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Sex and Age Characteristics in Acute or Chronic Myocarditis A Descriptive, Multicenter Cohort Study

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.

Abstract

BACKGROUND—Understanding the clinical features of myocarditis in various age groups is required to identify age-specific disease patterns.

OBJECTIVES—The objective of this study was to examine differences in sex distribution and clinical outcomes in patients with myocarditis of various ages.

METHODS—Patients with acute or chronic myocarditis in 3 centers in Berlin, Germany from 2005 to 2021 and in the United States (National Inpatient Sample) from 2010 to 2019 were included. Age groups examined included “prepubescent” (below 11 years for females and below 13 years for males), adolescents (11 [female] or 13 [male] to 18 years), young adults (18–35 years), “middle-aged adults” (35–54 years), and older adults (age >54 years). In patients admitted to the hospital, hospital mortality, length of stay, and medical complication rates were examined.

RESULTS—Overall, 6,023 cases in Berlin and 9,079 cases in the U.S. cohort were included. In both cohorts, there were differences in sex distribution among the 5 age categories, and differences in the distribution were most notable in adolescents (69.3% males vs 30.7% females) and in young adults (73.8% males vs 26.3% females). Prepubescent and older adults had the highest rates of in-hospital mortality, hospital length of stay, and medical complications. In the Berlin cohort, prepubescent patients had higher levels of leukocytes ($P < 0.001$), antistreptolysin antibody ($P < 0.001$), and NT-proBNP ($P < 0.001$) when compared to young adults.

CONCLUSIONS—In this study, we found that sex differences in myocarditis and clinical features of myocarditis were age-dependent.

Keywords

age; biomarkers; diagnosis; gender differences; myocarditis; sex differences

One consistent characteristic of clinical myocarditis is the report of sex differences with more males having myocarditis than females.[1–6] Studying the clinical nature of myocarditis by sex and age is necessary to learn about risk factors and patterns of disease. In addition to having a higher incidence of myocarditis, men also tend to have a more severe clinical course compared to women.[7,8] Various potential contributing factors have been reported for this sex difference including the influence of sex hormones.[9] It has been shown that the immune response, in particular innate immune signaling molecules on mast cells, macrophages, and T cells, differs in the inflamed myocardium by sex.[4,10–12] Also, men with myocarditis tend to develop more myocardial fibrosis on cardiac magnetic resonance (CMR) imaging, which has been suggested to be a potential explanation for their higher risk of arrhythmias and sudden cardiac death.[8] Fibrotic remodeling in patients with myocarditis has been demonstrated in animal models to be testosterone-dependent.[13,14] Other factors that may affect the clinical course in myocarditis are sex-specific differences in gene expression, as observed in patients with heart failure.[1,15–18]

Since the beginning of the COVID-19 pandemic, myocarditis has gained significant public attention due to its increasing incidence caused by SARS-CoV2 infection and, to a much lesser degree, mRNA vaccines.[19] Notably, there has been a significantly higher occurrence

of myocarditis in young men compared to women among both COVID-19 and vaccine-related cases. The underlying reasons for this phenomenon remain unknown.

Overall, data is limited on the differences in clinical characteristics of myocarditis in various age groups. There have been 3 inpatient registry studies of more than 2,500 patients hospitalized for myocarditis, reporting on hospital length of stay (LOS), medical complications, and mortality outcomes.[20–22] However, these studies published either preliminary data or were focused on patients below the age of 20. Furthermore, laboratory and echocardiographic markers were not included.

To evaluate sex differences and clinical features in patients with myocarditis according to age, we performed a multicenter analysis of clinical data from over 15,000 patients diagnosed with myocarditis across all age groups presenting to either 3 large tertiary care centers in Berlin, Germany from 2005 to 2021 (“Berlin cohort”) or hospitals in the United States from 2010 to 2019 (“U.S. cohort”).

METHODS

For detailed methods, see the Supplemental Appendix.

STUDY POPULATION.

The study population included patients diagnosed with myocarditis who were treated at 3 multidisciplinary tertiary care hospitals in Berlin, Germany, as well as a sample of data from U.S. hospitals. The study was approved by the local ethics committees. The diagnosis of myocarditis in the Berlin cohort was made based on the recommendations of the European Society of Cardiology.[23] Acute vs chronic myocarditis was based on the duration of clinical symptoms with symptoms persisting longer than 3 months being classified as chronic.[23] In the Berlin cohort, clinicians diagnosed myocarditis by a combination of clinical, laboratory, electrocardiographic findings, endomyocardial biopsies (EMB, 25.0% of the Berlin cohort), and/or CMR (16.0% of the Berlin cohort). Patients with a past medical history of myocarditis or missing baseline data were excluded from the study (Figure 1). The Berlin cohort was further divided into a subgroup of patients with myocarditis who received an EMB (“biopsy-proven myocarditis”).

AGE GROUPS.

The study cohort was divided into 5 age groups based on common age definitions in the medical literature: Age group 1 (“prepubescent”) was defined based on prepubescent age, which is defined as below 11 years for female and below 13 years for male patients.[24–26] Age group 2 (“adolescents”) ranged from 11 (female) or 13 (male) to 18 years; age group 3 (“young adults”) between 18 and 35 years; age group 4 (“middle-aged adults”) between 35 and 54 years; and age group 5 (“older adults”) was defined as age above 54 years based on the average age of menopause in women.[27] Age group 3 was the reference age group used for comparison purposes.

PRIMARY AND SECONDARY OUTCOMES.

Within each age group, the sex distribution in patients with myocarditis was examined (primary outcome). After the exclusion of outpatient cases, hospital mortality, hospital LOS, and medical complication rates (secondary outcomes) were examined in patients admitted to the hospital for inpatient treatment. Hospital mortality was defined as a mortality event that occurred during the patient's hospital stay. Hospital LOS was defined as the number of days between hospital admission and discharge. Medical complications were defined as the occurrence of malignant arrhythmias, cardiogenic shock, heart transplantation, or the implantation of a left ventricular assist device, extracorporeal membrane oxygenation, Impella micro-axial pump, or intraaortic balloon pump.

EXPLORATORY ANALYSIS IN THE BERLIN COHORT.

With an exploratory intent, the level of laboratory values, such as C-reactive protein (CRP), troponin T, leukocytes, antistreptolysin antibody, and NT-pro BNP were analyzed by age group. Additionally, left ventricular ejection fraction (LVEF) within a subgroup of patients who had documented transthoracic echocardiograms (N = 1,171) was analyzed by age. Causes of death were manually retrieved from the medical record for deceased patients, and in all patients who received an EMB and died, the pathologic EMB reports were retrieved.

STATISTICAL ANALYSIS.

Normality was assessed using Shapiro-Wilk analysis. Categorical and continuous variables were compared using chi-square tests and Student's *t*-tests (normally distributed) or Fisher's exact test and Wilcoxon-Mann-Whitney U-test (non-normally distributed), respectively. Normally distributed continuous variables are expressed as mean SD, non-normally distributed variables as median (IQR), and categorical variables as frequency (percentage). Results are presented as adjusted odds ratios (ORs) or incidence rate ratios (IRR) with 95% CIs and *P* values. A 2-tailed *P* value <0.05 was considered statistically significant. A Poisson regression model was used to analyze hospital LOS between age groups, Cox proportional hazard model to analyze hospital mortality, and logistic regression to analyze medical complication rates. Data analyses were performed using R Core Team 2020.

RESULTS

In the Berlin cohort, a total of 6,023 patients were treated between January 2005 and March 2021 with a primary diagnosis of acute or chronic myocarditis, while there were 9,079 patients in the U.S. cohort between 2010 and 2019. The following age distributions were observed in the Berlin and the U.S. cohort: 194 patients (3.2%) and 480 (5.3%) were in age group 1, 365 (6.1%) and 561 (6.2%) in age group 2, 1,821 (30.2%) and 2,945 (32.4%) in age group 3, 2,113 (35.1%) and 2,663 (29.3%) in age group 4, and 1,530 (25.4%) and 2,430 (26.8%) in age group 5 (Figure 1). Within the Berlin cohort, 3,944 patients had acute myocarditis and 2,079 patients had chronic myocarditis. Within both cohorts, the average Charlson comorbidity index of the study cohort was 1 (0–2). A total of 1,864 (12.3%) received an EMB, while a CMR was performed in 1,056 (7%) patients (Table 1). In the Berlin cohort, the rate of performed EMBs gradually decreased from 89 (38.2%) in 2005 to

38 (31.9%) in 2021, while the rate of CMR has more than doubled from 25 (10.7%) to 28 (23.5%) within the same time period (Supplemental Table 2).

PRIMARY OUTCOME: SEX DIFFERENCES ACROSS AGE GROUPS.

In age group 2 “adolescents”, 642 (69.3%) of male patients and 284 (30.7%) of female patients were diagnosed with myocarditis (Central Illustration), of which 224 (61.4%) male and 141 (38.6%) female patients were from the Berlin and 418 (74.5%) male and 143 (25.5%) female patients were from the U.S. cohort (Figures 2A, 2C, and 2D). Within age group 3 (“young adults”), there were 3,516 (73.8%) male and 1,250 (26.2%) female patients diagnosed with myocarditis, out of which the Berlin cohort was comprised of 1,328 (72.9%) male and 493 (27.1%) female patients, while the U.S. cohort was comprised of 2,188 (74.3%) male and 757 (25.7%) female patients. Sex differences were more balanced in the older age group (age group 5): 808 males (52.8%) vs 722 females (47.2%) in the Berlin cohort and 1,114 (45.8%) males vs 1,316 (54.2%) females in the U.S. cohort. Similar patterns were observed in the biopsy-proven cohort (Figure 2B).

SECONDARY OUTCOMES: HOSPITAL LENGTH OF STAY, HOSPITAL MORTALITY, AND MEDICAL COMPLICATION RATE.

Hospital LOS of the youngest (age group 1: 9 [IQR: 3–18] days in the Berlin cohort and 8 [IQR: 3–20] days in the U.S. cohort) and of the eldest patients (age group 5: 6 [IQR: 3–13] days in the Berlin cohort and 5 [IQR: 2–9] days in the U.S. cohort) were longer compared to the hospital LOS of young adults (age group 3: 5 [IQR: 3–9] days in the Berlin cohort and 3 [IQR: 2–5] days in the U.S. cohort) (Figures 3A and C): IRR 1.67 (95% CI: 1.58–1.76), P <0.001 and IRR 1.41 (95% CI: 1.36–1.45) for the Berlin cohort (P < 0.001) and IRR 3.38 (95% CI: 3.3–3.47), P <0.001 and IRR 1.39 (95% CI: 1.36–1.42) for the U.S. cohort (P < 0.001), respectively. Hospital LOS of age group 4 was similar to age group 3 in the Berlin and the U.S. cohorts, respectively.

Similar patterns were observed for hospital mortality: age group 1 (1.6% in the Berlin cohort and 8.1% in the U.S. cohort) and age group 5 (1.9% in the Berlin cohort and 7.7% in the U.S. cohort) had a higher mortality risk than young adults (age group 3: 0.5% in the Berlin cohort and 2.7% in the U.S. cohort) (Figures 4A and 4C): HR: 1.80 (95% CI: 0.34–9.39), P = 0.487 and HR: 2.17 (95% CI: 0.79–5.99), P = 0.135 for the Berlin cohort, as well as IRR 0.91 (95% CI: 0.62–1.34), P = 0.65 and IRR 1.29 (95% CI: 0.99–1.68), P = 0.063 for the U.S. cohort, respectively. The hospital mortality rate was also plotted across the continuous patient age in the Berlin and U.S. cohorts (Supplemental Figure 1). The largest difference in mortality between male and female patients were observed in age group 2 in the Berlin (0 [0%] male vs 1 [1.4%] female) and U.S. cohort (10 [2.4%] male vs 12 [8.4%] female) (Supplemental Figure 2), while there were no sex-based mortality differences in the remaining age groups.

Causes of death were available for 38 patients in the Berlin cohort (Supplemental Table 3). The most frequent causes were circulatory failure in 19 patients (50.0%) and cardiac arrest in 6 patients (15.8%). Of the 38 deceased patients, 10 (26.1%) received an EMB. Myocarditis was diagnosed by EMB in 7 (18.4%) patients, while CMR, clinical

or laboratory parameters were used in 29 (76.31%) patients to make the diagnosis of myocarditis (Supplemental Table 4). Compared to the U.S. cohort, deceased patients in the Berlin cohort were older (58.5 ± 19.5 years vs 46.3 ± 24.5 years), had more comorbidities (Charlson comorbidity index (3 [IQR: 2–6] vs 1 [IQR: 0–2]), a higher percentage of male patients (26 [68.4%] vs 245 [55.8%]), longer hospital LOS (9.5 [IQR: 3.25–29.75] vs 7.0 [IQR: 2–15.5] days), but less frequent medical complications (23 [60.5%] vs 311 [70.8%]) (Supplemental Table 5).

With regard to rate of medical complications, there was a similar trend: complications were higher in age group 1 (6.3% in the Berlin cohort and 39.4% in the U.S. cohort) and age group 5 (5.9% in the Berlin cohort and 26.9% in the U.S. cohort) compared to young adults (age group 3: 3.7% in the Berlin cohort and 15.5% in the U.S. cohort) (Figures 5A and 5C): OR: 1.89 (95% CI: 1.09–3.16), $P = 0.017$ and 1.87 (95% CI: 1.40–2.50), $P < 0.001$ in the Berlin cohort, as well as OR: 3.55 (95% CI: 2.88–4.36), $P < 0.001$ and OR: 2.01 (95% CI: 1.76–2.3), $P < 0.001$ in the U.S. cohort, respectively. Of note, differences in medical complications were attenuated across age groups in the biopsy-proven myocarditis cohort (Figure 5B). Paralleling the pattern in mortality, the most pronounced difference in medical complications between male and female patients was observed in age group 2 in the Berlin (20 [12.5%] male vs 20 [27%] female) and U.S. cohort (74 [17.%] male vs 50 [22.1%] female) (Supplemental Figure 3). In the remaining age groups, male patients had more frequent medical complications than female patients in the Berlin cohort, while in the U.S. cohort, female patients had more medical complications than male patients. Overall, the mortality rate (1.2% vs 4.8%) and medical complication rate (13.6% vs 22%) were lower in the Berlin cohort compared to the U.S. cohort.

EXPLORATORY ANALYSES IN THE BERLIN COHORT.

All age groups presented with elevated levels of CRP (26.7 ± 53.1 mg/L) and troponin T (278 ± 958 ng/L) (Table 2). In Berlin, the youngest patients had higher levels of leukocytes (11.4 ± 4.8/nL, $P < 0.001$), CRP (29.9 ± 60.0 mg/L, $P = 1.00$), anti-streptolysin antibody (380 ± 555 kU/L, $P < 0.001$), and NT-proBNP (15,300 ± 21,700 ng/L, $P < 0.001$) compared to young adults.

Additionally, in patients who had a documented transthoracic echocardiogram, LVEF decreased with age: 59.9% ± 11.0% in age group 2 compared to 44.3% ± 16.1% in age group 5 (Supplemental Figure 4). Apart from an age-dependent decrease in LVEF, LVEF appeared to be better in younger male patients compared to female patients (age groups 1 and 2). Notably, male patients had a stronger deterioration in LVEF until age groups 3 and 4, such that female patients showed a better LVEF than male patients with older age (Supplemental Table 6).

DISCUSSION

Myocarditis is defined as inflammation of the myocardium. In developed countries, the most common etiologies of myocarditis are viral infections and autoimmunity, which may result in a broad heterogeneity of clinical symptoms. Patients may report dyspnea and chest pain, while in rare cases, myocarditis may present as potentially life-threatening

acute heart failure or cardiogenic shock leading to death.[23,28] The objective of the present study was to examine the clinical features of myocarditis in different age groups and to examine differences in sex distribution in 2 large cohorts. In this multicenter cohort study of patients who were treated for a primary diagnosis of acute or chronic myocarditis, the most pronounced differences in sex were observed in patients between the ages of puberty and 54 years. The youngest and eldest patients had the longest hospital LOS and the highest mortality rates compared to young adults, presumably due to more comorbidities and a more complicated clinical disease course.

SEX-BASED DIFFERENCES IN CARDIAC INFLAMMATION.

The terms “sex” and “gender” are not interchangeable terms. “Sex” is a biological term based on the patientś reproductive organs and functions dependent on chromosomal complement.[29] Gender describes what a patient identifies as based on social and environmental influences.

In a historic context, myocarditis has been considered a male-predominant disease.[30] Multiple trials and registries have confirmed a greater frequency of myocarditis in men than women with a reported sex ratio between 1.5:1 and 1.7:1, which is in alignment with the findings in our study, where the sex ratio was 2.7:1 for the Berlin cohort and 2.9:1 for the U.S. cohort in age group 3—the group with the largest sex difference in frequency.[7,8,31–35] In accordance with these findings, animal studies have also shown an increased severity of myocarditis in male mice.[10,36,37] There is increasing clinical and preclinical evidence indicating differential pathogenesis and prognosis of myocarditis between sexes.

Myocarditis is associated with myocardial infiltration of immune cells, predominantly T-cells and macrophages, into the myocardium due to viral or toxic activation of the immune response.[38–41] Preclinical models reveal a Th1 vs Th2 dichotomy in adaptive immune responses between both sexes. It has been shown that male mice develop a predominantly Th1-type response, while female mice develop a Th2-type response containing more Foxp3+, Tim-3+, and CTLA4+ regulatory T cell populations.[10,42–44] Male mice were found to demonstrate enhanced infiltration by activated M1 and M2b macrophages and mast cells during myocarditis, while females showed increased infiltration by activated M2a macrophages.[9,45–48] Apart from different immune response patterns between both sexes, cardiac remodeling during myocarditis has also been shown to be sex-dependent. Multiple studies in mice and humans have reported that men with myocarditis have an increased deposition of extracellular matrix proteins and prevalence of myocardial fibrosis compared to women.[8,14,15,49] Testosterone signaling was shown to be associated with adverse cardiac remodeling, while estrogen signaling appeared to prevent cardiac hypertrophy and fibrosis.[8,50–52] Furthermore, the severity of myocardial inflammation was shown to be dependent on testosterone and estradiol levels.[9,43,44,53,54] These findings may explain why we observed a stronger difference in myocarditis frequency in patients between puberty and age 54, indicating an underlying sex hormone-dependent pathogenesis for clinical manifestation of cardiac inflammation.

HEALTH CARE UTILIZATION.

The prognosis after myocarditis is dependent on the severity of the cardiac inflammatory process and clinical manifestation of symptoms. Poor prognostic factors have been identified, such as reduced LVEF, left bundle branch block, and syncope.[55] In our study cohort, patients in age group 2 had an LVEF of 59.9% ± 11%, while patients in age group 5 had a moderately impaired LVEF of 44.3% ± 16.1%.

The youngest and eldest patients in our study cohort were more susceptible to a more severe disease outcome, reflected by an increased frequency of cardiac complications such as cardiogenic shock, cardiac arrest, or ventricular arrythmias, as well as a higher mortality rate. Cardiogenic shock has been shown to be the most frequent cause of death in patients with myocarditis.[55] Thus, prolonged hospitalization in both aforementioned age groups could be explained by a higher need for close patient monitoring and comprehensive medical treatment caused by a complex clinical course. Notably, the differences in complication rates between the Berlin and the U.S. cohorts are remarkable. A probable reason for the observed differences between both cohorts might be the circumstance that highly specialized tertiary care centers from Berlin with capacities for EMBs, CMR examinations, and intensive care unit care were compared to a heterogeneous nationwide data cohort including community and/or rural hospitals in the U.S.

Hospital mortality rates in our study cohort appear to differ from findings in a recent nationwide study in Poland with 3,659 myocarditis patients below the age of 20 years, in which no difference in 30-day mortality between male and female patients was found regardless of the age group.[20] Patient selection, which was limited to young patients, may have masked any significant trends in sex differences in the Polish registry study.

Additionally, in our study population, the overall 30-day mortality rate was lower compared to the mortality rate published in the Polish registry study, a U.S.-based registry study (preliminary data from abstract) with 8,875 myocarditis patients, and a Danish registry study with 2,523 myocarditis patients.[21,22] These data suggest that the prognosis of myocarditis may also be affected by socioeconomic, geographical, and institutional factors. Furthermore, since the analysis of the U.S. database was based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes, while CMR or EMB data were not accessible, some limitations on the accuracy of ICD codes may have to be considered. With regard to hospital LOS, the U.S.-based registry study reported an average LOS of 3 days.[21] In the Berlin study cohort, the hospital LOS was a function of patient age. Patients in age group 3 had a similar hospital LOS of 5 days, while it was almost doubled in patients in age group 1 (9 days).

LABORATORY VALUES.

The finding that the youngest age group had the highest levels of leukocytes and CRP is biologically plausible given that immune response mechanisms in general decrease with age due to cellular senescence.[56] This enhanced immune response may explain the associated elevation of NT-proBNP in that age group and the more severe clinical course that was observed.

STUDY LIMITATIONS.

The strengths of this study include the use of large, multicenter cohorts with a primary diagnosis of myocarditis over a period of 16 years. Patient heterogeneity was reduced by the exclusion of patients with missing information and past medical history of myocarditis. We included granular data on patient characteristics and hospital data, which were manually validated by 4 independent and blinded investigators. However, there are certain limitations to this cohort study. In the Berlin cohort, 25.0% of cases received an EMB, which is considered the diagnostic gold standard. Alternatively, CMR was used in 16.0% of cases in the Berlin cohort. The remaining patients were diagnosed based on clinical symptoms, 12-lead electrocardiogram, and laboratory values, resulting in a less definitive diagnosis. However, data retrieved from biopsy-proven patients were comparable to the overall Berlin cohort indicating high diagnostic accuracy. Additionally, clinical symptoms of included patients, CMR results, severity of disease, and time of myocarditis diagnosis were not retrieved from the data.

CONCLUSIONS

In this multicenter study of patients with myocarditis, sex distribution and clinical outcomes varied according to age of the patient. The most obvious differences in sex distribution were observed in age groups between puberty and age 54 years. The youngest and eldest patients had the most severe clinical manifestations of myocarditis with the longest length of stay and the highest rates of in-hospital mortality and cardiac complications. This study highlights the age-dependent features of myocarditis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

CMR	cardiac magnetic resonance
CRP	C-reactive protein
EMB	endomyocardial biopsy
IRR	incidence rate ratio
ICU	intensive care unit

ICD	International Statistical Classification of Diseases and Related Health Problems
LVEF	left-ventricular ejection fraction
LOS	length of stay
NT-pro BNP	N-terminal fragment of B-type natriuretic peptide

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

When treating patients with myocarditis, clinicians should be aware of sex differences and clinical outcomes of patients presenting at different ages. Identifying the highest-risk groups may help with the optimized utilization of health care resources.

TRANSLATIONAL OUTLOOK:

When planning future research studies on myocarditis, sex- and age-related differences in clinical presentation should be considered.

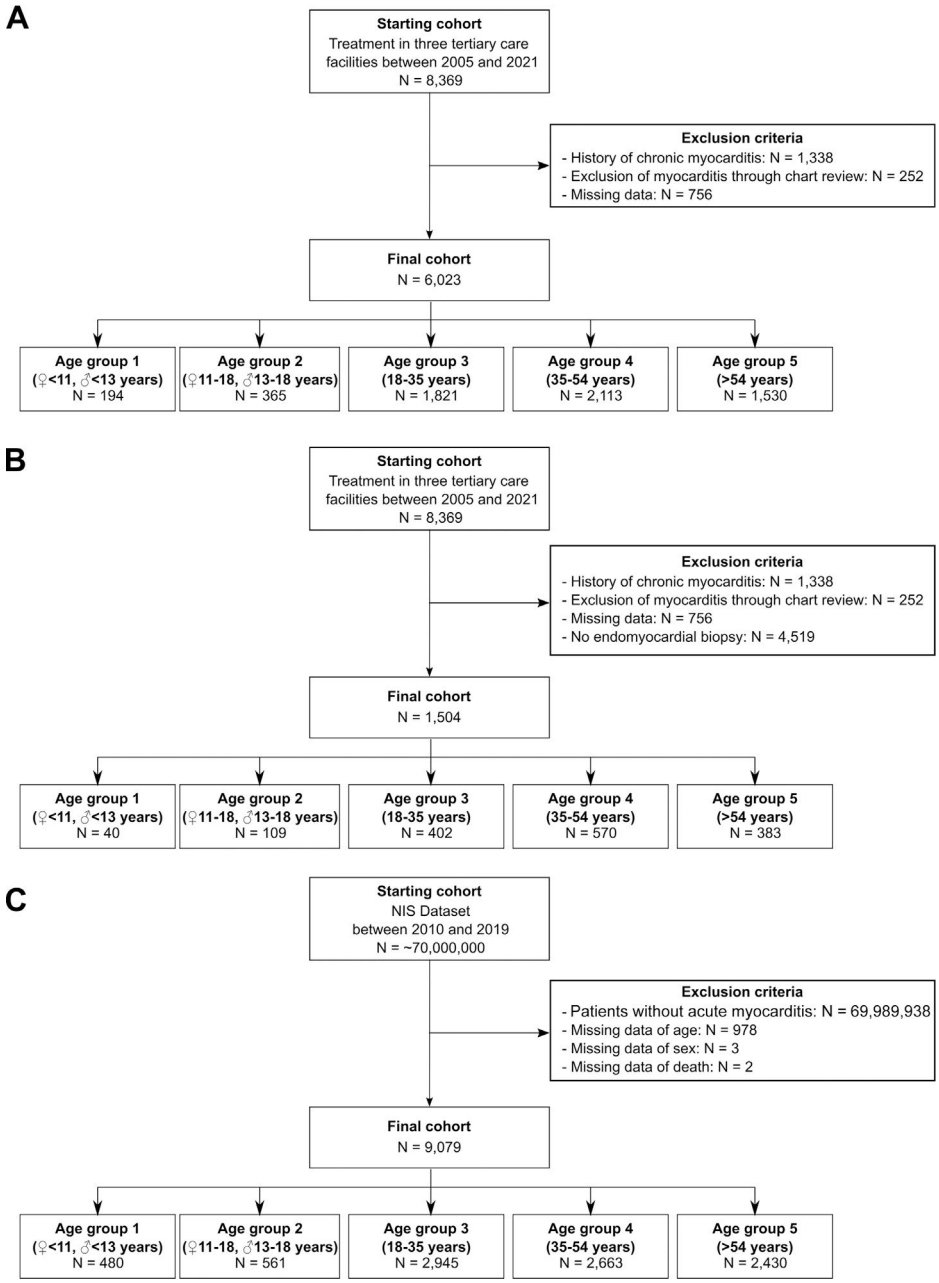


FIGURE 1. Study Subject Flow Diagram

(A) Berlin cohort, (B) Berlin cohort, biopsy proven, (C) U.S. cohort.

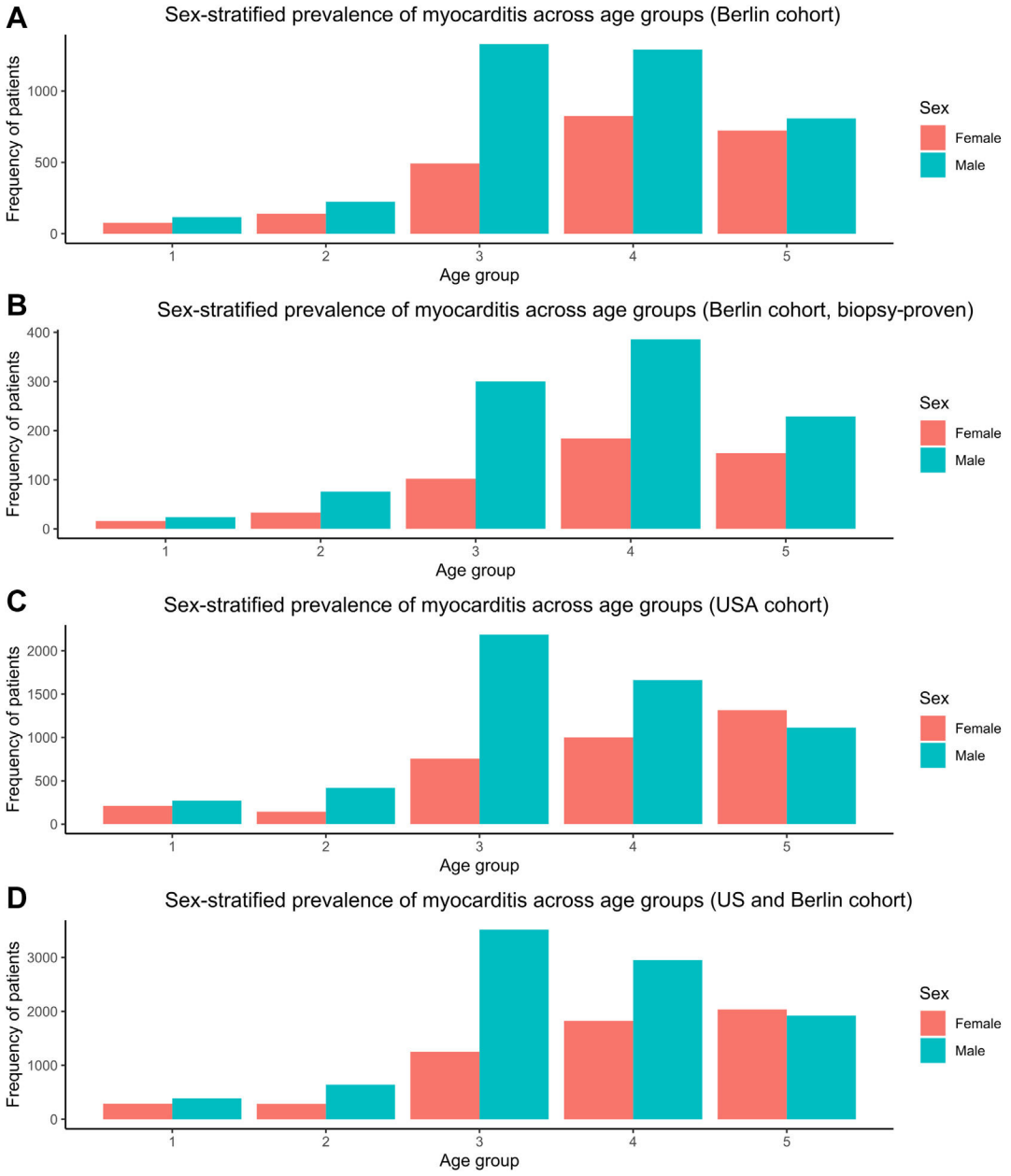


FIGURE 2. Sex Distribution in Cases of Myocarditis Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) U.S. cohort. (D) Total cohort (Berlin and U.S.). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

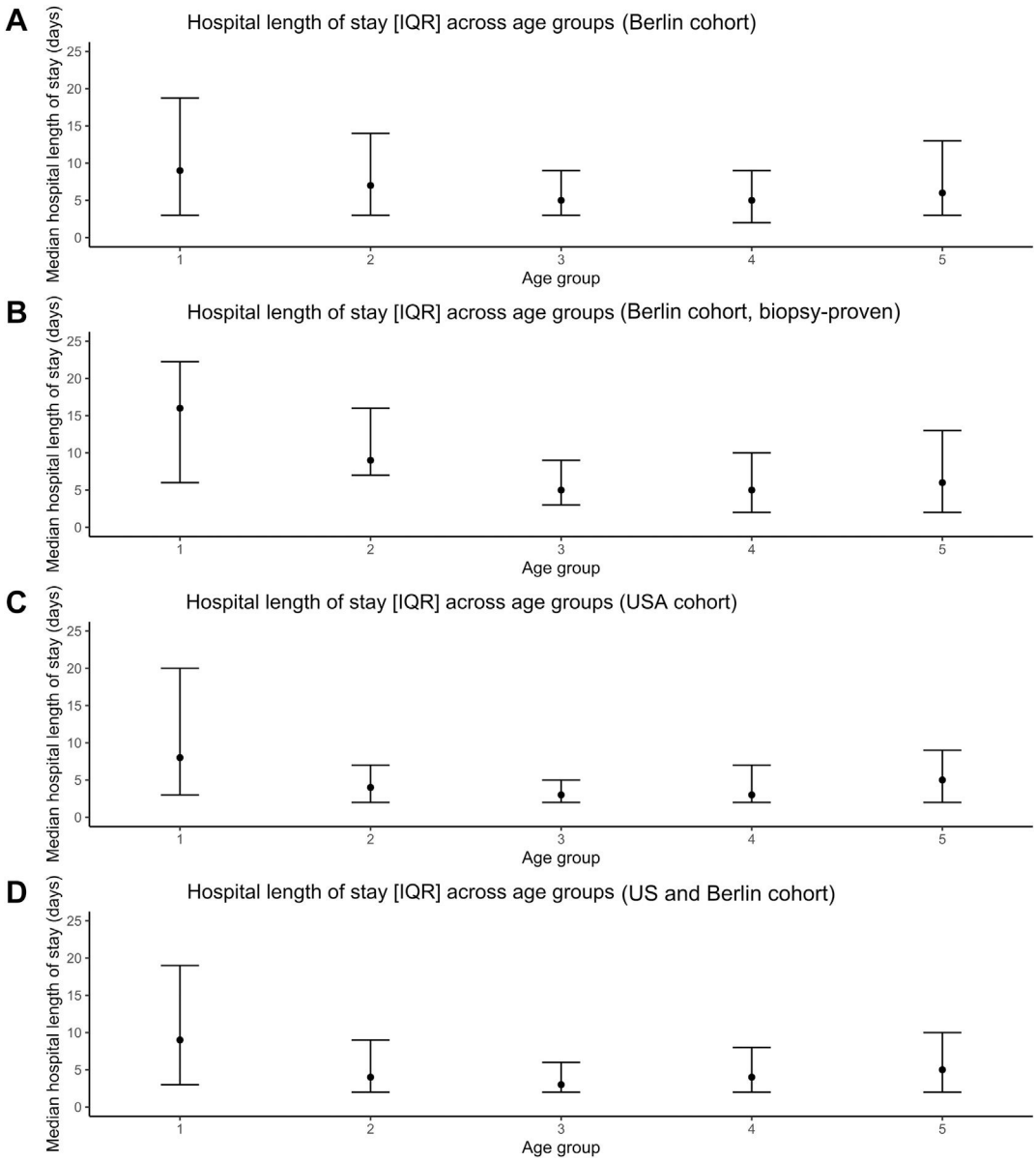


FIGURE 3. Hospital Length of Stay (IQR) Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) U.S. cohort. (D) Total cohort (Berlin and U.S.). IQR, interquartile range; age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

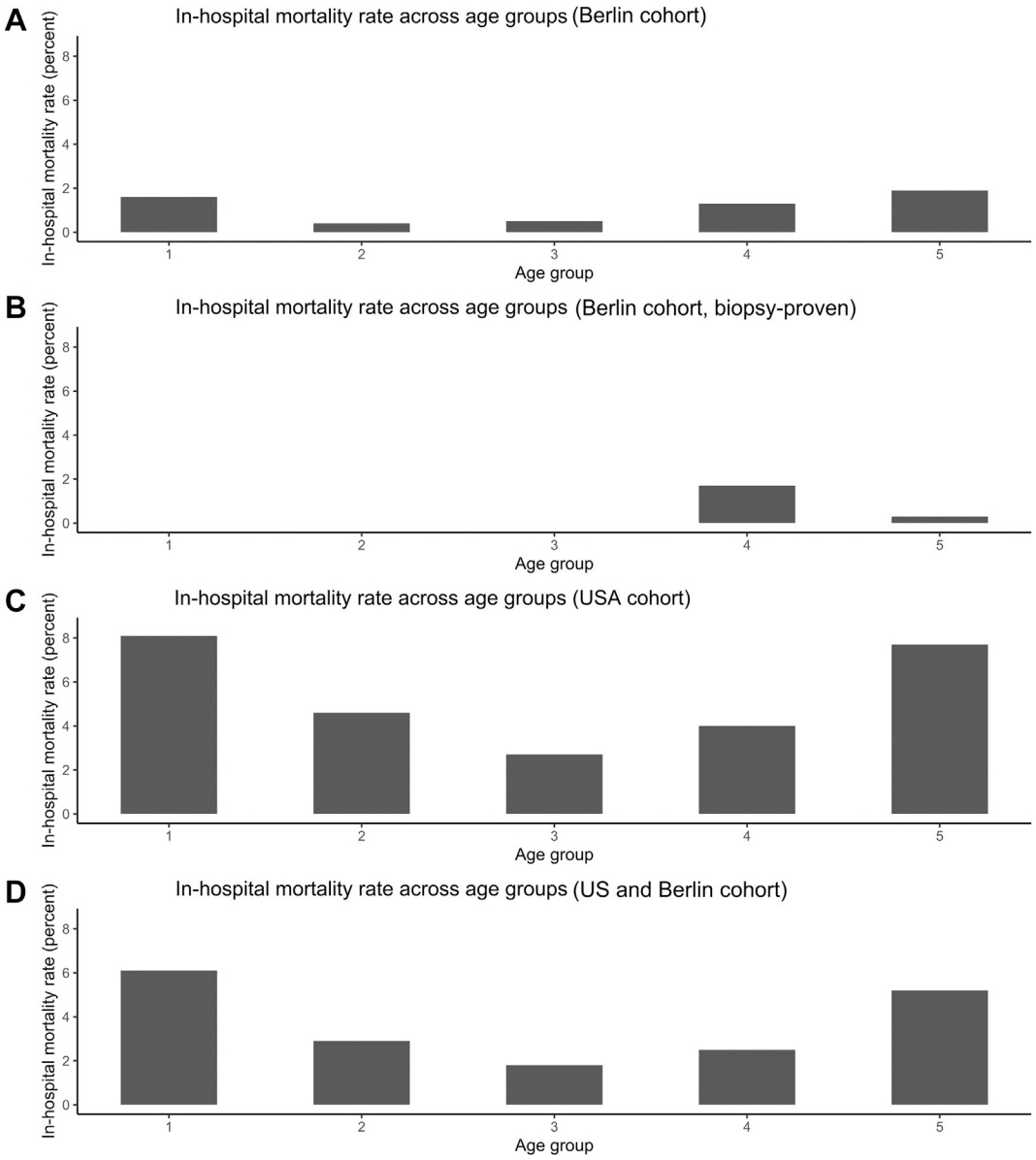


FIGURE 4. In-Hospital Mortality Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) U.S. cohort. (D) Total cohort (Berlin and U.S.). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

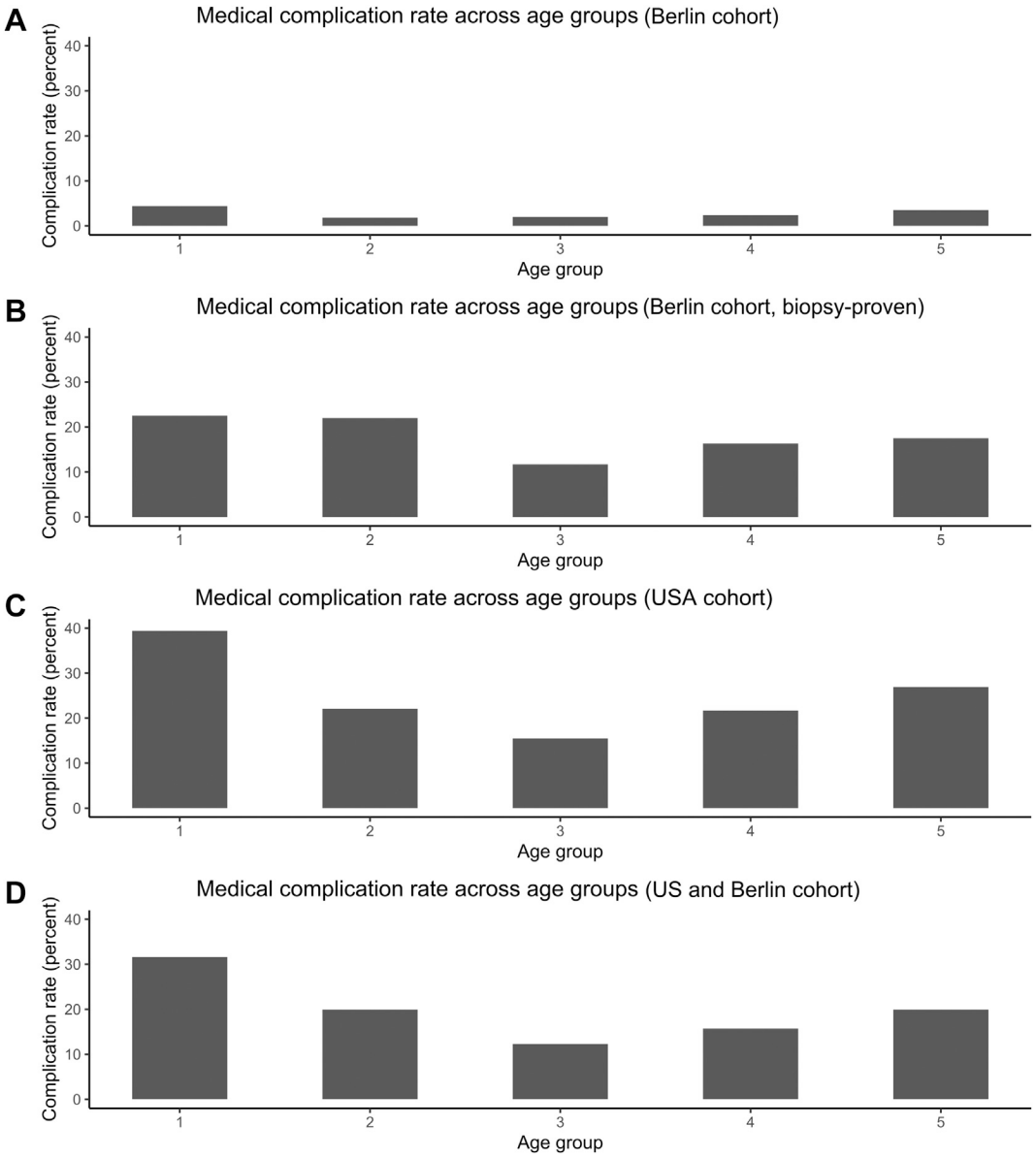
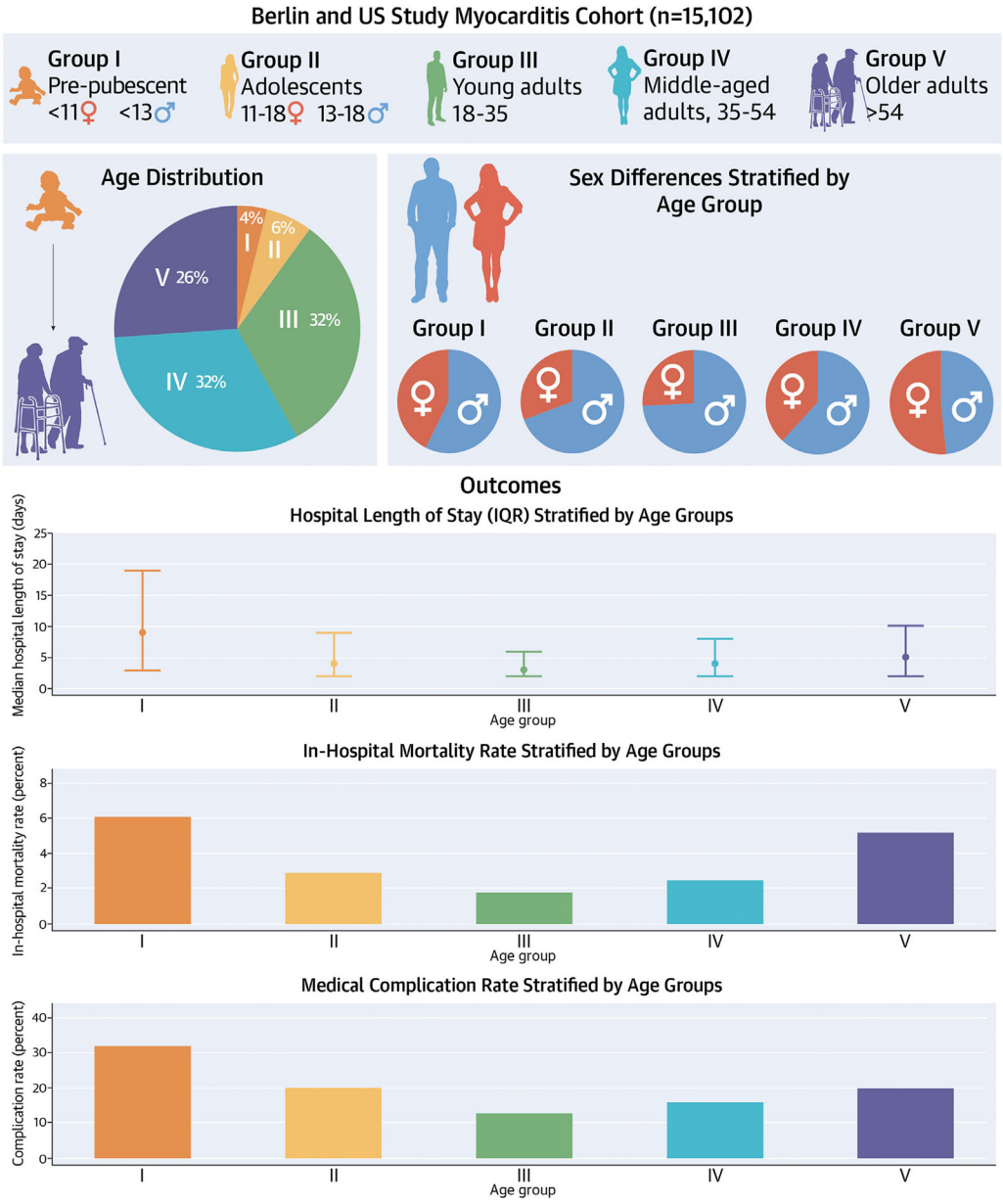


FIGURE 5. Medical Complication Rate Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) U.S. cohort. (D) Total cohort (Berlin and U.S.). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.



Thevathasan T, et al. JACC Adv. 2024;3(4):100857.

CENTRAL ILLUSTRATION.
Demographic Characteristics of Acute and Chronic Myocarditis

Table 1

Baseline Characteristics and Cardiac Procedures Stratified by Age Groups in the Berlin and U.S. Cohorts

	Age Group 1 (n = 674)	Age Group 2 (n = 926)	Age Group 3 (n = 4,766)	Age Group 4 (n = 4,776)	Age Group 5 (n = 3,960)	Overall (n = 15,102)
Baseline characteristics						
CCI	1 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 2)	1 (0, 3)	1 (0, 2)
CCI						
CCI ≤3	662 (98.2%)	910 (98.3%)	4,637 (97.3%)	4,445 (93.1%)	3,220 (81.3%)	13,874 (91.9%)
CCI >3	12 (1.8%)	16 (1.7%)	129 (2.7%)	331 (6.9%)	740 (18.7%)	1,228 (8.1%)
Cardiac procedures						
Endomyocardial biopsy	70 (10.4%)	149 (16.1%)	498 (10.4%)	681 (14.3%)	466 (11.8%)	1,864 (12.3%)
Cardiac catheterization	1 (0.1%)	6 (0.6%)	7 (0.1%)	31 (0.6%)	41 (1%)	86 (0.6%)
Cardiac MRI	43 (6.4%)	153 (16.5%)	382 (8%)	302 (6.3%)	176 (4.4%)	1,056 (7%)

Values are median (IQR) or n (%). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

CCI = Charlson comorbidity index; MRI = magnetic resonance imaging.

Table 2

Laboratory Values (Within 48 Hours After Hospital Admission) in Patients With Primary Diagnosis of Acute Myocarditis or Acute on Chronic Myocarditis Stratified by Age Group in the Berlin Cohort

	Age Group 1 (n = 194)	Age Group 2 (n = 265)	Age Group 3 (n = 1,821)	Age Group 4 (n = 2,113)	Age Group 5 (n = 1,530)	Overall (n = 6,023)
Electrolytes						
Sodium (mmol/L)	137 ± 4.04	139 ± 2.78	139 ± 3.95	139 ± 6.00	139 ± 4.71	139 ± 4.92
Potassium (mmol/L)	4.19 ± 0.567	4.00 ± 0.443	4.06 ± 1.88	4.15 ± 1.55	4.21 ± 0.525	4.13 ± 1.42
Complete blood count						
Hemoglobin (g/dL)	11.7 ± 2.18	14.3 ± 1.45	14.6 ± 1.96	14.3 ± 2.06	13.6 ± 2.25	14.1 ± 2.13
Leukocytes (n/nL)	11.4 ± 4.83	8.75 ± 3.82	8.67 ± 4.00	8.62 ± 4.19	8.55 ± 3.50	8.69 ± 3.99
Renal function						
Creatinine (mg/dL)	0.437 ± 0.207	0.969 ± 1.38	0.906 ± 0.332	0.969 ± 0.450	1.04 ± 0.458	0.952 ± 0.503
Inflammatory markers						
CRP (mg/L)	29.9 ± 60.0	29.4 ± 47.0	29.9 ± 55.9	21.4 ± 47.8	28.9 ± 56.4	26.7 ± 53.1
Procalcitonin (μg/L)	1.65 ± 4.29	0.473 ± 1.03	1.67 ± 10.4	0.627 ± 1.64	2.13 ± 8.74	1.38 ± 7.48
Anti-streptolysin antibody (kU/L)	380 ± 555	118 ± 98.0	152 ± 85.2	151 ± 153	52.6 ± 28.4	176 ± 267
Cardiac markers						
Troponin T (ng/L)	225 ± 537	491 ± 1,620	301 ± 713	238 ± 1,000	228 ± 908	278 ± 958
Creatine kinase (U/l)	158 ± 146	380 ± 710	265 ± 417	195 ± 319	231 ± 774	238 ± 529
Myoglobin (μg/L)	271 ± 6.23	241 ± 578	172 ± 534	548 ± 2,930	522 ± 1,430	375 ± 1,850
NT-proBNP (ng/L)	15,300 ± 21,700	906 ± 2,760	1,850 ± 11,500	1,740 ± 5,500	3,630 ± 8,390	2,610 ± 9,480

Values are mean ± SD. Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

CRP = C-reactive protein; NT-proBNP = N-terminal fragment of brain natriuretic peptide.