Research Article

Big Data From TriNetx on the Association of Retinal Vascular Occlusion and COVID-19 Vaccinations

Sunny, Chi Lik Au[1]

1. Department Ophthalmology, Tung Wah Eastern Hospital, Hong Kong, China

Hypercoagulability and thromboembolic abnormalities were observed in patients with coronavirus disease (COVID-19). COVID-19 has been suggested to cause retinal vascular damage. Uncertain associations of COVID-19 and its vaccines with retinal vascular occlusion (RVaO) were previously published. We believe that big data are needed for analysis of the association of RVaO and COVID-19. TriNetX is a federated cloud-based health research network providing access to anonymized, deidentified patient-specific electronic health records of >100 million patients from >70 healthcare organizations, which majority were located in the United States of America. Our team conducted thorough literature search on 31st May 2023 via PubMed, MEDLINE, EMBASE, Scopus, Web of Science on TriNetx related studies concerning RVaO and COVID-19. Big data studies were only available in May 2023. We summarized the results of the two TriNetX big data studies in table and text. Li et al. study showed no significant risk of RVaO at 12 weeks after vaccinations for each individual type of COVID-19 vaccine, no matter the mRNA or viral vector-based vaccines studied. However, when analyses were done with all brands of vaccines mixed together, there were increased risk at every bi-weekly time points up to 12 weeks. Dorney et al. study found no increased risk of RVaO by receiving the COVID-19 mRNA vaccines when compared to Influenza or Tdap vaccines. However, COVID-19 infection has a higher risk (4.25 times) of RVaO than COVID-19 vaccinations. Our review compared the similarities and differences on the two currently available TriNetX big data literature on the association of RVaO and COVID-19 vaccinations. These studies have different comparison groups, and possible limitations on the study design as we discussed in the main text. Despite they are not presenting directly conflicting results, further meta-analysis or other epidemiologic studies would be needed to answer the scientific question on the association of RVaO and COVID-19.

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Corresponding author: Sunny, Chi Lik Au, kilihcua@gmail.com

Hypercoagulability and thromboembolic abnormalities were observed in patients with coronavirus disease (COVID-19). COVID-19 has been suggested to cause retinal vascular damage. Uncertain associations of COVID-19 and its vaccines with retinal vascular occlusion (RVaO) were previously published, but mainly at the level of case reports or case series. [1] Concerning original researches, Feltgen *et al.* conducted multi-center case-control study on 1st dose of COVID-19 vaccines, but showed no increased risk of RVaO after that. [2] Another Japanese cohort by Hashimoto *et al.* investigated 2nd booster doses of COVID-19 vaccines, it showed no increased risk of retinal vein occlusion (RVO) after 1st dose of COVID-19 vaccination, but increased risk of RVO after 2nd dose of booster COVID-19 vaccination. [3] However, in this research, retinal artery occlusion (RAO) was not studied. We believe that big data are needed for analysis of the association of RVaO and COVID-19. [4]

TriNetX, which provided big data information, is gaining popularity during the COVID-19 era. [4] It is a federated cloud-based health research network providing access to anonymized, deidentified patient-specific electronic health records of >100 million patients from >70 healthcare organizations, which majority were located in the United States of America. Similar to many big data studies, TriNetX is an information retrieval system using 1:1 propensity score matching method for the analysis output, information bias and uncontrollable residual confounding patient characteristics could have present. Besides, diagnosis coding entry errors in daily clinical practice could occur, and thus reporting errors might exist. Although human errors might be unavoidable, diagnosis of retinal vascular occlusion is usually clear, as retinal manifestations are very characteristic.

Our team conducted thorough literature search via PubMed, MEDLINE, EMBASE, Scopus, Web of Science on 31st May 2023, there was no TriNetX related study on RVaO with primary COVID-19 infection. Concerning RVaO with COVID-19 vaccinations, previous literature review was limited, [5] big data studies were only available in May 2023. [6][7] Here, we summarized the results of the two TriNetX big data studies. [6][7] (Table 1)

	Li *et al.*'s study[6]	Dorney *et al.*'s study[7]
Article title	Risk assessment of retinal vascular occlusion after COVID-19 vaccination	Risk of New Retinal Vascular Occlusion After mRNA COVID-19 Vaccination Within Aggregated Electronic Health Record Data
Journal published	npj Vaccines	JAMA Ophthalmology
Inclusion criteria on the age of studied subjects	≥18 years old	Not mentioned
Time points of COVID-19 vaccination	Individuals vaccinated between 1st January 2020 and 31st December 2022:Data collection date was not mentioned	Individuals vaccinated between 15th December 2020 and 15th June 2022; Data collected on 20th October 2022
Types of COVID-19 vaccination studied	Both mRNA and viral vector-based vaccine	mRNA vaccines only
Dose of COVID-19 vaccination studied	1st and 2nd dose	1st and 2nd dose
Comparison group	Unvaccinated cohort	1st vs 2nd dose of COVID-19 vaccination, Influenza vaccination, Tdap (tetanus, diphtheria, and acellular pertussis) vaccination
Categories of RVaO analysis	Separated analysis for branch retinal artery occlusion (ICD-10 H34.2), branch retinal vein occlusion H34.83, central retinal artery occlusion H34.1, central retinal vein occlusion H34.81	Combined analysis of the whole spectrum of diseases coded under ICD-10 H34
Timeframe of RVaO after vaccination	Bi-weekly time points up to 12 weeks and at 2 years	Within 21 days
Number of COVID-19 vaccination subjects included for analysis	739,066	At least 718,400 out of the 3,108,829 were used for comparison after matching

	Li *et al.*'s study[6]	Dorney *et al.*'s study[7]
Mean age of COVID-19 vaccination subjects	52.5+/-18.5	Overall 3,108,829 subjects: 50.7+/-20.4
Conclusion	COVID-19 vaccinations have a higher risk of RVaO at 2 years	COVID-19 vaccinations do not have an association with RVaO

Table 1. Comparison of the similarities and differences across the two TriNetx studies on the association of retinal vascular occlusion (RVaO) and COVID-19 vaccinations.

Li et al. studied the risks of RVaO separately into branch RAO, branch RVO, central RAO, and central RVO across COVID-19 vaccinations (1st and 2nd dose) versus unvaccinated cohorts. [6] They analyzed the risk on bi-weekly basis up to 12 weeks, as well as calculated the hazard ratio (HR) of cumulative incidences up to 2 years. Both mRNA (BNT162b2, mRNA-1273) and viral vector-based (Ad26.COV2.S) vaccines were included. (Table 1) From their big data analysis, there was no significant risk of RVaO at 12 weeks after vaccinations for each individual type of COVID-19 vaccine, no matter the mRNA or viral vector-based vaccines studied. However, when analyses were done with all brands of vaccines mixed together, there were increased risk at every bi-weekly time points up to 12 weeks. Excluding Asians which had a small number of RVaO incidents of <10 for most subgroups, the HRs for branch RAO, branch RVO, central RVO were >1 at 2 years post-vaccination among different ages sub-group analyses. Central RAO in the age group of 18 – 64 remains the only exception.

Dorney et al. studied the risk of RVaO as a whole category under International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic coding of H34 by comparing 1st and 2nd dose of mRNA only COVID-19 vaccinations versus Influenza vaccinations, and Tdap (tetanus, diphtheria, and acellular pertussis) vaccinations received from 1st June 2018 to 31st December 2019. [7] There was no separate subgroup analysis for branch RAO, branch RVO, central RAO, central RVO; nor different brands of mRNA vaccines. Limiting to RVaO occurred within 21 days after vaccination, their big data study found no increased risk of RVaO by receiving the COVID-19 mRNA vaccines when compared to Influenza or Tdap vaccines. (Table 1) Despite the above negative

results, they found COVID-19 infection has a higher risk (4.25 times) of RVaO than COVID-19 vaccinations.

In summary, our review compared the similarities and differences on the two currently available TriNetX big data literature on the association of RVaO and COVID-19 vaccinations. These studies have different comparison groups, and possible limitations on the study design. Despite they are not presenting directly conflicting results, further meta-analysis or other epidemiologic studies would be needed to answer the scientific question on the association of RVaO and COVID-19.

Key messages

- What is known: Literature has conflicting results regarding the association of retinal vascular occlusion with COVID-19 vaccinations
- New information highlights: Big data from TriNetX Analytics Network are now available to explore the association of retinal vascular occlusion with COVID-19 vaccinations

Statements and Declarations

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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Declarations

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