JKMS Manuscripts Title Page

Title: Baseline and predictive incidence of Myocarditis and Pericarditis for safety monitoring of Koreans vaccinated with mRNA COVID-19 vaccines

Running title: Baseline Incidence of Myocarditis and Pericarditis in Korea

Authors: Jong Youn Moon[1,3*], Taemo Bang[2,3*], Munkhzul Radnaabaatar[3*], Dong Wook Kim[4], Young-Eun Kim[4], Jaehun Jung[2,3]

Affiliations:

[1] Center for Public Healthcare, Gachon University Gil Medical Center, Incheon, Korea

[2] Department of Preventive Medicine, Gachon University College of Medicine, Incheon, Korea

[3] Artificial Intelligence and Big-Data Convergence Center, Gil Medical Center, Gachon University College of Medicine, Incheon, Korea.

[4] Department of Big Data Strategy, National Health Insurance Service, Wonju, Korea.

Address for Correspondence:

Jaehun Jung, MD, PhD.

Department of Preventive Medicine, Gachon University College of Medicine, 38 Dokjeom-ro, 3-beon-gil, Namdong-gu, Incheon 21565, Republic of Korea. Email: eastside1st@gmail.com

Young-Eun Kim, PhD.

Department of Big Data Strategy, National Health Insurance Service, 32, Geongang-ro, Wonju, Gangwon-do, 26464, Republic of Korea. Email: kimyes4454@gmail.com

*Jong Youn Moon, Taemo Bang and Munkhzul Radnaabaatar contributed equally to this work

Baseline and predictive incidence of Myocarditis and Pericarditis for safety monitoring of Koreans vaccinated with mRNA COVID-19 vaccines

Abstract

The incidence of myocarditis and pericarditis is known to increase following vaccination with the Moderna (mRNA-1273) and Pfizer-BioNTech coronavirus disease-2019 (BNT162b2) vaccines. The monthly occurrence of myocarditis and pericarditis in 2021 was predicted based on data from 2006 to 2020 using National Health Insurance Service data. Six categories of myocarditis and pericarditis were operationally defined. The mean predicted monthly incidence of acute myocarditis, acute pericarditis, myocarditis/pericarditis case definition by Brighton collaboration was expected to occur in 2.367/100,000 (95% confidence interval[CI], 0.000-9.302) and 0.295/100,000 (95% CI, 0.241-0.348) and 0.634/100,000 (95% CI, 0.490-0.779), respectively. The baseline incidence of myocarditis and pericarditis in Korea has been stable for last 5years and had strong seasonality peaked in winter. And the predicted incidence of myocarditis is relatively high in the groups of male and age under 40 in 2021.

Keywords: COVID-19; Myocarditis; Pericarditis; Vaccine adverse effects

MAIN TEXT

Acute myocarditis and pericarditis are immune responses occurring in the myocardium and surrounding tissues. Viral infection is the most common cause of acute myocarditis and pericarditis. However, it is rarely induced by vaccination, such as the smallpox vaccine. [1,2]

The incidence of myocarditis and pericarditis is known to increase following vaccination with the coronavirus disease-2019 (COVID-19) mRNA-1273 and Pfizer-BioNTech COVID-19 (BNT162b2) vaccines. The reported rates of myocarditis after the second dose of the mRNA COVID-19 vaccination were 40.6/1,000,000 for males aged 12-29 years, 2.4/1,000,000 for males aged over 30 years, and 4.2/1,000,000 for females aged 12-29 years.[3] The Advisory Committee on Immunization Practices announced that despite the high incidence of myocarditis, the benefits of vaccination outweighed the

risks of vaccination in all age groups. On June 25, the Food and Drug Administration included the rare occurrence of myocarditis among younger individuals in the vaccination warning statement.[4]

As the vaccination with the Moderna and Pfizer-BioNTech COVID-19 vaccines continues in Korea, the incidence of myocarditis and pericarditis may increase. To determine its relationship with vaccination, the reference value should be determined and compared against the existing incidence rate. This study predicted the monthly occurrence of myocarditis and pericarditis in 2021 based on National Health Insurance Service (NHIS) data from 2006 to 2020.

Monthly cases of myocarditis and pericarditis were extracted from the NHIS medical claims database. The NHIS is a mandatory single-payer healthcare system for all residents of the Republic of Korea. The monthly number of cases for each condition was obtained using the primary diagnosis code and admission code or emergency department visit fee code from January 2006 to December 2020. The International Classification of Diseases and Related Health Problems, 10th edition (ICD-10) codes were used to identify the diagnoses codes.

The six categories of myocarditis and pericarditis included acute myocarditis (I40, I42, I51.4, A36.8, A52.0, B26.8), infectious myocarditis (A36.8, A39.5, A52.0, B26.8, I40.0, I41.0, I41.2, B33.2, J10.8, J11.8), myocarditis/pericarditis case definition by Brighton collaboration (I51.4, I30, I31.9, I32.8, I40, I41.8), acute pericarditis (I30, I31.9, I32, I01.0), rheumatic myocarditis (I09.0, M05.3, I01.2), and rheumatic pericarditis(I01.0) (Supplementary Table 1).

To calculate the monthly incidence per 100,000, the monthly number of cases was divided by the mid-year population of each year. Based on the monthly incidence of each condition, the seasonal autoregressive integrated moving average (ARIMA) model was used to predict the incidences and 95% confidence intervals (CIs) for January to December 2021. The parameters for the models were determined by the "ARIMA" function in the "fable" package of R software. The mean predicted monthly incidence was calculated by the mean of predicted monthly incidence in 2021. The predicted annual incidence was calculated by the sum of predicted monthly incidence in 2021. A subgroup analysis was performed for age groups of 10 years and sex. The parameters of the ARIMA model are

2

listed in Supplementary Table 2. These study designs are similar to the previous two studies published in Journal of Korean Medical Science in the past. And the scope of the study was extended to myocarditis and pericarditis to respond to adverse events after COVD-19 vaccination. These study designs are similar to previous studies Statistical analyses were performed using R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

The mean predicted monthly incidence of acute myocarditis and acute pericarditis were 2.367/100,000 (95% CI, 0.000-9.302), 0.295/100,000 (95% CI, 0.241-0.348) and myocarditis/pericarditis case definition by Brighton collaboration was 0.634/100,000 (95% CI, 0.490-0.779), respectively. The incidences of all conditions have been relatively stable since 2016. And the incidence of myocarditis, pericarditis, and myocarditis/pericarditis case definition by Brighton collaboration had strong seasonality peaked in winter. (Table 1, Figure 1).

Subgroup analysis was conducted with age groups of 10 years and sex. The baseline incidence of myocarditis/pericarditis case definition by Brighton collaboration and pericarditis among males aged 10-19 and 20-29 years was relatively higher than those of women from the same age group. The incidence of acute myocarditis was similar between males and females aged 10-19 and 20-29 years (Supplementary Figures 1 and 2).

The global incidence rate of myocarditis was reportedly 10-22/100,000 person-years.[5] The US population-based background incidence rates of myocarditis were investigated for use in assessing the safety of the COVID-19 vaccines in the US.[6] The incidence rate of acute pericarditis was 5.73-26/100,000 person-years, while the incidence rate of myopericarditis was 0.95-2.16/100,000 person-years. In a retrospective study of health insurance claims data in Taiwan, among 2,150,590 live births, 965 patients were hospitalized for myocarditis with an overall incidence of 0.45/1,000.[7] In a prospective study to monitor the adverse reactions of smallpox vaccination in the US military, the incidence rate was 2.16/100,000 (95% CI, 1.90-2.34) in the unvaccinated group.[8] The mean age was 27.8 years, and 30 cases were identified among 1,390,352 duty service members. The incidence rate in the smallpox-vaccinated group was 7.46/100,000 (95% CI, 6.89-8.48).

This study had several limitations similar to previous studies.[9,10] This study did not conduct detailed subgroup analyses, it is does not provide any information about risk factors in a specific population. Also, there are limitations that arise from the use of health insurance claim data. There is a problem with misclassification or incorrect input. Thus, this study only provides the rough baseline for myocarditis and pericarditis, and does not provide causal relationship with vaccination. Therefore, even if the monthly incidences of myocarditis and pericarditis exceed the baseline, a case-by-case review is necessary in order to determine the causal relationship with the vaccine.

In conclusion, the baseline incidence of myocarditis and pericarditis in Korea has been stable for last 5years and had strong seasonality peaked in winter. The predicted incidence of myocarditis is relatively high in the groups of male and age under 40. Even if the monthly incidences of myocarditis and pericarditis exceed the baseline after vaccination, a case-by-case review is necessary to determine its relationship with the vaccine.

Ethics statement

The study protocol was approved by the institutional review board of the Gil Medical Center, Gachon University College of Medicine (GFIRB2020-284). And the requirement to obtain written consent was waived due to the retrospective nature of this study; patients and the public were not involved in the study design, data collection, analysis, or interpretation of data. All study methods were carried out based on the Declaration of Helsinki.

ACKNOWLEDGMENTS

ORCID iDs

Jong Youn Moon https://orcid.org/0000-0001-5278-6816

Taemo Bang https://orcid.org/0000-0002-0497-9936

Munkhzul Radnaabaatar https://orcid.org/0000-0003-4968-5031

Dong Wook Kim https://orcid.org/0000-0002-4478-3794

Young-Eun Kim https://orcid.org/0000-0003-0694-6844

Jaehun Jung https://orcid.org/0000-0002-4856-3668

REFERENCES

1.   Cooper LT, Jr. Myocarditis. *The New England journal of medicine*. 2009;360:1526-1538

2.   Sagar S, Liu PP, Cooper LT, Jr. Myocarditis. *Lancet (London, England)*. 2012;379:738-747

3.   Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mrna covid-19 vaccine after reports of myocarditis among vaccine recipients: Update from the advisory committee on immunization practices - united states, june 2021. *MMWR*. Morbidity and mortality weekly report. 2021;70:977-982

4.   Coronavirus (covid-19) update: June 25. [Updated 2021]. [Accessed July 17, 2021]. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021

5.   Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;386:743-800

6.   Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, et al. U.S. Population-based background incidence rates of medical conditions for use in safety assessment of covid-19 vaccines. *Vaccine*. 2021;39:3666-3677

7.   Wu M-H, Wu E-T, Wang C-C, Lu F, Chen H-C, Kao F-Y, et al. Contemporary postnatal incidence of acquiring acute myocarditis by age 15 years and the outcomes from a nationwide birth cohort. *Pediatric Critical Care Medicine*. 2017;18:1153-1158

8.   Engler RJ, Nelson MR, Collins LC, Jr., Spooner C, Hemann BA, Gibbs BT et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PloS one*. 2015;10:e0118283

9.   Huh K, Kim Y-E, Radnaabaatar M, Lee DH, Kim DW, Shin S-A, et al. Estimating baseline incidence of conditions potentially associated with vaccine adverse events: A call for surveillance

system using the korean national health insurance claims data. *J Korean Med Sci*. 2021;36

10. Huh K, Na Y, Kim Y-E, Radnaabaatar M, Peck KR, Jung J. Predicted and observed incidence of thromboembolic events among koreans vaccinated with chadox1 ncov-19 vaccine. *J Korean Med Sci*. 2021;36

Figure legends

Figure 1. Baseline and predicted incidence of myocarditis and pericarditis (A) Acute myocarditis, (B) Infectious Myocarditis, (C) Myocarditis/pericarditis case definition by Brighton collaboration, (D) Acute pericarditis, (E) Rheumatic myocarditis, (F) Rheumatic pericarditis

Table 1. Monthly and annual predictive incidence of myocarditis and pericarditis

Condition		Mean predicted monthly incidences per 100,000 (95% CI)	Predicted annual incidences per 100,000 (95% CI)
Overall			
Acute myocarditis		2.367 (0.000-9.302)	28.407 (0.000-111.622)
Infection origin myocarditis		0.295 (0.241-0.348)	3.535 (2.893-4.176)
Myocarditis/pericarditis case definition by Brighton collaboration		0.634 (0.490-0.779)	7.613 (5.882-9.343)
Acute pericarditis		2.225 (0.000-9.142)	26.697 (0.000-109.703)
Rheumatic myocarditis		0.070 (0.032-0.108)	0.842 (0.388-1.295)
Rheumatic pericarditis		0.001 (0.000-0.003)	0.007 (0.000-0.039)
Age 1-9 yr			
Acute myocarditis	F	11.873 (0.000-47.985)	142.477 (0.000-575.819)
	M	11.779 (0.000-48.671)	141.347 (0.000-584.051)
Infection origin myocarditis	F	0.042 (0.000-0.131)	0.508 (0.000-1.572)
	M	0.046 (0.000-0.130)	0.555 (0.000-1.560)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.239 (0.000-0.516)	2.866 (0.000-6.192)
	M	0.222 (0.000-0.541)	2.664 (0.000-6.494)
Acute pericarditis	F	11.662 (0.000-47.732)	139.946 (0.000-572.785)
	M	11.562 (0.000-48.430)	138.739 (0.000-581.160)
Rheumatic myocarditis	F	0.002 (0.000-0.019)	0.023 (0.000-0.231)
	M	0.002 (0.000-0.021)	0.028 (0.000-0.255)
Rheumatic pericarditis	F	0.000 (0.000-0.012)	0.000 (0.000-0.139)
	M	0.000 (0.000-0.006)	0.000 (0.000-0.074)
Age 10-19 yr			
Acute myocarditis	F	4.802 (0.992-15.984)	57.621 (11.908-191.804)
	M	5.020 (0.722-16.919)	60.245 (8.660-203.033)
Infection origin myocarditis	F	0.101 (0.004-0.199)	1.217 (0.047-2.387)
	M	0.196 (0.000-0.397)	2.356 (0.001-4.763)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.283 (0.092-0.475)	3.397 (1.100-5.694)
	M	0.463 (0.161-0.765)	5.553 (1.928-9.177)

Acute pericarditis	F	4.704 (0.983-15.841)	56.446 (11.798-190.092)
	M	4.755 (0.681-16.612)	57.057 (8.175-199.338)
Rheumatic myocarditis	F	0.006 (0.000-0.035)	0.078 (0.000-0.422)
	M	0.005 (0.000-0.036)	0.066 (0.000-0.435)
Rheumatic pericarditis	F	0.000 (0.000-0.010)	0.000 (0.000-0.117)
	M	0.000 (0.000-0.004)	0.000 (0.000-0.052)
Age 20-29 yr			
Acute myocarditis	F	1.906 (0.035-6.928)	22.873 (0.425-83.135)
	M	0.840 (0.000-3.981)	10.078 (0.000-47.775)
Infection origin myocarditis	F	0.097 (0.000-0.201)	1.163 (0.000-2.408)
	M	0.262 (0.095-0.429)	3.143 (1.140-5.146)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.280 (0.088-0.472)	3.361 (1.060-5.661)
	M	0.504 (0.253-0.755)	6.050 (3.041-9.060)
Acute pericarditis	F	1.788 (0.033-6.793)	21.454 (0.395-81.518)
	M	0.700 (0.000-3.781)	8.401 (0.000-45.370)
Rheumatic myocarditis	F	0.011 (0.000-0.058)	0.131 (0.000-0.696)
	M	0.006 (0.000-0.043)	0.073 (0.000-0.521)
Rheumatic pericarditis	F	0.002 (0.000-0.016)	0.018 (0.000-0.189)
	M	0.000 (0.000-0.008)	0.000 (0.000-0.093)
Age 30-39 yr			
Acute myocarditis	F	1.855 (0.123-6.408)	22.264 (1.47-76.902)
	M	1.021 (0.000-4.109)	12.257 (0.000-49.313)
Infection origin myocarditis	F	0.090 (0.000-0.190)	1.074 (0.000-2.284)
	M	0.217 (0.066-0.368)	2.605 (0.788-4.422)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.229 (0.067-0.391)	2.748 (0.803-4.693)
	M	0.483 (0.235-0.731)	5.795 (2.819-8.772)
Acute pericarditis	F	1.781 (0.117-6.317)	21.369 (1.407-75.806)
	M	0.923 (0.000-3.992)	11.076 (0.000-47.91)
Rheumatic myocarditis	F	0.016 (0.000-0.069)	0.186 (0.000-0.823)
	M	0.015 (0.000-0.055)	0.181 (0.000-0.662)
Rheumatic pericarditis	F	0.001 (0.000-0.009)	0.009 (0.000-0.111)
	M	0.001 (0.000-0.009)	0.008 (0.000-0.103)
Age 40-49 yr			

Acute myocarditis	F	0.778 (0.000-4.031)	9.341 (0.000-48.370)
	M	0.758 (0.000-3.236)	9.091 (0.000-38.834)
Infection origin myocarditis	F	0.129 (0.015-0.243)	1.549 (0.183-2.915)
	M	0.231 (0.056-0.406)	2.770 (0.669-4.871)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.392 (0.195-0.589)	4.703 (2.339-7.067)
	M	0.434 (0.145-0.722)	5.203 (1.741-8.666)
Acute pericarditis	F	0.703 (0.000-3.929)	8.439 (0.000-47.144)
	M	0.603 (0.000-3.110)	7.236 (0.000-37.319)
Rheumatic myocarditis	F	0.037 (0.000-0.115)	0.443 (0.000-1.376)
	M	0.021 (0.000-0.066)	0.252 (0.000-0.793)
Rheumatic pericarditis	F	0.001 (0.000-0.011)	0.013 (0.000-0.130)
	M	0.000 (0.000-0.005)	0.000 (0.000-0.065)
Age 50-59 yr			
Acute myocarditis	F	0.880 (0.000-5.633)	10.554 (0-67.592)
	M	0.572 (0.000-3.107)	6.862 (0-37.282)
Infection origin myocarditis	F	0.180 (0.044-0.315)	2.156 (0.527-3.784)
	M	0.304 (0.112-0.496)	3.645 (1.339-5.951)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.576 (0.309-0.843)	6.914 (3.713-10.115)
	M	0.781 (0.438-1.123)	9.368 (5.258-13.479)
Acute pericarditis	F	0.783 (0.000-5.524)	9.393 (0.000-66.287)
	M	0.472 (0.000-3.004)	5.662 (0.000-36.043)
Rheumatic myocarditis	F	0.084 (0.000-0.235)	1.005 (0.000-2.815)
	M	0.040 (0.000-0.107)	0.476 (0.000-1.287)
Rheumatic pericarditis	F	0.001 (0.000-0.012)	0.011 (0.000-0.138)
	M	0.001 (0.000-0.01)	0.009 (0.000-0.119)
Age 60-69 yr			
Acute myocarditis	F	0.979 (0.000-6.518)	11.754 (0.000-78.214)
	M	0.706 (0.000-4.051)	8.473 (0.000-48.609)
Infection origin myocarditis	F	0.256 (0.003-0.527)	3.077 (0.030-6.323)
	M	0.505 (0.197-0.812)	6.057 (2.364-9.749)
Myocarditis/pericarditis case definition by Brighton collaboration	F	0.880 (0.434-1.325)	10.555 (5.208-15.903)
	M	1.181 (0.679-1.684)	14.177 (8.148-20.205)

Acute pericarditis	F	0.999 (0.000-6.361)	11.988 (0.000-76.336)
	M	0.683 (0.000-3.927)	8.191 (0.000-47.125)
Rheumatic myocarditis	F	0.260 (0.020-0.508)	3.117 (0.234-6.100)
	M	0.114 (0.000-0.273)	1.373 (0.000-3.275)
Rheumatic pericarditis	F	0.001 (0.000-0.012)	0.009 (0.000-0.145)
	M	0.000 (0.000-0.009)	0.004 (0.000-0.107)
Age 70+ yr			
Acute myocarditis	F	1.646 (0.000-9.955)	19.749 (0.000-119.464)
	M	1.624 (0.000-8.997)	19.493 (0.000-107.966)
Infection origin myocarditis	F	0.924 (0.533-1.315)	11.090 (6.394-15.785)
	M	1.166 (0.477-1.856)	13.995 (5.722-22.267)
Myocarditis/pericarditis case definition by Brighton collaboration	F	2.248 (1.364-3.132)	26.976 (16.364-37.589)
	M	1.899 (0.849-2.948)	22.782 (10.186-35.378)
Acute pericarditis	F	2.082 (0.064-10.647)	24.982 (0.774-127.766)
	M	2.312 (0.000-10.392)	27.747 (0.000-124.701)
Rheumatic myocarditis	F	0.445 (0.116-0.810)	5.340 (1.388-9.720)
	M	0.212 (0.003-0.460)	2.549 (0.030-5.519)
Rheumatic pericarditis	F	0.004 (0.000-0.028)	0.043 (0.000-0.337)
	M	0.000 (0.000-0.039)	0.000 (0.000-0.473)

CI: confidence interval ; F: Female; M: Male; yr: years

Baseline and predictive incidence of Myocarditis and Pericarditis for safety monitoring of Koreans vaccinated with mRNA COVID-19 vaccines

ONLINE SUPPLEMENTS

Supplementary Table 1. ICD-10 codes used to primary diagnoses codes for myocarditis and pericarditis

Supplementary Table 2. The parameters and mean root mean squared error of the autoregressive integrated moving average modeling

Supplementary Figure 1. Subgroup baseline and predicted incidence of myocarditis and pericarditis of age group of 10-19 years by sex (A) Acute myocarditis, (B) Infectious Myocarditis, (C) Myocarditis/pericarditis case definition by Brighton collaboration, (D) Acute pericarditis, (E) Rheumatic myocarditis, (F) Rheumatic pericarditis

Supplement Figure 2. Subgroup baseline and predicted incidence of myocarditis and pericarditis of age group of 20-29 years by sex (A) Acute myocarditis, (B) Infectious Myocarditis, (C) Myocarditis/pericarditis case definition by Brighton collaboration, (D) Acute pericarditis, (E) Rheumatic myocarditis, (F) Rheumatic pericarditis

Supplementary Table 1. ICD-10 codes used to primary diagnoses codes for myocarditis and pericarditis

Condition	ICD-10 codes
Acute myocarditis	I40, I40.0, I40.1, I40.8, I40.9, I41, I41.0, I41.1, I41.2, I41.8, I51.4, A36.8, A52.0, B26.8
Infection origin myocarditis	A36.8, A39.5, A52.0, B26.8, I40.0, I41.0, I41.1, I41.2, B33.2, J10.8, J11.8
Myocarditis/pericarditis case definition by Brighton collaboration	I51.4, I30, I30.0, I30.1, I30.8, I30.9, I31.9, I32.8, I40, I40.0, I40.1, I40.8, I40.9, I41.8
Acute pericarditis	I30, I30.0, I30.1, I30.8, I30.9, I31.9, I32, I32.0,I32.1, I32.8, I01.0
Rheumatic myocarditis	I09.0, M05.3, I01.2
Rheumatic pericarditis	I01.0

ICD-10 = International Classification of Diseases and Related Health Problems, 10th ed.

Supplementary Table 2. The parameters and mean root mean squared error of the
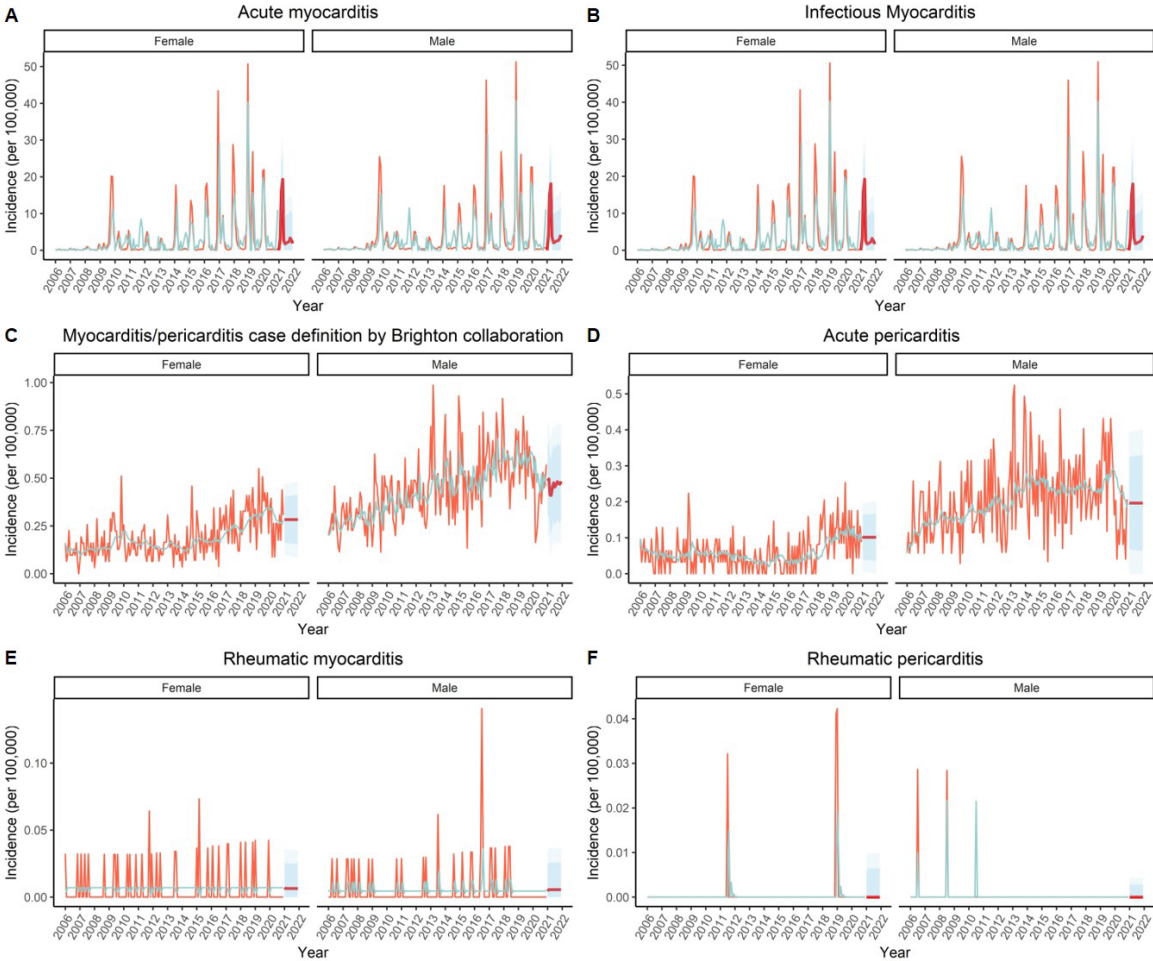
autoregressive integrated moving average modeling

Condition		Model parameters	Root mean
		(p, d, q)(P, D, Q)[S]	squared error
Overall			
Acute myocarditis		(0,1,2)(0,0,2)[12]	2.962
Infection origin myocarditis		(1,0,0)(0,1,2)[12]	0.026
Myocarditis/pericarditis case definition by Brighton collaboration		(1,0,1)(0,1,2)[12]	0.056
Acute pericarditis		(0,1,2)(0,0,2)[12]	2.957
Rheumatic myocarditis		(1,0,1)(2,1,0)[12]	0.018
Rheumatic pericarditis		(1,1,2)	0.001
Age 1-9 yr			
Acute myocarditis	F	(0,1,3)(0,0,2)[12]	13.659
	M	(0,0,2)(0,0,2)[12]	14.012
Infection origin myocarditis	F	(0,0,0)(2,0,0)[12]	0.045
	M	(0,0,0)(1,0,0)[12]	0.043
Myocarditis/pericarditis case definition by Brighton collaboration	F	(0,1,1)	0.135
	M	(0,1,1)	0.151
Acute pericarditis	F	(0,1,3)(0,0,2)[12]	13.664
	M	(0,0,2)(0,0,2)[12]	14
Rheumatic myocarditis	F	(0,0,1)(1,0,0)[12]	0.009
	M	(3,0,0)(1,0,0)[12]	0.009
Rheumatic pericarditis	F	(0,0,0)	0.006
	M	(0,0,0)	0.003
Age 10-19 yr			
Acute myocarditis	F	(0,1,4)(0,0,2)[12]	4.847
	M	(0,1,4)(0,0,2)[12]	5.053
Infection origin myocarditis	F	(1,1,1)	0.048
	M	(1,1,1)	0.099
Myocarditis/pericarditis case definition by Brighton collaboration	F	(0,1,1)	0.093
	M	(1,1,1)(0,0,2)[12]	0.145
Acute pericarditis	F	(0,1,4)(0,0,2)[12]	4.833
	M	(0,1,4)(0,0,2)[12]	5.058
Rheumatic myocarditis	F	(1,0,0)	0.015
	M	(0,0,1)	0.015
Rheumatic pericarditis	F	(0,0,1)	0.005
	M	(0,0,0)(2,0,0)[12]	0.002
Age 20-29 yr			
Acute myocarditis	F	(0,1,2)(0,0,2)[12]	2.219
	M	(1,0,1)(0,0,2)[12]	1.261

Infection origin myocarditis	F	(0,1,2)(1,0,0)[12]	0.051
	M	(0,1,1)(0,0,1)[12]	0.084
Myocarditis/pericarditis case definition by Brighton collaboration	F	(1,1,1)	0.094
	M	(0,1,1)(1,0,2)[12]	0.122
Acute pericarditis	F	(0,1,2)(0,0,2)[12]	2.209
	M	(1,0,1)(0,0,2)[12]	1.248
Rheumatic myocarditis	F	(0,1,1)(0,0,1)[12]	0.024
	M	(0,1,4)(0,0,1)[12]	0.017
Rheumatic pericarditis	F	(0,0,0)(2,0,0)[12]	0.007
	M	(1,0,1)(1,0,0)[12]	0.004
Age 30-39 yr			
Acute myocarditis	F	(0,1,3)(0,0,2)[12]	1.867
	M	(0,1,3)(0,0,2)[12]	1.279
Infection origin myocarditis	F	(1,0,1)	0.05
	M	(0,0,1)	0.076
Myocarditis/pericarditis defined by Brighton collaboration	F	(0,1,3)(1,0,2)[12]	0.078
	M	(2,1,1)(0,0,1)[12]	0.111
Acute pericarditis	F	(0,1,3)(0,0,2)[12]	1.866
	M	(0,1,3)(0,0,2)[12]	1.277
Rheumatic myocarditis	F	(0,1,1)(0,0,1)[12]	0.027
	M	(1,0,2)(2,0,0)[12]	0.02
Rheumatic pericarditis	F	(1,0,1)(1,0,0)[12]	0.004
	M	(0,0,0)	0.004
Age 40-49 yr			
Acute myocarditis	F	(0,1,2)(0,0,2)[12]	1.478
	M	(0,1,2)(0,0,2)[12]	1.13
Infection origin myocarditis	F	(1,1,2)	0.057
	M	(0,0,0)(1,0,0)[12]	0.089
Myocarditis/pericarditis case definition by Brighton collaboration	F	(0,1,1)	0.098
	M	(0,1,1)(0,0,1)[12]	0.133
Acute pericarditis	F	(0,1,2)(0,0,2)[12]	1.473
	M	(0,1,3)(0,0,2)[12]	1.111
Rheumatic myocarditis	F	(1,1,2)(2,0,0)[12]	0.039
	M	(0,0,0)	0.023
Rheumatic pericarditis	F	(0,0,0)(1,0,0)[12]	0.005
	M	(0,0,0)(2,0,2)[12]	0.003
Age 50-59 yr			
Acute myocarditis	F	(0,1,2)(0,0,2)[12]	2.106
	M	(0,1,2)(0,0,2)[12]	1.13
Infection origin myocarditis	F	(0,0,0)	0.069
	M	(0,0,0)	0.098
Myocarditis/pericarditis case definition by Brighton collaboration	F	(0,1,1)(1,0,0)[12]	0.132
	M	(0,1,1)	0.164

Acute pericarditis	F	(0,1,2)(0,0,2)[12]	2.105
	M	(0,1,2)(0,0,2)[12]	1.124
Rheumatic myocarditis	F	(0,1,3)(0,0,1)[12]	0.071
	M	(0,0,0)(1,0,1)[12]	0.034
Rheumatic pericarditis	F	(0,0,0)	0.005
	M	(0,0,3)	0.004
Age 60-69 yr			
Acute myocarditis	F	(0,1,3)(0,0,2)[12]	2.396
	M	(0,0,2)(0,0,2)[12]	1.464
Infection origin myocarditis	F	(1,1,2)(1,0,0)[12]	0.135
	M	(0,0,0)(2,0,0)[12]	0.156
Myocarditis/pericarditis case definition by Brighton collaboration	F	(0,0,1)(1,0,0)[12]	0.223
	M	(0,1,1)	0.253
Acute pericarditis	F	(0,1,2)(0,0,2)[12]	2.415
	M	(0,1,2)(0,0,2)[12]	1.467
Rheumatic myocarditis	F	(1,0,0)(1,0,0)[12]	0.126
	M	(0,0,0)	0.081
Rheumatic pericarditis	F	(0,0,0)	0.006
	M	(2,0,0)(2,0,1)[12]	0.004
Age 70+ yr			
Acute myocarditis	F	(0,1,2)(0,0,2)[12]	3.694
	M	(0,1,2)(0,0,2)[12]	3.265
Infection origin myocarditis	F	(0,0,1)(2,1,1)[12]	0.19
	M	(2,1,1)(1,0,0)[12]	0.344
Myocarditis/pericarditis case definition by Brighton collaboration	F	(1,0,1)(2,1,1)[12]	0.401
	M	(1,1,1)(0,0,2)[12]	0.514
Acute pericarditis	F	(2,1,1)(1,0,0)[12]	3.715
	M	(2,1,1)(0,0,1)[12]	3.44
Rheumatic myocarditis	F	(1,0,1)(0,1,1)[12]	0.176
	M	(0,0,0)(2,0,0)[12]	0.125
Rheumatic pericarditis	F	(0,0,0)(2,0,0)[12]	0.012
	M	(0,1,3)(2,0,0)[12]	0.019

CI: confidence interval ; F: Female; M: Male; yr: years

Supplementary Figure 1. Subgroup baseline and predicted incidence of myocarditis and pericarditis of age group of 10-19 years by sex (A) Acute myocarditis, (B) Infectious Myocarditis, (C) Myocarditis/pericarditis case definition by Brighton collaboration, (D) Acute pericarditis, (E) Rheumatic myocarditis, (F) Rheumatic pericarditis

Supplement Figure 2. Subgroup baseline and predicted incidence of myocarditis and pericarditis of age group of 20-29 years by sex (A) Acute myocarditis, (B) Infectious Myocarditis, (C) Myocarditis/pericarditis case definition by Brighton collaboration, (D) Acute pericarditis, (E) Rheumatic myocarditis, (F) Rheumatic pericarditis