Prevalence and Prognostic Impact of Septal Late Gadolinium Enhancement in Acute Myocarditis With or Without Preserved Left Ventricular Function

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Prevalence and Prognostic Impact of Septal Late Gadolinium Enhancement in Acute Myocarditis with or without Preserved Left Ventricular Function

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Running title: **Septal Late Gadolinium Enhancement in Acute Myocarditis**

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Abstract (248 words)

Recent data suggest that myocardial septal late gadolinium enhancement (LGE) may have an independent prognostic value in patients with acute myocarditis undergoing cardiac magnetic resonance (CMR). Aim of the present paper is to evaluate its prevalence and prognostic implications in these patients with or without preserved LV function.

Retrospective cohort study including all cases of clinically suspected acute myocarditis referred for CMR. A diagnosis of acute myocarditis was confirmed by CMR according to Lake Louise Criteria. Cardiovascular mortality, heart failure, heart transplantation, and sustained ventricular arrhythmias were considered adverse events at follow-up.

Seventy-one patients were included in the present study (mean age 47 years 95% CI 42-51, 53 males; 75%). LVEF was preserved in 45 cases (63%) and pericardial effusion was detected in 26 cases (38%). CMR was performed at a mean time of 11 days (95% CI 7.5-14.4) from symptoms onset. Myocardial hyperemia and edema was detected in 53 cases (75%), myocardial LGE in 66 cases (93%). Septal LGE was reported in 21 cases (30%). After a mean follow-up of 60.8 months, the mean LVEF increased from 51.6±14.0% to 56.6±10.9% (p=0.021) and combined adverse events were only recorded in 4 patients (6%) with reduced basal LVEF. These patients had more commonly septal LGE (respectively 58%vs.13%,p<0.0001). However, on multivariable analysis septal LGE had no additional predictive value over reduced basal LVEF.

In conclusion our study suggests that septal LGE is not uncommon in patients with acute myocarditis but has no added prognostic value over reduced LVEF at presentation.

Key words: myocarditis; cardiac magnetic resonance; late gadolinium enhancement

In clinical practice, acute myocarditis has a spectrum of clinical presentation ranging from asymptomatic, infarct-like, arrhythmic course, heart failure, to sudden cardiac death.[1] Infarct-like presentations with preserved LV function seem to have the best outcomes without mortality and evolving LV dysfunction.[2,3] Cardiac magnetic resonance (CMR) is a well-established imaging tool for the non-invasive diagnosis of acute myocarditis providing evidence of myocardial hyperemia, edema and fibrosis.[4,5] In this setting, myocardial late gadolinium enhancement (LGE) may have prognostic implications.[2,3,6,7] Recent data have been published showing that septal LGE may be associated with a worse prognosis regardless of basal LVEF.[8] Aim of the present paper is to evaluate the prevalence and prognostic implications of septal LGE in unselected patients with acute myocarditis with or without preserved LV function.

Methods

Retrospective cohort study including all cases of clinically suspected acute myocarditis referred for CMR from January 2010 to June 2016 in our center (referral center for myopericardial diseases in Torino, Italy). All patients were evaluated by echocardiography and CMR. In cases with an initial suspicion of an acute coronary syndrome, coronary angiography was performed before additional assessments. CMR studies were performed with a 1.5 Tesla GE scan.

A diagnosis of acute myocarditis was confirmed by CMR according to Lake Louise Criteria with presence of at least 2 of 3 CMR criteria including: (1) myocardial hyperemia, (2) myocardial edema in STIR-T2-weighted imaging, and (3) myocardial LGE.[9]

Baseline data were recorded including type of presentation, markers of inflammation and myocardial lesion, LV function, and CMR data. The following events were

considered as adverse events during follow-up: cardiovascular mortality, heart failure, heart transplantation, and sustained ventricular arrhythmias.

A structured clinical follow-up was performed at 6 months and then every year.

Continuous data are reported as mean and 95% CI. Patients subgroups were compared by use of the t test for continuous variables and Fisher's exact test for categorical variables as appropriate. Time to event distributions were estimated with the Kaplan-Meier method and compared by use of the log-rank test. A value of $p<0.05$ was considered to show statistical significance. Analyses were performed by MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Results

Seventy-one patients were eligible to be included in the present study. The mean age was 47 years (95% CI 42-51), with 53 males (75%). The following clinical presentations were recorded: infarct-like in 47 cases (66%), heart failure in 18 cases (25%), sustained arrhythmias in 6 cases (9%), with 1 case as resuscitated sudden cardiac death due to ventricular fibrillation during exertion (1%). LVEF was preserved in 45 cases (63%) and pericardial effusion was detected in 26 cases (38%) on basal echocardiography.

CMR was performed at a mean time of 11 days (95% CI 7.5-14.4) from symptoms onset. Myocardial hyperemia and edema were detected in 53 cases (74%), myocardial LGE in 66 cases (93%). Septal LGE was found in 21 cases (30%), while lateral LGE was detected in 58 cases (83%) (Figure 1).

Data on relevant medical therapy according to basal LVEF are reported in table 1. After a mean follow-up of 60.8 months (95% CI 55.9-65.6), the overall mean LVEF increased from 51.6 ± 14.0% to 56.6 ± 10.9% (p=0.021; Figure 2) and adverse events were 3

cases of heart failure (4%), and 1 case of sustained ventricular arrhythmia terminated by an ICD (1%). All adverse events were recorded in patients with reduced basal LVEF, but only 2 of them had also septal LGE (Table 1 and 2). Table 1 summarizes the main clinical features of patients with and without reduced LVEF at presentation, while table 2 summarizes main clinical features in patients with and without septal LGE.

Patients with a reduced basal LVEF, but not only septal LGE, has a worse event-free survival compared with those with a preserved LVEF at presentation (see Figure 3 and 4). The presence of septal LGE is more common in patients with a reduced baseline LVEF: respectively in 15/26 (58%) vs. 6/45 (13%, $p<0.0001$; see also table 1). However, on multivariable analysis (including age, gender, clinical presentation, LVEF<50% and septal LGE), it has no additional predictive value over reduced basal LVEF.

Discussion

The main findings of this study are that overall event rate is low after acute myocarditis and is restricted to those with reduced LVEF at baseline (LVEF<50%). Infarct-like presentation is the most common type of presentation in acute myocarditis and is associated with preserved LVEF and good prognosis without adverse events. Adverse events are confined to patients with a non-infarct like presentation (e.g. heart failure and sustained arrhythmias) and reduced LVEF. Myocardial septal LGE is more common in patients with reduced LVEF but is not an independent prognostic marker in these patients. This study supports the concept that reduced LVEF at baseline is the major prognostic determinant in such patients.

Previous studies on patients with acute myocarditis have demonstrated that major types of clinical presentations in myocarditis include infarct-like myocarditis, heart failure and sustained arrhythmias. Preserved LVEF is usually associated with infarct-

like myocarditis, and the cardiac transplantation (tx) free-survival is better in such patients with no need for cardiac tx compared with patients with myocarditis and arrhythmias, who have an intermediate prognosis and patients with heart failure, who have the worst prognosis.[2,3] A recent Italian study has retrospectively evaluated 386 patients with acute myocarditis and preserved LVEF.[8] A clinical combined endpoint of cardiac death, appropriate implantable cardioverter-defibrillator firing, resuscitated cardiac arrest, and hospitalization for heart failure was considered. Septal LGE was recorded in 135 cases (36%) and was associated with a worse prognosis also in patients with preserved LV function. After a mean follow-up of 52 months, the authors reported 4 cases of SCD, 2 cases with appropriate ICD shocks and 15 hospitalizations for heart failure in patients with septal LGE.[8] The study had a retrospective design and we suppose that it is possible that some patients with dilated cardiomyopathy (DCM) and myocarditis were included. In the setting of DC, septal LGE has a well-established negative prognostic meaning. In agreement with other Italian studies,[2,3] our study confirms that patients with preserved LVEF have a good overall prognosis without SCD and need for ICD implantation after a mean follow-up of 60.8 months. In our study, septal LGE is associated with lower LVEF and greater LVEDVi but does not seem to be an independent prognostic marker from reduced LVEF.

We acknowledge possible study limitations related to the limited sample size, the selection of relatively stable group of patients able to perform a CMR study and the retrospective design. However also in previous studies, the design was retrospective and only stable patients able to perform CMR were selected. The strength of this paper is that represent a real life study of non-selected patients with acute myocarditis undergoing a CMR study within 2 weeks from symptoms onset and with or without reduced LVEF.

In conclusion, septal LGE is not uncommon in patients with acute myocarditis and reduced LVEF performing a CMR study, but does not seem to have an independent prognostic value compared with reduced LVEF. Most patients have an infarct-like presentation with preserved LVEF and a good prognosis without SCD, heart failure and need for cardiac tx or ICD implantation. The worse prognosis is confined in patients with reduced LVEF at presentation. However, it should be remarked that LVEF generally improves in those patients and that stable patients who are able to perform a CMR study have a low event rate even at long term follow-up.

Disclosures: None

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Figures legends

Figure 1. Examples of septal and lateral myocardial LGE in patients with acute myocarditis.

Figure 2. Comparison of baseline and final LVEF at the end of follow-up for each patient.

Figure 3. Event-free survival in patients with or without reduced LVEF (LVEF <50%).

Figure 4. Event-free survival of patients with or without septal LGE.

Table 1

Table 1. Comparison of main clinical features and follow-up data of patients with and without preserved LVEF at baseline.

Variable	LVEF		
	<50% (n= 26)	≥50% (n= 45)	p value
Age (years)	53.3 (46.5-60.2)	53.3 (46.5-60.2)	0.999
Male	21 (84%)	32 (70%)	0.256
Clinical presentation:			
(1) Infarct-like			
(2) Non-infarct-like	10 (39%)	37 (82%)	0.0003
	16 (62%)	8 (18%)	
Hs-troponin T (μg/L)	0.66 (0.13-1.20)	0.71 (0.40-1.04)	0.853
C-reactive protein (mg/L)	70.6 (33.9-107.3)	40.2 (26.5-53.8)	0.057
Pericardial effusion	6 (23%)	20 (44%)	0.190
LVEF (%)	36.4 (32.3-40.5)	60.4 (58.9-62.0)	<0.0001
LVEDVi* (ml/m2)	226.4 (201.0-251.8)	158.1 (147.8-168.4)	<0.001
LGE (%)	25 (96%)	41 (91%)	0.646
Number of involved LV segments	3.2 (1.7-4.7)	3.7 (2.9-4.5)	0.857
Septal LGE	15 (58%)	6 (13%)	<0.0001
Use of betablockers	26 (100%)	34 (76%)	0.0106
Use of ACEi/ ARB	22 (85%)	26 (58%)	0.0198
Use of antiarrhythmics	2 (8%)	4 (9%)	0.8859
IC	1 (4%)	1 (2%)	0.6210
Sotalol	0	2 (4%)	0.4713
Amiodarone	1 (4%)	1 (2%)	0.6210
Follow-up (months)	60.2 (52.4-68.0)	61.2 (54.8-67.6)	0.844
Combined adverse events*	4 (15%)	0	0.015
(1) CV mortality	0	0	
(2) Heart Failure	3 (12%)	0	
(3) Cardiac Tx	0	0	

(4) Arrhythmias°	1 (4%)	0

ACEi= ACE inhibitors/ ARB= Angiotensin II Receptor Blockers; *= cardiovascular mortality + heart failure + cardiac transplantation + sustained ventricular arrhythmias; °= sustained ventricular arrhythmias.

Table 2

Table 2. Comparison of main clinical features and follow-up data of patients with or without myocardial septal LGE at baseline.

Variable	Septal LGE		
	Yes (n= 21)	No (n= 50)	p value
Age (years)	56.2 (48.6-63.8)	43.2 (38.2-48.2)	0.0053
Male	17 (81%)	36 (72%)	0.556
Clinical presentation:			0.0273
(1) Infarct-like	10 (48%)	38 (76%)	
(2) Other	11 (52%)	12 (24%)	
Hs-troponin T (μg/L)	0.70 (0.17-1.22)	0.70 (0.37-1.03)	0.987
C-reactive protein (mg/L)	72.5 (34.0-111.0)	41.4 (26.6-56.2)	0.061
Pericardial effusion	8	18	0.999
LVEF (%)	39.6 (33.1-46.1)	57.0 (54.0-60.0)	<0.0001
LVEF<50%	15	10	<0.0001
LVEDVi* (ml/m2)	215.6 (181.8-249.0)	169.7 (157.8-181.6.0)	0.0015
LGE (%)	21	45	0.312
Number of involved LV segments	3.1 (1.9-4.3)	3.7 (2.8-4.6)	0.474
Follow-up (months)	64.6 (55.0-74.2)	59.2 (53.5-64.9)	0.306
Combined adverse events*	2 (10%)	2 (4%)	0.576
(3) CV mortality	0	0	
(4) Heart Failure	2 (10%)	1 (2%)	
(5) Cardiac Tx	0	0	
(6) Arrhythmias	0	1 (2%)	

Figure 1

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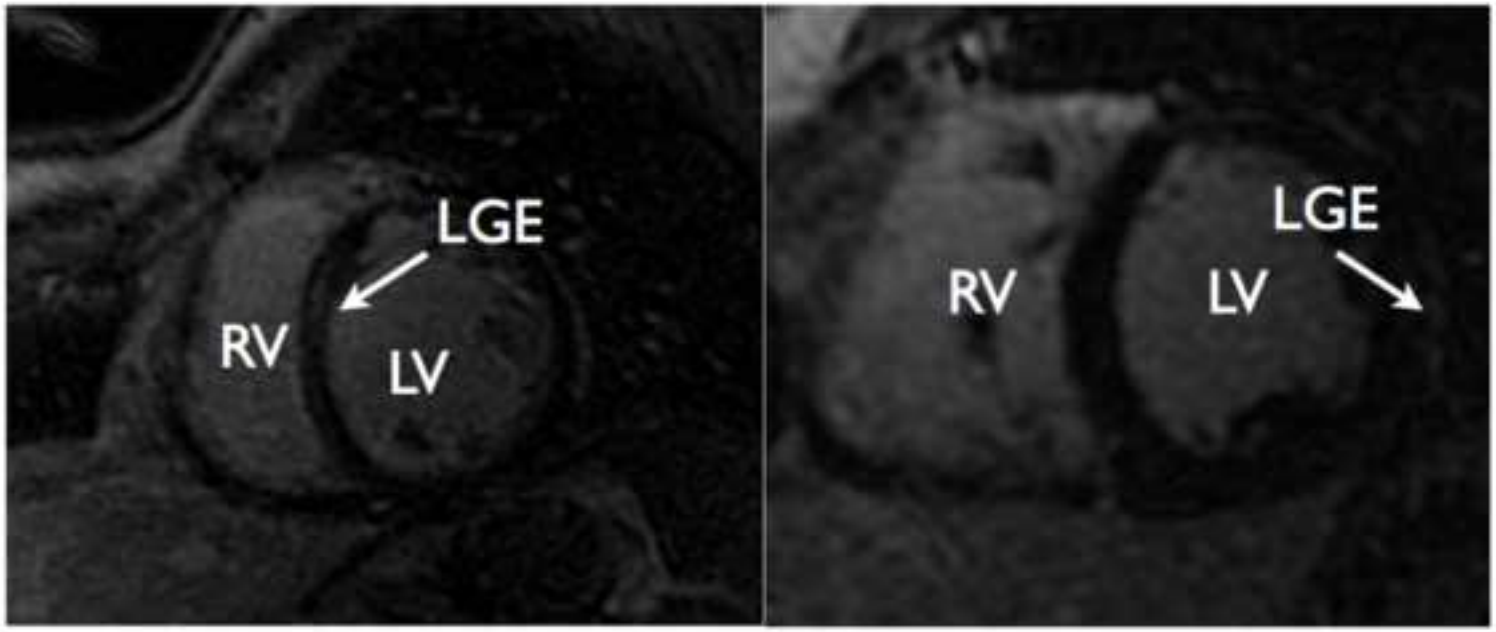

Septal LGE

Lateral LGE

Figure 2

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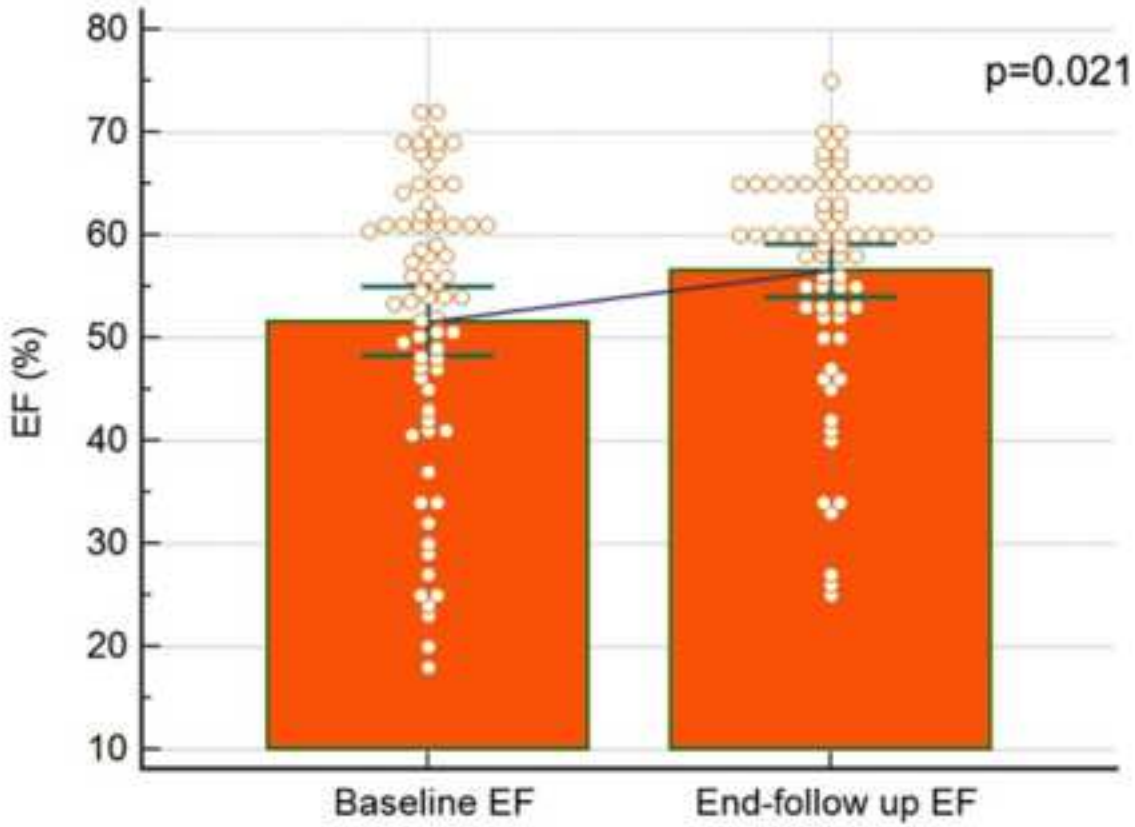

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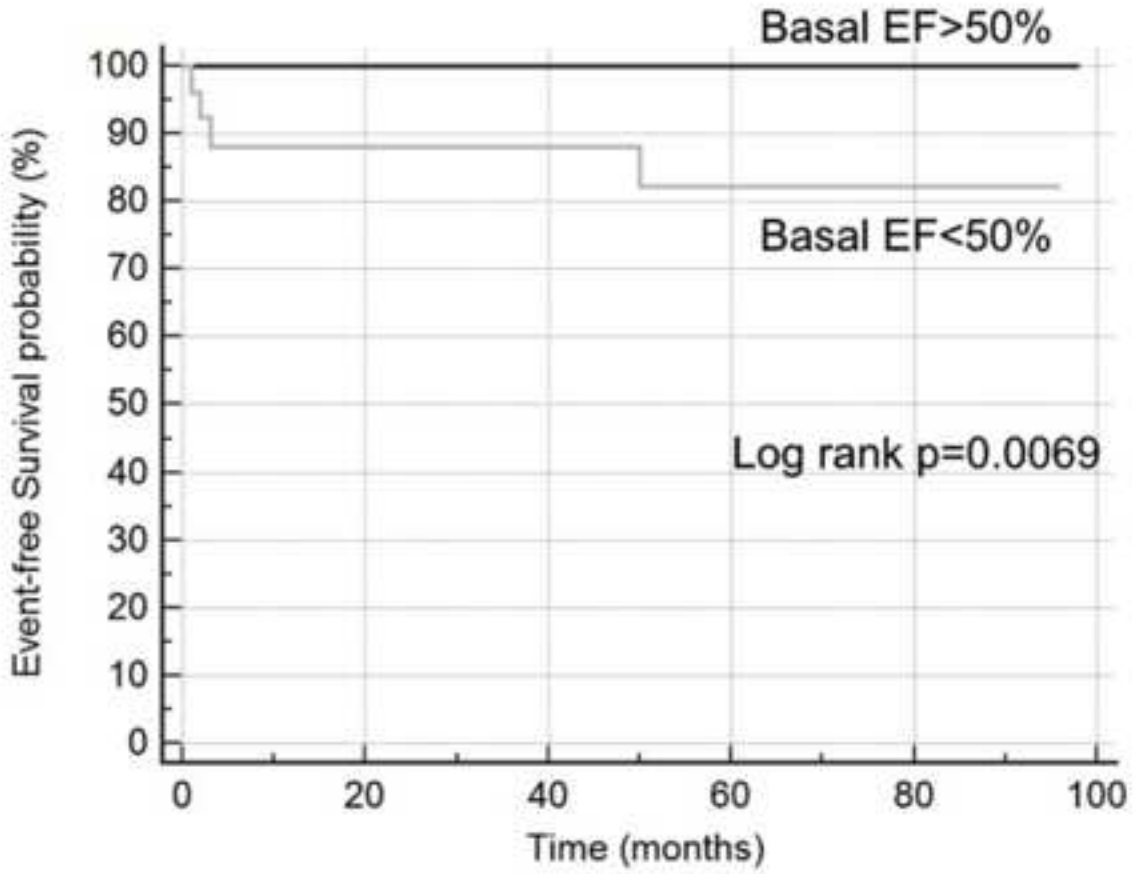

Figure 4

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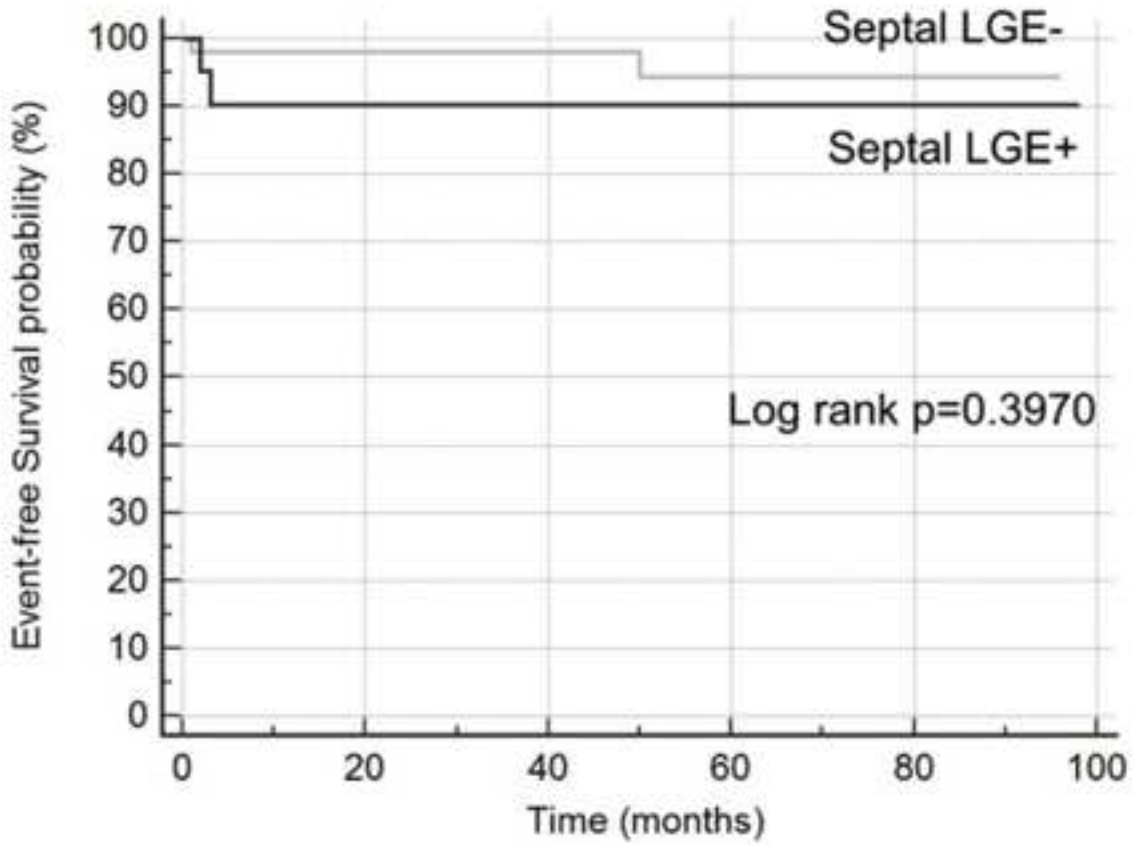

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