Biological Sex and Its Impact on Clinical Characteristics in Patients Presenting with Myocarditis

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Highlights of the Study

- Biological sex has a known influence on immunological processes and pathophysiology of diseases.
- Sex-specific differences in laboratory parameters and diagnostic procedures were observed in patients presenting with myocarditis.
- The inflammatory process underlying myocarditis may differ between biological men and women.

Keywords

Cardiology · Myocarditis · Gender · Inflammation ·
Electrocardiogram · Echocardiography

Abstract

Introduction: Biological sex has a paramount influence on the pathophysiology of diseases, and thus on clinical presentation. In this study, we provide a comprehensive analysis of sex-specific differences in patients with myocarditis. **Materials and Methods:** Patients with myocarditis who were admitted to our study center in the time-period of 2009–2019 were retrospectively enrolled in this study. Clinical data, laboratory parameters, and measurements from transthoracic echocardiography were extracted from hospital records. Follow-up was acquired for 2 years after admission. **Results:** Two hundred twenty-four patients with myocarditis were enrolled in this study. Of these, 78% were men and 22% women. Female patients were older (median 50 years vs. 35 years, $p < 0.0001$), had a higher prevalence of respiratory tract infec-

tions, and had less frequently ST-segment elevations on electrocardiogram (ECG) (28% vs. 59%, $p = 0.003$). Furthermore, C-reactive protein was lower in women (median 0.60 mg/dL vs. 3.90 mg/dL, $p < 0.0001$), but showed a less pronounced decrease within 3 days when compared to men (fold-change 1.00 vs. 0.80, $p = 0.002$). Cardiac magnetic resonance imaging was conducted less often in women, whereas time to coronary angiography was significantly longer. We found no difference in left ventricular systolic function or all-cause-mortality between the 2 sexes. **Conclusion:** We observed sex-specific differences in laboratory parameters, abnormalities on ECG, and diagnostic procedures conducted in patients with myocarditis. Understanding these differences, both at the cellular level and in regard to the clinical presentation of patients, could be helpful in the diagnosis and treatment of this disease, and could further expand our understanding of its pathophysiology.

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Introduction

The term “myocarditis” refers to inflammatory reactions within the myocardium, which are most frequently a result of preceding infections with cardiotropic viruses. Interestingly, while old age was identified as a risk factor for several other cardiovascular diseases, this does not particularly apply to myocarditis. In contrast, previous studies identified male sex as a pivotal risk factor for the development of myocarditis, with an estimated male to female ratio of 3:1 in affected patients [1, 2].

In contrast to “gender identity,” which refers to the extent of a person’s identification with masculinity, femininity, and the spectrum in between [3], “biological sex” is determined by the expression of genes of an individual’s sex chromosomes (X and Y chromosomes). The expression of these genes results in differing concentrations of sex hormones, which in turn results in differential development of internal and external sexual organs, cardiovascular physiology, and even differences in cellular biology between biological men and women [2].

Due to the increasing understanding of pathophysiology, the possible influence of biological sex on the development and presentation of diseases has gained increasing scientific attention and recognition in recent years. However, while sex-specific differences have been thoroughly investigated in cardiovascular diseases like coronary artery disease or heart failure [4–7], the impact of biological sex on the presentation and outcomes of patients with myocarditis was relatively less well addressed by previous studies. In a large retrospective study involving 27,129 hospitalizations for myocarditis, Shah et al. [8] recently reported that female patients had a higher risk of in-hospital complications than males, and female gender was identified as an independent risk predictor for in-hospital mortality in myocarditis. Furthermore, another study found that female patients with myocarditis presented with dyspnea rather than with chest pain and that plasma levels of creatinine kinase (CK) were significantly higher in the male subgroup. However, the authors of the latter study did not find any other sex-specific differences in laboratory parameters, probably due to the low number of patients enrolled in their study [9].

Biological sex has a considerable influence on several intra- and intercellular processes, and thus on the development and progression of several disease entities [10, 11]. To the best of our knowledge, there is currently no evidence regarding sex-specific differences in inflammatory parameters, such as C-reactive protein (CRP), leukocyte count, or neutrophil-to-lymphocyte ratio (NLR) in

patients with myocarditis. Furthermore, studies investigating the sex-specific impact on echocardiographic changes after acute myocarditis are also not available. Our study aimed to study differences between men and women because they could provide additional information on the pathophysiology of the disease and could aid in the sex-specific adaption of diagnosis and treatment.

Materials and Methods

The study protocol was reviewed and approved by the Ethics Committee of the State of Salzburg, Austria (EK Nr: 1181/2020). The study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki.

A database search of all consecutive patients admitted to the University Hospital of Salzburg, Austria, in the time-period of 2009–2019 was conducted. Patients with myocarditis were identified through a search on discharge diagnoses recorded in hospital discharge forms, which were classified according to the *International Classification of Diseases, Tenth Revision (ICD-10)* diagnostic codes (I40.0, I40.1, I40.8, I40.9, and I51.4). The presence of acute myocarditis, as defined by the current recommendations of the European Society of Cardiology [12], was confirmed by revision of all clinical records. Admissions for elective procedures or follow-up visits were excluded from the study. Clinical and laboratory data were extracted from the hospital records and discharge letters of enrolled patients. Laboratory data of the day of presentation and after 3 days of treatment were analyzed. Data from transthoracic echocardiography (TTE) and electrocardiogram (ECG) were acquired from the 1st available set of data after presentation, that is, from the emergency department, the intensive care unit, or the hospital ward. Data on follow-up TTE were acquired from exams conducted within 3–6 months after the initial presentation. Follow-up on mortality was acquired for 2 years after presentation; death was defined as that from any cause within 2 years after the index hospitalization. The classification of histopathological findings was graded according to the Dallas criteria [13], whereas findings of magnetic resonance imaging (MRI) were graded according to the Lake Louise criteria [14].

Statistical analyses were performed with SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) and R (version 4.0.2., R Core Team [2013], R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>). Data distribution, skew, and kurtosis of continuous data were assessed visually and by performing a Shapiro-Wilk test. Since data were not normally distributed, median $\pm$ interquartile range (IQR) are depicted and medians were compared using a Mann-Whitney U test. Categorical data were analyzed by applying Fisher’s exact test. A p value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 224 patients were enrolled in this study. Of these, 78% ($n = 174$) were men and 22% ($n = 50$) were

Table 1. Baseline characteristics, vital signs, ECG abnormalities, and TTE measurements in male and female patients with myocarditis

Baseline characteristics	Female (n = 50)		Male (n = 174)		p value
	median	IQR	median	IQR	
Age, years	50	36–62	35	24–45	<0.0001
	%	n	%	n	p value
Season					
Spring (20 March to 20 June)	20	10	23	40	0.973
Summer (21 June to 22 September)	24	12	24	42	
Autumn (23 September to 21 December)	24	12	23	40	
Winter (22 December to 19 March)	32	16	30	52	
Previous infection	59	29	68	117	0.305
Infection					
Gastrointestinal tract	7	2	23	27	0.029
Respiratory tract	69	20	40	47	
Urinary tract	7	2	3	3	
Ear, nose, and throat	7	2	15	17	
Other	10	3	19	23	
Diabetes mellitus	10	5	4	6	0.072
Hyperlipidemia	18	9	15	26	0.660
Obesity (BMI >30 kg/m ²)	14	7	13	23	0.524
Arterial hypertension	26	13	23	39	0.704
History of smoking	18	9	38	65	0.010
CAD	2	1	4	6	0.698
Cerebral artery disease	4	2	0	0	0.049
Peripheral artery disease	2	1	1	1	0.399
Vital signs	median	IQR	median	IQR	p value
Systolic blood pressure, mm Hg	124	114–146	130	120–146	0.431
Diastolic blood pressure, mm Hg	84	66–91	80	70–88	0.745
Heart frequency, bpm	75	68–90	75	62–88	0.279
Peripheral oxygen saturation (%)	98	93–99	98	97–99	0.917
Temperature	36.4	36.3–37.2	36.4	36.1–36.8	0.646
Initial ECG and TTE	%	n	%	n	p value
ECG changes	70	33	72	123	0.856
ST-seg. elevation	28	9	59	73	0.003
ST-seg. depression	25	8	18	22	0.451
Wall motion abnormalities on TTE	38	15	27	41	0.240
	median	IQR	median	IQR	p value
LV end-diastolic diameter, mm	44	40–46	48	45–51	<0.0001
Interv. septum thickness, mm	11	10–13	10	9–12	0.417
Posterior wall thickness, mm	11	9–13	10	9–12	0.325
EF (%)	55	47–60	55	50–60	0.324

IQR, interquartile range; BMI, body mass index; ECG, electrocardiogram; TTE, transthoracic echocardiography; LV, left ventricular; CAD, coronary artery disease; EF, ejection fraction.

Fig. 1. Sex-specific FC of CRP within 3 days after hospital admission. FC, fold-change; CRP, C-reactive protein.

women. Female patients were significantly older than males (median 50 years [IQR 36–62] versus median 35 years [IQR 24–45], $p < 0.0001$) and had a higher prevalence of cerebral artery disease as known comorbidity (4% vs. 0%, $p = 0.049$, see Table 1).

Although there was no sex-specific difference in the frequency of infections occurring 4–6 weeks before admission to the hospital (males [m]: 68%, females [f]: 59%, $p = 0.305$), female patients who had an infection prior to myocarditis had a significantly higher prevalence of respiratory tract infections and lesser gastrointestinal infections than males (respiratory tract: 69% vs. 40%; gastrointestinal: 7% vs. 23%, $p = 0.029$). Despite a high prevalence of infections prior to myocarditis, we neither observed seasonal clustering nor sex-specific differences in this regard (Table 1).

Vital Signs, ECG, and TTE

At presentation, there was no statistically significant difference in blood pressure, heart frequency, peripheral oxygen saturation, or body temperature between men and women. In the ECG, female patients had significantly less frequent ST-segment elevations (28% vs. 59%, $p = 0.003$); upon TTE, females had a significantly smaller left ventricular (LV) end-diastolic diameter (median 44 mm vs. median 48 mm, see Table 1) than male patients. There was no difference in LV systolic function between men and women.

Laboratory Findings

In the initial laboratory exam at presentation, women had significantly lower plasma levels of CRP (median 0.60

mg/dL vs. median 3.90 mg/dL, $p < 0.0001$) and CK (median 97.5 IU/L vs. 211.0 IU/L, $p < 0.0001$) than men. Furthermore, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), LDH, and hemoglobin were lower, whereas the thrombocyte count was higher than that in male patients (Table 2). Despite a higher CRP at the initial laboratory exam, men had a higher fold-change (FC) and delta (Δ) of CRP after 3 days than women (FC CRP 0.80 vs. 1.00, $p = 0.002$, see Table 2; Fig. 1). Furthermore, serum levels of CK showed a more pronounced decline after 3 days than those in the female patients (Δ CK -87.0 IU/L vs. -30.0 IU/L, $p = 0.029$, see Table 2). It is important to note that we did not observe sex-specific differences in the NLR, eosinophil-to-lymphocyte ratio, basophil-to-lymphocyte ratio, or monocyte-to-lymphocyte ratio but observed a statistically insignificant trend toward higher plasma concentrations of high-sensitivity troponin in men (median 179 ng/L vs. median 73 ng/L, $p = 0.101$).

Diagnostic Procedures and Outcome

Within 24 months of the index hospitalization, 4 patients died, resulting in an all-cause mortality rate of 2.8%. We did not observe a statistically significant difference in all-cause mortality between the 2 sexes; however, our study might have been underpowered in this regard.

In the total cohort, 95 patients (42%) underwent coronary angiography, 27 patients (12%) coronary computed tomography, and 3 patients (1%) myocardial scintigraphy. Cardiac MRI was conducted in 166 patients (74%), whereas endomyocardial biopsy was performed in 17 patients (8%). In women, MRI was conducted significantly less often (61% vs. 79%, $p = 0.015$), whereas endomyocardial biopsy was performed significantly more often (16% vs. 5%, $p = 0.019$, see Table 3). In females who underwent coronary angiography, the time from admission to procedure was significantly longer than that in male patients (median 2 days vs. median 0 days, $p = 0.001$, see Table 3).

Furthermore, we did not observe a statistically significant difference in Δ or FC of ejection fraction when compared to follow-up TTE at 3–6 months after the index hospitalization (see Table 3). Regarding the findings of MRI, we observed a slightly higher yet statistically insignificant prevalence of myocardial edema (57.1% vs. 46.8%, $p = 0.457$) in women. Furthermore, the location of inflammatory infiltrates was more evenly distributed than that in men, in whom a trend toward a predominance of lateral myocardial segments was observed ($p = 0.273$; see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520870).

Table 2. Laboratory findings in male and female patients with myocarditis

Laboratory findings	Female (n = 50)		Male (n = 174)		p value
	median	IQR	median	IQR	
Creatinine, mg/dL	0.80	0.70–0.90	0.92	0.83–1.10	<0.0001
eGFR, mL/min/1.73 m ²	70.0	68.0–70.0	70.0	70.0–70.0	0.098
CRP, mg/dL	0.60	0.60–3.98	3.90	0.60–8.30	<0.0001
Bilirubin, mg/dL	0.30	0.40–0.50	0.60	0.40–0.80	<0.0001
AST, IU/L	28.0	21.0–40.0	42.5	29.0–60.3	0.007
ALT, IU/L	18.0	14.0–32.0	31.5	21.0–46.5	0.001
LDH, IU/L	170.0	154.0–237.5	206.0	173.0–242.3	0.024
CK, IU/L	97.5	58.3–184.5	211.0	106.0–412.5	<0.0001
CK-MB (%)	10.1	8.3–19.4	10.2	7.1–13.5	0.386
hsTnT, ng/L	73.0	8.5–302.5	179.0	17.4–543.5	0.101
pBNP, ng/L	287.8	129.0–2,799.5	294.6	101.3–760.3	0.188
Fibrinogen, mg/dL	371.5	281.0–555.0	405.0	312.0–552.0	0.600
Hemoglobin, mg/dL	12.9	12.2–13.6	14.9	14.0–15.7	<0.0001
Leukocyte count, G/L	8.72	6.83–11.70	8.69	7.07–11.55	0.895
Thrombocyte count, G/L	261.5	217.3–299.8	215.0	174.3–247.8	<0.0001
IL-6, pg/mL	54.3	7.2–74.3	27.7	8.0–83.0	0.990
Procalcitonin, µg/L	0.15	0.10–0.20	0.20	0.10–0.40	0.324
NLR	3.39	1.49–4.73	2.20	1.51–4.71	0.465
ELR	0.05	0.03–0.13	0.07	0.02–0.16	0.967
BLR	0.01	0.00–0.02	0.02	0.00–0.02	0.734
MLR	0.42	0.32–0.54	0.42	0.27–0.60	0.903
Δs and FCs	median	IQR	median	IQR	p value
Δ CRP, mg/dL	0.0	–0.7 to 0.8	–1.0	–3.6 to 0.0	0.001
FC CRP	1.00	0.70–1.58	0.80	0.42–1.00	0.002
Δ hsTnT, ng/L	–4.0	–116.5 to 23.5	1.5	–77.3 to 257.0	0.209
FC hsTnT	0.98	0.59–1.56	1.06	0.73–2.17	0.255
Δ pBNP, ng/L	–24.8	–1,169.3 to 235.5	–28.0	–400.7 to 92.8	0.720
FC pBNP	0.75	0.66–1.22	0.83	0.44–1.49	0.699
Δ CK, IU/L	–30.0	–90.0 to 6.0	–87.0	–283.0 to 4.5	0.029
FC CK	0.70	0.46–0.90	0.57	0.31–0.94	0.177

IQR, interquartile range; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; CK-MB, creatinine kinase myocardial band; FC, fold-change; hsTnT, high-sensitivity troponin; pBNP, Pro-brain natriuretic peptide; Δ, delta; IL-6, interleukin 6; NLR, neutrophil-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.

There were no statistically significant differences in the findings of endomyocardial biopsy between both sexes, probably because of the low number of procedures conducted.

Discussion

Current evidence suggests that biological sex has a paramount influence on cellular processes, and thus on the development and progression of several disease entities

[2, 11]. Previous studies identified male sex as a risk factor for the development of myocarditis, whereas female sex was associated with worse outcomes in affected patients [1, 8]. Although these findings suggest that biological sex plays a pivotal role during the course of myocarditis, previous evidence on this aspect is limited. Therefore, we aimed to provide a comprehensive analysis of sex-specific differences of baseline characteristics, vital signs, abnormalities in the ECG and TTE, as well as of laboratory findings, diagnostic procedures, and outcomes of patients presenting with acute myocarditis. Interestingly,

Table 3. Diagnostic procedures conducted and outcomes in male and female patients with myocarditis

Diagnostic procedures and outcome	Female (n = 50)		Male (n = 174)		p value
	%	n	%	n	
Coronary angiography	40	20	43	75	0.747
Coronary CT	16	8	11	19	0.460
Myocardial scintigraphy	2	1	1	2	0.990
Cardiac MRI	61	30	79	136	0.015
Endomyocardial biopsy	16	8	5	9	0.019
All-cause mortality (24 months)	2	1	2	3	0.990
	median	IQR	median	IQR	p value
Δ EF to 3–6 months (%)	0.0	–9.0 to 5.0	0.0	–3.1 to 9.8	0.510
FC EF to 3–6 months	1.00	0.85–1.15	1.00	0.95–1.20	0.638
Time to coronary angiography, days	2	0–4	0	0–1	0.001
Time to cardiac MRI, days	8	2–17	6	3–16	0.864
Time to endomyocardial biopsy, days	11	1–238	3	2–23	0.536
Time to coronary CT, days	3	1–4	1	0–3	0.198
Time to myocardial scintigraphy, days	30	30–30	5	4–5	0.990

CT, computed tomography; MRI, magnetic resonance imaging; FC, fold-change; EF, ejection fraction; Δ, delta; IQR, interquartile range.

we found that plasma levels of CRP at baseline were significantly lower in women; however, men showed a higher FC of CRP, indicating a more pronounced decrease in inflammatory parameters within 3 days of admission to the hospital. Furthermore, cardiac MRI was conducted less often in women, and the time from admission to coronary angiography was significantly longer. Hence, biological sex affects not only cellular processes and pathophysiology but probably also the clinical management of patients with myocarditis.

Some sex-specific differences in patients with myocarditis have been reported previously. For example, male sex is more prevalent among patients with myocarditis, and females tend to be older [1]. Furthermore, a recent study by Patriki et al. [9] demonstrated that plasma levels of CK were higher in male patients with myocarditis than those of CK in the biological females. The same observation was also made in our study cohort, but additionally, we found statistically significant differences in CRP, bilirubin, AST, ALT, LDH, hemoglobin, and thrombocyte count between the 2 sexes. While sex-specific differences in bilirubin, AST, ALT, LDH, hemoglobin, and thrombocyte count are well known [15–17] and supposedly independent of the presence of myocarditis, the difference in CRP in our study cohort is of special interest. Female patients in our study had significantly lower plasma concentrations of CRP at baseline (median 0.6 mg/dL vs. 3.9 mg/

dL, $p < 0.0001$), but they showed a less pronounced decrease in CRP within 3 days after admission to the hospital, as assessed by Δ and FC of CRP (FC 1.00 vs. 0.80, $p = 0.002$). Furthermore, we observed a trend toward higher levels of interleukin 6 and NLR in women, which, however, remained statistically insignificant (interleukin 6: median 54.3 pg/mL vs. median 27.7 pg/mL, $p = 0.990$; NLR: 3.39 vs. 2.20, $p = 0.465$), probably because our study was underpowered in this regard. Nevertheless, taken together, these findings could indicate that the inflammatory process in acute myocarditis differs between men and women, which is also underlined by statistically insignificant trends toward the higher prevalence of myocardial edema and differently affected myocardial segments in women. In this regard, the fact that we observed significantly more respiratory tract infections and less gastrointestinal tract infections 4–6 weeks prior to myocarditis in biological women might also refer to immunological differences between men and women. In fact, previous studies found that biological sex has a marked influence on the immune system and its response to pathogens and autoantigens, which also becomes apparent with the increased risk for autoimmune diseases such as systemic lupus erythematosus or autoimmune thyroid disease in women [18, 19]. In inflammatory processes, sex hormones have been reported to elicit diverging effects, with male androgens eliciting predominantly anti-inflamma-

tory, and estrogens eliciting both anti- and pro-inflammatory properties, depending on several other factors [20–22]. Furthermore, sex-specific differences in T-cell activation and differentiation were observed in a previous study [23]. Kverneland et al. [23] reported significant differences in lymphocyte subsets between the 2 sexes, with a male predominance for CD8+ T cells and a female predominance for CD4+ T cells. Since CD4+ T lymphocytes have been identified as key mediators in the pathophysiology of myocarditis and its progression to inflammatory cardiomyopathy [24–26], the observed sex-specific divergence in laboratory parameters in our study could thus indicate differences in the inflammatory process between the 2 sexes, which could also in part explain the sex-specific variations in clinical outcomes observed in previous studies [1, 8].

However, the fact that women were significantly older than men in our study could have had an influence on our findings. As such, older age has been associated with a dysregulation of inflammatory and immunological responses, declining T-lymphocyte function and enhanced secretion of pro-inflammatory cytokines [27–29]. Whether beginning “immunosenescence” could have an impact on the inflammatory processes underlying myocarditis should be further addressed by future investigative studies.

Concerning the ECG, we observed significantly less ST-segment elevations in women than in men (28% vs. 59%, $p = 0.003$), which is in line with the findings of a previous study by Younis et al. [30]. However, upon TTE, we did not observe differences in LV systolic function at baseline (median 55%), or in the Δ and FC of ejection fraction 3–6 months after the index hospitalization between men and women. Although women had a significantly smaller LV end-diastolic diameter on the initial TTE, this finding has to be interpreted in consideration of the higher body surface area of men and is thus unlikely to be associated with the presence of myocarditis.

Interestingly, we further found a statistically significant variation between men and women in diagnostic procedures conducted. Hence, although coronary angiography, coronary computed tomography, and myocardial scintigraphy were roughly equally frequent between the 2 sexes, MRI was conducted less often (61% vs. 79%, $p = 0.015$), while endomyocardial biopsy was performed more often (16% vs. 5%, $p = 0.019$) in the female patients. Furthermore, time from admission to coronary angiography was significantly longer in women (median 2 days vs. median 0 days, $p = 0.001$). While the true reason for this variation remains elusive, we can only speculate that biological sex can also bias clinical reasoning and decision-

making. For example, since coronary artery disease is generally more prevalent in men [31] and men had a higher prevalence of ST-segment elevations in our study cohort, the significantly shorter time to coronary angiography in male patients could be a result of the attending physicians' priority to rapidly rule out myocardial ischemia in men in contrast to women. Similarly, the lower utilization of cardiac MRI in women was also observed in the study by Younis et al. [30], and could be a result of the often atypical clinical presentation of female patients, which could have had an impact on the clinical decisions made by physicians. Nevertheless, our study was conducted at a single study center, and these findings need to be confirmed by large multi-center studies in the future.

Our study has several limitations. First, because of the low prevalence of myocarditis, we chose a retrospective study design to test our hypotheses. Due to the low level of evidence of this design, however, a prospective multi-center study would have been preferable. Second, data from follow-up TTE were only available from 49 patients, and a possible selection bias cannot be excluded (i.e., patients with echocardiographic abnormalities during the index hospitalization could have been examined earlier than those with a normal exam). Large prospective multicenter studies should address this issue further. Last, in contrast to previous studies [8], we did not observe sex-specific differences in mortality. However, our study was probably underpowered to detect these differences, and therefore, prospective trials are warranted.

In summary, we observed sex-specific differences in laboratory parameters, abnormalities on ECG, and diagnostic procedures conducted in patients with myocarditis. While biological sex has a known influence on cellular processes and thus on pathophysiology of diseases, several sex-specific differences are related to diagnostic procedures and can probably be attributed to differences in clinical management. Understanding these differences, both at the cellular level and in regard to the clinical presentation of patients, could be helpful in the diagnosis and treatment of this disease, and could further expand our understanding of its pathophysiology.

Conclusions

In patients with myocarditis, sex-specific differences can be observed in laboratory parameters, abnormalities on the ECG, and diagnostic procedures conducted. As such, female patients had lower plasma concentrations of CRP at baseline but showed a less pronounced decrease within 3

days after admission. Furthermore, cardiac MRI was conducted less often in women, whereas time to coronary angiography was significantly longer. Understanding these differences, both at the cellular level and in regard to the clinical presentation of patients, could be helpful in the diagnosis and treatment of this disease, and could further expand our understanding of its pathophysiology.

Statement of Ethics

The study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. Informed consent was not obtained since it was a retrospective study. The study protocol was reviewed and approved by the Ethical Review Board of the state of Salzburg, Austria (EK Nr: 1181/2020), prior to data collection.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author Contributions

M.M. and L.S. designed the study protocol. L.S. performed data collection, while M.M. conducted all statistical analyses. M.M. and L.S. wrote the manuscript. A.T., U.H., and M.L. reviewed the article and provided substantial improvements prior to submission. All authors read the final version of the manuscript and agreed to its contents.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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