

AI-enabled electrocardiography alert intervention and all-cause mortality: a pragmatic randomized clinical trial

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Supplemental Table 1 | Characteristics of participating physicians.

	Academic medical center		Community hospital
	Emergency department (n = 9)	Department of internal medicine (n = 28)	Emergency department (n = 2)
Sex (male)	9 (100.0%)	27 (96.4%)	2 (100.0%)
Age	42.5±7.3	46.9±5.5	40.5±2.6
Years in attending physician	9.0±7.9	13.8±6.6	4.0±1.4
Specialty			
Emergency	9 (100.0%)	0 (0.0%)	2 (100.0%)
Cardiology	0 (0.0%)	11 (39.3%)	0 (0.0%)
Nephrology	0 (0.0%)	3 (10.7%)	0 (0.0%)
Pulmonology	0 (0.0%)	5 (17.9%)	0 (0.0%)
Gastroenterology	0 (0.0%)	3 (10.7%)	0 (0.0%)
Metabolism	0 (0.0%)	1 (3.6%)	0 (0.0%)
Oncology	0 (0.0%)	4 (14.3%)	0 (0.0%)
Infectious disease	0 (0.0%)	1 (3.6%)	0 (0.0%)
Numbers of cared patients	889.8±195.3	242.4±165.4	585.5±283.5

Supplemental Table 2 | Modified Early Warning Score (MEWS) components stratified by allocated groups.

	All patients		High risk identified by AI-ECG		Low risk identified by AI-ECG	
	Intervention (n = 8001)	Control (n = 7964)	Intervention (n = 709)	Control (n = 688)	Intervention (n = 7292)	Control (n = 7276)
Systolic blood pressure						
≤70 mmHg	9(0.1%)	11(0.1%)	2(0.3%)	6(0.9%)	7(0.1%)	5(0.1%)
71-80 mmHg	12(0.1%)	16(0.2%)	4(0.6%)	5(0.7%)	8(0.1%)	11(0.2%)
81-100 mmHg	298(3.7%)	305(3.8%)	74(10.4%)	75(10.9%)	224(3.1%)	230(3.2%)
101-199 mmHg	7527(94.1%)	7483(94.0%)	609(85.9%)	585(85.0%)	6918(94.9%)	6898(94.8%)
≥200 mmHg	55(0.7%)	53(0.7%)	3(0.4%)	0(0.0%)	52(0.7%)	53(0.7%)
Missing	100(1.2%)	96(1.2%)	17(2.4%)	17(2.5%)	83(1.1%)	79(1.1%)
Heart rate						
≤40 bpm	6(0.1%)	5(0.1%)	2(0.3%)	0(0.0%)	4(0.1%)	5(0.1%)
41-50 bpm	32(0.4%)	30(0.4%)	5(0.7%)	4(0.6%)	27(0.4%)	26(0.4%)
51-100 bpm	6898(86.2%)	6894(86.6%)	446(62.9%)	436(63.4%)	6452(88.5%)	6458(88.8%)
101-110 bpm	576(7.2%)	576(7.2%)	124(17.5%)	114(16.6%)	452(6.2%)	462(6.3%)
111-129 bpm	364(4.5%)	345(4.3%)	98(13.8%)	101(14.7%)	266(3.6%)	244(3.4%)
≥130 bpm	125(1.6%)	114(1.4%)	34(4.8%)	33(4.8%)	91(1.2%)	81(1.1%)
Respiratory rate						
<9 bpm	2(0.0%)	2(0.0%)	1(0.1%)	0(0.0%)	1(0.0%)	2(0.0%)
9-14 bpm	63(0.8%)	52(0.7%)	23(3.2%)	20(2.9%)	40(0.5%)	32(0.4%)
15-20 bpm	7552(94.4%)	7463(93.7%)	558(78.7%)	525(76.3%)	6994(95.9%)	6938(95.4%)
21-29 bpm	316(3.9%)	386(4.8%)	104(14.7%)	125(18.2%)	212(2.9%)	261(3.6%)
≥30 bpm	34(0.4%)	29(0.4%)	13(1.8%)	9(1.3%)	21(0.3%)	20(0.3%)
Missing	34(0.4%)	32(0.4%)	10(1.4%)	9(1.3%)	24(0.3%)	23(0.3%)
Temperature						
<35.0 °C	83(1.0%)	100(1.3%)	28(3.9%)	41(6.0%)	55(0.8%)	59(0.8%)
35.0-38.4 °C	7816(97.7%)	7775(97.6%)	666(93.9%)	635(92.3%)	7150(98.1%)	7140(98.1%)
≥38.5 °C	77(1.0%)	71(0.9%)	8(1.1%)	6(0.9%)	69(0.9%)	65(0.9%)
Missing	25(0.3%)	18(0.2%)	7(1.0%)	6(0.9%)	18(0.2%)	12(0.2%)
AVPU Score						
Awake	7099(88.7%)	7076(88.8%)	405(57.1%)	408(59.3%)	6694(91.8%)	6668(91.6%)
Reacts to voice	194(2.4%)	187(2.3%)	46(6.5%)	38(5.5%)	148(2.0%)	149(2.0%)
Reacts to pain	68(0.8%)	72(0.9%)	16(2.3%)	19(2.8%)	52(0.7%)	53(0.7%)
Unresponsive	193(2.4%)	186(2.3%)	90(12.7%)	89(12.9%)	103(1.4%)	97(1.3%)
Missing	447(5.6%)	443(5.6%)	152(21.4%)	134(19.5%)	295(4.0%)	309(4.2%)

Supplemental Table 3 | ECG features stratified by allocated groups.

	All patients		High risk identified by AI-ECG		Low risk identified by AI-ECG	
	Intervention (n = 8001)	Control (n = 7964)	Intervention (n = 709)	Control (n = 688)	Intervention (n = 7292)	Control (n = 7276)
ECG measurement						
Heart rate	83.0±20.0	82.9±19.9	103.8±28.6	102.4±27.2	81.0±17.7	81.1±18.0
PR interval	161.3±34.4	161.0±35.3	151.9±46.6	153.6±44.5	162.2±32.8	161.7±34.3
QRS duration	98.6±20.9	99.3±21.7	104.3±29.5	104.5±29.8	98.0±19.8	98.8±20.7
QT interval	388.0±48.1	388.9±49.5	374.0±70.6	376.6±70.6	389.4±45.1	390.1±46.8
QTc interval	449.1±43.5	449.5±45.5	477.2±54.0	477.6±58.9	446.3±41.3	446.8±43.1
P waves axes	48.9±35.4	48.8±35.3	47.3±52.0	42.9±46.9	49.0±33.4	49.4±33.9
QRS wave axes	37.9±46.6	36.5±46.7	38.1±62.3	33.5±60.4	37.9±44.8	36.7±45.2
T wave axes	44.5±50.2	43.4±50.5	57.3±78.4	51.7±77.0	43.2±46.4	42.6±47.2
Selected ECG pattern						
Sinus rhythm	7012(87.6%)	7000(87.9%)	434(61.2%)	481(69.9%)	6578(90.2%)	6519(89.6%)
Sinus arrhythmia	44(0.5%)	42(0.5%)	0(0.0%)	3(0.4%)	44(0.6%)	39(0.5%)
Sinus pause	13(0.2%)	18(0.2%)	2(0.3%)	3(0.4%)	11(0.2%)	15(0.2%)
Ectopic atrial rhythm	159(2.0%)	162(2.0%)	41(5.8%)	29(4.2%)	118(1.6%)	133(1.8%)
Junctional rhythm	51(0.6%)	41(0.5%)	23(3.2%)	13(1.9%)	28(0.4%)	28(0.4%)
Pacemaker rhythm	72(0.9%)	85(1.1%)	13(1.8%)	12(1.7%)	59(0.8%)	73(1.0%)
Early precordial R/S transition	614(7.7%)	594(7.5%)	32(4.5%)	42(6.1%)	582(8.0%)	552(7.6%)
ST elevation	2018(25.2%)	1974(24.8%)	83(11.7%)	99(14.4%)	1935(26.5%)	1875(25.8%)
ST depression	276(3.4%)	267(3.4%)	49(6.9%)	45(6.5%)	227(3.1%)	222(3.1%)
Abnormal T wave	1184(14.8%)	1103(13.8%)	109(15.4%)	100(14.5%)	1075(14.7%)	1003(13.8%)
Abnormal Q wave	101(1.3%)	96(1.2%)	11(1.6%)	10(1.5%)	90(1.2%)	86(1.2%)
RSR' wave	412(5.1%)	456(5.7%)	22(3.1%)	20(2.9%)	390(5.3%)	436(6.0%)
Low voltage	1017(12.7%)	985(12.4%)	200(28.2%)	181(26.3%)	817(11.2%)	804(11.1%)
Left axis deviation	413(5.2%)	405(5.1%)	48(6.8%)	57(8.3%)	365(5.0%)	348(4.8%)
Right axis deviation	216(2.7%)	225(2.8%)	24(3.4%)	24(3.5%)	192(2.6%)	201(2.8%)
Left ventricular hypertrophy	1004(12.5%)	1065(13.4%)	65(9.2%)	61(8.9%)	939(12.9%)	1004(13.8%)
Right ventricular hypertrophy	101(1.3%)	102(1.3%)	4(0.6%)	8(1.2%)	97(1.3%)	94(1.3%)
Left atrial enlargement	1093(13.7%)	1087(13.6%)	68(9.6%)	75(10.9%)	1025(14.1%)	1012(13.9%)
Right atrial enlargement	330(4.1%)	388(4.9%)	22(3.1%)	23(3.3%)	308(4.2%)	365(5.0%)
Nonspecific IVCD	476(5.9%)	514(6.5%)	47(6.6%)	52(7.6%)	429(5.9%)	462(6.3%)
Left fascicular block	300(3.7%)	326(4.1%)	42(5.9%)	44(6.4%)	258(3.5%)	282(3.9%)
Right bundle branch block	488(6.1%)	514(6.5%)	92(13.0%)	102(14.8%)	396(5.4%)	412(5.7%)
Left bundle branch block	149(1.9%)	130(1.6%)	27(3.8%)	27(3.9%)	122(1.7%)	103(1.4%)
First degree AV block	449(5.6%)	458(5.8%)	39(5.5%)	52(7.6%)	410(5.6%)	406(5.6%)
Second degree AV block	53(0.7%)	42(0.5%)	13(1.8%)	10(1.5%)	40(0.5%)	32(0.4%)
Complete degree AV block	6(0.1%)	8(0.1%)	1(0.1%)	0(0.0%)	5(0.1%)	8(0.1%)
Atrial fibrillation	507(6.3%)	504(6.3%)	149(21.0%)	122(17.7%)	358(4.9%)	382(5.3%)
Atrial flutter	124(1.5%)	111(1.4%)	30(4.2%)	13(1.9%)	94(1.3%)	98(1.3%)
Supraventricular tachycardia	15(0.2%)	13(0.2%)	9(1.3%)	6(0.9%)	6(0.1%)	7(0.1%)
WPW syndrome	4(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	4(0.1%)	0(0.0%)
Ventricular tachycardia	33(0.4%)	35(0.4%)	9(1.3%)	8(1.2%)	24(0.3%)	27(0.4%)
Atrial premature complex	265(3.3%)	255(3.2%)	30(4.2%)	30(4.4%)	235(3.2%)	225(3.1%)
Ventricular premature complex	659(8.2%)	663(8.3%)	111(15.7%)	117(17.0%)	548(7.5%)	546(7.5%)

Abbreviations: ECG, electrocardiography.

Supplemental Table 4 | Patient characteristics stratified by AI-ECG prediction.

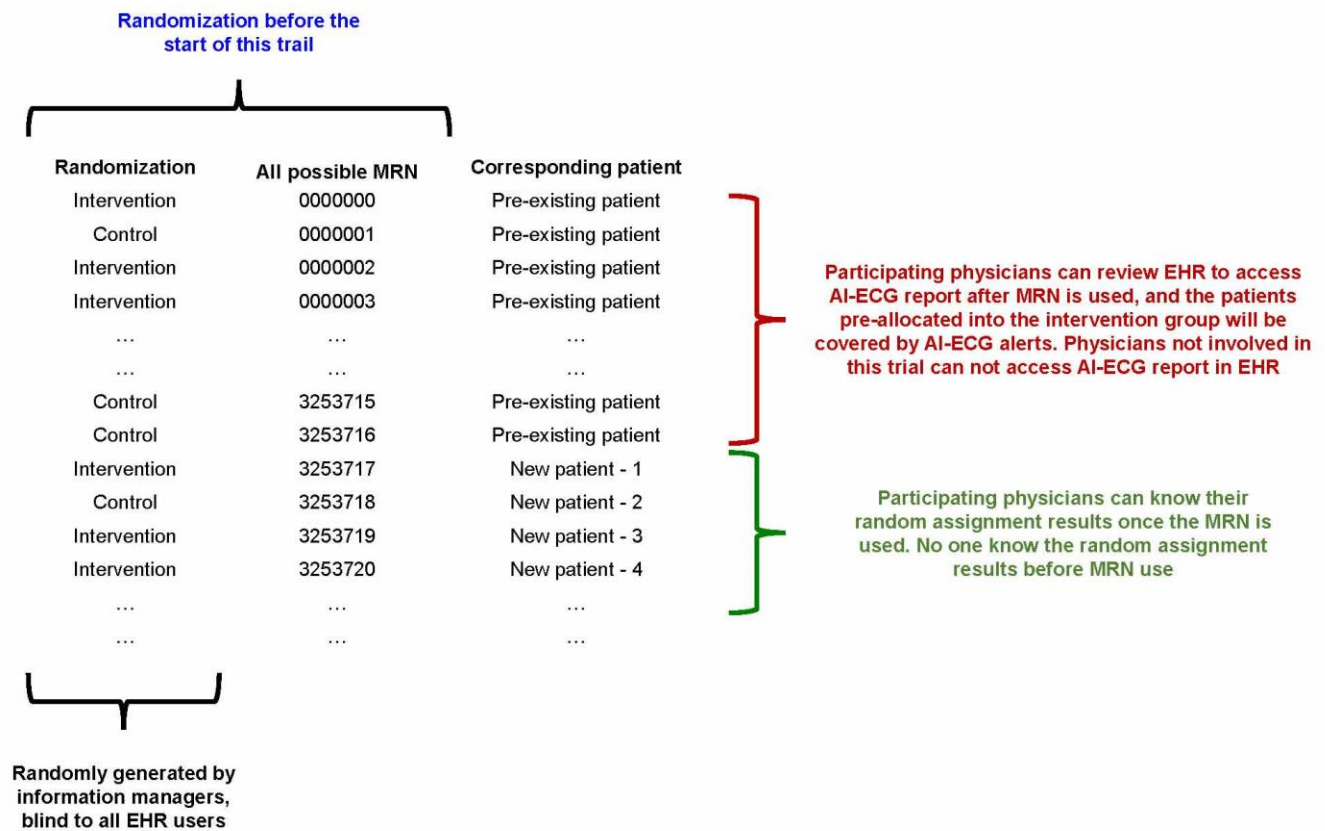
	High risk identified by AI-ECG (n = 1397)	Low risk identified by AI-ECG (n = 14568)	p value
Hospital			<0.001
Academic medical center	1333(95.4%)	13461(92.4%)	
Community hospital	64(4.6%)	1107(7.6%)	
Patient source			0.010
Emergency department	758(54.3%)	8421(57.8%)	
Inpatient department	639(45.7%)	6147(42.2%)	
Demographics and comorbidities			
Sex (male)	770(55.1%)	7474(51.3%)	0.006
Age (mean ± SD)	71.5±16.1	60.2±18.3	<0.001
Age group			<0.001
<65 y/o	447(32.0%)	8146(55.9%)	
65-74 y/o	338(24.2%)	3288(22.6%)	
≥75 y/o	612(43.8%)	3134(21.5%)	
Coronary artery disease	507(36.3%)	3680(25.3%)	<0.001
Heart failure	379(27.1%)	1408(9.7%)	<0.001
Atrial fibrillation	262(18.8%)	910(6.2%)	<0.001
Diabetes mellitus	604(43.2%)	3616(24.8%)	<0.001
Hypertension	832(59.6%)	6044(41.5%)	<0.001
Modified Early Warning Score†			
Score (mean ± SD)	2.5±1.8	1.4±0.9	<0.001
MEWS group			<0.001
0-2 (low risk)	836(59.8%)	13161(90.3%)	
3-4 (median risk)	382(27.3%)	1179(8.1%)	
≥5 (high risk)	179(12.8%)	228(1.6%)	
Systolic blood pressure			<0.001
≤70 mmHg	8(0.6%)	12(0.1%)	
71-80 mmHg	9(0.6%)	19(0.1%)	
81-100 mmHg	149(10.7%)	454(3.1%)	
101-199 mmHg	1194(85.5%)	13816(94.8%)	
≥200 mmHg	3(0.2%)	105(0.7%)	
Missing	34(2.4%)	162(1.1%)	
Heart rate			<0.001
≤40 bpm	2(0.1%)	9(0.1%)	
41-50 bpm	9(0.6%)	53(0.4%)	
51-100 bpm	882(63.1%)	12910(88.6%)	
101-110 bpm	238(17.0%)	914(6.3%)	
111-129 bpm	199(14.2%)	510(3.5%)	
≥130 bpm	67(4.8%)	172(1.2%)	
Respiratory rate			<0.001
<9 bpm	1(0.1%)	3(0.0%)	
9-14 bpm	43(3.1%)	72(0.5%)	
15-20 bpm	1083(77.5%)	13932(95.6%)	
21-29 bpm	229(16.4%)	473(3.2%)	
≥30 bpm	22(1.6%)	41(0.3%)	
Missing	19(1.4%)	47(0.3%)	
Temperature			<0.001
<35.0 °C	69(4.9%)	114(0.8%)	
35.0-38.4 °C	1301(93.1%)	14290(98.1%)	
≥38.5 °C	14(1.0%)	134(0.9%)	
Missing	13(0.9%)	30(0.2%)	
AVPU Score			<0.001
Awake	813(58.2%)	13362(91.7%)	
Reacts to voice	84(6.0%)	297(2.0%)	
Reacts to pain	35(2.5%)	105(0.7%)	
Unresponsive	179(12.8%)	200(1.4%)	
Missing	286(20.5%)	604(4.1%)	
Systolic blood pressure			<0.001
≤70 mmHg	8(0.6%)	12(0.1%)	
71-80 mmHg	9(0.6%)	19(0.1%)	
81-100 mmHg	149(10.7%)	454(3.1%)	
101-199 mmHg	1194(85.5%)	13816(94.8%)	

†: A total of 1079 (6.8%) individuals had missing data of the Modified Early Warning Score (MEWS) for at least one component. To account for these missing values, a score of zero was imputed in the analysis. The statistical tests were used by Student t-test and chi-square test where appropriate. The p value was two-sided, with no adjustment for multiple comparisons. Abbreviations: AI-ECG, artificial intelligence-enabled electrocardiogram; SD, standard deviation.

Supplemental Table 5 | ECG features stratified by AI-ECG prediction.

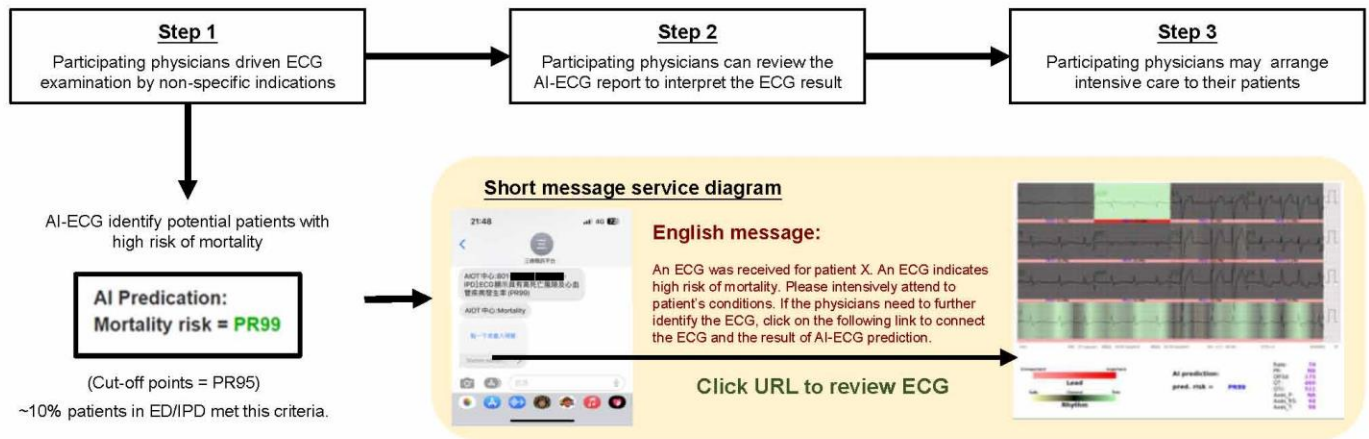
	High risk identified by AI-ECG (n = 1397)	Low risk identified by AI-ECG (n = 14568)	p value
ECG measurement			
Heart rate	103.1±27.9	81.0±17.9	<0.001
PR interval	152.7±45.6	162.0±33.6	<0.001
QRS duration	104.4±29.6	98.4±20.2	<0.001
QT interval	375.3±70.5	389.7±46.0	<0.001
QTc interval	477.4±56.5	446.6±42.2	<0.001
P waves axes	45.1±49.6	49.2±33.6	<0.001
QRS wave axes	35.9±61.4	37.3±45.0	0.269
T wave axes	54.6±77.7	42.9±46.8	<0.001
Selected ECG pattern			
Sinus rhythm	915(65.5%)	13097(89.9%)	<0.001
Sinus arrhythmia	3(0.2%)	83(0.6%)	0.083
Sinus pause	5(0.4%)	26(0.2%)	0.188
Ectopic atrial rhythm	70(5.0%)	251(1.7%)	<0.001
Junctional rhythm	36(2.6%)	56(0.4%)	<0.001
Pacemaker rhythm	25(1.8%)	132(0.9%)	0.001
Early precordial R/S transition	74(5.3%)	1134(7.8%)	0.001
ST elevation	182(13.0%)	3810(26.2%)	<0.001
ST depression	94(6.7%)	449(3.1%)	<0.001
Abnormal T wave	209(15.0%)	2078(14.3%)	0.478
Abnormal Q wave	21(1.5%)	176(1.2%)	0.340
RSR' wave	42(3.0%)	826(5.7%)	<0.001
Low voltage	381(27.3%)	1621(11.1%)	<0.001
Left axis deviation	105(7.5%)	713(4.9%)	<0.001
Right axis deviation	48(3.4%)	393(2.7%)	0.108
Left ventricular hypertrophy	126(9.0%)	1943(13.3%)	<0.001
Right ventricular hypertrophy	12(0.9%)	191(1.3%)	0.150
Left atrial enlargement	143(10.2%)	2037(14.0%)	<0.001
Right atrial enlargement	45(3.2%)	673(4.6%)	0.016
Nonspecific IVCD	99(7.1%)	891(6.1%)	0.151
Left fascicular block	86(6.2%)	540(3.7%)	<0.001
Right bundle branch block	194(13.9%)	808(5.5%)	<0.001
Left bundle branch block	54(3.9%)	225(1.5%)	<0.001
First degree AV block	91(6.5%)	816(5.6%)	0.159
Second degree AV block	23(1.6%)	72(0.5%)	<0.001
Complete degree AV block	1(0.1%)	13(0.1%)	1.000
Atrial fibrillation	271(19.4%)	740(5.1%)	<0.001
Atrial flutter	43(3.1%)	192(1.3%)	<0.001
Supraventricular tachycardia	15(1.1%)	13(0.1%)	<0.001
WPW syndrome	0(0.0%)	4(0.0%)	1.000
Ventricular tachycardia	17(1.2%)	51(0.4%)	<0.001
Atrial premature complex	60(4.3%)	460(3.2%)	0.022
Ventricular premature complex	228(16.3%)	1094(7.5%)	<0.001

The statistical tests were used by Student t-test and chi-square test where appropriate. The *p* value was two-sided, with no adjustment for multiple comparisons. Abbreviations: ECG, electrocardiography; AI-ECG, artificial intelligence-enabled electrocardiogram; SD, standard deviation.

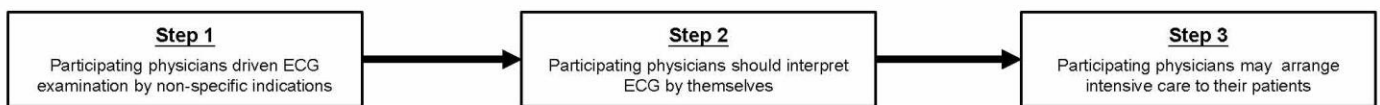


Supplemental Figure 1 | Randomization process in this trial. To ensure effective management of medical records within our hospital's information system, a unique Medical Record Number (MRN) is assigned to each patient as an identifier. Our hospital employs a 7-digit sequential numbering system for MRNs. Upon a patient's initial visit, irrespective of their entry point (emergency department, outpatient department, or inpatient admission), a new MRN is allocated to them in sequential order. Therefore, prior to the commencement of the trial, a random assignment of all possible case numbers was conducted, and the outcomes were stored in the database. It is important to highlight that access to this data is not provided through the Graphical User Interface (GUI) for Electronic Health Record (EHR) users. Given the access privileges granted to participating physicians, they have the capability to retrieve AI-ECG reports for their respective patients through the GUI, thereby indicating whether their patients were allocated to the intervention or control group. However, it should be noted that the GUI does not allow the inquiry of the allocated results for "unused MRNs."

Proposed AI-ECG supporting intensive care process



Traditional frontline physician driven intensive care process



Screenshot for the intervention group



Screenshot for the control group



Supplemental Figure 2 | Diagram illustrating the proposed and traditional intensive care process. Participating physicians may arrange ECG examination to their patients by all indications, and the only difference between proposed and traditional intensive care process is the AI-ECG involved. For the AI-ECG system, we demonstrated the screenshot at the bottom channel. The AI-ECG prediction was converted to a percentile (PR) rank from PR0 to PR99, and a higher PR indicated a higher risk of mortality. Of note, the reference of PR score is based on a whole hospital population prior to the trial, including outpatient department (OPD), inpatient department (IPD), and emergency department (ED), so we expected about 10% patients with a PR score higher than PR95 in IPD/ED. The top panel shows a sample allocated to the intervention group, and the middle panel shows a sample allocated to the control group.

Background

Cardiovascular diseases (CVDs) are critical causes of sudden cardiac death, which contribute to significant disease burden.¹ Most of in-hospital cardiac arrests are potentially avoidable and early intervention for critically ill patients was well-known to reduce mortality.² Unfortunately, the signs of acute deterioration may be difficult to identify early on.³ It had been proposed that 70% of patients died due to an incorrect diagnosis of acute CVDs in a study investigating medical disputes, with 28% of these deaths resulting from acute myocardial infarction.⁴ These results underscore the diagnostic challenges faced by front-line physicians who may lack sufficient experience or who are burdened by heavy workloads.

Rapid response systems (RRSs) have been implemented in hospitals since the early 21st century to aid physicians in promptly identifying and alerting them to high-risk patients.⁵ With the widespread adoption of electronic health records (EHRs) systems and advancements in information technology, the integration of alerts for acute cardiovascular events in hospitals has the potential to significantly enhance the quality of healthcare.⁶ The 12-lead electrocardiogram (ECG) is extensively applied in clinical practice, especially in emergency department (ED) and inpatient department (IPD). With the rapid development of deep learning model (DLM), artificial intelligences (AIs) algorithms were validated to extremely extracted ECG features.⁷ Recent study revealed a high area under the curve (AUC) of 0.88 on all-cause mortality prediction using AI-enabled ECG (AI-ECG).⁸ We aimed to integrate AI-ECG into a track-and-trigger system (TTS) that would have the capability to accurately identify acute cardiovascular events at an early stage during routine clinical practice.

Recently, we have developed a comprehensive AI-ECG system that enables timely notifications for patients exhibiting potential acute CVDs. The AI algorithm was seamlessly integrated into the EHRs system, enabling automatic generation of a report whenever an ECG is conducted. This study will evaluate whether the implementation of the new AI-ECG embedded RRS enhances physicians' diagnostic capabilities in detecting acute CVDs, ultimately leading to a reduction in subsequent mortality events.

Study Purpose and Rationale

Several AI applications have been developed and validated for health care. Among them, medical AIs for mortality risk stratification have been applied to the afferent limb of RRSs, which promptly initiate intensive care for critically ill patients to reduce the risk of mortality. However, very few studies regarding an AI-enabled ECG for stratifying the mortality risk have been prospectively evaluated by randomized controlled trials (RCTs). In this trial, we will introduce AI-ECG as the afferent limb of RRS and investigate the clinical impact of this intervention on critical care.

Since it is widely acknowledged that providing intensive care to critically ill patients reduces mortality,² we expect the AI-ECG based RRS will identify more underdiagnosed patients with critically illness to prompt physicians to arrange intensive care, which may reduce the adverse events of these patients. In this trial, the primary endpoint will be to evaluate whether the new AI-ECG embedded RRSs reduces all-cause mortality events within 90 days. Secondary objectives will include assessing the change of medical behaviors after physicians receive the AI-ECG warning messages.

Study Design and Methods

Overall study design

This study is a multi-site RCT in Tri-Service General Hospital, including an academic medical center and a community hospital. In Taiwan, the holistic patient care is delivered by the attending physician, who oversees and guides the nursing team along with other healthcare professionals involved in the patient's care. The attending physician assumes the responsibility of gathering all relevant patient information and making well-informed medical decisions after careful and comprehensive consideration. Therefore, this trial will involve attending physicians as participants who will receive the intervention by AI-ECG. We will present the clinical trial protocol during the monthly hospital meeting. All eligible attending physicians will be invited to participate this trial. Those who are willing to participate will be required to provide informed consent prior to the commencement of this trial. Since the research team does not directly interact with the patients and solely collects patient data from EHRs, informed consent will be sought from the attending physicians rather than the patients themselves. Moreover, as the ECGs used for AI analysis will be acquired as a routine part of clinical care and in accordance with the guidelines established by the Taiwan Food and Drug Administration (TFDA) (No. 1101603684), the AI-ECG software can be regarded as a medical device with minimal risk.

Study Population

The study participants will consist of the attending physicians responsible for providing care to the patients in ED or IPD. To reduce the heterogeneity of physicians in IPD, only the physicians from the department of internal medicine will be included in the study. All emergency physicians will be invited in the study due to the high homogeneity. Study participants should arrange all the necessary examinations and procedures for patients. A patient's data will be included in the analysis if the patient is ≥ 18 years old because the algorithms were trained by ECGs from adults. All included patients must undergo at least one ECG arranged or interpreted by the participating physicians.

Randomization

Randomization will be conducted at the patient level, and the sequence generation will be based on a MD5 hash transform of each medical record number. The medical record number in our hospital is a length of 7 digits and can be considered as a serial number. We will select the nineteenth value from the 128-bit hash value to assign patients into intervention or control groups.

Intervention

All the ECGs will be "real-time" uploaded after user click the "upload" button in ECG machines to our private cloud server. Subsequently, our AI-ECG platform will perform mortality risk prediction in both intervention and control groups at NVIDIA DGX-1. For patients allocated to the control group, the AI-ECG platform will conceal the results. As shown in [Study protocol Figure 1](#), during the RCT study period, physicians will have access to review the AI-ECG reports of patients in the intervention group within the EHRs, while access to such reports for patients in the control group will

be restricted. Importantly, irrespective of whether they are in the intervention or control group, physicians have the responsibility to examine and interpret the ECGs performed based on clinical indications. Our AI-ECG will be considered merely as an adjunctive tool for interpretation.

In the intervention group, when the AI-ECG indicates a high risk for mortality, a warning message will be promptly triggered and transmitted to the corresponding attending physicians. The notifications will appear in the recipient's smartphone message system immediately, which will indicate that "An ECG from patient X indicates a high risk for mortality. Please intensively monitor the patient's conditions. Please click on the following link to connect the ECG and the result of AI-ECG prediction." The short message will be sent only once for the earliest ECG indicating high risk for each patient. Of note, while we will actively send warning messages for high-risk cases, the AI-ECG results for low-risk cases will also be presented in the EHRs, allowing physicians in the intervention group to review and assess them.

Baseline measurements

This will be a single-blind study since the AI-ECG report system is only available for physicians in the AI-ECG group, instead of all physicians. At a participant level, the information will be collected by our human resource system, which provides the information of sex, age, years of experience, and specialties. Patient-level baseline data will be collected from EHR ([Study protocol Table 1](#)). All data will be ascertained at the time of their index time, defined as the time of ECG examination stratified by AI-ECG results. Since the active warning message may substantially change the medical behavior in intervention group, we will stratify our patients into high risk and low risk subgroups. The definition of these patients is shown in [Study protocol Figure 2](#). For the patients has at least one high risk ECG, whether in intervention or control groups, we will use the first high risk ECG identified by AI-ECG as the start of follow-up time. For the patients have no high risk ECG, the start of follow-up time will be defined as the time of first ECG examination.

Outcomes

The patient outcomes will be collected from EHR. The endpoint outcome in this study will be all-cause mortality within 90 days. Patient status (dead/alive) will be acquired through the EHR. Although it is important to note that there is a possibility that some patients may have passed away outside of our hospital, and as a result, their deaths might not be documented in our HER, we will make certain that the status of censored patients is accurately recorded as having survived until their most recent documented hospital encounter. The data for non-event visits will be censored at the patient's last known hospital live encounter to reduce bias from incomplete records.

The secondary endpoints will include the cardiac (including myocardial infarction, arrhythmia, and others) or noncardiac (including cancer, sepsis, and others) death, and the determination will be made through a manual review conducted at the end of this trial. Moreover, they will include follow-up examinations and medical treatments within 3 days after ECG exam, including intensive care unit (ICU) admission, arrhythmia-related intervention (Cordarone, Digoxin, Herbesser, Lidocaine, and defibrillation), heart function examinations (echocardiography, N-terminal pro-brain natriuretic peptide, high sensitivity troponin I, and coronary angiography), and electrolyte examinations (free calcium, magnesium, potassium, sodium, and chloride). Considering the potential lengthy waiting time for echocardiograms at our hospital, the follow-up period for echocardiograms will be extended to 7 days. [Study protocol Table 2](#) shows the detailed definition according to Taiwan National Health Insurance codes. We define the abnormalities of echocardiogram as follows: new-onset low ejection fraction ($\leq 40\%$), new-onset pulmonary arterial hypertension (≥ 40 mmHg), new-onset pericardial effusion (≥ 10 mm), and new-onset moderate-to-severe valvular diseases (aortic stenosis, aortic regurgitation, mitral regurgitation, pulmonary regurgitation, and tricuspid regurgitation), and progression of valvular diseases from moderate to severe. The definitions of other abnormalities are shown in [Study protocol Table 2](#).

Statistical analysis

The statistical analysis will be performed using the software environment R version 3.4.4 with a significance level of $p < 0.05$ without multiple comparison correction. The analyses will be performed at a patient level. We will compare the intervention and control groups in terms of baseline characteristics, which are the variables pre-considered to be likely to affect subsequent interventions after AI-ECG report. If any significant imbalance is detected for any baseline characteristics, an additional sensitivity analysis will be performed including the unbalanced characteristics in the regression models for outcomes.

The main results will be performed on an intention-to-treat basis, with patients analyzed according to randomly assigned groups, regardless of reception of any subsequent treatments. For primary endpoint, we will use mixed-effect Cox proportional hazard model with the physicians as random effects, which will be performed using the R package "coxme" version 2.2-18.1. We will conduct a stratified analysis based on baseline characteristics, and the results will be considered as exploratory. For the secondary endpoints, we will use the same statistical model as primary analysis. Since the patient may be received these interventions prior to ECG examination, we will generate a variable to describe the intervention history with corresponding time windows as below: (1) arrhythmia-related intervention (Cordarone, Digoxin, Herbesser, Lidocaine, and defibrillation): 3 days; (2) echocardiogram: 180 days; (3) coronary angiography: 180 days; (4) intensive care unit admission: 180 days; (5) laboratory examination (N-terminal pro-brain natriuretic peptide, high sensitivity troponin I, free calcium, magnesium, potassium, sodium, and chloride): 7 days.

Sample size

In our preliminary analysis, we assessed a total of 9,788 ED and IPD patients who had undergone an ECG prior to 30th April 2021. We found that 12.8-21.3% of the high-risk group patients exhibited the primary endpoint. Previous study has reported that high-intensity care is associated with lower mortality rate compared to conventional care (relative risk: 0.71, 95% CI: 0.62-0.82).² We will perform a sample size estimation using a significance level of 0.05, a statistical power of 0.80, a sample size ratio in intervention and control groups of 1.0, a hypothetical ratio of in patients from ED and IPD of 1.0, a hypothetical proportion of controls with primary endpoint of 0.17, and a relative risk of 0.71. The minimum number in intervention and control group both will be 801 per arm. Since approximately 10% ECGs in ED and IPD will be high risk, the final sample size of this trial will be 16,020. We will monthly review the total number of visits cared by participating physicians, and this trial will be terminated after the overall number achieved pre-estimated sample size.

Confidentiality of Study Data

To protect the privacies of patients, we will analyze the patient data on the hospital's internal network, ensuring that the server is not connected to any external networks. The Information Management Office at Tri-Service General Hospital will provide access to ECG records and their corresponding case codes, without disclosing any additional data that could reveal the patient identities. Furthermore, we will not extract any raw data after the completion of this trial, ensuring that there is no risk of data leakage which would compromise patient privacy.

Potential Conflict of Interest

We declare that there is no potential conflict of interest for any of the authors involved in this trial. We have no financial or personal relationships with any organizations that could potentially influence our work. Our focus is solely on the scientific integrity and the potential benefits of this study for patient care. Any findings for this study will be reported transparently and objectively, without any bias or influence from external sources.

Location of Study

This trial will be conducted at two separate institutions in the Tri-Service General Hospital system in Taiwan. The first site is an academic medical center located in NeiHu District, Taipei City, with a capacity of 1,800 beds and an approximately 100,000 annual ED volume. This center serves as the tertiary referral hospital for the surrounding region, boasting comprehensive medical resources and a large patient population. This environment is conducive to recruiting an ample number of eligible physicians and patients for the study. The second site is a community hospital located in Zhongzheng District, Taipei City, with a capacity of 100 beds and an approximately 15,000 annual ED volume. This community hospital plays an important role in providing healthcare services to the local residents, and the characteristics of the patient population at this hospital may be different from those at the academic medical center. Therefore, including both institutions in this trial will provide more comprehensive data and help to determine the generalizability of the study results.

Potential Risks/Discomforts

There are minimal risks and discomforts associated with this study. The study does not involve any experimental drugs, devices, or invasive procedures. All ECGs used in this study are part of routine clinical care and will not cause any additional discomfort to the patients. The AI-ECG software used in this study has been deemed a medical device with minimal risk by the Taiwan Food and Drug Administration, and its use in this study is not expected to pose any significant risks to patients. There is a potential risk of breaches in patient confidentiality if there is a security breach in the hospital's internal network. However, we will take strict measures to ensure patient data security, and the risk of such a breach is minimal. Additionally, patients will not be directly contacted or involved in this study, and their data will be de-identified and kept confidential. Overall, the risks and discomforts to subjects in this study are expected to be minimal.

Compensation to Subjects

Compensation to subjects is not applicable in this study as patient participation is not involved. Instead, attending physicians are the study participants, and their participation is voluntary. They will not receive any financial incentives or other forms of compensation for their participation in this trial. However, attending physicians will benefit from the knowledge gained from this study, which may improve the patient outcomes and the quality of care they provide. The results of this trial may also lead to the implementation of AI-ECG systems in clinical practice, which could potentially benefit future patients.

Cost to Subjects

There will be no cost to subjects associated with participating in this study. All data will be collected from routine medical care, and there will be no additional medical interventions or procedures required for the purpose of this study. There will be no fees associated with the use of the AI-ECG software, and subjects will not be required to purchase any equipment or supplies. Subjects will bear any costs associated with their routine medical care, which will remain the responsibility of the subjects and their healthcare providers.

Patient Benefits

An accurate risk detection model can make a crucial contribution to patient safety, and we will develop a model that uses ECG data to identify potential risks of acute CVDs. We are confident that implementing this model at Tri-Service General Hospital will greatly support physicians in making accurate and timely diagnoses, ultimately leading to significant benefits for the patients. Furthermore, after the trial, the model will be available to all patients at the hospital, potentially offering them significant welfare as well.

Study protocol Table 1. Patient baseline characteristics.

Patient Characteristics	Definition or supplementary note
1. Socio-demographic	
Source	emergency department or inpatient department
Gender	male or female, biological sex
Age	years old
2. Medical history	
Diabetes mellitus	ICD-9 (250) and ICD-10 (E11)
Hypertension	ICD-9 (401 to 404) and ICD-10 (I10 to I16)
Coronary artery disease	ICD-9 (410 to 414) and ICD-10 (I20 to I25)
Heart failure	ICD-9 (428, 398.91, 402) and ICD-10 (I50)
Atrial fibrillation	ICD-9 (427.31, 427.32) and ICD-10 (I48)
3. ECG measurement	
Heart rate	estimated by from the Philips system®
PR interval	estimated by from the Philips system®
QRS duration	estimated by from the Philips system®
QT interval	estimated by from the Philips system®
QTc interval	estimated by from the Philips system®
P waves axes	estimated by from the Philips system®
QRS waves axes	estimated by from the Philips system®
T waves axes	estimated by from the Philips system®
4. Selected ECG pattern	
Sinus rhythm	Philips statements code: SR; ST; TWRV; SB
Sinus arrhythmia	Philips statements code: SA; SAB; SAT
Sinus pause	Philips statements code: SP; SARSV; SARA
Ectopic atrial rhythm	Philips statements code: EAR; EAB; EAT; SEAR; SEAB; SEAT
Junctional rhythm	Philips statements code: JER; JRA; JT; SDJ
Pacemaker rhythm	Philips statements code: PMR; WPACE; PSAR; NFAD; NFRA
Early precordial R/S transition	Philips statements code: ET
ST elevation	Philips statements code: STE; MSTEL; BSTEL; EREPOL; STELVH; MSTEL; CINJI; BSTEA; MSTEI; CINJA; MSTEA; CINJL; MSTED; BSTEI; BSTE; PINJA; PINJL; PINJAL; CINJAL; SD0IN; BSTEL
ST depression	Philips statements code: STD; SD1AL; SDJ; SDPRR; SD1IN; SD0DI; SD2AN; SD2WI; SD1AN; SD0AN; SDM; SD2IN; SD2AL; SD0AL; SD0LA; SD1LA; SD2NS; SD1DI
Abnormal T wave	Philips statements code: ATW; T1LA; T0IN; T0LA; T1LA; T1AN; T1IN; T0AN; T0DI; T1DI; TONS; TTW10; T1AL; T3AL; T3LA; T6AL; T3WI; T3IN; T3AN; T0AL
Abnormal Q wave	Philips statements code: AQW; LATQ; INFQ; IMI3; ASQLVH; AMI57; AQLVH; PQIN; IMI18; PIMI; AMI17; AMI48; LMI10; ANTQ; LMI28
RSR' wave	Philips statements code: RSRW; RSR1; ETRSR1
Low voltage	Philips statements code: LVOL; LVOLFB; LVOLF; LVOLP; LVORAD; LVOLT
Left axis deviation	Philips statements code: LAD; AXL; CAFBII; NIVCDL
Right axis deviation	Philips statements code: RAD; AXR; LVORAD
Left ventricular hypertrophy	Philips statements code: LVH; LVH1; LVHVP; LVHSR; LVHR56; LVHV; LVHREP; STELVH; LVHCNP; LVHPRE; LVHSR; LVHCNV; ASQLVH; LVHR56; LVHCO; LVHV; AQLVH; TIALVH; LVHCOL; AMI57; AMI17; AMI48; LMI28
Right ventricular hypertrophy	Philips statements code: RVH; PRVH; CRVH; RVHR; PRVHR; CRVHR
Left atrial enlargement	Philips statements code: LAE; PLAE; CLAE; LAECB
Right atrial enlargement	Philips statements code: RAE; LAECB; BAE; RAECB; CRAE
Nonspecific IVCD	Philips statements code: NIVCD; BIVCD; IVCDP; LVHCO; NIVCDL
Left fascicular block	Philips statements code: LFB; LAFB; LPFB; CLAFB; RLAFB; CAFBII; IRAFB; RLPFB
Right bundle branch block	Philips statements code: RBBB; IRBBB; RLAFB; IRAFB; RLPFB; ARBBB
Left bundle branch block	Philips statements code: LBBB; ILBBB
First degree AV block	Philips statements code: 1AVB
Second degree AV block	Philips statements code: 2AVB; AFL2; AFLT2; AFLT3; AFLT4; WENCK; MOBII
Complete degree AV block	Philips statements code: CAVB; 3AVB; 3AVBFF; 3AVBIR
Atrial fibrillation	Philips statements code: AFIB; AFIB0; 3AVBFF; VPACCF; VPACF; FLFIB; AFIBT; AVDPCF
Atrial flutter	Philips statements code: AFLT; AFL2; AFLT2; AFLT3; AFLT4; 3AVBFF; AFLTV; FLFIB; VPACCF; VPACF
Supraventricular tachycardia	Philips statements code: SVT

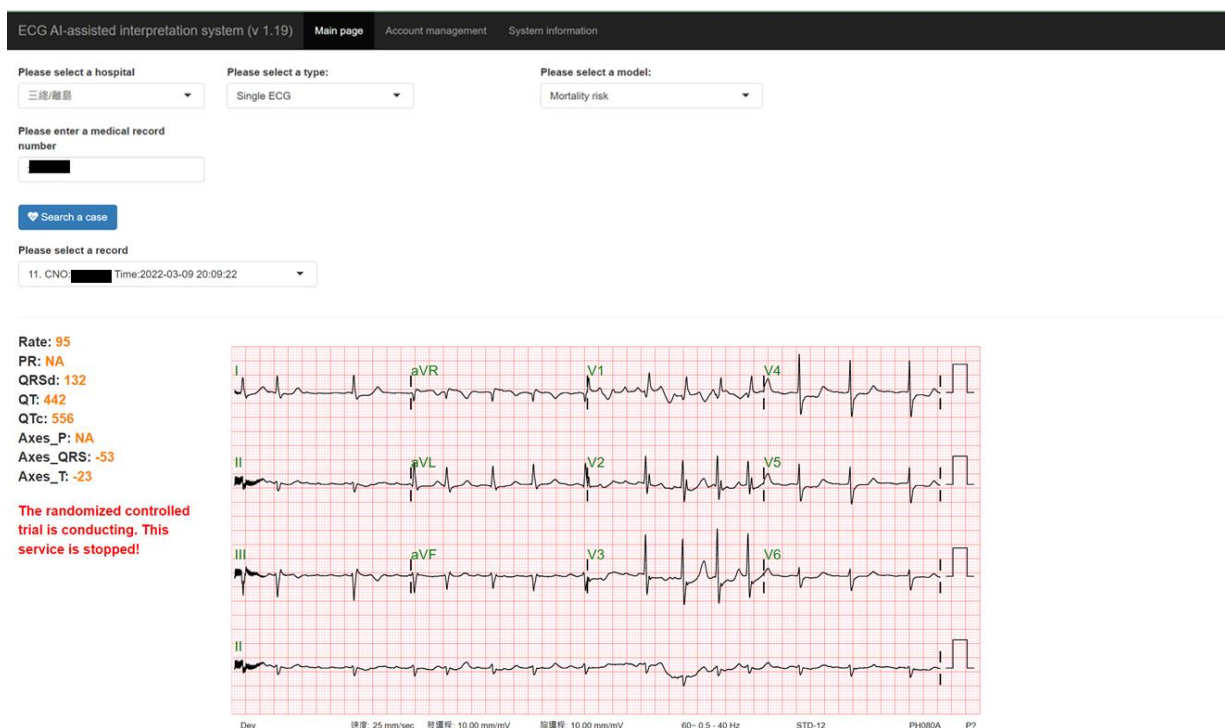
WPW syndrome	Philips statements code: VPE
Ventricular tachycardia	Philips statements code: RVPC
Atrial premature complex	Philips statements code: APC; MAPC; APCPR
Ventricular premature complex	Philips statements code: VPC; PVPC; APCPR; VBIG; MVPC; VTRI; MFVPC; IVPC

Abbreviation: ICD, International Classification of Disease.

Study protocol Table 2. Patient outcomes.

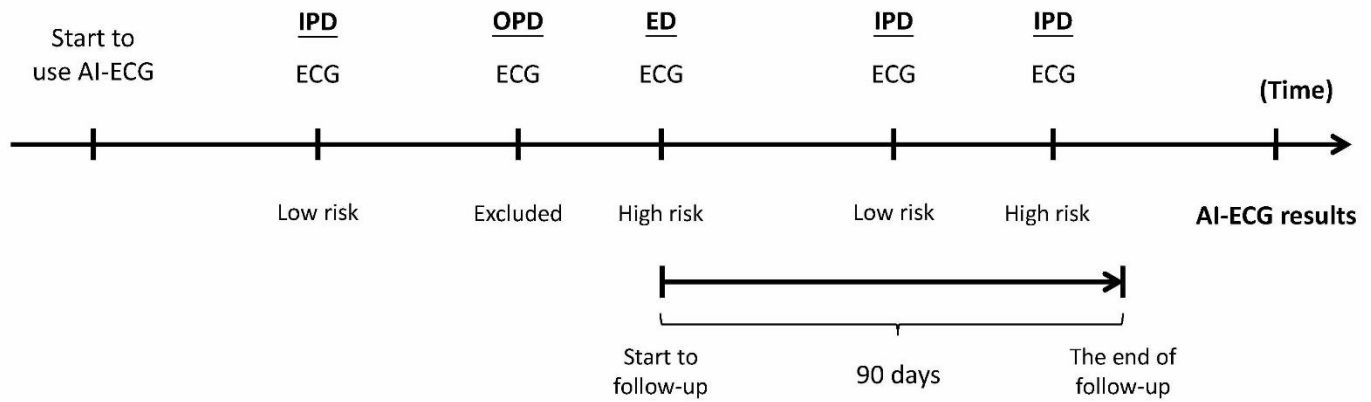
Event	Definition or supplementary note
1. Primary endpoint All-cause mortality	Defined by the death records in EHR.
2. Secondary endpoint	
Cardiac death	Manually review the cause of death
Non-cardiac death	Manually review the cause of death
Cordarone	NHI code (B014861216)
Digoxin	NHI code (BC09554100, B009714212)
Herbesser	NHI code (B018540248, AC103581G0, A010358100)
Lidocaine	NHI code (A010914221)
Defibrillation	NHI code (47028C)
Echocardiogram	NHI code (18005C, 18006C, 18007C)
Coronary angiography	NHI code (18020B, 18021B)
Intensive care unit admission	NHI code (03010E, 02011K)
N-terminal pro-brain natriuretic peptide	Collected by our laboratory information system
high sensitivity troponin I	Collected by our laboratory information system
Free calcium	Collected by our laboratory information system
Magnesium	Collected by our laboratory information system
Potassium	Collected by our laboratory information system
Sodium	Collected by our laboratory information system
Chloride	Collected by our laboratory information system
3. Secondary endpoint (examination results)	
Significant echocardiographic findings	Automatically review the structuralized echocardiogram report
Percutaneous coronary intervention	NHI code (33076B, 33077B, 33078B)
N-terminal pro-brain natriuretic peptide	≥1000 pg/mL
high sensitivity troponin I	≥200 pg/mL
Free calcium	<4.5 or >5.3 mg/dL
Magnesium	<1.7 or >2.2 mg/dL
Potassium	<3.5 or >5.1 mmol/L
Sodium	<136 or >145 mmol/L
Chloride	<98 or >107 mmol/L

Abbreviation: EHR, electronic health records; NHI, national health insurance.

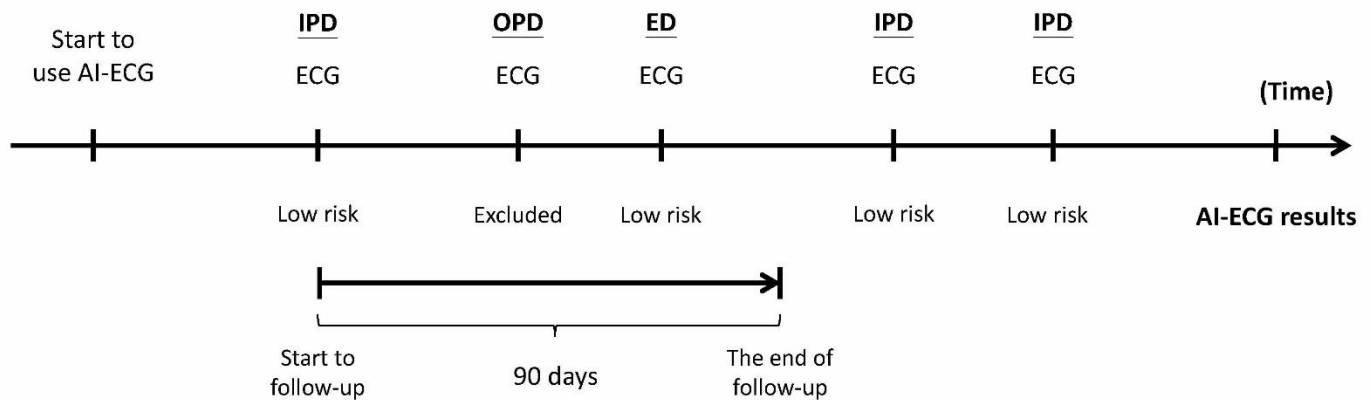


Study protocol Figure 1. The screenshot of system to review AI-ECG report. The AI-ECG prediction will be converted to percentile (PR) rank from PR0 to PR99, which the higher PR indicates the higher risk of mortality. Top panel shows a sample allocated to intervention group, and the bottom panel shows a sample allocated to control group.

For patients with at least one high risk ECG in the study period



For patients without high risk ECG in the study period



Study protocol Figure 2. Schematic the samples with and without high risk ECG identified by AI-ECG. For the patients with at least 1 high risk ECG, we will use the time of first high risk ECG identified by AI model as the reference time to follow-up. For the patients without 1 high risk ECG, we will use the time of first ECG as the reference time to follow-up. All ECGs in OPD will be excluded in this experiment.

Study protocol references

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