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Clinical Characteristics and Outcomes of Acute Myocarditis: An Analysis of Korean Multicenter Registry

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AUTHOR'S SUMMARY

Acute myocarditis presents diverse clinical manifestations and courses, yet systematic evaluations of this condition in the Republic of Korea are limited. We retrospectively collected data on acute myocarditis patients from seven tertiary centers to address this. Approximately half of the patients with acute myocarditis presented with fulminant myocarditis, with half of these patients requiring extracorporeal membrane oxygenation support. Diagnosis of acute myocarditis was made based on pathological findings in 27.8%, while 72.2% were diagnosed clinically. Despite the high proportion of fulminant myocarditis, in-hospital survival rates were favorable. The study identified variability in diagnosis and treatment patterns across centers, indicating a need for standardization in the management of acute myocarditis.

ABSTRACT

Background and Objectives: Data are limited on the clinical manifestations and outcomes of acute myocarditis from a large-scale registry. We investigated acute myocarditis's clinical characteristics and prognosis from a large-scale, multi-center registry in the Republic of Korea.
Methods: We collected data from seven hospitals between 2001 and 2021. Clinical variables and outcomes during the index hospitalization and follow-up periods were analyzed. We also evaluated inter-center and temporal differences in diagnostic and treatment patterns.
Results: Eight hundred forty-one patients diagnosed with acute myocarditis were included. Common symptoms included chest pain (60.4%), followed by fever or myalgia (46.3%), and dyspnea (45.7%). Fulminant myocarditis occurred in 421 (50.1%), with 217 requiring

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Conflict of Interest Disclosures
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
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extracorporeal membrane oxygenation (ECMO) support. Endomyocardial biopsy (EMB) was performed in 276 (32.8%) patients, and biopsy-proven diagnosis was made in 234 (27.8%). Based on the EMB results, lymphocytic myocarditis was the predominant form (69.6%), followed by eosinophilic (13.8%) and giant cell myocarditis (1.4%). Eighty-three in-hospital (9.9%) and 16 (1.9%) additional mortality during the follow-up occurred. An increase in the use of EMB, cardiac imaging, and immunosuppressive therapy was noted over time, but in-hospital mortality remained unchanged. Remarkable variations in diagnosis and treatment were observed across different centers.

Conclusions: This study unveiled clinical features of acute myocarditis in the Republic of Korea, including a high incidence of fulminant myocarditis and complex cases requiring ECMO. Given the considerable inter-center variation in diagnostic and treatment patterns and prognosis, protocolized future trials are needed to clarify diagnosis and treatment in patients with acute myocarditis.

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Keywords: Myocarditis; Diagnosis; Prognosis

INTRODUCTION

Acute myocarditis, an inflammatory condition of the myocardium, has the potential to result in catastrophic outcomes. The presentation of acute myocarditis varies widely, from asymptomatic to devastating cardiogenic shock, covering a broad spectrum of clinical presentations. Its clinical manifestations can overlap with those of heart failure, acute coronary syndrome, and arrhythmias.[1] While endomyocardial biopsy (EMB) is considered the gold standard for diagnosis, it is underutilized due to its low sensitivity and invasive nature.[2]

Despite existing guidelines, the evidence level to guide diagnostic and treatment strategies remains relatively weak;[3] clinical presentation heterogeneity leads to practice variability. Recently, there has been an increased use of cardiac magnetic resonance (CMR) imaging for diagnosis,[4] while the etiology of acute myocarditis has expanded to include immune checkpoint inhibitors, coronavirus disease 2019 (COVID-19), and vaccines. Advances in mechanical circulatory support (MCS) have made it possible to secure time for myocardial recovery in fulminant cases.[5][6] However, the prognostic implications of these advancements remain unclear.[7] Moreover, large cohort analyses have predominantly been based on analyses of populations from specific regions or ethnic backgrounds, resulting in a lack of diversity in findings. Thus, we aimed to analyze a large cohort of acute myocarditis patients drawn from an Asian population, focusing on their clinical characteristics and current diagnostic and treatment practices.

METHODS

Ethical statement

The study protocol was approved by the Institutional Review Board of the center (Asan Medical Center, 2022-0550) and conducted in compliance with the Declaration of Helsinki(2013).

Study design and population

This retrospective, multicenter cohort study included patients diagnosed with acute myocarditis from 7 hospitals in the Republic of Korea between January 2001 and December 2022. Diagnosis of acute myocarditis was defined and adjudicated as clinically suspected or biopsy-proven according to the recommendations of the European Society of Cardiology.[8] Briefly, patients with suspected myocarditis should be met following diagnostic criteria in the absence of significant coronary artery stenosis, pre-existing cardiac or non-cardiac disease that could explain the clinical situation: at least one of typical clinical presentation (acute pericarditic or pseudo-ischemic chest pain, new onset or worsening dyspnea, palpitation or unexplained arrhythmic symptoms or syncope or aborted sudden cardiac death, unexplained cardiogenic shock) and one diagnostic criteria (electrocardiography or Holter or stress testing, elevated cardiac troponin, abnormalities on cardiac imaging, and CMR evidence of myocardial edema or classical late gadolinium enhancement pattern compatible to myocarditis). Pathologic diagnosis was defined by the Dallas histopathologic criteria,[9] and diagnostic criteria of CMR were by recommendation.[10] Patients with suspected or confirmed myocarditis with a subacute (1–3 months) or chronic course (>3 months), ischemic heart disease, or cardiac sarcoidosis were excluded. Fulminant myocarditis (FM) was defined as the presence of hemodynamic instability or evidence of end-organ hypoperfusion necessitating vasoactive or inotropic agents or MCS.

Study outcomes

The primary outcome of the current study was the characterization of clinical features, including patient characteristics, clinical course, treatment, and outcomes of those with acute myocarditis. Additionally, the study aimed to assess temporal trends and inter-center differences in diagnostic patterns, treatment approaches, and in-hospital mortality among hospitals. Patient information was collected via a review of medical records.

Statistical analysis

The significance of differences in continuous variables among groups was analyzed using Student's t-test or the Mann-Whitney U test as appropriate, and results are presented as means ± standard deviations or medians (interquartile range; IQR). The significance of differences in categorical variables among groups was analyzed using the χ^2 test or Fisher's exact test as appropriate, and results are presented as numbers with percentages. A comparison of continuous variables over four eras—pre-2010, 2011–2014, 2015–2018, and 2019–2022—was conducted by analysis of variance. Event rates of in-hospital death and the composite of in-hospital death or heart transplantation were estimated using the Kaplan-Meier method. All comparisons were 2-sided, and p values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical characteristics

From 2001 to July 2022, a total of 841 patients (mean age, 35.9 years) diagnosed with acute myocarditis were enrolled. Among the total study population, 442 (52.6%) patients presented directly to the participating centers, while the remaining (47.4%) were transferred from other hospitals where they had been admitted. Overall, the prevalence of underlying comorbidities was low, as detailed in **Table 1**. Sixteen (1.9%) patients had a history of prior

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Table 1. Baseline characteristics of the study population

Variables	Total cohort population (n=841)
Demographic findings	
Age (years)	35.9±20.0
Male	495 (58.9)
Height (cm)	161.6±20.2
Body weight (kg)	61.7±18.1
Hypertension	130 (15.5)
Diabetes	55 (6.5)
Chronic kidney disease	18 (2.1)
Stroke	14 (1.7)
Current smoking	138 (16.4)
Malignancy	30 (3.6)
Autoimmune disease	14 (1.7)
Prior myocarditis	16 (1.9)
Use of immune checkpoint inhibitors	10 (1.2)
COVID-19 vaccination	64 (11.2)
Symptoms	
Onset before admission (days)	3 (1–5)
Dyspnea	384 (45.7)
NYHA functional class	
II	141 (18.2)
III	88 (11.3)
IV	90 (11.6)
Cough	164 (19.5)
Chest pain	508 (60.4)
Febrile sense or myalgia	389 (46.3)
Nausea or vomiting	237 (28.2)
Syncope	66 (7.8)
Vital signs*	
Systolic BP (mmHg)	93.5 (77.0–101.0)
Diastolic BP (mmHg)	56 (46–64)
Heart rate (beats per minute)	96.0 (74.0–108.0)
Body temperature (°C)	37.2±1.0

Values are presented as means ± standard deviations, number (%), or medians (interquartile range).
BP = blood pressure; COVID-19 = coronavirus disease 2019; NYHA = New York Heart Association.
*Vital signs of the study subjects represent the worst values obtained during shock.

myocarditis, while 64 (11.2%) had a recent history of COVID-19 vaccination. Symptoms related to myocarditis started a median of 3 days before hospitalization, with chest pain (45.7%), a febrile sensation, or myalgia (46.3%), followed by dyspnea (45.7%) being common symptoms. Sinus rhythm was a frequent initial electrocardiographic finding upon presentation, while 45 (5.3%) patients presented with ventricular tachyarrhythmia and 11 (1.4%) with atrioventricular (AV) block (**Table 2**). Throughout the hospital stay, ventricular tachyarrhythmia increased to 11.4% and AV block to 7.0%. ST-segment changes were observed in 558 patients (66.7%). Median peak cardiac troponin I and creatinine kinase-MB levels reached 9.08 and 29.73 ng/mL, respectively. The mean left ventricular ejection fraction (LVEF) was 43.5%, with over half of the patients exhibiting left ventricular systolic dysfunction (LVEF less than 50%).

Diagnostic patterns

Of the 841 patients, 508 (60.4%) underwent imaging evaluation for coronary artery disease, with 423 (50.3%) assessed via coronary angiography. EMB was performed in 276 (32.8%) of myocarditis patients at a median of 2 days (IQR, 1–5). Histopathologic findings indicated lymphocytic myocarditis in 192 (69.6%) patients, eosinophilic myocarditis in 38 (13.8%), and giant cell myocarditis in 4 (1.4%) (**Figure 1**). Non-diagnostic or negative results were observed in 42 (15.2%). Acute myocarditis was pathologically diagnosed in 234 (27.8%) patients, while

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Table 2. Electrocardiographic, laboratory, and echocardiographic findings of the study population

Variables	Results
ECG findings	
Sinus rhythm	
Initial presentation	698 (86.2)
During admission	618 (73.5)
Atrial fibrillation or flutter	
Initial presentation	21 (2.6)
During admission	56 (6.7)
Ventricular tachyarrhythmia	
Initial presentation	43 (5.3)
During admission	96 (11.4)
Any AV block	
Initial presentation	11 (1.4)
During admission	59 (7.0)
Asystole	
Initial presentation	8 (1.0)
During admission	23 (2.7)
ST segment changes	558 (66.7)
Elevation	229 (27.6)
Other ST changes	329 (39.1)
Bundle branch block	184 (22.1)
Longest QRS duration (ms)	108±31
Laboratory findings*	
WBC (/μL)	11,130±6,158
CRP (mg/dL)	2.6 (0.7–7.5)
Lactate dehydrogenase (IU/L)	650 (444–1,087)
Creatinine (mg/dL)	0.9 (0.5–1.0)
Cardiac troponin I (ng/mL)	5.55 (1.13–18.92)
Peak value (ng/mL)	9.08 (2.27–28.20)
Median hours to reach peak value	10.6
Creatinine kinase-MB (ng/mL)	20.04 (6.50–53.82)
Peak value (ng/mL)	29.73 (9.64–76.17)
Median hours reaching peak value	11.8
NT-proBNP (pg/mL)	3693 (517–12,740)
Peak value, pg/mL	4476 (636–17,217)
Median hours to reach peak value	14.3
Lactic acid (mmol/L)	2.0 (1.2–3.6)
Peak value (mmol/L)	2.6 (1.4–6.3)
Median hours to reach peak value	16.9
Echocardiographic parameters†	
LVEF (%)	43.5±18.0
LVEF <50%	478 (56.8)
LVEDD (mm)	47.7±7.5
IVS thickness (mm)	9.6±2.4
LA diameter (mm)	34.3±7.3
TV S'	10.4±3.3

Values are presented as means ± standard deviations, number (%), or medians (interquartile range).
AV = atrioventricular; CRP = C-reactive protein; ECG = echocardiography; IVS = interventricular septum; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; TV = tricuspid valve; TV S' = tricuspid lateral annular systolic velocity; WBC = white blood cells.
*Data for cardiac troponin I, creatinine kinase-MB, NT-proBNP, and lactic acid at initial presentation were available in 710, 825, 591, and 538 subjects, respectively. Data for troponin I, creatinine kinase-MB, NT-proBNP, and lactic acid at peak level were available in 689, 797, 547, and 562 subjects, respectively.
†Data regarding echocardiographic parameters were available in 823 subjects.

the remaining 607 (72.2%) were clinically diagnosed. CMR imaging was conducted in 273 (32.5%) patients at a median of 3 days (IQR, 2–5); 104 (12.4%) patients underwent EMB and CMR imaging, while 169 (20.1%) underwent CMR imaging only. Of the 607 (72.2%) patients with a clinical diagnosis who did not undergo an EMB or had non-diagnostic results, 187

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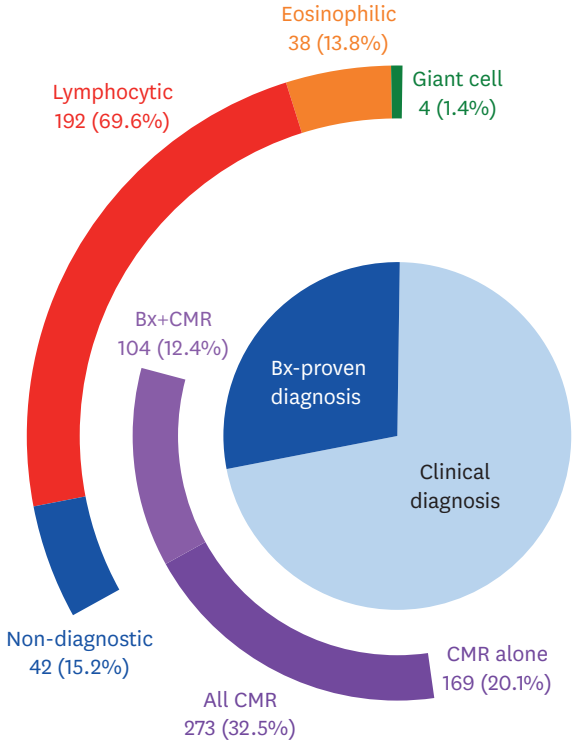

Figure 1. Patterns of acute myocarditis and modalities used for diagnosis.
Bx = biopsy; CMR = cardiac magnetic resonance.

(34.8%) underwent CMR imaging, among whom 167 (89.3%) had findings consistent with myocarditis. EMB was more frequently utilized in patients who received extracorporeal membrane oxygenation (ECMO) (105 out of 217, 48.4%) compared to those who did not (171 out of 624, 27.4%; p<0.001), whereas CMR was more commonly used for diagnosis in patients who did not undergo ECMO (39.7% vs. 11.5%, p<0.001). Diagnosis with EMB (p=0.002) and CMR (p<0.001) was significantly delayed in patients with ECMO support (median with IQR of EMB, 3 days [1–9] and CMR, 16 days [9–24]) than those without ECMO support (EMB, 2 days [1–4] and CMR, 3 days [2–5], respectively).

Management details

Six hundred (71.3%) patients were initially admitted to the intensive care unit, and 421 (50.1%) patients were classified as having FM. Vasoactive and/or inotropic agents were administered in 401 (47.7%) patients, and 217 (25.8%) patients received ECMO support. Among the vasoactive and/or inotropic agents used, dopamine was the most administered to 232 (27.6%) patients, followed by dobutamine to 216 (25.7%), norepinephrine to 194 (23.1%), epinephrine to 95 (11.3%), vasopressin to 39 (4.6%), and milrinone to 28 (3.3%). Of the 42 (5.0%) patients who received an intra-aortic balloon pump (IABP), 19 (2.3%) had IABP treatment alone, while 23 (2.7%) received combined therapy with ECMO. Details on the clinical characteristics, diagnosis, and outcomes in patients with and without FM were described in **Supplementary Table 1**. During the entire hospital stay, 63 (7.5%) patients had a temporary pacemaker inserted due to an AV block or asystole. Immunosuppressive therapies were administered to 305 (36.3%) patients, with corticosteroids used in 264 (31.4%) and intravenous immunoglobulin (IVIg) in 98 (11.7%) patients. Corticosteroid therapy was used in 22.8% of patients who did not undergo EMB, and based on pathologic findings,

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it was used in 41.1% of patients with lymphocytic myocarditis, 68.4% with eosinophilic myocarditis, 100% of giant cell myocarditis, and 61.9% of those with non-diagnostic results.

Clinical outcomes

Median hospital and intensive care unit stay was 9 days (IQR, 5–16) and 4 days (IQR, 2–10), respectively. Among the 217 FM patients who received ECMO, 136 of 215 (63.3%) were successfully weaned off ECMO. There were 83 (9.9%) in-hospital deaths, and 35 (4.2%) patients proceeded to heart transplantation. The cumulative incidence of in-hospital survival or the composite of free from in-hospital death and heart transplantation for 30 days is presented in **Figure 2**. The rate of in-hospital mortality was 34 (11.1%) of 305 patients treated with immunosuppressive therapies and 49 (9.1%) of 536 patients who did not receive immunosuppressive treatments (p=0.348). For a median period of 361 days (IQR, 41–1,416) after discharge, all-cause death during index admission and follow-up period occurred in 99 (11.8%) patients. An additional 16 mortality events occurred during the follow-up period after discharge. One-year and two-year mortality rates were 10.3% (n=87) and 11.1% (n=93), respectively. In-hospital mortality did not differ significantly according to the intensity of corticosteroid therapy in the overall study population and subgroups with and without ECMO use (**Supplementary Figure 1**). Throughout the follow-up period, 11 (1.3%) patients required the implantation of a permanent pacemaker.

Temporal trends and inter-center differences

We evaluated temporal differences in diagnostic and treatment patterns as well as in-hospital mortality (**Figure 3**, **Supplementary Figure 2**). While patient age did not vary significantly over time, the use of EMB (p<0.001) and CMR imaging (p<0.001) increased significantly over time (**Table 3**). Moreover, the use of corticosteroids (p<0.001) and IVIg (p=0.013) showed an increasing trend, while in-hospital mortality did not change significantly (p=0.483). There were notable differences in diagnostic patterns across the seven centers, especially in the performance of EMB (**Figure 4A**), administration of immunosuppressive therapies (**Figure 4B**), ECMO (**Figure 4D**), and the number of patients with a vasoactive-inotropic score (VIS) of more than 10 in the first 24 hours (**Figure 4F**). However, there were no remarkable variations in in-hospital mortality, which ranged from 3.0% to 20.0% (**Figure 4C**) or in the use of IABP (**Figure 4E**). Types of vasoactive and/or inotropic agents varied among the hospitals (**Supplementary Figure 3**). Three hospitals preferred dobutamine, while the other four preferred to use vasopressors.

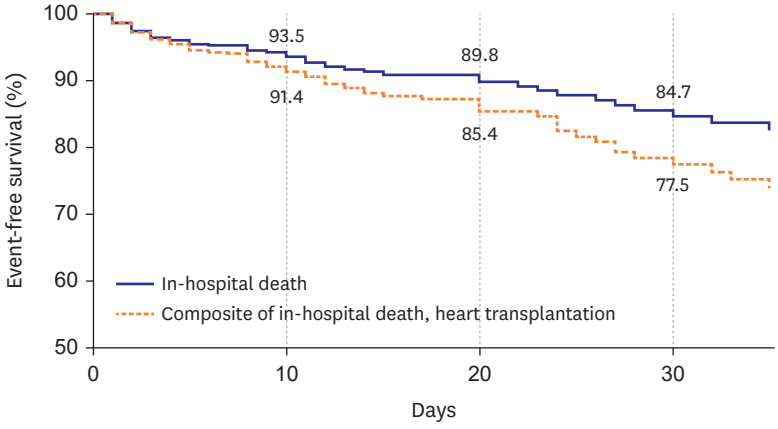

Figure 2. Cumulative event-free survival of in-hospital outcomes.
Red and blue graphs demonstrate in-hospital survival and free from the composite of in-hospital death and heart transplantation, respectively.

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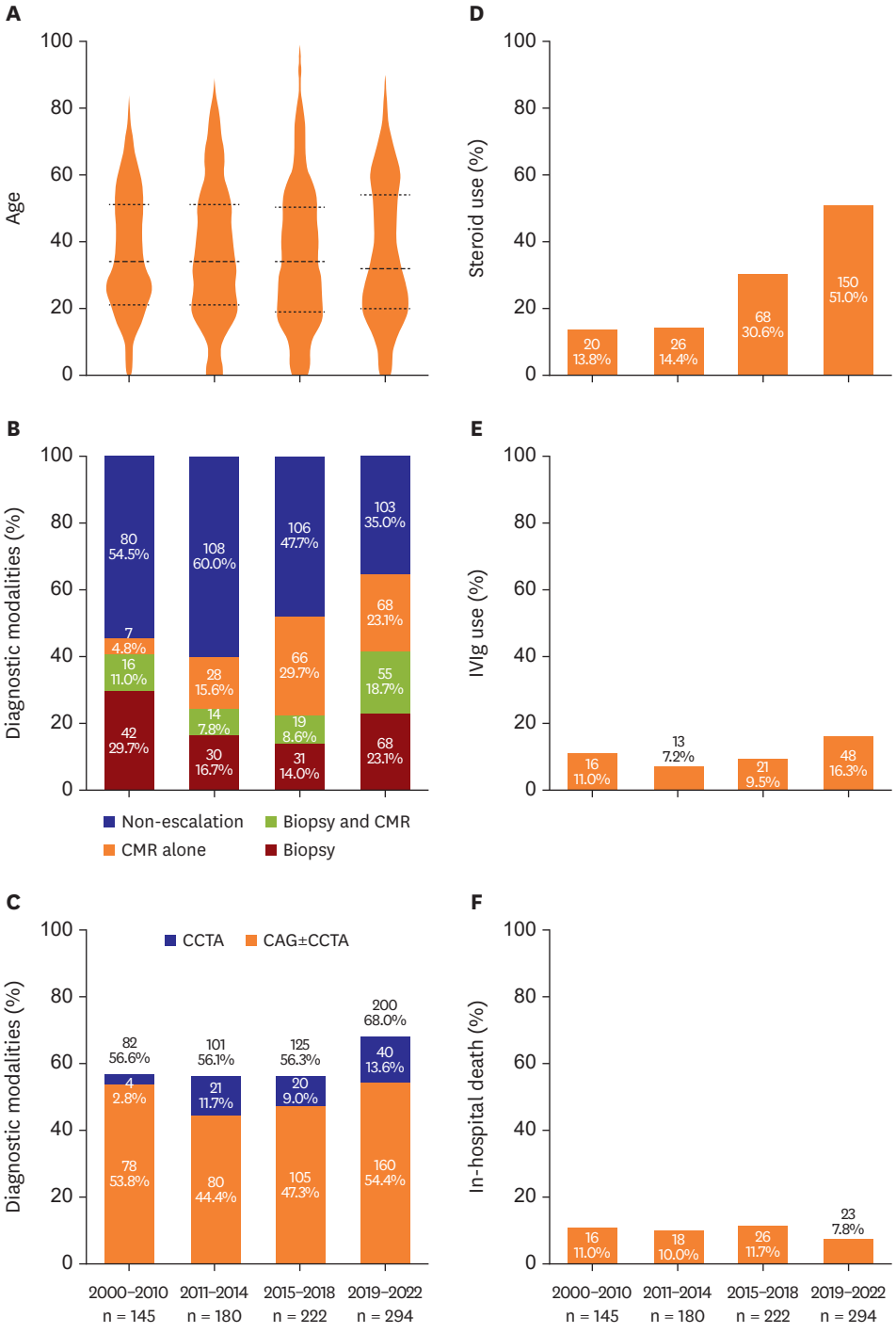

Figure 3. Temporal trends in diagnostic and treatment patterns as well as in-hospital death.
Graphs show temporal trends in (A) mean age at diagnosis; (B) proportion of diagnostic modalities used, (C) coronary imaging performance including coronary angiography and CCTA, (D) steroid use, (E) IVIg use, and (F) in-hospital death.
CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; IVIg = intravenous immunoglobulin.

DISCUSSION

This study presents findings from analyses of a large-scale acute myocarditis cohort from Asia, offering valuable insights into the characteristics of this patient population and current clinical

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Table 3. Temporal differences in patients, diagnosis, treatment, and mortality

Variables	2001–2010 (n=145)	2011–2014 (n=180)	2015–2018 (n=222)	2019–2022 (n=294)	p value
Age (years)	37.0±17.5	36.3±20.2	35.3±20.7	36.1±20.4	0.890
FM	81 (55.9)	81 (45.0)	121 (54.5)	134 (45.6)	0.050
Diagnosis					
Biopsy	59 (40.7)	44 (24.4)	50 (22.5)	123 (41.8)	<0.001
CMR	23 (15.9)	42 (23.3)	81 (36.5)	120 (40.8)	<0.001
Coronary imaging	82 (56.6)	101 (56.1)	125 (56.3)	200 (68.0)	0.012
Angiography	78 (53.8)	80 (44.4)	105 (47.3)	160 (54.4)	0.113
CCTA	4 (2.8)	32 (17.8)	29 (13.1)	53 (18.0)	<0.001
Treatment					
Steroids	20 (13.8)	26 (14.4)	68 (30.6)	150 (51.0)	<0.001
IVIg	16 (11.0)	13 (7.2)	21 (9.5)	48 (16.3)	0.013
ECMO	35 (24.1)	43 (23.9)	57 (25.7)	82 (27.9)	0.747
Outcome					
In-hospital death	16 (11.0)	18 (10.0)	26 (11.7)	23 (7.8)	0.483

CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; ECMO = extracorporeal membrane oxygenation; FM = fulminant myocarditis; IVIg = intravenous immunoglobulin.

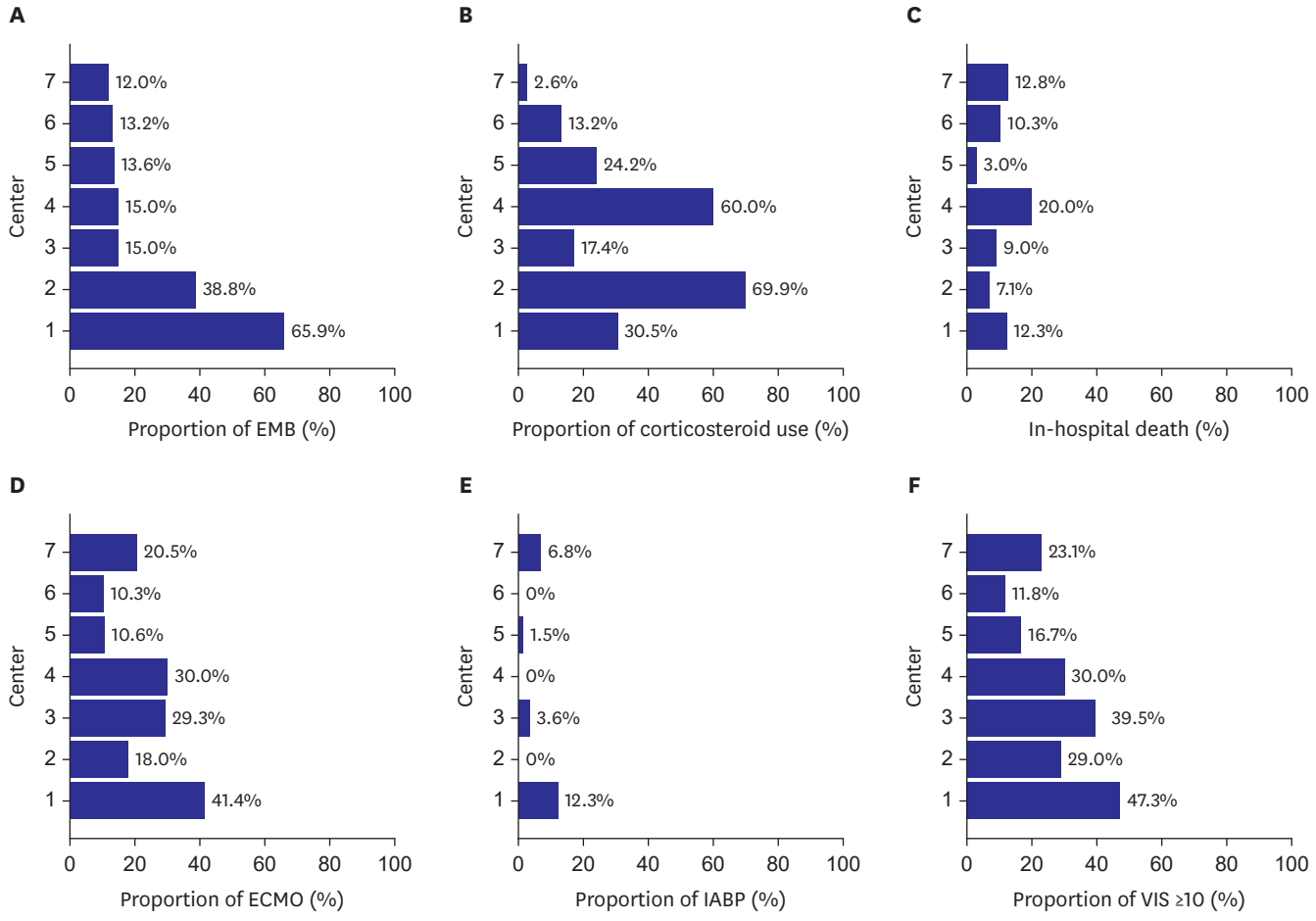

Figure 4. Differences in diagnostic and treatment patterns and in-hospital death according to center.
Graphs show the proportion of (A) EMB use, (B) steroid use, (C) in-hospital death, (D) ECMO use, (E) IABP use, and (F) VIS equal to or more than 10.
ECMO = extracorporeal membrane oxygenation; EMB = endomyocardial biopsy; IABP = intra-aortic balloon pump.

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practice. Despite advances in diagnosis and treatment, in-hospital mortality has not changed over time. Half of all acute myocarditis patients presented with FM, and half of these FM patients required hemodynamic support with ECMO. Despite the high incidence of FM, EMB was performed in only one-third of the study population, indicating underutilization of EMB. There was significant heterogeneity in diagnosis and management among hospitals, which suggests that current protocols and recommendations need to be standardized and adhered to.

This study represents the largest investigation into the characteristics of acute myocarditis in individuals of Asian ethnicity. Acute myocarditis predominantly occurred in relatively young adults, with approximately two-thirds of the patients being male. In addition, only 1–2% of cases had a prior history of myocarditis, consistent with the findings of previous studies (**Supplementary Table 2**).[11-13] Over time, the age of patients who present with acute myocarditis has not changed. The most common clinical presentation was chest pain, although the incidence of dyspnea was higher than that reported in previous studies.[11] Pathological diagnoses were made in 27.8% of patients based on EMB results, while the remaining 72.2% were clinically diagnosed. Overall, there has been an increase in the use of EMB, CMR, and other imaging modalities to rule out other cardiovascular diseases such as acute coronary syndrome, stress-induced cardiomyopathy, and chronic inflammatory cardiomyopathy. This suggests a growing effort to achieve accurate diagnosis and prognostic prediction of acute myocarditis. Among those in whom the diagnosis was not confirmed by EMB, only about 30% received CMR imaging. The reported incidence of performing EMB was 6.8% based on analyses of a nationwide database in the United States and 12.6% in the study of Ammirati and colleagues.[11][14] The rate of performing EMB for diagnosis of acute myocarditis in the current study was higher than that reported in previous studies, which may be due to the higher proportion of patients with FM in this study. Although EMB has low sensitivity,[15] the diagnostic yield in our study was high, and only 15% of patients with EMB had a negative pathologic result. Among patients with a pathologic diagnosis, about 70% had lymphocytic myocarditis, similar to what has been reported in the literature (**Supplementary Table 2**).[11] However, the incidence of giant cell myocarditis was 1.4%, lower than in previous reports, possibly due to underestimation or differences in patient selection.[11][16] The proportion of FM was higher than that reported in previous studies, with a quarter of patients requiring ECMO support, which is a very high rate. This discrepancy may stem from differences in defining FM, adopting early hemodynamic management using temporary MCS, and selecting severe cases in which most centers in the study were referring hospitals.

Immunosuppressive therapy was administered in more than one-third of the study population, a high rate considering that only 15% of patients had either eosinophilic or giant cell myocarditis. This suggests that a substantial number of patients received empirical immunosuppressive therapies despite the lack of clearly proven effectiveness.[17][18] Nevertheless, there were no significant differences in in-hospital mortality according to immunosuppressive therapies. Furthermore, the rate of corticosteroids and IVIg use showed a gradual increase, yet in-hospital mortality has not changed significantly over time.[7][19] These findings suggest that empirical immunosuppressive therapy does not benefit patients with acute myocarditis significantly. We did not investigate viral infections or cytokine levels. However, previous studies have suggested that immunosuppressive therapy might be effective in the absence of viral load and the presence of a cytokine storm due to its neutralizing effects.[20][21] It is difficult to determine the effectiveness of immunosuppressive therapy based on findings from the current study.

Significant variations were also observed in diagnosing and managing acute myocarditis across institutions. Notably, the rate of performing EMB varied widely, ranging from as low as 10% to over 60%. Furthermore, the rates of corticosteroid use showed remarkable variation, with usage patterns independent of EMB rates. Specifically, some centers with lower EMB rates showed high frequencies of corticosteroid use. This observation suggests the empirical usage of immunosuppressive therapies without objective pathologic diagnosis. Furthermore, some centers with lower EMB performance rates used corticosteroid therapy more frequently than those with the highest EMB rate. Despite these variations, in-hospital mortality did not differ significantly among centers. Preferred agents for hemodynamic support during cardiogenic shock varied, particularly the preference for inodilators. Although norepinephrine is regarded as preferable to dopamine,[22] issues regarding first-line agents and optimal combinations of agents for medical therapy of FM have not yet been resolved. They should be elucidated in large-scale prospective studies. Concerning hemodynamic support, the low use rate of IABP also reflects insufficient hemodynamic support with this device alone and limited LV unloading of IABP during ECMO support.[23] Furthermore, peak VIS before the ECMO application varied across institutions. This finding suggests that the threshold for applying MCS is different for each institution and physician for the treatment of FM complicated by profound cardiogenic shock.

This study had several limitations. First, its retrospective design inherently limits the interpretation of the results. Second, differences in diagnostic and treatment patterns and patient characteristics across the centers may have affected institutional outcomes. However, due to the lack of available information on the specific cause of death, it is challenging to perform a comparative analysis of in-hospital mortality between hospitals with high and low clinical performance, as well as to identify the underlying causes of these differences. Third, the incidence of FM was higher than that reported in previous studies, which may be attributed to the fact that participating centers were referral hospitals, potentially introducing selection bias. Therefore, the study population may not represent whole myocarditis patients in Korea. Fourth, the rates of MCS use and heart transplantation varied among institutions, likely due to differences in access and practices among institutions. Fifth, we did not evaluate the evidence of viral infection in blood or tissue samples. Some studies have reported that patients with chronic inflammatory cardiomyopathy with a negative viral genome status benefited from immunosuppressive therapies.[20] However, the evidence supporting these therapies is mostly based on single-center studies with a small number of patients.

In conclusion, although we noted a high incidence of FM cases and frequent use of temporary MCS in an Asian population, the in-hospital prognosis was overall favorable. Efforts to diagnose acute myocarditis have increased, while there is considerable variation across institutions, and empirical immunosuppressive therapy is commonly administered. This suggests that further efforts should be made to standardize the diagnosis and treatment of acute myocarditis.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Clinical characteristics, diagnosis, and outcomes among the patients with and without fulminant myocarditis

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Supplementary Table 2
Clinical characteristics and outcomes compared to previous studies

Supplementary Figure 1
Rates of in-hospital death according to the overall study population (A) and subgroups without (B) and with (C) extracorporeal membrane oxygenation use.

Supplementary Figure 2
Annual incidence and mortality rate of acute myocarditis.

Supplementary Figure 3
Proportion of vasoactive and inotropic agents used according to different center.

REFERENCES

1. Sagar S, Liu PP, Cooper LT Jr. Myocarditis. *Lancet* 2012;379:738-47. PUBMED | CROSSREF
2. Lorusso R, Centofanti P, Gelsomino S, et al. Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: a 5-year multi-institutional experience. *Ann Thorac Surg* 2016;101:919-26. PUBMED | CROSSREF
3. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation* 2007;116:2216-33. PUBMED | CROSSREF
4. Ammirati E, Frigerio M, Adler ED, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail* 2020;13:e007405. PUBMED | CROSSREF
5. Hunziker L, Radovanovic D, Jeger R, et al. Twenty-year trends in the incidence and outcome of cardiogenic shock in AMIS Plus Registry. *Circ Cardiovasc Interv* 2019;12:e007293. PUBMED | CROSSREF
6. Salter BS, Gross CR, Weiner MM, et al. Temporary mechanical circulatory support devices: practical considerations for all stakeholders. *Nat Rev Cardiol* 2023;20:263-77. PUBMED | CROSSREF
7. Pahuja M, Adegbala O, Mishra T, et al. Trends in the incidence of in-hospital mortality, cardiogenic shock, and utilization of mechanical circulatory support devices in myocarditis (analysis of national inpatient sample data, 2005-2014). *J Card Fail* 2019;25:457-67. PUBMED | CROSSREF
8. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;34:2636-48. PUBMED | CROSSREF
9. Aretz HT. Myocarditis: the Dallas criteria. *Hum Pathol* 1987;18:619-24. PUBMED | CROSSREF
10. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardiol* 2009;53:1475-87. PUBMED | CROSSREF
11. Ammirati E, Cipriani M, Moro C, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: multicenter Lombardy registry. *Circulation* 2018;138:1088-99. PUBMED | CROSSREF
12. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. *Circulation* 2008;118:639-48. PUBMED | CROSSREF
13. McCarthy RE 3rd, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000;342:690-5. PUBMED | CROSSREF
14. Singh V, Mendirichaga R, Savani GT, et al. Comparison of utilization trends, indications, and complications of endomyocardial biopsy in native versus donor hearts (from the nationwide inpatient sample 2002 to 2014). *Am J Cardiol* 2018;121:356-63. PUBMED | CROSSREF
15. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. *J Am Coll Cardiol* 1989;14:915-20. PUBMED | CROSSREF
16. Kanaoka K, Onoue K, Terasaki S, et al. Features and outcomes of histologically proven myocarditis with fulminant presentation. *Circulation* 2022;146:1425-33. PUBMED | CROSSREF
17. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;333:269-75. PUBMED | CROSSREF

18. Chen HS, Wang W, Wu SN, Liu JP. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev* 2013;2013:CD004471. PUBMED | CROSSREF

19. Yang JH, Choi KH, Ko YG, et al. Clinical characteristics and predictors of in-hospital mortality in patients with cardiogenic shock: results from the RESCUE registry. *Circ Heart Fail* 2021;14:e008141. PUBMED | CROSSREF

20. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 2009;30:1995-2002. PUBMED | CROSSREF

21. Kishimoto C, Shioji K, Kinoshita M, et al. Treatment of acute inflammatory cardiomyopathy with intravenous immunoglobulin ameliorates left ventricular function associated with suppression of inflammatory cytokines and decreased oxidative stress. *Int J Cardiol* 2003;91:173-8. PUBMED | CROSSREF

22. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779-89. PUBMED | CROSSREF

23. Cheng R, Hachamovitch R, Makkar R, et al. Lack of survival benefit found with use of intraaortic balloon pump in extracorporeal membrane oxygenation: a pooled experience of 1517 patients. *J Invasive Cardiol* 2015;27:453-8. PUBMED