openheart

Epidemiology of myocarditis following COVID-19 or influenza and use of diagnostic assessments

Oisin Butler ,[1] Zahra Raisi-Estabragh ,[2,3] Yuchi Han,[4] Ann Kathrin Frenz,[5] Cornelia Harz,[1] Sebastian Kelle,[6,7] Jeanette Schulz-Menger,[8,9] Alexander Michel,[10] Jiwon Kim[11]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2024-002947).

To cite: Butler O, Raisi-Estabragh Z, Han Y, *et al*. Epidemiology of myocarditis following COVID-19 or influenza and use of diagnostic assessments. *Open Heart* 2024;**11**:e002947. doi:10.1136/openhrt-2024-002947

Received 20 September 2024
Accepted 27 September 2024

For numbered affiliations see end of article.

Correspondence to
Dr Oisin Butler; oisin.butler@bayer.com

ABSTRACT

Background Previous research has suggested a heightened risk of acute myocarditis after COVID-19 infection. However, it is not clear from existing work whether this risk is higher than would be expected after comparable viral respiratory infections. This information is important to guide risk assessments and clinical practice.

Methods A retrospective cohort study of US administrative health claims was conducted to compare the rates of myocarditis after COVID-19 with that after influenza infection and describe the clinical use of diagnostic assessments.

Patients with either incident COVID-19 diagnosis (between 1 January 2020 and 31 December 2021) or incident influenza diagnosis (between 1 January 2016 and 31 December 2018), with at least 12 months of continuous enrolment prior to index date and without a previous diagnosis of myocarditis were included.

The primary outcome was clinically diagnosed acute myocarditis recorded after COVID-19 or influenza infection. Results are reported as covariate-adjusted subdistribution HRs from competing risk regression with COVID-19 considered as the exposure of interest and influenza as the reference group. Death was considered a competing risk.

Results 1 120 760 adult COVID-19 patients and 439 278 adult influenza patients were identified, of which 669 (0.06%) adult COVID-19 patients and 91 (0.02%) adult influenza patients received a diagnosis of myocarditis. The myocarditis rate per 1000 person-years was 0.73 (95% CI 0.67 to 0.78) for adult COVID-19 patients and 0.24 (95% CI 0.19 to 0.28) for adult influenza populations. In models comprehensively adjusted for demographic and clinical risk factors, COVID-19 diagnosis (compared with influenza diagnosis), cardiac comorbidities, being male and under the age of 30 were independently associated with an increased risk of myocarditis in the year after diagnosis.

Conclusions These findings support a distinct link between COVID-19 and myocarditis, which appears greater than after a similar viral respiratory infection. As such, a greater degree of clinical suspicion and investigation according to existing diagnostic pathways is recommended.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Existing literature, including large-scale analysis of real-world data, has demonstrated a substantially increased risk of myocarditis following COVID-19. However, no study has assessed if the risk of myocarditis linked to COVID-19 is greater than after exposure to other common viral respiratory infections and if demographic factors differ between patients with myocarditis following COVID-19 compared with other viral infections.

WHAT THIS STUDY ADDS

⇒ In this large retrospective cohort study of 1 560 038 adults and 293 438 paediatric patients, COVID-19 was shown to be associated with increased rates of myocarditis compared with influenza.

⇒ Being male and under the age of 30 was also independently associated with an increased risk of myocarditis in the year after diagnosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study results can be used to inform clinicians and healthcare professionals seeking to identify which clinical and demographic factors may lead to an increased risk of myocarditis, and therefore, which patients should be monitored more closely.

INTRODUCTION

Myocarditis is an inflammatory process of the myocardium, and the most common cause is a viral infection such as influenza or coronaviruses.[1] While most cases of viral myocarditis are mild with good prognosis, life-threatening cardiac dysfunction and arrhythmias may occur.[2 3] Myocarditis can result in heart failure and sudden cardiac death and has been recognised as a rare complication of acute SARS-CoV-2 infection, the strain of coronavirus that causes COVID-19.[3 4] A large international study reported acute myocarditis in 2.4–4.1 out of 1000 patients hospitalised with COVID-19 and demonstrated greater haemodynamic instability in these

patients.[5] Myocardial injury with diffuse oedema has been identified even in COVID-19 patients with mild or asymptomatic infection.[6 7] The clinical significance of these findings is unclear. While existing literature suggests association of COVID-19 exposure with an increased risk of myocarditis,[8] it is not known whether the increased risk of myocarditis linked to COVID-19 is greater than that expected after exposure to other common viral respiratory infections and if demographic factors differ between patients with myocarditis following COVID-19 compared with other viral infections.

Accurate diagnosis of COVID-19-related myocarditis is essential for tailoring treatment strategies and mitigating the associated morbidity and mortality. Cardiovascular MR (CMR) is the primary diagnostic tool for non-invasive assessment of myocardial inflammation in patients with known or suspected cardiomyopathy and myocarditis[9] including inflammatory cardiomyopathy due to COVID-19,[10] where contrast enhancement protocols (ie, late gadolinium enhancement) are essential in the diagnosis, risk stratification and prognosis. The Society for Cardiovascular Magnetic Resonance, the European Society of Cardiology and the American College of Cardiology collectively affirm that CMR is a potentially valuable diagnostic tool in patients with COVID-19 presenting with myocardial injury and evidence of cardiac dysfunction.[11–13] However, no contrast agent is approved in the USA for use in the assessment of inflammatory cardiomyopathy in patients with active or convalescent COVID-19.

The objective of the study was to assess the rates of incident myocarditis in patients diagnosed with COVID-19 against patients diagnosed with influenza, while accounting for potential confounders, and to describe the diagnostic assessments surrounding myocarditis events including CMR and contrast agents, among a very large cohort of patients drawn from a US administrative claims database.

METHODS

Study design and data source

This was a retrospective comparative cohort study using secondary healthcare data from Optum's deidentified Clinformatics Data Mart Database (CDM). CDM is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. CDM is statistically deidentified under the Expert Determination method consistent with the Health Insurance Portability and Accountability Act and managed according to Optum customer data use agreements. The population is geographically diverse, spanning all 50 states. At the time of analysis, data were available until 31 March 2023.

Study population

For the COVID-19 cohort (exposure group), patients were included if they had an incident COVID-19 diagnosis (ie, index date) between 1 January 2020 and 31 December 2021. For the influenza cohort (referent group), patients were included if they had an incident influenza diagnosis (ie, index date) between 1 January 2016 and 31 December 2018. Our cohort includes both inpatient and outpatient populations. Different time periods for exposure and referent groups were selected in order to clearly differentiate between influenza and COVID cases. Due to protection measures, for example, social distancing and mask wearing, implemented during the COVID-19 pandemic, influenza rates significantly decreased.[14] As such, it was felt that a prepandemic period was more appropriate for the influenza cohort.

Patients were excluded if they met any of the following criteria in the 365 days prior to the index date: diagnosis of myocarditis, diagnosis of COVID-19 (exposure group only) or diagnosis of influenza (referent group only), or had missing age or gender at index date. No patients were excluded from the analysis on the basis of racial, socioeconomic or regional factors.

Two nested cohorts were defined using patients from the main comparative cohorts. The eligibility criterion was a diagnosis of myocarditis within the 365 days after index date in the respective group (exposure or referent). The date of first recorded myocarditis diagnosis was the nested cohort index date.

Each nested cohort described was composed of two subpopulations, adults (patients aged 18 years old and above at index date and paediatrics (patients aged <18 years old at index date).

COVID-19, influenza and myocarditis diagnoses, along with relevant comorbidities, were identified in the claims using relevant International Classification of Diseases (ICD)-10 and ICD-9 codes (online supplemental eTable 1).

Patients in the main comparative cohorts were followed for a maximum of 1 year, disenrolment or death, whichever occurs first. Patients in the nested cohorts were followed until the end of the assessment period, occurrence of outcome, end of data, disenrolment or death, whichever occurs first. No minimum follow-up was required for any cohort.

The study involved no personally identifiable information and the data used in this study were deidentified and anonymised before use. Our study practices were performed in accordance with the Declaration of Helsinki guidelines and followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline. There was no patient or public involvement in this study.

Outcomes

The endpoint for the primary objective was the first recorded occurrence of myocarditis following either COVID-19 or influenza. These conditions were defined based on a recorded diagnosis in inpatient and outpatient records documented according to ICD code (online supplemental eTable 1). Incident myocarditis

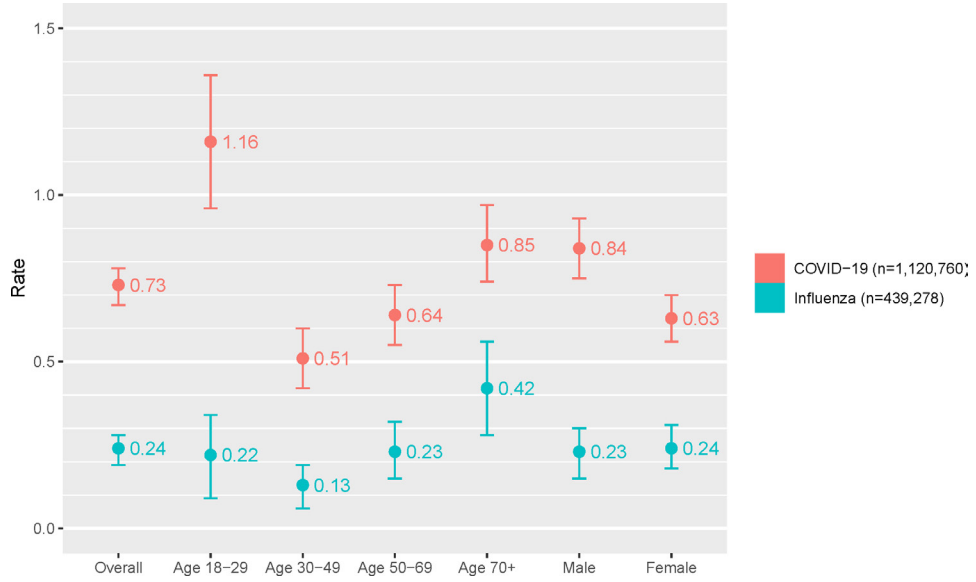

Figure 1 Rates of myocarditis per 1000 person-years.

was considered as a record of myocarditis within 365 days after the index date.

A 12-month follow-up period was employed based on established precedents in the literature, particularly from two large-scale US healthcare database studies on the long-term cardiovascular outcomes of COVID-19,[8 15] both of which employed a 12-month follow-up. While we note that a shorter follow-up period may capture a more direct temporal relationship between COVID-19 and myocarditis but would also limit our ability to detect late-onset cases, potentially underestimating the true burden of myocarditis related to COVID-19.

The endpoints for the secondary objectives were the occurrence of the following diagnostic assessments: ECG, echocardiography, blood tests (brain natriuretic peptide, C reactive protein, troponin, sedimentation rate, erythrocyte, myocardial antibody screen), fluorodeoxyglucose-positron emission tomography, invasive coronary angiography, endomyocardial biopsy and CMR (contrast-enhanced and non-contrast enhanced) (online supplemental eTable 2).

Covariates

The following baseline characteristics of patients for all cohorts were assessed at index date or over the 365 days prior to the index date: age, sex, race (white, black, Asian, Hispanic) hypertension, hyperlipidaemia, tobacco use, obesity, history of coronary artery disease (CAD), myocardial infarction (MI), diabetes, (online supplemental eTable 3), Charlson Comorbidity Index (CCI) score (online supplemental eTable 4). Relevant ICD codes were used to define these measures. A full list of relevant codes for the patient characteristics and comorbidities is included in online supplemental file.

Statistical analysis

Rates of myocarditis are reported per 1000 person-years using a Poisson model (figure 1).

Competing risk regression models were used to calculate the association of COVID-19 (exposure group) with incident myocarditis, relative to the influenza population (reference group). The event of death was considered a competing risk. In step 1 of the model-building procedure, the outcome was adjusted for age group and gender (figure 2). In step 2, an extended number of variables was accounted for by including all 11 baseline covariates into the model (figure 2). In step 3, additional sensitivity analyses were conducted, controlling for influenza vaccination status, influenza infection in the COVID-19 group and COVID-19 vaccination status in the COVID-19 group separately (online supplemental eFigures 1–4). Results are reported as subdistribution HRs (SHRs) with 95% CIs and p values.

The secondary endpoint (diagnostic assessments) was described for the nested cohorts by crude and relative numbers of patients in each of the diagnostic assessment categories and is reported as stratified by population. Only the first assessment in each category is considered for this analysis (table 3). The contrast media used was reported for all recorded CMR procedures (online supplemental eFigure 5).

Both endpoints were analysed for the adult subpopulation. Due to the low number of paediatric myocarditis cases, only the crude myocarditis rates were analysed for the paediatric subpopulation.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

76 631 192 patients were available for analysis in the CDM database, of which 1 120 760 adult COVID-19 patients and 439 278 adult influenza patients, and 98 425 paediatric

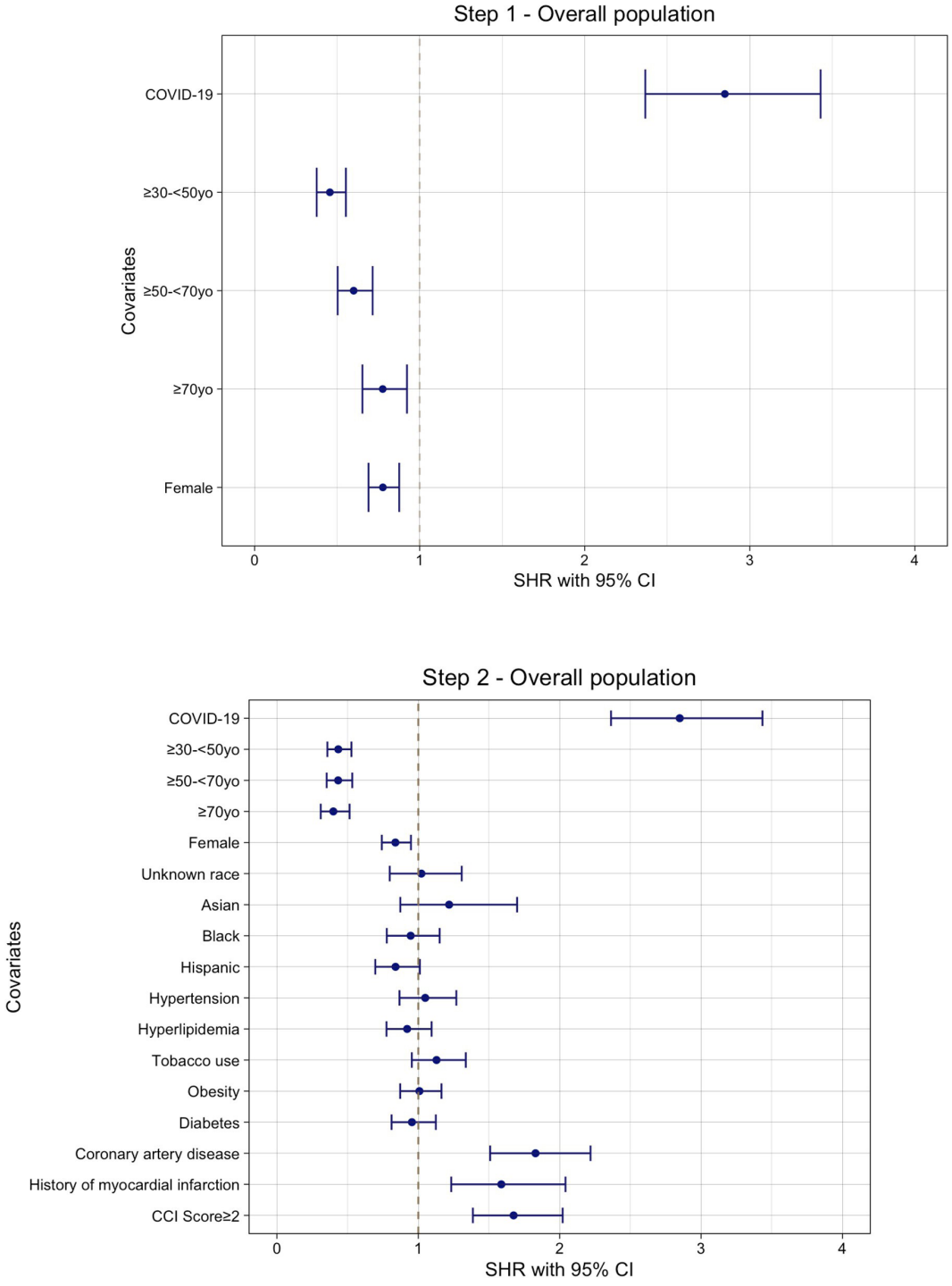

Figure 2 Step 1: Subdistribution hazard model limited to exposure, sex and age. Step 2:. Subdistribution hazard models with all covariates. CCI, Charlson Comorbidity Index; SHR, subdistribution HR.

COVID-19 patients and 194923 paediatric influenza patients were identified with 12-month baseline enrolment and at least 1 day of follow-up.

Demographic characteristics were comparable across the COVID-19 and influenza groups, with similar distributions of age, gender and race (table 1).

The median follow-up time for all patients was 365 days.

Regarding cardiovascular risk factors, the adult COVID-19 population had higher rates of hypertension (46% vs 40%), hyperlipidaemia (39% vs 34%), obesity (26% vs 20%), CAD (14% vs 11%), diabetes (22% vs 17%) and a higher number of patients with a CCI score of 2 or higher (30% vs 24%) as compared with the influenza cohort (table 1).

Myocarditis incidence rates

669 (0.06%) adult COVID-19 patients and 91 (0.02%) adult influenza patients received a diagnosis of

Table 1 Demographic characteristics and comorbidities at index date

Demographic characteristics (at index date)	Adult population		Paediatric population	
	COVID-19 patients	Influenza patients	COVID-19 patients	Influenza patients
	n=1 120 760	n=439 278	n=98 425	n=194 923
Age (years)				
Mean (SD)	54.84 (19.58)	51.32 (18.95)	10.71 (4.77)	8.55 (4.70)
Median (IQR)	56.00 (39.00–71.00)	51.00 (36.00–67.00)	11.00 (7.00–15.00)	8.00 (5.00–12.00)
Age (categorical); n (%)				
<18	0 (0.0)	0 (0.0)	98 425 (100.0)	194 923 (100.0)
≥18 to <30	144 184 (12.9)	65 120 (14.8)	0 (0.0)	0 (0.0)
≥30 to <50	308 309 (27.5)	146 291 (33.3)	0 (0.0)	0 (0.0)
≥50 to <70	353 544 (31.5)	135 538 (30.9)	0 (0.0)	0 (0.0)
≥70	314 723 (28.1)	92 329 (21.0)	0 (0.0)	0 (0.0)
Sex; n (%)				
Male	520 104 (46.4)	190 349 (43.3)	49 466 (50.3)	101 279 (52.0)
Female	600 656 (53.6)	248 929 (56.7)	48 959 (49.7)	93 644 (48.0)
Race; n (%)				
White	721 317 (64.4)	301 719 (68.7)	47 093 (47.8)	132 042 (67.7)
Asian	31 919 (2.8)	18 646 (4.2)	2933 (3.0)	12 483 (6.4)
Black	124 133 (11.1)	46 966 (10.7)	5075 (5.2)	14 112 (7.2)
Hispanic	169 839 (15.2)	59 728 (13.6)	9548 (9.7)	28 369 (14.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	73 552 (6.6)	12 219 (2.8)	33 776 (34.3)	7917 (4.1)
Comorbidities (during the baseline period)				
Hypertension, n (%)	515 081 (46.0)	174 505 (39.7)	323 (0.3)	489 (0.3)
Hyperlipidaemia, n (%)	433 490 (38.7)	147 267 (33.5)	747 (0.8)	859 (0.4)
Tobacco use, n (%)	154 998 (13.8)	55 267 (12.6)	112 (0.1)	127 (0.1)
Obesity, n (%)	289 060 (25.8)	87 214 (19.9)	3510 (3.6)	4202 (2.2)
History of coronary artery disease, n (%)	151 246 (13.5)	48 173 (11.0)	31 (0.0)	46 (0.0)
History of myocardial infarction, n (%)	31 410 (2.8)	10 661 (2.4)	<5 (0.0)	<5* (0.0)
Diabetes (types 1 and 2), n (%)	245 185 (21.9)	76 124 (17.3)	447 (0.5)	676 (0.3)
Charlson Comorbidity Index (last recorded value during baseline period)				
Mean (SD)	1.31 (2.07)	1.06 (1.86)	0.09 (0.33)	0.13 (0.37)
Median (IQR)	0.00 (0.00–2.00)	0.00 (0.00–1.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
<2; n (%)	790 643 (70.5)	335 632 (76.4)	97 891 (99.5)	193 943 (99.5)
≥2; n (%)	330 117 (29.5)	103 646 (23.6)	534 (0.5)	980 (0.5)
Vaccination during baseline				
Any vaccine	303 315 (27.1%)	66 936 (15.2%)	26 611 (27.0%)	27 931 (14.3%)
Influenza vaccine	276 485 (24.7%)	66 936 (15.2%)	25 039 (25.4%)	27 931 (14.3%)
COVID-19 vaccine	36 673 (3.3%)	N/A	2298 (2.3%)	N/A

*Categories with small sample counts (n<5) were masked to ensure no reidentification of patients.
N/A, not available.

myocarditis in the follow-up period while 44 (0.04%) paediatric COVID-19 patients and 11 (0.01%) paediatric influenza patients received a diagnosis of myocarditis in the follow-up period (table 2).

In the adult population, the myocarditis rate per 1000 person-years was 0.73 (95% CI 0.67 to 0.78) for COVID-19 patients and 0.24 (95% CI 0.19 to 0.28) for influenza populations. By age group, the myocarditis rate per 1000 person-years for COVID-19 patients was

Table 2 Myocarditis diagnosis rates overall and by age and gender

	Adult population		Paediatric population	
	COVID-19 patients	Influenza patients	COVID-19 patients	Influenza patients
	n=1 120 760	n=439 278	n=98 425	n=194 923
Follow-up descriptive				
Mean (SD), days	299.77 (117.97)	321.67 (94.63)	309.86 (107.39)	320.85 (94.14)
Median (IQR); days	365.00 (290.00–365.00)	365.00 (361.00–365.00)	365.00 (340.00–365.00)	365.00 (343.00–365.00)
Time-to-Myocarditis event (days)*				
Mean (SD), days	78.81 (99.56)	88.89 (113.82)	65.80 (90.46)	174.50 (149.41)
Median (IQR); days	30.00 (6.00–118.00)	20.00 (5.00–154.00)	27.00 (8.75–95.00)	118.00 (27.00–330.00)
Primary endpoint: myocarditis diagnosis				
Incidence of myocarditis diagnosis; %	0.06	0.02	N/A	N/A
Number of patients with an event	669	91	N/A	N/A
Number of person-years	920 454.03	387 134.60	N/A	N/A
Rate per 1000 person-years (95% CI)	0.73 (0.67, 0.78)	0.24 (0.19, 0.28)	N/A	N/A
Incidence of myocarditis diagnosis (age <18); %	N/A	N/A	0.04	0.01
Number of patients with an event	N/A	N/A	44	11
Number of person-years	N/A	N/A	83 557.36	171 347.15
Rate per 1000 person-years (95% CI)	N/A	N/A	0.53 (0.37, 0.68)	0.06 (0.03, 0.10)
Incidence of myocarditis diagnosis (age ≥18–30); %	0.09	0.02	N/A	N/A
Number of patients with an event	134	12	N/A	N/A
Number of person-years	115 485.17	54 901.14	N/A	N/A
rate per 1000 person-years (95% CI)	1.16 (0.96, 1.36)	0.22 (0.09, 0.34)	N/A	N/A
Incidence of myocarditis diagnosis (age ≥30–50); %	0.04	0.01	N/A	N/A
Number of patients with an event	130	16	N/A	N/A
Number of person-years	254 978.51	126 902.98	N/A	N/A
Rate per 1000 person-years (95% CI)	0.51 (0.42, 0.60)	0.13 (0.06, 0.19)	N/A	N/A
Incidence of myocarditis diagnosis (age ≥50–70); %	0.05	0.02	N/A	N/A
Number of patients with an event	191	28	N/A	N/A
Number of person-years	299 594.85	121 491.15	N/A	N/A
Rate per 1000 person-years (95% CI)	0.64 (0.55, 0.73)	0.23 (0.15, 0.32)	N/A	N/A
Incidence of myocarditis diagnosis (age ≥70); %	0.07	0.04	N/A	N/A
Number of patients with an event	214	35	N/A	N/A
Number of person-years	250 395.50	83 839.34	N/A	N/A
Rate per 1000 person-years (95% CI)	0.85 (0.74, 0.97)	0.42 (0.28, 0.56)	N/A	N/A
Incidence of myocarditis diagnosis (gender=male); %	0.07	0.02	0.05	0.00
Number of patients with an event	357	38	24	5
Number of person-years	425 100.78	167 273.91	42 060.99	89 002.83
Rate per 1000 person-years (95% CI)	0.84 (0.75, 0.93)	0.23 (0.15, 0.30)	0.57 (0.34, 0.80)	0.06 (0.02, 0.13)
Incidence of myocarditis diagnosis (gender=female); %	0.05	0.02	0.04	0.01
Number of patients with an event	312	53	20	6
Number of person-years	495 353.25	219 860.70	41 496.37	82 344.32
Rate per 1000 person-years (95% CI)	0.63 (0.56, 0.70)	0.24 (0.18, 0.31)	0.48 (0.27, 0.69)	0.07 (0.03, 0.16)

*Time-to-myocarditis event is the time in days to the first event among those with an event.
N/A, not available.

highest in the group aged 18–29 years (young adults) at 1.16 and highest for the influenza group in the group aged over 70 years (older adults) at 0.42 (figure 1). In the paediatric population, the myocarditis rate per 1000 person-years was 0.53 (95% CI 0.37, 0.68) for COVID-19 patients and 0.06 (95% CI 0.03, 0.10) for the influenza population.

By gender, the myocarditis rate per 1000 person-years was higher for males with COVID-19 at 0.84 than females with COVID-19 at 0.63, while there was no

difference in rates for males with influenza at 0.23 and females with influenza at 0.24.

Myocarditis rates by index date (year) showed a slight decrease for COVID-19 between 2020 at 0.82 and 2021 at 0.67, while rates following influenza were highest in 2017 at 0.29 compared with 2016 at 0.22 and 2018 at 0.20, presumably driven by different variants.

SHR model

Step 1: In step 1, the SHR model was limited to exposure (COVID-19 and influenza), sex and age group. In the age-adjusted and sex-adjusted model, COVID-19 infection was associated with almost threefold greater risk of myocarditis (SHR 2.85; 95% CI 2.37, 3.43) compared with influenza infection.

Step 2: In step 2, the SHR model was expanded to include race and clinical comorbidities. The additional covariates did not meaningfully change the results.

Step 3: In step 3, additional sensitivity analyses were conducted including stratification by influenza vaccination status, censoring the COVID-19 population in the event of influenza diagnosis, controlling for COVID-19 vaccination status by excluding patients based on prior COVID-19 vaccination during baseline and censoring on COVID-19 vaccination during follow-up (online supplemental eFigures 1–4).

These additional sensitivity analyses did not alter the direction of the results, and COVID-19 infection was consistently the most strongly associated risk factor for the development of myocarditis.

Diagnostic assessments

The majority of all patients who received a myocarditis diagnosis underwent some diagnostic assessments, with 94% of adult COVID-19 patients, 79% of adult influenza patients, 98% of paediatric COVID-19 patients and 90% of paediatric influenza patients having at least one of the procedures recorded in the period around their myocarditis diagnosis (table 3). To note, categories with small sample counts (N<5) were masked to ensure no reidentification of patients.

The most commonly used diagnostic assessments were ECGs and echocardiography. Blood tests were also common, of which troponin was the most frequently used.

Among patients with myocarditis diagnosis, CMR was conducted in approximately 25% of COVID-19 and 22% of influenza patients and in 41% of paediatric COVID-19 patients and 27% of influenza patients and the most commonly used contrast agent was Gadobutrol (Gadavist, online supplemental eFigure 5).

DISCUSSION

This retrospective healthcare claims database analysis including more than 1 million patients with COVID-19 and almost 440 000 with influenza demonstrates a heightened risk of myocarditis in the 12 months after COVID-19 infection compared with after influenza, independent of demographics and baseline clinical profile. The risk appears the highest among young adult men under the age of 30 years. The observed relationships were not altered in sensitivity analyses considering the potential modifying effects of vaccination.

The overall rate of patients developing myocarditis after COVID-19 infection was three times the rate of influenza patients in the adult population and almost nine times of the rate in the paediatric population.

Myocarditis rates differed between viral illnesses based on age distribution: patients aged 18–29 years present the highest rate among COVID-19 patients while those aged over 70 record the highest incidence rate among the influenza patient group. In addition, within the COVID-19 group, there was a bimodal distribution, with higher rates also observed in the over 70 population. Within the influenza the distribution was more unimodal, with more comparable rates in the 18–29, 30–49 and 50–69 groups compared with those aged over 70.

A history of CAD and male gender were risk factors for myocarditis.

Echocardiogram, ECG and troponin were the most commonly performed diagnostic tests among patients with myocarditis while approximately a quarter of patients underwent CMR.

In both the adult and paediatric populations, the distribution of age, gender and race were similar across both COVID-19 and influenza adult populations, although the COVID-19 adult population had higher rates of cardiovascular risk factors and CAD and the COVID-19 paediatric population was slightly older than the influenza paediatric population.

The overall rate comparison between the COVID-19 and the influenza population shows a decreasing trend over the different age groups. The rate is increased by factor 8.8 in the paediatric population, by factor 5.3 in the 18–29 age group, by 3.9 in the 30–50 age group, by factor 2.8 in the 50–70 age group and by factor 2 in the over 70 years group for the COVID-19 population compared with the influenza population. This comparison of rates not only highlights the increased rates of myocarditis in COVID-19 as compared with influenza in every age group but also shows that the risk elevation becomes less prominent with increasing age groups.

In the SHR model, COVID-19 diagnosis (compared with influenza diagnosis), CAD, history of MI or a CCI of 2 or above shows an elevated risk of myocarditis in the year after diagnosis, while older adults (compared with 18–29 age) and females (compared with males) showed a reduced relative risk.

The models were remarkably stable, between step 1 controlling only for age and gender, step 2 controlling for race and clinical covariates, and step 3, sensitivity analyses that included additional variables such as vaccination status and HCRU, indicating that the results are robust.

In all models, the most strongly associated risk factor for myocarditis was COVID-19.

Table 3 Diagnostic assessments

	Adult population		Paediatric population	
	COVID-19 patients	Influenza patients	COVID-19 patients	Influenza patients
Nested cohorts	n=669	n=91	n=44	n=11
Follow-up				
Mean (SD), days	214.15 (92.56)	243.76 (67.31)	242.61 (63.83)	206.64 (110.43)
Median (IQR); days	270.00 (165.00–270.00)	270.00 (270.00–270.00)	270.00 (251.25–270.00)	270.00 (90.00–270.00)
Secondary end point: diagnostic assessment, n (%)				
Any diagnostic test	630 (94.2)	72 (79.1)	43 (97.7)	10 (90.9)
ECGs—total number of assessments	515 (77.0)	47 (51.6)	40 (90.9)	7 (63.6)
Echocardiography—total number of assessments	484 (72.3)	50 (54.9)	38 (86.4)	8 (72.7)
Any blood tests—total number of assessments	388 (58.0)	36 (39.6)	31 (70.5)	6 (54.5)
Brain natriuretic peptide lab test—total number of assessments	191 (28.6)	16 (17.6)	17 (38.6)	<5 (<45)
C-reactive protein lab test—total number of assessments	177 (26.5)	15 (16.5)	21 (47.7)	5 (45.5)
Troponin lab test—total number of assessments	300 (44.8)	31 (34.1)	28 (63.6)	<5 (<45)
Sedimentation rate—total number of assessments	150 (22.4)	19 (20.9)	16 (36.4)	5 (45.5)
Myocardial antibody screen—total number of assessments	17 (2.5)	<5 (<5)	0 (0.0)	<5* (<45)
Fluorodeoxyglucose-positron emission tomography—total number of assessments	10 (1.5)	<5 (<5)	0 (0.0)	0 (0.0)
Invasive coronary angiographies—total number of assessments	102 (15.2)	30 (33.0)	0 (0.0)	0 (0.0)
Endomyocardial biopsies—total number of assessments	7 (1.0)	<5 (<5)	0 (0.0)	0 (0.0)
Cardiac MRI contrast enhanced (CMR-CE)—total number of assessments	162 (24.2)	20 (22.0)	18 (40.9)	<5* (<45)
CMR non-CE—total number of assessments	6 (0.9)	0 (0.0)	<5* (<45)	0 (0.0)
CMR—total number of assessments	165 (24.7)	20 (22.0)	18 (40.9)	<5* (<45)

*Categories with small sample counts (n<5) were masked to ensure no reidentification of patients.

Regarding diagnostic assessments performed among adults having myocarditis in the year following COVID-19 or influenza diagnosis, almost all COVID-19 patients and the majority of influenza patients underwent some diagnostic assessment, with echocardiography and ECGs being the most frequently used assessments and troponin being the most commonly used blood test, while approximately a quarter of patients in both groups underwent CMR. Contrast-enhanced CMR represented almost the entirety of CMR performed.

Our findings regarding comparing COVID-19 and influenza infection with respect to risk factors and rate of myocarditis extend to those from prior research. Isath *et al* examined characteristics and outcomes of adult patients hospitalised with myocarditis and either concomitant COVID-19 (n=5840) or influenza (n=1045) infection using a national inpatient sample from 2019 to 2020.[16] In this study, investigators found the age and prevalence of cardiovascular comorbidities to be higher in patients with myocarditis and COVID-19 versus those with influenza. While our study observed a similar higher prevalence of cardiovascular comorbidities among patients with COVID-19 infection, the discordance observed with respect to age distribution might be due to a variety of factors including heterogeneous study population. For example, whereas Isath *et al* examined only hospitalised patients with myocarditis, our study included all available patients with a COVID-19 or influenza infection and examined myocarditis rates within this population, and thus our findings may be of greater applicability to the general population.

Limitations

The reasons that led to an individual receiving a diagnosis of influenza in the period 2016–2018 might differ from the reasons that led to an individual receiving a diagnosis of COVID-19 in the period 2020–2021. Widespread testing for COVID-19 was implemented in the period 2020–2021, potentially resulting in individuals with a broader spectrum of disease severity being diagnosed with COVID-19. Conversely, individuals who received a diagnosis of influenza in the period 2016–2018 might have proactively sought out medical treatment for their illness, and therefore, might represent a subgroup with more severe or acute disease. As such, the rates of complications such as myocarditis may be overestimated in the influenza cohort compared with the COVID-19 cohort, in which case the true relative risk of COVID-19-related myocarditis would be even greater than that described here. Alternatively, greater awareness of the link between COVID-19 and myocarditis might have led to a surveillance bias[17] and overestimation for the COVID-19 population, although the lower rates of myocarditis following COVID-19 in 2021 compared with 2020 count against this.

While both COVID and influenza vaccination status were ascertained via ICD coding, we recognise that these data may be incomplete and thus the impact of vaccination on our findings may not be fully accounted for. Additionally, while we recognise that laboratory and imaging data to confirm myocarditis diagnosis was not performed in all patients, we note that our study encompasses a large sample size from a national database and thus has the potential to overcome biases that may be present in single-centre studies.

One of the limitations inherent in administrative claims databases is that data are primarily collected for billing purposes and not for clinical research. Coding errors and variability in data quality among different healthcare providers can affect the accuracy of the data and outcomes recorded are often limited to what is billed and might not accurately reflect clinical efficacy or the patient's quality of life. The population included in the database may also not be representative of the entire population. For example, it might predominantly consist of individuals with commercial insurance or Medicare Advantage, excluding those without insurance or those covered by Medicaid.

In addition, diagnoses are recorded by healthcare professionals who may have used a variety of diagnostic methods. The exact diagnostic criteria employed to make a diagnosis and test results are not detailed within the database making it impossible to verify the accuracy of the diagnosis or to limit the cohort to those confirmed via a specific diagnostic approach. In the current study, limiting the analysis to patients with CMR-confirmed myocarditis or biopsy-proven cases would increase the specificity of the analysis, but this is not feasible given the data limitations. Future studies with access to more detailed clinical data, including CMR and biopsy results, are needed to validate our observations.

A 12-month follow-up was employed, based on precedents observed in the literature[8 15]. We acknowledge that while some cases may be directly attributable to viral infection, others could result from heightened susceptibility to myocarditis from other causes postinfection. However, the same follow-up period was applied for both COVID-19 and influenza populations and it is not expected that different follow-up periods would alter the proportional difference in myocarditis cases observed between the two populations.

CONCLUSIONS

In this large population-based assessment of the epidemiology of myocarditis following COVID-19 and influenza, the overall rate of myocarditis after COVID-19 infection was three times higher than after influenza in the adult population. Young adults as well as males are at an elevated risk of myocarditis after COVID-19 infection, although the absolute rate is very low.

Although CMR is the primary diagnostic tool for non-invasive assessment of myocardial inflammation in patients with known or suspected cardiomyopathy and myocarditis,[9 10] in the current study, we observed that only approximately a quarter of patients with myocarditis following COVID-19 underwent contrast-enhanced CMR, indicating a potential underutilisation of CMR in routine clinical practice.

In addition, although no contrast agent is currently approved in the USA for use in assessing inflammatory cardiomyopathy in patients with active or convalescent COVID-19, almost all CMR conducted was contrast enhanced.

Author affiliations
[1]Radiology Medical Affairs, Bayer AG, Berlin, Germany
[2]William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University, London, UK
[3]Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, UK
[4]Cardiovascular Division, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA
[5]Medical Affairs Statistics, Bayer AG, Leverkusen, Germany
[6]Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Berlin, Germany
[7]DZHK, Berlin, Germany
[8]Working Group Cardiovascular MRI, Charité Medical University Berlin - ECRC, Berlin, Germany
[9]Department of Cardiology and Nephrology, HELIOS Klinikum Berlin-Buch, Berlin, Germany
[10]Bayer Consumer Care, Basel, Switzerland
[11]Greenberg Division of Cardiology, Department of Medicine, Weill Cornell Medicine, New York, New York, USA

Acknowledgements The authors thank James Horwill for his support with study coordination and Coralie Lecomte and Mireia Aguilà Bargués for their support with data analysis.

Contributors All authors contributed to the study design and were responsible for the interpretation of the data and writing the paper and agreed to publish the manuscript. OB, AKF and ZR-E were responsible for development of the methods. OB, AKF and AM were responsible for formal analysis and verification of the results. OB planned the study, reviewed the manuscript and is the guarantor. All authors reviewed the final manuscript.

Funding Bayer AG, Berlin, Germany.

Competing interests This study was performed as an academic and commercial partnership and funded by Bayer AG. OB, AKF and CH are Bayer AG employees. AM is an employee of Bayer Consumer Care AG. The academic authors were not paid to write this article and report no competing interests.

Patient consent for publication Not applicable.

Ethics approval Analysis of Optum's deidentified Clinformatics Data Mart Database (CDM) does not constitute human patient research as defined in 45 CFR 46.102 of the HHS regulations for the protection of human subjects in research (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html) and does not require an institutional review board assessment or approval for secondary analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data were obtained from Optum's deidentified Clinformatics Data Mart Database (CDM), consisting of deidentified administrative health claims for members of large commercial and Medicare Advantage health plans. These data cannot be made publicly available, as commercial restrictions apply to data availability, used under licence for the current study.

ORCID iDs
Oisin Butler http://orcid.org/0000-0001-6462-1664
Zahra Raisi-Estabragh http://orcid.org/0000-0002-7757-5465

REFERENCES

1 Kang Y, Chen T, Mui D, *et al*. Cardiovascular manifestations and treatment considerations in COVID-19. *Heart* 2020;106:1132–41.
2 Müller M, Cooper LT, Heidecker B. Diagnosis, risk stratification and management of myocarditis. *Heart* 2022;108:1486–97.
3 Ammirati E, Moslehi JJ. Diagnosis and Treatment of Acute Myocarditis: A Review. *JAMA* 2023;329:1098–113.
4 Gluckman TJ, Bhave NM, Allen LA, *et al*. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2022;79:1717–56.
5 Ammirati E, Lupi L, Palazzini M, *et al*. Prevalence, Characteristics, and Outcomes of COVID-19-Associated Acute Myocarditis. *Circulation* 2022;145:1123–39.
6 Puntmann VO, Carerj ML, Wieters I, *et al*. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1265.
7 Puntmann VO, Martin S, Shchendrygina A, *et al*. Long-term cardiac pathology in individuals with mild initial COVID-19 illness. *Nat Med* 2022;28:2117–23.
8 Xie Y, Xu E, Bowe B, *et al*. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28:583–90.
9 Ferreira VM, Schulz-Menger J, Holmvang G, *et al*. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation. *J Am Coll Cardiol* 2018;72:3158–76.
10 Kelle S, Bucciarelli-Ducci C, Judd RM, *et al*. Society for Cardiovascular Magnetic Resonance (SCMR) recommended CMR protocols for scanning patients with active or convalescent phase COVID-19 infection. *J Cardiovasc Magn Reson* 2020;22:61.
11 Rudski L, Januzzi JL, Rigolin VH, *et al*. Multimodality Imaging in Evaluation of Cardiovascular Complications in Patients With COVID-19: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2020;76:1345–57.
12 Phelan D, Kim JH, Elliott MD, *et al*. Screening of Potential Cardiac Involvement in Competitive Athletes Recovering From COVID-19: An Expert Consensus Statement. *JACC Cardiovasc Imaging* 2020;13:2635–52.
13 Petersen SE, Friedrich MG, Leiner T, *et al*. Cardiovascular Magnetic Resonance for Patients With COVID-19. *JACC Cardiovasc Imaging* 2022;15:685–99.
14 Olsen SJ, Azziz-Baumgartner E, Budd AP, *et al*. Decreased Influenza Activity During the COVID-19 Pandemic - United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1305–9.
15 Wang W, Wang C-Y, Wang S-I, *et al*. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks. *eClin Med* 2022;53:101619.
16 Isath A, Malik A, Bandyopadhyay D, *et al*. A Comparison of COVID-19 and Influenza-Associated Myocarditis: A Nationwide Study in the United States. *Curr Probl Cardiol* 2023;48:101680.
17 Haut ER, Pronovost PJ. Surveillance bias in outcomes reporting. *JAMA* 2011;305:2462–3.