Amsterdam, 26 February 2026
EMADOC-1700519818-2693539
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

COMIRNATY

Common name: COVID-19 mRNA vaccine

Procedure no.: EMA/PAM/0000316475

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	2 February 2026	2 February 2026
☐	CHMP comments	16 February 2026	16 February 2026
☐	Updated CHMP Rapporteur AR	19 February 2026	N/A
☒	CHMP outcome	26 February 2026	26 February 2026

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List of Abbreviations

Term	Definition
API	Application Programming Interface
CCI	Charlson Comorbidity Index
CI	confidence interval
COVID-19	coronavirus disease 2019
CPT	Current Procedure Terminology
EC	European Community
ED	Emergency Department
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EpiChron	EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HCU	Healthcare Utilization
HEOR	Health Economics and Outcomes Research
HIPAA	Health Information Insurance Portability and Accountability Act
ICD	International Classification of Diseases
IDN	integrated delivery network
IP/ED	inpatient/emergency department
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
mRNA	messenger ribonucleic acid
NI	non-interventional
NDC	National Drug Center
NLP	natural language processing
OR	odds ratio
PASS	post-authorization safety study
PPV	positive predictive value
RAPID3	Routine assessment of patient index data 3
RNA	ribonucleic acid
QC	quality control
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SQL	Structured Query Language
US	United States
WHO	World Health Organization

1. Introduction

On 27 November 2025, the MAH submitted a completed paediatric study for Comirnaty, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study C4591055 - *Assessment of Risk Factors for Myocarditis in the United States (US) Using Electronic Health Records and Claims Data* is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

Study C4591055 - Assessment of Risk Factors for Myocarditis in the United States (US) Using Electronic Health Records and Claims Data.

This study examined and compared demographic and clinical characteristics that may be associated with the risk of myocarditis after any dose of mRNA COVID-19 vaccine, myocarditis after SARS-CoV-2 infection (2020-later), or acute/viral myocarditis prior to COVID-19 era (pre-2020). Please note that individuals of all age groups were included and may have received any mRNA COVID-19 vaccine due to the study design. No specific analyses were performed for the paediatric population or for those receiving Comirnaty.

This non-interventional study was designated as a PASS. This C4591055 final study report is being submitted to EMA in fulfillment of Article 46 of the REGULATION (EC) NO, 1901/2006 "Pediatric regulation". The aim with the study was to address the following question: "What are the risk factors for myocarditis among the following three cohorts? 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020)."

2.3.2. Clinical study C4591055

Methods

Study Design

This was a non-interventional (NI), observational, retrospective cohort study that employed a nested case-control design, utilizing deidentified US-based Electronic Health Record (EHR) data from Optum. The broader cohort for this study was derived from the Optum EHR database during the study period of 01 January 2010 to most recent available at the time of start of data collection (31 March 2023). The C4591055 study included individuals with Post-mRNA COVID-19 vaccination myocarditis (Cohort 1),

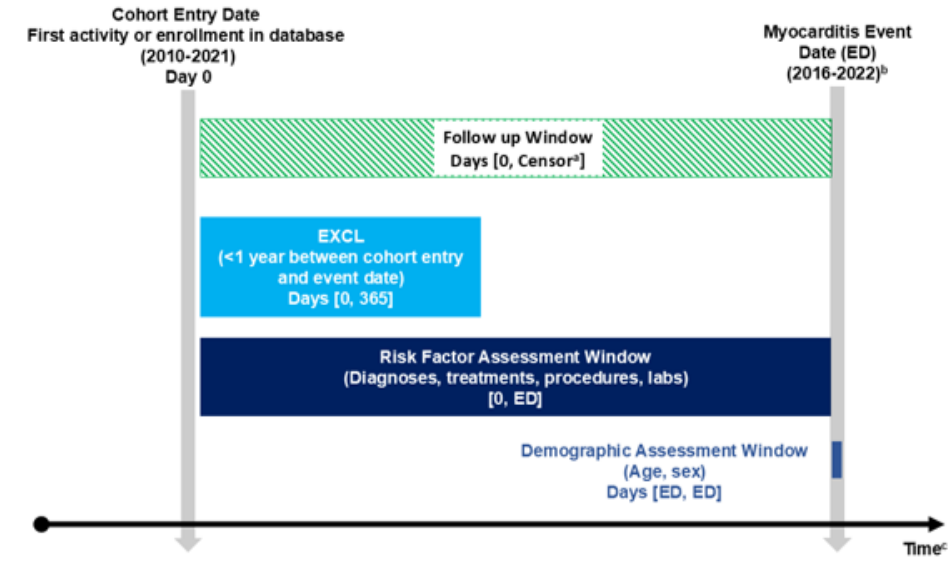
individuals with Post-SARS-CoV-2 infection myocarditis (Cohort 2), and individuals with Pre-COVID myocarditis (Cohort 3); as well as a random sample of matched individuals without myocarditis.

The broader cohort for this study was derived from the Optum EHR database during the study period of 01 January 2010 to most recent available at the time of start of data collection (31 March 2023). This study period was chosen to reflect the most current and complete data in the Optum database, with sufficient baseline time to examine risk factors of patients with myocarditis in each of the cohorts with index dates of 01 January 2016 and later.

Figure 1 summarizes the overall study design. Among the overall Optum EHR study population, the following mutually exclusive cohorts and index dates, and follow-up periods were defined to address the study objectives:

- Cohort 1 - Post-mRNA COVID-19 vaccination myocarditis cohort: first date of a myocarditis diagnosis code within 21 days after vaccination from 11 December 2020 to most recent data available, allowing for at least 30 days pre and post index myocarditis diagnosis for medical notes to confirm diagnosis through end of study period.
- Cohort 2 - Post-SARS-CoV-2 infection myocarditis: first date of a myocarditis diagnosis code within 8 weeks after a positive SARS-CoV-2 test from 01 January 2020 to most recent data available, allowing for at least 30 days pre and post index myocarditis diagnosis for medical notes to confirm diagnosis through end of study period.
- Cohort 3 - Pre-COVID myocarditis: most recent date of a myocarditis diagnosis from 01 January 2016 to 01 November 2019, allowing for at least 30 days pre and post index myocarditis diagnosis for medical notes to confirm diagnosis through end of study period.
- Controls - for the multivariable risk factor analysis, a random sample of matched patients without myocarditis was selected, i.e. by age, sex, an encounter date within the same month as the index date for the myocarditis case, and with a similar amount of follow-up time from entry into the cohort and activity in the database. Furthermore, controls met additional criteria pertaining to each cohort: controls for the vaccination cohort received an mRNA COVID-19 vaccination and controls for the SARS-CoV-2 infection cohort received a COVID-19 diagnosis. Controls for the pre-COVID cohort did not have additional therapeutic or diagnostic requirements.

Figure 1. Study Design



a. Censored at minimum of myocarditis diagnosis, death, disenrollment, or end of the study period
b. Controls risk-set matched on e.g. month/year of cohort entry, duration of follow up (from cohort entry). Matching criteria will be detailed in the SAP.
c. Timeframe for each myocarditis sub-cohort:
   1) Post-vaccination myocarditis: December 11, 2020 – March 31, 2023
   2) Post-SARS-CoV-2 myocarditis: January 01, 2020 – March 31, 2023
   3) Pre-COVID era myocarditis: January 01, 2016 – November 01, 2019

Study participants

Inclusion Criteria

Patients must have met all of the following criteria to be eligible for inclusion in the study:

1. All ages

Myocarditis cases:

2. Diagnosis of myocarditis identified using International Classification of Diseases (ICD) codes in EHR and/or claims when available.
3. At least one myocarditis inpatient record or two myocarditis records of any type dated greater than or equal to 30 days apart
4. Myocarditis diagnosis date between 01 January 2016 – most recent EHR data available (31 March 2023)
5. At least 365 days of enrollment or activity in the EHR prior to the index myocarditis diagnosis.

Myocarditis cases meeting the above criteria were divided into the following three cohorts with their own unique inclusion criteria:

a) Cohort 1 - Post- mRNA COVID-19 vaccine myocarditis cases:
   1. Myocarditis diagnosis dated 11 December 2020 or later
   2. Record of mRNA vaccination within 21 days prior to the myocarditis diagnosis without a record of SARS-CoV-2 positive test within 8 weeks prior to myocarditis diagnosis
   3. Availability of medical notes to use for confirmation of myocarditis post-mRNA COVID-19 vaccination thirty days before and after the index event

b) Cohort 2 - Post- SARS-CoV-2 infection myocarditis cases:

1. Myocarditis diagnosis date 01 January 2020 or later
2. Record of SARS-CoV-2 positive test within 8 weeks prior to myocarditis diagnosis, with no record of mRNA COVID-19 vaccination during that time
3. Availability of medical notes to use for confirmation of myocarditis post-SARS-CoV-2 infection thirty days before and after the index event

c) Cohort 3 - Pre-COVID-19-era acute/viral myocarditis cases:

1. Most recent Myocarditis diagnosis dated prior to 01 November 2019
2. Availability of medical notes to use for confirmation of myocarditis within thirty days before and after the index event

Controls for risk factor analysis:

1. Medical encounter and during the same month as their matched myocarditis case (index date for control – selected date closest to matched myocarditis case if ≥1 date/encounters were present)
2. At least 365 days of enrollment or activity in the EHR prior to index
3. No evidence of myocarditis prior to the index date
4. Details of matching criteria provided in Module 5.3.5.4 SAP.

Exclusion Criteria

Patients meeting any of the following criteria were not included in the study:

1. Less than 365 days between the first recorded date a patient had activity of any kind recorded the Optum EHR database and a patient's first recorded ICD code of myocarditis based on the cohort criteria above, or the index date for the controls.

Data Sources

Optum's Electronic Health Record (EHR) and Integrated Claims-Clinical dataset, which combines adjudicated claims data (where available) with Optum's EHR data, were the data sources for this study. Optum integrates EHR data with claims, prescribing, dispensing, and practice management data by partnering directly with several multi-specialty medical groups, integrated delivery networks (IDN)s and hospital chains to extract data from their EHR and various information technology systems in the US. By normalizing, validating, and aggregating the de-identified data, Optum generates a longitudinal view of patient care.

Optum's longitudinal EHR repository is derived from dozens of healthcare provider organizations in the US, that include more than 57 contributing sources and 111K sites of care: treating more than 106 million patients receiving care in the US. The data is certified as de-identified by an independent statistical expert following Health Information Insurance Portability and Accountability Act (HIPAA) statistical de-identification rules and managed according to Optum customer data use agreements[1],[2] .Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory EHRs, practice management systems and numerous other internal systems. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and

[1] 45 CFR 164.514(b)(1).
[2] Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Information Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Dated as September 4, 2012, as first released on November 26, 2012).

outpatient visits. Optum data elements include demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. In addition, Optum uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores (i.e. Routine assessment of patient index data 3 (RAPID3) for rheumatoid arthritis, or CHADS2 for stroke risk), genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR.

Diagnosis data, laboratory data, and surgical procedure data for the study period of interest was first obtained from structured data (via International Classification of Diseases, Ninth Revision/Tenth Revision, Clinical Modification [ICD-9-CM/ICD-10-CM], International Classification of Diseases, Ninth Revision/Tenth Revision, Procedure Classification System [ICD-9-PCS/ICD-10-PCS], or Current Procedure Terminology (CPT) codes where applicable. Drug treatment data may also have been pulled from prescription written, medication administration, and procedure tables when appropriate (via ICD-9-CM/ICD-10-CM, National Drug Center [NDC], CPT, and Healthcare Common Procedure Coding System [HCPCS] codes where applicable). In addition, Optum used data available in the medical records for a subset of myocarditis patients that have clinical patient notes and other data that cannot be mapped into the larger structured database. These data may have contained verbatim medical data, including text-based descriptions of medical information, such as medical records, physician notes, neurological scans, X-rays, or narrative fields in a database. When possible/appropriate, for validation of myocarditis diagnoses and analyses of risk factors and background epidemiology, lab data were also used to augment the structured electronic health data.

Two major data sources for this study are described in greater detail in various sections throughout the Study C4591055 Protocol. Their collection, retrieval, preparation, and storage are summarized as follows:

1. Optum's EHR database: The EHR Database is a longitudinally linked structured data source. It has been formally de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum customer data use agreements. [3],[4] The EHR includes structured fields rendered by NLP technology, wherein Optum data experts mine provider notes and then normalize, validate, and integrate them into the electronic database.

In addition to these structured data, Optum has clinical notes available from some EHR systems and is able to use technology to search the verbatim text for phrases of interest and extract a small portion of those notes for review and clinical assessment. All data elements from this source are stored on Optum's firewalled, password-protected database. These data can only be extracted by approved Optum study personnel using standard and commercially available software (e.g., SAS, SQL, Python).

2. Optum's Integrated Claims-Clinical database: The EHR were supplementally linked to patients in Optum's Integrated Claims-Clinical adjudicated claims database. For a subset of these

[3] 45 CFR 164.514(b)(1).

[4] Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Information Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Dated as September 4, 2012, as first released on November 26, 2012).

patients, electronic clinical notes underwent manual clinician review to confirm myocarditis cases.

For the validation process using the electronic clinical notes (which were converted to deidentified structured data for analyses), the Optum NLP team determined if clinical notes were available for all qualifying patients with post-vaccine myocarditis, all qualifying post-SARS-CoV-2 infection myocarditis, as well as random samples of myocarditis diagnosed pre-2020. Optum performed a series of "enhanced search" queries on the patient notes to determine key term content. Next, the Optum NLP team used the key terms to extract note snippets into a file for review by the Optum Clinical team. These notes snippets were then used to validate myocarditis cases per the Brighton Collaboration Criteria. After clinical review of the notes involving two clinicians from Optum, and categorization of the content for analysis, the resulting table of criteria was created. The myocarditis cases were then classified as validated or not validated (cases were considered validated myocarditis diagnoses if they qualified as Brighton Collaboration Levels 1−3 of certainty), and relevant information was entered into a spreadsheet which served as the data collection tool. Finally, the Optum clinical review team provided these results of the case validation to the Optum Health Economics and Outcomes Research (HEOR) analytics team, whose members identified matched controls for each case and conducted the multivariable analyses to assess risk factors for myocarditis using the structured data. This information was also used to calculate the PPV of the algorithm used to initially identify the myocarditis cases in the structured EHR database.

Data was transferred from the clinical review team to Optum's HEOR team via standard Data Transfer API (application programming interface). Extraction, merging, and cleaning of EHR and NLP-rendered data was performed and adjudicated by at least two HEOR programmers and two HEOR analysts/directors. All data steps and code locations were formally documented in a data dictionary and were reviewed by the directing analyst and researcher before commencement of programming.

All analyses for this study were conducted in SAS (version 9.4 or higher, SAS Institute, Cary, North Carolina, US).

Treatments

Individuals of all age groups were included who may have received any mRNA COVID-19 vaccine due to the study design. No specific analyses were performed for the paediatric population or for those receiving Comirnaty.

Objectives

The research question addressed by this study was, "What are the risk factors for myocarditis among the following three cohorts? 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020)."

Primary Objective

1. To assess and compare demographic, medical history, and comorbidities that may be risk factors for myocarditis in each of three cohorts: 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020).

Secondary Objective

1. To examine the risk factors in each myocarditis cohort stratified by age group at diagnosis, sex, time period and follow-up time (years).
2. To assess and compare the validity of myocarditis diagnosis case definitions in administrative data for each cohort, via calculating the positive predictive value (PPV) using electronic medical record review.

Outcomes/endpoints

The outcome in this study was myocarditis, categorized into three cohorts: 1) myocarditis post mRNA COVID-19 vaccination, 2) myocarditis post-SARS-CoV-2 infection, or 3) acute/viral myocarditis pre-2020. Myocarditis was identified with ICD-10-CM codes in EHR and claims data. In addition, Brighton Collaboration Criteria were used as the basis during manual reviews of electronic medical notes by two clinicians at Optum to validate a subset of the cases.

Statistical Methods

Descriptive statistics included counts and percentages for categorical data. For continuous variables, statistics such as mean, median, standard deviation, and range were provided. Odds ratios (ORs) and 95% confidence intervals (CIs) were provided for associations between potential risk factors and myocarditis in univariable and multivariable models.

Statistical Analyses for the Primary Objective:

In primary analyses, descriptive statistics were presented to characterize myocarditis patients in terms of demographic and clinical characteristics (including clinical characteristics of the myocarditis episode, as well as clinical history of the patient) as of the index date (date of myocarditis diagnosis code for myocarditis cases, or matched month/year among the control group).

Univariable association analyses for validated cases of myocarditis were conducted using baseline subject characteristics and historic diagnoses, procedures, and medications, defined using ICD-10 diagnostic/procedure codes, National Drug Center drug codes, Healthcare Common Procedure Coding System and Current Procedure Terminology drug codes during the period before the myocarditis diagnosis. Data on both long-term exposures up to 6 years earlier (i.e., long lookback) and short-term exposures up to 90 days earlier (i.e., short lookback) were collected and modelled separately. ORs, CIs and p-values for associations between the potential risk factors and myocarditis were estimated for the univariable models. Through a hybrid approach based on review of the top statistically significant univariable associations and manual selection-based clinical judgment considering biologically plausible risk factors (e.g., roadside accident not considered), a total of 24 top potential risk factors were selected for further assessment via multivariable modelling. The initial multivariable logistic regression model included patient demographic and baseline clinical characteristics. Medical history risk factors were assessed individually by adding each one separately to the initial multivariable logistic regression model. This process was repeated for each of the 24 potential biologically plausible risk factors, repeated for each of the 3 cohorts, repeated for ICD-based myocarditis outcome, and repeated for both short and long lookback windows. ORs, CIs and p-values for associations between the potential risk factors and myocarditis were estimated for multivariable models. Generalized linear modelling with log link and binary distribution was used for both univariable and multivariable models.

Statistical Analyses for the Secondary Objective:

In secondary analyses, all analyses above were attempted in the following *a priori* specified subgroups: 1) myocarditis case definition; 2) age group at index date; 3) sex; and 4) available follow-up time (years), as sample sizes allowed.

Results

Participant flow

Recruitment

Initially, 64,052 subjects were identified from January 1, 2016 to March 31, 2023. After applying the stated selection criteria, the study included 800 subjects with ICD-based myocarditis and 3200 matched controls, including 120 subjects in the post-mRNA COVID-19 vaccination case group (Cohort 1), 435 subjects in the post-SARS-CoV-2 infection case group (Cohort 2), and 245 subjects in the pre-COVID-19 era case group (Cohort 3). After clinical review, 554/800 (69.3%) patients had validated myocarditis by Brighton Collaboration criteria Levels 1–3, including 59/120 (49%), 335/435 (77%), and 160/245 (65%) validated in Cohorts 1, 2, and 3, respectively. Overall, 246/800 (30.8%) subjects had either insufficient information for validated myocarditis (Brighton Collaboration Level 4) or the data revealed information that the diagnosis was not compatible with myocarditis (Level 5).

Baseline data

Demographics

Baseline demographics, recent healthcare use, and comorbidities among cases and matched controls are shown in Table 1 for ICD-based myocarditis and Table 2 for validated myocarditis cases.

Table 1. Baseline demographics, medical history, and comorbidities by myocarditis case group for A) all ICD-code identified myocarditis cases, B) Brighton Collaboration criteria-validated cases.

	Cohort 1 Post-mRNA COVID-19 vaccination		**Cohort 2 Post-SARS-CoV-2 infection**		**Cohort 3 Pre-COVID-19 era**	
	Myocarditis (n=120)	**Controls (n=480)**	**Myocarditis (n=435)**	**Controls (n=1740)**	**Myocarditis (n=245)**	**Controls (n=980)**
Age,[a] y, median (Q1, Q3)	54.5 (34, 63.5)	54.5 (34, 63.5)	51 (28, 64)	51 (28, 64)	48 (32, 61)	48 (32, 61)
Sex, n (%)						
Female	44 (36.7)	176 (36.7)	188 (43.2)	752 (43.2)	101 (41.2)	404 (41.2)
Male	76 (63.3)	304 (63.3)	247 (56.8)	988 (56.8)	144 (58.8)	576 (58.8)
Race, n (%)						
Black	31 (25.8)	43 (9.0)	100 (23.0)	215 (12.4)	50 (20.4)	124 (12.7)
Asian	<5	17 (3.5)	12 (2.8)	36 (2.1)	6 (2.4)	13 (1.3)
White	78 (65.0)	345 (71.9)	266 (61.1)	1157 (66.5)	168 (68.6)	736 (75.1)
Other/unknown	10 (8.3)	75 (15.6)	57 (13.1)	332 (19.1)	21 (8.6)	107 (10.9)
Ethnicity, n (%)						
Hispanic	9 (7.5)	32 (6.7)	50 (11.5)	142 (8.2)	24 (9.8)	62 (6.3)
Not Hispanic	84 (70.0)	373 (77.7)	285 (65.5)	1165 (67.0)	200 (81.6)	775 (79.1)
Unknown	27 (22.5)	75 (15.6)	100 (23.0)	433 (24.9)	21 (8.6)	143 (14.6)
Region, n (%)						
Midwest	35 (29.2)	200 (41.7)	127 (29.2)	714 (41.0)	87 (35.5)	496 (50.6)
Northeast	57 (47.5)	106 (22.1)	164 (37.7)	414 (23.8)	100 (40.8)	150 (15.3)
South	15 (12.5)	104 (21.7)	113 (26.0)	376 (21.6)	34 (13.9)	197 (20.1)
West	8 (6.7)	49 (10.2)	13 (3.0)	156 (9.0)	8 (3.3)	78 (8.0)
Other/unknown	5 (4.2)	21 (4.4)	18 (4.1)	80 (4.6)	16 (6.5)	59 (6.0)
Insurance type,[a] n (%)						

	Cohort 1 Post-mRNA COVID-19 vaccination		Cohort 2 Post-SARS-CoV-2 infection		Cohort 3 Pre-COVID-19 era	
	Myocarditis (n=120)	**Controls (n=480)**	**Myocarditis (n=435)**	**Controls (n=1740)**	**Myocarditis (n=245)**	**Controls (n=980)**
Commercial	66 (55.0)	235 (49.0)	214 (49.2)	933 (53.6)	123 (50.2)	435 (44.4)
Medicaid	17 (14.2)	46 (9.6)	93 (21.4)	258 (14.8)	48 (19.6)	132 (13.5)
Medicare	18 (15.0)	33 (6.9)	83 (19.1)	232 (13.3)	56 (22.9)	142 (14.5)
HCU,[b] n (%)						
Inpatient	32 (26.7)	29 (6.0)	168 (38.6)	342 (19.7)	124 (50.6)	196 (20.0)
ED	29 (24.2)	47 (9.8)	108 (24.8)	347 (19.9)	76 (31.0)	222 (22.7)
Outpatient visit	105 (87.5)	366 (76.3)	326 (74.9)	1407 (80.9)	200 (81.6)	827 (84.4)
CCI score,[c] n (%)						
0	49 (40.8)	355 (74.0)	210 (48.3)	1115 (64.1)	91 (37.1)	569 (58.1)
≥1	71 (59.2)	125 (26.0)	225 (51.7)	625 (35.9)	154 (62.9)	411 (41.9)

CCI, Charlson Comorbidity Index; ED, emergency department; HCU, healthcare use; Q, quartile.
To reduce risk of re-identification, cells with fewer than n=5 were masked as "<5."

a. At index.
b. In previous 182 days.
c. In previous 365 days.

Table 2. Baseline demographics, medical history, and comorbidities by myocarditis case group for A) all ICD-code identified myocarditis cases, B) Brighton Collaboration criteria-validated cases (continued).

	Cohort 1 Post-mRNA COVID-19 vaccination		Cohort 2 Post-SARS-CoV-2 infection		Cohort 3 Pre-COVID-19 era	
	Myocarditis (N=59)	**Controls (N=236)**	**Myocarditis (N=335)**	**Controls (N=1340)**	**Myocarditis (N=160)**	**Controls (N=640)**
Age,[a] y, median (Q1, Q3)	40 (21, 61)	40 (21, 61)	52 (29, 64)	52 (29, 64)	46.5 (31.5, 59)	46.5 (31.5, 59)
Sex, n (%)						
Female	22 (37.3)	88 (37.3)	153 (45.7)	612 (45.7)	68 (42.5)	272 (42.5)
Male	37 (62.7)	148 (62.7)	182 (54.3)	728 (54.3)	92 (57.5)	368 (57.5)
Race, n (%)						
Black	15 (25.4)	20 (8.5)	85 (25.4)	175 (13.1)	33 (20.6)	82 (12.8)
Asian	1 (1.7)	6 (2.5)	10 (3.0)	25 (1.9)	5 (3.1)	10 (1.6)
White	40 (67.8)	172 (72.9)	197 (58.8)	892 (66.6)	109 (68.1)	474 (74.1)
Other/unknown	3 (5.1)	38 (16.1)	43 (12.8)	248 (18.5)	13 (8.1)	74 (11.6)
Ethnicity, n (%)						
Hispanic	8 (13.6)	20 (8.5)	36 (10.7)	111 (8.3)	16 (10.0)	39 (6.1)
Not Hispanic	36 (61.0)	181 (76.7)	225 (67.2)	893 (66.6)	133 (83.1)	511 (79.8)
Unknown	15 (25.4)	35 (14.8)	74 (22.1)	336 (25.1)	11 (6.9)	90 (14.1)
Region, n (%)						
Midwest	17 (28.8)	101 (42.8)	94 (28.1)	541 (40.4)	60 (37.5)	334 (52.2)
Northeast	28 (47.5)	59 (25.0)	126 (37.6)	314 (23.4)	63 (39.4)	98 (15.3)
South	8 (13.6)	46 (19.5)	92 (27.5)	295 (22.0)	23 (14.4)	118 (18.4)
West	2 (3.4)	22 (9.3)	11 (3.3)	129 (9.6)	5 (3.1)	49 (7.7)
Other/unknown	4 (6.8)	8 (3.4)	12 (3.6)	61 (4.6)	9 (5.6)	41 (6.4)
Insurance type,[a] n (%)						
Commercial	34 (57.6)	118 (50.0)	169 (50.4)	714 (53.3)	79 (49.4)	279 (43.6)
Medicaid	9 (15.3)	28 (11.9)	73 (21.8)	197 (14.7)	35 (21.9)	92 (14.4)
Medicare	7 (11.9)	8 (3.4)	66 (19.7)	172 (12.8)	34 (21.3)	83 (13.0)
Other/Unknown	9 (15.3)	82 (34.7)	27 (8.1)	257 (19.2)	12 (7.5)	186 (29.1)
HCU,[b] n (%)						
Inpatient	15 (25.4)	11 (4.7)	131 (39.1)	263 (19.6)	90 (56.3)	126 (19.7)
ED	11 (18.6)	27 (11.4)	84 (25.1)	1081 (80.7)	53 (33.1)	149 (23.3)
Outpatient visit	48 (81.4)	175 (74.2)	249 (74.3)	263 (19.6)	120 (75.0)	533 (83.3)
CCI score,[c] n (%)						

Table 2. Baseline demographics, medical history, and comorbidities by myocarditis case group for A) all ICD-code identified myocarditis cases, B) Brighton Collaboration criteria-validated cases (continued).

	Cohort 1 Post-mRNA COVID-19 vaccination		**Cohort 2 Post-SARS-CoV-2 infection**		**Cohort 3 Pre-COVID-19 era**	
	Myocarditis (N=59)	**Controls (N=236)**	**Myocarditis (N=335)**	**Controls (N=1340)**	**Myocarditis (N=160)**	**Controls (N=640)**
0	31 (52.5)	183 (77.5)	159 (47.5)	849 (63.4)	62 (38.8)	373 (58.3)
≥1	28 (47.5)	53 (22.5)	176 (52.5)	491 (36.6)	98 (61.3)	267 (41.7)

CCI, Charlson Comorbidity Index; ED, emergency department; HCU, healthcare use; Q, quartile. To reduce risk of re-identification, cells with fewer than n=5 were masked as "<5."

a. At index.
b. In previous 182 days.
c. In previous 365 days.

A higher percentage of case subjects with validated myocarditis had inpatient hospitalizations in the previous 182 days from the index date compared with the matched controls (Table 2). Specifically, the percentage with inpatient hospitalizations was 25.4% for case subjects versus 4.7% for control subjects in the post-COVID-19 vaccination (Cohort 1), 39.1% versus 19.6% in the post-SARS-CoV-2 infection (Cohort 2), and 56.3% versus 19.7% in the pre-COVID-19 era (Cohort 3) case groups. Similarly, a higher percentage of case subjects with validated myocarditis had outpatient visits in the previous 182 days from the index date compared with the matched controls for Cohort 2 (74.3% vs 19.6%), but this trend was less apparent in Cohort 1 (81.4% vs 74.2%) and was not observed in Cohort 3 (75.0% vs 83.3).

A higher percentage of case subjects with validated myocarditis had a CCI score of ≥1 (i.e., higher comorbidity burden) in the previous 365 days from the index date compared with the matched controls (Table 2). Specifically, the percentage of subjects with a CCI score of ≥1 in the previous 365 days was 47.5% for case subjects versus 22.5% for control subjects in the post-mRNA COVID-19 vaccination (Cohort 1), 52.5% versus 36.6% in the post-SARS-CoV-2 infection (Cohort 2), and 61.3% versus 41.7% in the pre-COVID-19 era (Cohort 3) case groups.

Between validated myocarditis cases from the three cohorts, Cohort 1 had the largest proportion of subjects who were male (62.7%, 54.3%, and 57.5% from Cohorts 1, 2, and 3, respectively), of younger age (median ages of 40.0, 52.0, and 46.5 years from Cohorts 1, 2, and 3, respectively), and from the Northeast region (47.5%, 37.6%, and 39.4% from Cohorts 1, 2, and 3, respectively). Cohort 3 had the largest proportion of subjects of non-Hispanic ethnicity (61.0%, 67.2%, and 83.1% from Cohorts 1, 2, and 3, respectively), and with comorbidities (47.5%, 52.5%, and 61.3% with CCI ≥1 from Cohorts 1, 2, and 3, respectively).

Number analysed

The most common myocarditis ICD-10 codes among validated cases across all study groups are shown in Table 3. Among the 65 unvalidated myocarditis cases (Brighton Collaboration criteria Levels 4 and 5) from subjects in the post-mRNA COVID-19 vaccination case group (Cohort 1), 37 (57%) had a D86.85—sarcoid myocarditis diagnosis code, with 71% (17/24) of all Brighton Collaboration criteria Level 5 cases having this code.

Table 3. Number and percentage of most common myocarditis ICD-10 codes by Cohort and Brighton Collaboration criteria level.

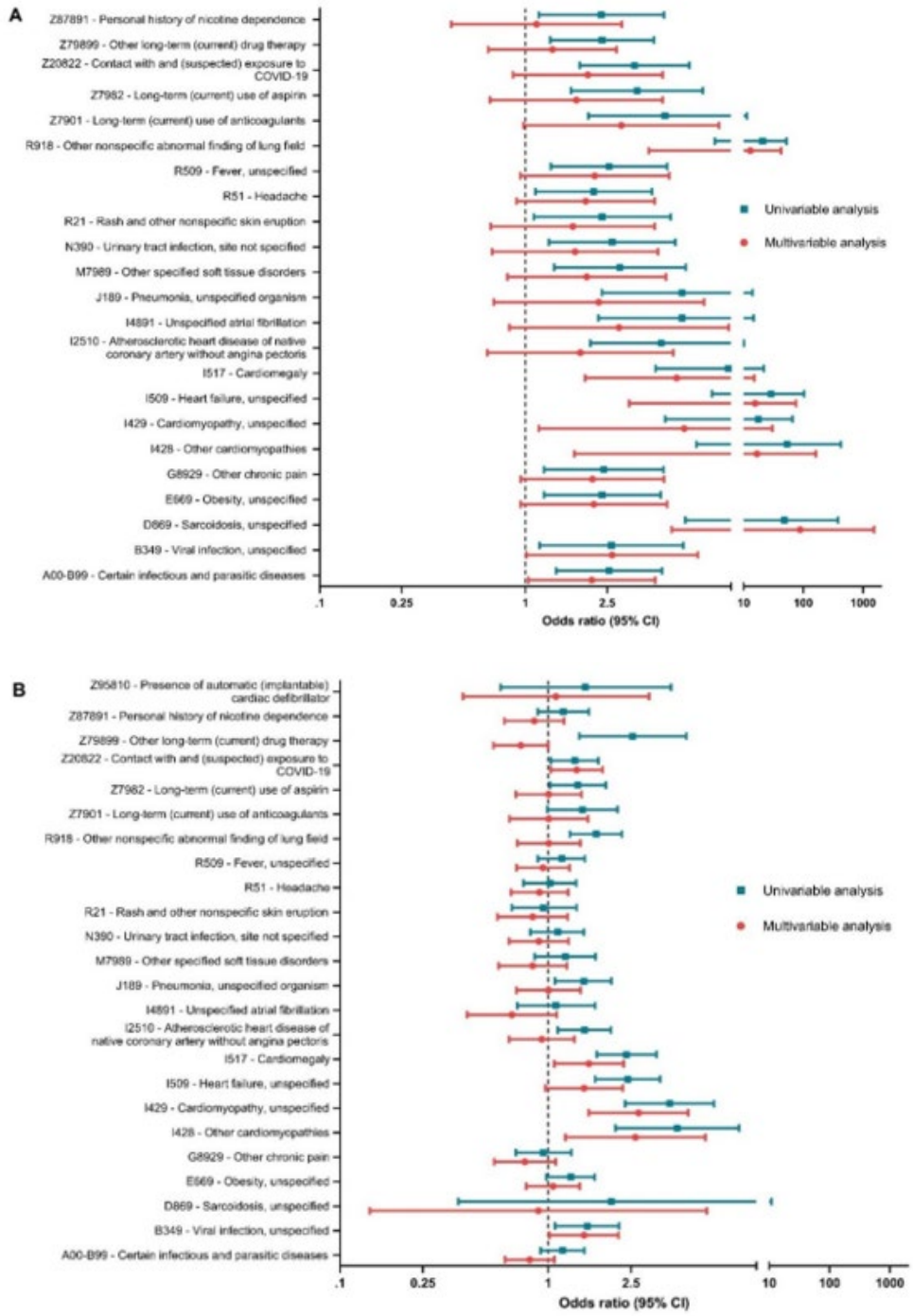
		Cohort 1 **Post-mRNA COVID-19 vaccinated** **Brighton criteria level n (%)**		**Cohort 2** **Post-SARS-CoV-2 infected** **Brighton criteria level n (%)**		**Cohort 3** **Pre-COVID-19 era** **Brighton criteria level n (%)**	
Code	**Description**	**1, 2, 3**	**4, 5**	**1, 2, 3**	**4, 5**	**1, 2, 3**	**4, 5**
	Total*	**66**	**65**	**378**	**109**	**186**	**88**
B33.22	Viral myocarditis	<5	<5	12 (3.2)	8 (7.3)	11 (5.9)	<5
D86.85	Sarcoid myocarditis	12 (18.2)	37 (56.9)	<5	<5	<5	<5
I40.0	Infective myocarditis	<5	<5	47 (12.4)	10 (9.2)	7 (3.8)	<5
I40.1	Isolated myocarditis	<5	<5	<5	5 (4.6)	12 (6.5)	8 (9.1)
I40.8	Other acute myocarditis	5 (7.6)	<5	13 (3.4)	<5	6 (3.2)	<5
I40.9	Acute myocarditis, unspecified	8 (12.1)	<5	44 (11.6)	10 (9.2)	30 (16.1)	12 (13.6)
I51.4	Myocarditis, unspecified	29 (43.9)	17 (26.2)	254 (67.2)	70 (64.2)	114 (61.3)	56 (63.6)

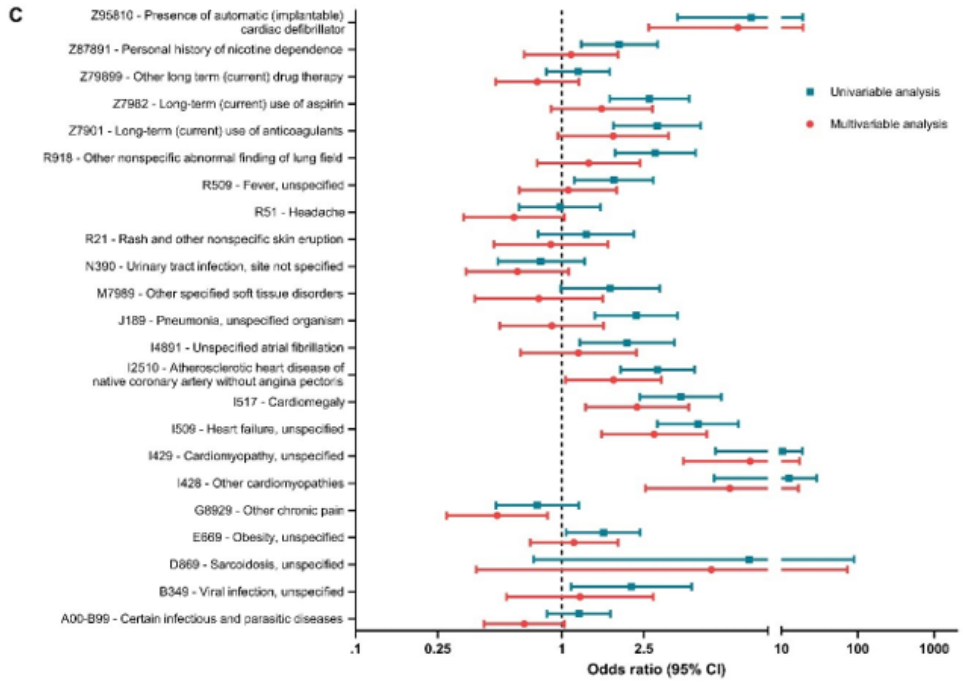
To reduce risk of re-identification, cells with fewer than n=5 were masked as "<5".
*Less frequently occurring ICD-10 codes are not included in this table.

Primary Analyses: Univariable (unadjusted) association analysis

Twenty-four top potential risk factors were selected for further examination via multivariable logistic regression after conducting a hybrid selection approach based on manual review of top statistically significant univariable associations and selection based on clinical judgment considering biologically plausible risk factors. The univariable associations for top risk factors during the long lookback window with validated myocarditis are shown as unadjusted odds ratios in forest plots Figure 2 and Table 4.

Figure 2. Risk factors during the long lookback window for validated myocarditis with unadjusted (univariable) and adjusted (multivariable) odds ratios (95% CIs) for (A) Cohort 1, (B) Cohort 2, and (C) Cohort 3.





Cohort 1: post-mRNA COVID-19 vaccination myocarditis; Cohort 2: post-SARS-CoV-2 infection myocarditis; Cohort 3: pre-COVID-19 era myocarditis. The multivariable associations were adjusted for the following covariates: race, ethnicity, geographic region, insurance type, Charlson Comorbidity Index, and healthcare utilization in the previous 182 days.

Table 4. Top risk factors during the long lookback window for validated myocarditis with unadjusted (univariable) odds ratios (95% CIs)

ICD-10 code–description	Cohort 1 Post-mRNA COVID-19 vaccination				Cohort 2 Post-SARS-CoV-2 infection				Cohort 3 Pre-COVID-19 era			
	Cases n (%)	Controls n (%)	OR	95% CI	Cases n (%)	Controls n (%)	OR	95 % CI	Cases n (%)	Controls n (%)	OR	95% CI
A00_B99 - Certain infectious and parasitic diseases	38 (64.4 %)	98 (33.2 %)	2.55	1.41-4.61	192 (57.3 %)	715 (53.4 %)	1.17	0.92 - 1.49	70 (43.8 %)	250 (39.1 %)	1.21	0.85-1.72
B349 - Viral infection, unspecified	11 (18.6 %)	19 (8.1%)	2.62	1.17-5.86	49 (14.6 %)	134 (10.0 %)	1.54	1.08 - 2.19	14 (8.8 %)	27 (4.2%)	2.18	1.11-4.26
D869 - Sarcoidosis, unspecified	10 (16.9 %)	1 (0.4%)	47.96	6.00-383.34	2 (0.6 %)	4 (0.3%)	2.01	0.37 - 11.00	2 (1.3 %)	1 (0.2%)	8.09	0.73-89.77
E669 - Obesity, unspecified	18 (30.5 %)	37 (15.7 %)	2.36	1.23-4.55	96 (28.7 %)	321 (24.0 %)	1.28	0.98 - 1.67	40 (25.0 %)	111 (17.3 %)	1.59	1.05-2.40
G8929 - Other chronic pain	17 (28.8 %)	34 (14.4 %)	2.40	1.23-4.70	63 (18.8 %)	262 (19.6 %)	0.95	0.70 - 1.29	26 (16.3 %)	130 (20.3 %)	0.76	0.48-1.21
I428 - Other cardiomyopathies	11 (18.6 %)	1 (0.4%)	53.85	6.79-427.02	17 (5.1 %)	17 (1.3%)	4.16	2.10 - 8.24	22 (13.8 %)	8 (1.3%)	12.59	5.49-28.88
I429 - Cardiomyopathy, unspecified	11 (18.6 %)	3 (1.3%)	17.80	4.78-66.22	32 (9.6 %)	36 (2.7%)	3.83	2.34 - 6.26	35 (21.9 %)	17 (2.7%)	10.26	5.57-18.89

ICD-10 code–description	Cohort 1 Post-mRNA COVID-19 vaccination				Cohort 2 Post-SARS-CoV-2 infection				Cohort 3 Pre-COVID-19 era			
	Cases n (%)	Controls n (%)	OR	95% CI	Cases n (%)	Controls n (%)	OR	95 % CI	Cases n (%)	Controls n (%)	OR	95% CI
I509 - Heart failure, unspecified	16 (27.1 %)	3 (1.3%)	28. 90	8.07-103.46	53 (15.8 %)	97 (7.2%)	2. 41	1.68 - 3.45	44 (27.5 %)	49 (7.7%)	4. 57	2.91-7.20
I517 - Cardiomegaly	19 (32.2 %)	11 (4.7%)	9.7 2	4.30-21.95	64 (19.1 %)	121 (9.0%)	2. 38	1.71 - 3.31	40 (25.0 %)	52 (8.1%)	3. 77	2.39-5.95
I2510 - Atherosclerotic heart disease of native coronary artery without angina pectoris	14 (23.7 %)	15 (6.4%)	4.5 8	2.07-10.16	76 (22.7 %)	220 (16.4 %)	1. 49	1.11 - 2.00	47 (29.4 %)	80 (12.5 %)	2. 91	1.93-4.40
I4891 - Unspecified atrial fibrillation	11 (18.6 %)	9 (3.8%)	5.7 8	2.27-14.71	29 (8.7 %)	107 (8.0%)	1. 09	0.71 - 1.68	23 (14.4 %)	48 (7.5%)	2. 07	1.22-3.52
J189 - Pneumonia, unspecified organism	12 (20.3 %)	10 (4.2%)	5.7 7	2.36-14.14	65 (19.4 %)	188 (14.0 %)	1. 48	1.08 - 2.01	33 (20.6 %)	65 (10.2 %)	2. 30	1.45-3.64
M7989 - Other specified soft tissue disorders	14 (23.7 %)	23 (9.7%)	2.8 8	1.38-6.03	52 (15.5 %)	177 (13.2 %)	1. 21	0.86 - 1.69	20 (12.5 %)	49 (7.7%)	1. 72	0.99-2.99
N390 - Urinary tract infection, site not specified	15 (25.4 %)	27 (11.4 %)	2.6 4	1.30-5.37	72 (21.5 %)	266 (19.9 %)	1. 11	0.82 - 1.48	23 (14.4 %)	112 (17.5 %)	0. 79	0.49-1.29
R21 - Rash and other nonspecific skin eruption	12 (20.3 %)	23 (9.7%)	2.3 6	1.10-5.09	42 (12.5 %)	175 (13.1 %)	0. 95	0.67 - 1.37	20 (12.5 %)	63 (9.8%)	1. 31	0.77-2.24
R51 - Headache	18 (30.5 %)	40 (16.9 %)	2.1 5	1.12-4.12	74 (22.1 %)	292 (21.8 %)	1. 02	0.76 - 1.36	28 (17.5 %)	114 (17.8 %)	0. 98	0.62-1.54
R509 - Fever, unspecified	19 (32.2 %)	37 (15.7 %)	2.5 5	1.33-4.89	99 (29.6 %)	357 (26.6 %)	1. 16	0.89 - 1.50	34 (21.3 %)	84 (13.1 %)	1. 79	1.15-2.78
R918 - Other nonspecific abnormal finding of lung field	23 (39.0 %)	7 (3.0%)	20. 90	8.36-52.24	82 (24.5 %)	215 (16.0 %)	1. 70	1.27 - 2.26	38 (23.8 %)	63 (9.8%)	2. 85	1.82-4.46
Z7901 - Long term (current) use of anticoagulants	12 (20.3 %)	12 (5.1%)	4.7 7	2.02-11.26	39 (11.6 %)	111 (8.3%)	1. 46	0.99 - 2.15	31 (19.4 %)	49 (7.7%)	2. 90	1.78-4.72
Z7982 - Long term (current) use of aspirin	15 (25.4 %)	21 (8.9%)	3.4 9	1.67-7.30	67 (20.0 %)	204 (15.2 %)	1. 39	1.02 - 1.89	38 (23.8 %)	67 (10.5 %)	2. 66	1.71-4.15
Z20822 - Contact with and (suspected) exposure to COVID-19	25 (42.4 %)	42 (17.8 %)	3.4 0	1.84-6.28	105 (31.3 %)	341 (25.4 %)	1. 34	1.03 - 1.74	0	0	-	-
Z79899 - Other long term (current) drug therapy	30 (50.8 %)	72 (30.5 %)	2.3 6	1.32-4.21	143 (42.7 %)	562 (41.9 %)	1. 03	0.81 - 1.31	63 (39.4 %)	225 (35.2 %)	1. 20	0.84-1.71

ICD-10 code–description	Cohort 1 Post-mRNA COVID-19 vaccination				Cohort 2 Post-SARS-CoV-2 infection				Cohort 3 Pre-COVID-19 era			
	Cases n (%)	Controls n (%)	OR	95% CI	Cases n (%)	Controls n (%)	OR	95 % CI	Cases n (%)	Controls n (%)	OR	95% CI
Z87891 - Personal history of nicotine dependence	15 (25.4 %)	30 (12.7 %)	2.34	1.16-4.71	80 (23.9 %)	281 (21.0 %)	1.18	0.89 - 1.57	38 (23.8 %)	90 (14.1 %)	1.90	1.24-2.92
Z95810 - Presence of automatic (implantable) cardiac defibrillator	10 (16.9 %)	0	-	-	6 (1.8 %)	16 (1.2%)	1.51	0.59 - 3.89	17 (10.6 %)	9 (1.4%)	8.33	3.64-19.08

OR, odds ratio; CI confidence interval.

The same general patterns of associations (i.e. ORs >1) are observed across all three cohorts for the univariable unadjusted association analyses of top risk factors, albeit with varying levels of significance depending on the specific risk factor. Some risk factors, such as heart conditions "Cardiomyopathy, unspecified" (ORs 3.83 – 17.80), "Other cardiomyopathies" (ORs 4.16 – 53.85), "Heart failure, unspecified" (ORs 2.41–28.90), and "Cardiomegaly" (ORs 2.38 – 9.72) are consistently significantly associated with myocarditis across all three cohorts in univariable analyses, with 95% CI intervals excluding 1 (Table 4).

Primary Analyses: Multivariable (adjusted) association analyses

The initial multivariable model showed demographic characteristics associated with validated myocarditis diagnoses, including Black race, Hispanic ethnicity, residence in the Northeast region of the United States, and other/unknown insurance status; these results were observed across groups (Table 5). Consistent with the initial descriptive analysis, previous inpatient hospitalization was associated with greater odds of myocarditis across case groups (OR, 2.28–5.57; P≤0.001).

Table 5. Multivariable logistic regression of myocarditis (initial model) for Brighton Collaboration criteria-validated cases.

Independent variable (reference)	Cohort 1 Post-mRNA COVID-19 vaccinated		Cohort 2 Post-SARS-CoV-2 infection		Cohort 3 Pre-COVID-19 era	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P* -value	Odds ratio (95% CI)	*P* -value
Race (ref. White)						
Black	2.52 (1.00, 6.32)	0.049	1.74 (1.26, 2.42)	<0.001	1.37 (0.79, 2.35)	0.263
Asian	1.03 (0.10, 10.41)	0.978	1.69 (0.76, 3.74)	0.196	3.42 (1.03, 11.36)	0.045
Other/unknown	0.14 (0.03, 0.70)	0.016	0.57 (0.39, 0.85)	0.006	0.36 (0.16, 0.80)	0.013
Ethnicity (ref. non-Hispanic/unknown)						
Hispanic	5.21 (1.44, 18.88)	0.012	1.52 (0.98, 2.37)	0.064	2.59 (1.14, 5.85)	0.023
US region (ref. Northeast)						
Midwest	0.48 (0.22, 1.06)	0.068	0.36 (0.26, 0.50)	<0.001	0.23 (0.14, 0.38)	<0.001

Table 5. Multivariable logistic regression of myocarditis (initial model) for Brighton Collaboration criteria-validated cases.

Independent variable (reference)	Cohort 1 Post-mRNA COVID-19 vaccinated		Cohort 2 Post-SARS-CoV-2 infection		Cohort 3 Pre-COVID-19 era	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P* -value**	**Odds ratio (95% CI)**	***P* -value**
South	0.29 (0.10, 0.81)	0.019	0.66 (0.47, 0.93)	0.018	0.25 (0.13, 0.47)	<0.001
West	0.31 (0.06, 1.70)	0.177	0.25 (0.13 0.49)	<0.001	0.18 (0.06, 0.53)	0.002
Other/unknown	1.44 (0.33, 6.28)	0.631	0.38 (0.19, 0.77)	0.007	0.24 (0.10, 0.59)	0.002
Insurance type at index (ref. commercial)						
Medicaid	0.49 (0.17, 1.41)	0.187	1.18 (0.83, 1.67)	0.353	1.03 (0.58, 1.81)	0.932
Medicare	1.24 (0.32, 4.81)	0.760	1.10 (0.76, 1.59)	0.615	1.22 (0.69, 2.15)	0.487
Other/unknown	0.19 (0.08, 0.49)	<0.001	0.33 (0.21, 0.52)	<0.001	0.16 (0.08, 0.33)	<0.001
CCI score previous 365 days (ref. 0)						
1+	1.81 (0.85, 3.88)	0.125	1.46 (1.09, 1.96)	0.012	1.41 (0.87, 2.30)	0.167
HCU previous 182 days (ref. no specified visit)						
Inpatient hospitalization	5.57 (1.98, 15.67)	0.001	2.28 (1.68, 3.08)	<0.001	5.14 (3.25, 8.11)	<0.001
Emergency department	1.76 (0.66, 4.72)	0.259	1.21 (0.88, 1.66)	0.234	1.55 (0.97, 2.48)	0.066
Outpatient visit	0.87 (0.36, 2.08)	0.752	0.57 (0.42, 0.78)	<0.001	0.25 (0.15, 0.42)	<0.001

CCI, Charlson Comorbidity Index; HCU, healthcare utilization; ref, reference.

The multivariable associations for top risk factors during the long lookback window with validated myocarditis are shown as adjusted odds ratios in forest plots in Figure 2 (Values provided in Table 6). Among the 24 risk factors assessed from top univariable associations, four remained associated with greater odds of myocarditis across all 3 case groups even after adjusting for covariates of the initial model in the adjusted multivariable analyses. This included history of ICD diagnoses of heart conditions, "Cardiomyopathy, unspecified", "Other cardiomyopathies", "Heart failure, unspecified", and "Cardiomegaly" (OR [P value] 2.72–8.20 [≤0.032], 2.62–16.72 [≤0.015], 1.49–15.56 [≤0.07], and 1.57–5.44 [≤0.021], respectively). The point estimates for the ORs of these cardiac risk factors were the highest for Cohort 1 (ORs: 5.44-16.72), followed by Cohort 3 (ORs: 2.32-8.20), and were the most modest for Cohort 2 (ORs: 1.49-2.72), although the confidence intervals were also wider for Cohorts 1 and 3.

For some risk factors the associations were significant for only some cohorts in the multivariable analyses. This included "Sarcoidosis, unspecified" and "Other nonspecific abnormal finding of lung field" (OR 88.6; P=0.002 and OR 13.0; P <0.001, respectively) for Cohort 1, "Contact with and (suspected) exposure to COVID-19" (OR 1.37; P =0.032) for Cohort 2, and "Atherosclerotic heart disease of native coronary artery without angina pectoris" and "Presence of automatic (implantable) cardiac defibrillator" (OR 1.49; P=0.043 and OR 7.15; P <0.001, respectively), for Cohort 3.

Some associations ("Obesity, unspecified", "Long term [current] use of anticoagulants") were only observed during the shorter lookback period (<90 days before myocarditis diagnosis) among validated

cases across groups, but not in the long lookback period (up to 5 years; Figure 3). However, there was no consistent trend when comparing between long and short lookback windows.

Most of the remaining top risk factors from the univariable association analyses were no longer significantly associated with validated myocarditis upon adjustment of covariates in the multivariable analyses, including "Atherosclerotic heart disease of native coronary artery without angina pectoris", "Unspecified atrial fibrillation", "Pneumonia, unspecified organism", "Other specified soft tissue disorders".

Table 6. Top risk factors during the long lookback window for validated myocarditis with adjusted (multivariable) odds ratios (95% CIs).

Independent variables	**Cohort 1** **Post-mRNA COVID-19 vaccinated**		**Cohort 2** **Post-SARS-CoV-2 infection**		**Cohort 3** **Pre-COVID-19 era**	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P* - value**	**Odds ratio (95% CI)**	***P* - value**
A00_B99 - Certain infectious and parasitic diseases	2.10 (1.03,4.28)	0.040	0.82 (0.62,1.07)	0.142	0.66 (0.42,1.03)	0.068
B349 - Viral infection, unspecified	2.64 (1.01,6.89)	0.047	1.49 (1.01,2.18)	0.043	1.23 (0.54,2.78)	0.627
D869 - Sarcoidosis, unspecified	88.57 (5.15,1524.63)	0.002	0.90 (0.14,5.78)	0.908	5.31 (0.38,73.61)	0.213
E669 - Obesity, unspecified	2.15 (0.95,4.88)	0.067	1.05 (0.78,1.42)	0.726	1.15 (0.7,1.88)	0.584
G8929 - Other chronic pain	2.12 (0.95,4.73)	0.067	0.77 (0.55,1.09)	0.138	0.49 (0.28,0.85)	0.012
I428 - Other cardiomyopathies	16.72 (1.73,161.76)	0.015	2.62 (1.21,5.69)	0.015	6.54 (2.55,16.81)	<0.001
I429 - Cardiomyopathy, unspecified	5.92 (1.16,30.23)	0.032	2.72 (1.57,4.71)	<0.001	8.20 (3.89,17.30)	<0.001
I509 - Heart failure, unspecified	15.56 (3.20,75.77)	<0.001	1.49 (0.97,2.28)	0.07	2.81 (1.56,5.06)	<0.001
I517 - Cardiomegaly	5.44 (1.95,15.16)	0.001	1.57 (1.07,2.3)	0.021	2.32 (1.30,4.13)	0.004
I2510 - Atherosclerotic heart disease of native coronary artery without angina pectoris	1.85 (0.65,5.24)	0.246	0.93 (0.65,1.34)	0.698	1.78 (1.04,3.04)	0.034
I4891 - Unspecified atrial fibrillation	2.85 (0.84,9.75)	0.094	0.67 (0.41,1.1)	0.112	1.20 (0.63,2.30)	0.57
J189 - Pneumonia, unspecified organism	2.28 (0.70,7.38)	0.171	1.00 (0.70,1.43)	0.989	0.89 (0.50,1.60)	0.705
M7989 - Other specified soft tissue disorders	1.99 (0.82,4.82)	0.129	0.84 (0.58,1.23)	0.372	0.77 (0.38,1.58)	0.481
N390 - Urinary tract infection, site not specified	1.75 (0.69,4.41)	0.239	0.90 (0.65,1.25)	0.533	0.61 (0.34,1.08)	0.091
R21 - Rash and other nonspecific skin eruption	1.70 (0.68,4.26)	0.256	0.84 (0.57,1.24)	0.384	0.89 (0.47,1.67)	0.707
R51 - Headache	1.97 (0.91,4.26)	0.087	0.91 (0.66,1.25)	0.55	0.59 (0.33,1.03)	0.063
R509 - Fever, unspecified	2.18 (0.95,5.00)	0.067	0.94 (0.70,1.27)	0.701	1.07 (0.62,1.85)	0.8

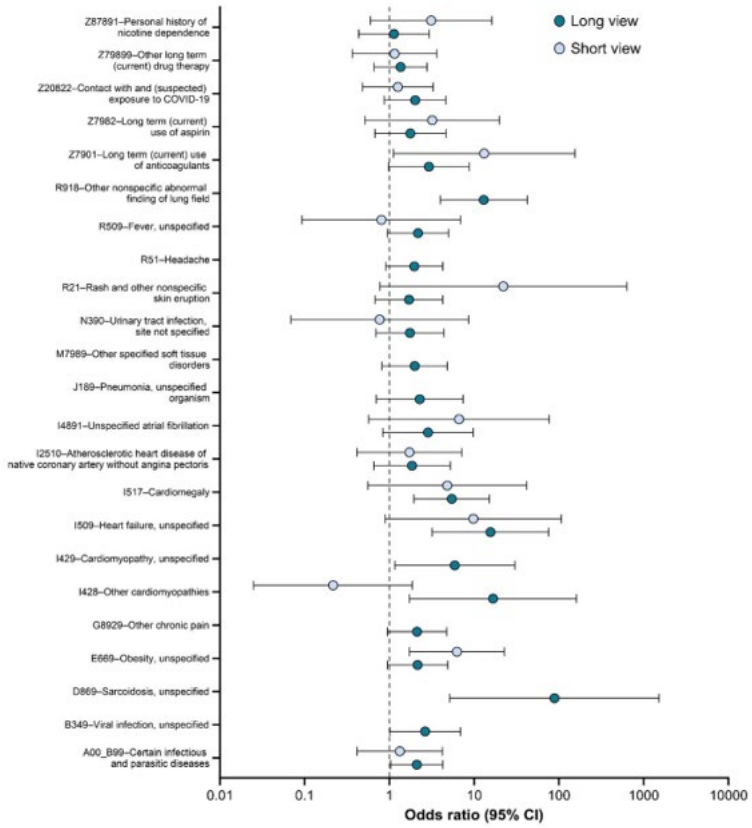
Table 6. Top risk factors during the long lookback window for validated myocarditis with adjusted (multivariable) odds ratios (95% CIs).

Independent variables	Cohort 1 Post-mRNA COVID-19 vaccinated		Cohort 2 Post-SARS-CoV-2 infection		Cohort 3 Pre-COVID-19 era	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P* - value**	**Odds ratio (95% CI)**	***P* - value**
R918 - Other nonspecific abnormal finding of lung field	12.99 (3.99,42.36)	<0.001	1.01 (0.71,1.43)	0.968	1.35 (0.76,2.4)	0.305
Z7901 - Long term (current) use of anticoagulants	2.93 (0.98,8.74)	0.054	1.01 (0.65,1.55)	0.98	1.78 (0.96,3.30)	0.068
Z7982 - Long term (current) use of aspirin	1.77 (0.67,4.66)	0.247	1.01 (0.70,1.45)	0.979	1.56 (0.89,2.75)	0.122
Z20822 - Contact with and (suspected) exposure to COVID-19	2.01 (0.87,4.65)	0.102	1.37 (1.03,1.83)	0.032	--	--
Z79899 - Other long term (current) drug therapy	1.35 (0.66,2.78)	0.409	0.74 (0.55,1.00)	0.048	0.76 (0.48,1.21)	0.25
Z87891 - Personal history of nicotine dependence	1.13 (0.44,2.95)	0.798	0.86 (0.62,1.19)	0.355	1.11 (0.66,1.87)	0.699
Z95810 - Presence of automatic (implantable) cardiac defibrillator	--	--	1.09 (0.39,3.05)	0.871	7.15 (2.64,19.32)	<0.001

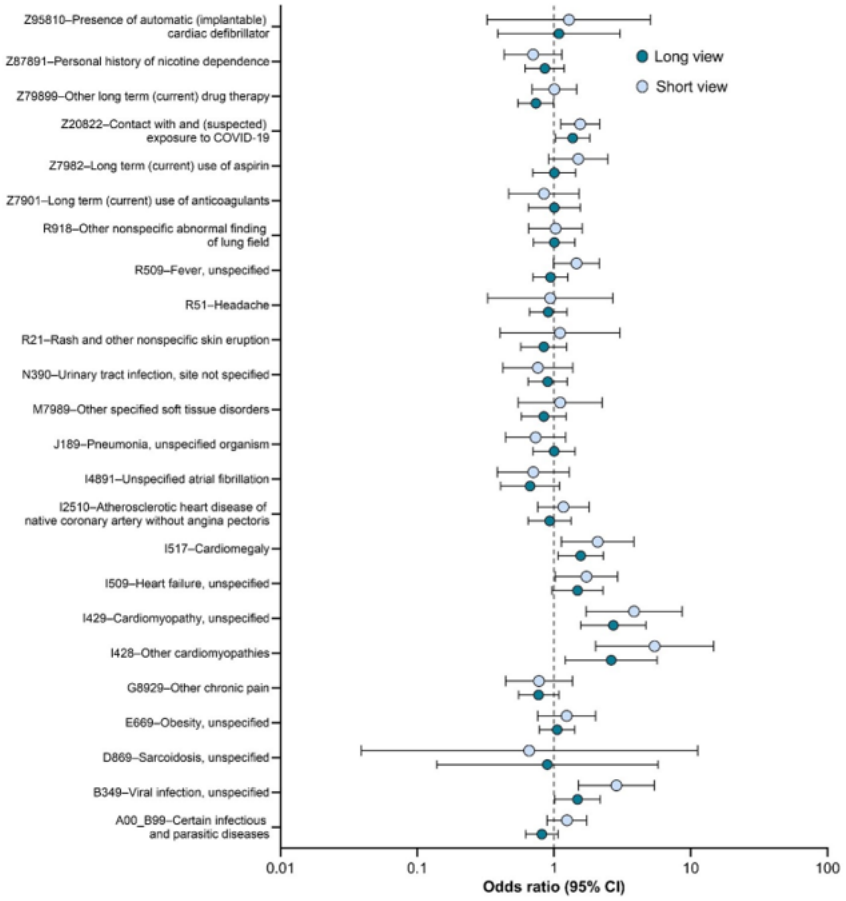
ICD-10, International Classification of Diseases, Tenth Revision; OR, odds ratio.
Associations were adjusted for the following covariates: race, ethnicity, geographic region, insurance type, Charlson Comorbidity Index, and healthcare utilization in the previous 182 days.

Figure 3. Adjusted multivariable analyses of odds ratios and 95% CI of validated myocarditis cases during the long lookback (all previous time in the database up to 6 years) and short lookback (up to 90 days) windows for (A) Cohort 1, (B) Cohort 2, and (C) Cohort 3.

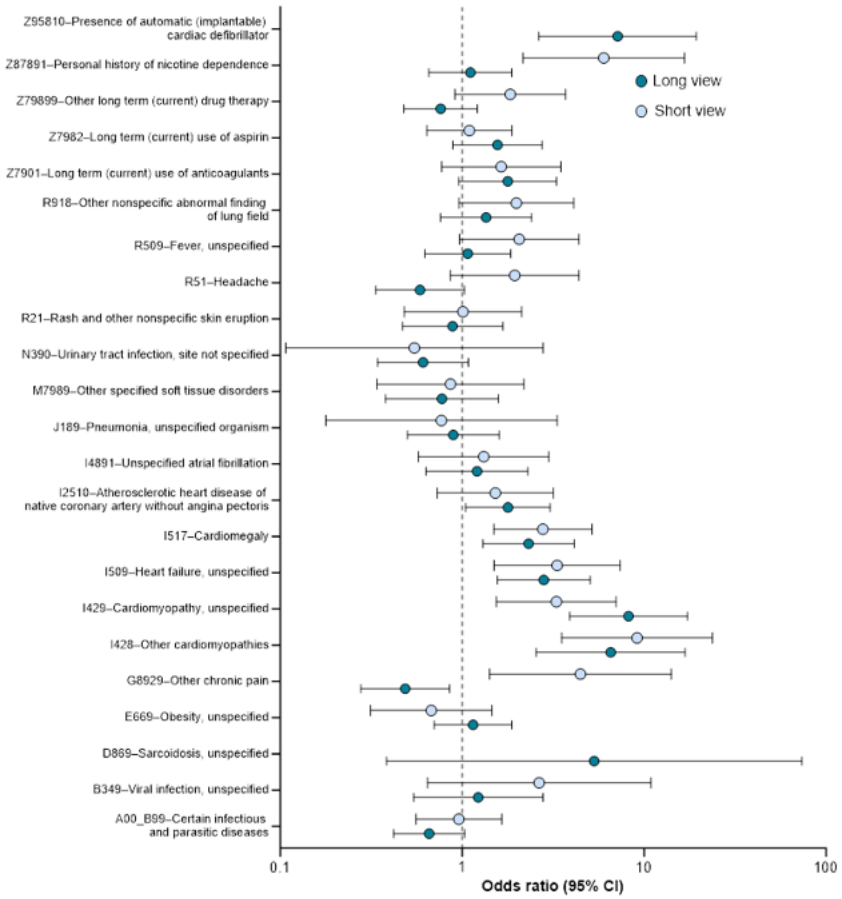
A



B


Z95810–Presence of automatic (implantable) cardiac defibrillator
Z87891–Personal history of nicotine dependence
Z79899–Other long term (current) drug therapy
Z20822–Contact with and (suspected) exposure to COVID-19
Z7982–Long term (current) use of aspirin
Z7901–Long term (current) use of anticoagulants
R918–Other nonspecific abnormal finding of lung field
R509–Fever, unspecified
R51–Headache
R21–Rash and other nonspecific skin eruption
N390–Urinary tract infection, site not specified
M7989–Other specified soft tissue disorders
J189–Pneumonia, unspecified organism
I4891–Unspecified atrial fibrillation
I2510–Atherosclerotic heart disease of native coronary artery without angina pectoris
I517–Cardiomegaly
I509–Heart failure, unspecified
I429–Cardiomyopathy, unspecified
I428–Other cardiomyopathies
G8929–Other chronic pain
E669–Obesity, unspecified
D869–Sarcoidosis, unspecified
B349–Viral infection, unspecified
A00_B99–Certain infectious and parasitic diseases
Long view
Short view
0.01
0.1
1
10
100
Odds ratio (95% CI)

C



Cohort 1: post-mRNA COVID-19 vaccination myocarditis; Cohort 2: post-SARS-CoV-2 infection myocarditis; Cohort 3: pre-COVID-19 era myocarditis. The multivariable associations were adjusted for the following covariates: race, ethnicity, geographic region, insurance type, Charlson Comorbidity Index, and healthcare utilization in the previous 182 days.

Secondary Analyses 1

Multivariable modelling was not possible for the *a priori* specified subgroups due to the small counts observed.

Secondary Analyses 2

The PPV for myocarditis ICD-10 codes compared with Brighton Collaboration criteria Levels 1–3 was 49% in Cohort 1, 77% in Cohort 2, and 65% in Cohort 3, and varied by age, ethnicity, comorbidities, care setting, and group (Table 7). Of note, in Cohort 1, PPV was higher in subjects <25 versus ≥25 years old (90% vs 41%), in Hispanic versus non-Hispanic subjects (89% vs 46%), in subjects with a Charlson Comorbidity Index (CCI) score of 0 versus ≥1 (63% vs 39%), and in subjects diagnosed in the inpatient/emergency department (IP/ED) versus outpatient settings (70% vs 30%). In Cohorts 2 and 3, PPV was also higher in IP/ED versus outpatient settings (80% vs 62% and 76% vs 51%, respectively), but similar by age, ethnicity, and CCI score. No PPV differences were noted by sex, race, geographic region, insurance type, or previous healthcare use for any group.

Table 7. Positive predictive values for myocarditis ICD-10 codes compared with Brighton Collaboration-defined myocarditis by age, race/ethnicity, CCI, and diagnosis setting.

	All Settings	IP/ED	Outpatient
Cohort 1: Post-COVID-19 vaccinated (all ages and comorbidity profiles)	49% (59/120)	70% (40/57)	30% (19/63)
Ages <25	90% (18/20)	88% (15/17)	100% (3/3)
Ages 25+	41% (41/100)	63% (25/40)	27% (16/60)
CCI 0	63% (31/49)	83% (25/30)	32% (6/19)
CCI 1+	39% (28/71)	56% (15/27)	30% (13/44)
Hispanic	89% (8/9)	100% (8/8)	0% (0/1)
Non-Hispanic/unknown	46% (51/111)	65% (32/49)	31% (19/62)
Cohort 2: Post-SARS-CoV-2 infection (all ages and comorbidity profiles)	77% (335/435)	80% (294/369)	62% (41/66)
Ages <25	69% (65/94)	73% (58/80)	50% (7/14)
Ages 25+	79% (270/341)	82% (236/289)	65% (34/52)
CCI 0	76% (159/210)	80% (142/178)	53% (17/32)
CCI 1+	78% (176/225)	80% (152/191)	71% (24/34)
Hispanic	72% (36/50)	75% (30/40)	60% (6/10)
Non-Hispanic/unknown	78% (299/385)	80% (264/329)	63% (35/56)
Cohort 3: Pre-COVID-19 era (all ages and comorbidity profiles)	65% (160/245)	76% (106/140)	51% (54/105)
Ages <25	60% (26/43)	55% (16/29)	71% (10/14)
Ages 25+	66% (134/202)	81% (90/111)	48% (44/91)
CCI 0	68% (62/91)	74% (45/61)	57% (17/30)
CCI 1+	64% (98/154)	77% (61/79)	49% (37/75)
Hispanic	67% (16/24)	67% (10/15)	67% (6/9)
Non-Hispanic/unknown	65% (144/221)	77% (96/125)	50% (48/96)

CCI, Charlson Comorbidity Index; ED, emergency department; IP, inpatient.

MAH Discussion on Study Limitations

The study has several limitations. The final data set of validated myocarditis was small, limiting the power to detect weaker associations. As is the case with any study based on secondary data sources, outcome misclassification is a possibility, as delayed and misdiagnosis of myocarditis are potentially high as previously noted[5,6,7] . Furthermore, ICD-10 codes may be incorrect or may be included as part of the diagnostic rule-out process or a record of a historical myocarditis event rather than an indication of a recent myocarditis. However, the validation by clinical note review, which was conducted concurrently, enabled evaluation of potential misclassification of myocarditis using the Brighton Collaboration criteria. Of note, this adjudication approach was also subject to some potential misclassification as the clinical assessment was based on technology-enabled extraction of note snippets rather than full medical record review, and the clinicians performing the review were not trained specifically in the field of cardiology. Another potential limitation is that conditions not requiring treatment or office visits may be systematically under-recorded; therefore, it is possible that this study only captured severe conditions in the risk factor models. Finally, we cannot exclude the possibility that

[5] Harvell B, Henrie N, Ernst AA, Weiss SJ, Oglesbee S, Sarangarm D, Hernandez L. The meaning of elevated troponin I levels: not always acute coronary syndromes. Am J Emerg Med 2016;34:145-148

[6] Albertson TE, Hansen C, Bihari S, Gayed J, Xu X, Simon-Campos JA, Dever ME, Cardona JF, Mitha E, Baker JB, Keep G, Oladipupo I, Mensa FJ, Feng Y, Ma H, Koury K, Mather S, Ianos CA, Anderson AS, Tureci O, Sahin U, Gruber WC, Gurtman A, Sabharwal C, Kitchin N, C CCTG. Serum troponin I assessments in 5- to 30-year-olds after BNT162b2 vaccination. *Infect Dis Ther* 2024;13:699-714.

[7] Deady M, Duncan R, Sonesen M, Estiandan R, Stimpert K, Cho S, Beers J, Goodness B, Jones LD, Forshee R, Anderson SA, Ezzeldin H. A computable phenotype algorithm for postvaccination myocarditis/pericarditis detection using real-world data: validation study. J Med Internet Res 2024;26:e54597

a patient was diagnosed with myocarditis or had other risk factors before entry into the Optum Market Clarity database.

MAH Discussion and Conclusion

Results of the primary objective identified top risk factors including histories of heart conditions and recent healthcare utilization, suggesting that predisposing risk factors contributed to myocarditis across all three settings.

Results could not be generated for the secondary objective of multivariable modelling for the *a priori* specified subgroups due to the small counts observed for validated myocarditis cases.

Results of the secondary objective of assessing and comparing the concordance of ICD-based myocarditis case definitions to the Brighton Collaboration criteria validated case definition showed variation in PPV by patient characteristics and diagnostic settings, indicating a high degree of potential misclassification using ICD-based diagnoses.

In conclusion, the accurate ascertainment of myocarditis diagnosis and adequate capture of medical history during the assessment of patients' longitudinal journeys is important to allow contextualization of safety events, enabling better public health insights and potential mitigation efforts.

As a descriptive study intended to characterize the risk factors for myocarditis across three different settings and to assess the validity of myocarditis diagnosis case definitions in administrative data, the study was not intended to specifically evaluate safety. However, given that a cohort of COVID-19 mRNA vaccinated individuals was evaluated alongside two unvaccinated cohorts, the opportunity for comparisons exists. This analysis shows that a history of ICD-based diagnoses of heart conditions such as "Cardiomyopathy, unspecified", "Other cardiomyopathies", "Heart failure, unspecified", and "Cardiomegaly" was associated with greater odds of myocarditis across all 3 case groups, indicating that such predisposing factors may be contributors the development of myocarditis of any cause.

Therefore, no new significant safety data has emerged from this study that could impact the benefit-risk of the Pfizer-BioNTech COVID-19 vaccine.

The results from Study C4591055 do not alter the benefit-risk profile of the Pfizer-BioNTech COVID-19 vaccine. The primary and secondary objectives did not assess risks associated with any mRNA COVID-19 vaccines in general nor the Pfizer-BioNTech COVID-19 vaccine specifically. None of the analyses conducted in this study provide any new significant information that would impact the benefit-risk profile of the Pfizer-BioNTech COVID-19 vaccine.

2.3.3. Discussion on clinical aspects

This application concerns the final report of the PASS study C4591055 - Assessment of Risk Factors for Myocarditis in the United States (US) Using Electronic Health Records and Claims Data.

No specific analyses were performed for the paediatric population or for those receiving Comirnaty.

The primary objective of the study was to examine and compare demographics, medical history and comorbidities that may be associated with the risk of myocarditis in each of three cohorts: Myocarditis after mRNA COVID-19 vaccine; myocarditis after SARS-CoV-2 infection (2020-2022); or acute/viral myocarditis prior to the COVID-19 era (pre-2020).

The study was a non-interventional, retrospective, observational cohort study with a nested case-control design, based on data from deidentified individuals diagnosed with myocarditis including in the US-based Electronic Heath Record (HER) data from Optum.

Initially, 64,052 subjects were identified from 1 January 2016 to 31 March 2023. After applying the stated selection criteria, the study included 800 subjects with ICD-based myocarditis and 3200 matched controls, including 120 subjects in the post-mRNA COVID-19 vaccination case group (Cohort 1), 435 subjects in the post-SARS-CoV-2 infection case group (Cohort 2), and 245 subjects in the pre-COVID-19 era case group (Cohort 3). After clinical review, 554/800 (69.3%) patients had validated myocarditis by Brighton Collaboration criteria Levels 1–3, including 59/120 (49%), 335/435 (77%), and 160/245 (65%) validated in Cohorts 1, 2, and 3, respectively. The median age was 40-46,5 years in the three cohorts. The overall C4591055 cohort consists of 4000 patients in total between cases and controls. Of this, the 0-10 year age category makes up about 3% and 11-20 year age category makes up about 10%.

The overall most common reported myocarditis code was "myocarditis unspecified", followed by sarcoid myocarditis (cohort 1), infective myocarditis (cohort 2) and acute myocarditis unspecified (cohort 2 and 3). Many risk factors were identified, and the same general pattern of associations were observed in all three cohorts. Risk factors such as heart conditions and recent hospitalisation were associated with greater odds of myocarditis in all three cohorts.

It can be agreed with the MAH that limitation of the study includes the limited final dataset, and the difficulties when using secondary data sources to get information on for example previous medical conditions and correct medical classification. In addition, the study was based on US data only. The presented data did not identify any new safety concerns for Comirnaty.

Myocarditis and pericarditis are already included in section 4.4 and 4.8 in the SmPC. The present warning in section 4.4 is worded as follows: "*There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition"*.

No SmPC updates has been proposed based on the presented study data, which is endorsed since no actionable additional information about risk factors concerning myocarditis and pericarditis has been presented through this study, nor were any new safety concerns identified. No specific paediatric data has been presented.

The B/R of Comirnaty remains positive.

3. CHMP overall conclusion and recommendation

The results obtained from one observational cohort study based on US data sources did not identify any new safety concerns for Comirnaty. Myocarditis and pericarditis are already included in sections 4.4 and 4.8 in the SmPC. No further, actionable information has been presented. Thus, no SmPC updates has been proposed based on the presented study data, which is acceptable.

☒ **Fulfilled**