CLINICAL RESEARCH STUDY

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Sex-Based Differences in Clinical Characteristics of Patients with Acute Myocarditis: A Cohort Study

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ABSTRACT

BACKGROUND: This study investigated sex differences in acute myocarditis patients during index hospitalization.

METHODS: We included 365 patients with acute myocarditis, hospitalized with continuous monitoring at the intensive care unit from 2000-2023 into the Basel Myocarditis Cohort study. We compared sex differences in clinical presentation, the presenting electrocardiogram, prior medical history, inflammatory and cardiac biomarkers, cardiac imaging, arrhythmia occurrence, and short- to midterm outcomes.

RESULTS: Mean age was 41.3 years, and 26.3% were female. Compared with men, women were older (median 49.7 vs 38.3 years, $P < .001$) at the time of diagnosis and presented more frequently with dyspnea (41 vs 26%, $P = .013$) and a higher Killip class ($P = .011$). In the presenting electrocardiogram, men had a higher occurrence of diffuse ST-elevation (38 vs 9%, $P < .001$) and PQ-depression (31 vs 20%, $P = .042$), compared with women. Women had higher N-terminal pro B-type natriuretic peptide levels (1180 vs 387 ng/L, $P = .015$), lower cardiac troponin T levels (389 vs 726 ng/L, $P = .006$), and fewer segments with nonischemic late gadolinium enhancement on cardiac magnetic resonance imaging (1 vs 3, $P = .005$), but similar left ventricular ejection fraction (55 vs 55%, $P = .629$), compared with men. Overall, hospital stay was longer in women compared with men (7 vs 5 days, $P = .018$), with a similar length of intensive care unit stay (2.6 vs 2.7 days, $P = .922$). Women more often developed severe arrhythmia (8.3 vs 2.2%, $P = .015$) and heart failure during the hospitalization (31.3 vs 16.4%, $P = .003$).

CONCLUSION: Compared with men, women with acute myocarditis were older at the time of diagnosis, presented more often with heart failure, and had an increased frequency of severe arrhythmia.

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KEYWORDS: Arrhythmia; Biomarkers; Heart failure; Inflammation; Myocarditis; Sex characteristics

INTRODUCTION

Acute myocarditis is a potentially life-threatening condition characterized by myocardial inflammation with increased risks for heart failure, fatal arrhythmias, or cardiac arrest.[1-3] While the underlying causes of acute myocarditis are diverse, prior studies have shown sex-specific differences in the epidemiology, clinical presentation, and diagnostic findings.[4-8] However, available data are limited and contradictory regarding sex differences in therapies, in-hospital outcomes, and severity of the course of acute myocarditis. While some studies showed a worse disease progression in female patients, with a higher occurrence of ventricular arrhythmias/cardiac arrest and higher in-hospital mortality,[3] others reported more ventricular arrhythmias in male patients.[8]

Differences in disease severity and clinical outcomes between males and females may be due to sex-specific

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immune responses and disease susceptibility, and influenced by sex hormones.[4,5] These different immune responses include variations in cytokine production and lymphocyte activity between sexes, suggesting a complex interplay of hormonal and immunological factors.[5,7,9] Better characterization of sex-specific differences in the clinical presentation, course, and outcomes may help to acknowledge these underlying mechanisms and allow sex-specific diagnostic criteria and therapy.

In this study, we sought to investigate sex-specific differences in acute myocarditis patients hospitalized in an intensive care unit (ICU) with continuous rhythm monitoring. We investigated differences in demographics, clinical presentation, cardiac and inflammatory biomarkers, cardiac imaging, in-hospital therapies, arrhythmia occurrence, and acute to mid-term outcomes.

CLINICAL SIGNIFICANCE

- Compared with men, women with acute myocarditis were older at the time of diagnosis, and presented with more severe heart failure symptoms and higher levels of N-terminal pro B-type natriuretic peptide.
- During hospitalization, women received more advanced therapies, experienced severe arrhythmia 3.8 times more often, and were 1.9 times more likely to develop incident or worsening heart failure.
- Men presented more often with chest pain and ST-elevation, and showed more nonischemic affected segments in cardiac magnetic resonance imaging compared with women.

METHODS

The study protocol was reviewed and approved by the local ethics committee of Northwest and Central Switzerland (project ID 2017-01783) and was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Patient Population, Myocarditis Diagnosis, and Clinical Investigations

We retrospectively included all patients ≥18 years of age hospitalized for acute myocarditis in the ICU of the University Hospital Basel between January 2000 and September 2023 into the Basel Myocarditis Cohort study. The University Hospital Basel is located in a mid-sized city and serves as a tertiary referral center for surrounding rural areas. We used main and supportive criteria of the updated Lake Louise Criteria[10] for the diagnosis of myocarditis, utilizing cardiac magnetic resonance imaging (CMR) with dedicated sequences for T2-weighted imaging to assess myocardial edema, T1-weighted imaging for evaluation of hyperemia, and late gadolinium enhancement (LGE) to identify areas of myocardial injury.[11,12] A cohort of 307 (84.1%) participants underwent comprehensive CMR following standardized protocols, and the results were analyzed by experienced cardiologists and radiologists to ensure reliable and reproducible assessment of myocardial inflammation and injury. Although endomyocardial biopsy (EMB) remains the gold standard for definitive diagnosis, it was not routinely performed due to procedural risks and availability. In our cohort, 22 (6.0%) patients underwent an EMB, while 315 (86.3%) patients received either an EMB or a CMR. Among the 50 (13.7%) patients who did not undergo CMR or EMB, we applied a combination of diagnostic criteria according to current guidelines,[1] including clinical presentations, ECG abnormalities, cardiac and inflammatory biomarkers, and sequential transthoracic echocardiography (TTE) findings. These cases were reviewed case by case by 2 independent investigators and included if the diagnosis was deemed to be acute myocarditis. Suspected acute coronary artery disease with ischemia was investigated either with coronary angiography or CMR. The decision for coronary angiography or CMR for ischemia detection was decided by the treating physician based on pretest probabilities for myocarditis and for myocardial infarction. CMR serves as the gold standard for detecting even the smallest myocardial infarctions (up to 1 gram) without the need for ischemia assessment.[10] Standard 12-lead ECGs were recorded at admission with standard paper speed of 25 mm/s and an amplification of 10 mm/mV. All ECGs were interpreted by a cardiologist. Diffuse ST-elevation was defined as ST-segment elevation >1 mm (2 mm in V2-V3), not attributable to one coronary artery territory. Diffuse T-wave inversion was defined as the presence of inverted T-waves not attributable to one coronary artery territory. Biomarkers included inflammatory biomarkers (C-reactive protein [CRP], leucocytes, neutrophils, lymphocytes, eosinophils, and procalcitonin), creatine kinase (CK), albumin, cardiac biomarkers (cardiac troponin T [cTnT], creatine kinase muscle and brain [CK-MB] and N-terminal pro B-type natriuretic peptide [NT-proBNP]) and rheumatological biomarkers (rheumatic factors, antinuclear antibodies, antineutrophil cytoplasmic antibodies). In our study, conventional cTnT was measured until 2010. Subsequently, high-sensitivity cTnT was used. For this analysis, we pooled conventional and high sensitivity cTnT measurements. NT-proBNP was measured to quantify the extent of hemodynamic stress and heart failure, and cTnT was measured to quantify the extent of acute cardiomyocyte injury. For each biomarker, we used the maximal or minimal value, as appropriate, in our statistical models.

Imaging and Endomyocardial Biopsy

TTE was performed during the hospital stay by a trained cardiologist or cardiac sonographer and analyzed by a board-certified cardiologist with particular attention to the assessment of left ventricular ejection fraction (LVEF), regional wall motion abnormalities, and pericardial

effusion. CMR was done with Magnetom Prisma 3T or Skyra 3T devices (Siemens Healthcare, Malvern, Pa) using SSFP Ax; T1- and T2-Mapping/Cine SSFP/KM-IR-GRE Ax/KA/LA sequences with assessment of signs of edema, LGE according to standardized 17 myocardial segments,[11] and assessment of pericardial effusion or enhancement, as well as standard biventricular volumetric assessment. EMB was performed at the clinician's discretion and interpreted according to the Dallas criteria.[12,13] Acute myocarditis etiology is reported only in patients with EMB. Suspected coronary artery disease was investigated with CMR or left heart catheterization. Patients with acute coronary artery occlusion were excluded from the study. Patients with concomitant chronic coronary artery disease not responsible for the index hospitalization were not excluded.

Monitoring During Hospital Stay

During the stay at the ICU, patients were continuously monitored by a bedside patient monitor (Philips IntelliVue MX800; Philips Healthcare, Amsterdam, Netherlands) with automatic arrhythmia detection. Arrhythmias were then transferred to a patient data management system (Metavision [V5.46.44; iMDsoft, Germany] or CareVueChart [V: Rev.D03.02; Philips Healthcare]). Recorded arrhythmias included atrial fibrillation, atrial flutter, nonsustained ventricular tachycardia, sustained ventricular tachycardia (>100 beats per minute, ≥30 s), ventricular fibrillation and cardiac arrest (due to asystole or pulseless electrical activity). For the current study we defined severe arrhythmia as sustained ventricular arrhythmia ventricular fibrillation or cardiac arrest.

Outcome/Follow-Up

Analyzed in-hospital outcomes included severe arrhythmia, in-hospital death, cardiogenic shock, incident or worsening heart failure, and heart transplantation, and were collected from the patient data management system. New-onset or worsening heart failure was diagnosed based on symptoms, clinical signs, TTE, or natriuretic peptides. In routine clinical practice, patients were offered a clinical consultation and TTE after the index hospitalization for acute myocarditis.

Statistical Analysis

Baseline characteristics were stratified by sex. Continuous variables were expressed as mean ± standard deviation for normal distribution, or as median (interquartile range) for non-normal distribution. Distribution of the studied variables was assessed using the Shapiro-Wilk test, and to determine normality graphically, the output of a normal Q-Q plot was used. We compared our cohort by using the paired *t* test when normally distributed, or the Mann-Whitney *U* test when not normally distributed. Categorical data were summarized as numbers (%) and compared using the chi-squared test or Fisher's exact test, as appropriate. Missing data are not replaced but are considered in the analysis. A P value of $< .05$ was considered statistically significant. All statistical analyses were done with statistical software R version 4.2.2.

RESULTS

Baseline Characteristics

We included 365 patients with acute myocarditis: 269 (73.7%) were men and 96 (26.3%) women. Baseline characteristics are shown in Table 1. Overall, mean age was 41.3 (SD 16.7) years; 80 (21.9%) patients had arterial hypertension, 28 (7.7%) had diabetes, and 15 (4.1%) had renal insufficiency. Compared with men, women were older (49.7 vs 38.3 years, $P < .001$) and more often had arterial hypertension (33.3 vs 17.8%, $P = .003$) and known autoimmune diseases (20.8 vs 9.7%, $P = .008$). The age distribution at the time of acute myocarditis is shown in Figure 1.

Clinical Presentation

Overall, the most common presenting symptoms were chest pain (83.6%), dyspnea (30.1%), and fever (28.8%). The median time from symptom onset to hospitalization was 2 (IQR 1-5) days. Compared with men, women presented more often with dyspnea (40.6 vs 26.4%, $P = .013$), with no other differences in symptoms or the time from symptom onset to hospitalization. In the clinical examination, cardiac murmurs (12.5 vs 3.3%, $P = .002$) and, numerically, peripheral edema (9.4 vs 3.7%, $P = .061$) were more frequent in women. Females were ranked higher in the Killip classification, with 10.4% of females in class IV compared with 3.0% of males ($P = .011$). The median overall hospital stay was longer in female compared with male patients (7 [IQR 5-10] vs 5 [IQR 4-8] days, $P = .018$), with no differences in the length of ICU stay (2.6 [IQR 1.6-4.0] vs 2.7 [IQR 1.7-3.9] days, $P = 0.922$) (Table 1).

ECG and Rhythm Monitoring

The most common ECG findings at presentation were diffuse T-wave inversion (33.2%) and diffuse ST-elevation (30.4%). Compared with men, women presented less often with ST-elevation (9.4 vs 37.9%, $P < .001$) and PQ-depression (19.8 vs 31.2%, $P = .042$), but there was no difference in T-wave inversion (Table 1).

During in-hospital monitoring, severe arrhythmia occurred in 14 (3.8%) patients, nonsustained ventricular tachycardia in 26 (7.1%), and atrial fibrillation/atrial flutter in 12 (3.3%). While we did not find a sex difference between women and men in atrial fibrillation/atrial flutter (5.2 vs 2.6%, $P = .194$) and nonsustained ventricular tachycardia (11.5 vs 5.6%, $P = .074$), women more often experienced severe arrhythmia (8.3 vs 2.2%, $P = .015$). The temporal occurrence of severe arrhythmia stratified by sex is shown in Figure 2.

Table 1 Baseline Characteristics Stratified by Sex

	Overall n = 365	Female n = 96	Male n = 269	*P* Value
Age, years: mean (SD)	41.3 (16.7)	49.7 (16.4)	38.3 (15.8)	< .001
In hospital stay, days: median (IQR)	6 (4, 9)	7 (5, 10)	5 (4, 8)	.018
ICU stay, days: median (IQR)	2.7 (1.7, 4.0)	2.6 (1.6, 4.0)	2.7 (1.7, 3.9)	.922
Onset of symptoms to hospitalization, days: median (IQR)	2 (1, 5)	2 (1, 6)	3 (1, 5)	.284
Arterial hypertension, n (%)	80 (21.9)	32 (33.3)	48 (17.8)	.003
Diabetes, n (%)	28 (7.7)	10 (10.4)	18 (6.7)	.340
Renal insufficiency, n (%)	15 (4.1)	3 (3.1)	12 (4.5)	.768
Autoimmune disease, n (%)	46 (12.6)	20 (20.8)	26 (9.7)	.008
Clinical presentation				
Chest pain, n (%)	305 (83.6)	75 (78.1)	230 (85.5)	.130
Dyspnea, n (%)	110 (30.1)	39 (40.6)	71 (26.4)	.013
Fever, n (%)	105 (28.8)	21 (21.9)	84 (31.2)	.108
Cardiac murmur, n (%)	21 (5.8)	12 (12.5)	9 (3.3)	.002
Peripheral edema, n (%)	19 (5.2)	9 (9.4)	10 (3.7)	.061
Arrhythmia, n (%)	13 (3.6)	2 (2.1)	11 (4.1)	.527
Killip classification, n (%)				.011
I	323 (88.5)	78 (81.3)	245 (91.1)	
II	15 (4.1)	6 (6.3)	9 (3.3)	
III	5 (1.4)	2 (2.1)	3 (1.1)	
IV	18 (4.9)	10 (10.4)	8 (3.0)	
ECG at presentation				
Normal ECG, n (%)	87 (23.8)	33 (34.4)	54 (20.1)	.008
Diffuse ST-elevation, n (%)	111 (30.4)	9 (9.4)	102 (37.9)	< .001
Diffuse T-wave inversion, n (%)	121 (33.2)	38 (39.6)	83 (30.9)	.159
PQ-depression, n (%)	103 (28.2)	19 (19.8)	84 (31.2)	.042

ECG = electrocardiogram; ICU = intensive care unit; IQR = interquartile range.

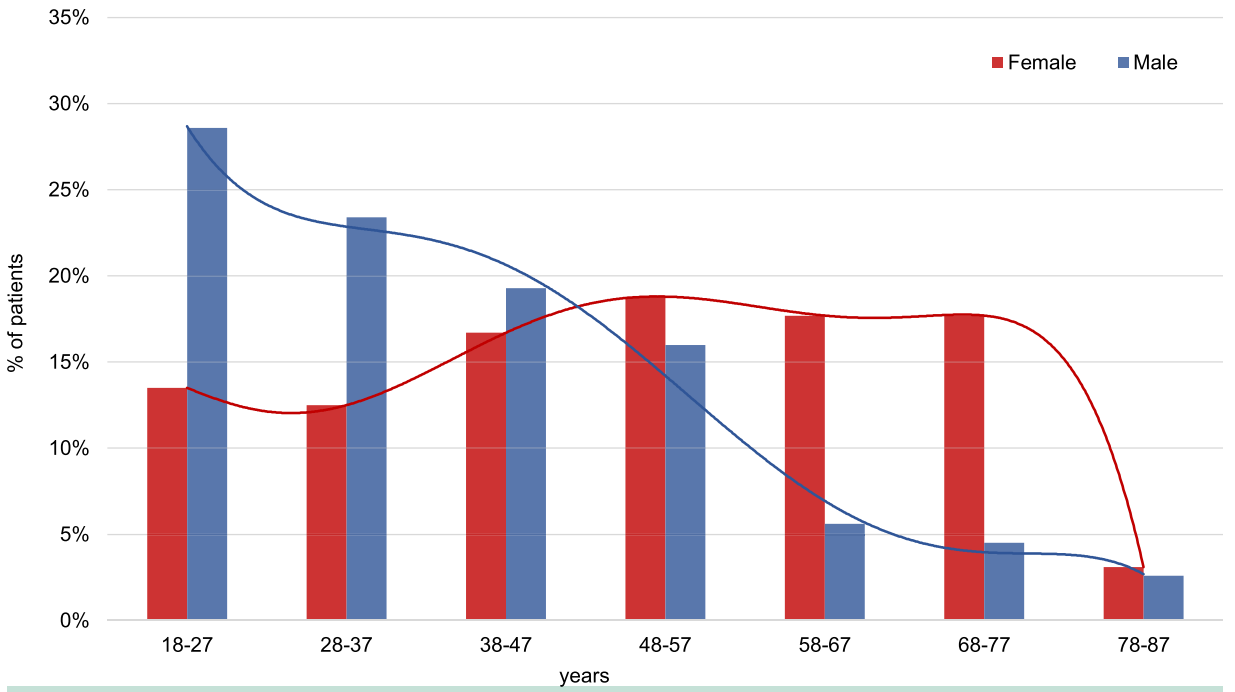


Figure 1 Age distribution at diagnosis of acute myocarditis stratified by sex. Bar chart with age groups (grouped in 10-year intervals) on the x-axis and the percentage of patients with acute myocarditis on the y-axis. For each age group, there are 2 columns representing male in blue color and female patients in red color, respectively. Additionally, trend lines have been added to demonstrate the age distribution.

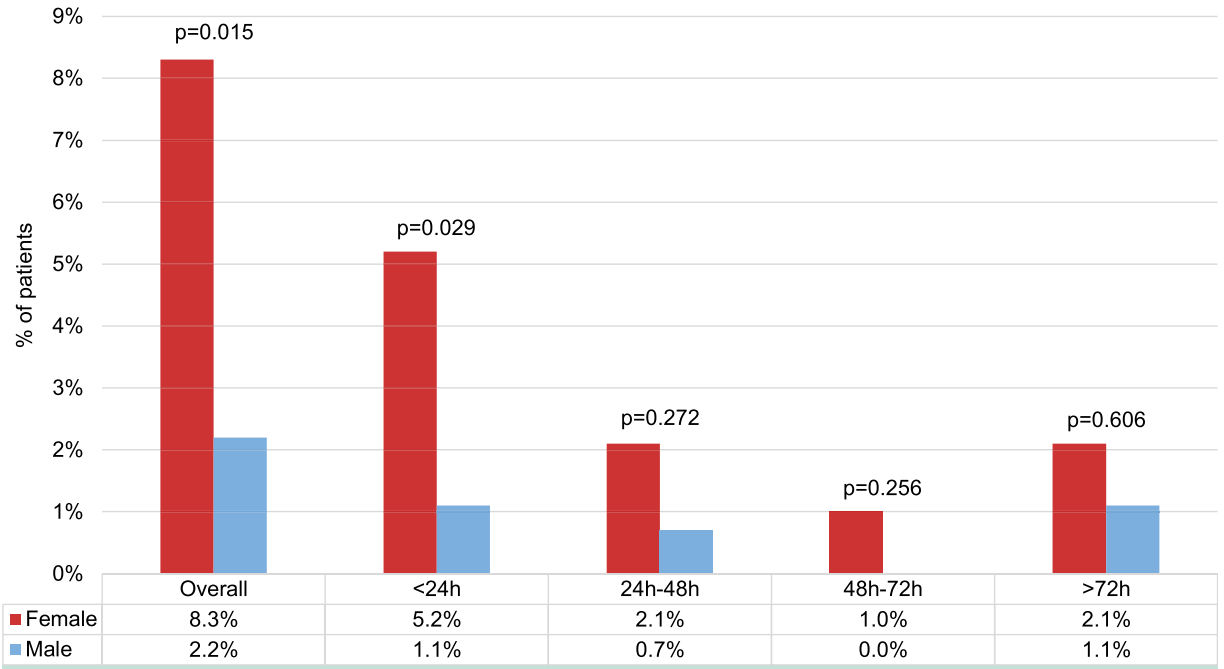


Figure 2 Temporal occurrence of severe arrhythmia stratified by sex. This bar chart compares the temporal occurrence of severe arrhythmia between sexes, male in blue and females in red.

Laboratory Findings

Women had higher median levels of NT-proBNP (1180 [IQR 319-5030] vs 387 [IQR 130-1250] ng/l, $P = 0.015$) and lower median levels of cTnT (389 [IQR 145-1000] vs 726 [IQR 245-1430] ng/l, $P = 0.006$) compared with men, but similar median levels of CK-MB. Women presented with lower levels of CK (239 [IQR 127-462] vs 378 [IQR 234-707] U/l, $P = .001$) and albumin (29 [IQR 24-32] vs 32 [IQR 29-35] g/l, $P < .001$) compared with men. For inflammatory biomarkers, women had numerically lower median levels of CRP (26.3 [IQR 4.3-77.2] vs 37.2 [IQR 12.6-84.2] mg/l, $P = .053$) and higher median levels of leucocytes (10.2 [IQR 8.2-13.6] vs 9.4 [IQR 7.5-11.5] x10S9/l, $P = .064$), but similar levels of lymphocytes, neutrophils, eosinophils, procalcitonin, and rheumatic factors (Table 2).

Cardiac Imaging and Endomyocardial Biopsy

In TTE, the overall median LVEF was 55% (IQR 50-60%), and 22.0% of the patients had a reduced LVEF <50%, with no sex differences. Pericardial effusion was detected more often in females compared with males (24.7 vs 10.9%, $P = .004$) (Table 3).

CMR was performed in 307 (84.1%) patients, with a similar rate in male and female patients (83.6 vs 85.4%, $P = .806$). Men had a higher occurrence of LGE (91.6 vs 76.8%, $P = .001$), but there was no difference in LVEF, pericardial effusion, regional wall motion abnormalities, and edema between sexes. In 65 (21.2%) patients with CMR, LGE distribution was assessed by standardized 17 segments (Figure 3). Of those, 69.2% showed nonischemic LGE in basal segments, 52.3% in mid-cavity segments, and 35.4% in apical segments with no sex differences. Men had a higher number of nonischemic LGE segments (3.0 [IQR 1.0−5.5] vs 1.0 [IQR 1.0-2.0], $P = .005$) compared with women (Table 3).

Overall, 22 (6.2%) patients received EMB, with a higher rate in female compared with male patients (12.5 vs 3.7%, $P = .004$). The etiology did not differ between the sexes. (Table 3)

Therapy

Overall, the most used therapeutics were renin-angiotensin-aldosterone system inhibitors in 283 (77.5%), nonsteroidal anti-inflammatory drugs in 245 (67.1%), and beta-blockers in 180 (49.3%) patients, with no sex differences. Compared with men, women were more often treated with steroids (24.0 vs 10.8%, $P = .003$), diuretics (24.0 vs 14.4%, $P = .040$), and more often received advanced treatments, including noninvasive ventilation (6.3 vs 1.9%, $P = .041$), mechanical circulatory support (6.3 vs 1.9%, $P = .041$), and numerically more often inotropes (8.3 vs 3.0%, $P = .056$) compared with men (Figure 4). Specific mechanical circulatory support devices are shown in the Supplementary Table (available online).

Outcomes

A follow-up TTE was available in 245 (67.1%) patients after a median of 46 [IQR 31-98] days. In 89 (36.3%) patients, the LVEF improved by >5% compared with the index hospitalization, with no difference between women and men (36.4 vs 36.3%, $P = 1.0$) (Table 3).

Overall, 8 (2.2%) patients died during hospitalization, 4 (4.2%) female and 4 (1.5%) male patients ($P = .215$).

Table 2 Comparison of Inflammatory and Cardiac Biomarkers Between Female and Male Patients

	Overall n = 365	Female n = 96	Male n = 269	*P* Value
cTnT (ng/L)	622 (192, 1350)	389 (145, 1000)	726 (245, 1430)	.006
NT-proBNP (ng/L)	505 (164, 2160)	1180 (319, 5030)	387 (130, 1,50)	.015
CK-MB (U/L)	21.5 (7.2, 44.3)	13.8 (5.0, 39.2)	23.2 (8.0, 45.2)	.129
Creatine kinase (U/L)	344 (193, 662)	239 (127, 462)	378 (234, 707)	.001
C-reactive protein (mg/L)	33.6 (9.6, 81.9)	26.3 (4.3, 77.2)	37.2 (12.6, 84.2)	.053
Leucocytes ($\times 10^9$/L)	9.6 (7.6, 12.2)	10.2 (8.2, 13.6)	9.4 (7.5, 11.5)	.064
Neutrophils ($\times 10^9$/L)	6.5 (4.8, 9.1)	6.5 (4.9, 9.6)	6.4 (4.8, 9.0)	.483
Lymphocytes ($\times 10^9$/L)	1.9 (1.4, 2.5)	2.0 (1.5, 2.7)	1.9 (1.4, 2.4)	.206
Eosinophils ($\times 10^9$/L)	0.19 (0.12, 0.31)	0.20 (0.12, 0.31)	0.19 (0.12, 0.31)	.556
Procalcitonin (ng/mL)	0.15 (0.06, 0.62)	0.20 (0.06, 0.90)	0.14 (0.07, 0.38)	.409
Albumin (g/L)	32 (28, 34)	29 (24, 32)	32 (29, 35)	< .001
Rheumatic factor (IU/mL)	9 (0, 11)	11 (0, 11)	0 (0, 11)	.175
ANA (1: XX Titer)	40 (0, 40)	40 (0, 60)	40 (0, 40)	.322
ANCA (1: XX Titer)	20 (0, 20)	20 (0, 20)	20 (0, 20)	.353

Values are median (interquartile range).

The maximum measured laboratory value was used except albumin where the minimum measured laboratory value was used.

ANA = antinuclear antibodies, ANCA = antineutrophil cytoplasmic antibodies CK-MB = creatine kinase muscle and brain; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro B-type natriuretic peptide.

Table 3 Cardiac Imaging and Endomyocardial Biopsy Stratified by Sex

	Overall	Female	Male	*P* Value
TTE at admission	n = 323	n = 85	n = 238	
LVEF, median (IQR), %	55 (50, 60)	55 (43, 61)	55 (50, 60)	.669
LVEF <50%, n (%)	71 (22.0)	25 (29.4)	46 (19.3)	.083
LVEF ≥50%, n (%)	242 (74.9)	58 (68.2)	184 (77.3)	.083
Pericardial effusion, n (%)	47 (14.6)	21 (24.7)	26 (10.9)	.004
Regional wall motion abnormalities, n (%)	145 (44.9)	38 (44.7)	107 (45.0)	1.0
Follow-up TTE	n = 245	n = 66	n = 179	
LVEF, median (IQR), %	60 (55, 64)	60 (54, 65)	60 (56, 64)	.58
LVEF improvement >5%, n (%)	89 (36.3)	24 (36.4)	65 (36.3)	1.0
LVEF improvement >10%, n (%)	47 (19.2)	16 (24.2)	31 (17.3)	.301
Days between TTE at admission and follow-up, median (IQR), d	46 (31, 98)	43 (31, 98)	49 (32, 98)	.672
CMR at admission	n = 307	n = 82	n = 225	
LVEF, median (IQR), %	56 (50, 62)	59 (49, 63)	56 (50, 61)	.140
LGE, n (%)	269 (87.6)	63 (76.8)	206 (91.6)	.001
LGE focal distributed, n (%)	172 (56.0)	40 (48.8)	132 (58.7)	.157
LGE diffusely distributed, n (%)	50 (16.3)	13 (15.9)	37 (16.4)	1.0
Pericardial effusion, n (%)	122 (39.7)	37 (45.1)	85 (37.8)	.302
Regional wall motion abnormalities, n (%)	166 (54.1)	47 (57.3)	119 (52.9)	.576
Edema, n (%)	171 (55.7)	44 (53.7)	127 (56.4)	.76
Segments with nonischemic LGE	n = 65	n = 13	n = 52	
Basal segments, n (%)	45 (69.2)	6 (46.2)	39 (75.0)	.073
Mid-cavity segments, n (%)	34 (52.3)	5 (38.5)	29 (55.8)	.351
Apical segments, n (%)	23 (35.4)	3 (23.1)	20 (38.5)	.346
Number of affected segments, median (IQR)	2.0 (1.0, 4.3)	1.0 (1.0, 2.0)	3.0 (1.0, 5.5)	.005
Endomyocardial biopsy etiology, n (%)	n = 22	n = 12	n = 10	
Viral/ idiopathic, n (%)	14 (63.6)	7 (58.3)	7 (70.0)	.675
Bacterial, n (%)	2 (9.1)	0 (0)	2 (20.0)	.195
Giant cell myocarditis, n (%)	4 (18.2)	3 (25)	1 (10.0)	.594
Connective tissue disease, n (%)	2 (9.1)	2 (16.7)	0(0)	.481

CMR = cardiovascular magnetic resonance imaging; IQR = interquartile range; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; TTE = transthoracic echocardiography.

Percentages refer to the number of the available, respective cardiac imaging studies.

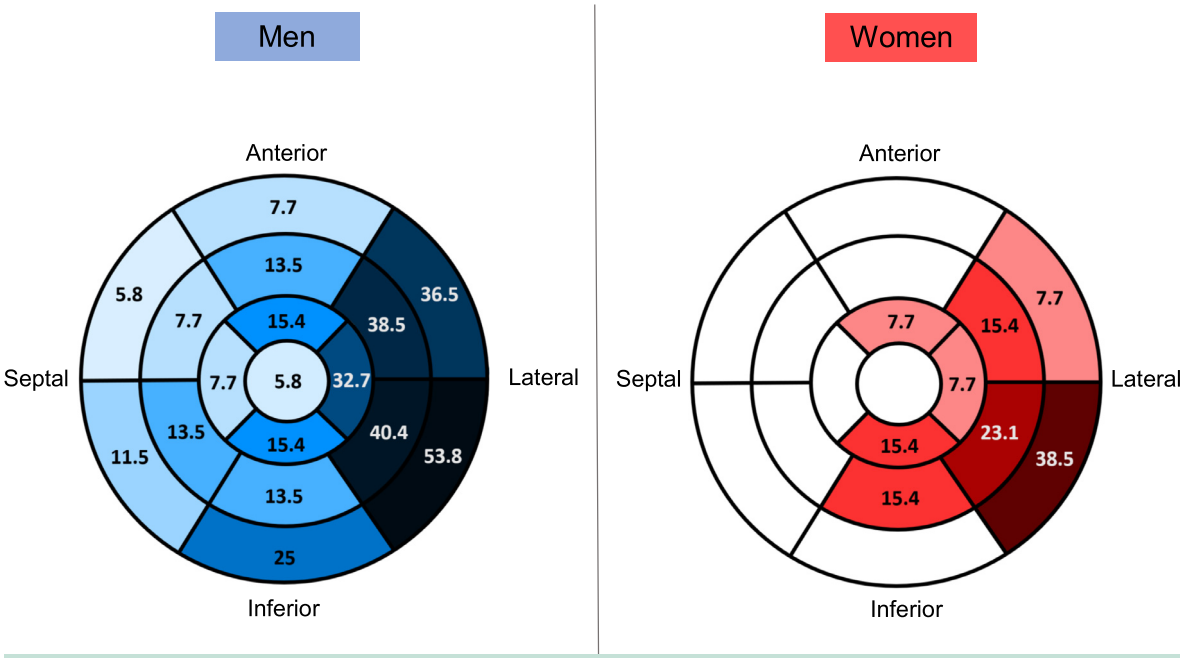


Figure 3 Seventeen-segment American Heart Association model shows nonischemic affected segments on CMR stratified by sex. Seventeen segments with nonischemic pattern in CMR stratified by sex. The blue-colored model represents the male patients, and the red-colored model the female patients. The numbers represent the percentage of patients with a nonischemic pattern in this segment. In total, 65 patients were available.

Cardiogenic shock was observed in 22 (6.0%) patients, with 11 (11.5%) female and 11 (4.1%) male patients (P = .019). During hospitalization, 74 (20.3%) patients developed new-onset or worsening heart failure: 31.3% of the female and 16.4% of the male patients (P = .003). Of these patients, 63 (85.1%) underwent a follow-up assessment, which revealed no difference in recovery rates between women and men (69.6 vs 71.4%, P = 1.0). There was no difference in the rate of heart transplantation after acute myocarditis (1.0% vs 0.4%, P = .457).

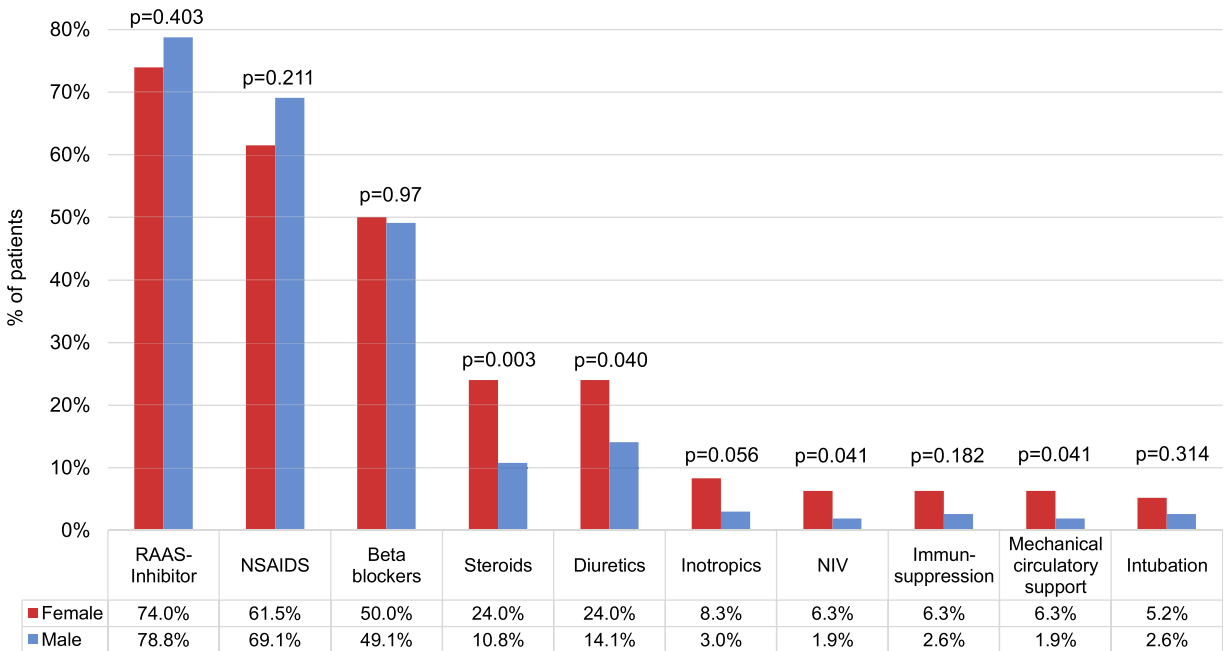
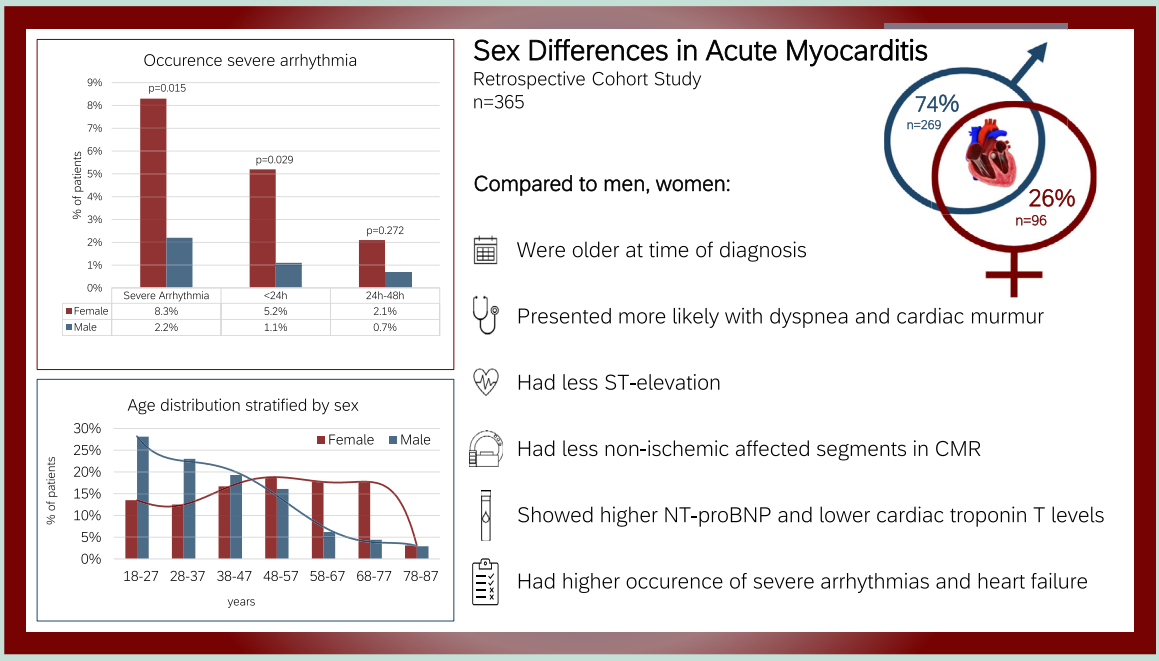


Figure 4 In-hospital therapy stratified by sex. Mechanical circulatory support includes left ventricular assist device, Impella pump (Abiomed, Inc., Danvers, Mass) and extracorporeal membrane oxygenation; NIV = noninvasive ventilation; NSAIDS = nonsteroidal anti-inflammatory drugs; RAAS = renin-angiotensin-aldosterone system.

CENTRAL ILLUSTRATION



DISCUSSION

Our study in an ICU revealed significant differences in clinical presentation, biomarkers, and in hospital outcomes between male and female with acute myocarditis, which underscore the need for sex-specific approaches in diagnosis and treatment. Compared with men, women with acute myocarditis were older at the time of diagnosis and presented with more severe heart failure symptoms and higher levels of NT-proBNP. During hospitalization, women received more advanced therapies, experienced severe arrhythmia 3.8 times more often, and were 1.9 times more likely to develop incident or worsening heart failure.

Data about sex-specific differences in acute myocarditis are scarce. Nevertheless, understanding these differences is crucial for accurate diagnosis and predicting patient outcomes. In our study, men presented more often with symptoms resembling acute myocardial infarction, whereas women more often showed heart failure symptoms. It is important to acknowledge the difference of the presenting symptoms to avoid missing the diagnosis in females due to their atypical presentation. This symptomatology might also indicate a worse clinical course in women. In the multicenter Lombardy registry, the proportion of women was higher in the group of complicated acute myocarditis (defined as LVEF <50%, ventricular arrhythmia, or fulminant presentation) compared with the group of uncomplicated acute myocarditis (31 vs 15%). The group of complicated acute myocarditis presented more often with dyspnea (56 vs 6%) and experienced a higher rate of adverse events.[14] In contrast, symptoms and clinical signs resembling acute myocardial infarction were shown to be associated with a better clinical outcome and more prevalent in males,[14-17] consistent with our study findings.

Sex-specific differences in the presentation and outcome might be due to different immunological responses and susceptibility to acute myocarditis. In our study, we found numerically lower levels of CRP, a trend toward higher levels of leucocytes, and lower levels of albumin in women compared with men, indicating differences in immune responses. These sex-specific differences in CRP and leucocytes were shown in some, but not all prior studies.[5-8] Higher CRP levels were associated with chest pain at presentation and a better clinical outcome, and normal CRP levels with higher New York Heart Association stages and arrhythmia occurrence.[15] These different inflammatory responses might, in part, be explained by differences in sex hormones. Estradiol has been shown in animal models to have a protective effect on the heart by preventing apoptosis in myocytes,[18] and estrogen receptors have been identified in coronary arteries, possibly affecting the immune response to infection and injury to the heart.[8,19-21] Considering decreasing estradiol levels throughout a woman's lifetime, women might become more vulnerable to developing acute myocarditis at a later stage in life. The presence of lower levels of protective estradiol and a higher burden of comorbidities during this later stage may expose women to

a more severe clinical course of acute myocarditis. In comparison, testosterone in male cardiac tissues has been shown to increase viral replication and inflammation in the heart.[6,8,22,23] Higher testosterone levels in males at a younger age might explain an earlier-age peak of acute myocarditis in men. A younger age at the time of infection might partly explain the more favorable outcome in males.

These sex-specific differences in immune responses might translate into different levels of cardiac biomarkers and adverse outcomes. We observed approximately twofold higher cTnT levels in males and threefold higher NT-proBNP levels in females, compared with each other. Based on prior evidence in patients with coronary artery disease, higher cTnT levels are expected to confer a higher risk for adverse outcomes.[24] However, the increase in cTnT levels in patients with acute myocarditis might be due to different mechanisms, potentially by increased permeability of cardiomyocyte cell membranes due to myocardial stress caused by inflammation, rather than due to cell necrosis.[25-28] In contrast, higher NT-proBNP levels seem to indicate increased myocardial wall stress in acute myocarditis and were associated with a poorer prognosis.[29] Similar to the increased incidence of heart failure, the observed 3.8-fold higher rate of severe arrhythmia in females might be due to more severe disease forms, inflammation, and myocardial wall stress.[30]

Strength and Limitations

Strengths of our study include the large and well-defined acute myocarditis cohort with continuous rhythm monitoring, available imaging parameters, and biomarkers. The following limitations need to be acknowledged in the interpretation of our study. First, the study was a retrospective, observational cohort study. Second, follow-up data were not available for all patients, introducing a possible survival bias. Third, patients were recruited at a tertiary hospital in the ICU. Our study population might therefore present patients with more severe forms of acute myocarditis, and the external validity to other patients in other countries or hospitals is limited.

CONCLUSION

Women with acute myocarditis presented more often with heart failure symptoms, more often experienced severe arrhythmias, and more often developed incident or worsening heart failure during hospitalization, compared with men. These sex-specific differences need to be considered in the diagnosis and treatment of acute myocarditis.

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SUPPLEMENTARY DATA

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Supplementary Table Types of Mechanical Circulatory Support Devices

	Overall n = 365	Female n = 96	Male n = 269	*P* Value
Impella pump, n (%)	9 (2.5)	5 (5.2)	4 (1.5)	.057
ECMO, n (%)	3 (0.8)	1 (1.0)	2 (0.7)	1.0
LVAD, n (%)	1 (0.3%)	1 (1.0)	0 (0)	.263

ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device.