-6: “SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection”
2. 94533-7: “SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection”
3. 94565-9: SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection
4. 94316-7: SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by NAA with probe detection
5. 94559-2: SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection
6. 94316-7: SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by NAA with probe detection
7. 94309-2: SARS-CoV-2 (COVID-19) RNA [Presence] in Specimen by NAA with probe detection

Patients in this cohort were excluded if they had any of record of receiving a COVID-19 vaccination within the timeframe.

Propensity Score Matching

Groups were matched using a 1:1 logistic regression model to balance the proportion of compared groups with respect to the following covariates:

1. AI: “Age at index” (Continuous)
2. F: “Female” (Present/Absent)
3. M: “Male” (Present/Absent)
4. UN: “Unknown Gender” (Present/Absent)
5. 2186-5: “Not Hispanic or Latino” (Present/Absent)
6. UN: “Unknown Ethnicity” (Present/Absent)
7. 2135-2: “Hispanic or Latino” (Present/Absent)
8. 2106-3: “White” (Present/Absent)
9. 2131-1: “Unknown Race” (Present/Absent)
10. 2054-5: “Black or African American” (Present/Absent)
11. 2028-9: “Asian” (Present/Absent)
12: 1002-5: “American Indian or Alaska Native” (Present/Absent)
13. 2076-8: “Native Hawaiian or Other Pacific Islander” (Present/Absent)
14. E08-E13: “Diabetes Mellitus” (Present/Absent)
15. I10-I16: “Hypertensive diseases” (Present/Absent)
16. E78.5: “Hyperlipidemia, unspecified” (Present/Absent)

All queries and analyses were performed on October 20th, 2022.

Post Hoc Table. Propensity matching results between COVID-19 infection cohort and first dose COVID-19 vaccine cohort.

	Before Matching			After Matching		
Characteristic	**COVID-19 Infection (n=4,084,221)**	**1st Dose COVID-19 (n=2,739,229)**	**Standardized Mean Difference**	**COVID-19 Infection (n=2,423,095)**	**1st Dose COVID-19 (n=2,423,095)**	**Standardized Mean Difference**
Age at Vaccination (mean ± SD)	40.7 (+/- 23.4)	51.5 (+/- 20.4)	0.492	49.7 +/- 20.4	49.2 +/- 20.2	0.025
Sex (%)						
Female	2239105 (54.8)	1545919 (56.4)	0.032	1352116 (55.8)	1361299 (56.2)	0.008
Male	1841883 (45.1)	1191788 (43.5)	0.032	1070139 (44.2)	1060343 (43.8)	0.008
Ethnicity (%)						
Hispanic or Latinx	382391 (9.4)	284555 (10.4)	0.034	252979 (10.4)	259,006 (10.7)	0.008
Not Hispanic or Latinx	2267076 (55.5)	1985128 (72.5)	0.359	1695575 (70.0)	1695687 (70.0)	<0.001
Unknown Ethnicity	1434754 (35.1)	469616 17.1)	0.418	474541 (19.6)	468,402 (19.3)	0.006
Race (%)						
Native Hawaiian or Pacific Islander	4943 (0.1)	4055 (0.1)	0.007	3606 (0.1)	3662 (0.2)	0.001
Asian	75929 (1.9)	122914 (4.5)	0.150	64965 (2.7)	83763 (3.5)	0.045
Black or African American	542595 (13.3)	285938 (10.4)	0.088	279085 (11.5)	276542 (11.4)	0.003
White	2227698 (54.5)	1862566 (68.0)	0.279	1626443 (67.1)	1606626 (66.3)	0.017
Unknown Race	1214582 (29.7)	450146 (16.4)	0.320	436337 (18.0)	440112 (18.2)	0.004
Comorbidities (%)						
Diabetes Mellitus	418413 (10.2)	376910 (13.8)	0.108	350919 (14.5)	325851 (13.4)	0.030
Hypertension	838879 (20.5)	795911 (29.1)	0.198	698522 (28.8)	671078 (27.7)	0.025
Hyperlipidemia	516889 (12.7)	573745 (20.9)	0.223	475866 (19.6)	460261 (19.0)	0.016