National Trends, Gender, Management, and Outcomes of Patients Hospitalized for Myocarditis

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Myocarditis is a major cause of acute and chronic cardiomyopathy. Data on patient characteristics utilization of healthcare, and outcomes of myocarditis-related hospitalizations are limited. We sought to analyze the outcomes of patients hospitalized with myocarditis from a large diverse, multicentric, nationwide cohort using Nationwide Inpatient Sample database. A total of 27,129 hospitalizations involving adult patients (age ≥ 18 years) with the primary discharge diagnosis of myocarditis from years 2007 through 2014 were included and patients who had diagnosis of myocardial infarction or coronary syndromes (including unstable angina) during the same hospitalization were excluded. More men were hospitalized compared with women (66% vs 34%, p <0.05). Patients hospitalized were young with a mean age of 37.3 ± 18.8 years with women being older compared with men (45.2 ± 20.9 vs 33.2 ± 16.2, p <0.001). In-hospital complications of cardiogenic shock and ventricular fibrillation/cardiac arrest occurred in 6.5% and 2.5% of hospitalizations, respectively, with females being affected significantly more than males (10.2% vs 4.6%; 3.6% vs 2%, respectively, p <0.001 for both comparisons). A total of 640 (2.4%) patients died during index hospitalization. Mortality was significantly higher in females compared with males (3.5% vs 1.8%; p <0.001). Multiple logistic regression analysis demonstrated female gender as an independent predictor of in-hospital mortality (odds ratio: 1.69, 95% confidence interval: 1.1 to 2.6; p = 0.007). In conclusion, myocarditis-related hospitalizations have increased during the study years and mostly affect young population with no significant co-morbidities. Female gender remains at high risk for myocarditis-related complications and in-hospital mortality. © 2019 Published by Elsevier Inc. (Am J Cardiol 2019;124:131−136)

Myocarditis is defined as an inflammatory state of the myocardium.[1,2] Clinical presentation of myocarditis can vary widely, from clinically silent to rapidly progressive heart failure resulting in cardiogenic shock (CS) and fatal arrhythmias.[1] The majority of information on the epidemiology, gender, and racial differences, in-hospital outcomes in myocarditis are derived from small studies, clinical trials, and case reports.[3−7] The majority of myocarditis-related deaths occur during the same hospitalization; however, little is known about the predictors of in-hospital mortality in these patients.[8] It is necessary for clinicians to be able to distinguish between patients with favorable prognosis and those who are at risk of fatal complications including death. To this end, we conducted a detailed analysis of Nationwide Inpatient Sample (NIS) database to investigate the recent trends, incidence of CS, use of diagnostic procedures, and advanced heart failure therapies; and mortality in the patients hospitalized with a primary discharge diagnosis of myocarditis. Another study objective was to identify independent predictors of in-hospital mortality in these patients.

Methods

We analyzed discharge data from the NIS for years 2007 through 2014 to identify all patients with primary discharge diagnosis of myocarditis. The NIS, developed by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project, is the largest all-payer inpatient database in the United States (US). The patients were identified by the presence of appropriate International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes (Supplemental Table 1) in the patient discharge records. Patients with ICD codes for myocardial infarction or coronary syndromes (including unstable angina) during same hospitalization were excluded. Differences in the baseline characteristics, including patient characteristics and co-morbidities, were compared between the cohorts stratified by gender and race, respectively.

For hospitalization trend analyses we calculated myocarditis hospitalization rate per 100,000 persons per year with numerator representing the national estimate of myocarditis hospitalizations and denominator representing the national estimate of adult population of Healthcare Cost and Utilization Project participating states from US Census.[9] Test for linear trend in hospitalization rate was performed using simple linear regression.

In-hospital outcomes and utilization of various diagnostic modalities were reported in the total cohort and compared between the cohorts stratified by gender and race.

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Utilization of temporary Mechanical Circulatory Support (tMCS) and advanced heart failure therapies, stratified by gender and race, was assessed in myocarditis patients with CS. Although this is not a true estimate of eligibility for tMCS and advanced therapies, this approach is a reasonable and practical surrogate for estimating the relation of CS burden, tMCS, and advanced therapies utilization in different demographic groups.

Categorical data were presented as frequency (percentage) and compared using svychisq function which performs second-order Rao-Scott correction to Pearson chi-square test and computes p-values based on Satterthwaite approximation. Continuous data were presented as either mean ± standard deviation or median (interquartile range) and compared using either *t* test or Wilcoxon rank sum test as deemed appropriate.

A stepwise logistic regression model was created to identify predictors of in-hospital mortality. We used Akaike information criterion based backward elimination method to identify the predictors in the final model and reported their odds ratios, 95% confidence intervals, and p values, respectively.

All statistical analyses were performed using R version 3.3.2-R Studio interface, on Mac OS x86_64-apple-darwin13.4.0. We used "tableone" package for R to generate all the tables and "Survey" package version 3.31-5 to set up survey design and obtain national estimates. For regression analyses we used svyglm function from survey package to fit generalized linear models to the data from a complex survey design, with inverse-probability weighting and design-based standard errors.

Results

A total of 27,129 hospitalizations were identified with primary discharge diagnosis of myocarditis from 2007 to 2014. Baseline characteristics are shown in Table 1. The overall number of hospitalizations with myocarditis has increased significantly from 2007 to 2014 (Ptrend = 0.002), as depicted in Figure 1. Women were significantly older as compared with men (45.2 ± 20.9 vs 33.2 ± 16.2 years, respectively, p <0.001). Caucasians were older than African-Americans and Hispanics with mean age of 39.6 years compared with 34.9 years and 31.3 years, respectively (p <0.001).

Diagnostic procedure utilization is shown in Table 2. Cardiac magnetic resonance imaging (CMRI) was utilized in 1.2% of patients, 52% underwent left heart catheterization (LHC), 7% underwent right heart catheterization and 3.5% underwent endomyocardial biopsy (EMB). Although, there was no significant difference in males and females for LHC and EMB utilization, more females underwent right heart catheterization as compared with males (9% vs 5.9%, respectively, p = 0.008).

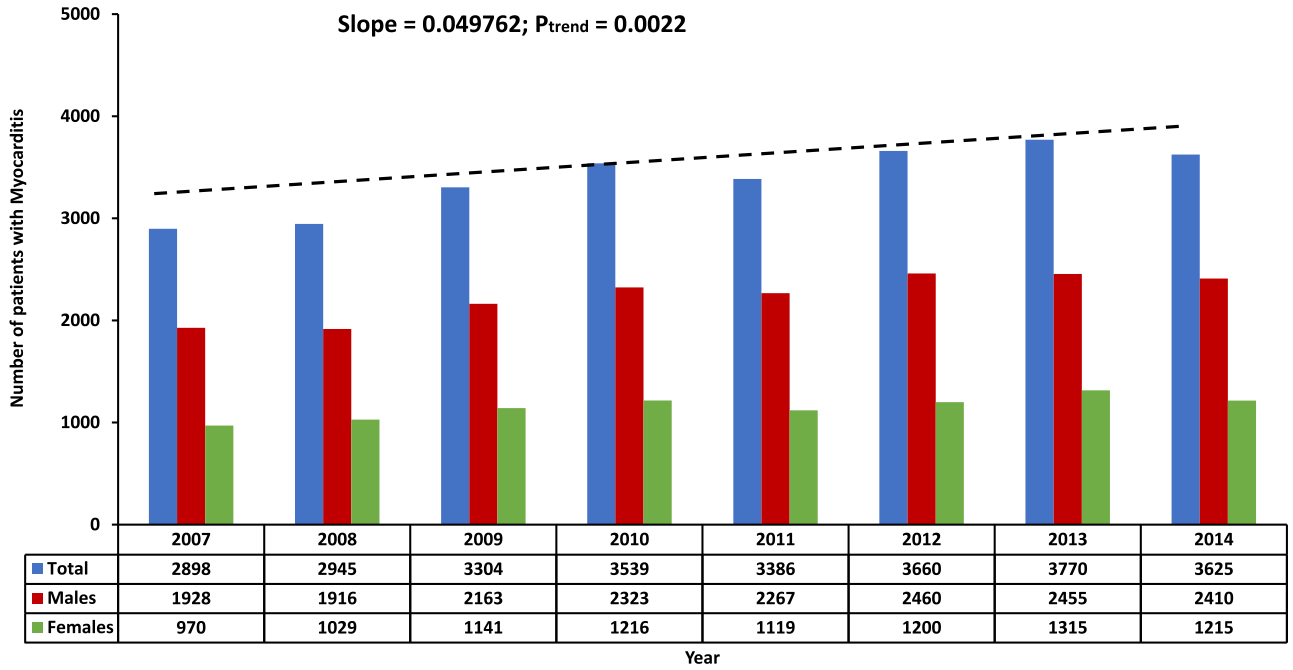
In-hospital complications of CS, ventricular fibrillation/cardiac arrest (VF/CA), and mortality were assessed as shown in Figure 2. There was a consistent increase in the occurrence of CS in myocarditis patients during the study period; 4% in 2007 and 6.7% in 2014; Ptrend < 0.05. CS occurred significantly more frequently in women as compared with men. This difference in the 2 gender groups was seen consistently across all the study years. There was no significant difference between the occurrence of CS in different racial groups. We also analyzed the use of tMCS and advanced heart failure therapies in patients with CS as shown in Table 3. A total of 67.7% (1189) of patients with CS underwent tMCS placement (intra-aortic balloon pump − 36.9%, percutaneous left ventricular assist device − 8%, and ECMO − 22.8%). A total of 15.9% of patients with CS underwent advanced heart failure therapies (left ventricular assist device − 8.3% and orthotropic heart transplant − 6.8%). No significant gender and racial differences were seen in the utilization of tMCS and advanced therapies in myocarditis patients with CS.

VF/CA was diagnosed in 2.5% (684) patients during the index hospitalization. There were significant gender differences in the occurrence of VF/CA with 3.6% women identified as having VF/CA compared with 2% of men (p <0.001). This difference was seen consistently across all the study years. When stratified by different racial categories there was no significant difference observed for patients with VF/CA.

The overall in-hospital all-cause mortality for the entire cohort was 2.4%. No significant trend in the mortality rates was found across the 8-year study period. In-hospital mortality was significantly higher in women compared with men (3.5% vs 1.8%, respectively; p <0.001). The gender differences in mortality were seen consistently across all the study years. Multivariate step-wise logistic regression analysis was done to analyze independent predictors of in-hospital mortality (Figure 3) which revealed female gender as an independent predictor of mortality in this cohort.

Table 1
Demographic and co-morbidities of study cohort

Patient characteristics (total)	% or Mean ± SD (n = 27,129)
Age ± SD (years)	37.3 ± 18.8
Male	17,921 (66%)
Female	9,208 (34%)
White	15,083 (64.5%)
Black	3,479 (14.9%)
Hispanic	3,063 (13.1%)
Other	1,760 (7.5%)
Primary insurance payer	
Medicare	3,115 (11.5%)
Medicaid	4,286 (15.8%)
Private	15,452 (57%)
Self-pay	2,879 (10.6%)
No charge	264 (0.97&)
Other	1,100 (4%)
Median household income (percentile)	
0-25th	5,503 (23.3%)
26th-50th	5,821 (24.6%)
51st-75th	6,117 (25.8%)
76th-100th	6,225 (26.3%)
Hypertension	7,069 (26%)
Chronic lung disease	3,398 (12.5%)
Obesity	2,904 (10.7%)
Diabetes mellitus	1,982 (7.3%)
Valvular heart disease	1,091 (4%)
Chronic kidney disease	979 (3.6%)
Chronic liver disease	442 (1.6%)
Peripheral vascular disease	357 (1.3%)



	2007	2008	2009	2010	2011	2012	2013	2014
Total	2898	2945	3304	3539	3386	3660	3770	3625
Males	1928	1916	2163	2323	2267	2460	2455	2410
Females	970	1029	1141	1216	1119	1200	1315	1215

Figure 1. Overall and gender-related trends in the myocarditis hospitalizations in US from 2007 to 2014. The dotted line represents linear trend of myocarditis admissions per year adjusted for total number of admissions during that calendar year utilizing linear regression analysis.

We also analyzed the use of diagnostic, therapeutic modalities, and in-hospital outcomes stratified by teaching status of the hospital as shown in Table 4. There were significantly higher number of hospitalizations at teaching hospitals as compared with nonteaching hospitals. The use of all diagnostic modalities except for LHC was significantly high in teaching hospitals. The outcomes of CS, VF/CA, and mortality remained significantly high in females at teaching hospitals.

Discussion

Our study included patients hospitalized with myocarditis and provides new and relevant information in regards to national trends, demographics, in-hospital management, and outcomes in these patients. This study is especially important as most of the information on myocarditis is from small studies or single center or regional experiences and national level information is lacking. The main findings of this study are: (1) there is a consistent increase in discharges for a diagnosis of myocarditis over the 8-year study period in the USA, (2) majority of patients are men, (3) women admitted with myocarditis are significantly older than men and Caucasians are older than other races, and (4) occurrence of CS, VF/CA, and in-hospital mortality is significantly higher in women.

We found an increase in the number of myocarditis-related hospitalizations during the study period. Myocarditis has diverse etiologies varying from infections to autoimmunity and toxins.[10] Viral etiology has been reported to be the most prevalent,[11] and 1 study[12] reported Adenovirus to be the most common cause using Polymerase Chain Reaction (PCR) technique. Recent report by Center for Disease Control (CDC) reported changes in circulating strains[13] and it is possible that this might have contributed to the trend. Another reason that can explain this trend, could be the diagnosis being based on non−EMB-related testing. Historically, myocarditis has been diagnosed by EMB.[14] However, sampling error and regional variation limit the sensitivity of biopsy for detecting cellular inflammation. Furthermore, histologic diagnosis seldom has an impact on therapeutic strategies and being an invasive procedure, it is associated with potentially fatal complications.[15,16] Thus, EMB remains a poor gold standard for defining myocardial inflammation. Given these limitations CMRI has increasing diagnostic role.[17] A combination of T2- weighted CMRI and postgadolinium early and

Table 2
Utilization of diagnostic procedures in myocarditis patients

	Total	CMRI	RHC	LHC	EMB
Overall	27,129	327 (1.2%)	1,891 (7%)	14,110 (52%)	951 (3.5%)
Male	17,921	238 (1.3%)	1,057 (5.9%)	9,344 (52.1%)	577 (3.2%)
Female	9,208	89 (0.97%)	828 (9%)	4,765 (51.8%)	369 (4%)
Caucasian	15,083	133 (0.9%)	1,087 (7.2%)	8,406 (55.7%)	453 (3%)
African American	3,479	41 (1.2%)	265 (7.6%)	1,510 (43.4%)	173 (5%)
Hispanic	3,063	67 (2.2%)	172 (5.6%)	1,402 (45.8%)	118 (3.9%)

CMRI = cardiac magnetic resonance imaging; EMB = endomyocardial biopsy; LHC = left heart catheterization/coronary angiography; RHC = right heart catheterization.

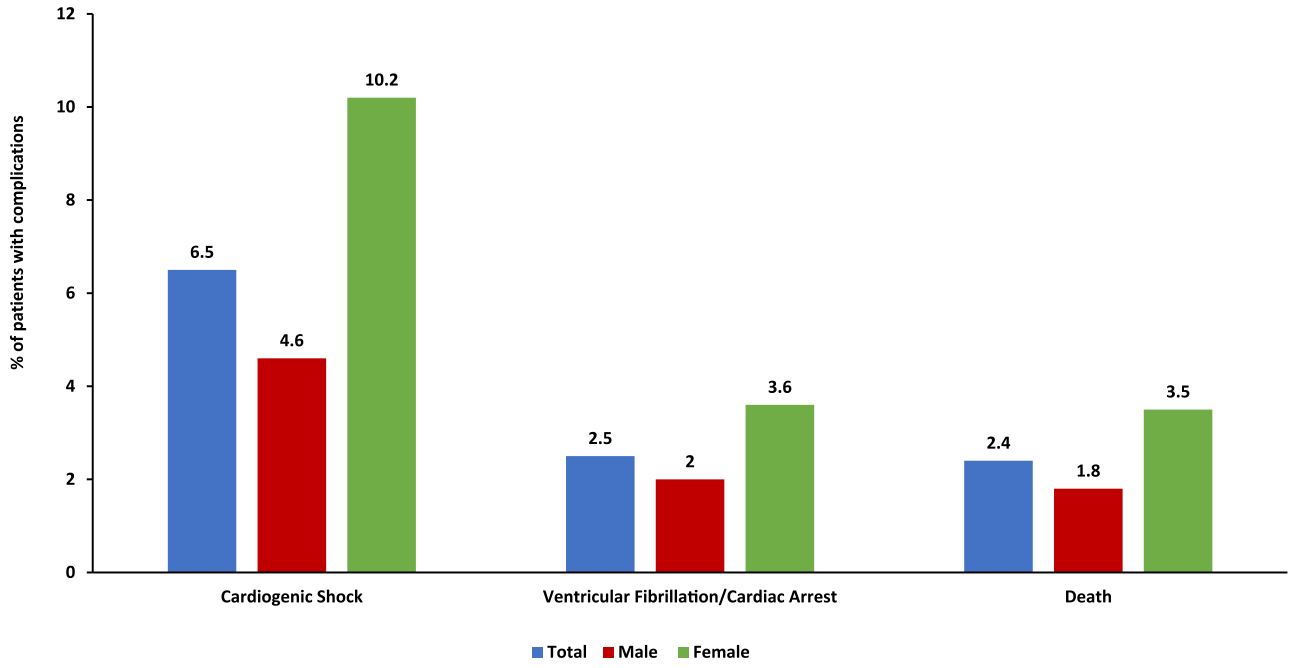


Figure 2. Complications related to myocarditis stratified by gender. Rate of cardiogenic shock, ventricular fibrillation/cardiac arrest and mortality was significantly higher in women as compared with men.

late T1-weighted CMRI has been found to have a high sensitivity and specificity to diagnose myocarditis.[18–20]

We reported that about 66% our total myocarditis admissions were men. Similar to our study, a higher prevalence of myocarditis in men has been reported in small trials and registries. Kyto et al utilized Finnish Hospital Discharge Registry and identified 3,198 myocarditis patients (by using discharge diagnosis codes [ICD-10]) and reported that 76% of the patients were men. Furthermore the study reported that the overall median age of the myocarditis patients was 33 years, with male patients being significantly younger than female patients (mean ages: 34.1 ± 15.1 years vs 49 ± 18.7 years, respectively).[7] In our significantly larger study of 27,129 patients we found that patient demographics were very similar. We also found racial differences with Caucasians being significantly older than other races.

Our study also evaluated the rate of CS in the patients admitted with myocarditis in a large and heterogeneous population. The overall rate of 6.5% is high and comparable to those hospitalized with STEMI.[21–24] The increasing rates of CS in myocarditis patients over the 8 years could be attributed to several factors. Possible explanations include a better recognition of myocarditis based on noninvasive imaging, early involvement of advanced heart failure teams and also increased diagnosis related to Diagnosis Related Group (DRG) creep (defined as changes in hospital record documentation to increase case mix and reimbursement). Since NIS is an administrative database such hypotheses are difficult to evaluate. Our study also reported higher rates of CS in women. The prevalence and severity of symptoms from cardiovascular disease have been consistently reported to be higher in women than men.[21,25,26]

Table 3
Utilization of temporary mechanical circulatory support and advanced heart failure therapies in myocarditis patients with cardiogenic shock

Total patients with CS (n = 1,757)		Stratified by sex		Stratified by race		
		Male (n = 814)	Female (n = 943)	Caucasian (n = 939)	African American (n = 267)	Hispanic (n = 142)
Patients requiring tMCS						
IABP	649 (36.9%)	297 (36.5%)	352 (37.3%)	391 (41.6%)	70 (26.2%)	19 (13.4%)
pLVAD	140 (8%)	76 (9.3%)	64 (6.8%)	96 (10.2%)	25 (9.4%)	10 (7%)
ECMO	400 (22.8%)	182 (22.4%)	218 (23.1%)	149 (15.9%)	86 (32.2%)	48 (33.8%)
Total tMCS	1,189 (67.7%)	555 (68.1%)	634 (67.2%)	636 (67.7%)	181 (67.8%)	77 (54.2%)
Patients requiring advanced heart failure therapies						
LVAD	145 (8.3%)	68 (8.4%)	77 (8.2%)	68 (7.2%)	22 (8.2%)	5 (3.5%)
BiVAD	14 (0.8%)	9 (1.1%)	5 (0.5%)	9 (1%)	0	0
OHT	120 (6.8%)	54 (6.6%)	66 (7%)	83 (8.8%)	13 (4.9%)	9 (6.3%)
Total advanced HF therapies	279 (15.9%)	131 (16.1%)	148 (15.7%)	160 (17%)	35 (13.1%)	14 (9.9%)

BiVAD = biventricular assist device; CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; HF = heart failure; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; OHT = orthotropic heart transplant; p-LVAD = percutaneous left ventricular assist device; tMCS = temporary mechanical circulatory support.

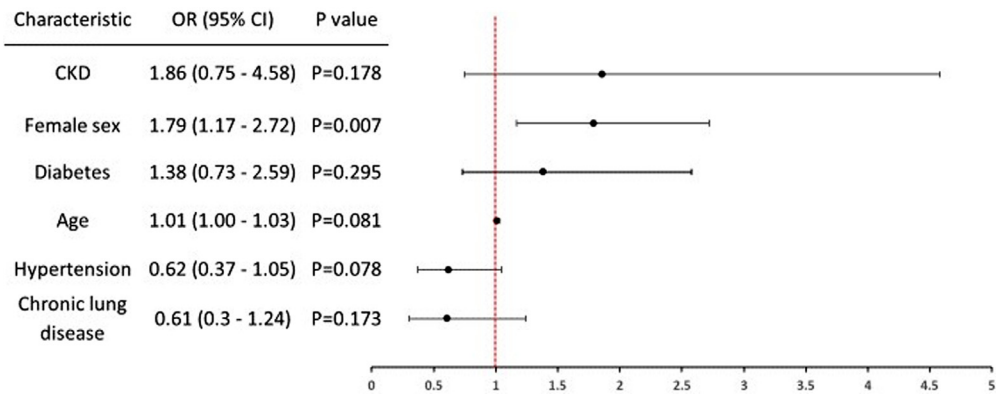


Figure 3. Foster plot for multivariate stepwise logistic regression analysis of in-hospital mortality.

Data from the Studies of Left Ventricular Dysfunction registry reported that more women with impaired systolic left ventricular function presented with CS than their male counter parts.[27] Similarly, several studies have reported higher rates of CS in female patients who present with STEMI.[21,24–26] To our knowledge, ours is the first study to reveal gender differences in the rates of CS in myocarditis patients. These will need to be confirmed in nonadministrative database studies.

We also found more women with myocarditis having VF/CA during the same hospitalization. Similar findings have been reported by Kyto et al in a smaller subset of patients.[6,7] The possible explanations could be higher incidence of CS in these patients predisposing them to CA, longer baseline segment of Electrocardiogram (QT) intervals and prolonged repolarizations than men. Although testosterone has been reported to protect men from arrhythmias by shortening action potential, the reduced expression of K-channel subunits, connexin 43, and fluctuating QT interval during menstrual cycle are implicated as causes of arrhythmia vulnerability in women.[28–30]

We report an overall mortality of 2.4% in myocarditis patients, with a significantly higher mortality in women as compared with men. Although there is paucity of data specifically in myocarditis patients, Kyto et al in a smaller study has reported higher in-hospital mortality in women admitted with myocarditis compared with men.[7] Multivariate sequential logistic regression analysis revealed female gender as independent predictor for in-hospital mortality. There were no other factors found, possibly because of the relatively young age of affected population without many co-morbid conditions.

There are several important limitations to our analysis. This is a retrospective analysis of registry data with the limitations inherent to such analyses. Although errors in ICD-9 coding and documentation are limited in this database, nondifferential misclassification bias cannot be entirely excluded. Myocarditis is a difficult diagnosis to make and it is very likely that this study is underestimating the actual estimates of hospitalizations for myocarditis. The study does not give any information on clinical presentation or cardiovascular study results (such as left ventricular systolic function,

Table 4
Utilization of diagnostic procedures, temporary mechanical circulatory support, advanced heart failure therapies and in-hospital outcomes in myocarditis patients stratified by teaching status of the hospital

	Nonteaching (n = 10,322)		Teaching (n = 16,677)		p Value
	Male (n = 6,764)	Female (n = 3,523)	Male (n = 11,001)	Female (n = 5,646)	
CMRI	9 (0.1%)	4 (0.1%)	200 (1.8%)	80 (1.4%)	<0.001
RHC	288 (4.3%)	260 (7.4%)	765 (7%)	568 (10%)	<0.001
LHC	3,853 (57%)	2,040 (57.9%)	5,438 (49.4%)	2,692 (47.7%)	<0.001
EMB	15 (0.2%)	10 (0.3%)	557 (5.1%)	359 (6.4%)	<0.001
IABP	92 (1.4%)	129 (3.7%)	205 (1.9%)	223 (4%)	<0.001
pLVAD	17 (0.2%)	9 (0.3%)	59 (0.5%)	55 (1%)	0.05
ECMO	5 (0.1%)	0	177 (1.6%)	218 (3.9%)	<0.001
LVAD	5 (0.1%)	5 (0.1%)	63 (0.6%)	72 (1.3%)	<0.001
BiVAD	0	0	9 (0.1%)	5 (0.1%)	0.614
OHT	5 (0.1%)	0	49 (0.4%)	66 (1.2%)	<0.001
CS	117 (1.7%)	234 (6.7%)	697 (6.3%)	709 (12.6%)	<0.001
VF/CA	79 (1.2%)	60 (1.7%)	273 (2.5%)	267 (4.7%)	<0.001
Death	72 (1.1%)	75 (2.1%)	243 (2.2%)	251 (4.4%)	<0.001

BiVAD = biventricular assist device; CMRI = cardiac magnetic resonance imaging; CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; EMB = endomyocardial biopsy; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; LHC = left heart catheterization; OHT = orthotropic heart transplant; p-LVAD = percutaneous left ventricular assist device; RHC = right heart catheterization; VF/CA = ventricular fibrillation/cardiac arrest.

troponin levels, myocardial histology, and CMRI results) of patients as this information is not available in the NIS. Further, the study only includes the sickest of patients with myocarditis who needed hospitalization and thus gives no information regarding the prognosis and management of less sick patients. Finally, since the NIS database is limited to single hospitalizations and does not contain information on long-term outcomes, including out-of-hospital mortality, this inference cannot be drawn from our analysis.

This large, national, multicentric study reveals baseline characteristics, co-morbidities, utilization of diagnostic modalities, tMCS, and advanced heart failure therapies in diverse patients hospitalized for myocarditis. Furthermore, this study also reports higher rates of CS, VF/CA, and mortality in women.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.03.036.

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