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ORIGINAL RESEARCH ARTICLE

Burden of Cardiovascular Outcomes After SARS-CoV-2 Infection in South Korea and Japan: A Binational Population-Based Cohort Study

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BACKGROUND: Despite the significant global impact of the COVID-19 pandemic, limited studies have investigated the long-term cardiovascular sequelae of SARS-CoV-2 infection, particularly among Asian populations. This large-scale, population-based binational cohort study with long-term follow-up aimed to investigate the association between SARS-CoV-2 infection and the risk of cardiovascular events.

METHODS: We used binational, large-scale, and population-based cohorts, including a Korean nationwide cohort (K-COV-N; discovery cohort; n=18 989 129) and a Japanese nationwide cohort (Japan Medical Data Center; validation cohort; n=12 218 680). Individuals aged 20 years or older were included from January 1, 2020, to December 31, 2022. We assessed the long-term risk of incident cardiovascular outcomes after SARS-CoV-2 infection. The primary outcome was the risk of cardiovascular diseases based on *International Classification of Diseases, Tenth Revision* code diagnosis. After propensity score–based overlap weighting, Cox proportional hazard models were used to estimate adjusted hazard ratios for cardiovascular outcomes. We assessed the time attenuation effect of cardiovascular outcomes after SARS-CoV-2 infection. Multiple subgroup analyses were conducted by 16 cardiovascular outcomes, COVID-19 severity, vaccination, and SARS-CoV-2 strain.

RESULTS: In the overlap-weighted discovery cohort, 7 960 357 individuals were included (mean age, 48.52 years [SD, 9.33]; men, 4 283 878 [53.82%]). SARS-CoV-2 infection was associated with a long-term increased risk of overall cardiovascular outcomes (adjusted hazard ratio, 1.62 [95% CI, 1.60–1.64]), particularly ischemic heart disease (1.81 [95% CI, 1.77–1.84]), heart failure (1.79 [95% CI, 1.73–1.85]), cerebrovascular disorders (1.65 [95% CI, 1.60–1.69]), major adverse cardiovascular events (1.65 [95% CI, 1.60–1.70]), inflammatory heart diseases (1.53 [95% CI, 1.31–1.80]), dysrhythmia (1.44 [95% CI, 1.42–1.46]), and thrombotic disorders (1.42 [95% CI, 1.35–1.48]). The increased risk persisted up to 18 months, with the highest association observed for 1 to 6 months after infection. The risk of cardiovascular diseases was pronounced with COVID-19 severity; however, it decreased with the administration of complete vaccination and subsequent booster doses. A similar risk of cardiovascular outcomes existed across every SARS-CoV-2 era (pre-delta, delta, and omicron). Similar patterns were observed in the validation cohort. The absolute risk of cardiovascular disease events after SARS-CoV-2 infection remained remarkably low (2.12% versus 1.31% in the noninfected population), particularly stroke (0.24% versus 0.13%) and ischemic heart disease (0.73% versus 0.39%).

CONCLUSIONS: This binational study observed associations between SARS-CoV-2 infection and cardiovascular events during extended follow-up across viral eras. Complete vaccination was linked to lower cardiovascular events. However, the absolute

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risk of cardiovascular disease events after SARS-CoV-2 infection remained remarkably low, particularly for stroke and ischemic heart disease. Although these findings suggest ongoing vigilance and preventive measures remain crucial, they should be interpreted within the context of these low absolute risks when considering long-term cardiovascular complications.

Key Words: cardiovascular outcomes ■ COVID-19 ■ pandemic ■ SARS-CoV-2 ■ vaccination

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Clinical Perspective

What Is New?

- This first comprehensive binational study of >30 million participants from South Korea and Japan presents consistently elevated cardiovascular risks across pre-delta, delta, and omicron eras after SARS-CoV-2 infection, with higher risks observed in severe COVID-19 cases.
- SARS-CoV-2 infection increased the risk of new-onset cardiovascular outcomes even in individuals without previous cardiovascular disease or behavioral risk factors, whereas complete vaccination or booster doses are associated with reduced cardiovascular risk after infection.
- The study reveals a time-dependent attenuation of cardiovascular risks, with most outcomes showing no statistically significant elevation beyond 18 months after infection.

What Are the Clinical Implications?

- Health care providers should maintain vigilant cardiovascular monitoring of individuals with SARS-CoV-2 infection, particularly during the first 18 months after infection.
- The protective effect of vaccination against cardiovascular complications underscores the importance of complete vaccination or booster doses in reducing COVID-19–related cardiovascular risks.
- Although SARS-CoV-2 infection is associated with increased relative risk of cardiovascular events, the low absolute risk of these events after infection suggests that excessive public concern is unwarranted.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
KDCA	Korea Disease Control and Prevention Agency
ICD	*International Classification of Diseases*
ICD-10	*International Classification of Diseases, Tenth Revision*
MACE	major adverse cardiovascular event
NHIS	National Health Insurance Service

Although 4 years have passed since the onset of the COVID-19 pandemic, its consequences remain a critical global concern.[1] SARS-CoV-2 infection has led to significant global mortality and morbidity, and the persistence of long-term effects continues to pose a substantial health burden worldwide.[2] Numerous reports have indicated that SARS-CoV-2 infection extends beyond an acute, self-limiting condition, potentially resulting in prolonged health consequences.[3] As of the end of 2023, the long-term effect of the COVID-19 pandemic was estimated to have affected >400 million people worldwide.[4]

The pervasive effects of the COVID-19 pandemic significantly influence individuals' quality of life, often necessitating ongoing medical care.[5] This condition contributes to increased disability-adjusted life years, resulting in economic and social burdens because of its effects on physical and mental health.[6] Previous studies have established that SARS-CoV-2 infection increases cardiovascular risks through multiple mechanisms, including cardiomyocyte invasion,[7] endothelial inflammation,[8] and systemic inflammatory responses.[9] Acute cardiovascular complications such as myocardial infarction and ischemic stroke were found to be 3 to 7 times more frequent within 2 weeks of COVID-19 diagnosis.[10] Despite its importance, few studies have examined long-term cardiovascular sequelae up to 2 years after infection.

Existing studies are based on limited hospital-based samples, or cohorts primarily comprising older White men, potentially misrepresenting the diverse population affected by this condition.[11] It is important to note that the role of vaccination in reducing cardiovascular outcomes remains understudied. Given the critical nature of cardiovascular diseases, there is a need to investigate the cardiovascular sequelae associated with SARS-CoV-2 infection.[12] Particularly the scarcity of research on long-term cardiovascular outcomes among Asian populations, coupled with limited data on the effect of vaccination on these outcomes, underscores the urgent need for comprehensive study.

In this study, we investigated the long-term cardiovascular outcomes after SARS-CoV-2 infection. Using large-scale, population-based, binational cohorts, we aimed to examine the long-term risk of cardiovascular outcomes associated with SARS-CoV-2 infection and quantify its overall health burden. Furthermore, we comprehensively

analyzed how various factors such as COVID-19 severity, vaccination status, and SARS-CoV-2 strains influence the cardiovascular manifestations after SARS-CoV-2 infection. This study will aid in identifying critical cardiovascular risks associated with SARS-CoV-2 infection, informing targeted prevention strategies, and enhancing long-term patient care for future public health challenges.

METHODS

Data Availability

The datasets analyzed during the current study are available in the National Health Insurance Service (NHIS), South Korea (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do), and the Japan Medical Data Center (JMDC), Japan (https://www.jmdc.co.jp/en/jmdc-claims-database/). This protects the confidentiality of the data and ensures that information governance is robust. Applications to access health data in South Korea should be submitted to the NHIS, South Korea. Information can be found at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do. Applications to access health data in Japan should be submitted to the JMDC, Japan. Information can be found at https://www.jmdc.co.jp/en/jmdc-claims-database/.

Ethical approval for this study was obtained from Kyung Hee University (KHSIRB-23-241[EA]), the Korea Disease Control and Prevention Agency (KDCA), the National Health Insurance Service of Korea (NHIS; KDCA-NHIS-2024-1-280), and JMDC (PHP-00002201-04). The requirement for informed consent was waived because of the use of de-identified administrative data. This study adhered to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) Statement guidelines (Table S1).

Discovery Cohort in South Korea

The K-COV-N cohort (total n=18 989 129) is a population-based nationwide dataset derived from the National Health Information Database in South Korea. This cohort was developed and shared collaboratively by the NHIS and the KDCA. South Korea has a comprehensive nationwide health care system that provides coverage for 98% of its population. Detailed descriptions of the discovery cohort are provided in the Supplemental Material.

The database uses *International Classification of Diseases* (*ICD*) codes for disease categorization.[13,14] In response to the COVID-19 pandemic, the Korean government provided free and mandatory medical services and insurance coverage to all individuals diagnosed with SARS-CoV-2 infection. The comprehensive dataset incorporated national health examination results, death records, health insurance data including individual information, pharmaceutical information from the NHIS, SARS-CoV-2 test results, SARS-CoV-2 vaccination status information, and SARS-CoV-2 infection–related outcomes from the KDCA.

The study analyzed data for participants aged 20 years and older from January 1, 2018, to December 31, 2022. The look-back period to assessing previous diagnostic history was from 2018 to the index date, and the follow-up period was from 2020 to 2022. The study identified participants who tested positive for COVID-19 during the follow-up period. A previous validation study reported an overall positive predictive value of 82% for diagnostic records in claims data.[15]

The study applied several exclusion criteria to the K-COV-N cohort participants: (1), those with insufficient socioeconomic status information or who had died during the look-back period, and (2), those with a previous history of cardiovascular events (cerebrovascular diseases such as stroke and transient ischemic attack; dysrhythmias such as atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmia, and atrial flutter; inflammatory heart diseases such as pericarditis and myocarditis; ischemic heart diseases such as acute coronary disease, myocardial infarction, and angina; other cardiac disorders such as heart failure, cardiac arrest, and cardiogenic shock; thrombotic disorders such as arterial thromboembolism, pulmonary embolism, and deep vein thrombosis; and major adverse cardiovascular events [MACEs]) during the look-back period.

Exposures

SARS-CoV-2 infection was confirmed through laboratory testing using real-time reverse-transcription polymerase chain reaction assays of nasal or pharyngeal swabs. These tests were authorized by the KDCA and adhered to World Health Organization guidelines. In the overlap-weighted COVID-19 cohort, SARS-CoV-2 infection was defined as a positive SARS-CoV-2 reverse-transcription polymerase chain reaction test result.[16] Participants who experienced reinfection were censored at the date of reinfection, which was defined as a positive SARS-CoV-2 test result occurring at least 90 days after the initial infection.[17–21]

Outcomes

The primary outcome was the onset of cardiovascular outcomes as follows: (1), cerebrovascular diseases such as stroke and transient ischemic attack; (2), dysrhythmia such as atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmia, and atrial flutter; (3), inflammatory heart diseases such as pericarditis and myocarditis; (4), ischemic heart diseases such as acute coronary disease, myocardial infarction, and angina; (5), other cardiac disorders such as heart failure, cardiac arrest, and cardiogenic shock; (6), thrombotic disorders such as arterial thromboembolism, pulmonary embolism, and deep vein thrombosis; (7), MACE defined as a composite end point comprising cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction.[22–24] Participants were categorized as having experienced a cardiovascular outcome if they were diagnosed with any of these events (Table S2).[25]

Covariates

The study collected a comprehensive set of demographic data on age, sex, household income, and region of residence from the insurance dataset. Clinical data were sourced from appropriate *ICD, Tenth Revision* (*ICD-10*) codes and national general health examinations, which included questionnaires and personal medical interviews. These data encompassed the Charlson Comorbidity Index and history of medication use for diabetes, dyslipidemia, and hypertension, as well as hospital admissions and outpatient contacts in the year preceding the index date.[13,14]

Body mass index was calculated and classified according to the Asia-Pacific criteria of the Western Pacific Regional Office 2000: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), and obese (≥25.0 kg/m^2).[13,14] National general health examinations provided data on blood pressure, fasting blood glucose, and glomerular filtration rate, measured using fasting serum samples. Information on smoking status, alcohol consumption, and aerobic physical activity was collected through questionnaires and personal medical interviews during these examinations. Sufficient aerobic physical activity was defined as an engagement in aerobic physical activity amounting to ≥600 Metabolic Equivalent Task scores (MET-min/week), based on World Health Organization guidelines on physical activity.[2,26,27] Missing data were addressed using multiple imputation by chained equation.[28] Representative population in our study is depicted in Table S3.

Propensity Score–Based Overlap Weighting

We implemented a propensity score–based overlap weighting algorithm to address the potential issue of extreme propensity scores thereby ensuring a balanced comparison between the COVID-19 group and noninfected controls.[17,18,29] All related covariates were incorporated into a multivariable logistic regression model to estimate propensity scores, which were then used for adjustment. We assigned the overlap weight as 1 − propensity score for the COVID-19 group and propensity score for the noninfected control. The effectiveness of the overlap-weighting process was assessed by comparing standardized mean differences between the groups. A standardized mean difference value <0.1 was considered indicative of no significant imbalance between the 2 groups. This approach allowed us to effectively control for confounding factors, enhancing our comparisons' validity and subsequent analyses.[30] A detailed explanation of overlap weighting is provided in the Supplemental Material, with an overview of the overlap weighting process in Figure S1.

Validation Cohort in Japan

The study applied similar methodologies to the JMDC (total n=12218680) as those used for the discovery cohort. This approach included using *ICD-10* codes, general health examination data, exposure and outcome definitions, and follow-up duration. Propensity score–based overlap weighting was implemented for the validation cohort. However, because of the absence of COVID-19 vaccination data in the validation cohort, this dataset was primarily used to validate the primary findings obtained from the discovery cohort. This approach allowed for a comprehensive validation of the primary results while accounting for potential differences between the 2 populations. More information is available in the Supplemental Material.

Statistical Analysis

The study used a Cox proportional hazards regression model to estimate hazard ratios and 95% CIs for the long-term risk of 16 cardiovascular outcomes after SARS-CoV-2 infection. Cause-specific Cox proportional hazards models were used, censoring participants at the competing risk of death.[31,32] Multiple subgroup analyses were conducted by 8 primary cardiovascular outcomes, COVID-19 severity (none, mild, moderate, and severe), COVID-19 vaccination dosage (unvaccinated or once [incomplete], twice [complete], and more [booster]), and SARS-CoV-2 era (original, delta, and omicron). Specifically, moderate COVID-19 cases were classified as patients requiring oxygen therapy, and severe COVID-19 cases were classified as patients admitted to the intensive care unit, requiring mechanical ventilation, extracorporeal membrane oxygenation, or renal replacement therapy. All other cases were categorized as mild COVID-19.[16] COVID-19 vaccination status was classified based on the number of vaccinations received before SARS-CoV-2 infection.[13,14] The study defined original SARS-CoV-2 cases as those with an index date for COVID-19 from the first infection to July 31, 2021. Delta era was defined as those with an index date from August 1, 2021, to December 31, 2021.[33] Omicron era was classified as those with an index date after January 1, 2022, until the end of the observation period (December 31, 2022).[19] Also, we assessed the time attenuation effect of cardiovascular outcomes after SARS-CoV-2 infection (<6, 6–12, 12–18, and ≥18 months). Further stratification analyses were performed by sex, age group, household income, Charlson Comorbidity Index, body mass index, and history of medication use (hypertension, diabetes, and dyslipidemia). All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc, Cary, NC),[34] and a 2-tailed *P* value <0.05 was considered statistically significant. To strengthen the credibility of our primary findings and the overall article, we performed multiple sensitivity analyses with accompanying justifications (Table S4).

Sensitivity Analysis

To enhance the reliability of the study, a sensitivity analysis was conducted using an influenza group as an additional comparator alongside the uninfected control group.[30,35] Furthermore, the short-term period was defined as the first 30 days after SARS-CoV-2 infection, during which cardiovascular outcomes were investigated.[3] To further explore the impact of COVID-19 severity, we used the COVID-19 group classified into subgroups based on severity within each cardiovascular risk factors.[36,37] In addition, to examine differential risks over time, a time attenuation analysis was performed, categorizing the index date by the pre-delta, delta, and omicron eras.[20] Last, to mitigate concerns about potential spurious biases, we conducted an analysis to replicate the expected null association between COVID-19 and a negative outcome control.[20] Using the same analytical approach, we examined the association between SARS-CoV-2 infection and incident malignant neoplasms, a condition for which there is no mechanistic or clinical evidence supporting a causal link with SARS-CoV-2 infection.[38] This approach aimed to reduce concerns about potential false associations in the study findings.[20,39] Further methodological details are provided in the Supplemental Material.

Patient and Public Involvement

The Korean government implemented data anonymization procedures for patient-related information, including personal identifiers for confidentiality. Although direct identification of individual participants became unfeasible because of the omission of names, all other relevant data remained intact and available for analytical purposes. Given that this study involved a retrospective analysis of a restricted-access administrative dataset, there was no direct engagement with patients or the

public during the research process. The study's design and execution were carried out independently, without external consultation. South Korea currently lacks an established framework for managing patient and public involvement in research. However, the findings of this investigation will be officially documented and submitted to the NHIS, a governmental institution in South Korea.

RESULTS

Descriptive Overview: Discovery and Validation Cohorts

In the discovery cohort from South Korea, encompassing 18 989 129 eligible participants, the mean age was 48.5 years (SD, 13.4), with men constituting 53.22% (n=10 106 148) of the cohort (Table S5). After propensity score–based overlap weighting, the final analysis included 7 960 357 individuals (3 980 141 patients with COVID-19 and 3 980 216 individuals from the noninfected control) (Table S6). These data formed the basis of our analysis within the South Korean context (Table 1; Figure 1). Similarly, in JMDC from Japan, after overlap weighting, the final sample included 1 247 450 (n=623 725 in individuals with SARS-CoV-2 infection; n=623 725 in noninfected population). Detailed characteristics of the validation cohort can be found in Tables S7 and S8.

Long-Term Risk of Incident Cardiovascular Outcomes: Discovery Cohort

Analysis of long-term cardiovascular risks after SARS-CoV-2 infection revealed an elevated risk compared with noninfected controls (adjusted hazard ratio [aHR], 1.62 [95% CI, 1.60–1.64]) (Figure 2; Table S9). In the overlap-weighted cohort, individuals with SARS-CoV-2 infection compared with noninfected controls, ischemic heart disease presented the highest hazard ratio (aHR, 1.81 [95% CI, 1.77–1.84]), followed by heart failure (aHR, 1.79 [95% CI, 1.73 –1.85]), cerebrovascular disorders (aHR, 1.65 [95% CI, 1.60–1.69]), inflammatory heart diseases (aHR, 1.53 [95% CI, 1.31–1.80]), dysrhythmia (aHR, 1.44 [95% CI, 1.42–1.46]), thrombotic disorders (aHR, 1.42 [95% CI, 1.35–1.48]), and MACE (aHR, 1.65 [95% CI, 1.60–1.70]).

Despite statistically significant differences in relative risk between infected and noninfected cohorts, the absolute risks of cardiovascular events remained low across both populations. The absolute risk of overall cardiovascular events in the infected cohort was 2.12%, compared with 1.31% in the noninfected cohort. MACE was observed in only 0.15% of cases, with stroke and myocardial infarction occurring at remarkably low rates of 0.24% and 0.05%, respectively. Even the conditions with the highest absolute risk, dysrhythmia (0.83%) and angina (0.53%), presented clinically low incidence rates.

Table 1. Baseline Characteristics for Overlap-Weighted Cohort in South Korea (Discovery Cohort, n=7 960 357)

Characteristic	Overlap-weighted cohort (n=7 960 357)	
	Noninfected control (n=3 980 216)	Patients with COVID-19 (n=3 980 141)
Age, y, n (%)		
20–39	1 162 024 (29.2)	1 162 023 (29.2)
40–59	1 894 243 (47.6)	1 894 203 (47.6)
≥60	923 950 (23.2)	923 915 (23.2)
Sex, n (%)		
Men	2 141 975 (53.8)	2 141 903 (53.8)
Women	1 838 241 (46.2)	1 838 238 (46.2)
Region of residence, n (%)		
Rural	1 767 226 (44.4)	1 767 200 (44.4)
Urban	2 212 990 (55.6)	2 212 942 (55.6)
Household income, n (%)		
Low (0–39 percentiles)	1 283 225 (32.2)	1 283 178 (32.2)
Middle (40–79 percentiles)	1 690 188 (42.5)	1 690 165 (42.5)
High (80–100 percentiles)	1 006 803 (25.3)	1 006 800 (25.3)
Charlson Comorbidity Index score, n (%)		
0	2 220 146 (55.8)	2 220 094 (55.8)
1	1 121 142 (28.2)	1 121 125 (28.2)
≥2	638 929 (16.1)	638 923 (16.1)
Previous medication history, n (%)		
Medication use for diabetes	215 035 (5.4)	215 028 (5.4)
Medication use for hyperlipidemia	194 164 (4.9)	194 162 (4.9)
Medication use for hypertension	498 987 (12.5)	498 976 (12.5)
Body mass index, n (%)		
Underweight (<18.5 kg/m²)	139 186 (3.5)	139 181 (3.5)
Normal weight (18.5–22.9 kg/m²)	1 410 366 (35.4)	1 410 337 (35.4)
Overweight (23.0–24.9 kg/m²)	904 356 (22.7)	904 340 (22.7)
Obesity (≥25.0 kg/m²)	1 526 310 (38.3)	1 526 285 (38.3)
Blood pressure, n (%)		
SBP <140 mm Hg and DBP <90 mm Hg	3 501 297 (88.0)	3 501 243 (88.0)
SBP ≥140 mm Hg or DBP ≥90 mm Hg	478 919 (12.0)	478 898 (12.0)
Fasting blood glucose, n (%)		
<100 mg/dL	2 555 745 (64.2)	2 555 715 (64.2)
≥100 mg/dL	1 424 472 (35.8)	1 424 426 (35.8)
Glomerular filtration rate, n (%)		
<60 mL/min/1.73 m²	78 937 (2.0)	78 936 (2.0)
60–89 mL/min/1.73 m²	1 663 362 (41.8)	1 663 332 (41.8)
≥90 mL/min/1.73 m²	2 237 918 (56.2)	2 237 874 (56.2)
Smoking status, n (%)		
Never	2 414 591 (60.7)	2 414 585 (60.7)
Ex-smoker	1 132 612 (28.5)	1 132 579 (28.5)
Current smoker	433 014 (10.9)	432 977 (10.9)

(*Continued*)

Table 1. Continued

Characteristic	Overlap-weighted cohort (n=7 960 357)	
	Noninfected control (n=3 980 216)	Patients with COVID-19 (n=3 980 141)
Alcohol consumption, n (%)		
<1 day per week	2 317 469 (58.2)	2 317 444 (58.2)
1 or 2 days per week	1 135 859 (28.5)	1 135 845 (28.5)
3 or 4 days per week	401 058 (10.1)	401 047 (10.1)
≥5 days per week	125 830 (3.2)	125 807 (3.2)
Aerobic physical activity, n (%)		
Insufficient	2 057 762 (51.7)	2 057 719 (51.7)
Sufficient	1 922 455 (48.3)	1 922 423 (48.3)

DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

Cardiovascular Outcomes After COVID-19 Severity, Vaccination, and SARS-CoV-2 Strain: Discovery Cohort

Severity of COVID-19 was proportionally associated with increased risk of cardiovascular outcomes (mild COVID-19: aHR, 1.56 [95% CI, 1.54–1.58]; moderate to severe COVID-19: aHR, 4.42 [95% CI, 4.27–4.56]). Individuals who received multiple vaccine doses showed lowered risks of cardiovascular events (complete dose: aHR, 0.72 [95% CI, 0.69–0.76]; booster dose: aHR, 0.68 [95% CI, 0.66–0.71]) compared with unvaccinated individuals or those with incomplete vaccination series (Table 2; Table S10). There was a similar risk of cardiovascular outcomes across every SARS-CoV-2 era (pre-delta: aHR, 1.48 [95% CI, 1.37–1.59]; delta: aHR, 1.55 [95% CI, 1.46–1.66]; omicron: aHR, 1.63 [95% CI, 1.61–1.64]) (Table 2; Table S10). Furthermore, patients with moderate COVID-19, defined as those requiring oxygen therapy, showed a 3.35-fold higher risk (95% CI, 3.22–3.49) compared with the noninfected group. Patients with severe COVID-19, characterized by admission to intensive care units, requirement of mechanical ventilation, extracorporeal membrane oxygenation, or renal replacement therapy, had a 10.6-fold (95% CI, 10.06–11.18) higher risk (Table S11).

Time Attenuation Effect: Discovery Cohort

Cardiovascular events were notably elevated during the first 30 days after SARS-CoV-2 infection (aHR, 2.37 [95% CI, 2.29–2.45]) (Table S12). The long-term risk of overall cardiovascular outcomes in individuals with SARS-CoV-2 infection exhibited a persistent elevation for up to 18 months after infection in the discovery cohort.

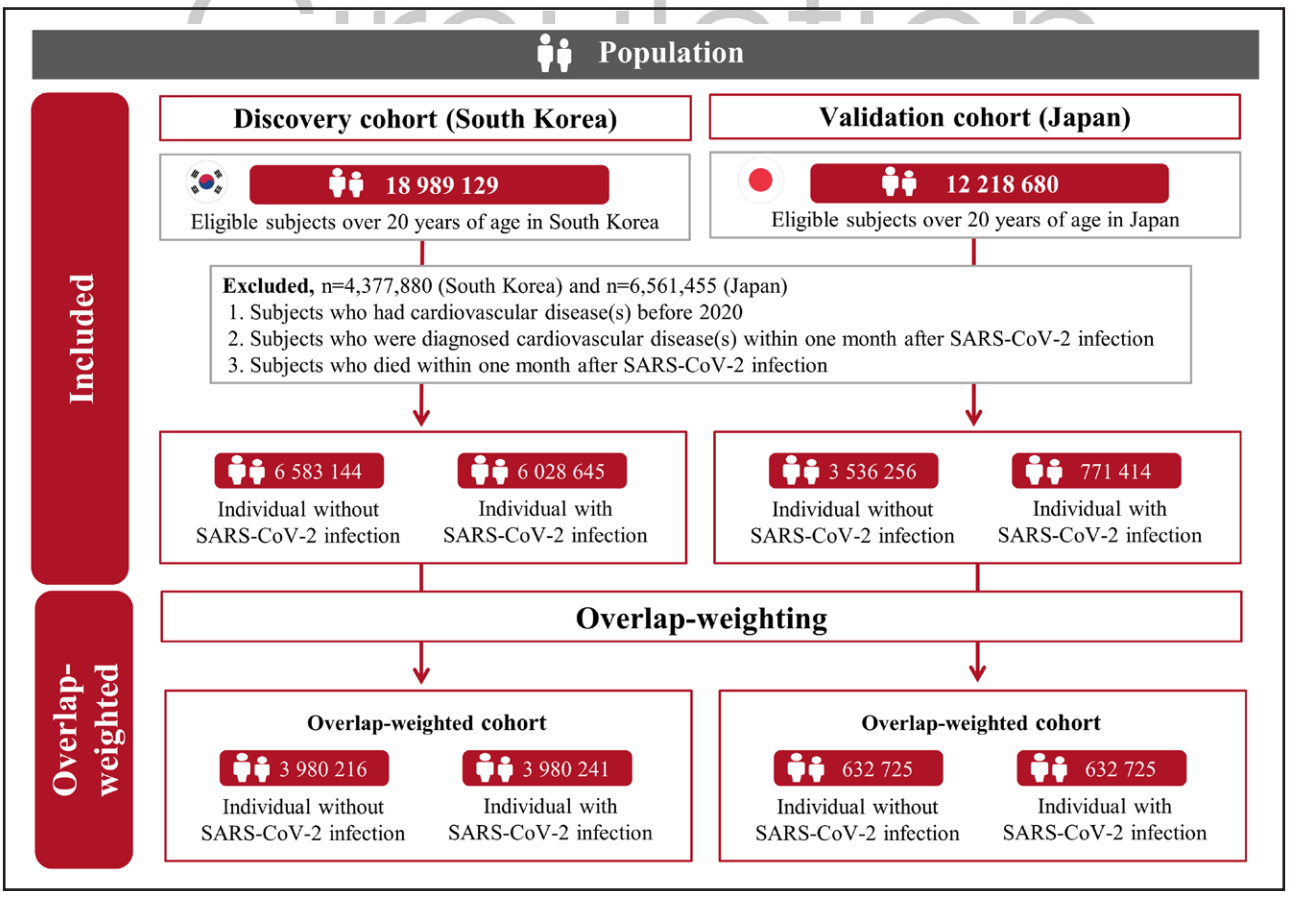

Figure 1. The study population of cohorts in discovery (South Korea) and validation (Japan).

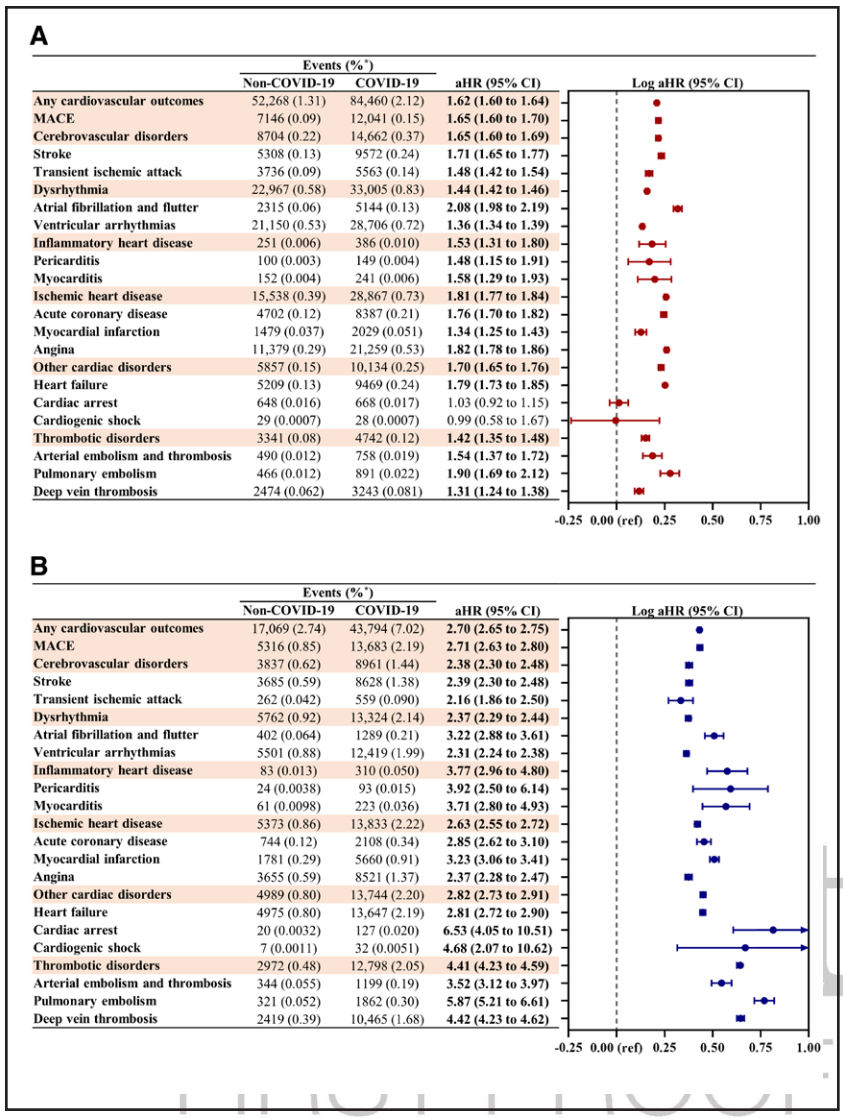

Figure 2. Overlap-weighted HR (95% CI) for the long-term incidence risk of cardiovascular disease events after COVID-19 diagnosis in the overlap-weighted cohorts.

A, South Korea (discovery). **B**, Japan (validation). The data in bold indicate significant differences ($P<0.05$). *Event rates represent the absolute risk of cardiovascular disease.aHR indicates adjusted hazard ratio; and MACE, major adverse cardiovascular event.

The association reached its peak at 1 to 6 months (<6 months: aHR, 1.81 [95% CI, 1.78–1.83]; 6–12 months: aHR, 1.25 [95% CI, 1.23–1.28]; 12–18 months: aHR, 1.19 [95% CI, 1.07–1.33]). Beyond 18 months, the risk of cardiovascular outcomes was no longer statistically significant (≥18 months: aHR, 1.24 [95% CI, 1.01–1.53]), suggesting a potential attenuation of the long-term effect of SARS-CoV-2 infection on cardiovascular outcomes (Figure 3; Table S13). Time attenuation effects of cardiovascular risks for each era are presented in Table S14.

Stratification and Sensitivity Analysis: Discovery Cohort

Our study incorporates a comprehensive justification for various sensitivity analyses, as outlined in Table S4. The association between incident cardiovascular outcomes and SARS-CoV-2 infection remained consistent across stratifications by sex, age group, income level, Charlson Comorbidity Index, and body mass index category (Tables S15 and S16). Within each stratification, every severity level of SARS-CoV-2 infection was associated with higher risks of any cardiovascular events and MACE compared with noninfected controls (Tables S17 and S18). When compared with influenza, individuals with SARS-CoV-2 infection showed elevated rates of cardiovascular events (Table S19). The rates of cardiovascular events were 2.12 times higher (95% CI, 2.04–2.20) in SARS-CoV-2 infection compared with influenza. The association between COVID-19 and incident neoplasm was examined as a negative outcome control (Table S20). Neutral association between COVID-19 and the negative outcome control was observed in noninfected control populations (aHR, 1.01 [95% CI, 0.98–1.03]).

Validation Cohort

Individuals with SARS-CoV-2 infection showed a long-term increased risk of cardiovascular outcomes compared with noninfected controls (aHR, 2.70 [95% CI,

Table 2. Subgroup Analysis of Overlap-Weighted Hazard Ratio (95% CI) for Incidence Risk of Cardiovascular Events in the Overlap-Weighted Cohort in South Korea (Discovery Cohort)

	aHR (95% CI)†							
	Any cardiovascular outcomes	MACE	Cerebrovascular disorders	Dysrhythmia	Inflammatory heart disease	Ischemic heart disease	Other cardiac disorders	Thrombotic disorders
Severity of COVID-19								
Noninfected control	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Mild COVID-19	1.56 (1.54–1.58)*	1.56 (1.54–1.59)*	1.59 (1.54–1.63)*	1.42 (1.39–1.44)*	1.49 (1.27–1.74)*	1.75 (1.72–1.79)*	1.60 (1.55–1.66)*	1.30 (1.25–1.36)*
Moderate to severe COVID-19	4.42 (4.27–4.56)*	7.06 (6.81–7.32)*	4.33 (4.02–4.66)*	3.08 (2.89–3.27)*	5.15 (3.15–8.40)*	4.81 (4.56–5.08)*	6.46 (5.99–6.96)*	7.54 (6.83–8.33)*
SARS-CoV-2 vaccination status								
Noninfected control	0.41 (0.40–0.42)*	0.42 (0.34–0.51)*	0.40 (0.37–0.43)*	0.46 (0.44–0.48)*	0.30 (0.21–0.43)*	0.37 (0.35–0.39)*	0.34 (0.31–0.37)*	0.42 (0.37–0.47)*
COVID-19 with incomplete vaccine (<2 dose)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
COVID-19 with complete vaccine (2 doses)	0.72 (0.69–0.76)*	0.70 (0.57–0.86)*	0.73 (0.65–0.83)*	0.70 (0.64–0.76)*	0.49 (0.21–1.14)	0.75 (0.69–0.82)*	0.59 (0.51–0.68)*	0.47 (0.37–0.60)*
COVID-19 with booster vaccine (≥3 doses)	0.68 (0.66–0.71)*	0.74 (0.61–0.91)*	0.72 (0.67–0.78)*	0.66 (0.63–0.69)*	0.44 (0.31–0.62)*	0.74 (0.70–0.78)*	0.60 (0.55–0.65)*	0.58 (0.52–0.65)*
SARS-CoV-2 infection in the pre-delta era								
Noninfected control at the same index date‡	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Infection in the pre-delta era	1.48 (1.37–1.59)*	1.81 (1.75–1.88)*	1.42 (1.18–1.71)*	1.46 (1.30–1.63)*	1.66 (0.78–3.55)	1.59 (1.40–1.81)*	1.50 (1.21–1.86)*	1.38 (1.05–1.81)*
SARS-CoV-2 infection in the delta era								
Noninfected control at the same index date‡	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Infection in the delta era	1.55 (1.46–1.66)*	1.23 (1.17–1.30)*	1.50 (1.28–1.76)*	1.44 (1.31–1.58)*	2.33 (1.20–4.54)	1.72 (1.54–1.91)*	1.45 (1.21–1.74)*	1.54 (1.21–1.97)*
SARS-CoV-2 infection in the omicron era								
Noninfected control at the same index date‡	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Infection in the omicron era	1.63 (1.61–1.64)*	1.26 (1.09–1.45)*	1.65 (1.61–1.70)*	1.44 (1.42–1.47)*	1.49 (1.26–1.76)	1.83 (1.79–1.86)*	1.72 (1.66–1.77)*	1.41 (1.35–1.48)*

aHR indicates adjusted hazard ratio; and MACE, major adverse cardiovascular event.

*Indicates significant differences ($P< 0.05$).

†aHR: adjusted for age (20–39, 40–59, and ≥60 years); sex (men and women); region of residence (urban and rural); household income (low [0–39 quartiles], middle [40–79 quartiles], and high [80–100 quartiles]); Charlson Comorbidity Index score (0, 1, and ≥2); body mass index (underweight [<18.5 kg/m^2], normal weight [18.5–22.9 kg/m^2], overweight [23.0–24.9 kg/m^2], and obesity [≥25.0 kg/m^2]); blood pressure (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg and systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg); fasting blood glucose (<100 and ≥100 mg/dL); glomerular filtration rate (<60, 60–89, and ≥90 mL/min/1.73 m^2); smoking status (never, ex-, and current smoker); alcohol consumption (drinks <1, 1 or 2, 3 or 4, and ≥5 days per week); aerobic physical activity (sufficient and insufficient); and history of medication use for diabetes, hyperlipidemia, and hypertension.

‡Comparators defined only overlap weighted comparators in each patient group at the same index date to reduce immortal bias.

2.45–2.55]) (Figure 2; Table S9). The risk of cardiovascular sequelae persisted for >18 months after infection (6 months: aHR, 3.12 [95% CI, 3.04–2.21]; 6–12 months: aHR, 2.22 [95% CI, 2.15–2.29]; 12–18 months: aHR, 2.10 [95% CI, 2.00–1.95]; ≥18 months: aHR, 1.94 [95% CI, 1.80–2.09]) (Figure 3; Table S13). Detailed stratification could be found in Tables S21 and S22.

DISCUSSION

Key Findings

This study is the first comprehensive binational investigation to examine the long-term cardiovascular outcomes of COVID-19, using large-scale population-based cohorts from South Korea (discovery) and Japan (validation)

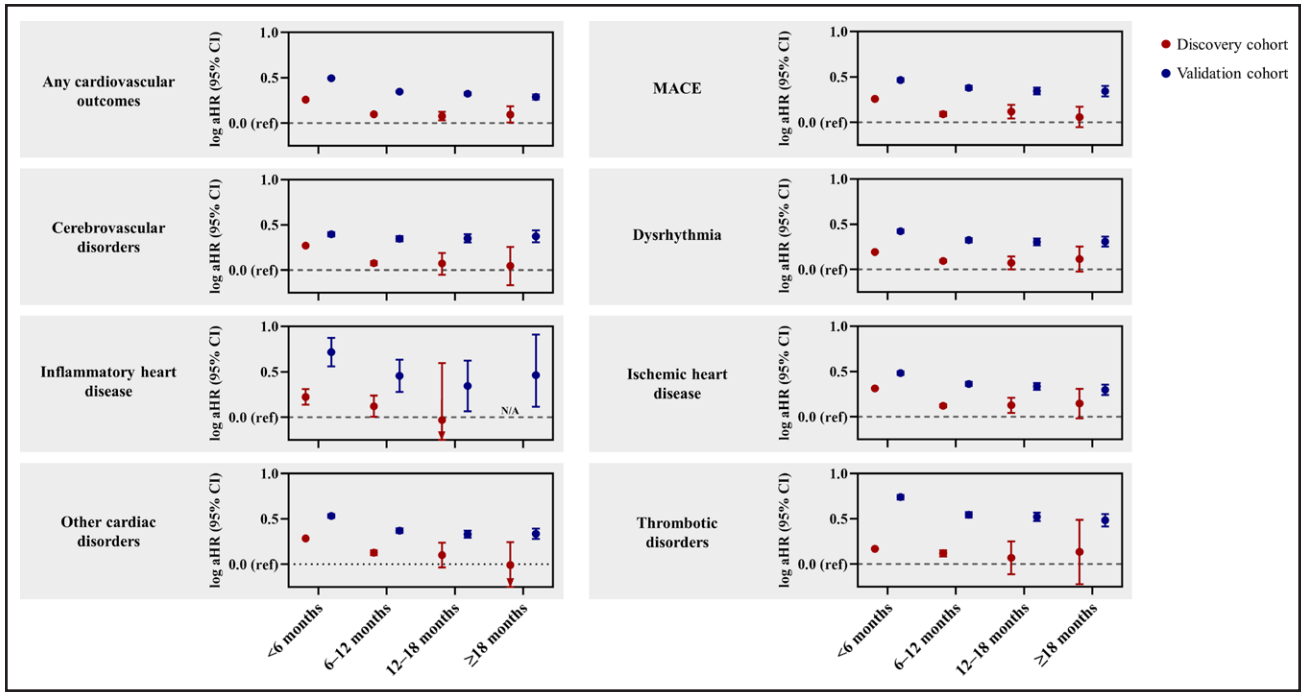

Figure 3. Time attenuation effect of SARS-CoV-2 infection on the incidence risk of cardiovascular disease events in the overlap-weighted cohort in South Korea (discovery) and Japan (validation).
The data in bold indicate significant differences (P<0.05). aHR indicates adjusted hazard ratio; and MACE, major adverse cardiovascular event.

consisting of >30 million participants. This study investigated the association between SARS-CoV-2 infection and cardiovascular events in comparison with the general population. First, an increased long-term risk of incident cardiovascular outcomes was observed in both discovery and validation cohorts. Second, severe COVID-19 was associated with a higher risk of developing cardiovascular outcomes. Third, individuals with complete vaccination and subsequent booster doses showed a lower risk of incident overall cardiovascular outcomes. Fourth, consistent elevated risks of incident cardiovascular outcomes were observed across the pre-delta, delta, and omicron eras. Fifth, there was a time attenuation effect on the risk of incident cardiovascular outcomes after SARS-CoV-2 infection. The risk associated with cardiovascular outcomes did not maintain statistical significance beyond the 18 months, suggesting a potential attenuation of cardiovascular risk over time for certain outcomes. Our findings indicate that infections across every era were consistently associated with increased cardiovascular risks. Although this elevated risk persisted during the follow-up period, it gradually attenuated over time. Adequate vaccination may mitigate these cardiovascular risks. In addition, although the increased cardiovascular relative risk after SARS-CoV-2 infection has been observed, given the low absolute risk of cardiovascular events even after infection, excessive public concern remains unwarranted.

Comparisons With Previous Studies

Although previous studies primarily focused on the first year after SARS-CoV-2 infection, this research extends the observation period, providing insights into longer-term cardiovascular risks. Meta-analyses and cohort studies have identified cardiometabolic risk factors such as age, sex, smoking status, body mass index, and comorbidities as contributors to the increased long-term effect of SARS-CoV-2 infection.[40–42] One cohort study has shown that SARS-CoV-2 infection elevates cardiovascular risk in populations including those with pre-existing cardiovascular conditions.[24] Our study extends beyond these findings by showing that even in individuals without previous cardiovascular disease, SARS-CoV-2 infection increased the risk of new-onset cardiovascular outcomes, regardless of behavioral risk factors and baseline health status. Previous research has shown persistent symptoms in individuals with mild SARS-CoV-2 infection.[43] Our study corroborates this, indicating increased cardiovascular risk after mild infection, although severe COVID-19 cases exhibited significantly higher risk. Two cohort studies with predominantly male, White participants >65 years of age, conducted over 2 and 3 years, highlighted the persistence of cardiovascular risks despite a decrease in some sequelae.[2,11] Another study focusing on East Asian populations reported increased cardiovascular outcomes after infection but was limited by small sample size and insufficient analyses.[44] Our research addresses these limitations through comprehensive analysis of large-scale cohorts. Furthermore, we investigated the protective role of vaccination on long-term cardiovascular outcomes associated with SARS-CoV-2 infection, an aspect insufficiently explored in previous studies.[19,45] Our results align with previous

findings suggesting that COVID-19 vaccination reduces the risk of postinfection cardiovascular events.

Plausible Underlying Mechanisms

SARS-CoV-2 infection induces systematic inflammation, which triggers hyperactivated immune responses, leading to persistent T-cell activation. The resulting tissue damage can cause myocardial fibrosis, chronically impairing ventricular compliance and myocardial perfusion.[41] Moreover, individuals with severe SARS-CoV-2 infection exhibited a more significant increased risk of cardiovascular outcomes. Research indicates that severe COVID-19 cases are characterized by widespread viral dissemination beyond the respiratory system, with SARS-CoV-2 RNA detected in multiple organ systems, potentially explaining the prolonged risks observed in our analysis.[46]

Strengths and Limitations

This comprehensive analysis investigates the long-term cardiovascular risks after SARS-CoV-2 infection, using a cohort of >30 million participants. It represents the first study to examine these risks specifically in an Asian population. Although previous research has indicated increased long-term cardiovascular risks, those studies were limited by small sample sizes[44] and biased cohort compositions, often focusing on older, predominantly male populations.[2,11,24] The cohort in this study, with its large and diverse composition, allows for a more generalizable understanding of the association between SARS-CoV-2 infection and cardiovascular events across age groups and sexes, including younger individuals and females. Furthermore, our methodology involved the exclusion of all cases with incomplete data, in contrast with other studies that used mean imputation for missing values.[24] This rigorous approach to data integrity facilitated more robust and precise analytical outcomes. In addition, unlike many previous studies that lacked vaccination data, this research presents the long-term protective effects of vaccination, categorized by dosage.

Despite its strengths, this study has several limitations. First, the lack of SARS-CoV-2 sequencing data hindered direct association between specific variants and long-term cardiovascular risks, despite categorization of variant eras. Second, although reinfected or breakthrough infection individuals may exist in the cohort, the study did not classify participants by the number of SARS-CoV-2 infections.[47] Third, despite efforts to minimize bias through data cleaning and propensity score–based overlap weighting, residual confounding factors may persist. Fourth, there is a possibility of detection bias because of undiagnosed COVID-19 cases, including asymptomatic infections or individuals who did not undergo polymerase chain reaction testing.[14] Fifth, variations in follow-up periods among participants may introduce bias when assessing the association between SARS-CoV-2 infection and cardiovascular risk. These limitations require careful interpretation of positive SARS-CoV-2 test outcomes within the study cohort. However, these limitations are mitigated by the robust features of our study, which used extensive nationwide cohorts from both countries, revealing consistent patterns. Furthermore, the comprehensive pandemic response strategies at the national level and the accessibility of health care services have further alleviated this concern.[48] Sixth, coinfections capable of evoking other respiratory infections were not considered. Seventh, although cardiovascular disease is less common in children than in adults, given that this study was limited to the adult population, future research focusing on children appears necessary.[49] This would allow for a comprehensive understanding of the cardiovascular effects of COVID-19 across all age groups. Eighth, as this study is limited to an Asian population, further research may be needed for other ethnicities. Last, the absence of COVID-19 vaccination status information in the validation cohort precluded validation analysis of vaccine influences on cardiovascular outcomes.[30] Although previous studies have suggested protective effects of vaccination against SARS-CoV-2 infection, the observational nature of these studies necessitates cautious interpretation of vaccination-related findings.

CONCLUSIONS

This binational large-scale study of >30 million participants from South Korea and Japan observed significant long-term associations between SARS-CoV-2 infection and cardiovascular events. The study presented increased cardiovascular sequelae across various viral eras, with severe COVID-19 cases showing higher risks. Although vaccination was associated with lower event rates, both vaccinated and unvaccinated groups showed higher frequencies of cardiovascular events compared with uninfected populations. Cardiovascular outcomes were observed consistently across the pre-delta, delta, and omicron periods, indicating a complex relationship between infection and outcomes. The risk of cardiovascular outcomes remained elevated during the extended follow-up period, gradually attenuating over time. These findings underscore the importance of continued vigilance and preventive measures, including adequate vaccination. However, despite these relative risk increases, the absolute risks of cardiovascular events remained remarkably low in the infected population. Thus, it is important to reassure individuals about the low absolute risk of cardiovascular complications after SARS-CoV-2 infection at the population level.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Expanded Methods
Figure S1
Tables S1–S22
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