BMJ Open Acute myocardial infarction or acute myocarditis? Discharge registry-based study of likelihood and associated features in hospitalised patients

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ABSTRACT

Objective: To evaluate the likelihood of and patient features associated with acute myocardial infarction (AMI) versus acute myocarditis in different population segments.

Design: Nationwide, multihospital observational retrospective registry study of 9.6 years in Finland.

Participants: All consecutive patients aged ≥ 18 years hospitalised with a primary diagnosis of AMI (n=89 399) or acute myocarditis (n=2131) in 22 hospitals with a coronary catheterisation laboratory.

Primary outcome measures: Likelihood of AMI versus acute myocarditis and associated patient features.

Results: Men were over-represented in patients with AMI (59.8%) and in patients with acute myocarditis (76.1%). Age distributions of AMI and acute myocarditis were opposite as a majority of patients with myocarditis were aged 18–29 years, while the number of patients with AMI increased gradually up to 80 years of age. Patients aged 18–29 years were more likely to have acute myocarditis as the cause of hospitalisation (relative risk (RR)=11.4; 95% CI 7.6 to 16.1 for myocarditis, $p<0.0001$), but after 30 years of age the likelihood of infarction was higher with exponentially increasing RR for AMI. In youngest patients (18–29 years), the likelihood of AMI was higher in women, but men had higher odds for AMI after 40 years of age. Overall, men had OR of 1.97 (95% CI 1.74 to 2.23, $p<0.0001$) for AMI versus myocarditis when compared with women.

Hypercholesterolaemia, chronic coronary artery disease, diabetes and hypertension predicted AMI in multivariate analysis. Odds for myocarditis were significantly higher if the patient had an otolaryngeal infection (OR 18.13; 95% CI 8.96 to 36.67, $p<0.0001$).

Conclusions: Acute myocarditis is more common than AMI in hospitalised patients aged 18–29 years, but the risk of AMI increases exponentially thereafter. Hypercholesterolaemia, diabetes and hypertension predict AMI regardless of age and gender.

INTRODUCTION

Acute myocardial infarction (AMI) and acute myocarditis have commonly similar clinical

Strengths and limitations of this study

- Characterises the likelihood of acute myocardial infarction (AMI) versus acute myocarditis in different segments of the general population.
- Large-scale nationwide study using obligatory and controlled registry data from hospitals with a coronary catheterisation laboratory.
- Diagnoses of AMI and acute myocarditis were carried out by treating physicians.

presentations.¹ As changes in ECG² and troponin levels³ are also alike, differential diagnosis may be very challenging and frequently requires invasive assessment of coronary arteries.⁴ Culprit-free coronary angiography is found in 5–13% of patients with suspected AMI,⁵ and a majority of patients with culprit-free angiography actually have myocarditis.⁶ Although epidemiology of AMI has been described in large patient series,^{7–12} epidemiology of acute myocarditis is less well established.¹³ Furthermore, there are currently no large-scale studies reporting on the risk of AMI versus acute myocarditis in different population segments. Therefore, we sought to estimate the likelihood of AMI versus acute myocarditis and associated patient features at the population level.

METHODS

Study patients and data collection

We included all consecutive patients aged ≥ 18 years who were admitted to a participating hospital between 29 April 2000 and 29 November 2009 with an AMI (ICD-10 code I21.x) or an acute myocarditis (ICD-10 code I40.x or I01.2) as the primary discharge diagnosis. Diagnoses were made by treating physicians. Confirmatory data of performed diagnostic tests were not available. Data were collected from all Finnish hospitals equipped with a coronary catheterisation laboratory

(n=22) by using the Finnish National Institute for Health and Welfare maintained Finnish Hospital Discharge Register (FHDR) database. The study was approved by the National Institute for Health and Welfare (permission no THL/1576/5.05.00/2010).

Statistical analysis

Categorical variables are presented as counts or percentages with 95% CIs (95% CI) as appropriate. Scale variables are presented as mean±SD. Count variables were analysed using negative binomial regression. Differences in dichotomous variables were analysed using logistic regression analysis with Firths correction and adjusted for study year. Results of regression analyses are given as OR or relative risk (RR) as appropriate. Multivariate analysis of patient features associated with the likelihood of myocardial infarction/myocarditis included features associated at $p<0.05$ in univariate analysis. CIs were calculated assuming Poisson distribution. The p values <0.05 were considered statistically significant. Statistical analyses were performed with SAS system V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient characteristics

During the study period, AMI resulted in 89 399 admissions, and acute myocarditis numbered 2131. Men were over-represented both in patients with AMI (59.8%) and

in patients with acute myocarditis (76.1%). Patients with AMI were significantly older than those with myocarditis (71.2 ± 12.7 vs 38.0 ± 16.9 years, $p<0.0001$). Diabetes, hypertension, hypercholesterolaemia, chronic pulmonary disease, neurovascular disease, malignancy and renal insufficiency, in addition to atrial fibrillation, heart failure and known atherosclerotic disease of coronary, cerebral or peripheral arteries were more common in patients hospitalised for AMI (table 1). By contrast, infections of the otolaryngeal tract and inflammatory bowel disease were more common in patients with myocarditis (table 1). The average duration of admission for AMI lasted, 6.9 ± 5.7 days, while admission due to acute myocarditis was shorter (5.3 ± 4.3 days, $p<0.0001$). Of patients with AMI, 0.03% had a co-diagnosis of myocarditis, while 0.37% of patients with myocarditis were also diagnosed with AMI.

Age distribution

Age distribution of patients with AMI and acute myocarditis were opposite (figure 1). The majority of patients with myocarditis were aged 18–29 years, after which the number of patients decreased (figure 1A). The number of patients with AMI increased gradually up to 80 years of age (figure 1B). Patients aged 18–29 years were more likely to have acute myocarditis as the cause of hospitalisation (RR=11.4; 95% CI 7.6 to 16.1 for myocarditis, $p<0.0001$), but after 30 years of age the likelihood of infarction was higher with exponentially increasing RR

Table 1 Co-diagnoses of patients hospitalised for acute myocardial infarction or myocarditis and differences between patients in univariate analyses

Co-diagnosis	Prevalence		Difference	
	Acute myocardial infarction % (95% CI)	Acute myocarditis % (95% CI)	Univariate analysis (infarction vs myocarditis) OR (95% CI)	p Value
Chronic coronary artery disease	15.36 (15.10 to 15.62)	1.55 (1.07 to 2.17)	11.52 (8.19 to 16.21)	<0.0001
Hypertension	13.12 (12.89 to 13.36)	4.04 (3.23 to 4.98)	3.59 (2.89 to 4.45)	<0.0001
Heart failure	11.57 (11.35 to 11.79)	2.25 (1.66 to 2.99)	5.63 (4.23 to 7.49)	<0.0001
Diabetes	7.84 (7.66 to 8.03)	1.13 (0.72 to 1.68)	7.32 (4.91 to 10.90)	<0.0001
Atrial fibrillation	6.64 (6.5 to 6.8)	1.55 (1.07 to 2.17)	4.44 (3.16 to 6.25)	<0.0001
Hypercholesterolaemia	6.52 (6.35 to 6.69)	1.03 (0.65 to 1.56)	6.51 (4.30 to 9.86)	<0.0001
Pneumonia	3.12 (3.00 to 3.23)	3.33 (2.60 to 4.20)	0.92 (0.73 to 1.17)	0.50
Chronic pulmonary disease	2.18 (2.08 to 2.28)	1.27 (0.83 to 1.84)	1.70 (1.17 to 2.49)	0.0059
Neurovascular disease	1.34 (1.27 to 1.42)	0.14 (0.03 to 0.41)	8.32 (2.91 to 23.77)	<0.0001
Ventricular arrhythmia or resuscitation	1.13 (1.07 to 1.21)	0.99 (0.61 to 1.51)	1.13 (0.73 to 1.73)	0.59
Malignancy	1.04 (0.98 to 1.11)	0.42 (0.19 to 0.80)	2.35 (1.24 to 4.46)	0.0089
Peripheral artery disease	0.86 (0.8 to 0.9)	0.05 (0.01 to 0.26)	12.39 (2.50 to 61.46)	0.0021
Renal insufficiency	0.83 (0.77 to 0.89)	0.09 (0.01 to 0.34)	4.15 (2.07 to 24.72)	0.0019
II or III degree AV block	0.59 (0.54 to 0.64)	0.89 (0.54 to 1.39)	0.65 (0.41 to 1.02)	0.060
Rheumatoid arthritis	0.44 (0.39 to 0.48)	0.52 (0.26 to 0.92)	0.81 (0.45 to 1.46)	0.50
Gastroenteral infection	0.38 (0.34 to 0.43)	0.38 (0.16 to 0.74)	0.96 (0.48 to 1.89)	0.89
Septicaemia	0.36 (0.32 to 0.40)	0.23 (0.08 to 0.55)	1.39 (0.60 to 3.23)	0.44
Systemic connective tissue disease	0.18 (0.16 to 0.21)	0.23 (0.08 to 0.55)	0.70 (0.30 to 1.64)	0.41
Otolaryngeal infection	0.12 (0.10 to 0.15)	2.49 (1.86 to 3.25)	0.05 (0.04 to 0.07)	<0.0001
Liver dysfunction	0.11 (0.09 to 0.13)	0.14 (0.03 to 0.41)	0.66 (0.23 to 1.93)	0.50
Inflammatory bowel disease	0.10 (0.08 to 0.12)	0.38 (0.16 to 0.74)	0.26 (0.13 to 0.52)	0.0002

for AMI (figure 2). In the total study population, the age-adjusted and gender-adjusted RR for AMI was 60.4 (95% CI 39.3 to 92.8, $p<0.0001$).

Patient features associated with AMI

The likelihood of AMI increased significantly with increasing age. In the total population, comorbidity adjusted OR for AMI was 4.69 (95% CI 4.48 to 4.91, $p<0.0001$) per 10-year increase in age. The gender-based difference in likelihood of AMI compared with myocarditis varied significantly by age (figure 3). In the youngest patients (18–29 years), the likelihood of AMI was higher in women, but men had higher odds for AMI after 40 years of age. Overall, men had significantly higher odds for AMI versus myocarditis when compared with women (OR 1.97; 95% CI 1.74 to 2.23, $p<0.0001$). Comorbidities predicting AMI in multivariate analysis included hypercholesterolaemia, chronic coronary artery disease, diabetes and hypertension (table 2). The odds for myocarditis were significantly higher if the patient had an otolaryngeal infection (OR 18.13; 95% CI 8.96 to 36.67, $p<0.0001$). In addition, atrial fibrillation and

Figure 1 Age distribution of patients with acute myocarditis (A) and acute myocardial infarction (B). Error bars represent upper 95% CIs.

Figure 2 Age-specific relative risk for acute myocardial infarction in patients hospitalised for acute myocardial infarction or acute myocarditis. Note the logarithmic scale of the x axis.

chronic pulmonary disease were more common among patients with acute myocarditis when adjusted for other comorbidities and patient features (table 2).

DISCUSSION

This multicentre study describes the likelihood and predictors of AMI versus acute myocarditis in hospitalised

Figure 3 Gender differences in odds for acute myocardial infarction versus acute myocarditis in different age groups. Error bars represent 95% CIs.

Table 2 Predictors of acute myocardial infarction in multivariate analysis

Patient characteristic	Multivariate analysis (infarction vs myocarditis)	
	OR (95% CI)	p Value
Age (per 10-year increase)	4.69 (4.48 to 4.91)	<0.0001
Male sex	1.97 (1.74 to 2.24)	<0.0001
Hypercholesterolaemia	8.68 (5.66 to 13.33)	<0.0001
Chronic coronary artery disease	6.10 (4.28 to 8.69)	<0.0001
Diabetes	4.85 (3.18 to 7.42)	<0.0001
Hypertension	1.42 (1.12 to 1.80)	0.0035
Chronic pulmonary disease	0.61 (0.38 to 0.98)	0.043
Atrial fibrillation	0.55 (0.38 to 0.80)	0.0017
Otolaryngeal infection	0.06 (0.03 to 0.11)	<0.0001
Neurovascular disease	2.77 (0.89 to 8.61)	0.078
Peripheral artery disease	2.70 (0.48 to 15.25)	0.26
Renal insufficiency	2.44 (0.66 to 9.04)	0.18
Heart failure	1.28 (0.93 to 1.76)	0.12
Inflammatory bowel disease	0.62 (0.19 to 1.96)	0.41
Malignancy	0.56 (0.28 to 1.14)	0.11

patients at the population level. Differential diagnosis between AMI and acute myocarditis is critical, as timely invasive treatment significantly improves outcomes in AMI.^{14 15} As clinical, ECG and biomarker presentations of AMI and acute myocarditis may be highly similar,²⁻⁴ the assumed probability of AMI or myocarditis is likely to act as a significant gatekeeper for coronary angiography and treatment. Although epidemiology of AMI has been described previously in large patient series,^{7-9 12 16} studies on epidemiology of myocarditis are scarce,¹³ and there are no estimations available for likelihood of AMI versus acute myocarditis in different population segments.

We found the youngest (18–29 years) patients to have an 11-fold risk for myocarditis compared with AMI, but AMI was more common in the population older than 30 years. This compares to a previous study of emergency department patients with chest pain that found 33% of patients aged 18–40 years positive for troponin to have AMI while myocarditis was present in 59%.¹⁷ Age distributions of patients with AMI and acute myocarditis were opposite in our data, resulting in the exponentially increasing likelihood of AMI with increasing age. AMI^{9 18} and myocarditis¹³ are more common in men than in women, but the current study is, to the best of our knowledge, the first to report on gender differences in the likelihood of AMI versus acute myocarditis. The gender bias in the occurrence of myocarditis is highest in young adults.¹³ Accordingly, we found women aged 18–29 years to have higher odds for AMI than equally aged men. High incidence of acute myocarditis in young men is most likely associated with effects of

testosterone,¹⁹ as testosterone treatment aggravates myocarditis²⁰ in experimental myocarditis, while gonadectomy reduces cardiac inflammation.²¹ In the population aged over 40 years, the odds for AMI were, however, higher in men, and in the total study population men had twofold odds for AMI when compared with women.

Classical risk factors for coronary artery disease, hypertension, hypercholesterolaemia and diabetes^{22 23} predicted AMI rather than acute myocarditis in our data regardless of age and gender. Although our data do not allow reporting directly on patients' smoking status, the association of chronic pulmonary disease with AMI is most likely to reflect the effects of smoking. Coronary angiography should also be considered in young patients with troponin-positive chest pain, especially if risk factors are present.⁴ However, of patients with suspected AMI, 5–13% have no detectable culprit lesion,^{5 24-28} and these findings are consistent regardless of whether ST-segment elevation AMI (STEMI)²⁷⁻³⁰ or non-ST-segment elevation AMI (NSTEMI)²⁴⁻²⁶ is suspected. Of culprit-free patients, myocarditis is detectable by cardiac MRI (CMR)³¹⁻³⁴ or scintigraphy⁶ in 50–78%. Since there are no effective special treatments available for common uncomplicated acute viral myocarditis, usage of imaging studies beyond echocardiography in suspected acute myocarditis is controversial and currently uncommon in clinical reality. CMR is an evolving entity for detection of myocarditis.^{35 36} It is, however, not feasible as the first-line diagnostic modality in suspected STEMI when diagnosis of AMI must be made immediately in order to enable efficient reperfusion therapy. Routine use of CMR in patients with suspected NSTEMI is currently under investigation.³⁷ Novel, clinically easy and rapidly applicable methods to differentiate between AMI and acute myocarditis are thus warranted.

The major limitation of our study is the retrospective nature of observational discharge registry data. The diagnoses were made by the treating physician and the nature of data does not allow us to report on used diagnostic tests or patient's risk-factor behaviour such as smoking. To optimise the balance between representation of all-comer real-life patients and diagnostic accuracy, only patients admitted to hospitals with a coronary catheterisation laboratory were included. Study data were collected from the FHDR registry that has proved to be a valuable source of information on acute cardiovascular disorders³⁸ and has been previously validated.^{39 40} Diagnostic inaccuracies are, however, possible, especially in recognition of comorbidities.²³ Confirmatory diagnosis of myocarditis requires endomyocardial biopsy, which is rarely indicated in a clinical setting of acute myocarditis.^{1 4} If biopsy is not obtained, myocarditis may be classified as clinically suspected⁴ or probable⁴¹ if cardiac symptoms are associated with changes in troponin, ECG or cardiac imaging studies in the absence of an acute coronary syndrome or other reasons. The majority of patients with acute myocarditis in our study probably belong to this category.

It is a common misbelief that acute myocarditis presents only with ST-segment elevations in ECG. Recent studies of CMR-detected acute/viral myocarditis have found 34–57% of patients to have ST-segment elevations, while ECG was normal at the presentation in approximately 30% of patients.^{42–43} Depressions of ST-segment are reported in 6–18% of patients.^{6–42} Thus, the need for differentiation between myocarditis and AMI includes all patients with suspected AMI regardless of ECG presentation.

In conclusion, acute myocarditis is more common than AMI in hospitalised patients aged 18–29 years, but the risk of AMI increases exponentially thereafter. Men aged ≥ 40 years are more likely to have AMI than myocarditis when compared with women. Hypercholesterolaemia, diabetes and hypertension predict AMI regardless of age and gender.

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