The long-term outcomes of early repolarization pattern and incidence of early repolarization syndrome in a population-based cohort study

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Abstract

Introduction: Early repolarization pattern (ERP) is associated with long-term cardiovascular death and early repolarization syndrome (ERS). However, the incidence of ERS has never been studied in a general population-based cohort study.

Purpose: To determine the prevalence and long-term outcome of ERP as well as the incidence of ERS in a general population-based cohort study.

Methods: Participants from the electricity generating authority of Thailand (EGAT) study during 1997 to 2015 were included in this study. ERP was defined either as "notching" or "slurring" and was localized into inferior leads, lateral leads, or both. ERS was defined according to recent expert consensus. The outcomes included cardiovascular death, deaths due to acute myocardial infarction, SCD, and all-cause mortality. A univariable and multivariable Cox-proportional hazard model, adjusted for all major cardiovascular risk factors, was used to determine the association between ERP and the outcomes.

Results: 2,689 participants with completed ECGs and risk factor profiles were included for the analysis. Most of the participants were male (80%) and mean age was 55±5.1 years. Mean follow up duration was 11.2±6.7 years. There were 444 (16.5%) participants with baseline ERP (slurr 54.3%, notching 38.3%, and both 7.4%). Inferior leads were the most common localization (49.8%), followed by lateral leads (35.6%), and both (14.6%). There were 566 deaths during the follow-ups; of these, 21 were SCD including 6 ERS. The prevalence and incidence of ERS in our study was 0.22% and 0.20 per 1000 person-year. The prevalence and incidence of ERS in ERP population was 1.35% and 1.21 per 1000 person-year. Overall, ERP was not associated with an increased risk of all-cause mortality (hazard ratio [HR]=1.04; 95% confidence interval [CI]:0.81 to 1.34; p=0.75). However, ERP was associated with an increased risk of all-cause mortality in the population ≤55 years old (HR = 2.36; 95% CI:1.47-3.77; p<0.01) in univariable analysis. There was a trend of increased risk of death due to acute myocardial infarction, cardiovascular death, and SCD in the population with ERP ≤55 years old versus >55 years old (HR of 1.59 versus 1.06, 1.37 versus 1.03, 1.55 versus 1.05, respectively). Notching ERP increased risk of SCD but the difference was not significant (HR=2.89; 95% CI: 0.25 to 32.98; p=0.393).

Conclusion: The incidences of ERS in general and in the ERP population were 0.22 and 1.35 per 1000 person-year respectively. The prevalence of ERP in the Thai population was higher than the prevalence in other countries in Asia. Our study supports previous studies that ERP is associated with a long-term increased risk of all-cause mortality in the young-middle age population.

Keywords ; incidence, early repolarization, mortality

Abbreviations

ERP	early repolarization pattern
VT	ventricular tachycardia
VF	ventricular fibrillation
SCD	sudden cardiac death
ERS	early repolarization syndrome
ECG	electrocardiogram
EGAT	Electricity Generating Authority of Thailand
LDL	low-density lipoprotein
HDL	high-density lipoprotein
HR	hazard ratio
CI	confidence interval

Introduction

The early repolarization pattern (ERP) is a common electrocardiographic finding. The term early repolarization has been used for more than 50 years. Its prevalence ranges from 1 to 13% of the general population (1-7). It is characterized by J-point elevation of ≥ 0.1mV in ≥2 leads in the inferior (II, III, aVF), lateral (I, aVL, V4-6) territories, or with or without ST elevation (1, 8). Early repolarization pattern had previously been considered a benign phenomenon (9, 10) until Gussak et al. reported in 2000 that ERP was a predictor of ventricular tachycardia (VT) and ventricular fibrillation (VF) in experimental models (11). Thereafter, many clinical studies supported the hypothesis, demonstrating that ERP was associated with sudden cardiac death (SCD) and long-term cardiac mortality in western countries (2, 12-14). In 2013, Priori et al. and colleagues first described early repolarization syndrome (ERS) in ERP patients with unexplained polymorphic VT/VF or SCD in an expert consensus statement. Because of the shared electrocardiogram (ECG) finding of J wave accentuation, ERS was later grouped with Brugada syndrome as a J wave syndrome in 2016 (8). We previously reported a very high prevalence of Brugada pattern (0.41%) in the Electricity Generating Authority of Thailand (EGAT) population-based cohort study in a Southeast Asian Thai population (15). However, the incidence of ERS in the general population has never been reported. This study aims to assess the long-term outcomes of ERP and incidence of ERS in a general population-based cohort study.

Methods

We conducted a retrospective review of the EGAT prospective population-based longitudinal cohort study of 2,765 participants from 1997 to 2015. The EGAT study identified cardiovascular risk factors in a Thai population with a comprehensive methodology described previously in Vathesatogkit P et al. (16). Standard 12-lead ECG (standard filter setting: 25 mm/s, 10 mm/mV, 40 Hz) has been performed in all participants and recorded in computer databases since 1997. The study was approved by the Ethics Committee of studies involving human subjects of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Patient baseline characteristics and sociodemographic data were collected by a questionnaire (age, sex, educational level, occupation, tobacco smoking and alcohol drinking) and physical examination (blood pressure, heart rate, weight, height and waist and hip circumference). A blood sample was taken to measure blood glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and creatinine. Of those 2,765 participants, 2,689 participants had completed ECG records and laboratory profiles and thus were included in our study.

Electrocardiogram Analysis

Standard 12-leads ECG of each participant was retrospectively interpreted without clinical information by 2 cardiac electrophysiologists independently. The third cardiac electrophysiologist adjudicated any disagreements. We also classified ERP into groups by morphology (notching and slurring) and localization (inferior and lateral leads).

Definition of early repolarization pattern

ERP was defined as an upward deflection (notching) or abrupt change in the slope of the last deflection (slurring) at the end of the QRS and J point elevation ≥1 mm above the isoelectric baseline at the end of QRS and the beginning of the ST segment in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG (Figure 1) (1). The anterior precordial leads (V_1–V_3) were excluded from the analysis of the ERP to avoid the inclusion of patients with right ventricular dysplasia or Brugada syndrome.

Definition of early repolarization syndrome

According to the 2013 expert consensus, ERS is diagnosed in a SCD or an unexplained polymorphic VT/VF patient with the presence of a J-point elevation≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG (1).

Outcomes retrieving and outcomes definition

Primary outcome is defined as all-cause mortality. Secondary outcomes include cardiovascular death, deaths due to acute myocardial infarction, and SCD. The outcome definitions were defined according to the 2017 Cardiovascular and Stroke Endpoint Definition for Clinical Trials (17). These vital statuses of all participants were obtained from the Thailand national registration system by the 10th iteration of the International Classification of Disease system as well as available medical records. We collected all deaths between 1997 and 2015.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Continuous variables were demonstrated as the mean ± SD. Comparisons of continuous data between 2 groups were tested by an unpaired *t*-test or Mann–Whitney *U*-test according to the data with or without normal distribution. All categorical variables were compared by a χ^2 analysis or Fisher exact test. A univariate analysis of the baseline characteristics was used to compare the ERP group and non-ERP group, then multivariable Cox proportional regression analysis was performed to calculate the hazard ratio (HR) with a 95% confidence interval (CI). A comparison of the probability in all-cause mortality, cardiovascular death, death due to acute myocardial infarction, and SCD between ERP and non-ERP was analyzed using a Kaplan–Meier survival analysis with a log-rank test.

Results

Demographic and Clinical Characteristics

A total of 2,689 people who had completed ECGs and risk factor profiles were included into our study. The mean age was 55±5.1 years. The majority of participants (80.0%) were male. ERP and non-ERP, age, gender, heart rate, weight, height, BMI, waist circumference, hip circumference were similar between both groups. ERP was more frequently observed in smokers (28.5 vs. 22.5%, p=0.08). Fasting plasma glucose, postprandial plasma glucose, HDL, triglyceride and creatinine were not different between both groups. On the other hand, total cholesterol and LDL were higher in the non-ERP group (p=0.017 and 0.023, respectively). Furthermore, blood pressure (both systolic and diastolic) was more elevated in the non-ERP group (p<0.001) and hypertension was diagnosed more frequently in the non-ERP group, which was statistically significant (p = 0.004). When non-

ERP and ERS were compared, all baseline characteristics were similar. Baseline characteristics are shown in Table 1.

ERP was present in 444 out of 2,689 subjects (16.5%). Slurr was found in 241 subjects (54.3%) followed by notching (170 subjects or 38.3%) and both (33 subjects or 7.4%). ERP in the inferior leads was the most common localization with 221 subjects (49.8%). Lateral leads localization was found in 158 subjects (35.6%) and both leads localization was seen in 65 subjects (14.6%). An example of ERP with notching in the inferior electrocardiogram leads and slurring in lateral electrocardiogram leads is shown in Figure 1A and 1B, respectively. Mean follow-up duration was 11.2±6.7 years. Five hundred and sixty-six participants expired during the follow-up. Causes of death in our study are presented in Table 2. Thirty-three patients expired from SCD, including six patients who had ERP and therefore, were diagnosed with ERS (Figure 2). One of six patients died from idiopathic VF according to the national registration system (Figure 2A) but the medical record could not be obtained. The prevalence and incidence of ERS in the general population was 0.22% and 0.20 per 1000 person-year respectively. The prevalence and incidence of ERS in participants with baseline ERP was 1.35% and 1.21 per 1000 person-year respectively, which are six fold higher compared to the overall population.

When ERP and non-ERP was compared, a univariable Cox proportional regression analysis revealed that ERP was not associated with an increased risk of all-cause mortality, which was 20.5% in ERP and 21.2% in non-ERP (HR=1.04; 95% (CI) 0.81 to 1.34; p=0.75). Risk of death due to acute myocardial infarction, cardiovascular death, and SCD was also not different between both groups, which were 7.2% in ERP and 7.6% in non-ERP 7.6% (HR = 1.06; 95% CI:0.71 to 1.56; p=0.790), 11.7% in ERP and 12.0% in non-ERP (HR =1.03; 95% CI:0.75 to 1.41; p=0.872) and 1.2% in ERP and 1.4% in non-ERP (HR =1.05; 95% CI:0.40 to 2.78; p=0.915), respectively.

Similar to the univariable analysis, in the overall population, multivariable Cox proportional regression analysis revealed that ERP was not associated with an increased risk of all-causes of death (HR = 1.09; 95% CI: 0.83 to 1.43; p=0.536). Risk of death due to acute myocardial infarction, cardiovascular death, and SCD were also not different between both groups, which were 7.2% in ERP versus 7.6% in non-ERP (HR = 1.13; 95% CI:0.75 to 1.71; p=0.563) 11.7% in ERP versus 12.0% in non-ERP (HR =1.12; 95% CI:0.80 to 1.57; p=0.516), and 5.6% in ERP versus 5.5% (HR =1.42; 95% CI:0.57 to 3.56; p=0.452), respectively.

In the subgroup analysis of the population age 55 years old and younger, a univariable Cox proportional regression analysis revealed that ERP was associated with an increased risk of all-cause mortality, which were 14.9% in ERP and 7.0% in non-ERP (HR = 2.36; 95% CI:1.47-3.77; p<0.01). Risk of death due to acute myocardial infarction, cardiovascular death, and SCD were also not different between both groups, which were 5.9% in ERP and 5.0% in non-ERP (HR = 1.59; 95% CI = 0.77 to 3.27; p=0.207), 10.4% in ERP versus 8.7% in non-ERP (HR =1.37; 95% CI = 0.76 to 2.45; p=0.0.291) and 1.1% in ERP versus 0.5% in non-ERP (HR =1.55; 95% CI = 0.31 to 7.75; p=0.596), respectively (Table 3). Kaplan–Meier curves of the participants age 55 years old and younger with baseline ERP on the 12-lead ECG showed an decreased survival from all-cause mortality in the population age 55 years old and younger (Figure 3) but was not significant by log-rank test (p=0.968)(Figure 3).

Our univariable statistical analysis demonstrated that the notching pattern of the terminal portion of the QRS complex and smoking may increase the risk of SCD in participants who had ERP (HR=2.89; 95% CI: 0.25 to 32.98; p=0.393 and 3.27; 95% CI: 0.83 to 12.89; p=0.09, respectively); however, this did not reach statistical significance (Table 4).

Discussion

The prevalence of ERP in our population-based study in Thailand was 16.5%. We report the incidence of ERS in the general population-based study for the first time. The prevalence and incidence of ERS in our study were 0.22% and 0.20 per 1000 person-year and increased by six fold in the ERP population. Male sex was predominant in ERP and ERS (80% and 83.3%, respectively). Our study also showed that ERP was significantly associated with an increased risk of all-cause mortality in the population age 55 years old and younger. ERP in the young-middle age population (55 years old and younger) also increased risk of death due to acute myocardial infarction, cardiovascular death, and SCD, but this did not reach statistical significant.

ERP prevalence ranges from 1 to 13% of the general population (1-7). In our study, ERP had a higher prevalence in Thailand compared to other countries in Asia (1.3-12%) (3, 5, 18, 19). ERP was associated with sudden cardiac death (SCD) and long-term cardiac mortality in western countries (2, 12-14). However, it has never been studied in a Southeast Asian population. Our study showed that ERP was not associated with an increased risk of all-cause mortality, deaths due to acute myocardial infarction, cardiovascular death, and SCD in the general Thai population. However, ERP was statistically significantly associated with an increased risk of all-cause mortality in the young-middle age population (55 years old and younger) (HR = 2.36; 95% CI:1.47-3.77; $p<0.01$). We also found a increased risk of death due to acute myocardial infarction, cardiovascular death, and SCD in the population age 55 years old and younger compared to the older population (HR of 1.59 versus 1.06, 1.37 versus 1.03, 1.55 versus 1.05, respectively). Due to a smaller sample size in the subgroup of the younger population, our study may have not enough power to test this hypothesis and thus did not reach statistical significance.

ERS was first described in ERP patients with unexplained polymorphic VT/VF or SCD in the expert consensus statement in 2016 (8). ERS is associated with younger age (20), increased prevalence of left ventricular hypertrophy, lower heart rate and blood pressure, healthier status, and a physically active phenotype (21). Previous studies reported the incidence and prevalence of ERS in specific high-risk populations including those with idiopathic VF (22, 23). However, the incidence of ERS in the general population is unknown and has never been reported. This study is the first to report the incidence of ERS in the general population. The prevalence and incidence of ERS in participants with baseline ERP was 1.35% and 1.21 per 1000 person-year, which is a six fold increase when compared to the overall population.

Previous studies clarified the morphology and amplitude of the J-wave in order to establish risk stratification for patients with ERP and J-wave syndrome (8). Haïssaguerre et al. found that a history of SCD was more frequent in patients with the combination of J-wave and descending/horizontal ST segment in inferior leads (24). Our analysis demonstrated that the notching pattern of the terminal portion of the QRS complex was the predominant morphology and might be associated with a risk of SCD in participants who had ERP. However, the numbers of events in each group were too small, which restricts statistical power and resulted in wide confidence intervals.

Conclusion

The prevalence and incidence of ERS was 0.22% and 0.20 per 1000 person-year and increased to six-fold when compared to the overall population. The prevalence of ERP in the Thai population was higher than the prevalence in other countries in Asia. Our study supports previous reports that suggest that ERP was significantly associated with an increased risk of all-cause mortality in the young-middle age population. ERP in the younger population may increase the risk of death due to acute myocardial infarction, cardiovascular death, and SCD.

Study limitations

In our study population, the age of subjects included was relatively higher compared to other studies. Therefore, the result may not be applicable to other subgroups. Also, our prevalence is somewhat less than the previous report in the general population. Hence, our clinical outcomes might have some limitation in regards to application to the general population with ERP. Due to a smaller sample size in the younger population, our study may have not enough power to reach statistical significance.

Table legends

Table 1: Baseline characteristics

Table 2: Causes of death between early repolarization pattern and non-early repolarization pattern groups.

Table 3: Univariate analyses of early repolarization pattern and primary and secondary outcomes in subgroup population age 55 years old and younger.

Table 4: Univariate analyses of early repolarization pattern and primary and secondary outcomes in subgroup population age 55 years old and younger.

Figure legends

Figure 1: J-point elevation with notching in the inferior electrocardiogram leads (A) and slurring in lateral electrocardiogram leads (B)

Figure 2: Electrocardiography of 6 early repolarization participants who had sudden cardiac death and were diagnosed with early repolarization syndrome; (A) Slurred J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 52-year-old female; past medical history: essential hypertension, dyslipidemia. This patient died from idiopathic ventricular fibrillation at the age of 65; (B) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 52-year-old male; past medical history: None. This patient died from sudden cardiac death at the age of 64; (C) Slurred J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 59-year-old male; past medical history: essential hypertension, dyslipidemia. This patient died from sudden cardiac death at the age of 64; (D) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 59-year-old sex: male; past medical history: dyslipidemia. This patient died from sudden cardiac death at the age of 65; (E) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 59-year-old male; past medical history: essential hypertension. This patient died from sudden cardiac death at the age of 60; (F) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). Age: 49-year-old male; past medical history: none. This patient died from sudden cardiac death at the age of 50.

Figure 3: Kaplan–Meier curves showed a non-significant trend of decreased survival from all-cause mortality in population ≤55 years old with early repolarization pattern compared with non-early repolarization pattern.

References

1. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932-63.
2. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529-37.
3. Sun GZ, Ye N, Chen YT, Zhou Y, Li Z, Sun YX. Early repolarization pattern in the general population: Prevalence and associated factors. Int J Cardiol 2017;230:614-8.
4. Rollin A, Maury P, Bongard V, et al. Prevalence, prognosis, and identification of the malignant form of early repolarization pattern in a population-based study. Am J Cardiol 2012;110:1302-8.
5. Makarawate P, Chaosuwannakit N, Ruamcharoen Y, et al. Prevalence and associated factors of early repolarization pattern in healthy young northeastern Thai men: A correlation study with Brugada electrocardiography. J Arrhythm 2015;31:215-20.
6. Greenfield JC, Jr., Rembert JC. The prevalence of lateral lead early repolarization in otherwise normal electrocardiograms as a function of age. J Electrocardiol 2013;46:334-5.
7. De Asmundis C, Conte G, Levinstein M, et al. Prevalence and electrocardiographic characteristics of early repolarization pattern in young teen athletes. Acta Cardiol 2014;69:3-6.
8. Antzelevitch C, Yan GX, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Heart Rhythm 2016;13:e295-324.
9. Kambara H, Phillips J. Long-term evaluation of early repolarization syndrome (normal variant RS-T segment elevation). Am J Cardiol 1976;38:157-6.
10. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. Am J Med 2003;115:171-7.
11. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol 2000;33:299-309.
12. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016-23.
13. Rosso R, Kogan E, Belhassen B, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008;52:1231-8.
14. Sinner MF, Reinhard W, Muller M, et al. Association of early repolarization pattern on ECG with risk of cardiac and all-cause mortality: a population-based prospective cohort study (MONICA/KORA). PLoS Med 2010;7:e1000314.
15. Rattanawong P, Ngarmukos T, Chung EH, et al. Prevalence of Brugada ECG Pattern in Thailand From a Population-Based Cohort Study. J Am Coll Cardiol 2017;69:1355-6.

16. Vathesatogkit P, Woodward M, Tanomsup S, et al. Cohort profile: the electricity generating authority of Thailand study. Int J Epidemiol 2012;41:359-65.
17. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021-34.
18. Haruta D, Matsuo K, Tsuneto A, et al. Incidence and prognostic value of early repolarization pattern in the 12-lead electrocardiogram. Circulation 2011;123:2931-7.
19. Takagi M, Aonuma K, Sekiguchi Y, et al. The prognostic value of early repolarization (J wave) and ST-segment morphology after J wave in Brugada syndrome: multicenter study in Japan. Heart Rhythm 2013;10:533-9.
20. Ahmed H, Czosek RJ, Spar DS, Knilans TK, Anderson JB. Early Repolarization in Normal Adolescents is Common. Pediatr Cardiol 2017;38:864-72.
21. Serra-Grima R, Donate M, Alvarez-Garcia J, et al. Long-term follow-up of early repolarization pattern in elite athletes. Am J Med 2015;128:192 e1-9.
22. Dalos D, Fiedler L, Radojevic J, Sponder M, Dichtl W, Schukro C. Prevalence of early repolarization syndrome and long-term clinical outcome in patients with the diagnosis of idiopathic ventricular fibrillation. Heart Vessels 2019;34:625-31.
23. Siebermair J, Sinner MF, Beckmann BM, et al. Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. Europace 2016;18:718-25.
24. Haissaguerre M, Sacher F, Nogami A, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. J Am Coll Cardiol 2009;53:612-9.

Table 1: Baseline characteristics

Characteristics	Non-ERP (N= 2,245)	ERP (N=444)	ERS (N=6)	P-value (ERP VS non-ERP)	P-value (ERS VS non-ERP)
Age [years; mean±SD]	54±4.8	54±5.0	55±4.7	0.156	0.833
Male sex [no (%)]	1,765 (78.6)	355 (80.0)	5(83.3)	0.498	0.778
Weight [kg; mean±SD]	66.3±16.3	64.8±10.5	62.8±10.1	0.081	0.608
Height [cm; mean±SD]	163.0±7.8	163.6±7.3	165.7±9.0	0.127	0.398
BMI (kg/m^2; mean±SD)	24.8±3.4	24.2±3.3	22.7±2.0	0.001	0.142
Waist circumference [cm; mean±SD]	87.8±26.5	87.3±9.8	87.5±6.5	0.700	0.980
Hip circumference [cm; mean±SD]	97.3±19.7	98.0±39.3	94.8±6.2	0.568	0.782
Pulse rate [beats/min; mean±SD]	79.2±11.5	78.711.1	85.5±18.0	0.382	0.931
Systolic blood pressure [mmHg; mean±SD]	136.8±21.6	132.4±20.4	152.9±17.6	<0.001	0.069
Diastolic blood pressure [mmHg; mean±SD]	82.2±13.3	79.4±12.3	89.3±7.9	<0.001	0.186
Mean arterial blood pressure [mmHg; mean±SD]	100.4±15.0	97.1±14.0	110.5±10.3	<0.001	0.098
Hypertension [no(%)]	1076 (50.1)	174 (39.5)	5(83.3)	<0.001	0.218
Hypertension on treatment [no (%)]	369 (17.2)	52(11.8)	3(50)	0.004	0.068
Diabetes [no(%)]	350 (16.8)	64 (14.6)	1(16.7)	0.287	0.734
Diabetes with Hypertension [no(%)]	235 (10.5)	39 (8.8)	1(16.7)	0.344	0.621
Dyslipidemia [no (%)]	181 (33.2)	782 (36.5)	3(50)	0.184	0.518
Fasting plasma glucose [mg/dL; mean±SD]	96.1±29.6	96.5±30.1	104.3±22.9	0.769	0.494
Postprandial Plasma glucose [mg/dL; mean±SD]	120.9±48.7	117.2±59.8	106.6±13.1	0.165	0.511
Total Cholesterol [mg/dL; mean±SD]	239.3±41.5	234. ±39.6	250±47.3	0.017	0.530
HDL- Cholesterol [mg/dL; mean±SD]	52.4±11.1	53.3±10.8	47±8.1	0.133	0.231
LDL- Cholesterol [mg/dL; mean±SD]	155.4±40.1	150.6±39.9	177±53.9	0.023	0.226
Triglyceride [mg/dL; mean±SD]	165.3±111.7	159.0±92.3	217±108.8	0.270	0.259
Creatinine [mg/dL; mean±SD]	1.08±0.4	1.07±0.4	1.28±0.3	0.541	0.158
GFR [1997:CKD-EPI equation] [ml/min*1.73m^2] Normal or increase GFR≥90 no (%) Mildly decreased 60-89 no (%) Moderately decreased 30-59 no (%) Severely decreased 15-29 no (%) Renal failure <15 no (%)	410 (20.7) 1296 (65.4) 269 (13.6) 6 (0.3) 1 (0.3)	101 (23.9) 270 (64.0) 50 (11.8) 0 (0.0) 1 (0.2)	1 (16.7) 1 (16.7) 2 (33.3) 0 (0) 0 (0)	0.049	0.088
Smoking [no (%)]	496 (22.5)	122 (28.5)	3(50)	0.080	0.108
Alcohol [no (%)]	774 (35.3)	171 (39.0)	0(0)	0.156	0.099

ERP: early repolarization pattern; ERS: early repolarization syndrome; SD: standard deviation; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein ; GFR: glomerular filtration rate.

Table 2: Causes of death between early repolarization pattern and non-early repolarization pattern groups.

Causes of death	**ERP (N=91)**	**Non-ERP (N= 475)**
Sepsis	3 (3.3%)	25 (5.3%)
Traffic accident	5 (5.5%)	33 (6.9%)
Malignancy	37 (40.7%)	143 (30.1%)
Cardiac events		
Acute myocardial infarction	16 (17.6%)	96 (20.2%)
Cardiomyopathy	0 (0%)	2 (0.2%)
Arrhythmias	0 (0%)	1 (0.3%)
Heart failure	1 (1.0%)	17 (3.5%)
SCD	6 (6.6%)	27 (5.7%)
Metabolic/renal failure	3 (3.3%)	7 (1.5%)
Neurovascular	4 (4.4%)	33 (6.9%)
Chronic obstructive pulmonary disease/other lung diseases	6 (6.6%)	35 (7.4%)
Gastrointestinal bleeding/cirrhosis	2 (2.2%)	27 (5.7%)
Unknown	8 (8.8%)	29 (6.1%)

ERP: early repolarization pattern; SCD: sudden cardiac death

Table 3: Univariate analyses of early repolarization pattern and primary and secondary outcomes in subgroup population age 55 years old and younger.

Outcomes	HR	95%CI	*P* value
All-cause mortality	2.36	1.47-3.77	<0.001
Death due to acute myocardial infarction	1.59	0.77-3.27	0.207
Cardiovascular death	1.37	0.76-2.45	0.291
SCD	1.55	0.31-7.75	0.596

Table 4: Univariate analyses of early repolarization pattern and primary and secondary outcomes in subgroup population age 55 years old and younger.

Variable	Hazard ratio	95% confidence interval	*P* value
Male sex	1.40	0.25-7.84	0.701
Hypertension	1.50	0.43-5.54	0.398
Diabetes Mellitus	0.81	0.10-6.83	0.854
Smoking	3.27	0.83-12.89	0.09
Notching	2.89	0.25-32.98	0.393

Figure 1: J-point elevation with notching in the inferior electrocardiogram leads (A) and slurring in lateral electrocardiogram leads (B)

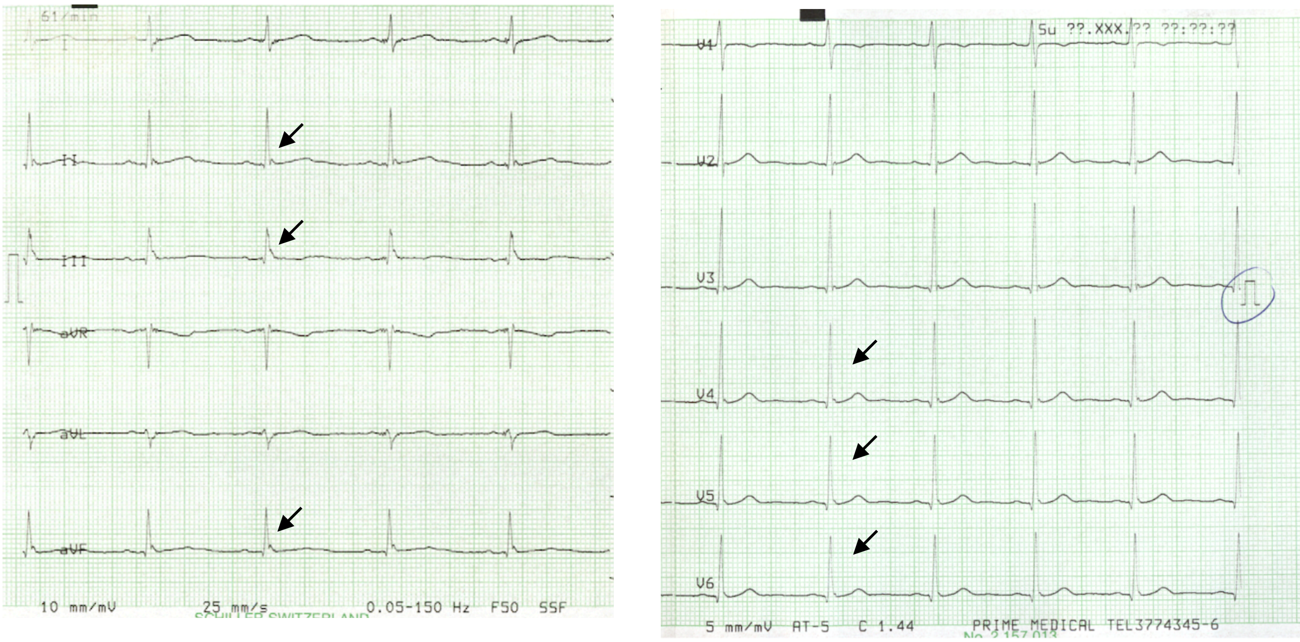
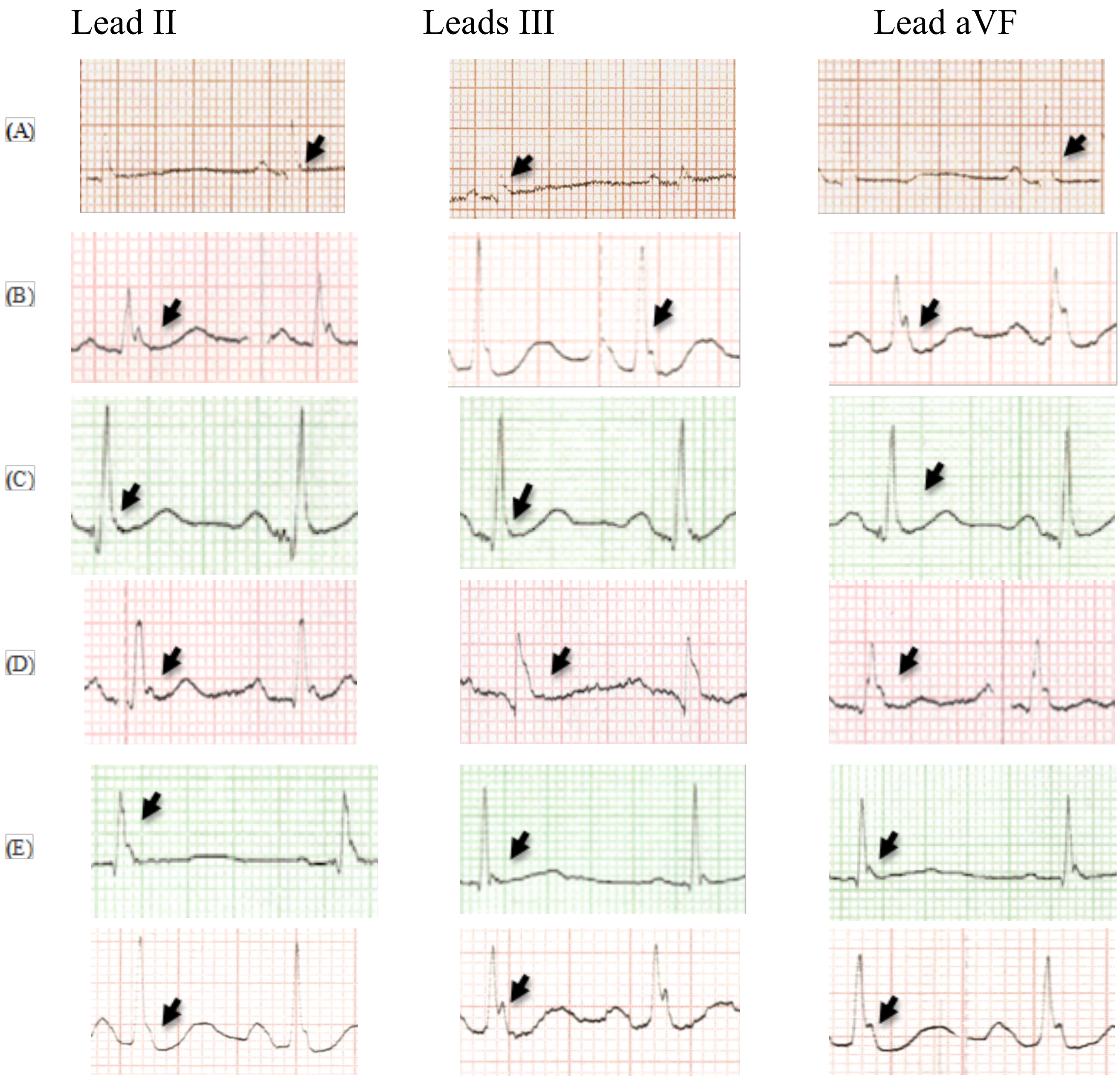
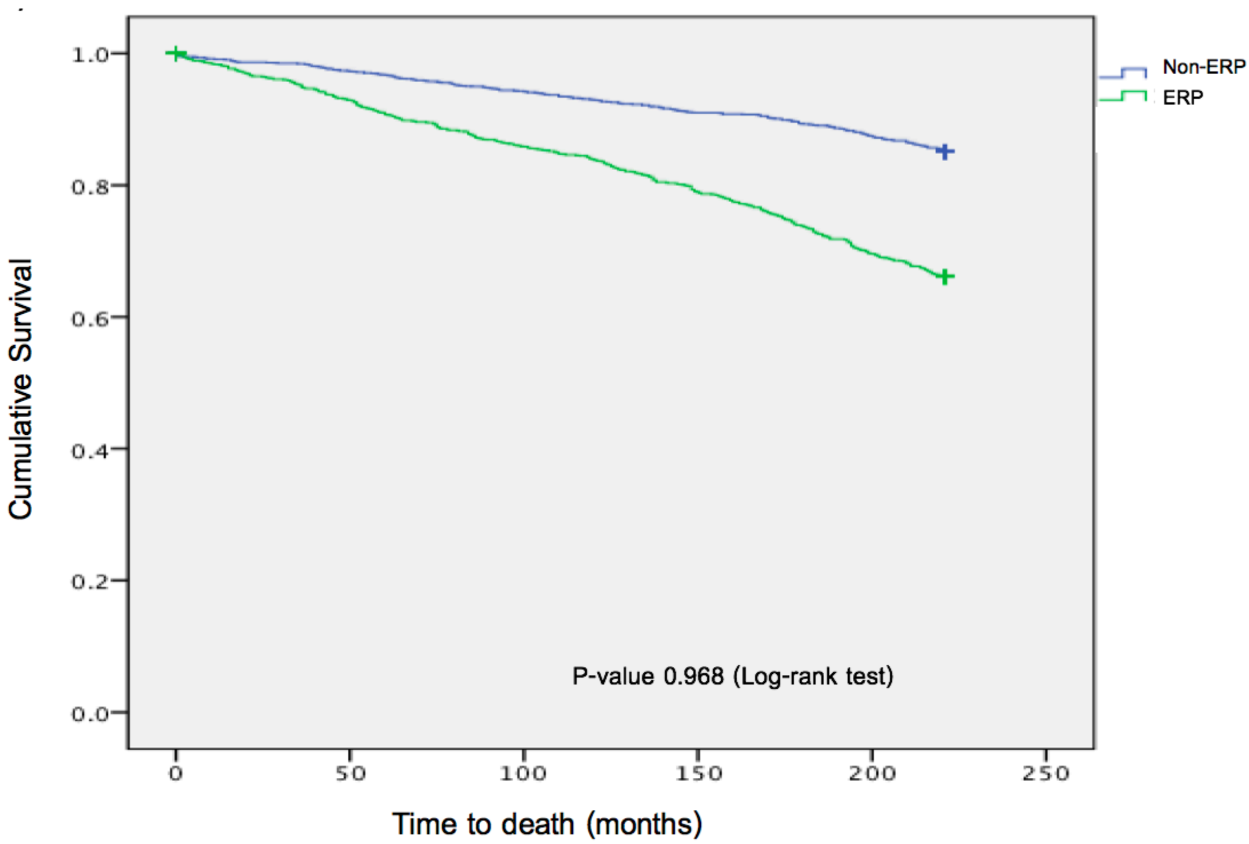


Figure 2: Electrocardiography of 6 early repolarization participants who had sudden cardiac death and were diagnosed with early repolarization syndrome.



(A) Slurred J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 52-year-old female; past medical history: essential hypertension, dyslipidemia. This patient died from idiopathic ventricular fibrillation at the age of 65. (B) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 52-year-old male; past medical history: None. This patient died from sudden cardiac death at the age of 64.(C) Slurred J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 59-year-old male; past medical history: essential hypertension, dyslipidemia. This patient died from sudden cardiac death at the age of 64.(D) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 59-year-old sex: male; past medical history: dyslipidemia. This patient died from sudden cardiac death at the age of 65. (E) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). 59-year-old male; past medical history: essential hypertension. This patient died from sudden cardiac death at the age of 60. (F) Notched J waves in inferior leads and a rapidly ascending ST-segment after a J-wave (solid arrows). Age: 49-year-old male; past medical history: none. This patient died from sudden cardiac death at the age of 50.

Figure 3: Kaplan–Meier curves showed non-significant trend of decreased survival from all-cause mortality in population ≤55 years old with early repolarization pattern compared with non-early repolarization pattern.



ERP: early repolarization pattern compared; non-ERP: non-early repolarization pattern.