The incidence of COVID vaccine-related myocarditis (VRM) varies among studies from 1.4 to 5.0 per 100,000 vaccinated persons. COVID VRM, which typically develops seven days after immunization and is more common in young males and after the second dose of the vaccine, has been reported in large cohort and epidemiologic studies. Some individuals experienced unfavorable clinical outcomes leading to fulminant myocarditis or even death, despite the fact that COVID VRM was generally reported to be mild. The Korean authors in this study investigated nationwide incidence and the clinical outcomes of myocarditis associated with the COVID vaccination in the entire vaccinated Korean population using a national reporting system for adverse events associated with COVID immunization.

About the study

The Korean Disease Control and Prevention Agency established a reporting system with a legal obligation for special adverse events, including myocarditis and pericarditis after COVID-19 vaccination. They also organized the Expert Adjudication Committee on pericarditis/myocarditis associated with COVID vaccination, which comprised seven experts in cardiology, one in infectious disease, and two in epidemiology. For the diagnosis and degree of certainty of COVID VRM diagnosis, the Committee adopted the definition and classification of the Brighton Collaboration. Acute myocarditis that developed within 42 days after COVID-19 vaccination was considered as COVID VRM.

Other possible causes of myocarditis, antibodies against various viruses, and autoimmune

markers were also investigated. Cardiac troponin was initially measured at the first hospital visit with symptoms after vaccination and followed up daily until levels normalized. Vaccination-related myocarditis requiring intensive care unit (ICU) admission, fulminant myocarditis, the use of extracorporeal membrane oxygenation, heart transplantation, or death were considered severe VRM in this study.

Results

This retrospective nationwide study included the entire vaccinated Korean population in 2021. 44,276704 individuals older than 12 years were vaccinated with at least one dose of vaccines (ChAdOx1, BNT162b2, mRNA-1273, or Ad26.COV2.S), 41,084830 persons with the second dose of vaccines (ChAdOx1, BNT162b2, or mRNA-1273), and 18,411821 persons with the third dose of vaccines (BNT162b2, mRNA-1273 or Ad26.COV2.S).

From 1533 cases of suspected acute COVID VRM reported to the Korean Disease Control and Prevention Agency, the Expert Adjudication Committee on COVID-19 vaccination pericarditis/myocarditis confirmed 480 cases of VRM.

Chest pain and discomfort were the most common presenting symptoms, and the median

time from the vaccination to symptom onset was 3 days.

The incidence of myocarditis related to COVID vaccination

The overall incidence of COVID vaccine-related myocarditis was 1.08 per 100,000 vaccinated persons. It was significantly higher in men than in women (1.35 *vs.* 0.82 per 100,000 persons).

The incidence of myocarditis was significantly higher after receiving the mRNA vaccines than other vaccines (1.46 vs. 0.14 per 100,000 persons), and it was highest after receiving the mRNA-1273 (2.30 per 100 000 persons), followed by BNT162b2 (1.23 per 100,000 persons), Ad26.COV2.S (0.20 per 100,000 persons), and ChAdOx1 (0.08 to 0.22 per 100,000 persons).

The incidence of COVID VRM was 0.47 per 100,000 persons after the first vaccination dose, 0.55 per 100,000 persons, after the second dose, and 0.24 per 100,000 persons after the third dose. The incidence of myocarditis did not differ between the first and second vaccination doses, but it was significantly lower after the third vaccination dose.

Sex-specific differences

COVID vaccine-related myocarditis was more common in males (62.3%) aged under 40 years (67.9%), and after receiving mRNA vaccines (96.3%). The incidence of COVID VRM was highest in males aged 12 to 17 years (5.29 per 100,000 persons) followed by males aged 18 to 29 years (2.93 per 100,000 persons), and lowest in females aged more than 70 years (0.16 per 100,000 persons).

The incidence of acute COVID VRM did not differ between sexes after the first vaccination dose, but, it was significantly higher in men than in women (0.76 vs. 0.31 per 100,000 persons) after the second dose.

Laboratory and imaging findings

Cardiac troponin levels were elevated in 97% (464/480) of VRM cases. In the remaining 16 cases, myocarditis was confirmed by the endo-myocardial biopsy or cardiac magnetic

resonance imaging (MRI) even though cardiac troponin levels were not measured or elevated.

Electrocardiography (ECG) was available in 67% (322/480 cases), and 68% had abnormal ECG findings. The most common ECG abnormality was ST-segment elevation, found in 41.6% of patients. During hospitalization, ECG of 16 cases (5%) showed sustained ventricular tachycardia or fibrillation.

Echocardiography was available in 59% (285/480) cases. 23% of them (66/285) had left ventricular ejection fraction (LVEF) <50%.

Cardiac MRI was available in 16% (78/480) cases. 73% of them (61/78) had acute myocarditis, 69% (54/78) had late gadolinium enhancement and 33% (26/78) had left ventricular ejection fraction <50%.

Clinical outcomes

Severe COVID-19 VRM was identified in 19.8% (95/480) cases and included ICU admissions in 18% (85/480) cases, fulminant myocarditis in 8% (36/480), extracorporeal membrane oxygenation in 4% (21/480), deaths in 4% (21/480), and 1 heart transplantation (0.2%). Heart transplantation was done successfully, and the histopathologic examination of the explanted heart demonstrated giant cell myocarditis.

Female sex, older age, symptoms of dyspnea or fever, and low blood pressure were more significantly associated with severe COVID VRM. Multivariate analysis showed that low systolic blood pressure (<100 mmHg) and age over 40 years were independent predictors of developing severe COVID VRM.

Eight out of 21 deaths were sudden cardiac deaths attributable to VRM proved by an autopsy. All sudden cardiac deaths developed within a week after the vaccination, the patients were under 45 years of age and all received the mRNA vaccines. Autopsy studies are presented in Table.

Table: Sudden cardiac death cases attributable to COVID-19 VRM

Case	Age	Sex	Vaccination to death (days)	Types of vaccine	Order of vaccination	Histopathologic findings
1	22	M	6	BNT162b2	1	Diffuse inflammatory infiltration, with neutrophil and histiocyte predominance in both atria and near AV node and SA node. Free of inflammatory infiltrates in ventricular myocardium.
2	30	F	3	BNT162b2	1	Diffuse inflammatory cell infiltration, myocardial fiber disarray, interstitial fibrosis, and localized necrosis of myocyte.
3	45	M	3	BNT162b2	2	Localized infiltration of neutrophils, lymphocytes, histocytes, and a few eosinophils was noted. A small number of cardiomyocyte necrosis were also seen.
4	25	M	3	BNT162b2	2	Myocarditis
5	45	M	3	BNT162b2	2	Interstitial infiltration of various inflammatory cells including lymphocyte, neutrophil, eosinophil, and focal necrosis suggesting the diagnosis of myocarditis.
6	36	F	2	mRNA-1273	1	Neutrophil, eosinophil, and histiocyte infiltration in the myocardium suggesting acute myocarditis.
7	33	M	1	mRNA-1273	2	Multiple focal infiltrations of acute inflammatory cells and chronic inflammatory cells in the myocardium.
8	33	M	3	mRNA-1273	2	Various inflammatory cells such as neutrophils, eosinophils, lymphocytes, macrophages, and cardiomyocyte necrosis in the myocardial interstitium and epicardium suggested myocarditis.

VRM, vaccine-related myocarditis; AV, atrioventricular; SA, sinoatrial.

Conclusion

This nationwide study conducted on more than 44 million vaccinated individuals in Korea demonstrated several clinically important findings on acute myocarditis associated with COVID vaccination. The incidence of COVID VRM was 1.08 cases *per* 100,000 vaccinated

persons for all vaccines (2.30 for mRNA-1273, 1.23 for BNT162b2). COVID VRM was mainly developed after receiving the mRNA vaccines, especially in young adult and adolescent males. The incidence of acute COVID VRM was significantly higher in men than in women after the second dose of the vaccine. These results are in line with those from a retrospective pharmacovigilance study that used the Vaccine Adverse Events Reporting System (VAERS) to analyze reporting rates of myocarditis/pericarditis after the primary and up to three booster doses of mRNA COVID-19 vaccination (BNT162b2, Pfizer-BioNTech, and mRNA-1273, Moderna). This analysis demonstrated a higher reporting rate mainly after the second dose, particularly among young males.
https://discovermednews.com/vaers-reporting-rates-of-myocarditis-pericarditis-after-mrna-vaccination/

The clinical outcomes found in the present study differed significantly from the previous studies, which reported a mild clinical course of COVID VRM with favorable short-term outcomes. In the present study, severe COVID VRM was recorded in 19.8% (95/480) of cases, including 36 cases of fulminant myocarditis and 21 deaths. Eight out of 21 deaths were sudden cardiac death attributable to VRM proved by an autopsy. All sudden cardiac deaths developed within a week after the vaccination, the patients were under 45 years of age and all received the mRNA vaccines. Vaccine-related myocarditis was the only possible cause of death in all cases. The authors emphasized that the reason for the different results regarding the clinical course of COVID VRM in the different studies may be due to a passive reporting system in some countries, whereas reporting of an adverse reaction to COVID-19 vaccination to the Korean Disease Control and Prevention Agency is required by law.

The authors concluded that the findings of sudden cardiac death attributable to COVID VRM warrant the careful monitoring or warning of sudden cardiac death as a potentially fatal complication of COVID-19 vaccination, especially in individuals younger than 45 years of age who received the mRNA vaccines.

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A Korean nationwide study conducted on more than 44 million vaccinated individuals found that the incidence of myocarditis associated with COVID vaccination was highest in males aged 12 to 17 years, and the most serious adverse effect was sudden cardiac death | 7 Access) https://doi.org/10.1093/eurheartj/ehad339