Research Paper

Role of electrocardiographic early repolarization pattern in long-term outcomes of a community-based middle-aged and geriatric ambulatory population: a prospective cohort study

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ABSTRACT

In some studies, electrocardiographic early repolarization pattern (ERP) has been associated with an increased risk of death from cardiac causes. However, little is known about the prognostic significance of ERP in the middle-aged and geriatric general populations. We investigated the prevalence and long-term prognostic significance of early repolarization pattern (ERP) on electrocardiograms (ECGs) in the Healthy Aging Longitudinal Study (HALST) cohort of 4615 middle-aged and geriatric community-dwelling Han Chinese adults from Taiwan. The study subjects were followed-up for 95±22 months. A positive ERP of ≥0.1 mV was observed in 889 (19.3%) of the subjects. Kaplan-Meier survival curve analysis showed that ERP was not associated with all-cause and cardiovascular mortality (log-rank test, *P*=0.13 and 0.84, respectively). Cox regression analysis after adjusting for covariables revealed that age, blood pressure, smoking, diabetes, stroke, chronic kidney disease, and corrected QT interval (QTc) were associated with increased risk of all-cause mortality (*P*<0.05). Age, and stroke were risk factors associated with increased risk of cardiovascular mortality (*P*<0.05). However, ERP alone was not associated with all-cause or cardiovascular mortality. These findings show that ERP is common in the middle-aged and geriatric Han-Chinese individuals from the HALST cohort and is not associated with all-cause or cardiovascular mortality.

INTRODUCTION

Sudden cardiac death (SCD) is a major health issue worldwide and accounts for 180,000 to 250,000 deaths annually in the United States [1]. The age-adjusted incidence of SCD in the United States is 60 per 100,000 population [2]. Ventricular tachyarrhythmia is the major cause of SCD, and is not associated with any structural heart disease in 6 to 14% of cases [3, 4]. In some cases, SCD is associated with electrocardiographic abnormalities that affect ventricular repolarization, such as long or short QT syndrome [5]. Early repolarization pattern (ERP) is characterized by elevation of the QRS-ST junction or

the J-point in a surface 12-lead electrocardiogram (ECG). Although ERP was considered benign, recent studies have suggested its potential association with cardiac arrhythmogenicity [6]. In case-control studies, the presence of ERP in the inferior or lateral leads is associated with susceptibility to ventricular fibrillation and SCD in patients without structural heart disease [7–9].

ERP is a common electrocardiographic finding that affects 1% to 13% of adults and is more common in young athletic males [7, 9–12]. The age of individuals enrolled in previous studies regarding ERP ranged widely from 25 to 95 years [13, 14]. Sinner et al conducted a large, prospective, population-based case-cohort study of individuals of Central-European descent (MONICA/KORA) and reported a high prevalence of ERP (13.1%) in individuals aged between 35-74 years and a 2- to 4-fold increased risk of cardiovascular mortality in individuals with ERP and aged between 35-54 years [15]. Haruta et al. reviewed ECG records of 5976 atomic bomb survivors in Nagasaki, Japan with a mean age of 47.2 years and reported that ERP was associated with elevated risk of unexpected death and decreased risk of cardiac and all-cause death [16]. However, the long-term prognostic significance of ERP is poorly characterized in older middle-aged and elderly population.

In this study, we investigated the prevalence and prognostic value of ERP regarding cardiac and all-cause mortality in a large, multi-site, Healthy Aging Longitudinal Study (HALST) cohort consisting of older middle-aged and elderly adults belonging to the Han Chinese population in Taiwan.

RESULTS

Study participants

The flowchart of enrollment and inclusion criteria of the study subjects is shown in Figure 1. We initially recruited 5,380 relatively healthy and ambulatory individuals from 7 communities across Taiwan. We then excluded 755 individuals with cancer and underlying severe cardiovascular diseases (e.g., myocardial infarction or pacemaker implantation), as well as those with missing follow-up information. Finally, we included 4,615 healthy individuals in this study. The prevalence of ERP in the study cohort was 19.3% (n=889/4,615). In the ERP (+) group, 122 out of 889 individuals died during follow-up (65.51±27.12 months). In the ERP (-) group, 561 out of 3726 individuals died during follow-up (62.63±28.44 months).

The baseline clinical and demographic data of the study population is shown in Table 1. The mean age was 69.1±8.2 years and 47.8% of the study subjects were males. The average age of study participants was lower and the proportion of males and current smokers was higher in the ERP (+) group compared to the ERP (-) group. The mean values for the body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension were significantly lower (all $P<0.005$) and the length of the corrected QT interval (QTc) was shorter ($P<0.001$) in the ERP (+) group compared to the ERP (-) group.

Figure 2 shows the representative ECGs of few selected individuals belonging to ERP (+) and ERP (-) groups. ERP was observed in the inferior and lateral leads, both separately and simultaneously. Among the 4,615 healthy individuals, 574 (12.4%) individuals were ERP-positive in the inferior leads (ERP-inf$^+$), 214 (4.6%) individuals were ERP-positive in the lateral leads (ERP-lat$^+$), and 101(2.2%) individuals were ERP-positive in both lateral and inferior leads (ERP-lat$^+$ inf$^+$). The agreement between the two initial interpreters was moderate to high (k=0.97, agreement proportion= 0.98).

Association between positive ERP and all-cause and cardiovascular mortality

We observed that all-cause and cardiovascular mortality rates were similar in ERP (+) and ERP (-) groups during a mean follow-up time of 95.1±21.9 months (log-rank test, $P=0.13$ and $P=0.84$, respectively; Figure 3A, 3B). Since previous studies showed that ERP in the inferior leads was a risk factor for all-cause and cardiovascular mortality [17], we performed Kaplan-Meier survival curve analysis to investigate the association between the two types of mortality and positive ERP in the inferior leads (ERP-inf$^+$). The results showed that all-cause and cardiovascular mortality rates were similar for individuals with and without ERP in the inferior leads (log-rank test, $P=0.58$, 0.66, Figure 3C, 3D).

Long-term outcomes of all-cause mortality and cardiovascular mortality and ERP stratified by age

Age is a known risk factor for both all-cause and cardiovascular mortality [18]. Therefore, we performed subgroup analyses in 3 age groups (55-64, 65-74, and ≥75 years) and observed no differences in all-cause or cardiovascular mortality rates in individuals with and without ERP in each subgroup (log-rank test, all $P>0.05$; Figure 4A, 4B). Moreover, the survival rates of individuals with and without ERP in the inferior leads among the 3 age subgroups were also similar (all $P>0.05$; Figure 5A, 5B).

Correlation between ERP and other risk factors with all-cause and cardiovascular mortality

As shown in Tables 2, 3 and Supplementary Figures 1, 2, multivariate Cox proportional hazards analyses after adjusting for covariables showed that ERP was not a risk factor for both all-cause and cardiovascular disease mortality (*P*=0.12 and 0.7, respectively). Furthermore, our study showed that age, gender, BMI, SBP, DBP, smoking, diabetes mellitus, stroke, chronic kidney disease, and QTc were risk factors for all-cause mortality (all *P* values <0.05) and age and stroke were risk factors for cardiovascular mortality (all *P* values <0.05, Supplementary Figure 2). Similarly, after adjusting for covariables, multivariate analysis showed that individuals with ERP in inferior leads alone (ERP-inf $^{+}$) were not associated with increased risk of all-cause and cardiovascular mortality (both *P* values >0.05; Supplementary Figures 3, 4). Moreover, multivariate analysis showed that patients with ERP in lateral leads alone (ERP-lat $^{+}$) and ERP in both inferior leads and lateral leads (ERP-inf $^{+}$/lat $^{+}$) were associated with risk of all-cause mortality (*P*=0.029, 0.048, respectively; Supplementary Figures 5, 6), but were not associated with the risk of cardiovascular mortality (both *P* values >0.05; Supplementary Figures 7, 8) after adjusting for covariables. Although patients with ERP-inf $^{+}$/lat $^{+}$ were associated with increased risk of all-cause mortality, the data was not sufficient to make a strong conclusion because only 5 deaths were reported in this group during the 10-year follow-up.

Since age is a strong predictor of both all-cause and cardiovascular mortality [18], we further compared mortality rates by stratifying ERP (+) and ERP (-) individuals into 3 age subgroups (55-64, 65-74, and ≥75 years). Multivariate Cox proportional hazard analyses after adjusting for covariables showed that ERP was not a risk factor for both all-cause and cardiovascular mortality in all the age subgroups (all *P* values >0.05; Tables 2, 3, Supplementary Figures 9–14). Moreover, study subjects with ERP in inferior leads alone (ERP-inf $^{+}$), lateral leads alone (ERP-lat $^{+}$), or both inferior and lateral leads (ERP-inf $^{+}$/lat $^{+}$) were not associated with increased risk of both all-cause and cardiovascular mortality in all age subgroups (all *P* values >0.05; Supplementary Figure 15–32).

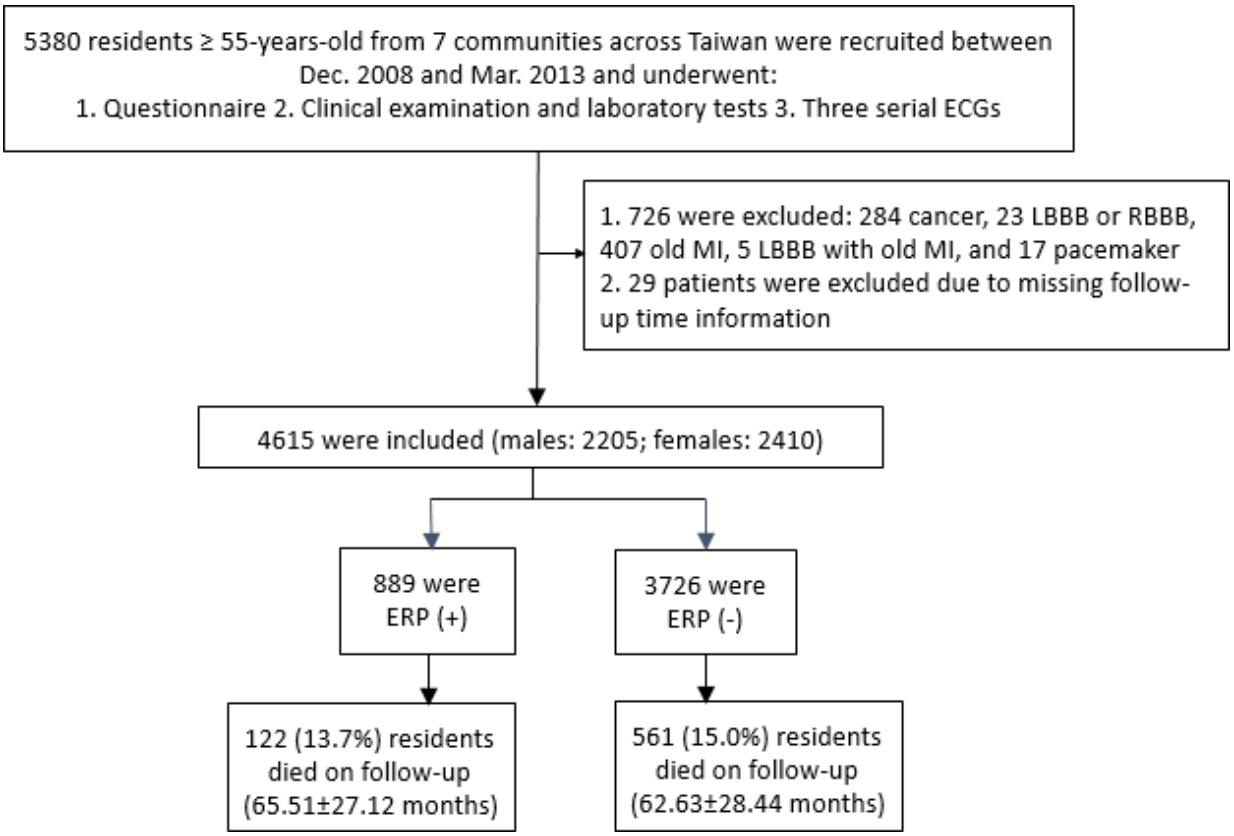

Figure 1. Schematic representation of the enrollment and inclusion criteria for the study subjects. ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; MI, myocardial infarction; ERP, early repolarization pattern

Table 1. Demographic and clinical characteristics of the study population*.

Parameters	All (N=4615)	ERP(+) (n=889)	ERP(-) (n=3,726)	*P*-value
Male, n (%)	2205 (47.8%)	470 (52.9%)	1735 (46.6%)	<0.001
Age at enrollment (years)	69.1±8.2	67.7±7.8	69.5±8.2	<0.001
BMI (kg/m^2)	24.5±3.5	24.1±3.3	24.6±3.5	<0.001
Systolic BP (mmHg)	128.4±18.7	125.89±18.7	128.9±18.7	<0.001
Diastolic BP (mmHg)	70.5±10.7	69.4±10.5	70.7±10.7	<0.001
Smoking				<0.001
Current	608 (13.2%)	168 (18.9%)	440 (11.8%)	
Quit	716 (15.5%)	132 (14.8%)	584 (15.8%)	
Never	3291 (71.3%)	589 (66.3%)	2702 (72.5%)	
Essential hypertension, n (%)	2011 (43.6%)	349 (39.3%)	1662 (44.6%)	0.004
Diabetes mellitus, n (%)	823 (17.8%)	159 (17.9%)	664 (17.8%)	0.99
Stroke, n (%)	231 (5%)	36 (4%)	195 (5%)	0.171
Hyperlipidemia, n (%)	1456 (31.5%)	269 (30.2%)	1187 (31.8%)	0.378
CKD, n (%)	667 (14.6%)	126 (14.1%)	541 (14.5%)	0.833
PR interval, *ms*	171.1±34.1	170.7±32.5	171.2±34.4	0.677
QTc, ms	437.0±22.6	431.4±20.7	438.3±22.9	<0.001

ERP: early repolarization pattern by the criteria adopted in 2015 [35]; BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; *Values are presented as n (%) or mean ± standard deviation; QTc was calculated by Bazett's equations.

Comparisons of the prevalence and clinical outcomes of ERP in community-based studies worldwide

As shown in Table 4, the prevalence of ERP ranged from ~1% to 25% in Caucasians and 3.5%-24% in Japanese according to the community based population studies worldwide [10, 13, 14, 16]. However, the association between all-cause and cardiovascular mortality and EPR was not consistent among the published studies. Most studies showed that ERP was not associated with all-cause mortality but was associated with cardiovascular mortality. Our study cohort included older middle-aged and geriatric individuals ≥55 years with an average age of 69.1±8.2 years (range: 55-103 years), which was the highest age average of a study cohort when compared with previous reports. Moreover, the prevalence of ERP was 19.26% in our study cohort. This was within the prevalence range reported by other studies (0.99-24.79%), but was higher than the mean worldwide prevalence of 6.42%. Overall, our study shows that ERP is not associated with increased risk of all-cause and cardiovascular mortality in older middle aged and geriatric Han-Chinese population in Taiwan.

DISCUSSION

The prevalence of cardiovascular disease is expected to increase because of a constant rise in the proportion of older individuals worldwide. ERP is not a rare event and has been reported in studies related to several ethnicities [19, 20], and has been associated with sudden cardiac arrest [15, 20]. To the best of our knowledge, this is the first study to examine the prevalence and prognostic value of ERP in a large cohort of older middle-aged and elderly individuals with a mean age ≥65 years.

Previous studies show that prevalence of ERP varies from ~1% to 25% in a general population [10, 13, 14, 16]. This wide range of ERP prevalence reflects differences in age range, proportions of male subjects, and inconsistent definition of ERP between studies. In the MONICA/KORA study that included 6,213 participants between 35-74 years, ERP prevalence of individuals above 55 years was 6.29% [15]. In the Japanese NIPPON DATA90 study with 7,630 participants aged 30-95 years, ERP prevalence of individuals above 60 years was 2.5% [14]. The number of participants in the older middle-aged and elderly population (aged 55-103 years) was highest in our study compared to previous studies. The prevalence of ERP in this age group was 19.2%— the highest overall ERP prevalence among all community-based studies that included study subjects with a mean age > 55 years. This may suggest that aging causes degeneration of the cardiac conduction pathways [21] or increased

fibrosis and fat deposition within the heart of elderly patients [22].

In the past years, the association between ERP and mortality has been tested in general populations by several epidemiologic studies [13, 15, 23–25]. The results are inconsistent and conflicting. The MONICA/KORA study screened 6,213 individuals aged 35-74 years and showed increased all-cause and cardiovascular mortality in individuals with ERP [15]. The CARDIA study enrolled 5,039 biracial young adults aged 18-30 years with a follow-up time >20 years

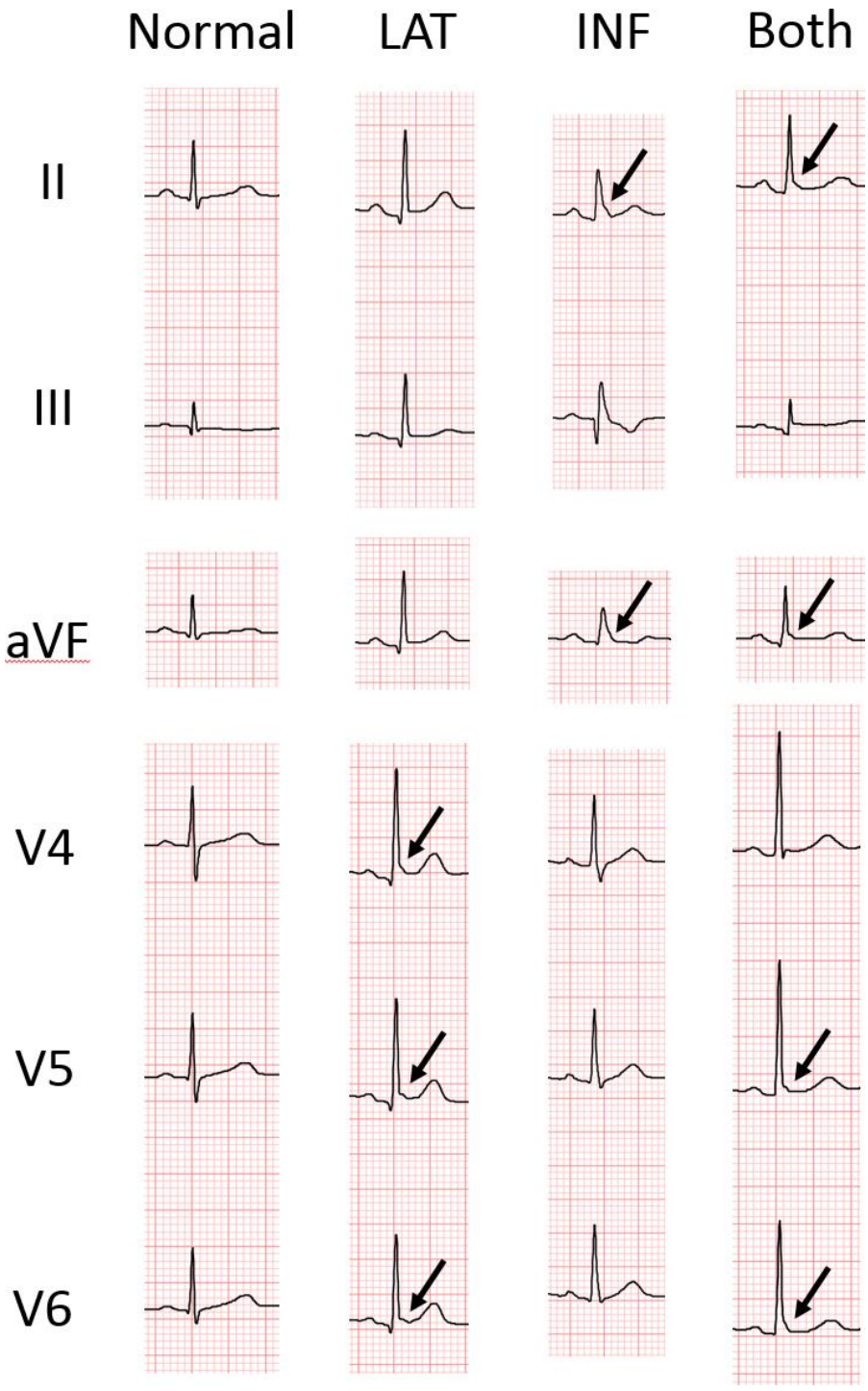

Figure 2. Representative ECGs of individuals with and without early repolarization pattern (ERP). LAT, ERP in lateral leads; INF, ERP in inferior leads; Both, ERP in both inferior and lateral leads. The arrow indicates junction (J)-point elevation greater than 0.1 mV.

and demonstrated that ERP was not associated with all-cause and cardiovascular mortality [13]. The CHD study consisting of 10,864 individuals aged 30-59 years concluded that ERP-positive in the inferior leads was associated with increased risk of cardiac mortality, but was not related to all-cause mortality [25]. A meta-analysis of 16 studies including 4 case-control and 12 prospective or retrospective studies (334,524 individuals from multiple ethnicities) showed that ERP was an electrocardiographic risk marker for deaths related to arrhythmia, cardiac diseases, and all-causes [23, 24]. However, there was considerable heterogeneity because of differences in study designs, ethnicity and potential misdiagnosis of ERP. Moreover, majority of these duties did not analyze older middle-aged and geriatric individuals. In the Japanese NIPPON DATA90 study of 2,433 individuals older than 60 years, subgroup analysis showed that J-point elevation was not associated with cardiovascular death or death from coronary artery disease [14]. Our random-sampling

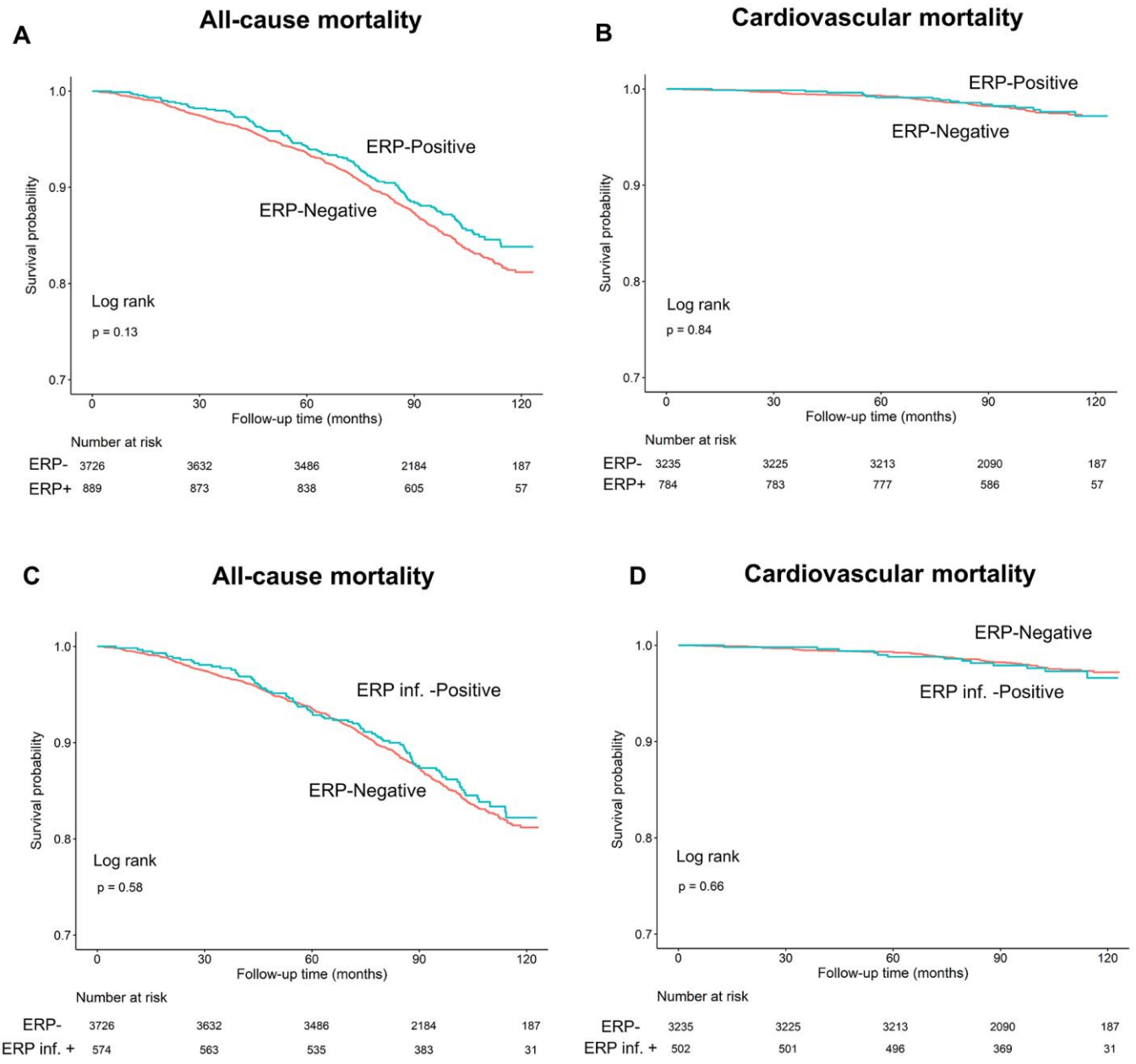

Figure 3. Kaplan–Meier survival curves show (**A**, **C**) all-cause and (**B**, **D**) cardiovascular mortality rates in individuals with and without early repolarization pattern, and individuals with and without early repolarization pattern in inferior leads.

community-based cohort study specifically enrolled older middle-aged and elderly individuals from the Han Chinese population, and prospectively followed up these individuals for 11years with less than 1% dropouts. Our analysis showed that ERP was not associated with both all-cause and cardiovascular mortality.

ECG is globally used as an inexpensive and noninvasive technique to detect electric abnormalities of the heart. Several individuals receive annual health examinations including ECG. ERP is an incidental and common finding on an ECG during a routine health examination. Our study provides an important reference for clinicians or health care providers when they encounter asymptomatic elderly individuals with an incidental ERP and without a family history of SCD in members younger than 40 years.

The results of the association between ERP and mortality in several epidemiologic studies are inconsistent and conflicting [13, 15, 23–25]. The possible reasons may be due to heterogeneity in observational studies, differences in study designs, as

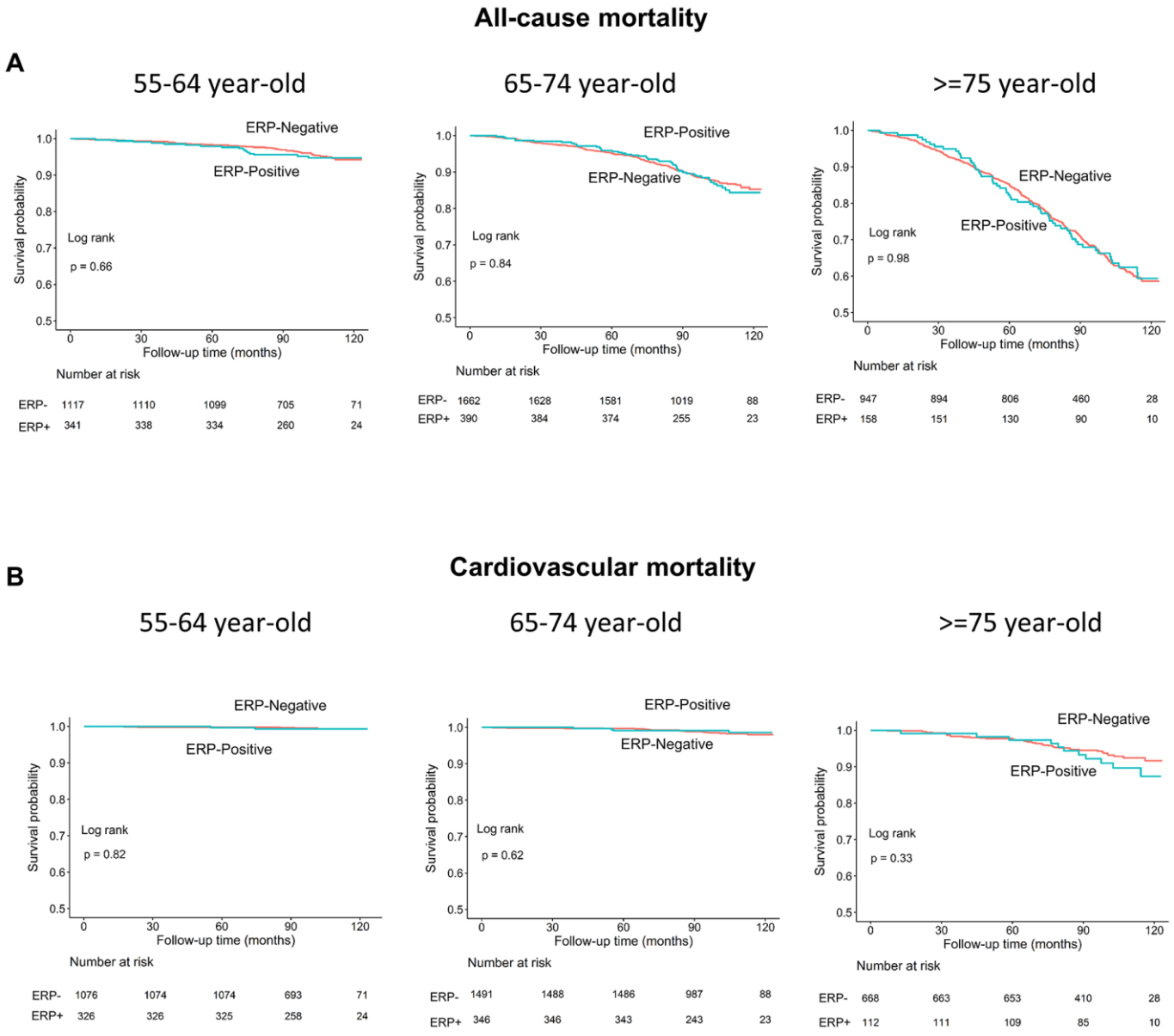

Figure 4. Kaplan–Meier survival curves show (**A**) all-cause and (**B**) cardiovascular mortality rates of individuals with and without early repolarization pattern stratified by age.

well as differences in age and ethnicity of the study subjects. Therefore, prospective long-term randomized clinical trials (RCTs) in different age groups (30-40 year or 60-70 year-olds) in specific ethnic populations are required in the future to minimize all possible confounding factors. Moreover, combining ERP with other ECG risk parameters (such as QTc interval) may provide better risk stratification of large community-based cohorts compared to ERP as a single ECG risk factor.

There are several limitations in our study. Firstly, our findings may not apply to younger individuals because our study consisted of individuals above the age of 55 years. Secondly, the HALST cohort was restricted to individuals of Han Chinese ethnicity, and may not be applicable to other ethnicities. Thirdly, detailed clinical information including echocardiographic assessments, coronary angiography, and medications were not available in the HALST database because this data was obtained during screening.

In summary, our study shows that prevalence of ERP in a standard 12-lead ECG is common in relatively healthy, community-dwelling, ambulatory individuals above 55 years. Moreover, ERP alone is not associated with all-cause and cardiovascular mortality.

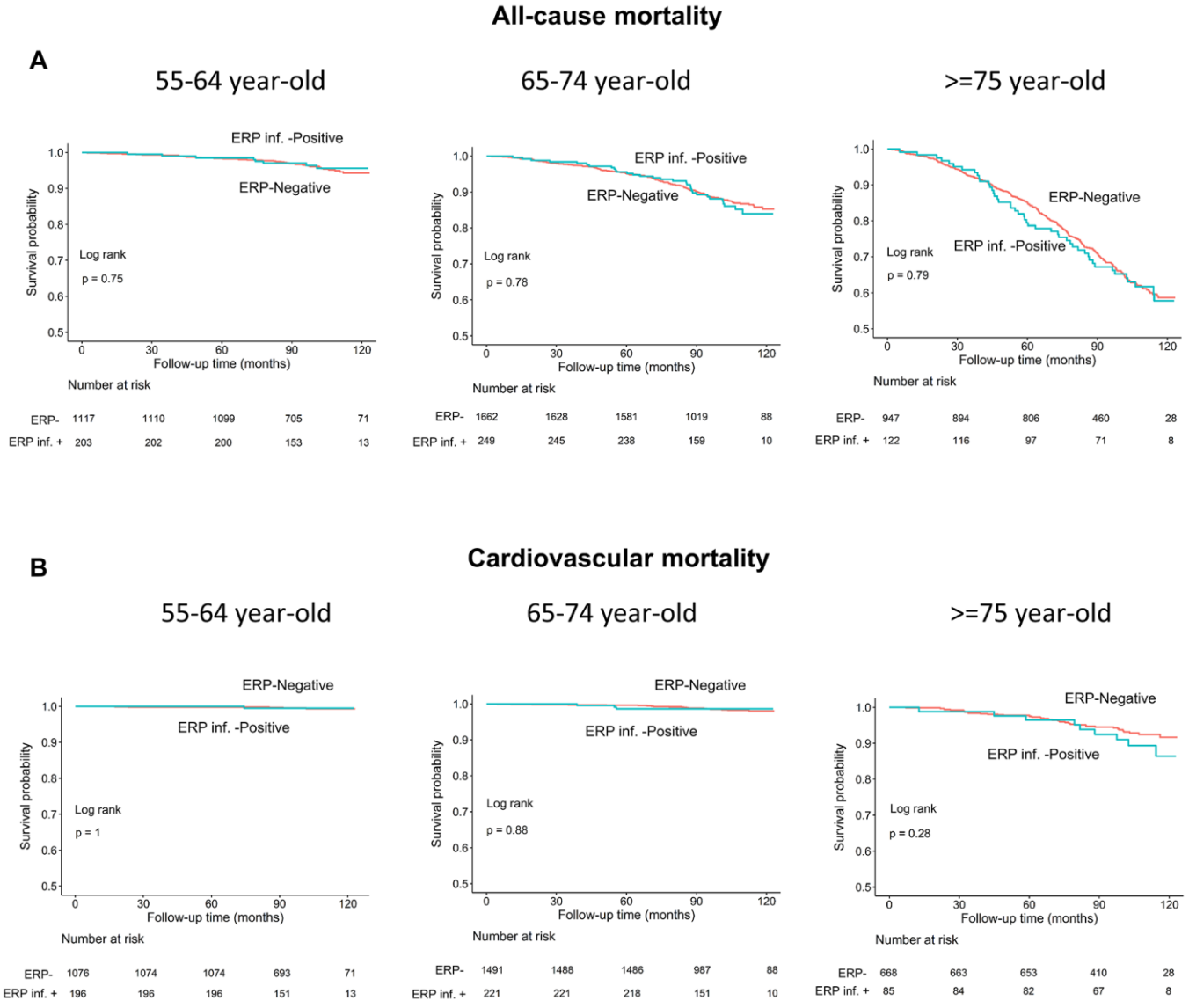

Figure 5. Kaplan–Meier survival curves show (**A**) all-cause and (**B**) cardiovascular mortality rates of individuals with and without early repolarization pattern in inferior leads stratified by age.

Table 2. Association between ERP and all-cause mortality*.

		Hazard ratio (95% CI)	*P*-value
All			
	ERP (reference: negative)	0.98 (0.81, 1.20)	0.877
	Gender (reference: male)	0.71 (0.57, 0.87)	0.001
	Age	1.11 (1.10, 1.12)	<0.001
	BMI (kg/m^2)	0.96 (0.94, 0.98)	<0.001
	Systolic BP (mmHg)	1.01 (1.01, 1.02)	<0.001
	Diastolic BP (mmHg)	0.99 (0.98, 0.99)	0.003
	Smoking (reference: current)		
	Quit	0.63 (0.50, 0.79)	<0.001
	Never	0.50 (0.40, 0.63)	<0.001
	Diabetes mellitus	1.51 (1.26, 1.81)	<0.001
	Stroke	1.94 (1.52, 2.48)	<0.001
	Chronic kidney disease	1.35 (1.10, 1.66)	0.005
	QTc	1.01 (1.00, 1.01)	<0.001
Age-stratified			
55-64 y			
	ERP (reference: negative)	1.04 (0.58, 1.86)	0.886
	Gender (reference: male)	0.34 (0.16, 0.73)	0.006
	Smoking (reference: current)		
	Quit	0.63 (0.31, 1.27)	0.198
	Never	0.40 (0.21, 0.79)	0.008
	QTc	1.01 (1.00, 1.03)	0.012
65-74 y			
	ERP (reference: negative)	1.01 (0.73, 1.39)	0.953
	Gender (reference: Male)	0.56 (0.39, 0.80)	0.001
	Systolic BP (mmHg)	1.02 (1.00, 1.03)	0.008
	Diastolic BP (mmHg)	0.97 (0.96, 0.99)	0.004
	Smoking (reference: current)		
	Quit	0.66 (0.45, 0.97)	0.032
	Never	0.44 (0.31, 0.64)	<0.001
	Stroke	1.98 (1.33, 2.95)	0.001
	QTc	1.01 (1.00, 1.01)	0.001
≥75 y			
	ERP (reference: negative)	0.87 (0.65, 1.17)	0.357
	BMI (kg/m^2)	0.92 (0.89, 0.95)	<0.001
	Systolic BP (mmHg)	1.02 (1.01, 1.03)	<0.001
	Diastolic BP (mmHg)	0.98 (0.97, 0.99)	0.002
	Smoking (reference: current)		
	Quit	0.78 (0.55, 1.09)	0.150
	Never	0.68 (0.48, 0.96)	0.030
	Diabetes mellitus	1.42 (1.11, 1.81)	0.005
	Stroke	1.89 (1.35, 2.64)	<0.001
	QTc	1.01 (1.00, 1.01)	0.008

ERP: early repolarization pattern; BMI: body mass index; BP: blood pressure; CI, confidence interval; *Except for ERP, only significant variables (*P*<0.05) are shown here; QTc was calculated by Bazett's equations.

Table 3. Association between ERP and cardiovascular mortality*.

		Hazard ratio (95% CI)	*P*-value
All			
	ERP (reference: negative)	1.27 (0.74, 2.20)	0.386
	Age	1.13 (1.10, 1.17)	<0.001
	Stroke	2.11 (1.01, 4.42)	0.048
Age-stratified			
55-64 y			
	ERP (reference: negative)	1.08 (0.21, 5.68)	0.928
	BMI	1.23 (1.02, 1.47)	0.027
	CKD	4.83 (1.03, 22.61)	0.046
65-74 y			
	ERP (reference: negative)	0.83 (0.28, 2.47)	0.744
	Stroke	3.59 (1.30, 9.92)	0.014
	QTc	1.02 (1.00, 1.04)	0.017
≥75 y			
	ERP (reference: negative)	1.54 (0.77, 3.07)	0.219
	Systolic BP (mmHg)	1.03 (1.01, 1.05)	0.014

ERP: early repolarization pattern; BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; *Except for ERP, only significant variables (*P*<0.05) are shown here. QTc was calculated by Bazett's equations.

Table 4. Summary of results from community-based studies worldwide regarding the prevalence of ERP, age distribution, and relationship with all-cause and cardiovascular mortality.

Study	Year	Country	Screened population N	Male (%)	Age (years)	ERP (+)			All-cause mortality	Cardiovascular mortality
						N (%)	M (%)	F (%)		
North America										
Klatsky et al.[10]	2003	USA	73,088	43.88	NA	670 (0.92)	583 (1.82)	87 (0.21)	Not increased	Increased
Olson et al.[19]	2011	USA	15,141	44.30	54.1	1866 (12.3)	1420 (21.17)	446 (5.29)	Not increased	SCD increased in whites and females
Uberoi et al.[40]	2011	USA	29,281	87.24	55±15	714 (2.44)	661 (2.59)	53 (1.42)	NA	Not increased
Perez et al.[41]	2012	USA	29,281	87	55	664 (2.27)	NA	NA	NA	Increased in non-African Americans but not in African Americans
Ilkhanoff et al.[13]	2014	USA	5,039	45.54	25 (18-30)	1249 (24.79)	1139 (49.63)	110 (4.01)	Not increased	Not increased
Pargaonkar et al.[42]	2015	USA	20,661	90.53	20-55	4219 (20)	3840 (20.53)	379 (19.38)	NA	Not increased
Leiderman et al.[43]	2019	USA	17,901	38.57	53±13	995 (5.6)	489 (7.08)	506 (4.60)	Not increased	NA
Europe										
Tikkanen et al.[25]	2009	Finland	10,864	52.40	44±8	630 (5.8)	407 (7.15)	223 (4.31)	NA	Increased
Sinner et al.[15]	2010	Germany	6,213	48.85	35-74	812 (13.1)	439 (14.46)	373 (11.74)	Increased	Increased
Rollin et al.[20]	2012	France	1,161	51.59	35-64	159 (13.7)	126 (21.04)	33 (5.87)	Increased	Increased
Asia										
Haruta et al.[16]	2011	Japan	5,676	43.71	47.2±15.4	779 (23.9)	815 (31.20)	614 (18.25)	Decreased	Decreased
Hisamatsu et al.[14]	2013	Japan	7,630	40.73	52.4 (30-95)	264 (3.5)	253 (8.14)	11 (0.24)	NA	Cardiac death and death from CAD increased
Juang et al.[present study]	2020	Taiwan	4,615	47.78	69.1±8.2 (55-103)	889 (19.26)	489 (7.08)	506 (4.60)	Not increased	Not increased
Total	-	-	226,851		-	14,560 (6.42)	10,642 (9.72)	3,254 (3.69)	-	-

ERP: early repolarization pattern; NA: not available, means no number was provided in the papers; USA: United States of America; M: male; F: female; SCD: sudden cardiac death; CAD: coronary artery disease

MATERIALS AND METHODS

Study subjects and inclusion criteria

Majority (>95%) of Taiwanese are of Han Chinese ancestry and nearly 2% are of aboriginal Austronesian ancestry [26]. In this study, we initially included 5,380 Han Chinese individuals of the HALST study cohort and excluded all aboriginal Taiwanese subjects [27–29]. This study was approved by the Ethics Committee of the National Health Research Institutes and conducted according to the principles of the Declaration of Helsinki. We obtained signed informed consent from the study subjects. The study cohort represented a random sample of the entire national population and was selected based on citizen IDs from 7 communities in the Northern, Central, Southern, and Eastern regions of Taiwan. The eligible and willing participants were enrolled from December 2008 to March 2013. At the time of enrollment, we prospectively collected three serial 12-lead ECGs and other relevant clinical and demographic information from the study subjects.

We then excluded individuals with cancer, significant heart diseases such as myocardial infarction and severe valvular diseases, ventricular conduction delay (left or right bundle branch block or QRS>120 ms), atrial fibrillation or flutter, QTc interval corrected for heart rate with Bazett's formula (QTc) of less than 340 msec (short QT interval) or more than 440 msec (long QT interval) at baseline and before arrhythmia [30, 31], Brugada type 1 ECG [32], catecholaminergic arrhythmias [33], ventricular pre-excitation, and implanted pacemakers. The final study cohort consisted of 4,615 individuals, which was followed up for 95.1±21.9 months. During follow-up, 770 study subjects died of cardiac (n=87) or other causes (n=683).

All participants were prospectively followed on a regular basis according to the HALST study framework guidelines and the follow-up information was available until April 2019. We obtained death certificates from the National Taiwan Ministry of Health and Welfare and evaluated the cause using the 10th revision of the International Classification of Diseases (ICD-10). The death from cardiac causes was defined by ICD codes, I01-I02.0, I05-I09, I20-I25, I27, and I30-I52.

ECG recording and definition of ERP

The 12-lead ECGs (Hewlett Packard, USA) were recorded using standard settings of 10 mm/mV and 25 mm/s. PR and QRS were computed automatically, whereas, QTc was computed using the Bazett's formula [34]. ERP was defined as a J-point (QRS-ST junction) elevation of at least ≥0.1 mV from baseline in ≥2 adjacent leads with either QRS slurring or notching morphology, as described by Haissaguerre et al. and the 2015 consensus criteria [7, 35]. The anterior precordial leads (V1 to V3) were excluded from the analysis to avoid inclusion of patients with right ventricular arrhythmogenic dysplasia or the Brugada syndrome [36, 37].

ECGs were displayed on a 24-inch computer screen in multiple formats to enable careful classification of slurring on the downslope of the R and J waves. All ECGs were independently analyzed and interpreted in a random order by two trained cardiologists who were blinded to clinical data and the follow-up status. In case of divergent results, a third blinded cardiologist re-interpreted the ECG and a preliminary ERP status was achieved by a majority vote. After the preliminary decision on ERP status, two trained cardiologists jointly reassessed all the ECGs that were considered ERP-positive and reached a final consensus decision on the ERP status.

Long-term prognosis and follow-up

We collected clinical data regarding history of unexplained syncope, circumstances of sudden cardiac arrest, and a family history of unexplained sudden death (at <40 years of age).

The primary end point was death from cardiac causes, and the secondary end point was death from any cause before April 2019. An annual follow-up telephone interview of all the study participants was carried out by the study nurses to determine any new cardiovascular or frailty-related events after the initial enrollment. The cause of deaths was determined by examining the death certificates from the National Taiwan Institute of Health and Welfare and reviewed by 2 clinicians blinded to the ECG results. The cause of sudden death from arrhythmia was adjudicated by a committee of experienced cardiologists who were blinded to the data from the ECG analyses.

Statistical analysis

We used the Fisher exact test to compare categorical variables and Student's t test to compare continuous data between the groups. Linear regression was used for continuous variables and logistic regression was used for dichotomous variables to determine the relationship between ERP and mortality. Multivariate analysis was performed to determine hazard ratios (HRs) and confidence intervals (CIs). The models were primarily adjusted for age and sex, and further adjusted for covariates that were selected on the basis of previous evidence of an association with death from

cardiovascular causes or other causes. This included continuous variables such as BMI, SBP, DBP, and QTc, and categorical variables such as smoking status (current, quit, never), hypertension, diabetes mellitus, hyperlipidemia, stroke, and chronic kidney disease. The relationship between ERP and mortality was calculated using a weighted Cox proportional hazards model [38]. Kaplan-Meier survival curves and log rank tests were used to determine survival times of different groups of individuals. Clinical factors such as gender, age, smoking, SBP, DBP, BMI, stroke, diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease were used for multivariable analysis. $P < 0.05$ was considered statistically significant. Inter-observer agreement was based on the overall proportion of agreements and the Kappa statistic across all ECGs. Statistical analyses were performed using the R software, version 4.0.1 (R Foundation for Statistical Computing) [39].

AUTHOR CONTRIBUTIONS

Conceptualization and study design: SFSY, JJMJ, and CYJC; Enrollment of study subjects, data collection, and laboratory work: CAH, ISC, ICW, CCH, TYC, and WTT; Data analysis and interpretation: SFSY, JJMJ, CYJC; Resources and supervision: CAH and JJMJ; Manuscript writing, review, and editing: SFSY and JJMJ.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Abbreviations

BMI: body mass index; BP: blood pressure; CI: confidence interval; ERP: early repolarization pattern by the criteria adopted in 2015 [1]; HR: hazard ratio; QTcB: corrected QT interval (QTc) calculated by Bazett's equations.

inf^+ indicates ERP-positive in the inferior leads

lat^+ indicates ERP-positive in the lateral leads

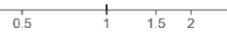
inf^+ lat^+ indicates ERP-positive in both inferior and lateral leads

Supplementary References

1. Macfarlane PW, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen JT, Wellens H, Yan GX. The Early Repolarization Pattern: A Consensus Paper. J Am Coll Cardiol. 2015; 66:470–77. https://doi.org/10.1016/j.jacc.2015.05.033 PMID:26205599

Supplementary Figures

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	3719		Reference	
	+	888		0.98 (0.81, 1.20)	0.877
Gender	Male	2202		Reference	
	Female	2405		0.71 (0.57, 0.87)	0.001
Age		4607		1.11 (1.10, 1.12)	<0.001
BMI		4607		0.96 (0.94, 0.98)	<0.001
Systolic_BP		4607		1.01 (1.01, 1.02)	<0.001
Diastolic_BP		4607		0.99 (0.98, 0.99)	0.003
Smoke	Current	605		Reference	
	Quitted	715		0.63 (0.50, 0.79)	<0.001
	Never	3287		0.50 (0.40, 0.63)	<0.001
Hypertension	0	2601		Reference	
	1	2006		0.87 (0.69, 1.11)	0.270
Diabetes_Mellitus	0	3785		Reference	
	1	822		1.51 (1.26, 1.81)	<0.001
Stroke	0	4377		Reference	
	1	230		1.94 (1.52, 2.48)	<0.001
Hyperlipidemia	0	3151		Reference	
	1	1456		0.89 (0.75, 1.06)	0.206
Chronic_Kidney_Disease	0	3941		Reference	
	1	666		1.35 (1.10, 1.66)	0.005
QTcB		4607		1.01 (1.00, 1.01)	<0.001

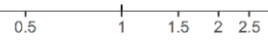


Supplementary Figure 1. Association between ERP and all-cause mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model adjusted for all covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	3231		Reference	
	+	784		1.27 (0.74, 2.20)	0.386
Gender	Male	1830		Reference	
	Female	2185		1.01 (0.55, 1.84)	0.980
Age		4015		1.13 (1.10, 1.17)	<0.001
BMI		4015		1.00 (0.94, 1.06)	0.919
Systolic_BP		4015		1.02 (1.00, 1.04)	0.092
Diastolic_BP		4015		0.99 (0.96, 1.01)	0.264
Smoke	Current	477		Reference	
	Quitted	583		0.83 (0.40, 1.73)	0.625
	Never	2955		0.57 (0.27, 1.20)	0.138
Hypertension	0	2313		Reference	
	1	1702		1.09 (0.57, 2.11)	0.794
Diabetes_Mellitus	0	3347		Reference	
	1	668		1.54 (0.93, 2.55)	0.090
Stroke	0	3851		Reference	
	1	164		2.11 (1.01, 4.42)	0.048
Hyperlipidemia	0	2722		Reference	
	1	1293		0.81 (0.50, 1.32)	0.399
Chronic_Kidney_Disease	0	3448		Reference	
	1	567		0.98 (0.51, 1.91)	0.957
QTcB		4015		1.01 (1.00, 1.02)	0.058

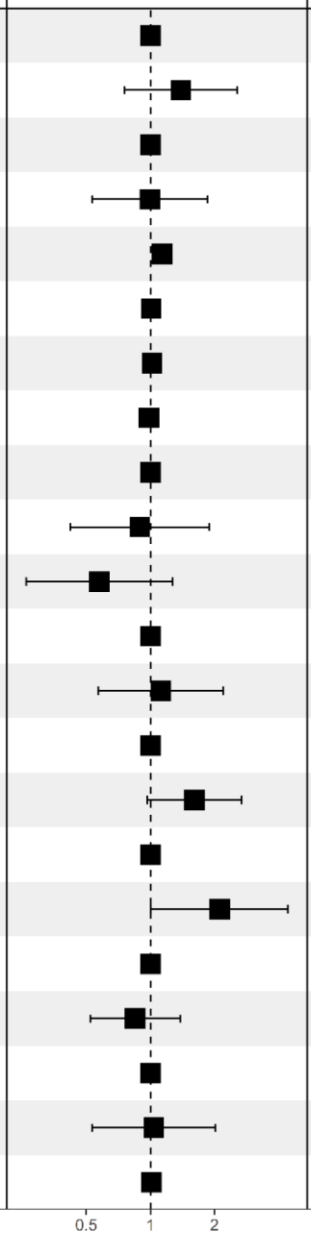
Supplementary Figure 2. Association between ERP and cardiovascular mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model adjusted for all covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	3719		Reference	
	inf. +	573		0.93 (0.74, 1.17)	0.534
Gender	Male	2038		Reference	
	Female	2254		0.72 (0.58, 0.89)	0.002
Age		4292		1.11 (1.10, 1.12)	<0.001
BMI		4292		0.95 (0.93, 0.98)	<0.001
Systolic_BP		4292		1.01 (1.01, 1.02)	<0.001
Diastolic_BP		4292		0.99 (0.98, 1.00)	0.004
Smoke	Current	554		Reference	
	Quitted	674		0.63 (0.49, 0.80)	<0.001
	Never	3064		0.49 (0.39, 0.63)	<0.001
Hypertension	0	2407		Reference	
	1	1885		0.88 (0.69, 1.12)	0.295
Diabetes_Mellitus	0	3517		Reference	
	1	775		1.54 (1.28, 1.85)	<0.001
Stroke	0	4072		Reference	
	1	220		1.97 (1.54, 2.53)	<0.001
Hyperlipidemia	0	2927		Reference	
	1	1365		0.88 (0.74, 1.06)	0.182
Chronic_Kidney_Disease	0	3670		Reference	
	1	622		1.36 (1.10, 1.69)	0.004
QTcB		4292		1.01 (1.00, 1.01)	<0.001

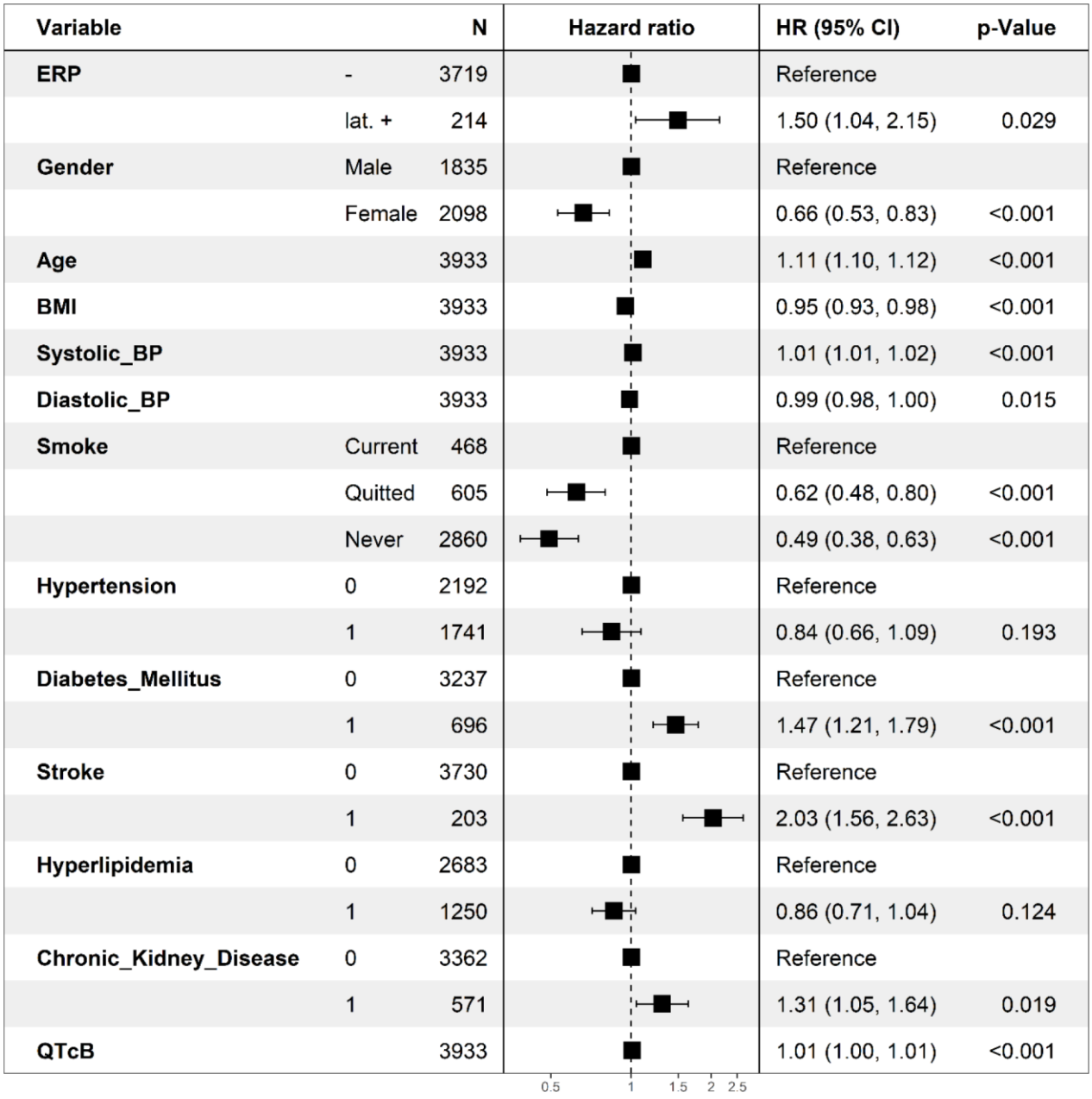


Supplementary Figure 3. Association between positive ERP in the inferior leads and all-cause mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model adjusted for all covariables.

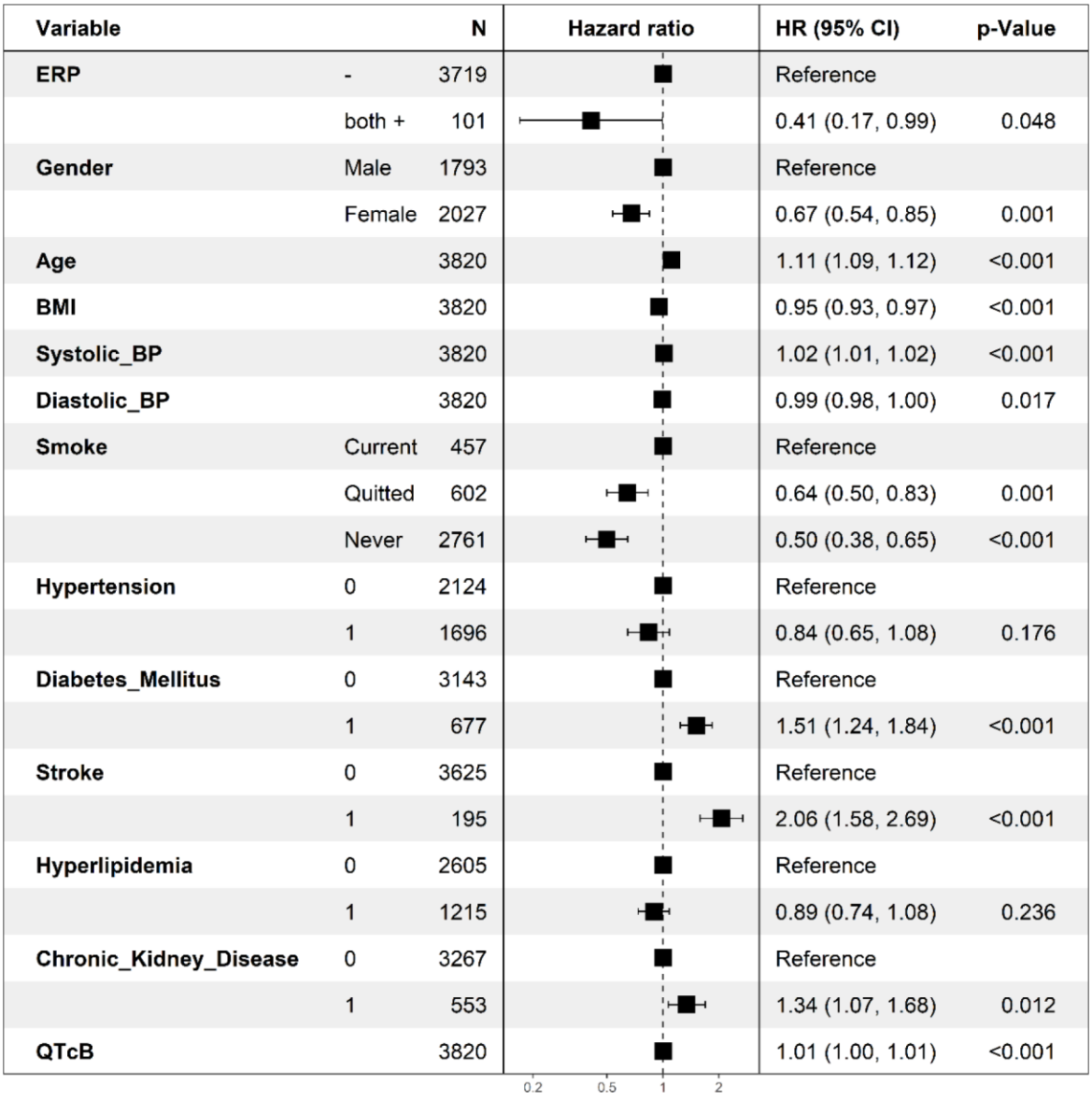
Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	3231		Reference	
	inf. +	502		1.39 (0.76, 2.55)	0.288
Gender	Male	1687		Reference	
	Female	2046		0.99 (0.53, 1.86)	0.987
Age		3733		1.13 (1.10, 1.17)	<0.001
BMI		3733		1.01 (0.94, 1.07)	0.843
Systolic_BP		3733		1.02 (1.00, 1.04)	0.051
Diastolic_BP		3733		0.99 (0.96, 1.01)	0.271
Smoke	Current	433		Reference	
	Quitted	548		0.89 (0.42, 1.89)	0.764
	Never	2752		0.58 (0.26, 1.27)	0.170
Hypertension	0	2137		Reference	
	1	1596		1.12 (0.57, 2.19)	0.743
Diabetes_Mellitus	0	3104		Reference	
	1	629		1.61 (0.97, 2.67)	0.067
Stroke	0	3577		Reference	
	1	156		2.11 (1.01, 4.43)	0.048
Hyperlipidemia	0	2521		Reference	
	1	1212		0.85 (0.52, 1.38)	0.504
Chronic_Kidney_Disease	0	3204		Reference	
	1	529		1.04 (0.53, 2.02)	0.918
QTcB		3733		1.01 (1.00, 1.02)	0.026



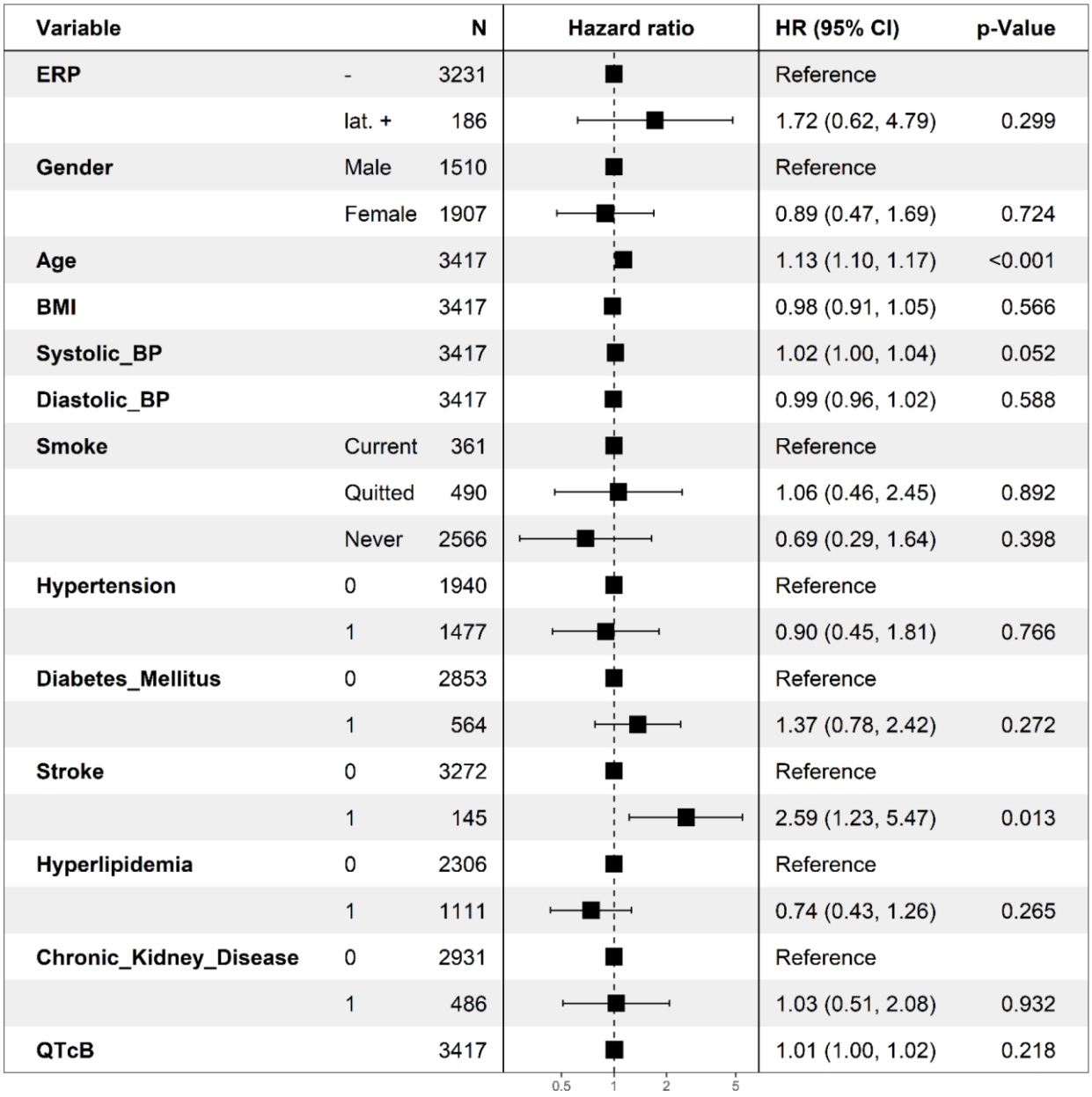
Supplementary Figure 4. Association between positive ERP in the inferior leads and cardiovascular mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



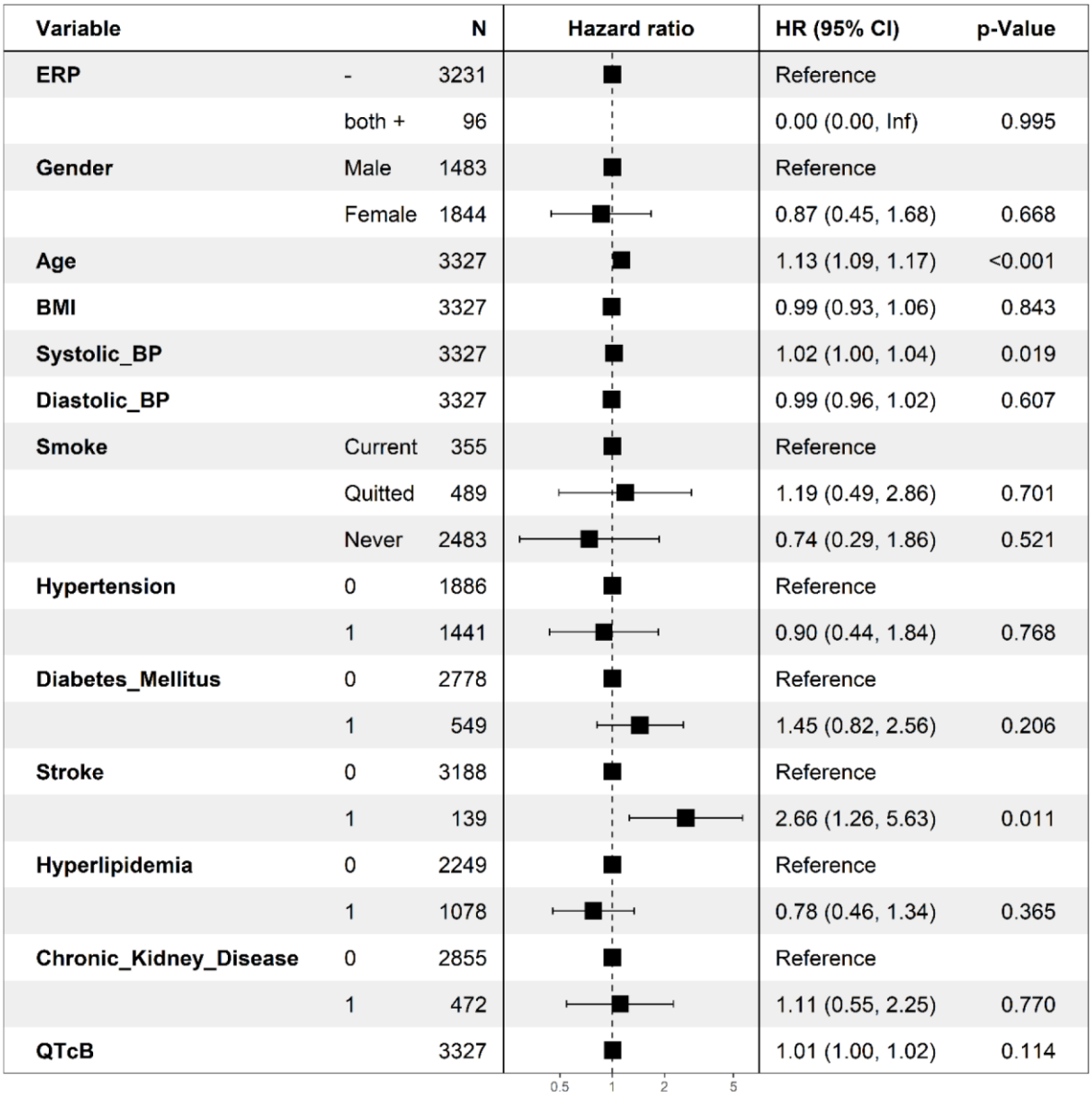
Supplementary Figure 5. Association between ERP-positive in the lateral leads and all-cause mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



Supplementary Figure 6. Association between positive ERP in both the inferior and lateral leads and all-cause mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



Supplementary Figure 7. Association between positive ERP in the lateral leads and cardiovascular mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



Supplementary Figure 8. Association between positive ERP in both inferior and lateral leads and cardiovascular mortality. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

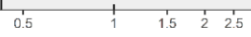
Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1117		Reference	
	+	341		1.04 (0.58, 1.86)	0.886
Gender	Male	704		Reference	
	Female	754		0.34 (0.16, 0.73)	0.006
BMI		1458		0.96 (0.89, 1.04)	0.339
Systolic_BP		1458		1.02 (1.00, 1.05)	0.093
Diastolic_BP		1458		0.96 (0.93, 1.00)	0.057
Smoke	Current	259		Reference	
	Quitted	181		0.63 (0.31, 1.27)	0.198
	Never	1018		0.40 (0.21, 0.79)	0.008
Hypertension	0	1012		Reference	
	1	446		0.94 (0.42, 2.10)	0.880
Diabetes_Mellitus	0	1278		Reference	
	1	180		1.80 (0.96, 3.35)	0.065
Stroke	0	1416		Reference	
	1	42		1.56 (0.55, 4.40)	0.404
Hyperlipidemia	0	993		Reference	
	1	465		0.93 (0.53, 1.64)	0.801
Chronic_Kidney_Disease	0	1223		Reference	
	1	235		1.62 (0.91, 2.88)	0.103
QTcB		1458		1.01 (1.00, 1.03)	0.012

Supplementary Figure 9. Association between ERP and all-cause mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1660		Reference	
	+	390		1.01 (0.73, 1.39)	0.953
Gender	Male	930		Reference	
	Female	1120		0.56 (0.39, 0.80)	0.001
BMI		2050		1.00 (0.96, 1.04)	0.906
Systolic_BP		2050		1.02 (1.00, 1.03)	0.008
Diastolic_BP		2050		0.97 (0.96, 0.99)	0.004
Smoke	Current	238		Reference	
	Quitted	282		0.66 (0.45, 0.97)	0.032
	Never	1530		0.44 (0.31, 0.64)	<0.001
Hypertension	0	1105		Reference	
	1	945		0.86 (0.57, 1.30)	0.480
Diabetes_Mellitus	0	1626		Reference	
	1	424		1.18 (0.88, 1.59)	0.264
Stroke	0	1939		Reference	
	1	111		1.98 (1.33, 2.95)	0.001
Hyperlipidemia	0	1376		Reference	
	1	674		0.97 (0.73, 1.28)	0.804
Chronic_Kidney_Disease	0	1748		Reference	
	1	302		1.30 (0.93, 1.82)	0.119
QTcB		2050		1.01 (1.00, 1.01)	0.001

Supplementary Figure 10. Association between ERP and all-cause mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

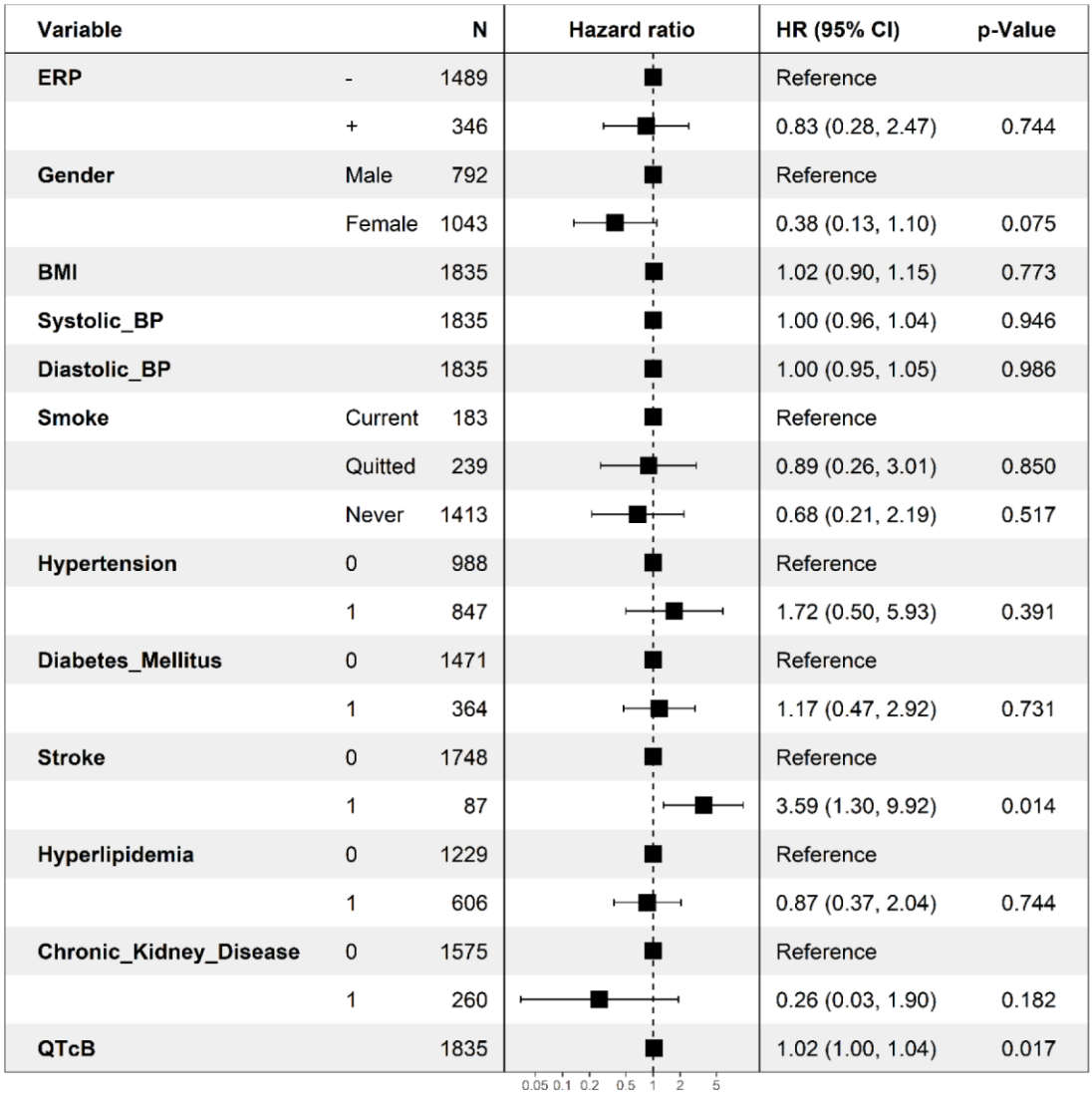
Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	942		Reference	
	+	157		0.87 (0.65, 1.17)	0.357
Gender	Male	568		Reference	
	Female	531		0.81 (0.62, 1.07)	0.143
BMI		1099		0.92 (0.89, 0.95)	<0.001
Systolic_BP		1099		1.02 (1.01, 1.03)	<0.001
Diastolic_BP		1099		0.98 (0.97, 0.99)	0.002
Smoke	Current	108		Reference	
	Quitted	252		0.78 (0.55, 1.09)	0.150
	Never	739		0.68 (0.48, 0.96)	0.030
Hypertension	0	484		Reference	
	1	615		0.85 (0.61, 1.17)	0.319
Diabetes_Mellitus	0	881		Reference	
	1	218		1.42 (1.11, 1.81)	0.005
Stroke	0	1022		Reference	
	1	77		1.89 (1.35, 2.64)	<0.001
Hyperlipidemia	0	782		Reference	
	1	317		0.82 (0.64, 1.04)	0.101
Chronic_Kidney_Disease	0	970		Reference	
	1	129		1.22 (0.90, 1.65)	0.196
QTcB		1099		1.01 (1.00, 1.01)	0.008



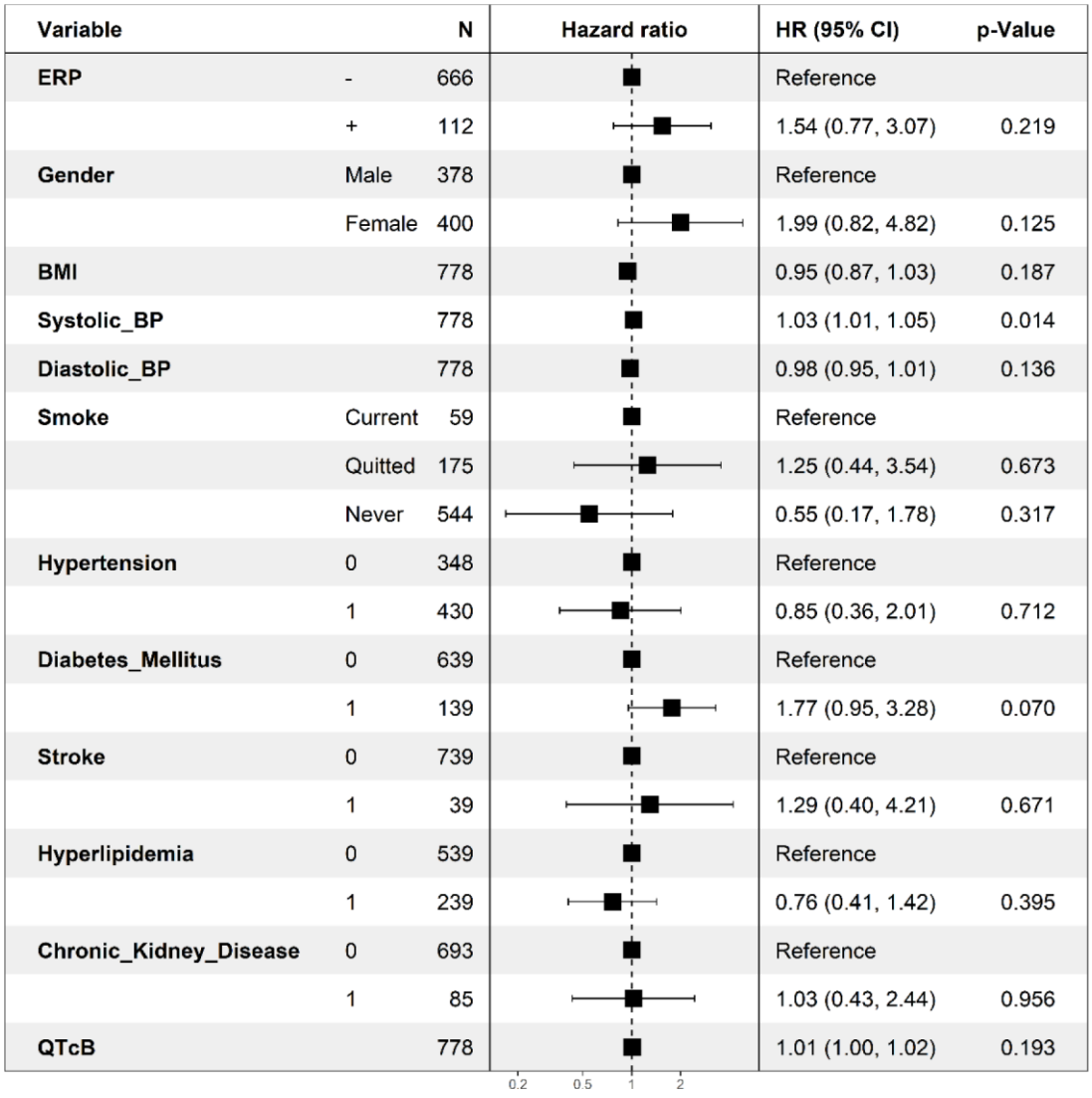
Supplementary Figure 11. Association between ERP and all-cause mortality among individuals aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1076		Reference	
	+	326		1.08 (0.21, 5.68)	0.928
Gender	Male	660		Reference	
	Female	742		0.25 (0.03, 1.91)	0.183
BMI		1402		1.23 (1.02, 1.47)	0.027
Systolic_BP		1402		1.02 (0.93, 1.13)	0.654
Diastolic_BP		1402		0.90 (0.79, 1.03)	0.139
Smoke	Current	235		Reference	
	Quitted	169		0.00 (0.00, Inf)	0.999
	Never	998		1.27 (0.21, 7.78)	0.798
Hypertension	0	977		Reference	
	1	425		1.46 (0.09, 24.09)	0.790
Diabetes_Mellitus	0	1237		Reference	
	1	165		0.00 (0.00, Inf)	0.999
Stroke	0	1364		Reference	
	1	38		0.00 (0.00, Inf)	0.999
Hyperlipidemia	0	954		Reference	
	1	448		1.09 (0.20, 6.03)	0.922
Chronic_Kidney_Disease	0	1180		Reference	
	1	222		4.83 (1.03, 22.61)	0.046
QTcB		1402		0.99 (0.95, 1.03)	0.503

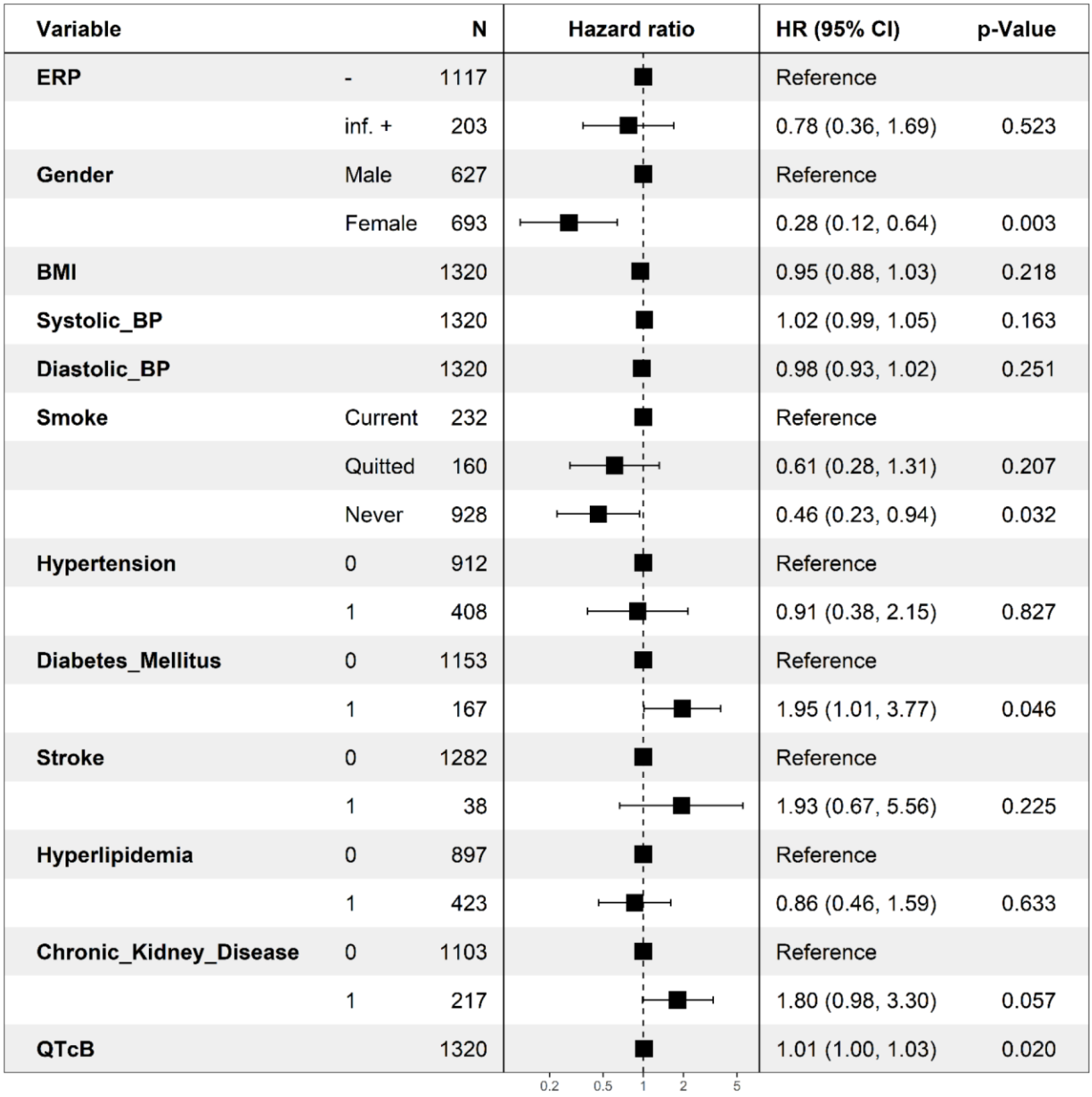
Supplementary Figure 12. Association between ERP and cardiovascular mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



Supplementary Figure 13. Association between ERP and cardiovascular mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

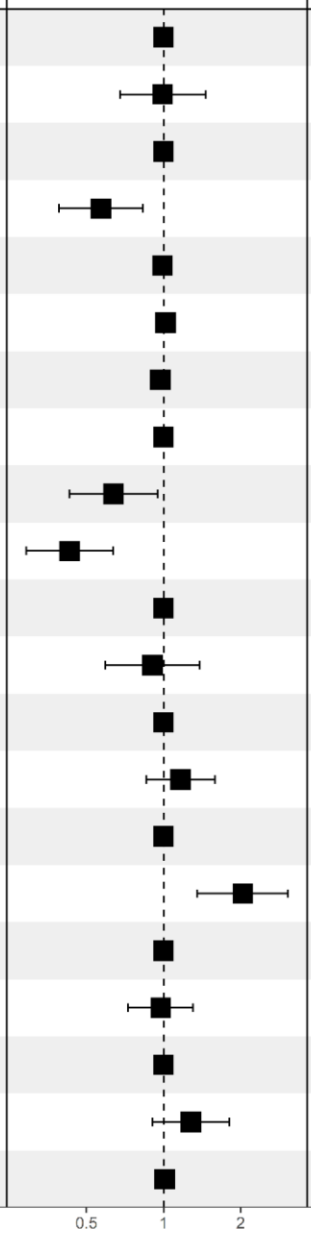


Supplementary Figure 14. Association between ERP and cardiovascular mortality among individuals aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

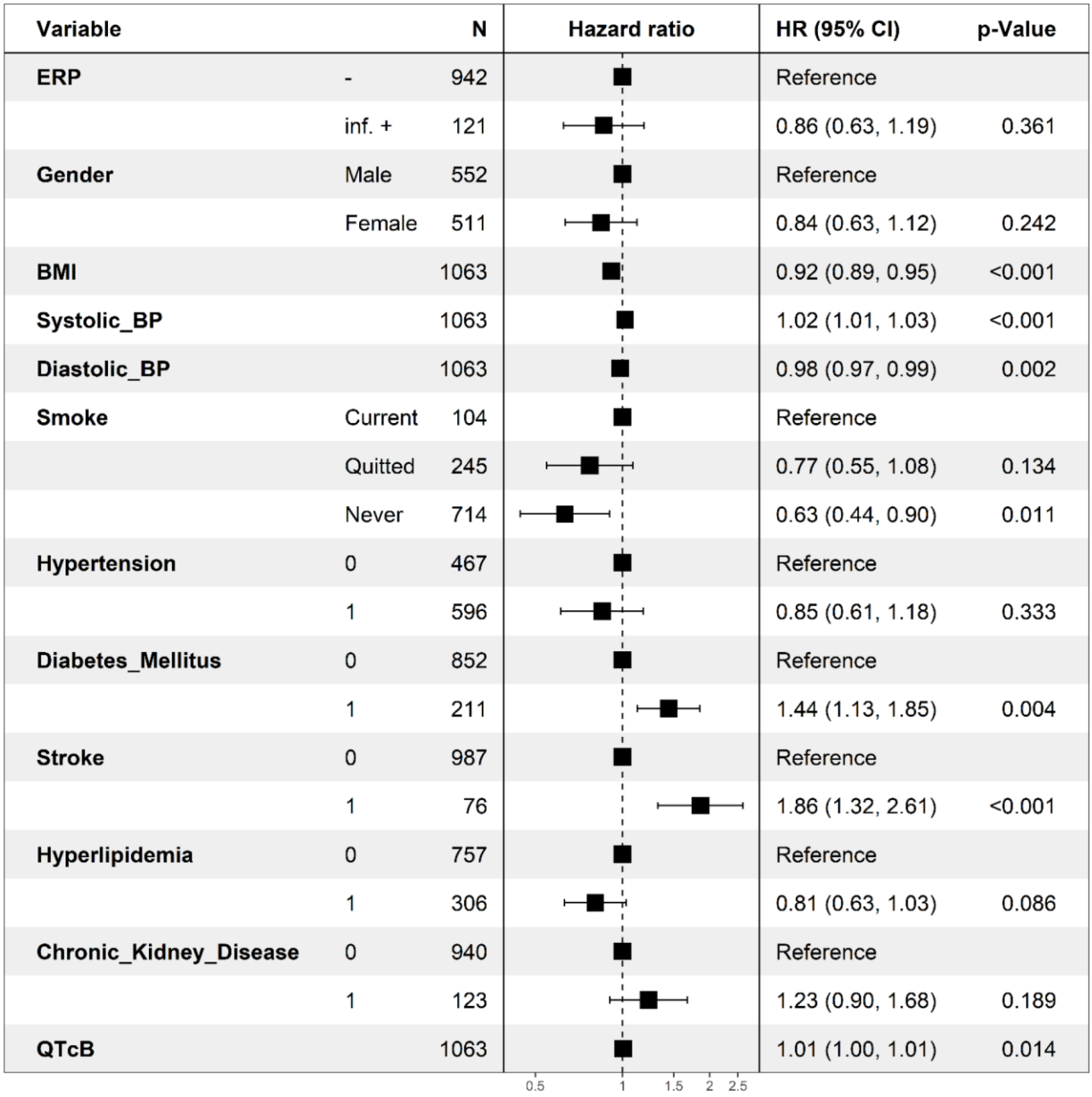


Supplementary Figure 15. Association between positive ERP in inferior leads and all-cause mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1660		Reference	
	inf. +	249		0.99 (0.68, 1.46)	0.966
Gender	Male	859		Reference	
	Female	1050		0.57 (0.39, 0.83)	0.003
BMI		1909		0.99 (0.95, 1.03)	0.583
Systolic_BP		1909		1.02 (1.00, 1.03)	0.016
Diastolic_BP		1909		0.97 (0.95, 0.99)	0.003
Smoke	Current	218		Reference	
	Quitted	269		0.64 (0.43, 0.95)	0.026
	Never	1422		0.43 (0.29, 0.64)	<0.001
Hypertension	0	1028		Reference	
	1	881		0.91 (0.59, 1.38)	0.646
Diabetes_Mellitus	0	1512		Reference	
	1	397		1.17 (0.86, 1.59)	0.329
Stroke	0	1803		Reference	
	1	106		2.04 (1.36, 3.06)	0.001
Hyperlipidemia	0	1273		Reference	
	1	636		0.97 (0.73, 1.30)	0.859
Chronic_Kidney_Disease	0	1627		Reference	
	1	282		1.28 (0.91, 1.81)	0.161
QTcB		1909		1.01 (1.00, 1.01)	0.003

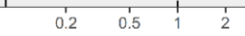


Supplementary Figure 16. Association between positive ERP in the inferior leads and all-cause mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



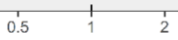
Supplementary Figure 17. Association between positive ERP in the inferior leads and all-cause mortality among individuals aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1117		Reference	
	lat. +	95		1.89 (0.88, 4.08)	0.104
Gender	Male	568		Reference	
	Female	644		0.26 (0.11, 0.60)	0.002
BMI		1212		0.96 (0.88, 1.04)	0.282
Systolic_BP		1212		1.02 (0.99, 1.05)	0.255
Diastolic_BP		1212		0.97 (0.93, 1.01)	0.157
Smoke	Current	193		Reference	
	Quitted	151		0.59 (0.28, 1.22)	0.154
	Never	868		0.39 (0.19, 0.79)	0.009
Hypertension	0	839		Reference	
	1	373		0.99 (0.41, 2.39)	0.985
Diabetes_Mellitus	0	1068		Reference	
	1	144		2.07 (1.06, 4.08)	0.034
Stroke	0	1180		Reference	
	1	32		1.47 (0.44, 4.88)	0.529
Hyperlipidemia	0	817		Reference	
	1	395		0.71 (0.38, 1.34)	0.289
Chronic_Kidney_Disease	0	1011		Reference	
	1	201		1.55 (0.83, 2.89)	0.166
QTcB		1212		1.01 (1.00, 1.03)	0.022



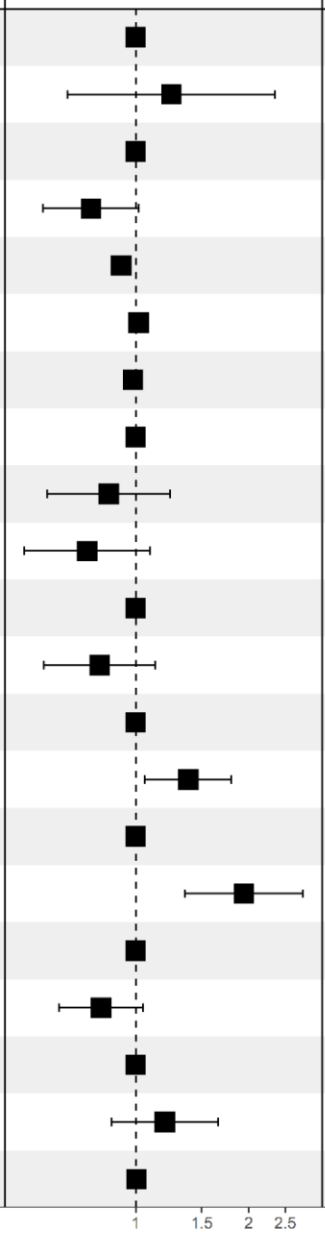
Supplementary Figure 18. Association between positive ERP in the lateral leads and all-cause mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1660		Reference	
	lat. +	95		1.36 (0.78, 2.35)	0.277
Gender	Male	778		Reference	
	Female	977		0.53 (0.36, 0.78)	0.001
BMI		1755		0.99 (0.95, 1.04)	0.783
Systolic_BP		1755		1.02 (1.01, 1.03)	0.005
Diastolic_BP		1755		0.97 (0.95, 0.99)	0.002
Smoke	Current	190		Reference	
	Quitted	235		0.58 (0.39, 0.89)	0.011
	Never	1330		0.40 (0.27, 0.59)	<0.001
Hypertension	0	929		Reference	
	1	826		0.85 (0.55, 1.32)	0.478
Diabetes_Mellitus	0	1394		Reference	
	1	361		1.10 (0.80, 1.52)	0.565
Stroke	0	1651		Reference	
	1	104		2.11 (1.40, 3.17)	<0.001
Hyperlipidemia	0	1186		Reference	
	1	569		0.96 (0.71, 1.31)	0.802
Chronic_Kidney_Disease	0	1496		Reference	
	1	259		1.24 (0.86, 1.78)	0.253
QTcB		1755		1.01 (1.00, 1.02)	0.001



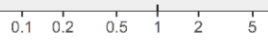
Supplementary Figure 19. Association between positive ERP in the lateral leads and all-cause mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	942		Reference	
	lat. +	24		1.24 (0.66, 2.35)	0.501
Gender	Male	489		Reference	
	Female	477		0.76 (0.57, 1.02)	0.066
BMI		966		0.91 (0.88, 0.95)	<0.001
Systolic_BP		966		1.02 (1.01, 1.03)	<0.001
Diastolic_BP		966		0.98 (0.97, 1.00)	0.012
Smoke	Current	85		Reference	
	Quitted	219		0.85 (0.58, 1.24)	0.393
	Never	662		0.74 (0.51, 1.09)	0.130
Hypertension	0	424		Reference	
	1	542		0.80 (0.57, 1.13)	0.206
Diabetes_Mellitus	0	775		Reference	
	1	191		1.38 (1.06, 1.80)	0.017
Stroke	0	899		Reference	
	1	67		1.94 (1.35, 2.79)	<0.001
Hyperlipidemia	0	680		Reference	
	1	286		0.81 (0.62, 1.05)	0.106
Chronic_Kidney_Disease	0	855		Reference	
	1	111		1.20 (0.86, 1.65)	0.280
QTcB		966		1.00 (1.00, 1.01)	0.052

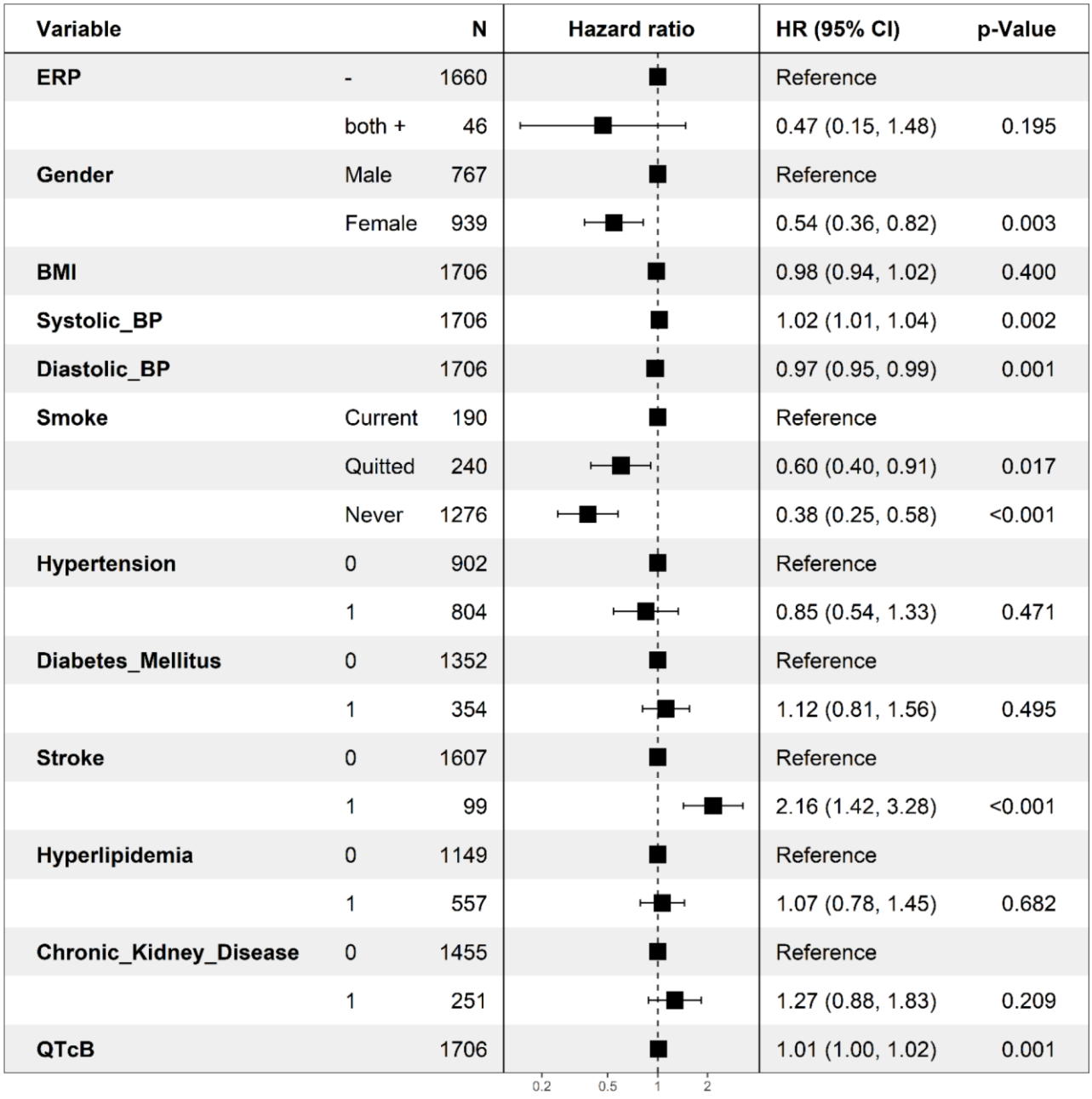


Supplementary Figure 20. Association between positive ERP in the lateral leads and all-cause mortality among those aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1117		Reference	
	both +	43		0.48 (0.07, 3.55)	0.475
Gender	Male	543		Reference	
	Female	617		0.24 (0.10, 0.59)	0.002
BMI		1160		0.94 (0.87, 1.03)	0.185
Systolic_BP		1160		1.01 (0.98, 1.04)	0.437
Diastolic_BP		1160		0.99 (0.94, 1.03)	0.547
Smoke	Current	182		Reference	
	Quitted	144		0.57 (0.25, 1.30)	0.181
	Never	834		0.47 (0.22, 0.97)	0.041
Hypertension	0	807		Reference	
	1	353		0.95 (0.37, 2.44)	0.923
Diabetes_Mellitus	0	1023		Reference	
	1	137		2.11 (1.04, 4.30)	0.039
Stroke	0	1130		Reference	
	1	30		1.67 (0.50, 5.61)	0.404
Hyperlipidemia	0	783		Reference	
	1	377		0.75 (0.39, 1.47)	0.406
Chronic_Kidney_Disease	0	967		Reference	
	1	193		1.67 (0.87, 3.21)	0.123
QTcB		1160		1.01 (1.00, 1.03)	0.020

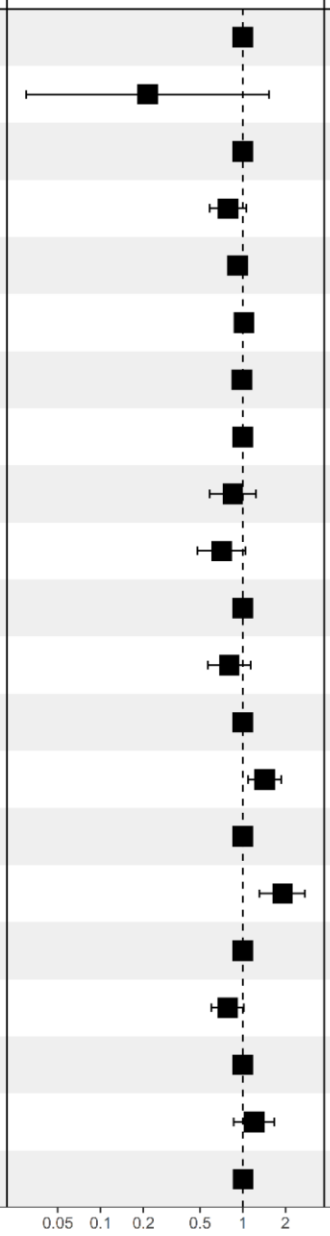


Supplementary Figure 21. Association between positive ERP in both inferior leads and lateral leads and all-cause mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



Supplementary Figure 22. Association between positive ERP in both inferior and lateral leads and all-cause mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

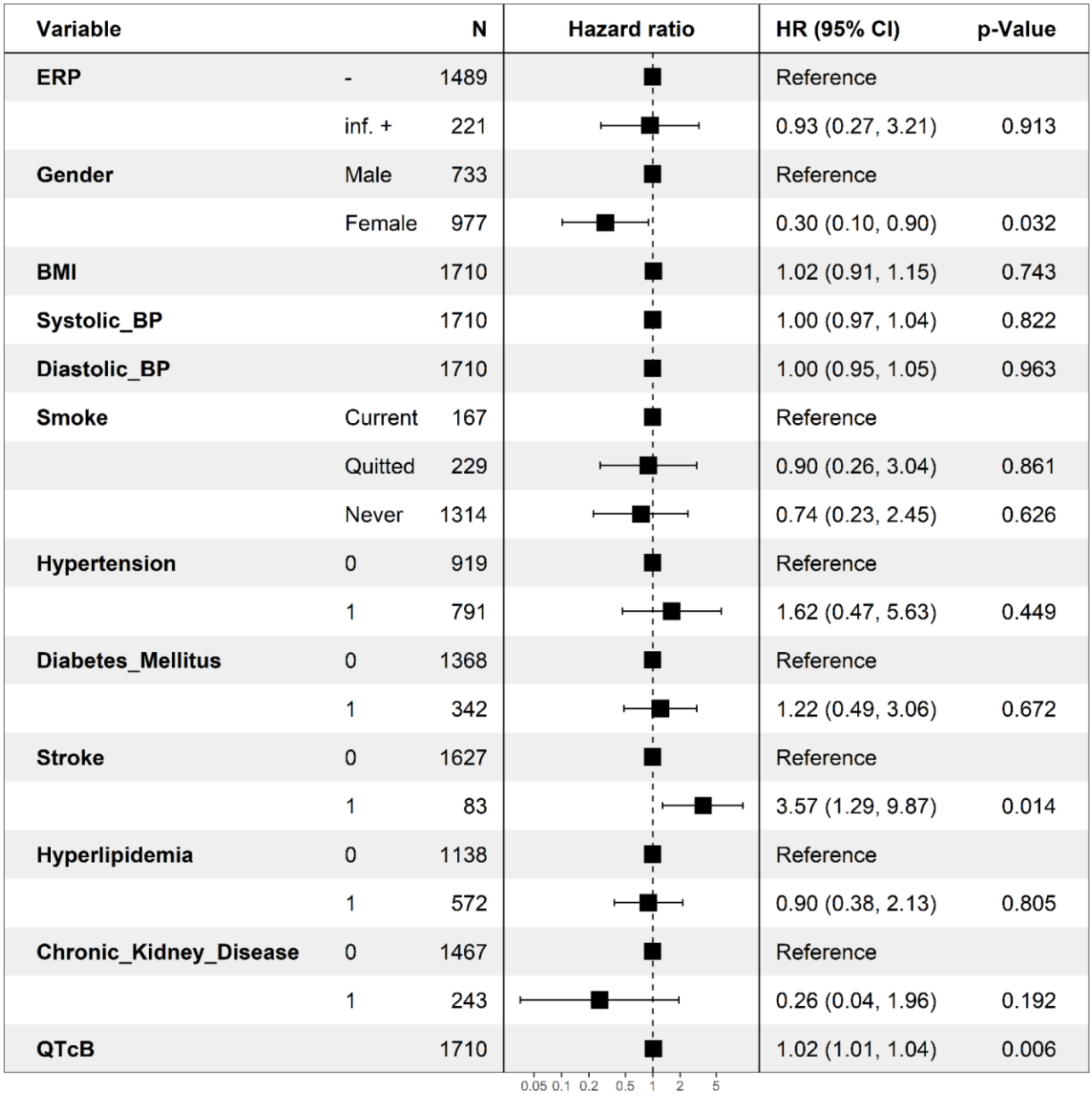
Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	942		Reference	
	both +	12		0.21 (0.03, 1.53)	0.124
Gender	Male	483		Reference	
	Female	471		0.79 (0.58, 1.06)	0.119
BMI		954		0.92 (0.89, 0.95)	<0.001
Systolic_BP		954		1.02 (1.01, 1.03)	<0.001
Diastolic_BP		954		0.98 (0.97, 1.00)	0.014
Smoke	Current	85		Reference	
	Quitted	218		0.85 (0.58, 1.24)	0.404
	Never	651		0.71 (0.48, 1.05)	0.083
Hypertension	0	415		Reference	
	1	539		0.80 (0.57, 1.13)	0.213
Diabetes_Mellitus	0	768		Reference	
	1	186		1.42 (1.09, 1.86)	0.010
Stroke	0	888		Reference	
	1	66		1.90 (1.32, 2.75)	0.001
Hyperlipidemia	0	673		Reference	
	1	281		0.78 (0.60, 1.02)	0.070
Chronic_Kidney_Disease	0	845		Reference	
	1	109		1.20 (0.86, 1.67)	0.278
QTcB		954		1.00 (1.00, 1.01)	0.072



Supplementary Figure 23. Association between positive ERP in both inferior and lateral leads and all-cause mortality among individuals aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

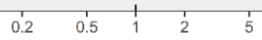
Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1076		Reference	
	inf. +	196		0.93 (0.10, 8.19)	0.944
Gender	Male	588		Reference	
	Female	684		0.26 (0.03, 2.05)	0.203
BMI		1272		1.24 (1.04, 1.48)	0.017
Systolic_BP		1272		1.03 (0.93, 1.14)	0.594
Diastolic_BP		1272		0.92 (0.79, 1.06)	0.244
Smoke	Current	211		Reference	
	Quitted	150		0.00 (0.00, Inf)	0.999
	Never	911		2.39 (0.24, 24.16)	0.462
Hypertension	0	883		Reference	
	1	389		1.35 (0.07, 25.99)	0.842
Diabetes_Mellitus	0	1119		Reference	
	1	153		0.00 (0.00, Inf)	0.999
Stroke	0	1238		Reference	
	1	34		0.00 (0.00, Inf)	1.000
Hyperlipidemia	0	863		Reference	
	1	409		1.18 (0.19, 7.18)	0.857
Chronic_Kidney_Disease	0	1067		Reference	
	1	205		5.62 (1.09, 28.99)	0.039
QTcB		1272		0.99 (0.95, 1.03)	0.542

Supplementary Figure 24. Association between positive ERP in the inferior leads and cardiovascular mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.



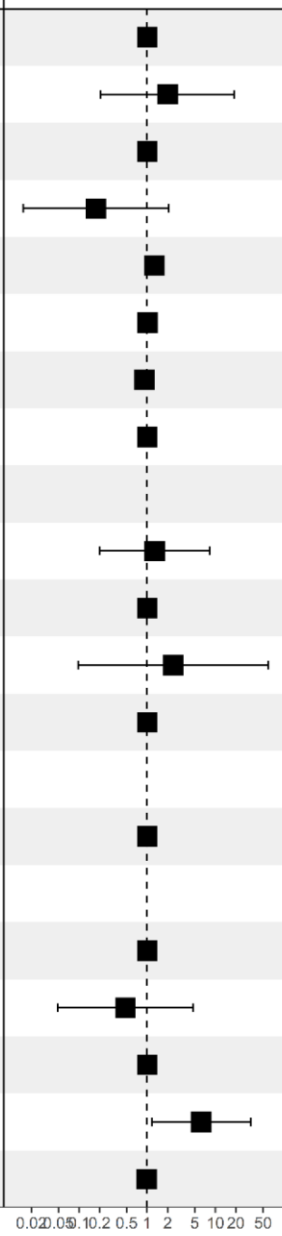
Supplementary Figure 25. Association between positive ERP in the inferior leads and cardiovascular mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	666		Reference	
	inf. +	85		1.72 (0.81, 3.63)	0.159
Gender	Male	366		Reference	
	Female	385		2.44 (0.94, 6.36)	0.067
BMI		751		0.96 (0.88, 1.04)	0.280
Systolic_BP		751		1.03 (1.00, 1.05)	0.017
Diastolic_BP		751		0.98 (0.94, 1.01)	0.121
Smoke	Current	55		Reference	
	Quitted	169		1.22 (0.43, 3.45)	0.713
	Never	527		0.42 (0.12, 1.45)	0.169
Hypertension	0	335		Reference	
	1	416		0.97 (0.40, 2.32)	0.941
Diabetes_Mellitus	0	617		Reference	
	1	134		1.83 (0.98, 3.41)	0.058
Stroke	0	712		Reference	
	1	39		1.25 (0.38, 4.07)	0.715
Hyperlipidemia	0	520		Reference	
	1	231		0.79 (0.42, 1.49)	0.471
Chronic_Kidney_Disease	0	670		Reference	
	1	81		1.08 (0.45, 2.57)	0.869
QTcB		751		1.01 (1.00, 1.02)	0.181



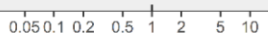
Supplementary Figure 26. Association between positive ERP in the inferior leads and cardiovascular mortality among individuals aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1076		Reference	
	lat. +	88		1.99 (0.21, 18.98)	0.549
Gender	Male	529		Reference	
	Female	635		0.18 (0.02, 2.06)	0.166
BMI		1164		1.27 (1.03, 1.58)	0.029
Systolic_BP		1164		1.01 (0.91, 1.12)	0.865
Diastolic_BP		1164		0.91 (0.79, 1.05)	0.189
Smoke	Current	173		Reference	
	Quitted	140		0.00 (0.00, Inf)	0.999
	Never	851		1.29 (0.20, 8.23)	0.788
Hypertension	0	809		Reference	
	1	355		2.42 (0.10, 60.13)	0.590
Diabetes_Mellitus	0	1033		Reference	
	1	131		0.00 (0.00, Inf)	0.999
Stroke	0	1135		Reference	
	1	29		0.00 (0.00, Inf)	1.000
Hyperlipidemia	0	782		Reference	
	1	382		0.48 (0.05, 4.70)	0.528
Chronic_Kidney_Disease	0	974		Reference	
	1	190		6.19 (1.17, 32.85)	0.032
QTcB		1164		0.98 (0.94, 1.02)	0.317



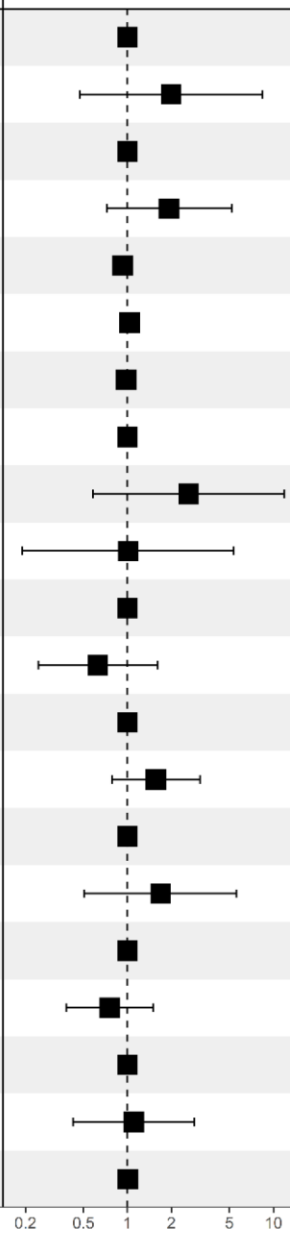
Supplementary Figure 27. Association between positive ERP in the lateral leads and cardiovascular mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1489		Reference	
	lat. +	82		1.05 (0.14, 7.98)	0.960
Gender	Male	661		Reference	
	Female	910		0.30 (0.10, 0.93)	0.038
BMI		1571		1.02 (0.90, 1.15)	0.786
Systolic_BP		1571		0.99 (0.95, 1.04)	0.678
Diastolic_BP		1571		1.02 (0.96, 1.08)	0.460
Smoke	Current	142		Reference	
	Quitted	200		0.99 (0.27, 3.65)	0.992
	Never	1229		0.75 (0.21, 2.66)	0.661
Hypertension	0	832		Reference	
	1	739		1.27 (0.34, 4.79)	0.727
Diabetes_Mellitus	0	1260		Reference	
	1	311		0.90 (0.32, 2.56)	0.850
Stroke	0	1490		Reference	
	1	81		4.27 (1.52, 11.97)	0.006
Hyperlipidemia	0	1058		Reference	
	1	513		0.75 (0.29, 1.93)	0.546
Chronic_Kidney_Disease	0	1347		Reference	
	1	224		0.28 (0.04, 2.08)	0.213
QTcB		1571		1.02 (1.01, 1.04)	0.010



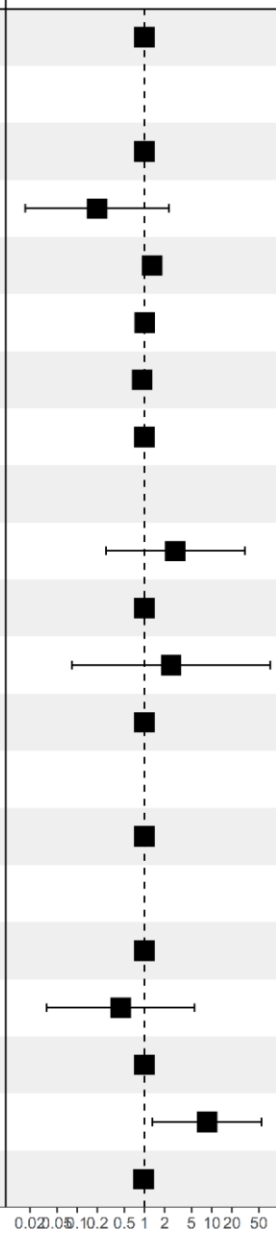
Supplementary Figure 28. Association between positive ERP in the lateral leads and cardiovascular mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	666		Reference	
	lat. +	16		1.99 (0.47, 8.37)	0.348
Gender	Male	320		Reference	
	Female	362		1.93 (0.72, 5.16)	0.191
BMI		682		0.93 (0.85, 1.01)	0.092
Systolic_BP		682		1.04 (1.01, 1.06)	0.002
Diastolic_BP		682		0.98 (0.95, 1.01)	0.220
Smoke	Current	46		Reference	
	Quitted	150		2.63 (0.58, 11.87)	0.210
	Never	486		1.01 (0.19, 5.35)	0.989
Hypertension	0	299		Reference	
	1	383		0.63 (0.25, 1.60)	0.329
Diabetes_Mellitus	0	560		Reference	
	1	122		1.57 (0.78, 3.14)	0.206
Stroke	0	647		Reference	
	1	35		1.69 (0.51, 5.59)	0.392
Hyperlipidemia	0	466		Reference	
	1	216		0.76 (0.38, 1.50)	0.424
Chronic_Kidney_Disease	0	610		Reference	
	1	72		1.11 (0.43, 2.87)	0.837
QTcB		682		1.00 (0.99, 1.02)	0.535



Supplementary Figure 29. Associations between positive ERP in the lateral leads and cardiovascular mortality among individuals aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1076		Reference	
	both +	42		0.00 (0.00, Inf)	1.000
Gender	Male	509		Reference	
	Female	609		0.20 (0.02, 2.31)	0.196
BMI		1118		1.30 (1.05, 1.60)	0.017
Systolic_BP		1118		1.01 (0.90, 1.13)	0.836
Diastolic_BP		1118		0.93 (0.78, 1.09)	0.363
Smoke	Current	165		Reference	
	Quitted	135		0.00 (0.00, Inf)	0.999
	Never	818		2.87 (0.27, 30.91)	0.384
Hypertension	0	781		Reference	
	1	337		2.49 (0.08, 74.50)	0.598
Diabetes_Mellitus	0	993		Reference	
	1	125		0.00 (0.00, Inf)	0.999
Stroke	0	1091		Reference	
	1	27		0.00 (0.00, Inf)	1.000
Hyperlipidemia	0	753		Reference	
	1	365		0.44 (0.04, 5.58)	0.530
Chronic_Kidney_Disease	0	935		Reference	
	1	183		8.56 (1.32, 55.47)	0.024
QTcB		1118		0.98 (0.93, 1.02)	0.316



Supplementary Figure 30. Association between positive ERP in both inferior and lateral leads and cardiovascular mortality among individuals aged 55-64 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	1489		Reference	
	both +	43		0.00 (0.00, Inf)	0.998
Gender	Male	656		Reference	
	Female	876		0.23 (0.07, 0.76)	0.016
BMI		1532		1.02 (0.90, 1.16)	0.767
Systolic_BP		1532		1.00 (0.96, 1.04)	0.941
Diastolic_BP		1532		1.02 (0.97, 1.08)	0.440
Smoke	Current	144		Reference	
	Quitted	204		0.97 (0.26, 3.56)	0.962
	Never	1184		0.80 (0.23, 2.85)	0.732
Hypertension	0	811		Reference	
	1	721		1.11 (0.29, 4.21)	0.878
Diabetes_Mellitus	0	1227		Reference	
	1	305		0.95 (0.33, 2.68)	0.915
Stroke	0	1455		Reference	
	1	77		4.47 (1.59, 12.57)	0.005
Hyperlipidemia	0	1033		Reference	
	1	499		0.79 (0.30, 2.08)	0.637
Chronic_Kidney_Disease	0	1315		Reference	
	1	217		0.29 (0.04, 2.15)	0.224
QTcB		1532		1.03 (1.01, 1.05)	0.003

Supplementary Figure 31. Association between positive ERP in both inferior and lateral leads and cardiovascular mortality among individuals aged 65-74 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.

Variable		N	Hazard ratio	HR (95% CI)	p-Value
ERP	-	666		Reference	
	both +	11		0.00 (0.00, Inf)	0.997
Gender	Male	318		Reference	
	Female	359		2.30 (0.82, 6.49)	0.115
BMI		677		0.94 (0.85, 1.03)	0.163
Systolic_BP		677		1.04 (1.01, 1.06)	0.002
Diastolic_BP		677		0.98 (0.94, 1.01)	0.189
Smoke	Current	46		Reference	
	Quitted	150		2.67 (0.59, 12.13)	0.205
	Never	481		0.81 (0.15, 4.44)	0.811
Hypertension	0	294		Reference	
	1	383		0.69 (0.27, 1.80)	0.451
Diabetes_Mellitus	0	558		Reference	
	1	119		1.64 (0.81, 3.31)	0.168
Stroke	0	642		Reference	
	1	35		1.65 (0.50, 5.48)	0.412
Hyperlipidemia	0	463		Reference	
	1	214		0.78 (0.39, 1.56)	0.485
Chronic_Kidney_Disease	0	605		Reference	
	1	72		1.18 (0.45, 3.07)	0.739
QTcB		677		1.00 (0.99, 1.02)	0.505

Supplementary Figure 32. Association between positive ERP in both inferior and lateral leads and cardiovascular mortality among those aged ≥75 years. The hazard ratios and *P*-values were calculated by the Cox proportional hazards model after adjusting for covariables.