NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) STUDY REPORT

Study Information

Title	Assessment of Risk Factors for Myocarditis in the United States (US) Using Electronic Health Records and Claims Data
Protocol number	C4591055
Version identifier of the study report	1.0
Date	28 October 2025
EU Post Authorization Study (PAS) register number	EUPAS104403
Active substance	Pfizer-BioNTech coronavirus disease 2019 (COVID-19) Vaccine is single-stranded, 5'-capped messenger ribonucleic acid (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine
Research question and objectives	Research 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). 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 objectives: 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
Country(-ies) of study	United States.
Author	[redacted]

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Not Applicable

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Not Applicable

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
API	Application Programming Interface
CCC	Complex chronic conditions
CDC	Centers for Disease Control and Prevention
CCI	Charlson Comorbidity Index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPT	Current Procedure Terminology
ECG	Electrocardiogram
ED	Emergency department
EHR	Electronic health records
EMA	European Medicines Agency
EMB	Endomyocardial biopsy
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HCU	Healthcare Utilization
HCUP CCS	Healthcare Cost and Utilization Project Clinical Classifications Software
HEOR	Health Economics and Outcomes Research
HHV-6	Human herpes virus-6
HIPAA	Health Information Insurance Portability and Accountability Act (HIPAA) Privacy
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IDN	Integrated delivery network
IEC	Independent Ethics Committee
IP/ED	Inpatient/emergency department
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

Abbreviation	Definition
mRNA	Messenger ribonucleic acid
NDC	National Drug Center
NI	Non-interventional
NLP	Natural language processing
OR	Odds ratio
PASS	Post-Authorization Safety Study
PPV	Positive Predictive Value
QC	Quality Control
RAPID3	Routine assessment of patient index data 3
RWD	Real world data
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SQL	Structured Query Language
US	United States
YRR	Your Reporting Responsibilities

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted] Inc.

4. OTHER RESPONSIBLE PARTIES

Not Applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	26 May 2023	24 May 2023	
End of data collection	30 May 2025	30 May 2025	
Registration in the EU PAS register	25 May 2023	23 May 2023	
Final report of study results	30 November 2025	28 October 2025	

6. RATIONALE AND BACKGROUND

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria. Clinically, myocarditis can present in a variety of ways, ranging from mild symptoms of chest pain and palpitations associated with transient electrocardiogram (ECG) changes to life-threatening cardiogenic shock and ventricular arrhythmia[1]. Myocarditis is a challenging diagnosis due to the heterogeneity of clinical presentations, and several classifications exist [2,7]. During the COVID-19 era, diagnostic criteria have been based on those from the Centers for Disease Control and Prevention (CDC) and the Brighton Collaboration.[3,4] The actual incidence of myocarditis is also difficult to determine as endomyocardial biopsy (EMB), the diagnostic gold standard, is used infrequently.[2] It is estimated that approximatively 1.5 million individuals experience myocarditis per year worldwide, with the incidence varying from 1 to 40 per 100,000 depending upon the population characteristics. [5,6]

Although the etiology of myocarditis often remains undetermined, a large variety of infectious agents, systemic diseases, drugs, and toxins can cause the disease. Molecular techniques suggest that viral infections are the most important cause of myocarditis in North America and Europe with genomes of enterovirus, adenovirus, influenza viruses, human herpes virus-6 (HHV-6), Epstein-Barr-virus, cytomegalovirus, hepatitis C virus, and parvovirus B19 reported in the myocardium of patients with myocarditis.[7] In almost 50-80% of cases, no cause is ever found.[8]

Outcome and prognosis of myocarditis depend on etiology, clinical presentation, and disease stage. The fatality rate for myocarditis varies according to the methodology, geographic region, or time of the study, and generally converge to a rate of 5% of myocarditis resulting in death in the short-term, and much higher if the acute episode required admission in intensive care or use of mechanical circulatory support, or if the myocarditis diagnosis was confirmed on histology.[9,10,11,12,13,14]

To date, few risk factors have been identified for myocarditis from any cause, including younger age, male gender, as well as engagement in competitive athletics. [9,12,15,16] Population studies show that the incidence of myocarditis tends to peak around adolescence through 40 years of age. [9] During the pre-COVID-19 timeframe, the female-to-male ratio was between 1:1.5 and 1:1.7 in a series of patients with myocarditis.[17,18] Outside of these characteristics, an understanding of risk factors that predispose individuals or contribute to the development of myocarditis after exposure to infections or drugs/vaccines is limited.

Higher myocarditis risk has been reported after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, ranging from 5.4 per 100,000 persons (54 per million) for girls 5-11 years to 57.2 per 100,000 persons (572 per million) for males 30 years of age or older within a 7-day risk window of infection.[19] Heymans and Cooper reviewed a variety of studies and concluded that SARS-CoV-2 infection caused 1000 to 4000 cases of myocarditis per 100,000 people, which was higher than most other reports.[20] In a large meta-analysis, Ling et al. reported that SARS-CoV-2 infection caused 1100 cases of myocarditis per 100,000 people.[21] After the acute natural infection, from which most recover, long-term cardiovascular sequelae are possible. The risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial, with increased risk of cerebrovascular disorders (stroke, transient ischemic attack), dysrhythmias, ischemic and

non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease.[22]

Myocarditis has been reported as an adverse event (AE) following immunization with COVID-19 mRNA vaccine. In aggregate, epidemiology studies reported higher risk after Dose 2 compared to Dose 1 [23], and among younger males compared to older males or females of any age post-vaccination, with the highest excess risk reported in young males with <1 case per 10,000 vaccine doses.[24] The clinical course of post-vaccination myocarditis and pericarditis tends to be mild, responds to standard of care treatments and requires a relatively short duration of hospitalization (2-4 days).[25] Short-term data on mortality are reassuring, with some studies showing a lower mortality compared with myocarditis from other causes, and other studies finding statistically comparable rates.[26,27] The prognosis of post-mRNA COVID-19 vaccine-associated myocarditis is comparable with myocarditis from other causes.[26] Apart from male gender, younger age, and second dose of the primary series, no other risk factors have been identified for post-vaccine myocarditis.

Given the limited information obtained to date, the objective of this study was to gain an understanding of the risk factors for myocarditis in the United States (US) prior to and during the COVID-19 era. This study examined the risk factors for myocarditis in general, as well as served to advance the knowledge of myocarditis of various etiologies. Specifically, 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). This study aimed to provide a broader context for myocarditis following mRNA COVID-19 vaccine using a data source that has sufficiently detailed demographic and clinical information on a large number of patients, with availability of medical chart review to adjudicate myocarditis cases via Brighton Collaboration criteria. [28] Identifying potential new risk factors for acute/viral myocarditis prior to the COVID-19 era, myocarditis after mRNA COVID-19 vaccine, or myocarditis after SARS-CoV-2 infection is important to contextualize and mitigate safety events while providing public health insights. In addition, this large-scale population-based study using real-world data (RWD) via electronic health records (EHR) may help to identify risk factors that may differ from tertiary/referral center studies. A population-based view of patients' longitudinal journey that captures adequate medical history may also help inform potential future clinical trial inclusion/exclusion criteria, as well as generate hypotheses for potential myocarditis mechanisms of action.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study was to characterize risk factors for myocarditis in the following three cohorts:

1) myocarditis diagnosed post any type of mRNA COVID-19 vaccine,

2) myocarditis diagnosed post SARS-CoV-2 infection (2020-2022), and

3) myocarditis diagnosed prior to the COVID-19 era (pre-2020).

Among patients defined as myocarditis cases, the study specific objectives are detailed below.

Research 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).

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 objectives:

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.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1.1	31 January 2024	Administrative	Section 3. RESPONSIBLE PARTIES	Principal Investigator Change	Some Principal Investigators are no longer with Pfizer
1.1	31 January 2024	Administrative	Section 6 Milestones	Update end of data collection and final study report planned date	Most recent data available in the database at time of data collection updated to 31 March 2023
1.1	31 January 2024	Administrative	Section 9.1. Study Design Section 9.2.1. Inclusion criteria	Removal of requirement for minimum of 3 medical notes for Cohorts 2 and 3	Requirements for notes now consistent for all three Cohorts
1.1	31 January 2024	Administrative	Section 9.6. Data management	Addition of sections	Missing from previous version of the protocol to describe the data collection tools and

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
					record retention requirements
1.2	25 July 2024	Administrative	Section 6 Milestones	Update end of data collection and final study report planned date	Delays with the vendor for case adjudication and construction of the controls
2.0	11 January 2025	Substantial	Section 6 Milestones	Update end of data collection and final study report planned date	Updated study milestone needs and incorporated all former changes

9. RESEARCH METHODS

The research methods based on the final protocol are described below and presented in full in Appendix 2.

9.1. Study design

This was a non-interventional (NI), observational, retrospective cohort study utilizing a nested case-control design with secondary data collection. 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 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.

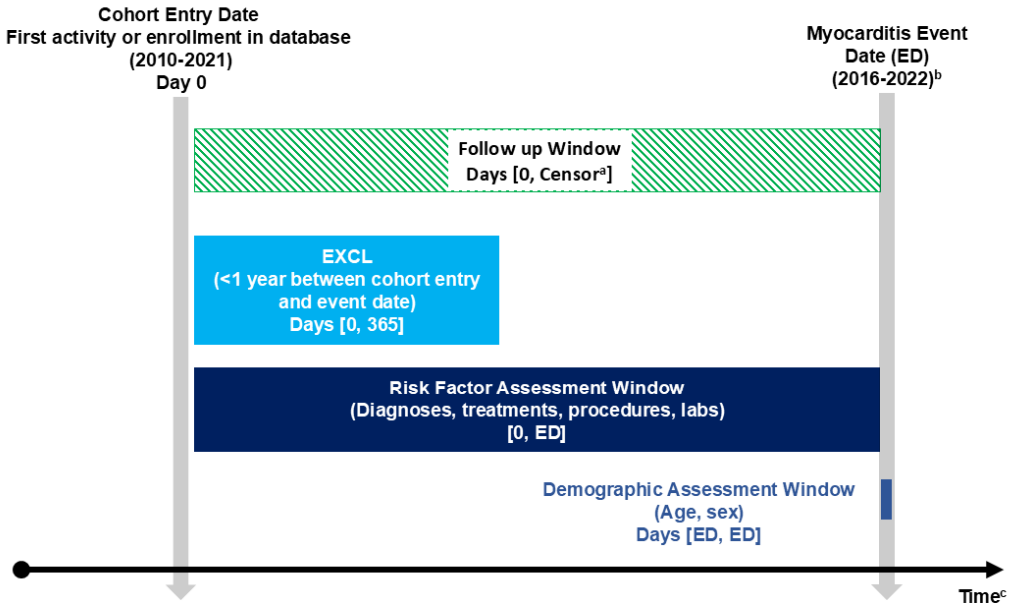
- Cohort 2 - Post-SARS-CoV-2 infection myocarditis: first date of a myocarditis diagnosis code within 8 weeks after a positive SARS-CoV-2 test from 01 January 2020 to most recent data available, allowing for at least 30 days pre and post index myocarditis diagnosis for medical notes to confirm diagnosis 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.

Additional details on index dates, episode definitions, matching criteria, matching methods, and appropriate modeling considerations were provided in the statistical analysis plan (SAP) (Appendix 4).

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

9.2. Setting

This study used the US-based Optum's deidentified Electronic Health Record (EHR) data, with supplemental linkage to Optum's Integrated Claims-Clinical adjudicated claims dataset for those patients in the EHR who also have claims data available. For a subset of patients in the EHR, data exist including patient electronic clinical notes, allowing manual clinician review at Optum to confirm myocarditis cases based on available data that align with the Brighton Collaboration criteria.[28] Review of clinical notes was not conducted for the random sample of patients without evidence of myocarditis that served as controls for the risk factor analysis. Optum's role, processes, and data are described in more detail in Section 9.5.

9.3. Subjects

9.3.1. 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. (ICD codes will be provided in the SAP)

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 date 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 date 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 the SAP (Appendix 4).

9.3.2. 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.

Relevant codes/operational criteria for this study were documented in the SAP (Appendix 4).

9.4. Variables

As described above, patients in the myocarditis cohorts were identified via ICD codes in the EHR data, and a subset were confirmed using Brighton Collaboration criteria [28] and medical record review. The main study variables of interest, including demographics, diagnostic, therapeutic and laboratory/examinations are listed in Table 2**.** Operational definitions, codes, more detailed listings of comorbidities, procedures and treatments, as well as any additional variables are provided in the SAP (Appendix 4).

Table 2. Variables and Associated Roles

Variable	Role
Year of birth	Demographic
Sex	Demographic

Table 2. Variables and Associated Roles

Variable	Role
Race/Ethnicity	Demographic
Geographic region (census regions)	Demographic
Payer type	Demographic
Date of matched encounter (index date for controls)	Index
Date of qualifying myocarditis diagnosis (index date for cases)	Diagnosis and index
Age at time of diagnosis (e.g., index date, or if unavailable then age entered or calculated in database closest to myocarditis diagnosis)	Diagnosis
Time to diagnosis (time from first Optum EHR record until first myocarditis diagnosis date)	Diagnosis
Time since diagnosis (time from first myocarditis diagnosis date until last date in the Optum EHR or date of death)	Diagnosis
Laboratory biomarkers *if feasible* (e.g. troponin, c-reactive protein, creatine kinase-myoglobin binding, creatine phosphokinase, additional lab markers to be determined)	Diagnosis
Imaging* (e.g. echocardiogram, Cardiac Magnetic Resonance Imaging, Cardiac Magnetic Resonance, ECG)	Diagnosis
Procedures* (Biopsy / cardiac biopsy)	Diagnosis
mRNA COVID-19 vaccination	Exposure
SARS-CoV-2 infection	Exposure
Medical comorbidities prior to diagnosis/index date** (e.g. Charlson categories, Feudtner Complex chronic conditions [CCC] for pediatric populations, Healthcare Cost and Utilization Project Clinical Classifications Software [HCUP CCS] groups, incl. cardiac, immune, inflammatory conditions)	Medical history
Treatments prior to diagnosis/index date* (e.g. prior cardiac or COVID-related treatments, frequency of other drug classes)	Medical history
Procedures prior to diagnosis/index date* (e.g. cardiac, HCUP CCS groups)	Medical history
Labs of interest prior to diagnosis/index date* (e.g. labs mentioned above, as well as other cardiac labs, basic metabolic panel, complete blood count, urinalysis, thyroid test, lipid panel, cultures)	Medical history
Prior HCU within the 6 months prior to diagnosis/index date (e.g. hospitalizations, emergency department, other outpatient visits)	Medical history

* Results of these tests will not be available, only whether the results supported the Brighton Criteria.

Table 2. Variables and Associated Roles

Variable	Role

** Detailed variables within each and relevant codes/operational criteria for each are documented in the SAP.

9.5. Data sources and measurement

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 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-

[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).

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 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[1],[2]. 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 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 that were

[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 04 September 2012, as first released on 26 November 2012).

identified in the EHR using the inclusion and exclusion criteria specified in Section 9.3. 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.

The Optum database is regularly updated. The date and version of the database were specified in the report of the cohort, and any intermediate datasets archived as necessary for these results that will be submitted to a regulatory agency or published.

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

9.6. Bias

Outcome misclassification was a possibility, as delayed and misdiagnosis of myocarditis is potentially high. However, the validation sub-study, which was conducted concurrently, allowed us to evaluate potential misclassification of myocarditis, as well as key risk factors of interest. Diagnostic codes may also be incorrect or may have been 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 by incorporating a multi-tier treatment and diagnostic algorithm to identify myocarditis, it allowed us to evaluate the robustness and accuracy of cases identified based on diagnosed criteria alone versus criteria that requires additional data such as medication or procedures for verification of myocarditis. Laboratory results and vital signs/other biometric measures may have been incomplete and therefore only available for a subset of the patients. Another limitation inherent to EHR databases is that information on prescriptions recorded for outpatients in this database does not necessarily indicate that the medication was consumed or taken as prescribed; similarly, medications filled over the counter or provided as samples by the physician may not have been recorded in the database. Vaccine administrations or SARS-CoV-2 infections may not have been recorded in the EHR, and so myocarditis after vaccination or COVID-19 infection may be missed. Similarly, due to the nature of EHR data, conditions not requiring treatment or office visits tend to be systematically under-recorded; therefore, it is possible that this study may only capture severe conditions that were considered in the risk factor models. Patients may have received health care outside of the network of providers and healthcare organizations that contributed to the Optum databases, or prior to having the index

diagnosis and we may not be able to exclude the possibility that a patient was diagnosed with myocarditis, as well as other risk factors, prior to entry into a healthcare system where Optum has EHR access.

9.7. Study Size

This was a NI study with no *a priori* hypotheses specified; therefore, sample size calculations were not applicable. Based on initial feasibility assessment of the Optum EHR database, there were approximately 240 myocarditis cases within 21 days of mRNA vaccination, 1,730 myocarditis cases after SARS-CoV-2 infection, and 7,200 myocarditis cases prior to 01 November 2019. In addition, the large size of the database would have allowed for matching of each myocarditis case with controls for the risk factor analyses.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the SAP, which is dated, filed and maintained by the sponsor (Appendix 4).

9.9. Statistical methods

9.9.1. Main summary measures

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.

Detailed methodology for summary of the data is documented in the SAP (Appendix 4).

9.9.2. Main statistical methods

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). Specific demographics and clinical characteristics of interest are described in Section 9.4.

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 (ie, long lookback) and short-term exposures up to 90 days earlier (ie, short lookback) were collected and modeled 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 (eg, roadside accident not considered), a total

of 24 top potential risk factors were selected for further assessment via multivariable modeling. 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 modeling with log link and binary distribution was used for both univariable and multivariable models.

Secondary objectives

In secondary analyses, all analyses above were attempted in the following *a priori* specified subgroups: 1) myocarditis case definition (based on criteria outlined in Section 9.3.1 – Inclusion Criteria); 2) age group at index date; 3) sex; and 4) available follow-up time (years), as sample sizes allowed.

In additional secondary analyses, we assessed the PPV of myocarditis diagnosis definitions that were created using algorithms in the EHR compared with those cases that were validated based on the review of the electronic medical notes as specified in Section 9.5.

Detailed methodology for summary and statistical analyses of data collected in this study were documented in the SAP (Appendix 4).

9.9.3. Missing values

None

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

None

9.10. Quality control

All codes and/or code algorithms were reviewed by the Safety Risk Lead in the Safety Surveillance and Risk Management group for the Pfizer COVID-19 vaccine program, as well as the protocol authors. The ICD-9-CM and ICD-10-CM codes used in the study were reviewed against relevant codes used in the Food and Drug Administration (FDA) Sentinel program whenever applicable; if there were any discrepancies, the Sentinel codes were used unless there was a strong rationale to use internally developed ICD codes and/or ICD algorithms instead. Additional validation of the code lists was performed if warranted. All efforts were made to ensure quality and safe storing of data and reports. Quality control (QC) checks were performed on all SAS programming, data tables, and reports generated in the course of this research. QC findings and documentation of remedial action were maintained. Storage of programming, data, and reports were carried out per standard procedures, and as specified in Section 9.5.

In the validation study, after the Optum NLP team created key term tags for use in the snippet review for the two Optum clinicians who reviewed patient notes with these key terms mentioned, the two clinicians recorded their findings from the notes regarding whether the notes supported a myocarditis diagnosis based on the Brighton Criteria. These results were provided to the HEOR team for review and any clarifications or questions were managed between the two groups until resolved.

9.11. Protection of human subjects

Subject information and consent

Not Applicable

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) review was not required.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) [29], European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [30], FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data [31], and Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)–International Society for Pharmacoepidemiology (ISPE) Special Task Force on real-world evidence in health care decision making [32].

10. RESULTS

10.1. Participants

Initially, 64,052 subjects were identified from January 1, 2016 to March 31, 2023 (Figure 2). 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 (Figure 3). 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).

Figure 2. Case identification attrition flowchart

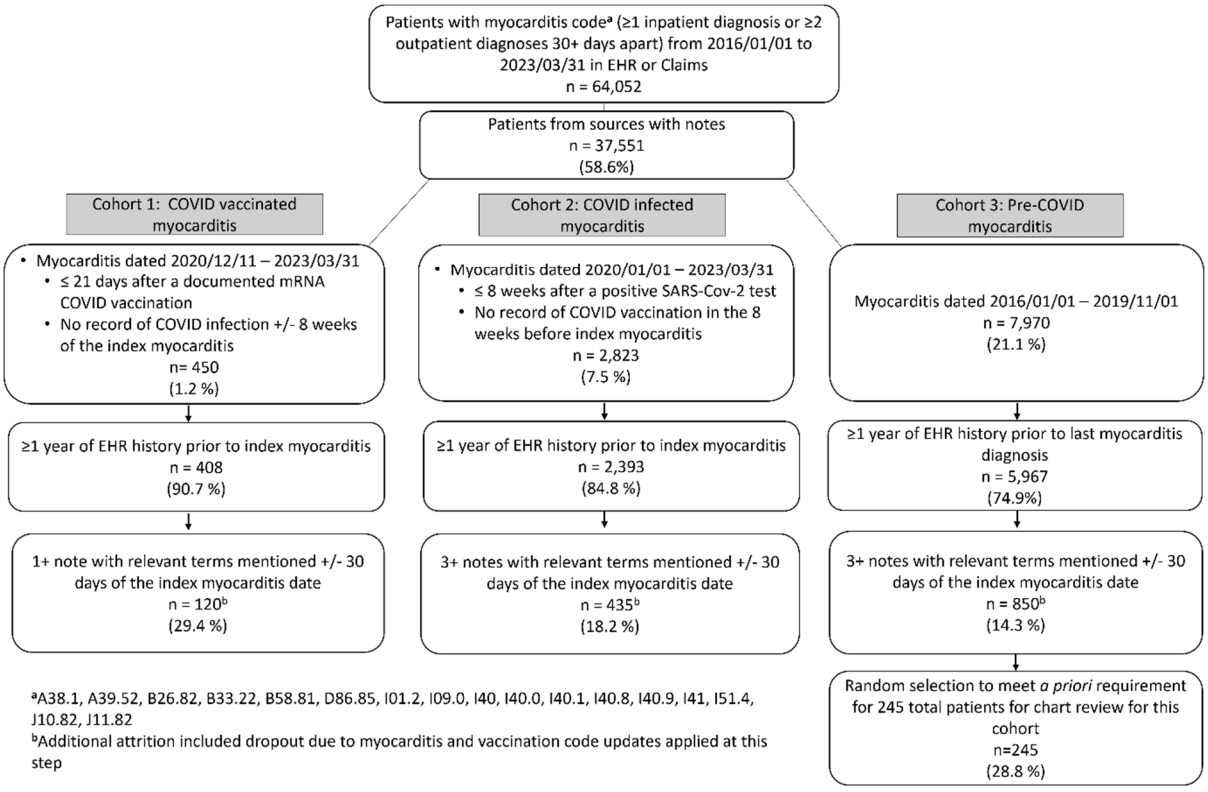
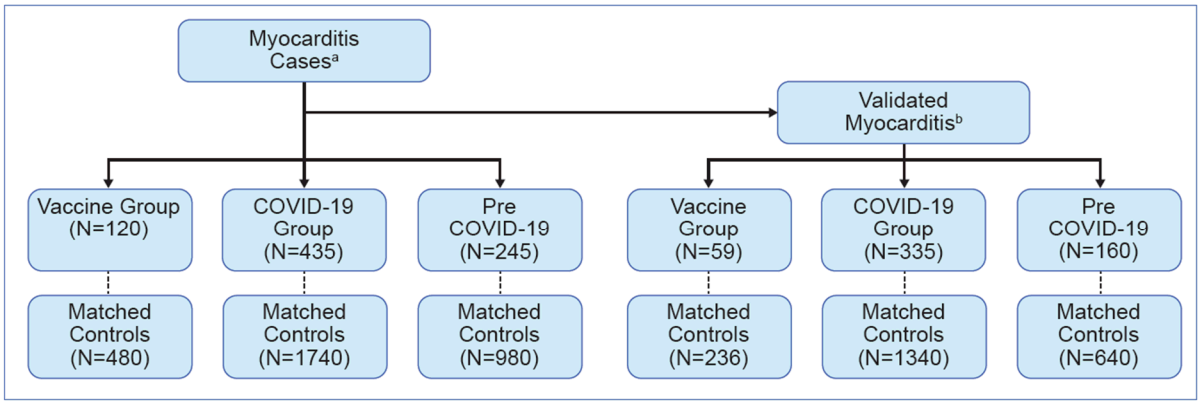


Figure 3. Matched case-control flowchart



[a] Cases identified via ICD-10 codes: A38.1, A39.52, B26.82, B33.22, B58.81, D86.85, I01.2, I09.0, I40, I40.0, I40.1, I40.8, I40.9, I41, I51.4, J10.82, J11.82.
[b] 2 clinicians reviewed medical records for myocarditis against the Brighton Collaboration criteria; levels 1-3 were considered "validated."

10.2. Descriptive data

Baseline demographics, recent healthcare use, and comorbidities among cases and matched controls are shown in Table 3A for ICD-based myocarditis and Table 3B for validated myocarditis cases. Case subjects with validated myocarditis were predominantly male sex (62.7%, 54.3%, and 57.5% from Cohorts 1, 2, and 3, respectively), with median

ages of 40.0, 52.0, and 46.5 years. The majority of myocarditis case subjects versus control subjects were White race (67.8% vs 72.9% in Cohort 1, 58.8% vs 66.6% in Cohort 2, and 68.1% vs 74.1% in Cohort 3), of non-Hispanic ethnicity (61.0% vs 76.7% in Cohort 1, 67.2% vs 66.6% in Cohort 2, and 83.1% vs 79.8% in Cohort 3), and from the Northeast (47.5% vs 25.0% in Cohort 1, 37.6% vs 23.4% in Cohort 2, and 39.4% vs 15.3% in Cohort 3) and Midwest regions of the United States (28.8% vs 42.8% in Cohort 1, 28.1% vs 40.4% in Cohort 2, and 37.5% vs 52.2% in Cohort 3).

Table 3A. 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 (%)						
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 3B. 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 (%)						
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 3B). 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 (ie, higher comorbidity burden) in the previous 365 days from the index date compared with the matched controls (Table 3B). 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)

10.3. Outcome data

The numbers of subjects across categories of outcomes, i.e. ICD-based and validated myocarditis cases, are as described in Section 10.2 Descriptive data.

The most common myocarditis ICD-10 codes among validated cases across all study groups are shown in Table 4. 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 4. 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

Table 4. 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**
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.

10.4. Main results

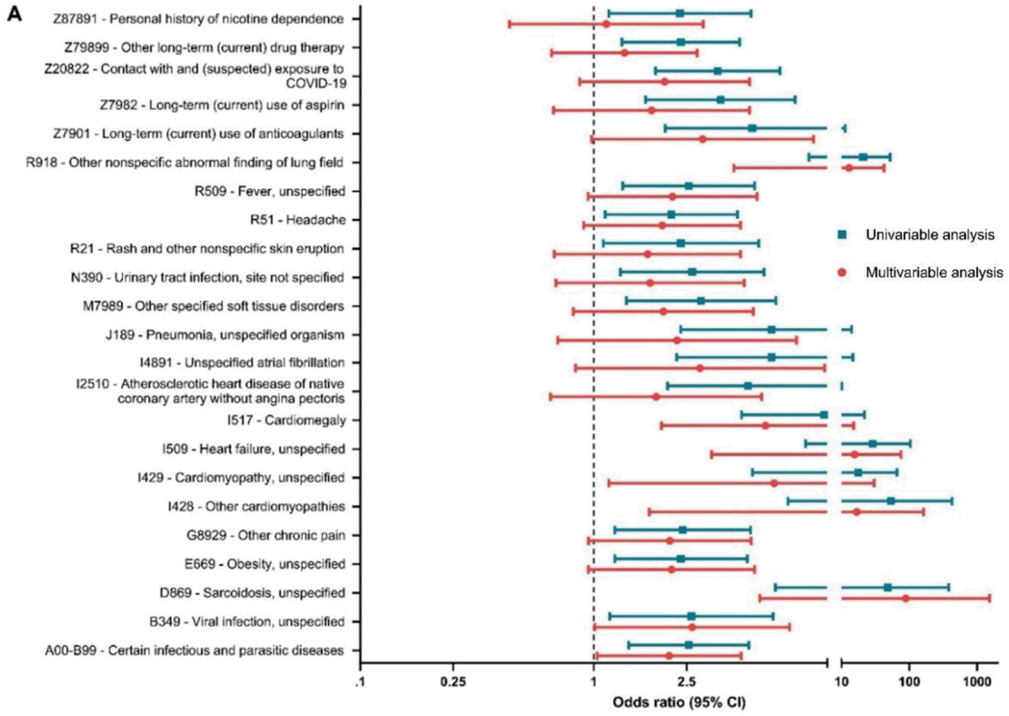
10.4.1 Primary Analyses

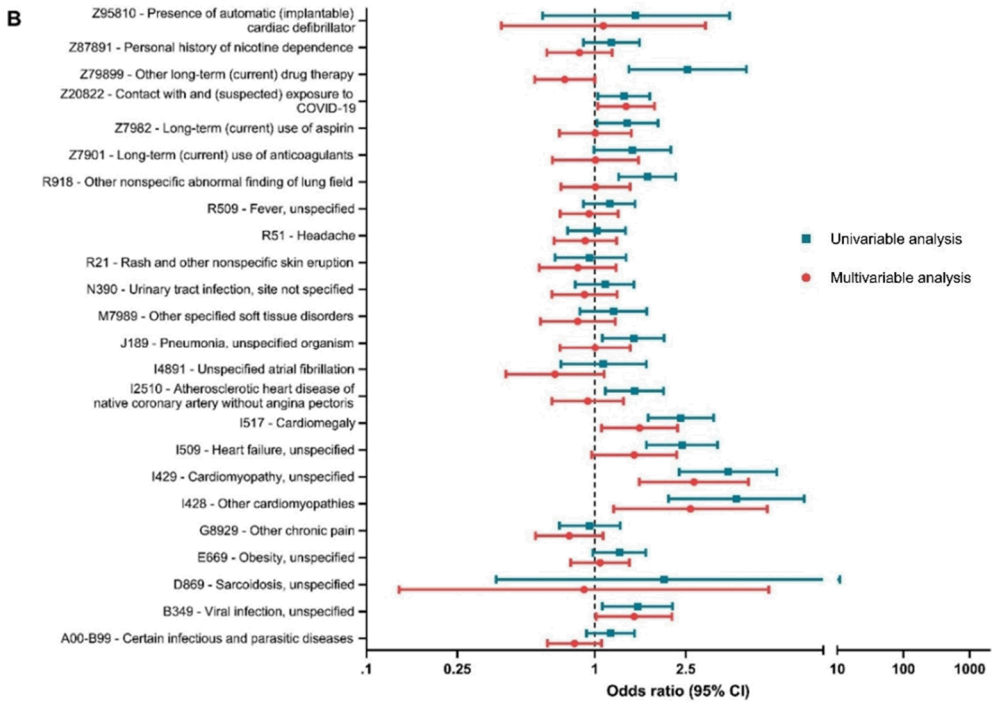
10.4.1.1 Univariable (unadjusted) association analyses

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 in Figure 4 (Values provided in Table 5). The comprehensive unadjusted univariable model results for all risk factors assessed during the long and short lookback windows for both ICD-based and validated myocarditis cases are provided in Appendix 8.1.

Figure 4. 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.





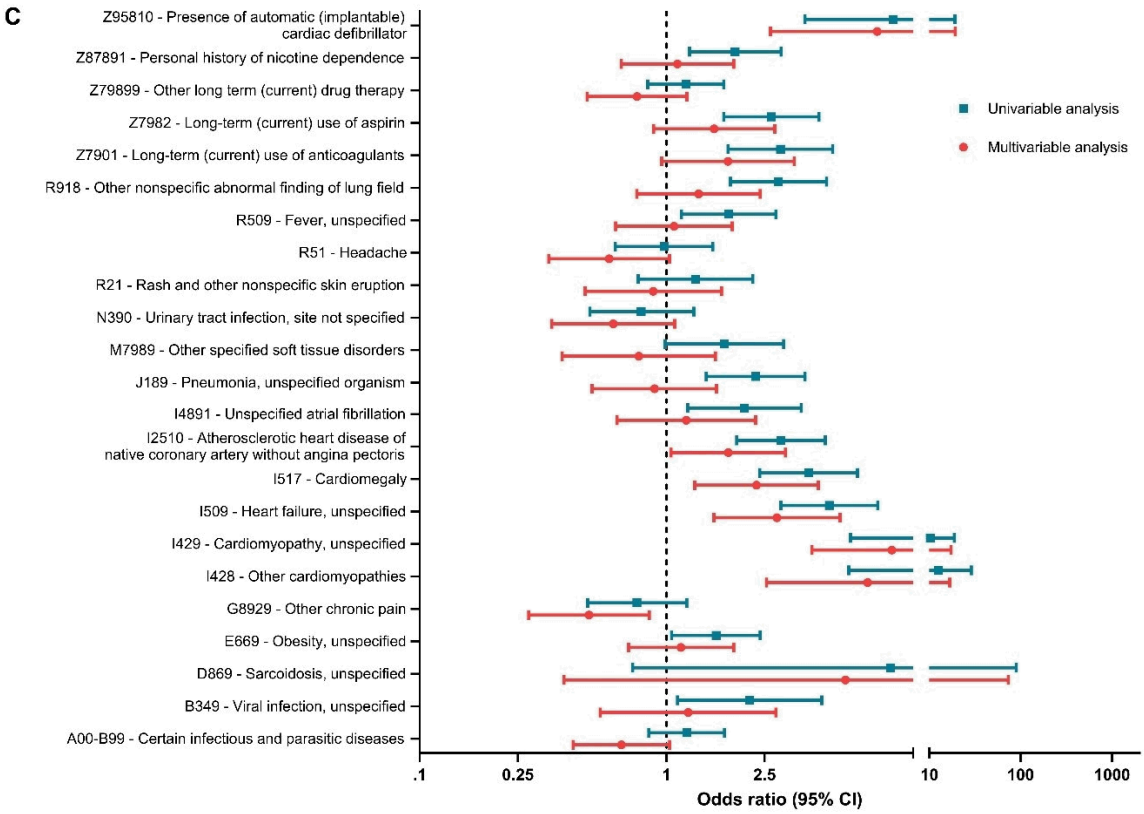


Table 5. Top risk factors during the long lookback window for validated myocarditis with unadjusted (univariable) odds ratios (95% CIs)

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
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%)	9.72	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%)	4.58	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%)	5.78	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%)	5.77	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%)	2.88	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

Table 5. 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
N390 - Urinary tract infection, site not specified	15 (25.4%)	27 (11.4%)	2.64	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%)	2.36	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%)	2.15	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%)	2.55	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%)	4.77	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%)	3.49	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%)	3.40	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%)	2.36	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
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 5).

10.4.1.2 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 6). 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). Corresponding initial multivariable model analyses data for ICD-based myocarditis cases are provided in Appendix 8.2.

Table 6. 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
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

Table 6. 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
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 4 (Values provided in Table 7). 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; Figure 4; Table 7). 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 5). 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”. The values corresponding to Figure 4 and Figure 5 for the comprehensive adjusted multivariable model results for the top 24 risk factors assessed during the long and short lookback windows for both ICD-based and validated myocarditis cases are provided in Appendix 8.2.

Table 7. 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

Table 7. Top risk factors during the long lookback window for validated myocarditis with adjusted (multivariable) odds ratios (95% CIs)

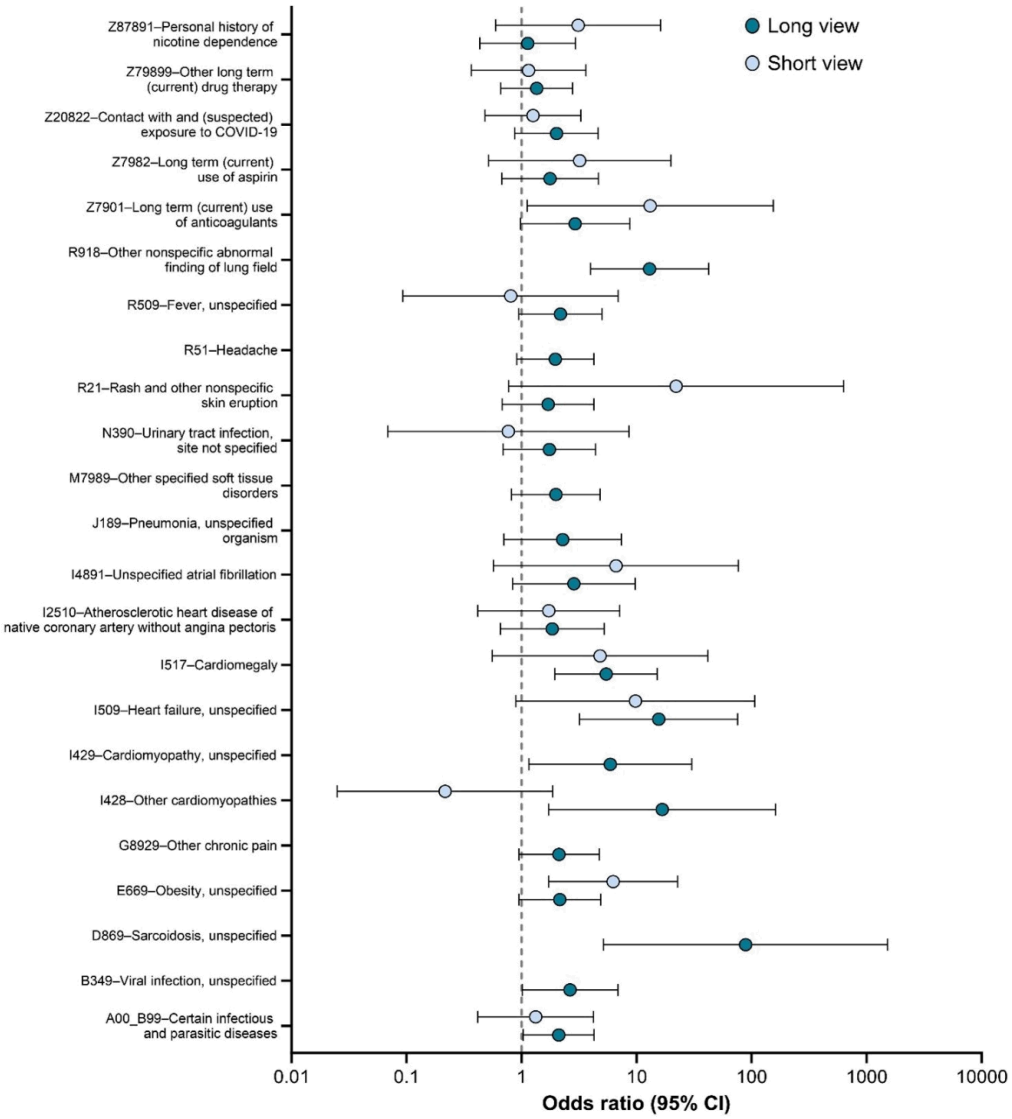
Independent variables	Cohort 1 Post-mRNA COVID-19 vaccinated		Cohort 2 Post-SARS-CoV-2 infection		Cohort 3 Pre-COVID-19 era	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P* - value	Odds ratio (95% CI)	*P* - value
R21 - Rash and other nonspecific skin eruption	1.70 (0.68,4.26)	0.256	0.84 (0.57,1.24)	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
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 5. 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.

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.

A



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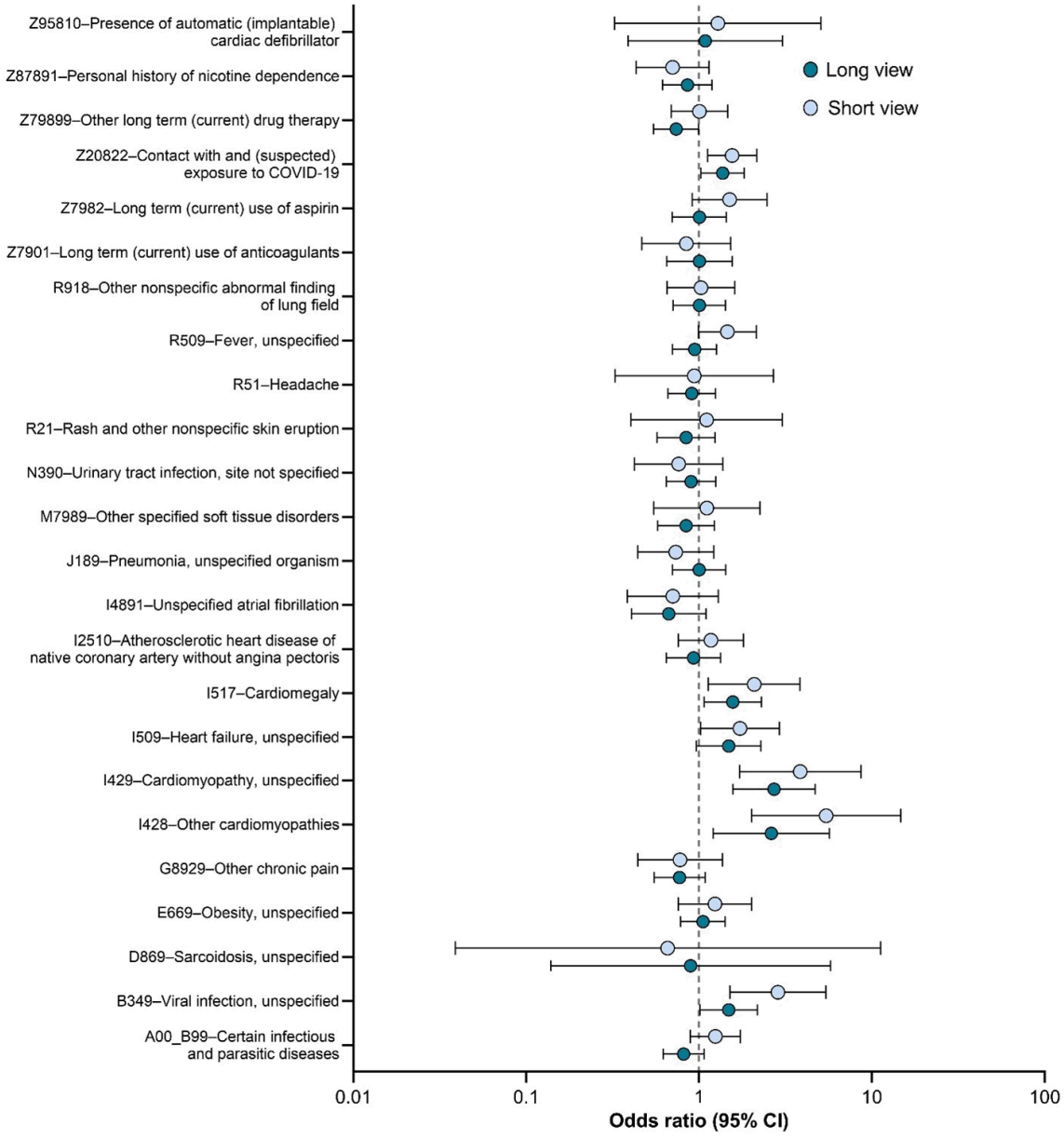
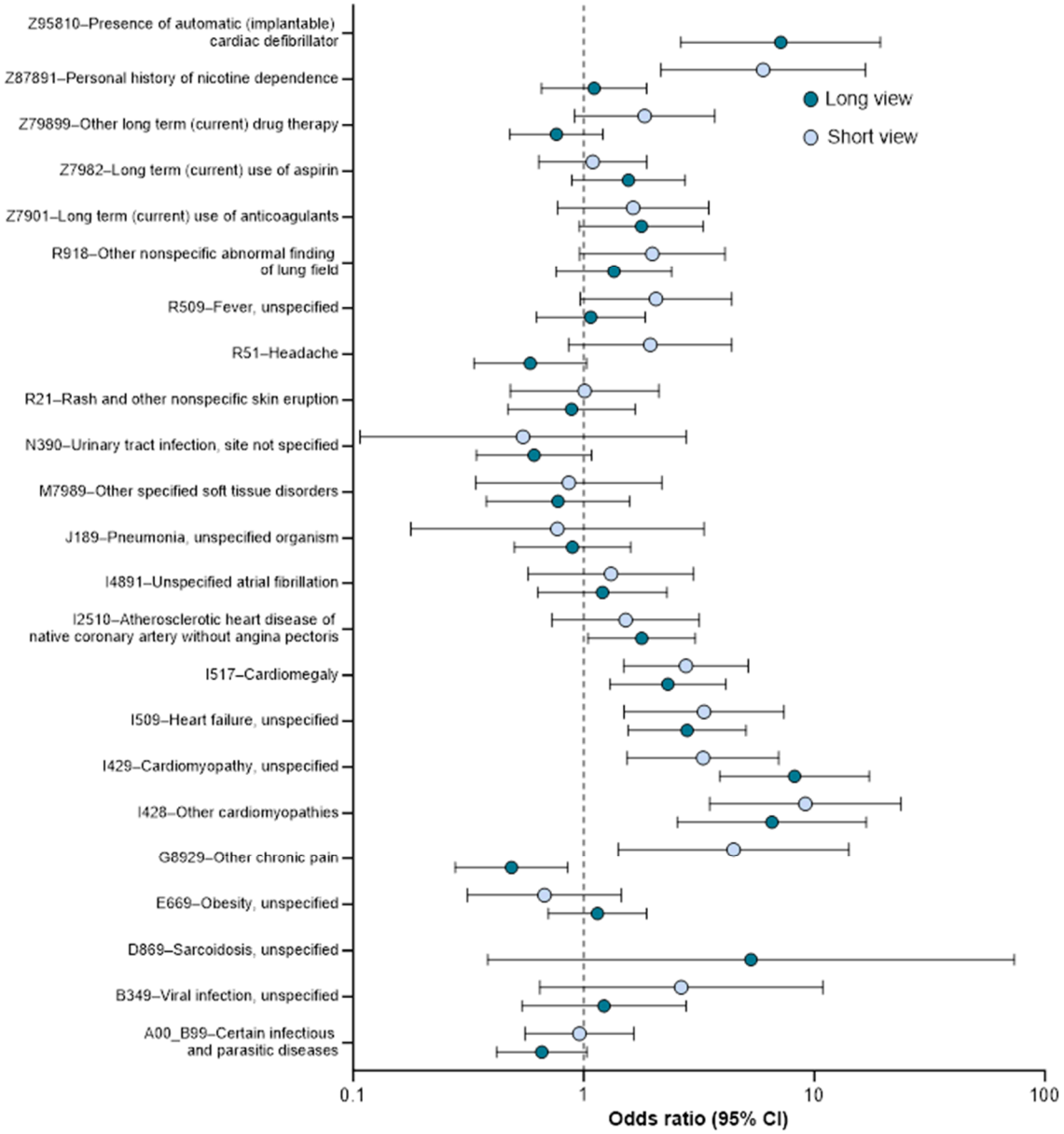


C.



10.4.2 Secondary Analyses

10.4.2.1 Secondary Analyses 1

Multivariable modeling was not possible for the *a priori* specified subgroups due to the small counts observed. Instead, descriptive tables showing counts for age and sex subgroups are provided in Appendix 8.3.

10.4.2.2 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 8). 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 (Appendix).

Table 8. 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)

Table 8. 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
Non-Hispanic/unknown	65% (144/221)	77% (96/125)	50% (48/96)

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

10.5. Other analyses

None

10.6. Adverse events/adverse reactions

This study involved data that exist as structured data. In these data sources, it was not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) could not be met.

This study also involved human review of patient-level unstructured data; unstructured data refers to verbatim medical data, including text-based descriptions such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewers were obligated to report AEs with explicit attribution to any Pfizer drug that appeared in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution was not inferred by a temporal relationship between drug administration and an AE but must have been based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety were as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appeared in the reviewed information must be recorded on the data collection tool (e.g., chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- For exposure during pregnancy in studies of pregnant women, data on the exposure to “PF-07302048 during pregnancy, were not reportable unless associated with serious or non-serious AEs.
- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed was captured in the Event Narrative section of the report form, and constituted all clinical information known regarding these AEs. No follow-up on related AEs was conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements were available due to privacy concerns with the use of secondary data sources. While not all demographic fields were completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) was reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers were limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers were removed.

Additionally, the onset/start dates and stop dates for “Illness,” “Study Drug,” and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members completed the following Pfizer training requirements:

- “Your Reporting Responsibilities (YRR) with Supplemental Topics.”

These trainings were completed by research staff members prior to the start of data collection. All trainings included a “Confirmation of Training Statement” (for signature by the trainee) as a record of completion of the training, which is kept in a retrievable format. Copies of all signed training statements were provided to Pfizer.

11. DISCUSSION

11.1. Key results

Among ICD-based myocarditis cases with clinical notes available, the proportions of validated cases were 59/120 (49%) for Cohort 1, 335/435 (77%) for Cohort 2, and 160/245 (65%) for Cohort 3, indicating a high degree of potential misclassification using ICD-based diagnoses. A substantially higher percentage of case subjects with validated myocarditis had healthcare resource use, specifically inpatient hospitalizations, in the previous 182 days from the index date compared with the matched controls. Similarly, a substantially higher percentage of case subjects with validated myocarditis had a greater comorbidity burden in the previous 365 days from the index date relative to the matched controls. However, we note that sample sizes for validated myocarditis cases were small (N=59; N=335; and N=160 among the post-COVID-19 vaccination, post-SARS-CoV-2 infection and pre-COVID-19 cohorts, respectively), which limits the precision of these estimates and warrants cautious interpretation of observed differences. In both unadjusted univariable analyses and adjusted multivariable analyses, history of cardiomyopathy (adjusted OR: 2.62−16.7; P<0.001−0.032), heart failure (adjusted OR: 1.49−15.6; P<0.001−0.070), and cardiomegaly (adjusted OR: 1.57−5.44; P=0.001−0.021) were associated with greater odds of myocarditis across all 3 case groups. Collectively, these findings suggest that patients may have certain predisposing risk factors prior to the development of myocarditis after exposure to mRNA COVID-19 vaccines, infections, and of any cause. These findings highlight the importance of evaluation of individuals who develop myocarditis to enable proper identification of their risk factors, medical histories, and comorbidities that may contribute to the event.

Diagnosis of myocarditis is challenging, with misclassification and low precision of diagnoses. [33, 34, 35] The accuracy of myocarditis ICD-10 codes varied by age, healthcare setting, and comorbidity burden. Notably, more than half of the unvalidated myocarditis cases (Brighton Collaboration criteria Levels 4 and 5) and 71% of the confirmed non-

myocarditis (Level 5) in the post-mRNA COVID-19 vaccination case group had a D86.85−sarcoid myocarditis diagnosis code. This suggests that D86.85−sarcoid myocarditis is among the most frequently misclassified ICD-10 codes when identifying true myocarditis cases in the post-mRNA COVID-19 vaccination setting. Cardiac sarcoidosis, which results from granulomatous inflammation of the myocardium, is diagnostically challenging.[36, 37] Although approximately one quarter of individuals with sarcoidosis are found to have cardiac involvement at autopsy, only ~5% of patients have clinically evident cardiac sarcoidosis.[38] Differentiation of sarcoidosis from other cardiac syndromes with similar presentations, including acute myocarditis, is important, but not always possible, and clinical misclassification is high.[37] Because of the difficulty of diagnosis, sarcoidosis may be initially overlooked;[39] thus cardiac symptoms in a patient with undiagnosed sarcoidosis may be assumed to be acute myocarditis. Collectively, this suggests difficulty in the diagnosis of myocarditis through administrative codes, particularly for cases of sarcoid myocarditis and in patients who have had a recent mRNA COVID-19 vaccination, and emphasizes the need for developing improved myocarditis case identification algorithms that take into account correlates of accuracy when using ICD-codes to identify myocarditis cases.

11.2. Strengths and limitations of the research methods

This study has several strengths. First, it is a population-based study in a real-world population, increasing generalizability and external validity. Second, the Optum® Market Clarity database has both inpatient and outpatient visits capturing diagnosis data, laboratory data, and surgical procedure data enabling the assessment of a wide range of prespecified procedures, health outcomes and clinical conditions from before myocarditis diagnosis. Finally, the longitudinal nature of the data, with its extended lookback period, enabled the assessment of clinical history that occurred further back in time.

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[33-35] 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 a patient was diagnosed with myocarditis or had other risk factors before entry into the Optum® Market Clarity database.

11.3. Interpretation

Top risk factors identified in this study include histories of heart conditions as well as prior recent healthcare utilization, suggesting that patients may have had predisposing risk factors that contributed to the development of myocarditis across all three settings assessed. Furthermore, the PPV of ICD-based myocarditis case definition compared with

the Brighton Collaboration criteria validated case definition varied by patient characteristics and diagnostic settings, indicating a relatively high degree of diagnostic misclassification in ICD-based diagnoses.

11.4. Generalizability

This study leverages Optum® Market Clarity database, a large, integrated US claims and electronic health record database, which enhances generalizability by capturing a real-world population across inpatient and outpatient settings and enabling longitudinal assessment of medical history. However, external validity may be limited by the inclusion criteria requiring sufficient clinical documentation for myocarditis validation and at least one year of prior database activity, which may result in underrepresentation of individuals with less healthcare engagement or incomplete records.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

Our study suggests that individuals diagnosed with myocarditis either before the COVID-19 pandemic, after mRNA COVID-19 vaccination, or after SARS-CoV-2 infection were more likely to have inpatient hospitalization in the past 182 days and previous history of heart conditions including cardiomyopathies, heart failure, and cardiomegaly. The capture of adequate medical history during the assessment of patients' longitudinal journey is therefore important to allow contextualization of safety events, enabling better public health insights and potential mitigation efforts.

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15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable

Document Approval Record

Document Name:	C4591055 Non-Interventional Study Report
Document Title:	C4591055

Signed By:	Date(GMT)	Signing Capacity
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]