PROTOCOL V.1.6: Clinical Outcomes after Myocarditis – a Nordic population-based cohort study

Background

Myocarditis is a rare adverse event following vaccination with the two available SARS-CoV-2 mRNA vaccines BNT162b2 and mRNA-1273. The association appears to be strongest in the younger age groups below the age of 40 years and after the second dose. The severity of clinical outcomes after myocarditis is nevertheless wide-ranging, from no sequelae to chronic heart failure or death. It is therefore important to characterize the outcome severity of myocarditis following SARS-CoV-2 mRNA vaccination compared with myocarditis not occurring immediately following vaccination and myocarditis following SARS-CoV-2 infection.

Objectives

To describe the risk of re-admission, heart failure, and death within 90-days of incident myocarditis diagnosis (occurring within 28 days of SARS-CoV-2 mRNA vaccination, occurring within 28 days of RT-PCR positive test for SARS-CoV-2, or unrelated to vaccination and infection).

Methods

Nordic Myocarditis Cohort

We will conduct a multi-country evaluation taking advantage of nationwide register data available in the Nordic countries (Denmark, Finland, Norway, and Sweden). Our study cohort will comprise all individuals aged 12 years or older who were first-time diagnosed with myocarditis as a main or secondary diagnosis (ICD-10 codes, I40.0, I40.1, I40.8, I40.9, I41.1, I41.8, or I51.4) at discharge from inpatient hospital care from January 1, 2018 to latest possible date of follow-up. Patients with any (in-patient or out-patient, main or secondary) pre-existing diagnosis of myocarditis (defined as above) or heart failure (defined as ICD-10 codes I11.0, I13.0, I13.2, I42.0, I42.7, I43.0, I50, I50.0, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9,) will be excluded from the study (3 years of wash-out prior to the day of first-time myocarditis admission[1]). To avoid potential duplicate case during 2018-2022, all individuals with matching person-specific variables will be removed from the cohort if appearing again after a first-time myocarditis diagnosis. All cases admitted for a myocarditis hospitalization within 28 days of vaccination with a SARS-CoV-2 mRNA vaccination are categorized as '*SARS-CoV-2 mRNA vaccine-associated myocarditis*', while all cases admitted for a myocarditis hospitalization within 28 days of a positive SARS-CoV-2 PCR test are categorized as '*SARS-CoV-2 infection-associated myocarditis*'. If both SARS-CoV-2 mRNA vaccinated and PCR test positive within 28 days, the latest exposure counts. Remaining cases will be categorized as '*regular myocarditis*'.

Only cases that were discharged (dead or alive) prior to 90 days before the end of the country-specific follow-up, and therefore having potential 90 days of follow-up, will be included in the study.

Outcomes

[1] For Norway, washout was only possible from January 1, 2017 onwards.

Outcomes following first-time myocarditis admission will be; a) a first-time diagnosis of heart failure (in-patient or out-patient, primary or secondary diagnosis during 90 days following *admission* for a first-time diagnosis of myocarditis, b) death during 90 days following *admission* for a first-time diagnosis of myocarditis, in addition to c) re-admission (in-patient hospitalization of any cause), during 90 days following *discharge* for a first-time diagnosis of myocarditis.

If a first-time heart failure diagnosis is diagnosed during the same hospitalization as a first-time myocarditis diagnosis, heart failure will be categorized as occurring at day 0, the day of the myocarditis in-patient admission.

Length-of-stay for a first-time myocarditis hospitalization will be estimated as 'day-of-discharge' minus 'day-of-admission' + 1. If a patient with first-time myocarditis has a subsequent in-patient hospitalization within on the day of discharge or the day after, then this hospitalization will be counted as a part of the initial first-time myocarditis hospitalization.

Cohort stratification

For comorbidity stratification will use a 'comorbidity' boolean variable which is '1' if the case has any pre-existing diagnoses (defined as 2 years prior to first-time myocarditis admission) of malignancy (ICD-10: C00-C97), cardiovascular disease (ICD-10: I00-I99), or autoimmune disease (ICD-10: K50.x, K51.x, M32.x, M05.x-M06.x, E05.0, E06.3, G35.x, L40.x, E27.1, E27.2, G12.2, M45.x, M08.1, K90.0, M33.x, L52.x, G61.0, D59.0-D59.1, D69.0, D69.3, M08.x, L93.x, G70.0, D51.0, L12.x, M31.3, M30.0, K74.3, I00.x-01.x, D86.x, M34.x, M31.5-M31.6, L80.x, M35.x), (in-patient or out-patient, main or secondary diagnoses), and otherwise '0'.

For length-of-stay stratification we will stratify length-of-stay in groups of ≤3 days, 4-6 days, and ≥ 7 days.

In addition, a stratification boolean variable will specify whether the admission of first-time myocarditis was on or after January 1, 2020 ('1') or prior this date ('0').

Statistical analysis

Outcomes by myocarditis group, given by time since myocarditis diagnosis will be compared by country-specific Kaplan-Meier plots and combined tables of 90-day relative risk and 90-day risk difference between myocarditis groups.

Country-specific cumulative incidences will be calculated for readmission (as a function of days from discharge) and heart failure and death (as a function of days from admission) as one minus the Kaplan-Meier estimate. Emigration will be a censoring event and death a censoring event for readmission and heart failure. If a first-time heart failure is diagnosed during the same hospitalization as the first-time myocarditis, the heart failure will be coded as occurring on day 1, the day after the myocarditis admission. Cumulative incidences at 10, 20, … and 90 days follow-up will be presented in figures.

In the combined aggregate tables there will not be censoring for emigration or death. Sensitivity analyses of combined numbers will be performed by age group (categorized as 12-39 years, and 40 years or older) and among women. As additional sensitivity analyses, we will restrict the cohort to individuals younger than 40 years without pre-existing diagnoses of malignancy, cardiovascular disease, or autoimmune disease.

Results

We will present a Table 1 with country-specific descriptive data on the age and sex distribution of myocarditis cases by myocarditis group, age group, and sex (cell counts between 1 and 5 will be described as '*'). In addition, we will present length-of-stay during the initial myocarditis admission, by myocarditis group. Tables 2-4 will present combined cumulative 90-day relative risk and combined cumulative 90-day risk difference between myocarditis groups of respectively heart failure, death, and readmission, with regular myocarditis as reference.

Figure 1A-D and 2A-D will present country-specific Kaplan-Meier estimates of heart failure and death, respectively, during 90-days of follow-up following diagnosis by myocarditis type, with day-of-admission as day 0 (with 10-day resolution, as described above). Figure 3A-D will present country-specific Kaplan-Meier estimates of re-admission (in-hospital of any cause), with day-of-discharge as day 0 (with 10-day resolution).