The Association between Electrophysiology Profile and Risk of Cardiovascular Events: A Systematic Review

Muhammad Haris F.[1], Mirza Alfiansyah[2]
[1]Kilisuci Regional Public Hospital, [2]Gambiran Regional Public Hospital Kediri, Indonesia

ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are the leading cause of death, accounting for 31% of global mortalities. This systematic review explores the role of electrophysiological profiles in cardiovascular prevention, focusing on their integration into risk management protocols. **Methods:** A comprehensive review was conducted using the PubMed database, adhering to PRISMA guidelines. Of the 1,050 identified studies, 10 met the inclusion criteria and were assessed for quality using the STROBE method. **Results:** Key electrophysiological markers were identified as significant predictors of cardiovascular events. Abnormalities in Holter monitoring, such as a turbulence slope (TS) ≤25 ms/RRI, are strongly correlated with sudden cardiac death (HR 4.7). Prolonged QT intervals in ECG were linked to increased mortality from cardiac arrest (HR 2.4) and heart failure (HR 1.74). ST-segment depression during exercise stress testing was a strong predictor of coronary heart disease death (HR 2.47), especially during the recovery phase (HR 4.01). **Discussion:** Electrophysiological markers like Holter monitoring, ECG findings and exercise stress testing are valuable for identifying high-risk individuals. Their integration into routine screening could improve early detection and prevention strategies, further research is needed to standardize protocols.

Keywords: Cardiovascular events, electrophysiology profile, mortality.

ABSTRAK

Pendahuluan: Penyakit kardiovaskular (CVD) merupakan penyebab 31% seluruh kematian di seluruh dunia. Tinjauan literatur sistematis ini mengeksplorasi peran profil elektrofisiologis dalam pencegahan kardiovaskular, dengan fokus pada integrasi mereka ke dalam protokol manajemen risiko. **Metode**: Tinjauan komprehensif menggunakan basis data PubMed, sesuai pedoman PRISMA. Dari 1.050 studi yang diidentifikasi, 10 memenuhi kriteria inklusi dan dinilai kualitasnya menggunakan metode STROBE. **Hasil**: Penanda elektrofisiologis utama diidentifikasi sebagai prediktor signifikan kejadian kardiovaskular. Abnormalitas dalam pemantauan Holter, seperti kemiringan turbulensi (TS) ≤25 ms/RRI, sangat berkorelasi dengan kematian jantung mendadak (HR 4,7). Interval QT memanjang pada temuan EKG dikaitkan dengan peningkatan mortalitas akibat serangan jantung (HR 2,4) dan gagal jantung (HR 1,74). Depresi segmen ST selama *exercise stress test* adalah prediktor kuat kematian akibat penyakit jantung koroner (HR: 2,47), terutama selama fase pemulihan (HR 4,01). **Diskusi**: Penanda elektrofisiologis seperti pemantauan Holter, temuan EKG, dan *exercise stress testing* sangat berguna untuk identifikasi individu dengan risiko tinggi. Integrasi profil elektrofisiologis ke dalam skrining rutin dapat meningkatkan deteksi dini dan strategi pencegahan, penelitian lebih lanjut diperlukan untuk menstandarkan protokol. **Muhammad Haris F., Mirza Alfiansyah. Hubungan antara Profil Elektrofisiologi dan Risiko Kardiovaskular: Sebuah Tinjauan Sistematik.**

Kata Kunci: Kejadian kardiovaskular, profil elektrofisiologi, mortalitas.

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading global cause of death, responsible for approximately 31% of all mortalities each year. Despite advancements in medical science, the burden of CVDs continues to rise, necessitating effective prevention strategies. Traditional risk factors for cardiovascular diseases, such as hypertension, diabetes, smoking, and dyslipidemia, are well-documented. Emerging evidence suggests that electrophysiological parameters might provide additional predictive value, enhancing our ability to identify individuals at high risk for cardiovascular events.[1]

Electrophysiology (EP) involves the study of the electrical properties of biological cells and tissues. In cardiovascular health, electrophysiological assessments focus on the heart's electrical activity, including rhythm and conduction abnormalities. Techniques such as electrocardiograms (ECG) findings, Holter monitoring, and exercise stress testing are commonly used to evaluate these parameters. By examining electrophysiological markers, healthcare providers can gain deeper insights

Alamat Korespondensi *email:*

into the underlying mechanisms of cardiac dysfunction and may identify early signs of cardiovascular risk.[2]

OBJECTIVE

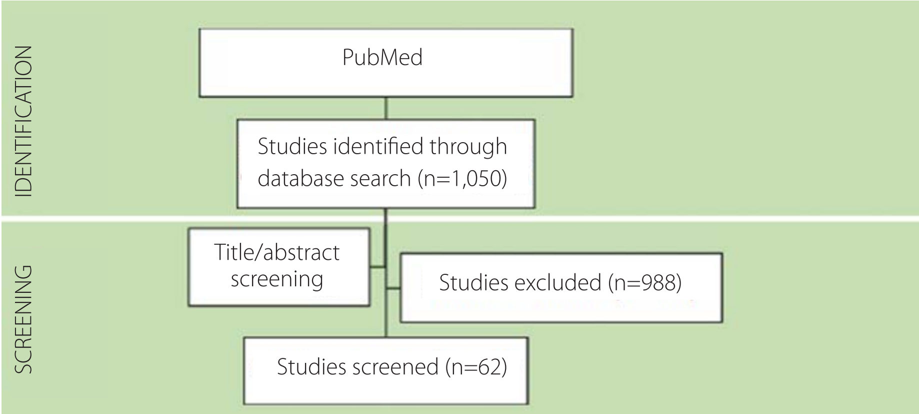
The primary objective is to evaluate the role of electrophysiological profiling in cardiovascular risk assessment and prevention. We aim to summarize the current evidence on the use of electrophysiological markers for predicting cardiovascular events and guiding preventive measures. Specifically, we seek to answer the following questions:

1. What are the key electrophysiological markers associated with cardiovascular risk?
2. How do these markers predict cardiovascular outcomes such as myocardial infarction, sudden cardiac death, and arrhythmias?
3. What interventions targeting electrophysiological abnormalities have been shown to improve cardiovascular outcomes?
4. What are the clinical implications of integrating electrophysiological assessments into routine cardiovascular screening and prevention?

METHODS

Literature Search

A comprehensive literature search was conducted across PubMed. The search terms used included "electrophysiological markers", "electrophysiological signals", "electrocardiogram", "ECG", "electrophysiology", "electrocardiographic parameters", "cardiovascular outcomes", "cardiovascular events", "heart disease", "cardiac events", "cardiovascular risk", "heart failure", "myocardial infarction", "coronary artery disease", "arrhythmias", "randomized controlled trial", "RCT", and "cohort study". The search has no limited published year. The strategy involved a combination of Medical Subject Headings (MeSH) terms and free-text keywords, utilizing Boolean operators (AND, OR, NOT) to refine the search results.



Scheme. Study selection process based on the PRISMA statement.

Inclusion Criteria

Studies were included if they met the following criteria:

- Human studies published in English.
- Focus on electrophysiological markers and their predictive value for cardiovascular outcomes.
- Observational studies include cohort, case-control, and cross-sectional studies.

Exclusion Criteria

Studies were excluded based on the following criteria:

- It is not directly related to electrophysiology and cardiovascular prevention.
- Non-human studies and articles not published in English.
- Case reports and studies with inadequate data or poor methodological quality.

Data Extraction

Data extraction was performed independently by two reviewers. The following information was extracted from each study:

Figure. Quality assessment by STROBE checklist.

	Title and Abstract	Background	Objective	Study design	Setting	Participant (methods)	Variables	Data mesurement	Bias	Study Size	Quantitative variables	Statistical methods	Participants(results)	Descriptive data	Outcome data	Main results	Other analyses	Key results	Limitations	Interpretation	Generalizability	Funding
Yap Y., *et al*., 2016	±	±	±	±	±	±	±	±	±	+	±	±	±	±	+	+	±	+	±	+	±	+
Gibbs C., *et al*., 2018	+	±	+	+	+	±	±	±	±	+	±	±	±	±	+	+	±	+	±	+	±	+
Laukkanen, *et al*., 2009	+	±	+	+	+	+	+	+	±	±	+	+	+	+	+	+	+	+	±	+	±	+
Timo M. H., *et al*., 2005	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+	+	+	+
Rankinen J, *et al*., 2022	±	+	+	±	+	+	+	+	-	±	±	+	+	+	+	+	+	±	±	±	+	+
Deedwania PC, Carbajal, 1990	±	+	+	±	+	+	+	+	±	-	+	+	+	+	+	±	+	+	±	+	+	+
Räihä IJ., *et al*., 2021	±	+	+	+	+	+	+	+	±	-	+	+	+	+	+	±	+	+	±	+	+	-
Lindow T., *et al*., 1994	±	+	+	+	+	+	+	+	±	-	+	+	+	+	+	+	+	+	±	+	+	+
Tsuji, H., *et al*., 2024	±	±	+	+	±	±	+	±	±	+	±	+	+	+	+	+	+	+	±	+	±	+
Cho Y., *et al*., 2024	+	+	+	+	+	+	+	+	±	±	±	+	+	+	+	+	+	±	±	±	±	+

- Study characteristics: author, year, study design, population, and sample size.
- Electrophysiological markers assessed: ECG findings, heart rate variability (HRV), and exercise stress testing.
- Outcomes measured: incidence of myocardial infarction, sudden cardiac death, arrhythmias, and overall cardiovascular events.
- Key findings and conclusions.

Quality Assessment

The available data from each publication were processed using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) as shown in the **Figure**.[3]

Study Selection

The initial search identified 1,050 articles. The titles and abstracts of these 1,050 articles were screened, leading to the exclusion of 988 articles that did not meet the inclusion criteria. This left 62 articles for full-text review**.** After further exclusion of 52 studies due to specific reasons, a total of 10 studies were included. This study selection is shown in **Scheme.**

RESULTS

Quality Assessment Using STROBE

Based on the STROBE assessment, the studies included in the review exhibited varying levels of reporting quality, as shown in **Table**. The median STROBE score was 18.5 (13.5-21.5), indicating overall high quality. The highest-rated study was conducted by Timo MH. et al. (2005), receiving a score of 21.5 out of 22, showcasing the most rigorous reporting. Major weaknesses identified in the studies included potential biases and limitations in generalizability. The research methods employed across these studies were diverse, reflecting the different approaches to cardiovascular research. Common methods included ECG findings, Holter monitoring, and exercise stress testing, which were crucial in identifying cardiovascular risk factors and outcomes.

The studies identified various cardiovascular risk factors, with several showing significant associations with mortality and cardiovascular events. For instance, a prolonged QT interval was linked to an increased risk of cardiovascular events and myocardial infarction, with hazard ratios (HR) of 1.20 (95% CI 1.01-1.43) and 1.22 (95% CI 1.01-1.47), respectively.[4] Similarly, prolonged QT interval (>500 ms) significantly raised the risk of mortality due to cardiac arrest (HR 2.4; 95% CI 1.44-4.01) and heart failure (HR 1.74; 95% CI 1.43-2.12).[5]

Regarding the exercise stress testing method, asymptomatic ST-segment depression during exercise was a strong predictor of coronary heart disease (CHD) death, with a hazard ratio of 2.47 (95% CI 1.52–3.99). Furthermore, the study revealed that ST-segment depression during the recovery phase of the exercise test was an even stronger predictor, with a hazard ratio of 4.01 (95% CI 2.12–7.58).[6]

Other studies highlighted the predictive value of specific ECG markers and Holter monitoring findings. For example, a turbulence slope (TS) ≤25 ms/RRI in Holter monitoring was a strong predictor of sudden cardiac death, with an HR of 4.7 (95% CI 2.3-9.8).[7] Additionally, a prolonged QRS duration (>110 ms) was significantly associated with cardiovascular mortality (HR 1.74; 95% CI 1.07-2.82) and new-onset heart failure (HR 3.39; 95% CI 1.60-7.17).[8] These findings underscore the importance of ECG, Holter monitoring, and exercise stress testing parameters as key indicators in assessing cardiovascular risk.

DISCUSSION

Summary of Findings

This systematic review highlights the critical role of electrophysiological markers in cardiovascular risk assessment and prevention. The three most significant electrophysiological markers as strong predictors of sudden cardiac death are abnormalities of Holter monitoring and exercise stress testing and ECG findings.

1. Abnormalities of Holter Monitoring

Ambulatory ECG monitoring, also known as Holter monitoring, is a crucial tool for identifying cardiac arrhythmias that can predict mortality in various populations. The presence of silent ischemia detected through ambulatory ECG monitoring was the most significant predictor of two-year cardiac mortality in patients with stable angina, with a hazard ratio of 3.93 (95% CI: 1.26-12.27).[9] Similarly, in elderly patients, the detection of sinoatrial pauses exceeding 1.5 seconds during the day and multifocal ventricular ectopy at night were strong independent predictors of increased mortality from cardiac causes, with odds ratios of 4.52 (95% CI 1.84-11.11) and 2.98 (95% CI 1.25-7.13), respectively.[10] Additionally, a Turbulence Slope (TS) of ≤25 ms/RRI detected via Holter monitoring in patients with an ejection fraction above 35% was a significant predictor of sudden cardiac death, with a hazard ratio of 4.7 (95% CI 2.3-9.8).[7] These findings underscore the importance of Holter monitoring in both the early detection and management of potentially fatal cardiac conditions, particularly in high-risk populations such as the elderly.

2. Exercise Stress Testing

Exercise stress testing involves a patient performing incremental physical exercise, typically on a treadmill or bicycle ergometer, while their ECG, heart rate, and blood pressure are continuously monitored to detect ischemic changes, arrhythmias, or other abnormalities. The test's predictive value for sudden cardiac death is enhanced by observing ST-segment depression during both the exercise and recovery phases, particularly in individuals with conventional cardiovascular risk factors. Exercise stress testing plays a critical role in identifying individuals at high risk for sudden cardiac death (SCD), even among asymptomatic populations. Asymptomatic ST-segment depression during exercise was a strong predictor of coronary heart disease (CHD) death, with a hazard ratio of 2.47 (95% CI 1.52–3.99).[6] Furthermore, the study revealed that ST-segment depression during the recovery phase of the exercise test was an even stronger predictor, with a hazard ratio of 4.01 (95% CI 2.12–7.58).[6] ST depression without accompanying angina was associated with an increased risk of acute coronary syndrome (ACS) and cardiovascular death, emphasizing the prognostic value of exercise stress testing in identifying individuals who may benefit from early interventions.[11]

3. ECG Findings

Prolonged QT interval, as identified through ECG monitoring, has been increasingly recognized as a critical marker for predicting adverse cardiovascular outcomes and mortality. QT interval prolongation was independently associated with a significant increase in all-cause mortality, with a hazard ratio of 1.27 (95% CI: 1.10-1.48, p=0.0015).[4] Additionally, this study demonstrated that a prolonged QT interval was linked to a higher risk of cardiovascular events, including myocardial infarction and stroke, with a hazard


ratio of 1.20 (95% CI: 1.01-1.43, p=0.0415).[4] Similarly, a QT interval exceeding 500 ms was a strong predictor of mortality due to cardiac arrest, with a hazard ratio of 2.4 (95% CI: 1.44-4.01).[5] Furthermore, there was also an association between prolonged QRS duration (>100 ms) and increased cardiovascular mortality, with hazard ratios of 1.38 (95% CI: 1.01-1.88, p=0.045) and 1.74 (95% CI: 1.07-2.82, p=0.025) for durations over 110 ms.[8] These studies collectively emphasize the prognostic value of ECG monitoring in detecting high-risk individuals and guiding early interventions to prevent fatal cardiovascular events.

Clinical Implications and Interventions

The studies highlight the critical need for early detection and preventive strategies in asymptomatic or seemingly healthy individuals who may harbor significant cardiovascular risks. Asymptomatic ST-segment depression, identified during routine exercise testing, serves as a strong predictor of sudden cardiac death, especially in middle-aged men with traditional risk factors such as smoking, hypertension, and hypercholesterolemia. The study recommends routine exercise stress testing and ECG monitoring as essential tools to uncover hidden risks in these individuals.[6] Once identified, targeted lifestyle modifications are crucial, including smoking cessation, dietary changes to lower cholesterol, regular physical activity to improve cardiovascular fitness, and stress management techniques to reduce hypertension.[12] In addition to lifestyle interventions, the document emphasizes the importance of pharmacotherapy, such as the use of statins to manage hypercholesterolemia, antihypertensive medications to control blood pressure, and possibly the use of anti-ischemic drugs or aspirin to prevent further cardiovascular complications.[13] These combined strategies aim to mitigate the risk of severe cardiovascular events before any symptoms manifest, thereby improving long-term outcomes for these individuals.

For individuals already diagnosed with cardiovascular disease, the studies emphasize the importance of continuous and comprehensive management to prevent further complications. Silent ischemia, prolonged QT intervals, and reduced heart rate variability are highlighted as significant predictors of mortality in patients with stable angina, heart failure, or post-acute myocardial infarction.[5,9,14] The studies advocate for routine monitoring using ambulatory ECG and Holter devices to detect these conditions early.[9,10] Aggressive management of underlying risk factors, including optimizing existing therapies such as antianginal medications, and considering advanced preventive interventions like ICD implantation, is crucial to reducing the likelihood of fatal cardiac events.[5,7,9] ICDs play a key role in preventing sudden cardiac death by correcting life-threatening arrhythmias in high-risk patients.[5,7] In patients with recent myocardial infarction and obstructive coronary artery disease, invasive treatment might be more effective than anti-ischemic drug therapy in lowering the long-term risk of major cardiac events.[15] Additionally, the studies recommend the use of AI-based ECG analysis as a powerful tool for risk identification, particularly in patients with acute heart failure, where it can enhance early detection and allow for more personalized management strategies.[16] Personalized treatment plans tailored to each patient's

Table. Characteristics and findings of included studies.

	Study Design	Origin	Sample Size	Age	Outcomes with OR Score	Analysis Method	STROBE Score (0-22)
Yap J, *et al*, 2016.[4]	Cohort Prospective study	Singapore	2,536	57-73	Prolonged QT interval and in-creased risk of cardiovascular events (HR 1.20, CI 1.01-1.43, p=0.0415)	Cox proportional hazards model	13.5
Gibbs C, *et al*, 2018.[5]	Retrospec-tive observa-tional study	Norway	1,531	55-85	Prolonged QT interval (>500ms) and mortality caused by cardiac arrest (HR 2.4, 95% CI 1.44-4.01)	Cox regression analysis	15
Laukkanen JA, *et al*, 2009.[6]	Population-based ob-servational prospective cohort study	Finland	1,769	42-60 years	Sudden Cardiac Death (SCD): ■ Asymptomatic ST-segment depression during exercise: HR 2.13 (95% CI 1.15–3.89, p=0.015) ■ During recovery: HR 3.17 (95% CI 1.68–5.96, p<0.001) Coronary Heart Disease (CHD) Death: ■ During exercise: HR 2.47 (95% CI 1.52–3.99, p<0.001) ■ During recovery: HR 4.01 (95% CI 2.12–7.58, p<0.001)	Cox proportionalhazards regression model	20
Timo MH, *et al*, 2005.[7]	Prospective cohort study	Finland and Ger-many	2,130	49-69	Turbulence Slope (TS) ≤2,5 ms/RRI in Holter monitoring in patients with an EF >0,35 as a predictor of Sudden Cardiac Death (HR 4.7, 95% CI 2.3-9.8)	Cox proportionalhazards model	21.5


Rankinen J, *et al*, 2022.[8]	Population-based observational prospective cohort study	Finland	6,033	>30 years (mean age 52.2 years)	Prolonged QRS (>100 ms) as cardiovascular mortality (HR 1.38; 95% CI 1.01-1.88, p=0.045). Prolonged QRS (>110 ms) as cardiovascular mortality (HR 1.74; 95% CI 1.07-2.82, p=0.025). Prolonged QRS (>110 ms) as all-cause mortality (HR 1.52; 95% CI 1.02-2.25, p=0.039). Prolonged QRS (100-109 ms) as a predictor of new-onset. Heart Failure (HR 2.18; 95% CI 1.32-3.61, p=0.003). Prolonged QRS (>110 ms) as a predictor of new-onset Heart Failure (HR 3.39; 95% CI 1.60-7.17, p=0.001).	Chi-square test, spline model, Kaplan-Meier method, cox proportional hazards regression model, fine and gray subdistribution hazard modeling	15.5
Deedwania PC, *et al*,1990[9]	Prospective cohort study	USA	107 patients	Mean age: 63 ± 6 years (Range: 45-79 years)	The presence of silent ischemia on ambulatory ECG monitoring was found to be the single most important predictor of 2-year cardiac mortality, with a HR of 3.93 (95% CI: 1.26-12.27)	Kaplan-Meier survival analysis, cox proportional hazard function analysis	18.5
Raiha IJ, *et al*, 1994.[10]	Retrospective cohort study	Finland	480 elderly people	65 years and older (No specific mean age provided)	Daytime sinoatrial pauses (>1.5 sec) OR 4.52 (95% CI 1.84-11.11) for increased mortality from cardiac causes. Night-time multifocal ventricular ectopy OR 2.98 (5% CI 1.25-7.13) for increased mortality from cardiac causes. Daytime multifocal ventricular ectopy OR 2.25 (5% CI 1.01-5.02) for increased mortality from cardiac causes.	Univariate and multivariate logistic regression	18.5
Lindow T, *et al*, 2021.[11]	Prospective Observational cohort study	Sweden	11,605	Mean age 58.3 (SD 14.9 years)	ST depression without angina was associated with ACS during complete follow-up, HR 1.7 (95% CI 1.4–2.0). ST depression without angina was associated with ACS within 1 year, HR 3.9 (95% CI 2.7–5.7). ST depression without angina was associated with death from cardiovascular cause, HR 1.7 (95% CI 1.3–2.2).	Kaplan-Meier, cox proportional hazards regression models, concordance statistics, sensitivity analyses	19.5
Tsuji, H, *et al*, 1994.[14]	Longitudinal cohort study	Japan	736	Middle-aged and older adults (mean age: 60)	Heart Rate Variability by measuring 2 Hours Standard Deviation NN intervals (2H SDNN) and cardiovascular event (HR 1.47, 95% CI 1.16-1.86).	Multivariate logistic regression	16.5
Cho Y, *et al*, 2024.[16]	Prospective Cohort Study	South Korea	1,254	Middle aged and older adults (mean age: 69,8)	In-hospital cardiac death (QCG-Critical score) with adjusted OR 1.68 (95% CI 1.47-1.92) per 0.1 increase; p<0.001 Long-term mortality (QCG-Critical score) with adjusted HR 2.69 (95% CI 2.14-3.39) for high vs low QCG-Critical scores (>0.5 vs 0.25); p<0.001	Cox proportional hazards model for HR, logistic regression for OR, Kaplan-Meier survival analysis	18.5


specific risk factors are crucial for improving outcomes in this high-risk group.[4,16]

CONCLUSION

This systematic review underscores the critical role of electrophysiological markers in the early detection and prevention of cardiovascular events. Key markers such as abnormalities in Holter monitoring, prolonged QT intervals in ECG findings, and ST-segment depression during exercise stress testing have been identified as significant predictors of adverse cardiovascular outcomes, including sudden cardiac death, myocardial infarction, and heart failure. The integration of these electrophysiological assessments into routine cardiovascular screening could significantly enhance the identification of high-risk individuals and guide timely preventive interventions. However, the variability in study designs and the need for standardized protocols highlight the importance of further research to develop evidence-based guidelines that can be universally applied in clinical practice. Overall, the findings advocate for the broader application of electrophysiological profiling as a valuable tool in cardiovascular risk management.

Conflict of Interest. None declared

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