

Late gadolinium enhancement pattern is not associated with ventricular arrhythmia event in non-ischemic cardiomyopathy

El patrón de realce tardío con gadolinio no se asocia con la presencia de arritmias ventriculares en la cardiomiopatía no isquémica

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Resumen

Arrhythmia is a leading cause of sudden cardiac arrest and a major cause of mortality in non-ischemic cardiomyopathy (NICM). The late gadolinium enhancement (LGE) pattern reveals myocardial fibrosis as an arrhythmogenic focus in cardiac magnetic resonance (CMR) imaging. This study aims to analyze the association between LGE patterns and baseline characteristics of subjects with the incidence of ventricular arrhythmias (VA) in NICM. Using a cross-sectional approach, this study is an analytical observational study involving 105 eligible outpatient patients from the cardiovascular clinic at RSUP Dr. Hasan Sadikin, Bandung. The researchers conducted bivariate analysis with Unpaired T-Test, Chi-Square, and Mann-Whitney tests using the Statistical Program for Social Science (SPSS) software. Ventricular arrhythmias occurred in 50.5% of subjects with NICM. The most common LGE patterns were mid-wall (52.4%), patchy (25.7%), and subepicardial (22.9%). The primary outcome of the study indicated no association between various LGE patterns and the incidence of VA in patients with NICM ($p > 0.05$). The secondary outcomes revealed an association between age ($p = 0.006$) and older female patients ($p = 0.043$) with the incidence of VA in NICM. There is no association between LGE patterns and the incidence of VA in NICM; however, age has a significant relationship with the occurrence of these arrhythmias.

Keywords: late gadolinium enhancement, non-ischemic cardiomyopathy, ventricular arrhythmias.

Resumen

La arritmia es una de las principales causas de paro cardíaco súbito y una de las principales causas de mortalidad en la miocardiopatía no isquémica (MNI). El patrón de realce tardío con gadolinio (RTG) revela fibrosis miocárdica como foco arritmogénico en la resonancia magnética cardíaca (RMC). Este estudio tiene como objetivo analizar la asociación entre los patrones de RTG y las características basales de los sujetos con la incidencia de arritmias ventriculares (AV) en la MNI. Mediante un enfoque transversal, este estudio observacional analítico incluyó a 105 pacientes ambulatorios elegibles de la clínica cardiovascular del Hospital Universitario Dr. Hasan Sadikin de Bandung. Los investigadores realizaron un análisis bivariado con la prueba t de Student para muestras independientes, la prueba de chi-cuadrado y la prueba U de Mann-Whitney utilizando el software SPSS (Statistical Program for Social Sciences). Se observaron arritmias ventriculares en el 50,5% de los sujetos con miocardiopatía no isquémica (MNI). Los patrones de realce tardío de gadolinio (RTG) más comunes fueron el de pared media (52,4%), el parcheado (25,7%) y el subepicárdico (22,9%). El resultado primario del estudio no mostró asociación entre los distintos patrones de RTG y la incidencia de arritmias ventriculares en pacientes con MNI ($p > 0,05$). Los resultados secundarios revelaron una asociación entre la edad ($p = 0,006$) y la edad avanzada ($p = 0,043$) con la incidencia de arritmias ventriculares en la MNI. No se encontró asociación entre los patrones de RTG y la incidencia de arritmias ventriculares en la MNI; sin embargo, la edad

sí mostró una relación significativa con la aparición de estas arritmias.

Palabras clave: realce tardío de gadolinio, miocardiopatía no isquémica, arritmias ventriculares.

Cardiomyopathy is a heterogeneous myocardial disorder associated with mechanical and/or electrical dysfunction, characterized by ventricular hypertrophy or dilation due to various etiologies. Non-ischemic cardiomyopathy (NICM) is caused by a range of etiologies without involvement of coronary artery disease or myocardial ischemic injury¹. (Wang et al., 2023) The global prevalence of NICM from 2005 to 2015 was 2.5 million cases, with a 3-year mortality rate due to heart failure and ventricular arrhythmias ranging from approximately 12% to 20%²⁻⁹.

Ventricular arrhythmia (VA) is a cardiac rhythm disorder caused by fibrosis in the ventricular myocardial wall, which serves as an arrhythmogenic substrate leading to disturbances in cardiac electrical conduction. The mortality rate due to arrhythmias in NICM is 8 per 100,000 patients¹⁰. Previous studies have indicated an increased risk of mortality due to heart failure associated with VA in NICM^{2,4,11-13}.

There are various diagnostic tests for myocardial fibrosis, with endocardial-myocardial biopsy considered the gold standard. Cardiac magnetic resonance (CMR) imaging, particularly with late gadolinium enhancement (LGE) patterns, is one of the main non-invasive imaging modalities for diagnosing myocardial fibrosis. Several previous studies have explored the relationship between LGE patterns and the incidence of arrhythmias in patients with cardiomyopathy¹⁴⁻²⁶.

Controversies and differences in results have been observed in several previous studies regarding the relationship between LGE patterns and the incidence of VA in cardiomyopathy^{27,28}. No similar studies have been conducted in the Indonesian population. This study aims to assess the association between LGE patterns on CMR imaging and the incidence of VA in patients with NICM.

Design and Setting

This study is an analytical observational study with a cross-sectional approach involving outpatient patients from the cardiovascular clinic at RSUP Dr. Hasan Sadikin Bandung, recorded from January 2021 to September 2023.

Study Population

The inclusion criteria for this study are all subjects aged 18 years and older with a diagnosis of NICM, based on the guidelines of the World Health Organization/International Society and Federation of Cardiology, with various underlying causes¹ Subjects with a family history of cardiomyopathy, electrolyte imbalances, and incomplete medical records were excluded. A total of 105 subjects who met the eligibility criteria and had complete medical records were included in the study.

Data Collection

Data collection was conducted after obtaining ethical approval from the Ethics Committee of RSUP Dr. Hasan Sadikin, Bandung. Secondary data on demographics, clinical information, laboratory blood tests, electrocardiography (ECG), echocardiography, and CMR were obtained from the outpatient medical records of RSUP Dr. Hasan Sadikin, Bandung. Age was calculated from the start of the study based on the date of birth. Data recording included comorbidities (hypertension and diabetes mellitus), medication history, and ejection fraction from echocardiography as documented in the medical records. The severity of chronic heart failure was classified according to the New York Heart Association (NYHA) functional classification. (McDonagh et al., 2021) Ventricular arrhythmias are any abnormalities in heart rhythm recorded on an ECG, including premature ventricular contractions (PVCs), non-sustained ventricular tachycardia (NSVT), sustained monomorphic ventricular tachycardia (SMVT), and polymorphic ventricular tachycardia or ventricular fibrillation (VF)²⁹. The LGE patterns observed on CMR imaging using the Siemens Skyra 3.5 T scanner include mid-wall, subepicardial, subendocardial, intramyocardial, patchy, and transmural patterns³⁰⁻³³.

Statistical Analysis

Basic characteristic data were described using percentages, standard deviations (SD), and median values through univariate analysis. The primary outcome of the study was to assess the association between LGE patterns, while the secondary outcome focused on the association between baseline characteristics of subjects and the incidence of VA in NICM patients. Bivariate analysis was performed using Unpaired T-Test, Chi-Square, and Mann-Whitney tests with the Statistical Program for Social Science (SPSS) version 23.0 to obtain prevalence ratios (PR) with 95% confidence intervals (CI), where a p-value <0.05 was considered statistically significant.

Analysis was performed on 105 outpatient patients from the cardiovascular clinic at RSUP Dr. Hasan Sadikin, Bandung, who met the eligibility criteria. (**Figure 1**) The mean age of the subjects was 47 ± 15 years, with 58.1% being female. Approximately 38% of the subjects had comorbid hypertension, while only 7.6% had diabetes mellitus (DM). The most commonly used medications were angiotensin-converting enzyme inhibitors (ACEIs) (88.6%) and beta-blockers (80.0%). The majority of the subjects with chronic heart failure were classified as NYHA functional class II (57.1%). The mid-wall LGE pattern (52.4%) was the most frequently observed compared to other patterns. The baseline characteristics of the study subjects are presented in **Table 1**.

Figure 1. Flow of Research Subject

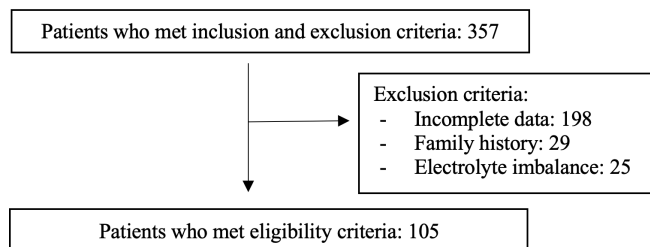


Table 1. Baseline Characteristics

Characteristics	n=105
Ages (Years), Mean \pm Standard Deviation (SD)	47 \pm 15
Sex, n (%)	
Male	44 (41.9)
Female	61 (58.1)
Comorbid, n (%)	
Hypertension	38 (36.2)
Diabetes Mellitus Tipe 2	8 (7.6)
Treatment, n (%)	
SGLT2	23 (21.9)
Mineralocorticoid antagonist receptor	58 (55.2)
Beta blocker	93 (88.6)
ACE inhibitor	84 (80.0)
NYHA Functional Class, n (%)	
Class I	10 (9.5)
Class II	60 (57.1)
Class III	23 (21.9)
Class IV	12 (11.4)
Left ventricular ejection fraction (%), median (min – max)	0.41 (0.16 – 0.78)
Ventricular Arrhythmia, n (%)	
Yes	53 (50.5)
No	52 (49.5)
Types of ventricular arrhythmia (n=53), n (%)	
Ventricular tachycardia	16 (30.2)
Frequent ventricular extrasystole	15 (28.3)
Infrequent ventricular extrasystole	22 (41.5)
LGE pattern, n (%)	
Midwall	55 (52.4)
Subepicardial	24 (22.9)
Subendocardial	14 (13.3)
Intramyocardial	23 (21.9)
Patchy	27 (25.7)
Transmural	7 (6.7)

Bivariate analysis between various LGE patterns and the incidence of ventricular arrhythmias in NICM did not show a significant association ($p > 0.05$). (**Table 2**) The mid-wall LGE pattern, which was the most frequently observed, also did not have an association with the incidence of ventricular arrhythmias ($p = 0.926$). The primary outcome of this study indicates that there is no association between the variables.

Table 2 Bivariate Association of LGE and Arrhythmia Event

	Event + (n=53)	Event - (n=52)	p-value
Midwall (n=55)	28 (50.9)	27 (49.1)	0.926
Non midwall (n=50)	25 (50.0)	25 (50.0)	

Note: Analyzed with *Chi Square* test, *significant value $p < 0.05$

The secondary outcome assessed the association between baseline characteristics of subjects and the incidence of VA in NICM (**Table 3**). There was a statistically significant association between age and the incidence of ventricular arrhythmias ($p = 0.006$). Subgroup analysis of mean age by gender revealed a significant association between older female patients and the occurrence of ventricular arrhythmias ($p = 0.043$).

Table 3 Association of LGE, Sex, and Arrhythmia Event

	Sex	Event +	Event -	p-value
Midwall	Male	16 (59.3)	11 (40.7)	0.242
	Female	12 (42.9)	16 (57.1)	0.363

Note: Analyzed with *Chi-Square* test, *significant value $p < 0.05$

The mid-wall LGE pattern was the most frequently observed in patients with cardiomyopathy in this study and others. This study found that the mid-wall LGE pattern was not associated with the incidence of VA in NICM ($p=0.926$). A similar study in Korea reported that 52.3% of patients with mid-wall LGE experienced arrhythmias, but this association was not statistically significant ($p=0.28$)²³. The studies by²⁶ (HR 10.22, CI 1.46–17.56, $p=0.02$) and²² Schiau et al. ($p=0.019$) reported differing results, showing a significant association between the mid-wall LGE pattern and the incidence of arrhythmias²². A study in the Netherlands demonstrated an association between mid-wall septal LGE and the incidence of VA in cases of ischemic cardiomyopathy (ICM) (HR 2.70, 95% CI 1.34 to 5.44, $p<0.01$) and dilated cardiomyopathy (DCM) (HR 2.80, 95% CI 1.34 to 5.87, $p<0.001$)²⁷. Other studies have demonstrated an association between the mid-wall LGE pattern and sudden cardiac death ($p=0.01$). However, that studies combined populations of ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) to evaluate both primary and secondary outcomes¹⁴. Analysis of other LGE patterns, such as subepicardial, subendocardial, patchy, and intramyocardial, did not show a significant association with ventricular arrhythmias in this study. However, another study in Korea found a significant association with the subepicardial pattern ($p = 0.008$)²⁵. That study did not assess the extent and location of LGE formation, unlike previous studies^{27,34}.

The relationship between the mid-wall LGE pattern and the incidence of ventricular arrhythmias remains controversial, as indicated by several previous studies and this study. A possible differentiating factor could be the differing subject populations. Both the study by²³ and this study involved Asian populations²³. The Multi-Ethnic Study of Atherosclerosis (MESA) found that Hispanic and Asian races have a lower risk of myocardial scarring compared to African and Caucasian races. However, further research is lacking in this area. (Turkhey et al., 2015) No further research has been conducted on the relationship between racial differences and the incidence of arrhythmias in NICM. There is a need for larger and more diverse populations to study LGE patterns across various racial groups worldwide and their association with arrhythmias in NICM.

Another quantitative measure for assessing myocardial fibrosis is the calculation of extracellular volume (ECV) on CMR. Previous studies have shown that a 1% increase in ECV can raise the risk of ventricular arrhythmias by up to 12%, and an ECV value greater than 30% can increase the risk of ventricular arrhythmias up to six-fold³⁶⁻³⁸. This study did not assess or examine the rela-

tionship between ECV and the incidence of VA in NICM.

Several similar studies have reported baseline characteristics with average ages comparable to those in this study. A meta-analysis by³⁶ reported an average age of 49-66 years with a standard deviation of $\pm 12-15$ years, while the study by²³ reported an average age of 54 years with a standard deviation of ± 15 years. The study by²⁸ demonstrated a significant association between age and the incidence of VA ($p<0.001$). That study had similar age criteria, with subjects being over 18 years old, consistent with the criteria used in this study²⁸. The study in Korea did not show an association between age and the incidence of VA in NICM ($p=0.32$), similar to the findings in this study²³. In²⁴ also found no association between age and the incidence of VA in NICM ($p=0.643$). However, that study had a broader age range in the population, from 9 to 81 years. (Schiau et al., 2021) Further research with a larger and more diverse population is needed due to the differing results in several studies regarding the relationship between age characteristics and the incidence of VA in NICM.

Female subjects with VA had a higher average age (52 ± 15 years) compared to those without a history of arrhythmias in this study. Further subgroup analysis revealed a significant association between age and the incidence of VA in female subjects with NICM. No previous studies have evaluated the relationship between age and VA based on gender in NICM. A possible underlying theory is that women may have a higher risk of electrophysiological disturbances, such as long QT syndrome and Torsades de Pointes. Estrogen has cardioprotective effects; in premenopausal women, estrogen has been shown to have anti-hypertrophic effects and protection against myocardial necrosis, which may reduce arrhythmogenic substrate and thereby decrease the incidence of arrhythmias. Conversely, postmenopausal women may experience exacerbated cardiac function and chronic myocardial changes, potentially increasing their risk of arrhythmias^{39,40}. Further studies are needed to explore the relationship between age within each gender group and the incidence of VA in NICM.

The limitations of this study include the cross-sectional design, which does not allow for causal inferences regarding the relationship between age and LGE patterns with the incidence of VA in NICM. Additionally, as a single-center study, it may not fully represent a broader population. The similar findings in one analysis compared to other studies conducted in Asia suggest that further research is needed to examine these variables across different racial groups worldwide with more diverse subject populations. Furthermore, the study lacks data on the location and extent of LGE on CMR, limiting the analysis of these variables.

In conclusion, there is no association between various LGE patterns and the incidence of VA in NICM. However, age is related to the occurrence of ventricular arrhythmias in NICM, both across all subjects and specifically within the female subgroup.

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Disclosure

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Consent for Publication

The authors declare that this manuscript *is* original, *has not been published* before, and *is not* currently being considered for *publication*. All authors consent to the publication of this manuscript.

Ethics Approval

This study received approval from the Health Research Ethics Committee of Hasan Sadikin General Hospital (Letter number: LB.02.01/X.6.5/375/2023). Ethical approval for this research complies with the provisions of the Declaration of Helsinki

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