Original Article

Rate and patient features associated with recurrence of acute myocarditis

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ABSTRACT

Background: Rate and patient features associated with recurrence after acute myocarditis are largely unknown.
Methods and results: First recurrence of acute myocarditis was studied in 1662 patients aged 16–70 years using a registry data of 29 hospitals in Finland (median follow-up 4.5 years). Matched intoxication patients served as controls. Incidence rate of first time hospitalization due to acute myocarditis was 5.52 (CI 5.26–5.79) per 100,000 person-years during 2001–2008. During the first 30 days 5.5% (CI 3.5–4.4%) of patients were re-admitted to hospital with acute myocarditis ($p < 0.0001$ vs. controls). After 30 days, recurrence rate was 7.0% (CI 5.7–8.6%; $p < 0.0001$ vs. controls). Acute myocarditis recurred after 365 days in 4.7% (CI 3.2–6.7%) of patients ($p < 0.0001$ vs. controls). During the whole follow-up, recurrence rate was 10.3% (CI 8.8–12.1%; $p < 0.0001$ vs. controls) with median recurrence time of 34.5 days. Prolonged (>7 days) initial admission was associated with recurrences during (HR 2.9; CI 1.6–5.2) and after first month (HR 1.8; CI 1.2–3.2), and overall (HR 2.0; CI 1.3–3.2). Ventricular arrhythmia at initial occurrence was associated with recurrence after 30 days (HR 8.6; CI 2.5–30.1), after 1 year (HR 22.6; CI 2.5–201.4) and overall (HR 6.7; CI 2.3–6.7). Other features associated with recurrence were younger age (>365 days), inflammatory bowel disease (during first month), and chronic pulmonary disease (≥30 days).
Conclusions: Acute myocarditis reoccurs in a significant proportion of patients. Prolonged initial admission, ventricular arrhythmias, younger age, inflammatory bowel disease and chronic pulmonary disease are associated with recurrences at different phases after acute myocarditis.

1. Introduction

Acute myocarditis is an inflammatory disease of myocardium. Myocarditis is commonly caused by viral infection, with entero-, adeno- and Parvovirus B19 recognized as the most common etiologies [1]. Clinical manifestation of acute myocarditis varies from chest pain to arrhythmias and heart failure [2,3]. Currently there are no effective treatments available for viral myocarditis as immunosuppression is found not be effective [1,2]. Both short and long-term outcomes of acute myocarditis are usually good [4], but development of heart failure or ventricular arrhythmias indicates poorer prognosis [5,6]. Acute pericarditis, inflammatory disease of pericardial sac, has similar causes and pathogenetical mechanisms with acute myocarditis [7]. Acute pericarditis is known to reoccur in 15–30% of patients [7]. Although recurrences of myocarditis have been reported in literature [8–10], the general recurrence rate of

acute myocarditis has however remained unknown. We studied the recurrence of acute myocarditis by using a multihospital, nationwide registry follow-up data.

2. Methods

2.1. Study patients and data collection

We studied 1662 consecutive patients aged 16–70 years hospitalized for acute myocarditis (primary discharge diagnosis code I40) during 2001–2008. Age- and sex-matched control population ($n = 1662$) was randomly selected from patients admitted due to drug intoxication (primary discharge diagnosis code T36). Discharge records of prior admissions were reviewed from May 1st 2000 and patients with any type of myocarditis, heart failure, cardiomyopathy, or heart transplant before index hospitalization were excluded ($n = 49$). Patients were followed for admission with acute myocarditis until October 31st 2009. Median follow-up was 4.5 years (IQR 2.2–6.6 years) after acute myocarditis and 4.7 years (IQR 2.6–6.8 years) for controls. Hospital

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transfers were joined as one admission. Readmissions with acute myocarditis (ICD-10 code I40) as primary, secondary or tertiary diagnosis were detected beginning from second day after initial discharge. Data was retrospectively collected from the Finnish Hospital Discharge Register (FHDR), a nationwide, obligatory registry maintained by the Finnish National Institute for Health and Welfare. Hospital discharge diagnoses from 29 hospitals (all university and central hospitals in addition to 8 regional hospitals) nationwide were studied. The study was conducted according to the National Institute for Health and Welfare permission (THL/1576/5.05.00/2010).

2.2. Statistical analysis

Proportion of patients with readmission was analyzed by Kaplan–Meier method. Association of acute myocarditis with sequential myocarditis admissions was studied using log-rank test stratified for study year. Patient features associated with recurrence were studied using exact Cox-regression models stratified by study year. Multivariate model included patient characteristics (Table 1) associated with readmission at the level of $p < 0.05$ in univariate analysis. Differences of dichotomous variables were analyzed with Fischer's exact test and differences in treatment times were analyzed with paired t-test. Incidence was calculated based on population data of whole Finland acquired from Statistics Finland, and standardized with European Standard Population 2013 with direct method. Scale variables are presented as mean $\pm$ standard deviation or median with interquartile range as appropriate. Categorical variables are presented as counts or percentages with 95% confidence intervals (CI) as appropriate. P-values <.05 were considered statistically significant. The SAS system version 9.3 (SAS Institute Inc, Cary, NC, USA) was used for statistical analyses.

3. Results

3.1. Patient features and incidence of acute myocarditis

Majority (81%) of acute myocarditis patients were male. Mean age of patients at index hospitalization was 34.4 ± 14.7 years. Most common sites of co-infection in acute myocarditis were respiratory and otolaryngeal tracts (Table 1). Chronic co-morbidities were rare among study patients (Table 1). Standardized incidence rate of first time hospitalization due to acute myocarditis in participating hospitals was 5.52 (CI 5.26–5.79) per 100,000 person-years during the study period. Incidence was highest in population aged 16–19 years, followed by a linear decline to 40 years and a steady state in older population (Fig. 1).

Table 1
Characteristics of acute myocarditis patients at index hospitalization.

|	%	95% CI
Female sex	19.0	17.0–21.2
Prolonged (>7 days) initial admission	9.1	7.7–10.7
Hypertension	3.7	2.5–4.4
Chronic pulmonary disease	1.1	0.6–1.7
Diabetes	0.8	0.4–1.3
Coronary artery disease	0.8	0.4–1.3
Systemic connective tissue disease*	0.7	0.4–1.3
Inflammatory bowel disease	0.6	0.3–1.1
Malignant disease	0.2	0.1–0.6
Heart failure	1.4	0.9–2.1
Conduction abnormality	0.7	0.4–1.3
Ventricular arrhyhtmia	0.5	0.2–0.9
Otolaryngeal infection	3.4	2.6–4.4
Lower respiratory tract infection	3.2	2.4–4.2
Gastro-intestinal infection	0.4	0.2–0.9
Septicemia	0.1	0.01–0.4
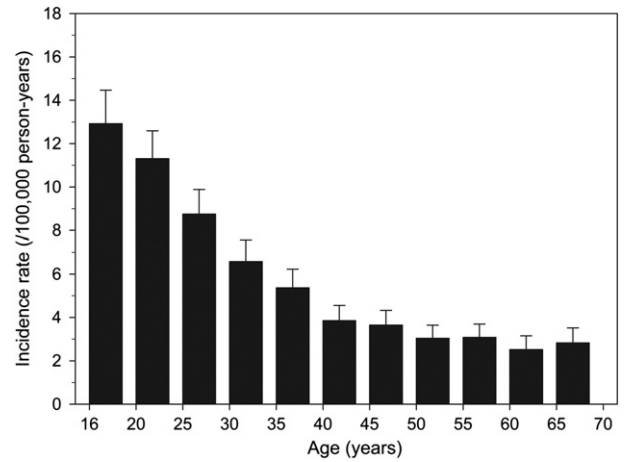
Fig. 1. Age-specific incidence rates of first time hospitalization due to acute myocarditis in participating hospitals during 2001–2008. Error bars represent upper limits of 95% confidence intervals.

3.2. Recurrence rate

During the first 30 days 5.5% (CI 3.5–4.4%) of patients with acute myocarditis were re-admitted to hospital with ongoing or recurrent acute myocarditis ($p < 0.0001$ vs. controls). Rate of re-admissions was highest during 10 first days after initial discharge and remained similar during following 20 days with median time of 10 (IQR 6–18) days to readmission (Fig. 2). After 30 days from acute myocarditis the cumulative recurrence rate was 7.0% (CI 5.7–8.6%; $p < 0.0001$ vs. controls) with 7.2 month (IQR 1.9–20.3) median time to recurrence (Fig. 3A). Acute myocarditis recurred late after onset (≥ 1 year after initial admission) in 4.7% (CI 3.2–6.7%) of patients ($p < 0.0001$ vs. controls). Median time to late onset recurrence was 2.3 (IQR 1.4–3.4) years (Fig. 3B). During the whole follow-up, the rate of readmission with acute myocarditis was 10.3% (CI 8.8–12.1%) with median time of 34.5 days (IRQ 11–257) to readmission ($p < 0.0001$ vs. controls). Twelve months after acute myocarditis 93% (CI 91–94%) of patients were free from recurrences (Fig. 4). None of the control patients had admissions with acute myocarditis during follow-up.

3.3. Features of recurrence admissions

Acute myocarditis was the primary cause of readmission in 89.7% of recurrences. Ventricular arrhythmias were diagnosed in 3.9% (CI 1.4–8.5%) of patients at readmission, which was significantly higher than
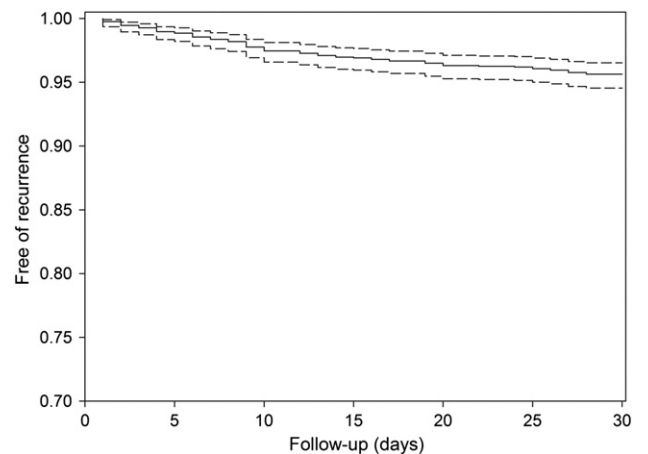

Fig. 2. Readmission due to acute myocarditis during first 2–30 days after initial discharge. Short-dashed lines mark 95% confidence intervals. Please note origin of y-axis.