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COVID-19 vaccination and cerebral small vessel disease progression—A prospective cohort study

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ABSTRACT

Objectives: The association between SARS-CoV-2 spike protein and cerebrovascular diseases raised a concern of cerebrovascular safety of COVID-19 vaccines. We aimed to determine the risk of radiologic cerebral small vessel disease (cSVD) progression with BNT162b2 and CoronaVac.

Methods: In this community-based prospective cohort study, community-dwelling subjects underwent brain magnetic resonance imaging (MRI) before and 4 months after vaccination with BNT162b2 or CoronaVac. Unvaccinated subjects received serial brain MRI over a comparable interval. The primary outcome was progression of a composite of six standard cSVD biomarkers. We compared the risk of cSVD progression between vaccinated and unvaccinated subjects and identified predictors of primary outcome within each vaccine subgroup.

Results: Of the 415 subjects recruited, 190 received BNT162b2, 152 received CoronaVac, and 73 remained unvaccinated. A total of 60 (14.4%) had COVID-19 infection before follow-up MRI, and 109 (26.3%) developed the primary outcome. Neither BNT162b2 (adjusted odds ratio [aOR] 0.61, 95% confidence interval [CI] 0.30-1.26, $P = 0.179$) nor CoronaVac (aOR 0.71, 95% CI 0.34-1.47, $P = 0.349$) was associated with cSVD progression. Among the BNT162b2 recipients, a higher surrogate virus neutralization test was associated (aOR 0.97, 95% CI 0.95-0.99, $P = 0.002$) with a lower risk of cSVD progression.

Conclusions: BNT162b2 and CoronaVac did not increase cSVD burden in community-dwelling citizens. The association between surrogate virus neutralization test and cSVD progression among BNT162b2 recipients requires further investigation.

Introduction

As of April 2024, the SARS-CoV-2 pandemic caused more than 7 million deaths worldwide [1]. Apart from the respiratory damage, compromise to the cerebrovascular system has been implicated in SARS-CoV-2 infection through viral spike protein–mediated endothelial dysfunction, hypercoagulability, and downregulation of angiotensin-converting enzyme 2 (ACE2) [2]. These postulations were supported by studies that demonstrated a much higher incidence of severe cerebral small vessel disease (cSVD) in patients with severe COVID-19, which could happen within weeks after infection [3,4].

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Similarly, the native-like mimicry of SARS-CoV-2 spike protein induced either by a nucleoside-modified messenger RNA (mRNA) vaccine (e.g. BNT162b2) or an inactivated virus vaccine (e.g. CoronaVac) may trigger endotheliopathy through binding to circulatory or endothelial ACE2 [5,6]. The subsequent downstream molecular signaling may promote vascular inflammation, fibrotic remodeling, and occlusions of cerebral terminal arterioles [7,8], which may potentiate cSVD, enhancing the long-term risk of stroke and dementia [9]. A prospective clinical study revealed transient endothelial dysfunction within 24 hours after mRNA vaccine injection [10]. Several self-controlled case series reported a safety concern of ischemic and hemorrhage stroke risk among BNT162b2 recipients over a 28-day period [11–13].

Although COVID-19 vaccines have covered majority of the world's population [1], effective bivalent booster vaccination is advocated in response to the evolving variants of interest [14,15]. Yet, uptake rate of booster vaccinations has been low. For instance, only 22.5% of the US population received bivalent boosters as of May 2024 [16]. Because concerns about side effects, including potential longer-term cerebrovascular safety, could be a reason for vaccine hesitancy [17,18], there is a compelling need to elucidate the potential cerebrovascular effects of COVID-19 vaccines.

In this prospective cohort study, we aimed to evaluate the risk of radiologic progression of cSVD in BNT162b2 and CoronaVac recipients who were SARS-CoV-2 infection–naïve. The study results would clarify the safety concerns of COVID-19 vaccines and inform immunization policy.

Methods

Study design and participants

Community-dwelling citizens in the CUHK Brain Health Cohort (CBHC) who received baseline cognitive assessment, cardiovascular risk factor screening, and a magnetic resonance imaging (MRI) brain scan before the COVID-19 pandemic offered a unique opportunity for this prospective study. The CBHC was a community-based cohort of adults aged 40-75 years without preexisting neurologic diseases recruited randomly from all geographical districts and socio-economic classes in Hong Kong, with reference to the government census data (NCT03592563).

From June 2021 to May 2022, we enrolled unvaccinated SARS-CoV-2 infection–naïve subjects from the CBHC. Exclusion criteria were (i) subjects with past or active SARS-CoV-2 infection; (ii) subjects who received only one COVID-19 vaccination; (iii) history of stroke, transient ischemic attack, or neurodegenerative disease; and (iv) contraindications to MRI examination. Based on personal choice, the recruited participants either remained unvaccinated or received BNT162b2 or CoronaVac vaccine, followed by homologous or heterologous booster(s) over time intervals, as recommended by World Health Organization (i.e. the first and second vaccinations were 1 month apart, followed by an optional booster in 3 months after the second dose). All subjects then had clinical follow-up, serologic assessment, and a follow-up MRI brain scan after the last COVID-19 vaccine dose (see *MRI and radiologic biomarkers)*. Unvaccinated controls had a follow-up MRI after a comparable interval. At the concluding visit, we measured blood pressure and repeated blood tests for cardiovascular risk factors. All study participants underwent serologic tests to ascertain the vaccine-induced antibody level and confirm whether natural SARS-CoV-2 infection had occurred (see *Serologic Tests*). The study was approved by the institutional review board (Joint CUHK-NTEC CREC Reference No. 2021.386) and registered at ClinicalTrials.gov (NCT04992195). All study participants provided a written informed consent. We followed the STrengthening the Reporting of OBservational studies in Epidemiology reporting guideline. Figure S1 shows a schematic diagram of the study algorithm.

Data collection

We collected demographic parameters, including age, sex, smoking, and alcohol status. We assessed the body mass index, blood pressure, Montreal cognitive assessment, glycated hemoglobin A1c, lipid profile, and renal and liver function tests at baseline [19]. These assessments were repeated 16 $\pm$ 4 weeks after the last vaccination (i.e. the second or third dose of COVID-19 vaccine) for vaccinated participants or at a comparable time interval for unvaccinated controls. Medical co-morbidities including hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease were clarified by self-reporting and the territory-wide public electronic health care database.

Vaccination groups and controls

CoronaVac and BNT162b2 were the two vaccines available during the study period. CoronaVac group included subjects with homologous CoronaVac vaccinations. Whereas the BNT162b2 group included subjects with either homologous or heterologous BNT162b2 vaccination, i.e. subjects given at least one dose of BNT162b2 in the immunization regimen. Controls were those remained unvaccinated throughout the study period. We verified the vaccine types and dates of vaccination through the government central electronic vaccination record system.

Magnetic resource imaging and radiologic biomarkers

Subjects with two or three doses of homologous/heterologous CoronaVac or BNT162b2 vaccinations had a follow-up MRI brain in 16 $\pm$ 4 weeks after the last vaccination (Figure S1). The 16-week interval between the last vaccination and follow-up MRI brain was determined based on (i) previous studies that reported detectable structural brain and cerebrovascular changes within 20 weeks of infection [20], (ii) self-controlled case series that detected potential safety signals for ischemic and hemorrhagic stroke within 28 days of COVID-19 vaccine [11–13], and (iii) radiologic studies that suggested a high incidence of radiologic cSVD within a few weeks after severe COVID-19 infection [3,4]. Unvaccinated controls underwent a follow-up MRI scan at a comparable time interval. We acquired all MRIs with the same Siemens MAGNETOM Prisma scanner, with a scan protocol containing 3D T-1 weighted, axial T2-weighted, coronal 2D FLAIR, time-of-flight MR angiogram, axial susceptibility-weighted imaging, and axial diffusion-weighted imaging (see Supplementary Methods for details).

The cSVD biomarkers selected in this study had been reported to be detectable shortly after SARS-CoV-2 infection and represent cerebrovascular pathologies resulted from inflammatory stenoocclusive disease of distal arterioles [4,21]. These cSVD biomarkers were quantified according to the Standards for Reporting Vascular Changes on Neuroimaging criteria [22]: (i) white matter hyperintensity (WMH) are FLAIR-hyperintense lesions. WMH volume and WMH ratio (WMH volume divided by intracerebral volume) were determined by Accubrain, a cloud-based automated brain quantification tool [23]. (ii) Lacunes are ischemic lesions either round or ovoid, subcortical, fluid-filled cavities of size $<$15 mm. (iii) Cerebral microbleed (CMB) were 2-5 mm lesions of low signal on susceptibility-weighted sequence. (iv) Cortical cerebral microinfarct (CMI) were T1-hypointense and fluid-attenuated inversion recovery (FLAIR)-hyperintense cortical lesions of size 0.5-4 mm. (v) Perivascular space (PVS) were fluid-filled round, ovoid, or linear spaces of size $<$3 mm that follow the typical course of small perforating vessels as they penetrate white or deep gray matter, with sig-

nal intensity similar to that for cerebrospinal fluid without a T2-hyperintense rim. A visual rating scale for PVS was described previously [24]. Manual radiologic assessments were performed by vascular neurologists or neuroradiologists with >10 years of experience (B.Y.I., S.M., J.A., and T.L.). All raters were blinded to the time sequence of the paired MRI scans, demographics, clinical parameters, COVID-19 vaccination, and infection status. We pre-processed T1-weighted imaging with bias field correction using Functional MRI of the Brain's Automated Segmentation Tool [25].

Serological tests

Details of the serologic test are provided in Supplementary Methods. In brief, the surrogate virus neutralization test (sVNT) detects the total immunodominant neutralizing antibodies targeting the viral spike protein receptor-binding domain. History of SARS-CoV-2 infection was determined by the enzyme-linked immunosorbent assay using either ORF8 (CoronaVac) or nucleoprotein (BNT162b2 or unvaccinated controls) [26,27]. The assay was validated from the results of 100 negative controls. We defined the sera sample as serologically positive for ORF8 or nucleoprotein if the optical density value was three SDs above the mean of the negative controls.

Primary and secondary outcomes

Primary outcome was radiologic progression of cSVD, as defined by (i) WMH progression, defined as an increase of WMH ratio ≥0.25 or a WMH volume increased by ≥0.58 ml, (ii) new CMB, (iii) new CMI, (iv) increase in PVS grading by ≥1, or (v) new lacunes. The criteria for WMH progression were based on a meta-analysis of community-based cohorts [28]. Secondary outcomes were the components of the primary outcome. These biomarkers are associated with increased risk of stroke and vascular cognitive impairment [22,29].

Statistical analysis

We expressed normally distributed continuous variables as means ± SD, non-normally distributed continuous variables as median (interquartile range) and categorical data as number (percentage). Skewness and kurtosis were used to determine normality of continuous variables. One-way analysis of variance or Kruskal–Wallis test was used for comparison of continuous variables among three groups (unvaccinated, CoronaVac, BNT162b2). The chi-square test was used for comparison of categorical variables for expected counts five or more, whereas Fisher's exact test was used for expected count less than five. Two-sided tests with P <0.05 were considered statistically significant.

In the primary analysis, we used multivariable logistic regression models to evaluate the effect of COVID-19 vaccination and other risk factors on the primary composite outcome. We first subjected covariates to univariate logistic regression models. The covariates that reached a significance level of P <0.1 or of clinical relevance were subjected to the final multivariable model, adjusting for covariates stated in Figure S2. In the primary model, we considered the longitudinal changes in laboratory findings (Model 1). Sensitivity analyses were performed using (i) baseline and follow-up laboratory findings at discrete time points, (ii) data-driven forward stepwise, covariate selection approach considering longitudinal laboratory changes, or (iii) data-driven forward stepwise, covariate selection approach considering laboratory results at discrete time points (Models 2-4). In a simplified model, we performed multivariable logistic regression, adjusting for age, sex, any cardiovascular co-morbidities as a binary variable (hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease), baseline radiologic findings as the cSVD score [30] (Model 5), and time-lapse between baseline and follow-up MRI. We also performed a complete-case analysis by excluding participants in the unvaccinated group who received COVID-19 vaccine after the follow-up MRI but before the blood tests (Model 6). Secondary outcomes (WMH progression, new CMB) were evaluated in a similar manner (Models 7 and 8). Logistic regression was performed to determine the risk factors associated with the primary outcome within the BNT162b2 and CoronaVac subgroups, with the addition of sVNT as one of the covariates (Models 9 and 10). Figure S2 summarizes the statistical analysis plan. Missing data were assumed to be missed at random and imputed by multiple imputation with chained equations with values kept within reasonable ranges (Table S1).

Results

Demographic and clinical characteristics of the study participants

From June 1, 2021 to February 28, 2023, we recruited 415 participants who were SARS-CoV-2 infection–naïve, with physical assessment, blood tests, and brain MRI completed before the COVID-19 pandemic (Figure 1). During the period when most recruitment took place, Hong Kong was relatively unaffected by COVID-19 and <60% of the 7.5 million population had received two vaccine doses (Figure S3).

Of the 415 subjects, 152 (36.6%) were in the CoronaVac group, 190 (46.3%) were in the BNT162b2 group, and 73 (17.6%) were unvaccinated controls. The mean age was 63.5 ± 7.2 years, 170 (41.1%) were female, 192 (46%) had hypertension, 82 (19.8%) had diabetes mellitus, and 220 (53.1%) had dyslipidemia. Unvaccinated controls had higher platelet count and hemoglobin level and slightly lower intracerebral volume (Tables 1, S2-3). The median interval between last vaccination and follow-up brain MRI was 118 days (interquartile range 108-129). Two unvaccinated subjects received COVID-19 vaccine after the follow-up MRI but before serologic blood tests.

Longitudinal changes in blood pressure, blood glucose, lipid levels, intracerebral volume, and Montreal cognitive assessment scores were comparable among the three groups. A total of 60 (14.4%) participants had evidence of SARS-CoV-2 infection before the follow-up brain MRI; none required hospitalization. No participant developed incident dementia, mild cognitive impairment, clinical strokes, or thromboembolic complications in the study period. The time intervals between baseline and follow-up MRI were comparable among the control, BNT162b2, and CoronaVac groups (1.6 ± 0.5 vs 1.4 ± 0.6 vs 1.4 ± 0.6 years, P = 0.174). Overall, 102 (24.6%) subjects had the radiologic primary end point.

Primary analysis

In the primary logistic regression model, we included age, sex, natural COVID-19 infection, time-lapse between baseline and follow-up MRI, baseline WMH volume, CMB, PVS grading, lacunes, CMI, dyslipidemia, and increase in white cell count as covariates (Table S4). Neither BNT162b2 (adjusted odds ratio [aOR] 0.61, 95% confidence interval [CI] 0.30-1.26, P = 0.179; incidence: 21.1% vs 27.4%) nor CoronaVac (aOR 0.71, 95% CI 0.34-1.47, P = 0.349; incidence: 27.6% vs 27.4%) was associated with the primary end point, compared with the no vaccination group (Model 1, Table 2). Dyslipidemia and increase in white cell count were significantly associated with the progression of cSVD. The sensitivity analyses (Models 2-5, Tables S5-8) and the exclusion of two participants with protocol violation (Model 6, Table S9) yielded similar results.

Secondary outcomes

There were 50 (12%) subjects with WMH progression and 29 (7.0%) subjects with new CMBs. BNT162b2 (WMH progression: aOR

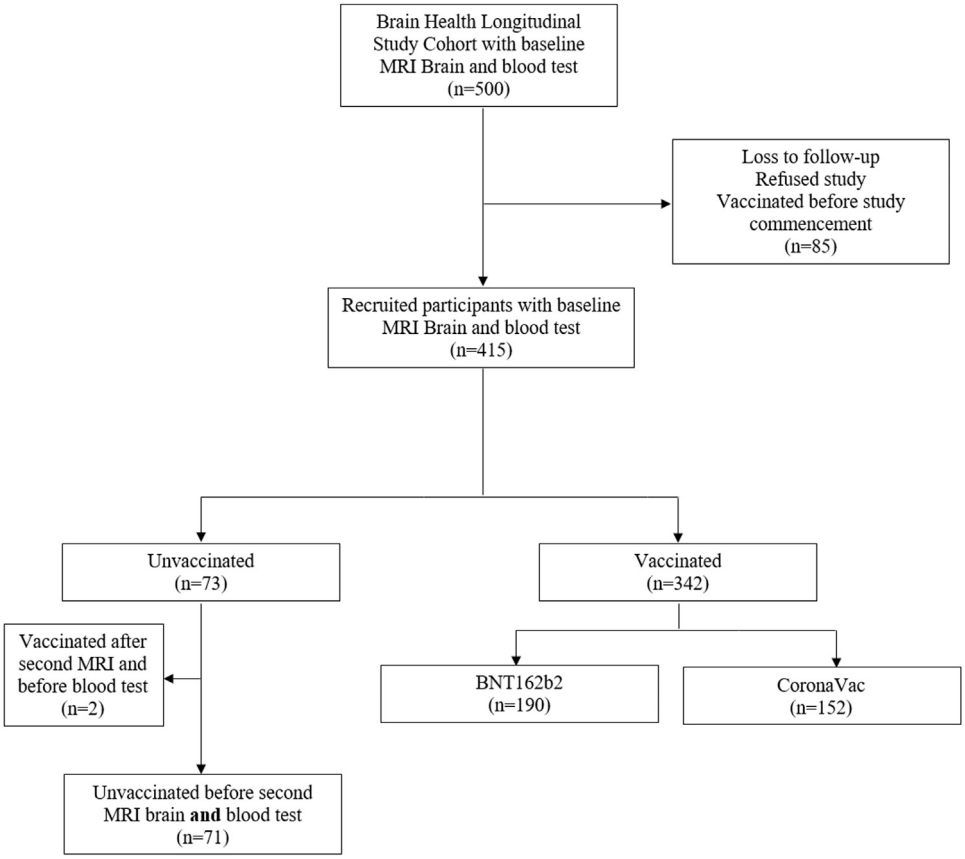

Figure 1. Study flow diagram.
MRI, magnetic resource imaging.

0.58, 95% CI 0.22-1.50, $P = 0.258$; incidences 11.1% vs 13.7%; new CMB: aOR 0.69, 95% CI 0.22-2.19, $P = 0.532$; incidence 5.3% vs 5.5%) and CoronaVac (WMH progression: aOR 0.44, 95% CI 0.16-1.21, $P = 0.117$; incidence 12.5% vs 13.7%; new CMB: aOR 1.19, 95% CI 0.39-3.56, $P = 0.761$; incidence 9.2% vs 6.8%) were not associated with WMH progression or new CMB (Models 7 and 8, Tables S10-11). New cortical microinfarct (n = 18), lacunes (n = 3), and progression of enlarged perivascular space (n = 18) were excluded from the secondary analyses due to the low event rates.

Subgroup analyses

In the BNT162b2 subgroup (n = 190), 117 (61.5%) participants received two doses of BNT162b2. Among 73 (38.4%) participants who had three doses of vaccine, 64 (33.4%) participants received a homologous regimen (three doses of BNT162b2), whereas nine (4.7%) received a heterologous regime (two doses of CoronaVac and one dose of BNT162b2). sVNT was negatively associated (aOR 0.97, 95% CI 0.95-0.99, $P = 0.002$) with the primary composite end point (Model 9, Figure 2). Such an association was not observed in the CoronaVac subgroup (Model 10, Table S12). COVID-19 infection was not associated with the primary end point in both vaccination groups (BNT162b2: aOR 1.17, 95% CI 0.56-2.45, $P = 0.674$; incidence 20.7% vs 23%; CoronaVac: aOR 0.94, 95% CI 0.34-2.59, $P = 0.889$; incidence 27.3% vs 30.8%).

Discussion

In a SARS-CoV-2 infection–naïve community cohort, we found that neither CoronaVac nor BNT162b2 vaccine was associated with subclinical progression of MRI cerebrovascular disease biomarkers.

To the best of our knowledge, this is the first prospective investigation on how COVID-19 vaccines might affect cerebrovascular health. Before our study, the reported stroke risk associated with COVID-19 vaccines had been inconsistent. Two self-controlled case series suggested an increased hemorrhagic stroke risk up to 13 days after a booster of BNT162b2 but not CoronaVac [11,12], such an association was absent in a meta-analysis [31]. One self-controlled case series in the United Kingdom showed a small increase in arterial thromboembolism with BNT162b2 [13]. Of note, retrospective collection of “adverse events after immunization” from pharmacovigilance systems limited the interpretation of these studies because avoidance and inaccessibility of medical care during the pandemic undermined the record of mild strokes, leading to reporting bias [32]. In addition, owing to the failure to adjust for time-dependent covariates, such as metabolic risk factor control and SARS-CoV-2 infection, self-controlled case series might only determine the short-term risks of vaccines, without untangling the confounders of SARS-CoV-2 infection, COVID-19 vaccination, and the probable deteriorated metabolic risk profile during the heavy hit of the pandemic. In contrast, our study provided a prospective baseline and post-vaccination cSVD assessments until 16 weeks after vaccination, covering the peaks of the circulating vaccine-induced spike protein and the neutralizing antibodies levels [33]. Moreover, radiologic cSVD biomarkers have been shown to predict long-term risk of stroke and cognitive impairment [8,9,22]. For instance, WMH is associated with increased likelihood of incident dementia and ischemic stroke over a period exceeding 5 years [34,35]. The current study, thus, unveiled important longer-term safety data of CoronaVac and BNT162b2 on cerebrovascular health. sVNT detects the total immunodominant neutralizing antibodies targeting the viral spike protein receptor-

Table 1
Characteristics of study participants.

	Control (n = 73)	BNT162b2 (n = 190)	CoronaVac (n = 152)	*P*-value
Demographic information (mean [SD])				
Age	64.58 (6.83)	62.37 (8.07)	63.99 (8.04)	0.058
Female sex (%)	38 (52.1)	69 (36.3)	63 (41.4)	0.066
Years between MRI scans	1.6 (0.5)	1.4 (0.6)	1.4 (0.6)	0.174
Days between last vaccine and second MRI (median [interquartile range])	-	119.00 [107.20, 128.00]	118.00 [108.00, 129.20]	–
Booster vaccine (%)	-	55 (28.9)	31 (20.4)	–
Ever-smoker (%)	9 (12.3)	21 (11.1)	21 (13.8)	0.741
Ever-drinker (%)	10 (13.7)	24 (12.6)	21 (13.8)	0.943
Body mass index	23.95 (3.38)	23.91 (3.40)	24.09 (3.89)	0.908
Medical comorbidities n(%)				
Hypertension	40 (54.8)	84 (44.2)	68 (44.7)	0.272
Dyslipidemia	36 (49.3)	108 (56.8)	76 (50.0)	0.355
Diabetes mellitus	20 (27.4)	38 (20.0)	24 (15.8)	0.122
Ischemic heart disease	5 (6.8)	28 (14.7)	21 (13.8)	0.216
Medications n(%)				
Antiplatelet	12 (16.4)	38 (20.0)	33 (21.7)	0.652
Statins	37 (50.7)	99 (52.1)	74 (48.7)	0.821
Oral anticoagulants	2 (2.8)	5 (2.7)	2 (1.3)	0.307
MoCA scores (mean [SD])				
Baseline MoCA	24.00 [21.00, 26.00]	26.00 [23.00, 28.00]	25.00 [22.75, 27.00]	0.070
Follow-up MoCA	24.00 [21.00, 26.00]	26.00 [23.00, 28.00]	25.00 [22.75, 27.00]	0.087
COVID-19 infection before follow-up MRI (%)	9 (12.3)	29 (15.3)	22 (14.5)	0.832
Serological tests (median [interquartile range])				
Surrogate virus neutralization test	0.00 [0.00, 10.45]	88.97 [71.72, 97.56]	20.18 [3.47, 44.60]	<0.001
Nucleocapsid protein	0.06 [0.05, 0.15]	0.07 [0.05, 0.14]	0.32 [0.12, 0.88]	<0.001
Primary composite event (%)	20 (27.4)	40 (21.1)	42 (27.6)	0.309

MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging.

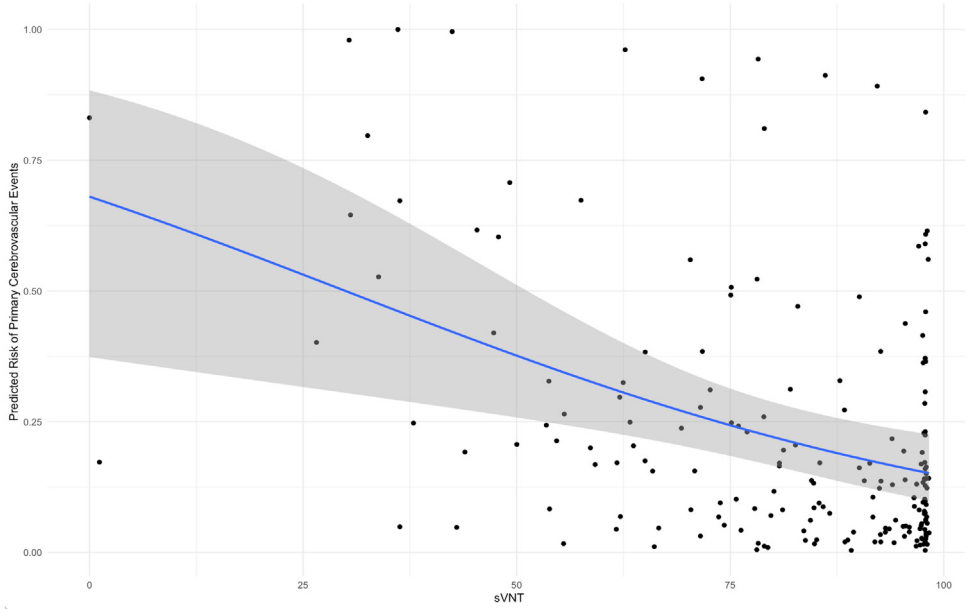

Figure 2. Estimated risk of primary outcome vs sVNT level by multivariable logistic regression. Higher sVNT level was associated with lower estimated risk of primary outcome: adjusted odds ratio 0.97, 95% confidence interval 0.95-0.99, $P = 0.002$.
sVNT, surrogate viral neutralization test.

Table 2
Predictors of primary composite outcome by multivariable logistic regression (model 1), adjusted for age, sex, COVID-19 infection, baseline radiologic findings, and time-lapse between baseline and follow-up brain imaging.

Covariates	Adjusted odds ratio (95% confidence interval)	*P*-value
BNT162b2 vs Unvaccinated	0.61 (0.30-1.26)	0.179
CoronaVac vs Unvaccinated	0.71 (0.34-1.47)	0.349
BNT162b2 vs CoronaVac	0.86 (0.47-1.58)	0.633
Dyslipidemia	1.81 (1.02-3.19)	0.041
Increase in white cell count	1.34 (1.09-1.64)	0.005
Increase in glucose	1.10 (1.00-1.22)	0.054

binding domain in an isotype- and species-independent manner [36] and, thus, is a reflection of vaccine immunogenicity. The negative correlation between sVNT and the primary outcome in the BNT162b2 subgroup suggested that higher neutralizing antibody levels against spike protein induced by BNT162b2 was associated with a lower risk of cSVD progression. Because circulating vaccine-induced spike protein is the key driver of mRNA vaccine-induced immune response and endotheliopathy [7,10], a poor neutralizing antibody response might lead to cerebrovascular insult due to a delayed antibody-mediated clearance of spike protein. Such a finding was not observed in the CoronaVac subgroup, possibly due to a smaller amount of spike protein produced [12]. However, this finding should be interpreted with caution because (i) we did not measure the spike protein level and endothelial function, (ii) aOR was close to 1 per unit increase of sVNT, (iii) there were no clinical strokes recorded. This potential signal may inform vaccination strategy in immunocompromised individuals who may mount a poor neutralizing antibody response to mRNA-based vaccines [37]; future studies are required to substantiate these findings.

Natural SARS-CoV-2 infection is a strong risk factor of clinical strokes and was associated with radiologic infarcts, white matter abnormalities, cerebral microbleeds, and intracerebral hemorrhage [21,38]. However, these radiologic changes were not observed in vaccine recipients who had natural infection. Because these individuals had no cSVD progression and recovered from SARS-CoV-2 infection without hospitalization, future studies should elucidate whether vaccination could attenuate the pro-stroke effect of SARS-CoV-2 infection, plausibly through minimizing infection severity, immune-mediated thrombosis, and endothelial damage [6,33].

Lastly, because dyslipidemia and increase in white cell count, which reflects vascular inflammation [39], were risk factors of cSVD progression in our study, long-term stringent control of cardiovascular risks, such as hypertension, diabetes, dyslipidemia, and systemic inflammation, is, overall, more important than short-term predispositions, if any, by SARS-CoV-2 vaccination.

Our study has the following limitations: first, compared with the vaccination group, the sample size of unvaccinated subjects was relatively small due to the steep increase in vaccination rate soon after the implementation of the territory-wide vaccination program in late 2021 [1]. The confounding effect of "healthy-vaccinee bias" was possible [40]. Second, based on the higher immunogenicity of mRNA-based vaccine and, thus, potentially, a higher cerebrovascular impact, we categorized recipients with a single BNT162b2 dose into the BNT162b2 group. Therefore, the cumulative effects of homologous BNT162b2 vaccinations on the primary outcome could have been diluted by those with heterologous BNT162b2 vaccinations. Third, our cohort recruited only citizens without preexisting cerebrovascular disease and the results could not be generalized to patients with established cerebrovascular diseases. Fourth, the study was conducted among Chinese participants receiving the primary vaccine series; thus, the results may not be generalized to people of other ethnicities who received bivalent COVID-19 vaccines. Last, longer-term monitoring for clinical events is needed to substantiate our study findings on radiologic cerebrovascular events.

In conclusion, CoronaVac and BNT162b2 appeared not to increase the radiologic cSVD burden in community-dwelling citizens. The higher risk of radiologic cSVD progression in poor responders of BNT162b2 may inform vaccination strategy in individuals who may have suboptimal neutralizing antibody response to mRNA-based vaccines. Because natural SARS-CoV-2 infection in vaccine recipients was not associated with cSVD progression, further studies should evaluate whether vaccination could mitigate cerebrovascular insult from subsequent SARS-CoV-2 infection.

Author contributions

B.Y.I. was involved in study design, data collection, analysis, interpretation, and writing the first draft of the manuscript. S.P. and H.L. performed data management and statistical analyses for the study. A.Y., L.L., A.M., K.C., H.K., A.K. were involved in study design, data collection, interpretation of results. H.Y.C., S.L., H.C., T.H. were involved in data collection, analysis, and reviewing the manuscript. B.L., V.H., L.S., J.A., X.L., S.M. were involved in the analysis of radiology results and interpretation. Y.S., V.C.M., H.S.M., C.M., D.H. were involved in analysis, interpretation, and reviewing the manuscript. T.W.L. were involved in analysis, interpretation, reviewing the manuscript and had the final responsibility for the decision to submit for publication.

Data availability statement

Anonymized data not published within this article will be made available by request from any qualified investigator. All authors declare no conflict of interest.

Declarations of competing interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107324.

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