



Original Contribution

Incidence of Fatal Myocarditis: A Population-based Study in Finland

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To study the incidence of fatal myocarditis in the general population, the authors retrospectively collected all death certificates recording myocarditis as the underlying cause of death in Finland in 1970–1998. The incidence of myocarditis and its proportion of all deaths were calculated from 141.4 million person-years and 1.35 million deaths. Myocarditis was recorded as the underlying cause of death in 639 cases. Thus, its death certificate-based incidence was 0.46 (95% confidence interval (CI): 0.43, 0.49) per 100,000 person-years, and it caused 0.47 (95% CI: 0.44, 0.51) of 1,000 deaths. The incidence of 0.51 (95% CI: 0.46, 0.56) in males was higher than the incidence of 0.42 (95% CI: 0.37, 0.47) in females, the odds ratio being 1.34 (95% CI: 1.15, 1.58) ($p < 0.001$). The proportion of deaths caused by myocarditis was highest (up to six of 1,000 deaths) in children and adults aged less than 45 years. Because previous histopathologic reanalysis showed that only 32% of cases fulfilled the Dallas criteria, the authors estimated the incidence of histopathologically certain fatal myocarditis to be 0.15 (95% CI: 0.13, 0.17) per 100,000. The death certificate-based incidence of fatal myocarditis was found to be 0.46 per 100,000, and the histopathologically corrected incidence was 0.15 per 100,000.

fatal outcome; incidence; myocarditis

Abbreviation: CI, confidence interval.

Myocarditis is commonly a mild or subclinical disease, but it may cause fatal heart failure or underlie sudden cardiac death (1). The incidence of myocarditis has been difficult to study because clinical presentations of disease vary widely and because histopathologic examination of the heart is needed to confirm the diagnosis (1, 2). In studies of consecutive autopsies, myocarditis has been reported in 0.1–5.6 percent of cases (3, 4). Myocarditis is a major cause of sudden death in children and young adults (5, 6). However, the significance of myocarditis as the cause of death in the general population still remains uncharacterized. The aim of this study was to assess the incidence of fatal myocarditis in the Finnish population.

MATERIALS AND METHODS

Study population

All death certificates issued in Finland with myocarditis recorded as the underlying cause of death (according to the World Health Organization's *International Classification of Diseases*) during the years 1970–1998 were retrospectively collected from the database of Statistics Finland (Helsinki, Finland). Age- and sex-specific population and mortality data of the whole Finnish population from the years 1970–1998 were obtained from Statistics Finland. The person-years of each study year were calculated as an arithmetic mean of populations on January 1st and December 31st.

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TABLE 1. Death certificate-based incidences of fatal myocarditis, Finland, 1970–1998

	Men			Women			Total		
	No.	Incidence*	95% confidence interval	No.	Incidence	95% confidence interval	No.	Incidence	95% confidence interval
Age (years)									
<1	15	1.61	0.97, 2.67	14	1.57	0.93, 2.65	29	1.59	1.05, 2.29
1–4	9	0.24	0.12, 0.45	9	0.25	0.13, 0.48	18	0.24	0.15, 0.39
5–14	9	0.09	0.05, 0.17	15	0.16	0.09, 0.26	24	0.12	0.08, 0.18
15–24	21	0.19	0.13, 0.30	15	0.14	0.09, 0.24	36	0.17	0.12, 0.23
25–34	44	0.39	0.29, 0.52	24	0.22	0.15, 0.33	68	0.31	0.24, 0.39
35–44	73	0.71	0.56, 0.89	31	0.31	0.22, 0.44	104	0.51	0.42, 0.62
45–54	75	0.88	0.70, 1.10	49	0.56	0.42, 0.74	124	0.72	0.60, 0.85
55–64	32	0.49	0.35, 0.70	38	0.49	0.36, 0.68	70	0.49	0.39, 0.62
65–74	44	1.02	0.76, 1.37	50	0.76	0.57, 1.00	94	0.86	0.70, 1.05
≥75	19	0.94	0.60, 1.48	53	1.17	0.89, 1.53	72	1.10	0.87, 1.39
Total	341	0.51	0.46, 0.56	298	0.42	0.37, 0.47	639	0.46	0.43, 0.49

* Per 100,000 person-years.

The study period of 29 years included a total of 141,438,176 person-years and 1,349,824 deaths.

Analysis

Age- and sex-specific incidences, as well as the age-adjusted incidence, of fatal myocarditis were calculated. In addition, age- and sex-specific proportions of deaths caused by myocarditis from all deaths were calculated. The time of death and comorbidities listed in death certificates were analyzed. Direct standardization with the European 1994 standard population was used for calculation of age-adjusted incidence. Ninety-five percent confidence intervals for incidences were calculated assuming that the number of cases of fatal myocarditis followed Poisson distribution. The differences among sex, age groups, years, and seasons were analyzed by use of logistic regression. Results were quantified by odds ratios and their 95 percent confidence intervals. Analyses were conducted with SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). $p < 0.05$ was considered statistically significant. The study was approved by the local ethical committee and the Finnish Ministry of Social Affairs and Health.

Histopathologic corrections

According to the death certificates, the diagnosis of myocarditis was based on autopsy in 97 percent of cases. Because diagnosis of myocarditis is known to be difficult, a previous subgroup study for the accuracy of histopathologic diagnosis was conducted (7). Autopsy materials of all the cases with myocarditis recorded as the underlying cause of death in 1970–1998 were requested from treating hospitals and departments of forensic medicine. Autopsy samples were received from 142 cases (22 percent of all cases), including both men ($n = 71$) and women ($n = 71$), all age

groups, the whole study period, both hospital and medico-legal autopsies, and all parts of Finland. Reanalysis of these autopsy samples according to the widely accepted histopathologic Dallas criteria for myocarditis (2) was carried out by three independent pathologists (7). Reanalysis showed that only 32 percent of the analyzed cases fulfilled the Dallas criteria (7). Accuracy was 75 percent in pediatric patients and 28 percent in adult patients. Gender or type of autopsy (hospital vs. medicolegal) did not affect the accuracy (7). In addition to results based on death certificates, we made estimations of the incidence based on the overall proportion of cases fulfilling the Dallas criteria for myocarditis (32 percent).

RESULTS

Myocarditis was recorded as the underlying cause of death in 639 cases (median age: 47 years; range: 6 days–93 years) during the years 1970–1998. Thus, the death certificate-based, age-adjusted incidence of fatal myocarditis was 0.46 (95 percent confidence interval (CI): 0.43, 0.49) per 100,000 person-years (table 1). The proportion of deaths recorded to be caused by myocarditis was 0.47 (95 percent CI: 0.44, 0.51) out of 1,000 deaths (table 2).

The death certificate-based incidence of fatal myocarditis was similar in the 1970s and 1980s, but there was a significant increase in incidence in the 1990s ($p < 0.001$) (figure 1). There was no significant seasonal variability in the incidence. The proportionate amount of deaths recorded to be caused by myocarditis demonstrated similar annual changes and lack of seasonal variability (data not shown).

The death certificate-based incidence of fatal myocarditis of 0.51 (95 percent CI: 0.46, 0.56) per 100,000 in males was higher than the incidence of 0.42 (95 percent CI: 0.37, 0.47) per 100,000 in females, the odds ratio being 1.34

TABLE 2. Death certificate-based proportions of fatal myocarditis of all deaths, Finland, 1970–1998

	Men			Women			Total		
	No.	Proportion*	95% confidence interval	No.	Proportion	95% confidence interval	No.	Proportion	95% confidence interval
Age (years)									
<1	15	2.01	1.21, 3.33	14	2.48	1.47, 4.19	29	2.21	1.54, 3.18
1–4	9	5.47	2.85, 10.51	9	7.66	3.99, 14.72	18	6.38	4.02, 10.13
5–14	9	2.84	1.48, 5.45	15	8.07	4.86, 13.38	24	4.77	3.20, 7.12
15–24	21	1.66	1.08, 2.54	15	3.86	2.33, 6.40	36	2.18	1.57, 3.02
25–34	44	2.27	1.69, 3.05	24	4.01	2.69, 5.98	68	2.68	2.11, 3.40
35–44	73	2.08	1.66, 2.62	31	2.56	1.80, 3.63	104	2.21	1.82, 2.67
45–54	75	1.12	0.89, 1.40	49	1.93	1.46, 2.55	124	1.34	1.12, 1.60
55–64	32	0.26	0.18, 0.36	38	0.67	0.49, 0.92	70	0.39	0.31, 0.49
65–74	44	0.23	0.17, 0.31	50	0.35	0.26, 0.46	94	0.28	0.23, 0.34
≥75	19	0.08	0.05, 0.13	53	0.13	0.10, 0.17	72	0.11	0.09, 0.14
Total	341	0.49	0.44, 0.54	298	0.46	0.41, 0.51	639	0.47	0.44, 0.51

* Out of 1,000 deaths.

(95 percent CI: 1.15, 1.58) ($p < 0.001$) (table 1). Myocarditis was significantly more often the cause of death in children and adults aged up to 44 years (by proportion, from 6.38 to 2.18 out of 1,000 deaths) than in the population aged over 55 years (by proportion, from 0.39 to 0.11 out of 1,000 deaths); for example, children aged 1–4 years were 56 times more likely to have myocarditis as the underlying cause of death than was the population aged 75 or more years ($p < 0.001$). The incidence of fatal myocarditis was highest in infants less than 1 year of age (incidence = 1.59, 95 percent CI: 1.05, 2.29, per 100,000 person-years).

Half of the patients with myocarditis recorded as the cause of death had comorbidities listed on the death certificates (table 3). The most commonly listed comorbidity was infection, recorded in 15.8 percent of cases. The respiratory

tract was the most common location of infection (10.6 percent of all cases). Psychiatric (12.7 percent) and cardiac (12.5 percent) diseases were the most commonly recorded chronic disorders. Coronary artery disease was the most common chronic cardiac disease (7.5 percent of all cases). Autoimmune disease was recorded in 2.0 percent and cancer in 1.1 percent (table 3) of cases.

Notably, when the incidence indicated by the death certificates was adjusted with the overall accuracy of histopathologic diagnosis based on reanalysis by the Dallas criteria (32 percent), the total incidence declined to 0.15 (95 percent CI: 0.13, 0.17) per 100,000 person-years. Histopathologic myocarditis would have therefore been the underlying cause of 0.15 (95 percent CI: 0.13, 0.17) out of 1,000 deaths.

DISCUSSION

This population-based study found that the death certificate-based incidence of fatal myocarditis was 0.46 per 100,000 person-years and that myocarditis was recorded to cause 0.47 out of 1,000 deaths in the general Finnish population during the years 1970–1998.

The epidemiology of fatal myocarditis in the general population has remained largely uncharacterized, because the clinical presentations and findings of myocarditis are highly variable and because the definite diagnosis is based on autopsy (2, 7). Clues about the epidemiology are provided by studies of consecutive autopsies. A Japanese study of over 350,000 autopsies from the general population found the frequency of myocarditis to be 0.1 percent (3). In an Italian study of over 17,000 autopsies from a general hospital, myocarditis was found in 0.5 percent of deaths (8), while another Italian study of 2,500 autopsies reported a 5.6 percent frequency (4). A study of the Swedish adult population found myocarditis in 1.1 percent of autopsies (9). In forensic

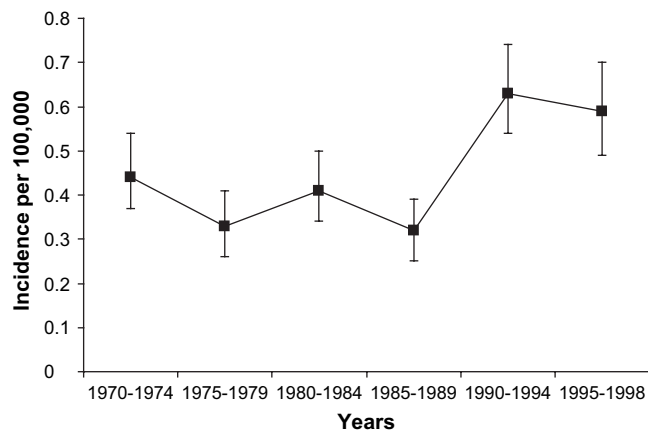


FIGURE 1. Death certificate-based incidence of fatal myocarditis in the general population, Finland, 1970–1998. Error bars represent 95% confidence intervals.

TABLE 3. Comorbidities listed on death certificates of patients with myocarditis recorded as the cause of death (n = 639), Finland, 1970–1998

Comorbidity	No.	%
Infection	101	15.8
Psychiatric disease	81	12.7
Cardiac disease	80	12.5
Gastrointestinal disease	37	5.8
Acute thromboembolism	27	4.2
Pulmonary disease	23	3.6
Endocrinologic disease	22	3.4
Neurologic disease	16	2.5
Autoimmune disease	13	2.0
Trauma	13	2.0
Cancer	7	1.1
Urogenital disease	3	0.5
Drug use	2	0.3
Down's syndrome	2	0.3
Liver transplant recipient	1	0.2
Pregnancy	1	0.2
Any comorbidity	325	50.1

autopsies of young Australians, myocarditis was detected in 0.7 percent (10). However, because an autopsy is more often performed when the cause of death is clinically obscure, the autopsy frequency of myocarditis is likely to overestimate the true proportion of deaths caused by myocarditis. Cases of nonfatal myocarditis may also be included in studies of consecutive autopsies. On the basis of analysis of over 1,340,000 death certificates of the whole population, we found myocarditis to cause 0.47 out of 1,000 deaths in Finland.

The death certificate-based incidence of fatal myocarditis was found to be similar in the 1970s and 1980s, but the incidence increased in the 1990s. This increase in incidence is similar to that previously reported in Italy (8). Although random factors certainly contribute for yearly changes, epidemics of infectious diseases may also affect the incidence.

The death certificate-based incidence of fatal myocarditis was found to be highest in infants (1.59 per 100,000 person-years), but a little surprisingly the incidence was lowest in the population aged 5–24 years (0.12–0.17 per 100,000). However, the proportion of deaths caused by myocarditis was higher in children aged 1–14 years (6.38–4.77 out of 1,000 deaths) than in infants (2.21 out of 1,000), because of the higher total mortality of infants. There was also an increase in the death certificate-based incidence in the population older than 45 years and particularly in the elderly (≥ 75 years), but the proportion of deaths caused by myocarditis was lowest because of the increase in total mortality.

We found that men are at significantly higher risk (odds ratio = 1.34) of fatal myocarditis than are females. Previous studies have resulted in contradictory results on whether myocarditis is more common in men (3) or in women (4). In the current study, half of the fatal myocarditis patients

were recorded to be otherwise healthy, while comorbidities were listed on the death certificates of the other half.

The determination of the cause of death is mandatory, and the collection of official death certificates is both mandatory and centralized in Finland, resulting in almost complete coverage of the population (99.7–99.9 percent during the study period) and providing excellent possibilities for population-based studies (11). The current large retrospective study covers practically the whole Finnish population over a period of 29 years. However, the fact that some cases of fatal myocarditis are never recognized if autopsy is not performed (e.g., patients with preexisting cardiac disorder) may cause underestimation of the incidence of myocarditis in our series. During the study period, the autopsy rate was 30–38 percent of all deaths in Finland (11).

Because diagnosis of myocarditis is known to be difficult, we conducted a previous subgroup study of the accuracy of histopathologic diagnosis (7) based on the widely accepted Dallas criteria for myocarditis (2). In order to eliminate the potential selection bias for this subgroup study, the autopsy material was requested from all 639 cases with myocarditis listed as the underlying cause of death (7). The autopsy material received was representative with respect to the sex and age of the patients, study period, type of autopsy, and regions of Finland. The overall accuracy for diagnosis of myocarditis in routine autopsies was found to be only 32 percent (7), suggesting that fatal myocarditis is less common in the general population than is reported on the death certificates. These data on the accuracy of diagnosis allow us to estimate that the true incidence of Dallas criteria-fulfilling fatal myocarditis would be as low as 0.15 per 100,000 person-years, and it caused 0.15 out of 1,000 deaths.

Although the current study describes the epidemiology of fatal myocarditis, the epidemiology of myocarditis in general remains largely unknown. Symptomatic myocarditis is reported to occur annually in 0.02 percent of conscripts (12). Myocarditis may, however, be more common, as 1 percent of patients with common respiratory and gastrointestinal infections and 9 percent of influenza patients are reported to have cardiac involvement, often without cardiac symptoms (13, 14), although a recent study suggests that influenza-associated myocarditis may not be that common (15). In some studies, myocarditis is accompanied by a quick and good recovery (12, 16, 17). However, a meta-analysis found spontaneous improvement in only 58 percent of myocarditis patients and deterioration in 15 percent (18), with mortality up to 30 percent being reported (19). In order to further clarify the epidemiology of nonfatal myocarditis, more studies are warranted.

In conclusion, we found the death certificate-based incidence of fatal myocarditis in the general population to be 0.46 per 100,000 person-years and the histopathologically corrected incidence to be 0.15 per 100,000 person-years. The incidence was highest in infants. Men were at higher risk of fatal myocarditis than were females.

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