Long-term cardiovascular, cerebrovascular, and thrombotic complications after SARS-CoV-2-Omicron infection: a retrospective cohort study

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INTRODUCTION

Evidence suggests that some COVID-19 survivors experience a wide range of post-COVID-19 sequelae, such an increase in major adverse-cardiac-events at 12 months post-infection (1). However, the majority of studies were conducted before the emergence of the milder Omicron variant. We examined the post-acute risk of new-incident **cardiovascular complications** after **SARS-CoV-2 infection** in a **multi-ethnic Asian population**, during **Omicron** predominance.

METHODOLOGY

Primary data collection

- Data was obtained from the Singapore national testing registry from adults with their first confirmed SARS-CoV-2 infection during the Omicron BA.1/2 wave
- Infections were confirmed using either PCR or rapid antigen tests (RAT)
- Data on vaccination status and infection severity were obtained from national databases
- Severe COVID-19 was defined as requiring oxygen therapy or ICU admission

Study population

- Singaporean citizens and permanent residents age ≥ 18 with ARI symptoms during the Omicron BA.1/2 wave period
- Test-negative controls were included from individuals presenting with ARI symptoms who tested negative

Exclusion criteria

- Death within 30 days of infection
- Missing demographic data
- Reinfection within 300 days

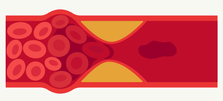
Complications measured (RISK and Excess burdens (EB))

CEREBROVASCULAR EVENTS

ISCHAEMIC AND HEMORRHAGIC STROKES

CARDIAC EVENTS

DYSRHYTHMIAS, ISCHEMIC HEART DISEASE, HEART FAILURE, MYOCARDITIS, AND PERICARDITIS



THROMBOTIC EVENTS

PULMONARY EMBOLISM, DEEP VEIN THROMBOSIS, AND ARTERIAL THROMBOSES

Covariates considered

VACCINATION STATUS: FULLY VACCINATED OR BOOSTED

DEMOGRAPHICS: AGE, SEX, ETHNICITY

INFECTION SEVERITY: 1. AMBULATORY, 2. HOSPITALIZED BUT NON-SEVERE 3. HOSPITALIZED AND SEVERE.

COMORBIDITIES: HYPERTENSION, DIABETES, HYPERLIPIDEMIA, CANCER, CHRONIC ORGAN DISEASES

SOCIOECONOMIC STATUS (SES): ASSESSED BY HOUSING TYPE.

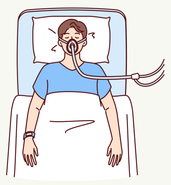
- Inverse probability weighting (including all relevant covariates) was used to account for differences in baseline characteristics.
- Baseline characteristics of the groups were analyzed, and the standardized mean difference (SMD) of each group compared.
- Risks and excess burdens (EBs) of new cardiovascular complications in individuals infected with SARS-CoV-2 were compared to those who tested negative, over a follow-up period of 300 days from the date of diagnosis (T0).
- A subgroup of participants without a history of that specific condition in the past five years was created for each complication.

RESULTS

- The study included 375,903 individuals with confirmed SARS-CoV-2 infection during the Omicron BA.1/2 period and 619,379 individuals who tested negative in the same timeframe.
- Baseline characteristics between groups yielded standardized mean differences (SMDs) <0.1.
- Among those infected, most (97.5%) had mild disease, while 2.5% were hospitalized. Of those hospitalized, 14.9% had severe disease. Additionally, 74.6% of the infected group had received booster vaccinations.

General cardiovascular risks

- No increased risk of composite cardiovascular complications or major adverse cardiovascular events (MACE) in infected individuals compared to test-negatives.
- Slight increase in the risk of dysrhythmias (aHR 1.09, p=0.04), but no significant increase in the risk of other cardiac disorders
- modestly increased risk of sinus bradycardia (aHR 1.35, p=0.03), other arrhythmias (aHR 1.16, p=0.04), and pericarditis (aHR 3.86, p=0.02) in infected individuals.
- However, these findings did not remain significant after adjusting for multiple comparisons.



Hospitalisations and severe cases

- Individuals who were hospitalized had a significantly higher risk of any cardiovascular complication (aHR 2.81) compared to test-negatives
- Pts with severe disease had an even greater risk (aHR 5.52), particularly for composite cardiovascular outcomes.

Vaccination status effect on risk

- Vaccinated and boosted individuals had a lower risk of cardiovascular complications compared to unvaccinated or unboosted individuals
- However, confidence intervals crossed one, suggesting no statistically significant difference.

DISCUSSION

- The mild, non-hospitalised sub-group of Omicron COVID cases did not experience any increased risk of MACE or cadiovascular complications.
- More vulnerable, hospitalised or severe cases did experience an increased risk.
- Other past research however, suggest the opposite, that COVID does increase risk of MACE and cardiovascular complications across all populations
- There are a few possible reasons for this:

1. **The studied variant of COVID in this paper is Omicron, different from past research which studied other COVID variants such as pre-delta.**
   - The majority of long-term (>4 weeks) patients with cardiovascular problems after COVID infection were afflicted with pre-delta variant (83.7%), compared to Omicron (3.1%)
   - The very nature of the Omicron variant could have made it less harmful than other variants
   - This phenomena is explained by lower levels of virus particles found in cardiomyocytes in Omicron infected populations relative to those infected with Delta variant

2. **Omicron generally caused milder infections, rather than severe / hospitalised cases.**
   - The small proportion of severe / hospitalised cases did see an increase in MACE and cardiovascular complications
   - Excess burden of other sequelae of disease such as influenza or sepsis are similar to that of MACE and cardiovascular complications
   - Innate physiological weakness in these groups could attribute to increased risk of complications (including MACE and cardiovascular complications) as a whole rather than the COVID infection specifically

	Excess Burden (weighted per 1000 persons)		
	Ambulatory, Mild	Hospitalised, non-severe	Hospitalised, severe
Any complication	-0.38 (-0.72 to -0.04)	13.32 (9.56 to 17.09)	36.45 (20.07 to 52.83)
MACE	-0.31 (-0.55 to -0.06)	6.71 (4.23 to 9.19)	21.27 (9.58 to 32.96)

Table of results showing similar / higher excess burden of complications as a whole compared to MACE, across all populations afflicted with Omicron variant COVID infection

3. **Other confounding factors such as quality of healthcare**
   - Healthcare is multi-factorial and there are many other dependent variables that cannot be controlled
   - In Singapore where this study was done, healthcare resources were not stretched, with adequate intensive care units, unlike in other regions where studies were done suggesting the opposite trend
   - Singapore also had a higher uptake rate of COVID booster vaccinations compared to other regions, which could have led to better outcomes, with fewer post-COVID recovery incidences of MACE and cardiovascular complications.

LIMITATIONS

- Undiagnosed / asymptomatic cases of COVID might have been wrongly misclassified, leading to bias of hazard ratios calculated. As much as possible this was mitigated through the use of comprehensive and reliable public health databases available in Singapore during a time where testing and reporting was mandated, so much so the risk of collecting biased data is limited.
- This study was conducted before the release of new oral antivirals specific to treating COVID-19. This could have possibly further lowered the excess burden of cardiovascular complications, and could be another topic of extension for this study.

CONCLUSION

- In the context of Singapore, with high rates of Omicron variant COVID-19 booster vaccine uptake, abundant provision of healthcare and mandated reporting with strict rules surrounding the management of COVID-19 infections, there is **no** reported increased risk of cardiovascular complications 300 days post-infection for the cohort with **mild infection without hospitalisation**.
- However, an **increased risk** was demonstrated in cohorts with **severe infection or infection requiring hospitalisation**.

SOURCES

1. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID- 19. Nat Med 2022;28:583e90. https://doi.org/10.1038/s41591-022-01689-3.