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ABSTRACT (242 words)

Objective. The electrocardiogram (ECG) has been traditionally used to support the diagnosis of acute pericarditis. However the pericardium is electrically silent and ECG changes may imply concomitant myocardial involvement rather than simple pericarditis. Aim of the present paper is to study the frequency, type, and clinical implications of ECG changes in patients with pericarditis.

Methods. Consecutive patients with pericarditis and myocarditis were included in a prospective cohort study from January 2017 to December 2020. A clinical and echocardiographic follow-up was performed at 1, 3, 6 months and then every 6 months. Cardiac magnetic resonance was used to rule out concomitant clinically suspected myocarditis.

Results. 166 patients (median age 47 years, 95% CI 44-51) with 66 males (39.8%) were included: 110 cases with pericarditis (mean age 47.7 years, 29.1% males), and 56 cases with myocarditis (mean age 44.8, 60.7% males) as control group. ECG changes were reported in 61 of 166 (36.7%) of patients: 24.5% of those with pericarditis and 60.7% of those with myocarditis ($p<0.0001$). In multivariable analysis, ECG changes were associated with male gender (OR 2.6 95% CI 1.28-5.42) and troponin elevation (OR 3.68 95% CI 1.77-7.65) suggesting myocardial involvement. ECG changes were not associated with a worse prognosis.

Conclusions. ECG changes can be recorded in about one quarter of patients with pericarditis, mainly widespread ST-segment elevation. These changes may reflect concomitant myocarditis, that should be ruled out. ECG changes are not associated with a worse prognosis in patients with pericarditis.

KEYWORDS: pericarditis; score; prognosis

Key questions

What is already known about this subject?

- In clinical practice current guidelines on the management of pericardial diseases suggest to use the electrocardiogram for the diagnosis of pericarditis.
- A limited number of patients with acute, and especially recurrent pericarditis, shows classical ECG changes during pericarditis.

What does this study add?

- In this study we evaluated the clinical meaning of ECG changes in the setting of pericarditis and myocarditis showing that ECG changes are features of myocardial involvement in most cases.
- ECG changes may be associated with myocardial involvement and do not carry necessarily a worse outcome.

How might this impact clinical practice?

- The presence of new ECG changes in the setting of clinically suspected pericarditis should prompt clinicians to rule out concomitant myocardial involvement by means of second level imaging (e.g. cardiac magnetic resonance).

INTRODUCTION

The electrocardiogram (ECG) has been traditionally used to support the diagnosis of acute pericarditis[1,2] and current international guidelines report ESC changes (especially new widespread ST elevation or PR depression) as a diagnostic criterion to be used for the clinical diagnosis of pericarditis.[3]

However, the pericardium is electrically silent and ECG changes may rise from the inflammation of the epicardium involving the adjacent myocardium and imply concomitant myocardial involvement rather than simple pericarditis. Aim of the present paper is to analyse the frequency, type, and clinical implication of ECG changes in patients with simple pericarditis compared to those with a diagnosis of myocarditis and to verify if ECG changes imply concomitant myocarditis rather than pericarditis.

METHODS

Study population. Consecutive patients with pericarditis and myocarditis were included in a prospective cohort study. Patients were recruited from January 2017 to December 2020 in a tertiary referral centre for pericardial diseases. The study was approved by the institutional review board (AOU Città della Salute e della Scienza di Torino), and participants gave written informed consent.

For the diagnosis of pericarditis, 2015 European Society of Cardiology (ESC) guidelines were followed.[3] Acute pericarditis was diagnosed with at least two out of the following criteria: (1) pericarditic chest pain, (2) pericardial friction rub, (3) electrocardiogram (ECG) changes with new widespread ST elevation or PR depression, and (4) new or worsening pericardial effusion. A clinical diagnosis of myocarditis was performed by clinical criteria plus confirmation by cardiac magnetic resonance and/or endomyocardial biopsy (EMB).[3,4] EMB was considered for complicated cases of myocarditis with heart failure, major ventricular arrhythmias or persistent troponin elevation and/or not responding to conventional medical

therapy according to international and national guidelines.[3,5] In patients with clinically suspected myocarditis and pericarditis with ST segment elevation, cardiac magnetic resonance (CMR) was performed to detect myocardial involvement by means of Lake Louise criteria for the diagnosis of myocarditis.[6]

Imaging studies. All patients had a comprehensive echocardiographic examination at presentation, after 1 week and during follow-up. CMR evaluations were performed on a 1.5 T magnetic resonance imaging scanner (multivendor scanners were included) as soon as possible after the onset of symptoms. All imaging was performed using commercially available software, electrographic triggering, and dedicated phased-array receiver coils. The CMR protocol included the detection of pericardial thickness on T1-weighted morphological imaging, myocardial and pericardial oedema/inflammation by STIR T2-weighted imaging and myocardial and pericardial late gadolinium enhancement (LGE). STIR T2-weighted and LGE images were obtained in the long- and short-axis orientations as the cine images. The LGE images were acquired 10 minutes after the intravenous injection of gadolinium contrast agent (0.1 to 0.2 mmol/kg body weight) using a phase-sensitive inversion recovery technique, and inversion time was selected for optimal nulling of the myocardium. A diagnosis of myocarditis by CMR was reached with at least 2 of 3 Lake Louise criteria using: early gadolinium enhancement (EGE) for the detection of myocardial hyperaemia, T2w images for the detection of myocardial oedema, and late gadolinium enhancement (LGE). The following CMR findings for pericarditis were considered: (1) pericardial thickening, (2) pericardial oedema by STIR-T2w imaging, (3) pericardial LGE, and (4) pericardial effusion. A diagnosis of pericarditis according to CMR was performed with at least 2 CMR criteria.[7] Pericardial thickness was considered normal with values< 3mm on CMR. For CMR studies two expert observers, blinded to clinical data and outcomes, analysed CMR studies offline. Interobserver and intraobserver reproducibility of assessment of pericardial oedema and LGE were excellent.

Follow-up. A clinical and echocardiographic follow-up was performed at 1, 3, 6 months and then every 6 months to assess the presence of clinical events and complications. We considered as major cardiac events (MACE): all-cause death, heart failure, recurrences of pericarditis or myocarditis, cardiac tamponade, and constrictive pericarditis.

Statistical Analysis. Continuous data were expressed as mean +/-SD or median and interquartile range ([IQR]) based on their distribution. Categorical data are presented as numbers and percentages. Comparisons between groups were performed using the t test, chi-square and Fisher's exact test, as appropriate. Multivariable analysis was performed to assess clinical features associated with ECG changes.

A survival analysis was performed in order to evaluate the effect of ECG changes on the risk of MACE during the follow up after the index episode. The Kaplan-Meier event-free survival curves of patients with pericarditis (with or without ECG changes) for combined adverse events were compared using the log-rank test. Data were censored at the time of the first event or last visit.

A probability value <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).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret

the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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RESULTS

Baseline data. Overall, we included 166 patients (median age 47 years, 95% CI 44-51) with 66 males (39.8%). Cases of clinically suspected pericarditis were 110 (mean age 47.7 years, 29.1% males), while cases of myocarditis were 56 (mean age 44.8, 60.7% males). Detailed clinical characteristics of the studied population are reported in table 1. Compared with pericarditis cases, patients with myocarditis were more commonly male (60.7% vs. 29.1%, p=0.0001), had more commonly ECG changes (60.7% vs. 24.5%, p<0.0001), elevation of troponin (80.4% vs. 0%, p<0.0001) and C-reactive protein (64.3% vs. 42.7%; p=0.0279), and reduced basal left ventricular ejection fraction (LVEF<50%; p=0.0213). Compared with myocarditis cases, patients with pericarditis had more commonly pericardial rubs (32.7% vs. 5.4%, p<0.0001) and pericardial effusion (65.5% vs. 46.4%; p=0.0288). The aetiology was similar in both subgroups of patients with pericarditis and myocarditis (see table 1).

Follow-up data. After a median follow-up of 21 months (95% CI 14-26), we recorded 67 major cardiac events (MACE) without mortality and heart failure (Table 2). The most common reported MACE was recurrence of pericarditis or myocarditis (67 events). Recurrences were more common among patients with pericarditis (50.0% vs. 21.4%; p=0.0006), while cardiac arrhythmias were more common in patients with myocarditis

(17.9% vs. 4.5%; p=0.0047). Cardiac arrhythmias were all supraventricular in patients with pericarditis, while non sustained ventricular arrhythmias were recorded only in patients with myocarditis (Table 2). Medical treatment of cases reflected current guidelines recommendations with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids, that were more commonly prescribed in patients with pericarditis, and betablockers in patients with myocarditis. Follow-up duration was similar in both groups.

ECG changes and its diagnostic and prognostic indications. ECG changes were reported in 61 of 166 (36.7%) of patients (Figure 1). Patients with ECG changes were younger (42.7 ± 16.6 vs. 49.1 ± 16.8; p=0.0181), more commonly male (59.0% vs. 28.6%; p=0.0001) and had more commonly C-reactive protein elevation (63.9% vs. 41.9%; p=0.0203) and troponin elevation (50.8% vs. 15.2%; p<0.0001). Patients with ECG changes had more commonly a clinical diagnosis of myocarditis (55.7% vs. 21.0%; p<0.0001) but few MACE during follow-up (29.5% vs. 46.7%; p=0.0303), due to the higher frequency of recurrences in patients with pericarditis. A detailed comparison of clinical features of patients with and without ECG changes is reported in table 2.

In multivariable analysis including age, gender and biomarkers, male gender (OR 2.6 95% CI 1.28-5.42) and troponin elevation (OR 3.68 95% CI 1.77-7.65) were independent predictors of ECG changes, suggesting that they are indicators of myocardial involvement.

ECG changes were reported in 27 of 110 cases of pericarditis (24.5%) but were not associated with a worse prognosis as assessed by Kaplan-Meier curves of survival from MACE (Figure 2, Log rank p=0.8732). Moreover the presence of myocarditis could be confirmed by CMR in 6 of 17 cases (35.0%) with pericarditis and ST-segment elevation on ECG at presentation (Figure 3) due to the limited diagnostic accuracy of CMR by standard diagnostic criteria to detect subtle degrees of myocardial involvement.

DISCUSSION

ECG changes (mainly widespread ST-segment elevation and PR depression as early or concomitant ECG sign) are considered a diagnostic criterion for the diagnosis of acute pericarditis[1,2] and mentioned in guidelines.[3] ECG changes derive from the inflammation of the epicardium and adjacent myocardium, because the pericardium is electrically silent. On this basis, many cases of pericarditis, especially in recurrences or in certain aetiologies, where serositis prevails on myocardial involvement, such as in uremic pericarditis, ECG changes are seen in less than 50-60% of patients, and patients may present atypical, subtle and non-diagnostic changes or even no changes at all.[8-10]

In this prospective cohort paper, we evaluated the presence of ECG changes in the setting of a sample of pericarditis, compared the clinical features with a control group with myocarditis, and assessed the diagnostic and prognostic implication of the finding of ECG changes in clinically suspected pericarditis.

We identified ECG changes in about one quarter of patients with pericarditis. The main reported ECG change in pericarditis was widespread ST-segment elevation (about 16% of unselected cases), followed by PR depression (about 5% of unselected cases). The majority of patients with a clinical diagnosis of pericarditis did not show any ECG change (about 76% of all cases). On the contrary, about 60% of patients with a clinical diagnosis of myocarditis showed some types of ECG changes. Patients with ECG changes are younger and especially males (about 60% of cases, OR 2.63) and had more commonly troponin elevation (OR 3.68) suggesting that ECG changes mean essentially myocardial involvement and not simple pericarditis. This finding was also confirmed by cardiac magnetic resonance that confirmed the presence of myocarditis in 35% of patients with pericarditis and ST-segment elevation on ECG at presentation. On this basis, under a diagnostic point of view, in clinical practice ECG changes should prompt the exclusion of concomitant myocarditis in patients with clinically suspected pericarditis.

Although ECG changes are more commonly associated with CRP elevation and concomitant myocardial involvement, these findings do not have a negative prognostic meaning as demonstrated by a similar MACE-free survival in patients with pericarditis with or without ECG changes (Log rank p= 0.8732, see Figure 2).

Study limitations. This study has some limitations. First of all, a limited sample size, that was however sufficient to assess the diagnostic and prognostic role of ECG changes in patients with pericarditis. Second, the setting was a single-centre and tertiary referral centre for pericarditis, where more complicated cases could be referred and this could lead to the selection of more severe cases with an increased frequency of ECG changes. Third, cardiac magnetic resonance was performed and allowed within 4 weeks from symptoms onset in the setting of pericarditis and original Lake Louise criteria were adopted for the diagnosis of myocarditis without the use of T1 and T2 mapping techniques[11] leading to a possible underestimation of the real frequency of myocardial oedema and fibrosis and a lower diagnostic accuracy. Moreover current CMR criteria can have a limited diagnostic accuracy to detect mild degrees of myocardial inflammation in the setting of pericarditis with ECG changes.

In conclusion, ECG changes are not so common, as previously reported, in the setting of simple pericarditis. They are generated by myocardial involvement and should prompt the exclusion of concomitant myocarditis in patients with clinically suspected pericarditis. Nevertheless, the presence of ECG changes is not a negative prognostic marker for patients with pericarditis since they showed a similar occurrence of MACE compared with those without ECG changes.

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Contributors

All other authors contributed to study design and conception, data collection, interpretation and analysis, article drafting, critical revision and approval of the final version.

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Competing interests None declared.

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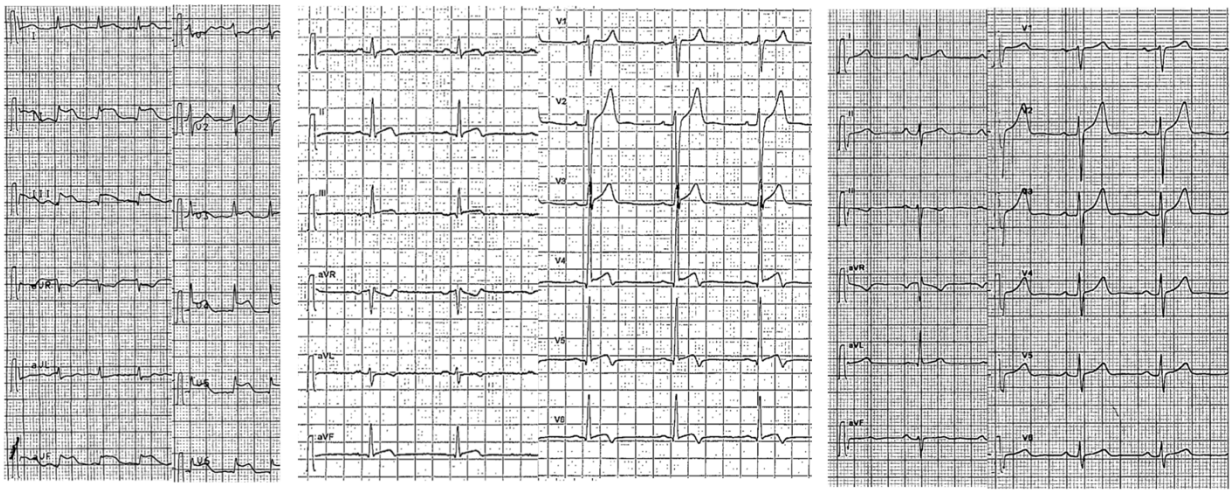
FIGURES LEGENDS

Figure 1. ECG changes in 3 illustrative cases. Case 1: a male patient with myocarditis and widespread ST-segment elevation at presentation. Case 2: a male patient with pericarditis with myocarditis and ECG changes with convex ST segment elevation and isodifasic T waves in inferolateral leads. Case 3: a case of simple pericarditis without ECG changes.



Case 1
Myocarditis with
ECG Changes

Case 2
Pericarditis with Myocarditis
and ECG Changes

Case 3
Simple Pericarditis
Without ECG changes

Figure 2. Kaplan-Meier survival curves of event-free survival from MACE in patients with or without ECG changes in the subgroup of patients with clinically suspected pericarditis. The presence of ECG changes is not associated with a worse event-free survival (Log rank p= 0.8732).

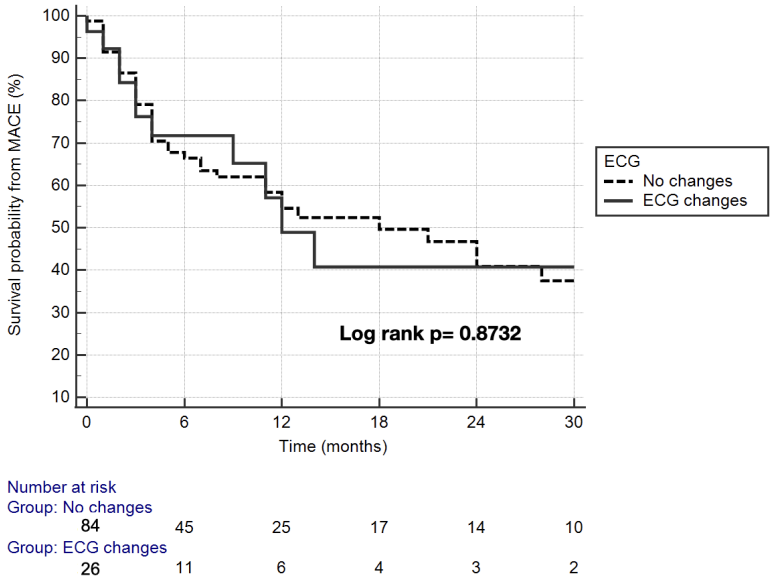
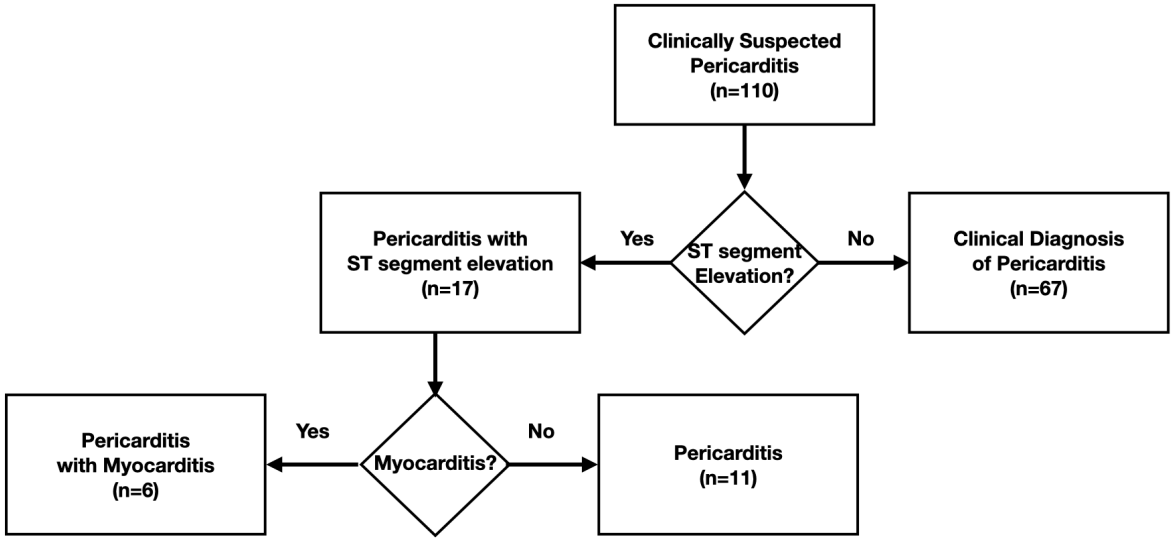


Figure 3. Patients with clinically suspected pericarditis and ST-segment elevation on ECG at presentation. A diagnosis of concomitant myocarditis was confirmed by CMR in 6/17 cases (35.0%) of patients with pericarditis and ST-segment elevation on ECG at presentation.



TABLES

Table 1. Clinical characteristics of enrolled patients.

Feature	Pericarditis (n=110)	Myocarditis (n=56)	p
Age (years)	47.7 ± 16.6	44.8 ± 17.6	0.3007
Male gender	32 (29.1%)	34 (60.7%)	0.0001
Chest pain at presentation	83 (75.5%)	35 (62.5%)	0.0827
Pericardial rubs	36 (32.7%)	3 (5.4%)	<0.0001
ECG changes: ST-segment elevation PR depression T wave inversion Other ST/T changes No changes	27 (24.5%) 17 (15.5%) 5 (4.5%) 9 (8.2%) 1 (0.9%) 83 (75.5%)	34 (60.7%) 24 (42.9%) 9 (16.1%) 11 (19.6%) 5 (8.9%) 0 (0.0%)	<0.0001 <0.0001 0.0118 0.0168 0.0059 <0.0001
Pericardial Effusion: Mild Moderate Severe	72 (65.5%) 50 (45.5%) 12 (10.9%) 10 (9.1%)	26 (46.4%) 19 (33.9%) 6 (10.7%) 1 (1.8%)	0.0288 0.0026
C-reactive protein elevation (mg/L)	47 (42.7%) 74.5 ± 12.9	36 (64.3%) 99.8 ± 19.2	0.0279 0.2679
Troponin T elevation (ng/L)	0 (0.0%) 0	45 (80.4%) 372.5 (208.6-536.4)*	<0.0001
LVEF (%)	60 ± 6	53 ± 13	0.0213
Aetiology Idiopathic Viral Pericardial injury syndrome Systemic autoimmune disease Neoplastic Unknown/not labelled	 84 (76.4%) 10 (9.1%) 10 (9.1%) 5 (4.5%) 1 (1.1%) 0 (0.9%)	 42 (75.0%) 4 (7.1%) 4 (7.1%) 4 (7.1%) 2 (3.5%) 0 (0.0%)	 0.2200

*= 95% CI for the mean

Table 2. Therapy and follow-up data of the studied population.

Feature	Pericarditis (n=110)	Myocarditis (n=56)	p
NSAID	91 (82.7%)	14 (25.0%)	<0.0001
Colchicine	86 (78.2%)	16 (28.6%)	<0.0001
Corticosteroids	38 (34.6%)	8 (14.2%)	<0.0001
Betablockers	14 (12.7%)	45 (80.4%)	<0.0001
Follow-up (months)	29 ± 4	36 ± 5	0.2468
Major Cardiac Events (MACE):	55 (50.0%)	12 (21.4%)	0.0004
Death or Heart Failure	0 (0.0%)	0 (0.0%)	NS
Recurrences	55 (50.0%)	12 (21.4%)	0.0006
Arrhythmias*	5 (4.5%)	10 (17.9%)	0.0047
Cardiac Tamponade	9 (8.2%)	2 (3.6%)	0.2603
Constrictive Pericarditis	5 (4.5%)	1 (1.8%)	0.3692

NSAID= non-steroidal anti-inflammatory drugs

*= all patients with pericarditis had supraventricular arrhythmias, while 4 of 10 patients with myocarditis had non sustained ventricular arrhythmias.

Table 3. Main clinical basal and follow-up characteristics of patients with ECG changes.

Feature	No ECG changes (n=105)	Any ECG change (n=61)	p
Age (years)	49.1 ± 16.8	42.7 ± 16.6	0.0181
Male gender	30 (28.6%)	36 (59.0%)	0.0001
Chest pain at presentation	72 (68.6%)	46 (75.4%)	0.3503
Pericardial Effusion: Moderate to Severe	62 (59.0%) 16 (15.2%)	34 (55.7%) 11 (18.0%)	0.6781 0.6391
C-reactive protein elevation	44 (41.9%)	39 (63.9%)	0.0203
Troponin T elevation	16 (15.2%)	31 (50.8%)	<0.0001
LVEF<50%	8 (7.6%)	9 (14.8%)	0.1450
LGE	21 (20.0%)	17 (27.9%)	0.2461
Final diagnosis of myocarditis	22 (21.0%)	34 (55.7%)	<0.0001
Non-idiopathic aetiology	36 (34.3%)	13 (21.3%)	0.0781
MACE	49 (46.7%)	18 (29.5%)	0.0303

LGE= late gadolinium enhancement on cardiac magnetic resonance (either pericardial or myocardial); MACE= major cardiac events during follow-up.

Table 4. Multivariable analysis to assess variables associated with ECG changes at presentation. Odds ratios are reported with 95% confidence intervals.

Variables	OR	95% CI
Age	0.9795	0.9590-1.0004
Male gender	2.6383	1.2840-5.4209
Elevation of C reactive protein	0.9644	0.8407-1.1063
Troponin elevation/myocarditis	3.6847	1.7725-7.6596