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Quantitative Cardiac MRI in COVID-19 Vaccine-Related Versus Other Types of Myocarditis: A Korean Multicenter Study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) vaccine-related myocarditis (C-VRM) is a potential adverse event following mRNA-based vaccination. Cardiac magnetic resonance imaging (CMR) is pivotal for diagnosing and monitoring myocarditis. This study compared quantitative CMR findings among C-VRM, COVID-19 myocarditis, and other myocarditis in the Korean population, and identified prognostic factors associated with adverse outcomes.
Methods: This retrospective multicenter study included patients diagnosed with various types of myocarditis who underwent CMR in four tertiary-care hospitals between October 2018 and January 2023. Clinical data and CMR findings, including cine, native T1, T2, extracellular volume (ECV), and late gadolinium enhancement (LGE) were analyzed. Differences in CMR parameters among myocarditis types were analyzed using linear regression. Predictors of adverse outcomes, defined as a composite of left ventricular ejection fraction (LVEF) of < 40% at follow-up and all-cause mortality, were assessed using logistic regression analysis.
Results: A total of 82 patients (mean age, 42.8 ± 19.2 years; 40 men) were included: 29 with C-VRM, 7 with COVID-19 myocarditis, and 46 with other myocarditis. C-VRM showed significantly lower native T1, T2, and ECV than other myocarditis ($P = 0.001$, 0.022, and 0.001, respectively), after adjustment for age, sex, and time from symptom onset to CMR. Among the 74 patients with follow-up LVEF data, seven (9.5%) experienced adverse outcomes. Maximum ECV z-score (odds ratio [OR], 1.457; 95% confidence interval [CI], 1.062–1.998; $P = 0.020$) and LGE extent (OR, 1.109; 95% CI, 1.029–1.194; $P = 0.007$) remained independent predictors after adjusting for age and initial LVEF, while myocarditis type was not associated with prognosis.
Conclusion: In this Korean multicenter cohort, CMR markers of myocardial injury were lower in C-VRM than in other myocarditis types, whereas prognosis was more strongly associated with injury severity than with disease subtype.

Keywords: Myocarditis; COVID-19; Magnetic Resonance Imaging; Parametric Mapping; Prognosis

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The authors have no potential conflicts of interest to disclose.

Data Availability Statement
Data generated or analyzed during the study are available from the corresponding author by request.

Author Contributions
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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic highlights the essential role of vaccines in preventing the spread of infectious diseases. As vaccination efforts worldwide aim to limit the transmission rates of COVID-19, understanding the potential side effects of these vaccines is crucial for public health and safety. Among the reported adverse events, myocarditis has garnered special attention, particularly among young men following mRNA-based COVID-19 vaccination.[1]

Myocarditis presents with a variety of symptoms, ranging from asymptomatic to heart failure or sudden death.[2] The diagnosis relies on evidence of myocardial edema and damage through cardiac magnetic resonance (CMR) imaging, along with elevated cardiac enzyme levels and the exclusion of other cardiac conditions, including coronary artery disease.[3] CMR is the most effective imaging tool for detecting myocardial edema and inflammation, assisting in the evaluation of disease severity and prognosis prediction. Quantitative parameters such as T1, T2, and extracellular volume (ECV) mapping provide precise representation of myocardial edema and fibrosis.[4]

Previous studies have indicated a relatively benign course and favorable prognosis for vaccine-induced myocarditis.[5-7] However, recent research from Korea has presented contrasting findings, revealing more severe clinical presentations and older age groups among the Korean population.[8,9] Despite previous studies, comprehensive research comparing CMR findings between coronavirus disease 2019 vaccine-related myocarditis (C-VRM) and other causes of myocarditis in Korean patients remains limited.

This study aimed to evaluate the differences in CMR parameters among C-VRM, COVID-19 myocarditis, and other myocarditis in the Korean population and to identify prognostic factors based on myocarditis type and quantitative CMR parameters.

METHODS

Study population

The inclusion criteria were as follows: 1) patients who presented with suspected myocarditis, defined by the presence of clinical symptoms (e.g., chest pain, fever, myalgia, or other symptoms), elevated cardiac biomarkers, and compatible CMR findings according to the updated Lake Louise Criteria[4]; 2) patients who underwent quantitative CMR, including cine imaging, T1 and T2 mapping, and late gadolinium enhancement (LGE) sequences, between October 2018 and January 2023. The study period encompassed myocarditis cases across pre-pandemic, pandemic, and post-vaccination phases in Korea, allowing the inclusion of diverse etiologies while maintaining consistent imaging protocols. The exclusion criteria were as follows: 1) patients with an uncertain diagnosis; and 2) patients with poor-quality CMR scans that hindered accurate analysis. Patients' medical records were collected from October 2018 to October 2023.

Patients were categorized into three groups based on clinical and temporal features, following a previous study[10]: 1) C-VRM, defined as myocarditis that developed shortly after COVID-19 vaccination, with elevated troponin levels and no alternative identifiable cause; 2) COVID-19 myocarditis, defined as myocarditis occurring in the setting of active or recent

SARS-CoV-2 infection confirmed by reverse transcriptase-polymerase chain reaction, without other identifiable causes; and 3) Other myocarditis, including all remaining patients who met the inclusion criteria but had no temporal association with COVID-19 vaccination or infection.

Clinical data

Clinical variables included demographics, underlying conditions, symptoms, laboratory results, family history of sudden cardiac death, history of COVID-19 infection or vaccination, and echocardiographic follow-up of left ventricular ejection fraction (LVEF). Definitions of the underlying conditions are provided in **Supplementary Data 1**.

CMR data

CMR studies were performed using 3-T scanners across four participating hospitals. The sequences included cine, T1 and T2 mapping, and LGE. The detailed scanner models and pulse sequence parameters are provided in **Supplementary Data 2**.

All CMR data were measured by a cardiac radiologist (Yoo Jin Hong with 15 years of experience) who was blinded to all clinical information using automated software (Myomics Lab, version 1.3; Phantomics, Seoul, Korea) with manual editing. The analyzed CMR findings included the cardiac function of both ventricles, LGE (presence and extent), mapping values (native T1, T2, and ECV fraction), and pericardial effusion. The extent of LGE was quantitatively assessed using a threshold of 5 standard deviations (SDs) above the mean signal intensity of remote myocardium. Mapping values were measured and converted to z-scores using site-specific normal references, a method supported by expert consensus[11] and used in previous multi-scanner studies[10,12,13] to reduce inter-scanner variability.

Clinical follow-up

Follow-up data, including outpatient visits, hospitalizations, and mortality documentation, were obtained from electronic medical records. The clinical endpoint was adverse outcomes, defined as a composite endpoint of all-cause mortality and LVEF < 40% on follow-up echocardiography. Follow-up LVEF was categorized as less than 40%, 40–50%, or greater than 50%.[14] The follow-up duration was defined as the interval from CMR to the last available clinical record or death.

Statistical analysis

Categorical data are presented as numbers and percentages, and continuous variables are presented as mean ± SD or median with interquartile range (IQR). To compare the clinical characteristics and CMR data among the three groups, we used one-way analysis of variance or the Kruskal–Wallis test for continuous variables, followed by post-hoc analysis with Bonferroni correction. For categorical variables, we used the χ^2 test or Fisher's exact test. Linear regression models were used to compare continuous CMR parameters between the myocarditis groups, with C-VRM as reference. Multivariable models included age, sex, and time from symptom onset to CMR as covariates. Logistic regression analyses were conducted to identify predictors of adverse outcomes. Candidate variables were selected based on their clinical relevance and univariable significance. Statistical significance was set at a *P* value of less than 0.05. Statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Ethics statement

This retrospective multicenter study was conducted in four Korean institutions. Approval for this study was obtained from the Institutional Review Boards (IRBs) of all four institutions, and the requirement for informed consent was waived. This retrospective multicenter study included four hospitals in South Korea. Hospital A: Keimyung University Dongsan Hospital (IRB approval No. 2024-02-018). Hospital B: Bundang Seoul National University Hospital (IRB approval No. B-2501-946-104). Hospital C: Seoul St. Mary's Hospital (IRB approval No. KC24RIDI0019). Hospital D: Severance Hospital, Yonsei University (IRB approval No. 4-2024-0022).

RESULTS

Patients characteristics

Among the 85 patients with suspected myocarditis who underwent quantitative CMR between October 2018 and January 2023, two were excluded due to an uncertain diagnosis, and one was excluded because of poor-quality CMR. Eighty-two patients were included in this study: 29 patients with C-VRM, seven with COVID-19 myocarditis, and 46 with other myocarditis (**Fig. 1**). The distribution of included cases by period and etiology is shown in **Supplementary Fig. 1**.

The demographic data for each group are presented in **Table 1**. The mean age of the total population was 42.8 ± 19.2 years, and 48.8% (40/82) were male. There were no significant differences in age, sex, body surface area, underlying diseases, or presenting symptoms between the groups (all $P > 0.05$). However, laboratory findings showed significant differences among the three groups, with the highest levels of troponin T ($P = 0.022$), troponin I ($P = 0.033$), and NT-proBNP ($P = 0.002$) in the other myocarditis group. The median interval from symptom onset to CMR imaging was 9 days (IQR, 5–17.5 days).

Among the 29 patients in the C-VRM group, 79.3% (n = 23) received the Pfizer-BioNTech vaccine, and 13.8% (n = 4) received the Moderna vaccine. One patient received

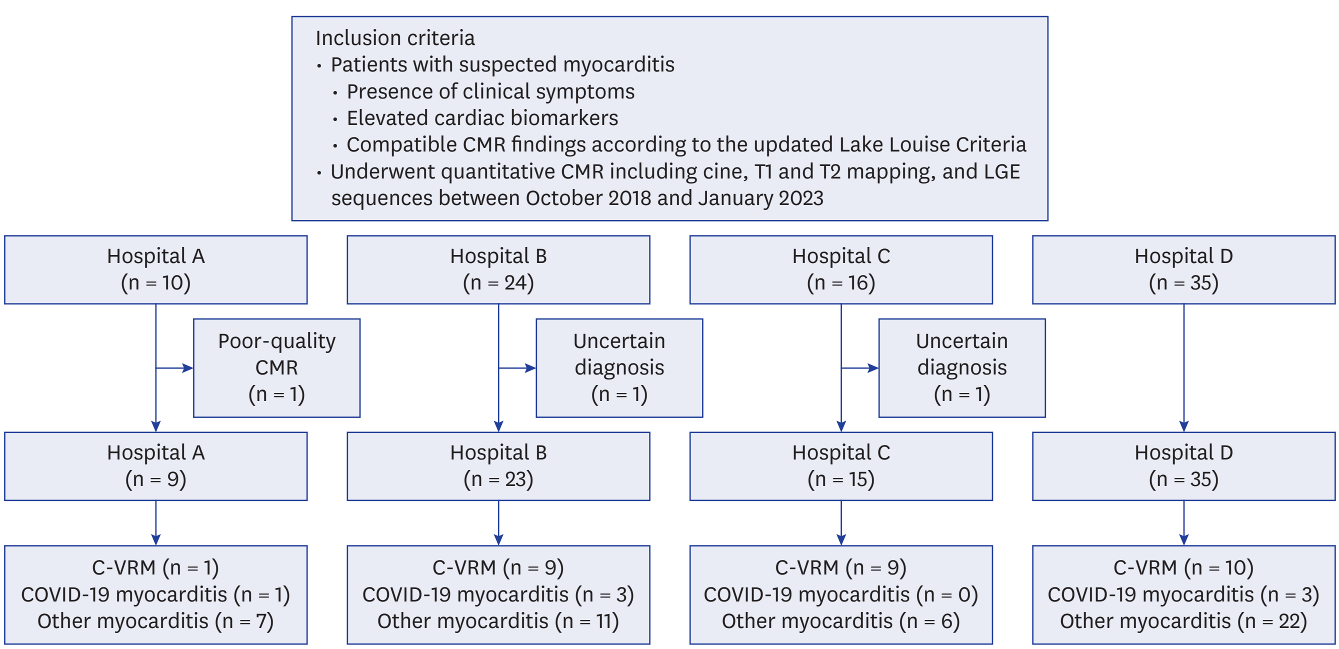

Fig. 1. Study participants.
CMR = cardiac magnetic resonance imaging, LGE = late gadolinium enhancement, C-VRM = coronavirus disease 2019 vaccine-related myocarditis.

Table 1. Baseline characteristics of study population

Variables	Total (N = 82)	C-VRM (n = 29)	COVID-19 myocarditis (n = 7)	Other myocarditis (n = 46)	*P* value
Age, yr	42.8 ± 19.2	40.9 ± 19.9	33.7 ± 13.9	45.3 ± 19.2	0.222
Sex, male	40 (48.8)	16 (55.2)	3 (42.9)	21 (45.6)	0.705
BSA, m^2	1.7 ± 0.2	1.8 ± 0.3	1.8 ± 0.2	1.7 ± 0.2	0.876
Underlying disease					
Hypertension	22 (26.8)	7 (24.1)	1 (14.3)	14 (30.4)	0.615
Diabetes	10 (12.2)	3 (10.3)	0 (0.0)	7 (15.2)	0.678
Hyperlipidemia	7 (8.5)	0 (0.0)	0 (0.0)	7 (15.2)	0.057
Coronary artery disease	10 (13.0)	6 (21.4)	0 (0.0)	4 (9.5)	0.251
Cardiomyopathy	17 (20.7)	6 (20.7)	1 (14.3)	10 (21.7)	0.902
Atrial fibrillation	5 (6.1)	0 (0.0)	0 (0.0)	5 (10.9)	0.241
Hear failure	29 (35.4)	6 (20.7)	3 (42.9)	20 (43.5)	0.129
Valvular heart disease	1 (1.2)	0 (0.0)	1 (14.3)	0 (0.0)	0.085
Family history of sudden death	11 (13.4)	6 (20.7)	1 (14.3)	4 (8.7)	0.272
Symptom					
Fever	21 (25.6)	4 (13.8)	2 (28.6)	15 (32.6)	0.188
Chest pain	52 (63.4)	23 (79.3)	3 (42.9)	26 (56.5)	0.059
Dyspnea	40 (48.8)	11 (37.9)	4 (57.1)	25 (54.4)	0.331
Palpitation	13 (15.8)	8 (27.6)	1 (14.3)	4 (8.7)	0.068
Syncope	10 (12.2)	5 (17.2)	0 (0.0)	5 (10.9)	0.586
Laboratory findings					
Troponin T, ng/mL[a]	0.47 ± 0.90	0.40 ± 1.06	0.02 ± 0.03	0.57 ± 0.84	**0.022**
Troponin I, ng/mL[b]	10.5 ± 22.3	1.9 ± 3.2	0.3 ± 0.4	19.4 ± 29.1	**0.033**
NT-proBNP, pg/mL[b]	4,360.8 ± 7,698.7	2,923.0 ± 6,842.6	1,442.6 ± 1,912.6	5,680.1 ± 8,508.8	**0.002**
ESR, mm/h	18.3 ± 26.8	14.0 ± 26.0	21.7 ± 23.7	20.6 ± 27.8	0.373
CRP, mg/L	5.9 ± 10.1	3.7 ± 5.7	6.1 ± 8.0	7.3 ± 12.2	0.126
WBC	8.1 ± 4.1	8.0 ± 4.6	7.3 ± 1.6	8.3 ± 4.2	0.675
Hematocrit, %	38.9 ± 6.6	41.2 ± 7.7	36.3 ± 6.2	37.8 ± 5.5	0.054
Adverse outcome[c]	7/74 (9.5)	2/25 (8.0)	1/7 (14.3)	4/42 (9.5)	0.715

Values are presented as number (%) or mean ± standard deviation. Bold indicates statistical significance. Troponin I data were available for 15 patients with C-VRM, 4 patients with COVID-19 myocarditis, and 19 patients with other myocarditis. NT-proBNP data were available for 28 patients with C-VRM, 7 patients with COVID-19 myocarditis, and 46 patients with other myocarditis. ESR data were available in 22 patients with C-VRM, 3 patients with COVID-19 myocarditis, and 37 patients with other myocarditis.

C-VRM = coronavirus disease 2019 vaccine-related myocarditis, COVID-19 = coronavirus disease 2019, BSA = body surface area, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, WBC = white blood cell.

[a]Significant difference between COVID-19 myocarditis and other myocarditis; [b]Significant difference between C-VRM and other myocarditis; [c]Adverse outcome was defined as follow-up left ventricular ejection fraction < 40% or all-cause mortality. Outcome status was available in 74 of 82 patients (25 in C-VRM, 7 in COVID-19 myocarditis, and 42 in other myocarditis).

Pfizer-BioNTech and AstraZeneca (3.4%), and the other received Moderna and AstraZeneca (3.4%) (**Fig. 2**). C-VRM occurred exclusively after mRNA vaccination, most frequently after the second dose (44.8%), followed by the first dose (31.0%) and the third dose (17.2%).

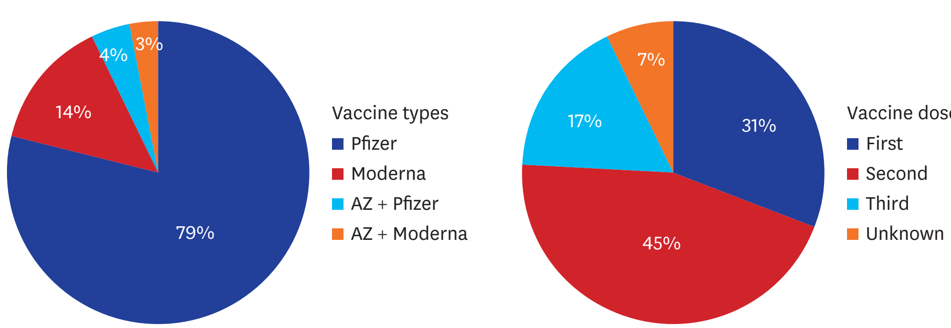

Fig. 2. Vaccine types and doses in patients with C-VRM. All cases of C-VRM occurred following mRNA vaccination, most frequently after the second dose (44.8%), followed by the first dose (31.0%) and third dose (17.2%).
C-VRM = coronavirus disease 2019 vaccine-related myocarditis, AZ = AstraZeneca.

CMR findings according to the types of myocarditis

The CMR findings of the three groups are presented in **Table 2**, with representative cases for each group shown in **Fig. 3**. There were no significant differences in the volumetric and functional CMR parameters among the groups (all $P > 0.05$). The mean LVEF and RVEF of the total population were 46.3% and 45.9%, respectively, both slightly below the normal ranges.

Significant differences were observed in myocardial tissue characteristics among the groups. Native T1 values were significantly lower in the C-VRM group than in other myocarditis group (mean native T1 z-score: 4.7 vs. 7.1, $P = 0.001$). Similarly, ECV values were lower in the C-VRM group than in the other myocarditis group (mean ECV z-score: 1.5 vs. 3.5; $P = 0.011$). The T2 values were also significantly lower in the C-VRM group than in the other myocarditis group (mean T2 z-score: 0.5 vs. 2.7, $P < 0.001$). The regional mapping values of the mid-septum and each slice showed similar results (**Supplementary Table 1**).

LGE was more common in the other myocarditis group (91.3%) than in the C-VRM (65.5%) and COVID-19 myocarditis (71.4%) groups ($P = 0.019$). No significant differences were observed in the LGE patterns ($P = 0.228$), with subepicardial LGE being the most common in all groups. LGE extent showed significant differences among the three groups ($P = 0.046$),

Table 2. CMR parameters of myocarditis

Parameters	Total (N = 82)	C-VRM (n = 29)	COVID-19 myocarditis (n = 7)	Other myocarditis (n = 46)	*P* value
Cardiac function					
LVEDVI, mL/m²	91.1 ± 39.5	96.0 ± 46.7	93.3 ± 35.8	87.7 ± 35.5	0.814
LVESVI, mL/m²	53.3 ± 40.5	59.0 ± 50.8	50.1 ± 31.9	50.1 ± 34.5	0.852
LVSV, mL	65.8 ± 21.5	63.8 ± 16.8	75.6 ± 15.1	65.5 ± 24.6	0.425
LVEF, %	46.3 ± 16.6	44.8 ± 17.4	49.3 ± 12.2	46.8 ± 16.8	0.771
LV mass index, g/m²	87.3 ± 29.7	87.6 ± 28.1	86.2 ± 28.0	87.2 ± 31.5	0.976
RVEDVI, mL/m²	81.9 ± 24.5	86.5 ± 29.7	76.8 ± 19.3	79.7 ± 21.5	0.718
RVESVI, mL/m²	46.0 ± 24.0	50.5 ± 31.6	35.9 ± 12.4	44.6 ± 19.1	0.611
RVSV, mL	62.6 ± 20.7	63.0 ± 19.1	71.9 ± 18.4	61.0 ± 21.9	0.428
RVEF, %	45.9 ± 13.4	45.0 ± 14.9	53.9 ± 9.4	45.3 ± 12.8	0.261
Mapping values					
Native T1, ms[a]	1,377.5 ± 105.2	1,326.3 ± 78.3	1,362.1 ± 103.5	1,412.1 ± 108.3	**0.002**
Maximum native T1 z-score[a]	9.2 ± 4.0	7.2 ± 2.9	8.5 ± 4.0	10.6 ± 4.1	**0.001**
Mean native T1 z-score[a]	6.2 ± 3.5	4.7 ± 2.8	5.8 ± 3.7	7.1 ± 3.6	**0.001**
T2, ms[a]	47.2 ± 6.7	44.4 ± 5.7	47.8 ± 6.7	48.9 ± 6.8	**0.036**
Maximum T2 z-score[a]	5.0 ± 4.3	3.0 ± 2.9	4.0 ± 2.9	6.4 ± 4.7	**0.001**
Mean T2 z-score[a]	1.8 ± 2.5	0.5 ± 2.1	1.5 ± 2.1	2.7 ± 2.5	**< 0.001**
ECV, %[a]	33.3 ± 7.1	30.1 ± 5.9	32.1 ± 8.0	35.5 ± 7.0	**0.004**
Maximum ECV z-score	5.0 ± 4.2	3.6 ± 3.6	4.6 ± 4.7	5.9 ± 4.3	0.056
Mean ECV z-score[a]	2.7 ± 2.7	1.5 ± 2.0	2.5 ± 2.8	3.5 ± 2.8	**0.011**
LGE					
LGE presence	66 (80.5)	19 (65.5)	5 (71.4)	42 (91.3)	**0.019**
LGE pattern					0.228
Subendocardial	2 (3.0)	1 (5.3)	1 (20.0)	0 (0.0)	
Mid-wall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Subepicardial	35 (53.0)	9 (47.4)	2 (40.0)	24 (57.1)	
Transmural	4 (6.1)	1 (5.3)	1 (20.0)	2 (4.8)	
Combined	14 (21.2)	4 (21.1)	0 (0.0)	10 (23.8)	
LGE extent (%), > 5SD	19.3 ± 18.2	14.3 ± 15.0	12.4 ± 16.8	23.4 ± 19.5	**0.046**
Pericardial effusion	42 (51.2)	10 (34.5)	3 (42.9)	29 (63.0)	**0.046**

Values are presented as number (%) or mean ± SD. Bold indicates statistical significance.
CMR = cardiac magnetic resonance, C-VRM = coronavirus disease 2019 vaccine-related myocarditis, COVID-19 = coronavirus disease 2019, LVEDVI = left ventricular end-diastolic volume index, LVESVI = left ventricular end-systolic volume index, LVSV = left ventricular stroke volume, LVEF = left ventricular ejection fraction, LV = left ventricular, RVEDVI = right ventricular end-diastolic volume index, RVESVI = right ventricular end-systolic volume index, RVSV = right ventricular stroke volume, RVEF = right ventricular ejection fraction, ECV = extracellular volume, LGE = late gadolinium enhancement, SD = standard deviation.
[a]Significant difference between C-VRM and other myocarditis.

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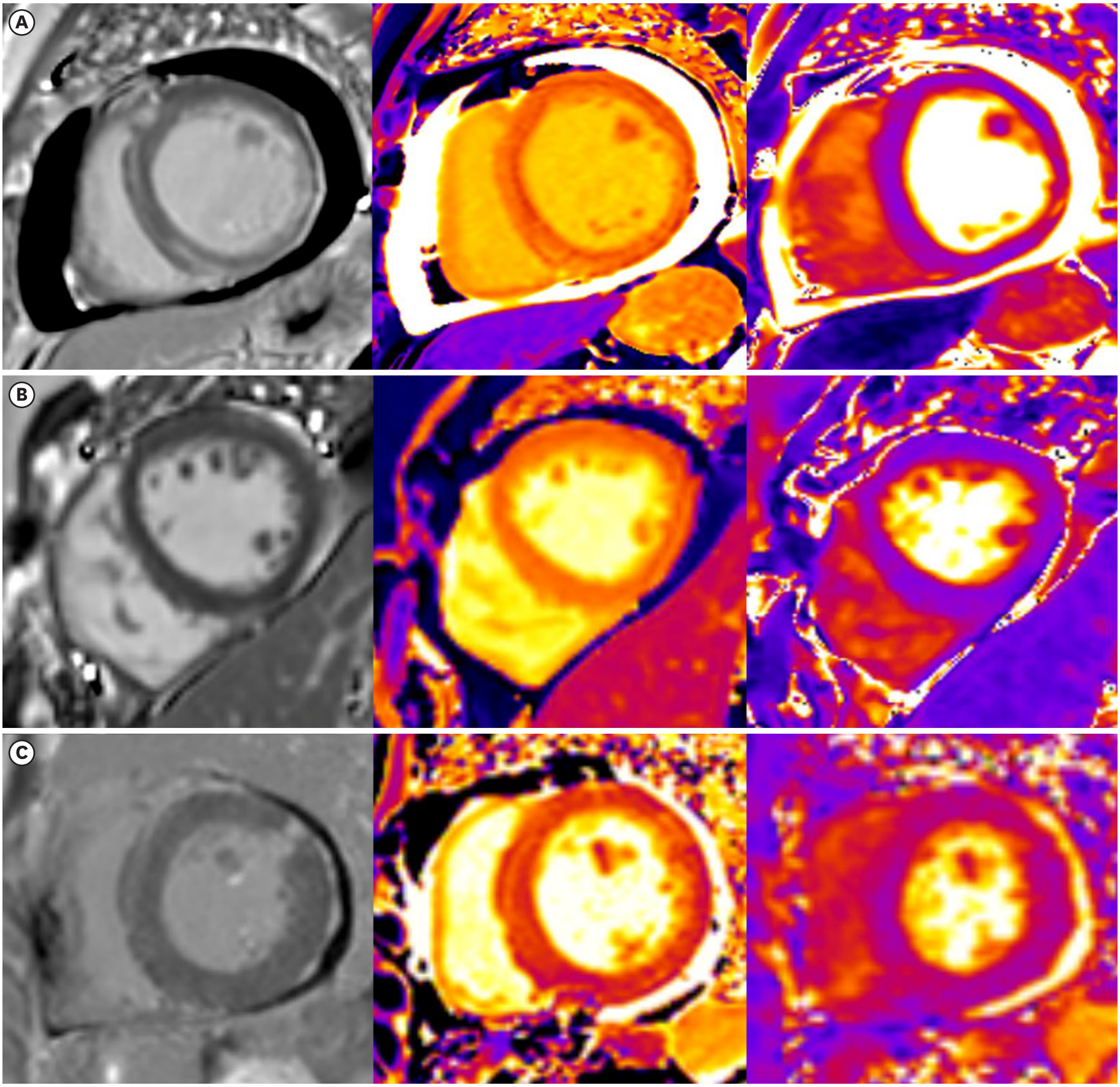

Fig. 3. Example cases of myocarditis demonstrating LGE, native T1 map, and T2 map (from left to right). (**A**) A 71-year-old man with COVID-19 vaccine-related myocarditis presented with dyspnea after receiving Moderna vaccine. His initial LVEF was 21.9%, improving to 44% on follow-up. LGE extent was 36.3%, with a maximum native T1 z-score of 2.86, maximum T2 z-score of 10.69, and maximum ECV z-score of 4.93. (**B**) A 53-year-old woman with COVID-19 myocarditis presented with dyspnea following a COVID-19 infection. Her initial LVEF was 43%, improving to 58% on follow-up. No LGE was observed, with a maximum native T1 z-score of 3.56, maximum T2 z-score of 2.54, and maximum ECV z-score of 1.16. (**C**) A 66-year-old man with other myocarditis presented with cough, rhinorrhea, sputum, and dyspnea. His initial LVEF was 22.21%, improving to 52% on follow-up. The LGE extent was 13.6%, with a maximum native T1 z-score of 5.56, maximum T2 z-score of 1.21, and maximum ECV z-score of 1.32. These cases show the importance of LGE extent and mapping values in predicting prognosis in patients with myocarditis.
LGE = late gadolinium enhancement, COVID-19 = coronavirus disease 2019, LVEF = left ventricular ejection fraction, ECV = extracellular volume.

with other myocarditis showing the highest value (23.4% ± 19.5%). However, in the pairwise comparison, no significant difference was observed between C-VRM and other myocarditis after Bonferroni correction (P = 0.087). Pericardial effusion also differed according to

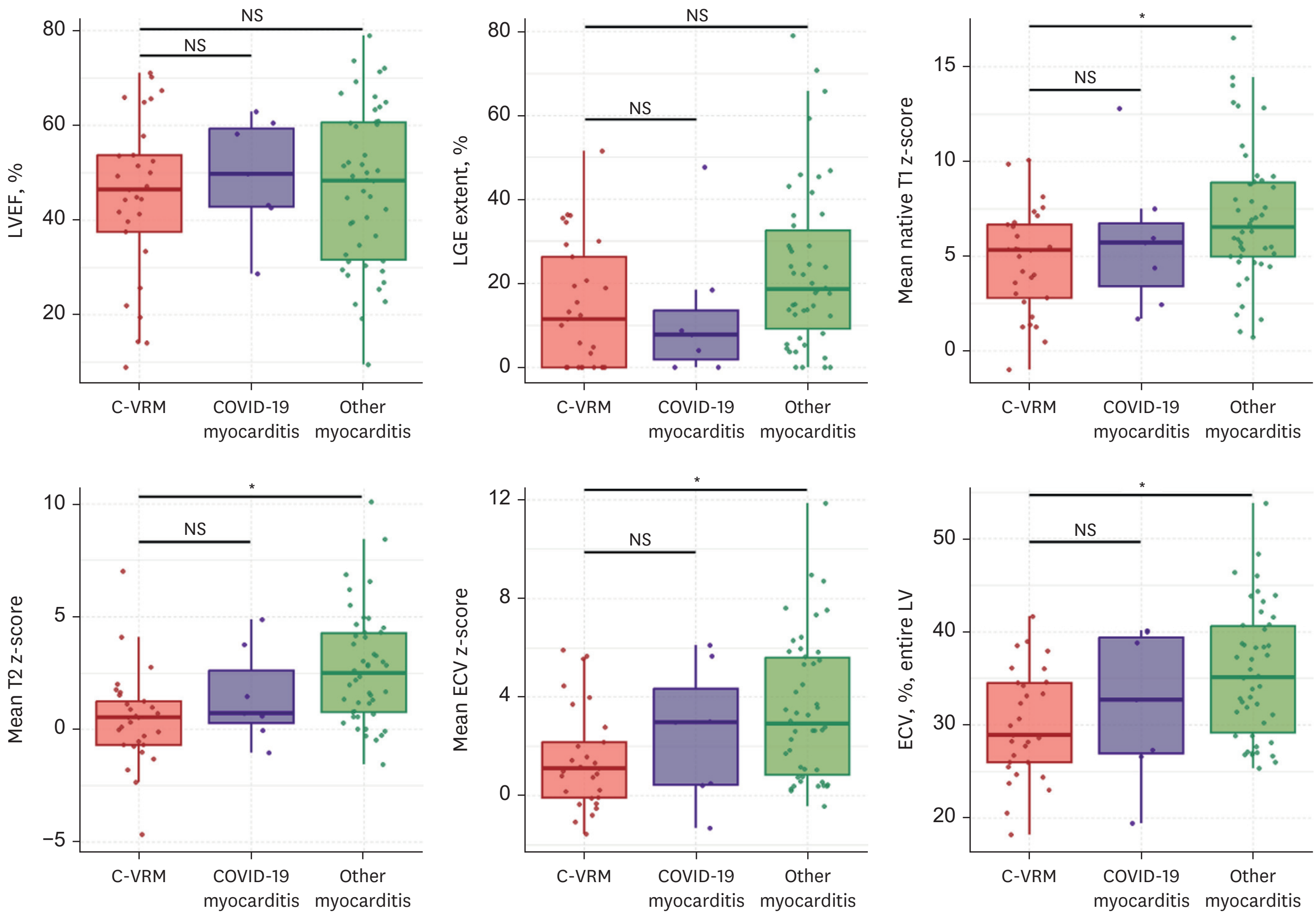

Fig. 4. Box plots show LVEF, LGE extent, native T1, T2, and ECV according to myocarditis group.
LVEF = left ventricular ejection fraction, C-VRM = coronavirus disease 2019 vaccine-related myocarditis, COVID-19 = coronavirus disease 2019, LGE = late gadolinium enhancement, ECV = extracellular volume, NS = not significant.
**P* < 0.05; statistically significant.

myocarditis type, with other myocarditis having the highest frequency ($P = 0.046$). These group-wise differences in functional parameters and myocardial tissue characteristics are visually summarized in **Fig. 4**.

Comparison of C-VRM with COVID-19 myocarditis and other myocarditis

Using linear regression with C-VRM as the reference group and adjusting for age, sex, and time from symptom onset to CMR, patients with other myocarditis showed significantly higher native T1 ($\beta = 77.48$, $P = 0.001$), T2 ($\beta = 3.73$, $P = 0.022$), and ECV ($\beta = 5.3$, $P = 0.001$) (**Table 3**). There were no significant differences in the CMR parameters between the C-VRM and COVID-19 myocarditis groups. No significant differences were found in the initial or follow-up LVEF values. Regional mapping values showed similar results (**Supplementary Table 2**).

Clinical follow-up

Clinical follow-up was performed for a median duration of 537 days (Q1–Q3, 233–768 days). The median follow-up durations for the myocarditis subtypes were 445, 488, and 641 days for C-VRM, COVID-19 myocarditis, and other myocarditis, respectively. Follow-up LVEF data were available for 74 patients. Among these, an LVEF < 40% at follow-up was observed in

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Table 3. Univariable and multivariable linear regression analyses of imaging parameters with C-VRM as the reference group

Parameters	Univariable model				Multivariable model (adjusted with age, sex, and time from symptom onset to CMR)			
	COVID-19 myocarditis		Other myocarditis		COVID-19 myocarditis		Other myocarditis	
	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value
Initial LVEF, %	4.58 (−9.46, 18.61)	0.518	2.07 (−5.84, 9.97)	0.604	2.70 (−11.12, 16.52)	0.698	1.45 (−6.64, 9.55)	0.721
Follow-up LVEF, %	−0.05 (−0.16, 0.07)	0.402	0.02 (−0.05, 0.09)	0.582	−7.45 (−18.88, 3.98)	0.198	2.77 (−4.01, 9.54)	0.418
Native T1, ms	35.76 (−46.64, 118.16)	0.390	85.78 (39.38, 132.17)	**< 0.001**	25.33 (−52.24, 102.91)	0.517	77.48 (32.04, 122.93)	**0.001**
Maximum native T1 z-score	1.25 (−1.89, 4.40)	0.430	3.33 (1.56, 5.10)	**< 0.001**	0.98 (−1.94, 3.90)	0.506	2.81 (1.10, 4.52)	**0.002**
Mean native T1 z-score	1.05 (−1.74, 3.83)	0.457	2.37 (0.80, 3.94)	**0.004**	0.78 (−1.94, 3.50)	0.569	2.12 (0.52, 3.71)	**0.010**
T2, ms	3.33 (−2.05, 8.72)	0.222	4.42 (1.39, 7.46)	**0.005**	3.26 (−2.15, 8.67)	0.234	3.73 (0.56, 6.90)	**0.022**
Maximum T2 z-score	1.05 (−2.33, 4.42)	0.539	3.38 (1.48, 5.28)	**0.001**	0.97 (−2.34, 4.27)	0.562	2.84 (0.90, 4.77)	**0.005**
Mean T2 z-score	1.00 (−0.94, 2.94)	0.308	2.24 (1.14, 3.33)	**< 0.001**	0.86 (−1.04, 2.77)	0.370	2.02 (0.91, 3.14)	**0.001**
ECV, %	2.06 (−3.55, 7.66)	0.467	5.47 (2.31, 8.62)	**0.001**	1.19 (−4.04, 6.41)	0.653	5.30 (2.24, 8.37)	**0.001**
Maximum ECV z-score	0.97 (−2.46, 4.41)	0.574	2.32 (0.38, 4.25)	**0.020**	0.80 (−2.63, 4.22)	0.644	1.95 (−0.05, 3.96)	0.056
Mean ECV z-score	1.00 (−1.19, 3.18)	0.367	2.01 (0.78, 3.24)	**0.002**	0.68 (−1.41, 2.78)	0.516	1.88 (0.65, 3.10)	**0.003**
LGE extent (%), > 5SD	−2.03 (−15.78, 11.72)	0.797	6.97 (−0.77, 14.71)	**0.034**	−0.35 (−15.55, 14.86)	0.964	7.56 (−1.35, 16.47)	0.095

Linear regression was used to evaluate the relationship between continuous magnetic resonance imaging parameters and patient groups. Multivariable models were adjusted for age, sex, and time from symptom onset to CMR. The β coefficient represents the estimated mean difference relative to the reference group (C-VRM). Bold indicates statistical significance.
C-VRM = coronavirus disease 2019 vaccine-related myocarditis, CMR = cardiac magnetic resonance, COVID-19 = coronavirus disease 2019, CI = confidence interval, LVEF = left ventricular ejection fraction, ECV = extracellular volume, LGE = late gadolinium enhancement, SD = standard deviation.

seven patients (9.5%): two with C-VRM (8%), one with COVID-19 myocarditis (14.3%), and four with other myocarditis (9.5%) (P = 0.715). The proportion of patients with LVEF > 50% at follow-up were 72% for C-VRM, 71.4% for COVID-19 myocarditis, and 90.5% for other myocarditis. Two deaths occurred during follow-up: one in the COVID-19 myocarditis group (due to cerebral infarction and hemorrhage related to an intracardiac thrombus) and one in the other myocarditis group (due to progressive myocarditis). Both patients had an LVEF < 40% at follow-up.

Predictors of adverse outcomes

In the univariable analysis, older age (odds ratio [OR], 1.050; 95% confidence interval [CI], 1.002–1.100; P = 0.040), low initial LVEF (OR, 0.916; 95% CI, 0.861–0.975; P = 0.006), higher maximum ECV z-score (OR, 1.246; 95% CI, 1.047–1.483; P = 0.013), and large LGE extent (OR, 1.085; 95% CI, 1.032–1.141; P = 0.001) were significantly related to adverse outcomes (**Table 4**, **Supplementary Table 3**). In multivariable analysis, both a higher maximum ECV z-score (OR, 1.457; 95% CI, 1.062–1.998; P = 0.020) and increased LGE extent (OR, 1.109; 95% CI, 1.029–1.194; P = 0.007) remained significant predictors of adverse outcomes after adjusting for age and initial LVEF.

DISCUSSION

In this Korean multicenter study, C-VRM exhibited lower native T1, ECV, and T2 values on CMR than other types of myocarditis, indicating milder myocardial injury. However, this interpretation should be viewed with caution due to potential selection bias and variability in CMR timing. In the outcome analysis, older age, lower initial LVEF, higher ECV, and greater LGE extent were independent predictors of adverse outcomes, whereas the type of myocarditis itself was not. These findings suggest that disease severity, rather than etiology, is the primary determinant of prognosis. Importantly, the ECV and LGE extent remained significant predictors even after adjusting for age and initial LVEF, suggesting the importance of CMR-based tissue characterization for prognostic prediction in patients with myocarditis.

Table 4. Univariable and multivariable logistic regression analyses of predictors of adverse outcomes in patients with follow-up LVEF (N = 74)

Variables	Univariable analysis		Multivariable analysis			
			Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, per yr	1.050 (1.002–1.100)	**0.040**	1.093 (1.009–1.184)	**0.030**	1.054 (0.983–1.130)	0.138
Sex (female as reference)	0.388 (0.070–2.143)	0.278				
Underlying disease						
Hypertension	2.391 (0.483–11.827)	0.285				
Diabetes	6.429 (1.187–34.814)	**0.031**				
Hyperlipidemia	2.067 (0.206–20.712)	0.537				
Coronary artery disease	4.833 (0.727–32.125)	0.103				
Cardiomyopathy	2.786 (0.557–13.923)	0.212				
Hear failure	2.551 (0.526–12.379)	0.245				
Family history of sudden death	0.292 (0.047–1.795)	0.292				
Myocarditis group						
C-VRM	Reference	-				
COVID-19 myocarditis	1.917 (0.148–24.871)	0.636				
Other myocarditis	1.211 (0.205–7.140)	0.873				
Initial LVEF, %	0.916 (0.861–0.975)	**0.006**	0.919 (0.858–0.985)	**0.016**	0.911 (0.842–0.987)	**0.022**
Native T1, ms	1.003 (0.996–1.010)	0.395				
Maximum native T1 z-score	1.069 (0.885–1.290)	0.488				
Mean native T1 z-score	1.054 (0.848–1.310)	0.636				
T2, ms	0.968 (0.849–1.104)	0.628				
Maximum T2 z-score	1.149 (0.996–1.326)	0.056				
Mean T2 z-score	1.030 (0.765–1.388)	0.845				
ECV, %	1.064 (0.956–1.185)	0.254				
Maximum ECV z-score	1.246 (1.047–1.483)	**0.013**	1.457 (1.062–1.998)	**0.020**		
Mean ECV z-score	1.215 (0.939–1.574)	0.139				
LGE extent (%), > 5SD	1.085 (1.032–1.141)	**0.001**			1.109 (1.029–1.194)	**0.007**

Bold indicates statistical significance. ORs were not estimated for atrial fibrillation, valvular heart disease, follow-up LVEF, and LGE presence due to complete separation or model non-convergence. In the multivariable analysis, Model 1 included age, initial LVEF, and ECV; Model 2 included age, initial LVEF, and LGE extent.
OR = odds ratio, CI = confidence interval, C-VRM = coronavirus disease 2019 vaccine-related myocarditis, COVID-19 = coronavirus disease 2019, LVEF = left ventricular ejection fraction, ECV = extracellular volume, LGE = late gadolinium enhancement, SD = standard deviation.

Previous studies have reported that C-VRM predominantly occurs in young men.[15] However, in this study, the mean age of C-VRM patients was 40.9 years, with 44.8% being female, aligning with recent Korean research that identified an older patient population and a weaker male predominance in VRM cases.[8] Moreover, a recent Korean nationwide study has shown that C-VRM is not confined to young men, but can also occur in broader clinical populations, including cancer patients.[16] These demographic differences highlight the importance of conducting population-specific analyses to better understand the characteristics and risks associated with C-VRM.

Although C-VRM is often regarded as having a favorable short-term prognosis,[5,6,17,18] only 72% of patients with C-VRM with follow-up data in our cohort achieved an LVEF > 50%. This aligns with recent studies reporting that 76% of C-VRM cases required emergency care or hospitalization,[19] and that unfavorable outcomes, including deaths, have been observed in some cases.[9,20] A Korean nationwide cohort study also reported that 19.8% of C-VRM cases were severe, including cases of intensive care unit admissions, fulminant myocarditis, extracorporeal membrane oxygenation, deaths including sudden cardiac death, and heart transplantation.[8] These findings suggest that C-VRM represents a broad clinical spectrum, ranging from mild to life-threatening presentations. Although the CMR findings in our study indicated mild myocardial injury and edema, severe or fulminant cases may have been underrepresented due to the exclusion of hemodynamically unstable patients who could not undergo CMR. In addition, variability in imaging timing may have influenced the degree of tissue abnormality observed.

A previous single-center study reported that C-VRM is characterized by higher LVEF, less extensive LGE, and lower native T1 compared to other myocarditis types, while ECV was not assessed.[10] Similarly, a Korean CMR study involving 39 patients found that native T1 and T2 values tended to be lower in C-VRM compared to other myocarditis, but the differences were not statistically significant.[21] Building upon these findings, our multicenter study demonstrated significant differences in native T1, T2, and ECV values between C-VRM and other myocarditis. These differences remained significant even after adjusting for age, sex, and the interval between symptom onset and CMR. Nevertheless, this should be interpreted with caution because of potential selection bias. We found no significant differences in the functional or volumetric parameters, emphasizing the greater diagnostic utility of myocardial tissue characterization than that of functional assessment in differentiating myocarditis subtypes. Notably, the cardiac enzyme levels in the COVID-19 myocarditis group were lower than those in the C-VRM group. This may be attributed to the small number of COVID-19 myocarditis cases and missing laboratory values, which led to a limited subset of patients being analyzed. Given the variability in myocardial injury patterns associated with COVID-19, larger studies with more comprehensive data collection are required to clarify the true differences in cardiac biomarker levels between these groups.

In this study, older age, lower initial LVEF, higher ECV, and a greater extent of LGE were identified as independent predictors of adverse outcomes. However, the type of myocarditis was not significantly associated with prognosis. These findings imply that disease severity, rather than myocarditis type, drives outcomes. Among Korean patients, who demonstrate a weaker young male predominance and a higher frequency of severe cases than Western populations,[8] CMR-based assessments may be particularly important. Both LGE extent and ECV have emerged as important prognostic markers; however, LGE quantification is influenced by protocol variations and requires subjective assessment. In contrast, ECV provides an absolute and reproducible quantitative value, supporting its potential to enhance objectivity and enable automated prognostic assessment in myocarditis.[22] Furthermore, in our multicenter setting involving diverse scanners and imaging protocols, ECV remained a consistent prognostic biomarker. This suggests that ECV may serve as a reliable and generalizable biomarker for risk stratification in patients with myocarditis, both in real-world practice and in multicenter studies.

This study had several limitations. First, its retrospective design and relatively small sample size may have introduced bias and limited the statistical power, particularly for subgroup comparisons. Second, selection bias was possible, because only patients who underwent CMR for suspected myocarditis and met the updated Lake Louise Criteria were included. Patients with severe or fulminant myocarditis may have been excluded because of the challenges of performing CMR in unstable individuals. Third, the timing of CMR imaging was not standardized relative to symptom onset, which may have influenced tissue characterization. To address this, we included the interval from symptom onset to CMR as a covariate in the multivariable linear regression. Fourth, inter-institutional variability in scanner models and contrast agents, including the use of contrast media with different relaxivities, may have affected the image parameters, particularly in LGE and post-contrast T1 mapping. To mitigate this, z-score standardization and threshold-based LGE quantification were applied across centers. However, the residual variability cannot be completely excluded. Finally, although the CMR-based parameters showed prognostic associations in our analysis, the study was not designed to determine the true prognosis, mortality, or long-term outcomes of myocarditis. Therefore, these associations should be interpreted within the limited context of CMR findings, and prospective studies with broader inclusion and standardized imaging protocols are needed to validate our results.

In conclusion, C-VRM in this Korean multicenter cohort demonstrated lower T1, ECV, and T2 values than other types of myocarditis. However, these imaging differences should be interpreted with caution given the potential selection bias and variability in imaging timing. Our findings suggest that disease severity, rather than the myocarditis type, is the primary determinant of prognosis. CMR-based tissue characterization, particularly LGE and ECV, serves as a crucial prognostic tool, regardless of the myocarditis type.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Definitions of underlying clinical conditions

Supplementary Data 2

CMR scanners and acquisition protocol

Supplementary Table 1

Regional mapping values of myocarditis

Supplementary Table 2

Linear regression of regional mapping values, with COVID-19 vaccine-related myocarditis as the reference group

Supplementary Table 3

Univariable logistic regression analysis of regional mapping values for predicting adverse outcomes in patients with follow-up left ventricular ejection fraction (N = 74)

Supplementary Fig. 1

Distribution of included myocarditis cases by etiology and study period.

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