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Opportunistic Screening for Asymptomatic Left Ventricular Dysfunction Using Electrocardiographic Artificial Intelligence: A Cost-Effective Approach

Wei-Ting Liu[1#] MD, Ping-Hsuan Hsieh[2#] PhD, Chin-Sheng Lin[1] MD, Wen-Hui Fang[3,4] MD, Chih-Hung Wang[5] MD, Chien-Sung Tsai[6] MD, Yi-Jen Hung[7] MD, Chung-Bao Hsieh [8] MD, Chin Lin[3,9,10] PhD, Dung-Jang Tsai[3,9,11*] MD

[1]Division of Cardiology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.

[2]School of Pharmacy, National Denfense Medical Center, Taipei, Taiwan, R.O.C.;

[3]Artificial Intelligence of Things Center, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.;

[4]Department of Family and Community Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.;

[5]Department of Otolaryngology-Head and Neck Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.;

[6]Division of Cardiovascular Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.

[7]Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.

[8]Division of General Surgery, Department of Surgery, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan, R.O.C.

[9]Medical Technology Education Center, School of Medicine, National Defense Medical Center, Taipei, Taiwan, R.O.C.

[10]School of Public Health, National Defense Medical Center, Taipei, Taiwan, R.O.C.;

[11]Department of Statistics and Information Science, Fu Jen Catholic University, New Taipei City, Taiwan, R.O.C.

[#]These authors contributed equally.

Running Head: Cost effect of AI-enabled ECG for LV Dysfunction

Address correspondence:

Dr. Dung-Jang Tsai, No.510, Zhongzheng Rd., Xinzhuang Dist., New Taipei City 242062, Taiwan (R.O.C.)

Tel: 886-2-29053974; E-mail: 157373@mail.fju.edu.tw

ABSTRACT

BACKGROUND

The burden of asymptomatic left ventricular dysfunction (LVD) is greater than that of heart failure; however, a cost-effective tool for asymptomatic LVD screening has not been well validated. We aimed to prospectively validate an artificial intelligence (AI)-enabled electrocardiogram (ECG) algorithm for asymptomatic LVD detection and evaluate its cost-effectiveness for opportunistic screening.

METHODS

In this prospective observational study, patients undergoing ECG at outpatient clinics or health check-ups were enrolled in two hospitals in Taiwan. Patients were stratified into LVD (LVEF <= 40%) risk groups using a previously developed ECG algorithm. The performance of AI-ECG was used to conduct a cost-effectiveness analysis of LVD screening compared with no screening. Incremental cost-effectiveness ratio (ICER) and sensitivity analyses were employed to examine the cost-effectiveness and robustness of the results.

RESULTS

Among the 29,137 patients, the algorithm demonstrated area-under-the-curves of 0.984 and 0.945 for detecting LVD within 28 days in the two hospital cohorts. For patients not initially scheduled for an echocardiogram, the algorithm predicted future echocardiograms (high-risk, 46.2%; medium-risk, 31.4%; low-risk, 14.6%) and LVD at 12 months (high-risk, 26.2%; medium-risk, 3.4%; low-risk, 0.1%). Opportunistic screening with AI-ECG could result in a negative ICER of -$7,439 for patients aged 65, with consistent cost-savings across age groups and particularly in men. Approximately 91.5% of the cases were found to be cost-effective at the willingness-to-pay of $30,000 in the probabilistic analysis.

CONCLUSIONS

The use of AI-ECG for asymptomatic LVD risk stratification is promising, and opportunistic screening in outpatient clinics has the potential to save costs.

KEYWORDS

Artificial intelligence; deep learning; electrocardiogram; left ventricular dysfunction; risk stratification

Introduction

Heart failure (HF) affects over 23 million people worldwide and has a high rate of morbidity and mortality, leading to a serious global public health problem[1]. The detection of HF mainly relies on clinical presentations such as dyspnea on exertion, orthopnea, and peripheral edema. However, some patients may have decreased left ventricular (LV) function before the appearance of obvious HF symptoms. This results in a prevalence of asymptomatic LV dysfunction (LVD) in the general population of approximately 3–6%, which is three to four times higher than that in clinical HF patients[2, 3]. In Taiwan, the prevalence of LVD varied between 1.4% (LV ejection fraction [LVEF] < 40%) and 6.1% (LVEF < 50%)[4]. Patients with asymptomatic LVD have an 8.4% risk of progression to clinical HF every year, and the risk of mortality is 1.6 times higher in patients with asymptomatic LVD compared to those with normal LVEF[3, 5]. Early detection of asymptomatic LVD and follow-up with adequate treatment can effectively reduce the risk of incident HF and mortality[5]. The brain-type natriuretic peptide (BNP) has been suggested as a cost-effective tool for asymptomatic LVD screening; however, its routine clinical use is limited by the possibility of false positives in various conditions[6]. Furthermore, echocardiography, which is an accurate assessment tool for LVD, requires specialized technical skills, and is unsuitable for widespread screening. Therefore, a precise and accessible screening test is required to identify individuals at risk of asymptomatic LVD.

Deep-learning techniques, an extensive field of artificial intelligence (AI), have been used to identify cardiovascular diseases using electrocardiograms (ECGs) with cardiologist-level precision[7]. Studies have shown that deep learning algorithms can identify LVD with area-under-the-curve (AUC) values exceeding 0.90[8, 9]. Screening for asymptomatic LVD using an AI-enabled ECG is promising. A study conducted by Tseng et al. in the United States found that screening for asymptomatic LVD using AI-ECG at ages 55 and 65 was cost-effective, but not at age 75, at a willingness-to-pay[A] threshold of $50,000[11]. Due to advanced age, the limited improvement in effectiveness resulting from screening and subsequent treatment leads to a higher incremental cost-effectiveness ratio (ICER) at age of 75 compared to the age of 65. However, the cost of

[A]This technique asks people to state explicitly the maximum amount they would be willing to pay to receive a particular benefit. It is based on the premise that the maximum amount of money an individual is willing to pay for a commodity is an indicator of the value to them of that commodity.[10]

screening, subsequent examinations, and treatment varies greatly because of differences in economic and health insurance systems between regions, which play a crucial role in determining cost-effectiveness.

In the present study, we aimed to validate the performance of AI-enabled ECG in detecting asymptomatic LVD at outpatient clinics in a prospective cohort. Furthermore, we conducted an economic evaluation to assess the cost-effectiveness of screening for asymptomatic LVD using AI-enabled ECG compared with no screening under a social insurance system.

Materials and Methods

Study design and participants

In this prospective observational study, patients who underwent an ECG examination at either the Tri-Service General Hospital (TSGH), a tertiary center hospital, or the Tingzhou branch of TSGH, a district hospital in Taiwan, were recruited between March 2020 and February 2022. Patients who were 18 years of age or older and had undergone an ECG in outpatient departments or health checkups were eligible to participate in the screening program. Patients who underwent ECG examinations in the emergency department or during hospitalization were excluded to avoid the inclusion of patients with obvious heart failure. Patients with a history of heart failure or prior echocardiography were also excluded. The recruited patients might subsequently undergo transthoracic echocardiography arranged by clinicians because of various indications, such as breathlessness, peripheral edema, chest pain, arrhythmia, or suspected valvular heart disease. The timing and results of the transthoracic echocardiograms of the recruited patients after the index ECG were analyzed. The study was reviewed and approved by the Institutional Ethics Committee of TSGH (C202105049).

Procedures

The use of an AI-based alarm system (AI-S) is described in this study. AI-S is designed to predict the LV ejection fraction (EF) automatically by analyzing ECGs uploaded in real time. The system uses a convolutional neural network trained on 58,431 independent pairings of 12-lead ECGs and echocardiograms from the TSGH[8]. The training process was published in our previous work[8] and it was reported in the Supplementary Methods. AI-S automatically calculates LVEF, with LVEF equal to or less than 40% defined as LVD. The AI-S uses the maximum Youden's index of AUC to establish a medium-risk LVD cutoff value and the area under the precision-recall curve (PRAUC) to establish a high-risk LVD cutoff value[12]. Every ECG was given an AI-predicted EF value, which was stored in electronic medical records.

Once the AI-S detected the LVD, a warning message was immediately sent to the frontline physician in charge of the patient and the on-duty cardiologist. A notification appeared on the recipient's smartphone message system to prompt attention during the shift. The short message was triggered only once for the earliest triggering rule and was not triggered by negative samples after multiple background calculations by AI-S. The study cohort was then categorized based on the risk of LVD predicted by the AI-S, and physicians determined whether the patient required a cardiac ultrasound examination.

Study Outcomes

The primary analysis aimed to evaluate the performance of the AI-S for LVD detection using the F-measure, precision, and recall, whereas the secondary analysis assessed the risk of future adverse events (such as all-cause mortality, hospitalization, and emergency department visits) in patients with and without echocardiograms. Additionally, cardiovascular events, including HF, atrial fibrillation, coronary artery disease, stroke, and acute myocardial infarction, were calculated.

Cost-effectiveness Analysis and Assumptions

To evaluate the cost-effectiveness of AI-enabled ECG (AI-ECG) screening for asymptomatic LVD compared to no screening, we used a decision analytic model incorporating Markov processes to simulate a cohort of 65-year-old patients followed up over the rest of their projected remaining lifetime horizon. Due to disease prevalence and health checkups policies in Taiwan, we focused our analysis on individuals aged 65 as the base-case scenario. The structure of the cost-effectiveness analysis used in this study was adopted from the literature[11]. The healthcare payer's perspective was chosen. The decision analytic model consists of a decision tree and a Markov model, taking into consideration the prevalence of asymptomatic LVD, AI-ECG screening performance, costs, and outcomes related to early intervention. This includes the associated costs and effects of LVD and HF on long-term mortality and quality of life. The short-term decision tree model is illustrated in the left part of Figure 1. Positive AI screening would lead to transthoracic echocardiography to confirm true-positive cases or rule out false-positive cases of asymptomatic LVD. After the confirmation of LVD through echocardiography, a thallium myocardial perfusion scan was conducted as a post-confirmatory test to evaluate the presence of coronary artery disease. The hypothetical cohort entered the Markov model in one of three health states following screening: (1) treated with asymptomatic LVD if positively screened using AI algorithm and TTE (true positive); (2) untreated with asymptomatic LVD if AI algorithm failed to detect existing condition (false negative); or (3) untreated without asymptomatic LVD if the condition was absent.

As shown in the right section of Figure 1, those treated and untreated for asymptomatic LVD could progress to symptomatic heart failure, leading all individuals to be treated upon disease advancement. Additionally, transitions to a dead state can occur annually from any of the predefined health conditions, following specified transition probabilities.

Health Outcomes, Costs and Discounting

Table 1 summarized estimated values of the AI-ECG performance, health outcomes, costs, utilities, and other factors in the model. The AI-ECG performance in detecting medium- and high-risk groups in the internal validation cohort was applied to the model. The sensitivity of AI-ECG for detecting medium risk of asymptomatic LVD was 0.926 (standard error [SE]:0.042), with a specificity of 0.927 (SE:0.003). The sensitivity and specificity for the detection of high-risk patients were 0.630 (SE:0.154) and 0.987 (SE:0.002), respectively. In this analysis, the prevalence of asymptomatic LVD was set at 1.6% among the 65-year-old cohort in Taiwan, according to the published literature[13]. Individuals were simulated to receive treatment for asymptomatic LVD using a combination of angiotensin-converting enzyme inhibitors (ACEi) and beta blockers. Annual transition probabilities to symptomatic heart failure from treated and untreated patients and their utility scores were built mainly on data used in previous studies and their calculations[11]. The transition of patients without LVD on initial screening to death is accounted for the age and sex-specific survival of general population, according to the Taiwan life tables[14].

The cost of the AI-ECG was assumed to be the same as that of an electrocardiogram ($ 4.96) in the base case and increased to five times higher in the sensitivity analysis as it is still unclear how to set the price of AI-ECG. The costs of health resources were calculated based on Taiwan National Health Insurance, as presented in Table 1. Cost and effectiveness were both discounted at 1.5%. Discounting accounts for time preference, with higher costs being valued or effectiveness gains being realized now rather than later.

Analytical methods

One-way deterministic sensitivity analyses were performed to evaluate the robustness of the model with respect to the starting ages of cohort, costs of AI-ECG screening, diagnosis, outpatient attendance, hospitalization, treatment, the performance of AI-ECG and discounting rates. To better assess the covariate uncertainty, a probabilistic sensitivity analysis was conducted. Probability distributions were assigned to each of the input variables; the estimate mean values, estimated standard errors, and types of distribution for each variable. Probabilities and utilities were modelled using beta distributions, as these take on values between 0 and 1. In contrast, costs were modelled as gamma distributions, which are non-negative, right-tailed distributions that are well-suited to modeling costs. Point estimates for ICER were calculated using a Monte Carlo simulation of 5,000 iterations of parameters from their estimated probability distributions. The model was constructed and analyzed using TreeAge Pro version 2022. Costs were converted to USD according to the currency rate obtained from the Bank of Taiwan on January 16, 2023. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and Canadian Agency for Drugs and Technologies in Health (CADTH) recommendations were used to serves as evidence of our adherence to the reporting elements outlined in the CHEERS guidelines[15] and to ensure the generalizability to Canadian standard (Table S2 to S3).

Statistical Analysis

Patient characteristics are presented as means with standard deviations, numbers of patients, or percentages, as appropriate. Comparisons between groups were made using either the student's t-test or the chi-square test, depending on the type of data being analyzed. Cox proportional hazards models adjusted for gender and age were used, presenting standardized hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). A normality distribution test was conducted using the "nortest" package. Statistical analysis was carried out using R software version 3.4.4, and a significance level of $p < 0.05$ was used throughout the analysis.

Results

AI-S Prediction and Future Echocardiograms

In this study, 29,137 patients were recruited and categorized based on their risk levels for LVD predicted by the AI-S. Of these patients, 244 (0.84%) were classified as high-risk, 974 (3.34%) as medium-risk, and 27,919 (95.82%) as low-risk. The number of echocardiographic examinations in each risk group was calculated, as shown in Figure 2. The patients recruited in the academic center were considered the internal validation cohort, while those in the district hospital were regarded as the external validation cohort. The high-risk group had a higher proportion of men, older age, and comorbidities than did the low- and medium-risk groups, as shown in Table S1. Moreover, in the internal validation set, the high- and medium-risk groups had a higher proportion of patients who underwent echocardiography within 28 days (42.7% and 40.4%, respectively) than the low-risk group (24.5% at 28 days) (Figure 3). The adjusted HR for receiving an echocardiogram within 28 days was 1.93 (95% CI:1.54-2.41) and 1.77 (95% CI:1.57-2.00) for the high-risk and medium-risk groups, respectively. Both the internal and external validation sets showed similar results. Furthermore, among patients who were not initially scheduled to undergo an echocardiogram within 28 days, the high- and medium-risk groups underwent more echocardiograms (high-risk, 46.2%; medium-risk, 31.4%) within 12 months than the low-risk groups (low-risk, 14.6%) (Figure 3).

The Performance of AI-S for LVD Detection

In the medium-risk group, the AI-S was able to predict an LVEF <= 40% by 12-lead ECG with an AUC of 0.984, a sensitivity of 92.6%, a specificity of 93.8%, a positive predictive value (PPV) of 6.9%, and a negative predictive value of 100% in the internal validation cohort. In the high-risk group, the AI-S achieved an F-score of 0.321, sensitivity of 63.0%, specificity of 98.9%, and PPV of 21.5% for identifying LVD. The AI-S also demonstrated robust performance, with an AUC of 0.945 in the external validation cohort, as shown in Figure 4. Additionally, the proportion of patients being diagnosed with an EF <= 40% within 12 months was significantly higher in the high-risk (26.2% and 17.9%) and medium-risk (3.4% and 2.5%) groups compared to the low-risk group (0.1% and 0.2%), in the internal and external validation sets, respectively. The adjusted HR for the diagnosis of LVD in the high-risk group was 65397.04 and 82.92 in the internal and external validation sets, respectively (Figure 5). Moreover, significant abnormal findings on echocardiograms, such as moderate-to-severe valvular heart disease or pulmonary artery systolic pressure greater than 50 mmHg, were more likely to be found in the medium- or high-risk groups than in the low-risk group (Figure S1). Although the presented AI algorithm's performance was limited to patients who received echocardiograms within 28 days, as the follow-up period extended to 12 months, the performance of the AI algorithm to detect LVD in this subgroup remained consistent (Figure S2 to S4).

We also assessed the prognostic capability of the AI-S in predicting future adverse events, including all-cause mortality, hospitalization, emergency department visits, and cardiovascular events, in patients who underwent an echocardiography exam as well as in those who did not, as depicted in Figures S5 to S8. The AI-S exhibited promising diagnostic and prognostic performance in screening for LVD and predicting future adverse events in patients undergoing ECG at the OPD or health checkups.

Cost-Effectiveness Analysis

In the base-case scenario, AI-ECG screening of 5,000 individuals resulted in 56 HF cases (33.5%) and 52 deaths (31.1%) cumulatively within the first 4 years among the 167 LVD individuals. In contrast, among those who were not screened for LVD, there were 70 HF cases (41.0%) and 51 deaths (30.1%) in the first 4 years among 170 individuals with LVD.

Regarding cost-effectiveness (Table 2), AI-ECG screening showed dominance, with lower average costs for the entire simulated AI-ECG group compared to non-screened patients. This pattern held true for both medium-risk and high-risk groups. In the medium-risk category, AI-ECG resulted in average cost reduction of $44 per patient, alongside a slight increase in quality-adjusted life years (QALYs) expectancy (0.006 QALYs gained per patient), yielding a negative ICER of -$7,439. This cost-saving effect was notably pronounced in men. While AI-ECG screening cost slightly more for women compared to no screening ($111 vs. $104) and had marginal QALY gains, the resulting ICER of $6,262 indicates continued cost-effectiveness.

One-way sensitivity analysis (Figure S9) revealed that the costs of outpatient attendance, treatment (ACEi and beta-blockers), hospitalization, asymptomatic LVD evaluation (post-confirmatory testing) and the specificity of AI-ECG had a significant effect on cost-effectiveness. Higher costs of outpatient attendance and hospitalization due to HF increased cost-effectiveness (ie, screening for asymptomatic LVD avoids more subsequent HF than no screening), whereas higher costs of treatment and asymptomatic LVD evaluation deceased cost-effectiveness. Of note, even the cost of AI-ECG screening was raised to 500% of the current cost, AI-ECG screening for asymptomatic LVD was still dominant over no screening.

In the probabilistic sensitivity analysis, Figure 6 graphically illustrates that 62.8% of the 5,000 simulations resulted in estimates for AI-ECG screening that were both more effective and less costly compared to no screening. Furthermore, for a willingness-to-pay of $30,000, most simulations (91.5%) yielded ICERs below the threshold. The cost-effectiveness increased even more for payers with a WTP exceeding 0 dollar/year (Figure 6B). Analysis of AI-ECG screening for asymptomatic LVD across various age groups consistently revealed cost-effective outcomes from age 45 onward, irrespective of sex and risk stratification strategies (Table 2). Optimal cost-effectiveness was observed with screening at age 65. These findings underscore the efficacy of widespread AI-ECG screening for detecting asymptomatic LVD.

Discussion

In this study, we conducted a prospective assessment of an AI-ECG to screen for LVEF <= 40% in patients at OPD or health checkups. The algorithm demonstrated high accuracy in detecting LVD, with AUCs of 0.984 and 0.945 for the internal and external validation sets, respectively. By stratifying patients into high-, medium-, and low-risk categories, the algorithm could detect those susceptible to LVD early. Additionally, among patients who were not initially scheduled to receive an echocardiogram, the algorithm accurately predicted the need for future echocardiograms as well as the risk of LVD and cardiovascular adverse events within one year. Using this powerful AI screening tool, we analyzed the cost-effectiveness of AI-enabled ECG screening for asymptomatic LVD compared with no screening in different age groups. The results showed that screening for asymptomatic LVD with the algorithm can lead to an improvement in QALYs and a reduction in medical costs by preventing future incident heart failure and associated costs, particularly in patients over the age of 65. To the best of our knowledge, this is the first study to evaluate the cost-effectiveness of asymptomatic LVD screening using AI-enabled ECG in a country with social insurance, indicating comprehensive insurance coverage and relatively low healthcare costs. These findings suggest that AI-ECG could be widely applied in clinical practice for the detection of asymptomatic LVD, resulting in improved patient outcomes and cost savings.

The AI algorithms used in ECG for LVD detection have been widely proposed in recent years. Yao et al. conducted a randomized controlled trial involving 22,641 patients to compare the diagnostic rate of LVEF <= 50% within 90 days of ECG between an AI-assisted group and a usual care group[16]. Compared to usual care, physicians with additional information from AI-ECG predictions could identify 32% more patients with LVEF <=50% using similar echocardiogram utilization rates between the two groups (18.2% in usual care and 19.2% in the AI-assisted group, $P = 0.17$)[16]. Similarly, another study prospectively enrolled 16,056 patients and used AI-enabled ECG to detect EF <= 35%.[17] The algorithm detected patients with LVEF <=35% with an AUC of 0.918 and 39.8% of the false-positive results had an LVEF of 36% to 50%.[17] Compared to previous studies, our study prospectively included 29,137 patients without previous cardiac evaluation, of whom 7,645 (26%) received echocardiograms within 28 days. The algorithm accurately identified patients who required an echocardiogram in advance in both the internal and external validation cohorts. Among patients who were not initially scheduled for echocardiography, the high-risk group identified by the AI underwent more echocardiograms during the follow-up period. Moreover, patients with normal LVEF but a high risk predicted by the AI had more structural abnormalities on echocardiograms. In clinical practice, physicians may encounter asymptomatic patients without traditional risk factors for LVD but with a positive AI alarm. With the risk stratification provided by our AI model, physicians can comprehensively evaluate the possibility of LVD and arrange subsequent examinations and treatments precisely.

The performance of the AI models in screening for various cardiovascular diseases was comparable to that of cardiologists. Moreover, the cost-effectiveness of opportunistic screening using these algorithms is promising. For instance, Pickhardt et al. conducted a cost-effectiveness analysis of an AI-based cardiovascular disease screening using abdominal computed tomography (CT).[18] The algorithm was able to automatically quantify abdominal aortic calcium; based on the results, moderate-to high-intensity statin treatment was recommended. Compared to the no-screening group, opportunistic screening using an AI-assisted CT scan was found to be a clinically effective and cost-saving strategy.[18]

In the case of diagnosing asymptomatic LVD, AI-enabled ECG has demonstrated excellent diagnostic ability compared to previous risk-prediction scoring models[19]. Because AI-ECG provides significant diagnostic improvements compared to usual care, the cost-effectiveness of AI in detecting asymptomatic LVD should be remarkable. In our model, early identification of asymptomatic LVD and subsequent intervention resulted in the avoidance of more cases of HF compared to the control group. Consequently, AI-ECG screening demonstrated dominance, with lower average costs and higher QALYs gained for the entire simulated AI-ECG group when compared to non-screened patients. Even with uncertainty in AI-ECG costs and potential variations in interventions, AI-ECG screening for asymptomatic LVD remained dominant compared to no screening, even when AI screening and healthcare costs increased fivefold from the base-case costs. Furthermore, it is noteworthy that increased costs associated with outpatient attendance and hospitalization resulting from HF contribute to improved cost-effectiveness. Conversely, escalated costs related to treatment and asymptomatic LVD evaluation have the opposite effect, diminishing cost-effectiveness. The probabilistic sensitivity analysis reveals that in 62.8% of the 5,000 simulations, the estimates for AI-ECG screening indicated both greater effectiveness and lower costs when compared to no screening. While the WTP threshold can vary in different countries and may not be a critical criterion for decision-making, the results suggest that cost-effectiveness improved even further for payers with a WTP exceeding $0 per year. Moreover, the probability of AI-ECG screening being considered acceptable was higher than 91.5% under a threshold of $30,000 and did not change significantly beyond this threshold.

Our study has several limitations. First, the lack of a control group posed challenges in assessing AI-ECG screening's effectiveness. Therefore, we used economic modeling to compare its cost-effectiveness against no screening. Although our focus was asymptomatic LVD detection, inclusion of mildly symptomatic patients might have impacted algorithm accuracy. Additionally, the extra cost of implementing the AI algorithm was not counted in the economic modeling. Despite AI-ECG pricing uncertainty, AI-ECG screening remained dominant over no screening even when assuming an ECG cost increase of up to 500% in the sensitivity analysis. Finally, transition and treatment data relied on a 30-year-old study, as recent relevant trials are absent. Due to the limitations of available data, our economic model is not exhaustive. Robust post-AI implementation studies are needed to assess real-world cost-effectiveness comprehensively.

In conclusion, the algorithm using ECG demonstrated high accuracy in detecting LVEF <= 40%, and the risk stratification predicted by AI suggested the probability of being diagnosed with LVD in both the short and long terms. Applying AI-ECG for systemic asymptomatic LVD screening could be cost-saving, especially in men, in a social insurance country.

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Disclosures

All authors declare that they have no conflict of interest.

Patient Consent Statements

The authors confirm that patient consent is not applicable to this article. This research received approval from the Institutional Review Board of Tri-Service General Hospital, Taipei, Taiwan (IRB No. C202105049). As we utilized encrypted and de-identified data from the hospital, a waiver for informed consent was granted by the data controller for this study.

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Table 1. Summary of Model and Parameter Estimates

Factor	Estimate (SE)	Distribution modelled	Source
Prevalence of asymptomatic LVD		Uniform	Wang et al. [13]
Age 40-59, Man; Woman	0.0084; 0.0020		
Age 60-69, Man; Woman	0.0288; 0.0032		
Age 70-79, Man; Woman	0.0452; 0.0040		
Age 80-99, Man; Woman	0.0572; 0.0076		
Probabilities and outcomes			
Sensitivity of AI (medium and high risk)	0.926 (0.042)	Beta	
Specificity of AI (medium and high risk)	0.938 (0.003)	Beta	
Sensitivity of AI (high risk)	0.630 (0.154)	Beta	
Specificity of AI (high risk)	0.989 (0.002)	Beta	
The annual transition from asymptomatic LVD to HF without treatment	0.098 (0.026)	Beta	SOLVD Investigators[20]
The annual transition from asymptomatic LVD to HF with	0.065 (0.011)	Beta	SOLVD Investigators[20]

treatment			
Annual probability of HF hospitalization	0.33 (0.13)	Beta	SOLVD Investigators[20, 21]
Annual subsequent HF hospitalization	0.11 (0.05)	Beta	SOLVD Investigators[20, 21]
Utility score for asymptomatic LVD without treatment	0.855 (0.005)	Beta	Göhler et al.[22]
Utility score for asymptomatic LVD with treatment	0.855 (0.005)	Beta	Göhler et al.[22]
Utility score for HF	0.771 (0.005)	Beta	Göhler et al.[22]
Additional mortality risk of asymptomatic LVD compared to no asymptomatic LVD (without treatment)	3.3 (1-4)	Uniform	SOLVD Investigators[20]
Additional mortality risk of asymptomatic LVD compared to no asymptomatic LVD (with treatment)	2.9 (1-4)	Uniform	SOLVD Investigators[20]
Additional mortality risk of HF compared to no asymptomatic LVD.	4.9 (3-9)	Uniform	Heidenreich et al. [23]
Age-specific mortality		Taiwan Life Tables[14]	
Costs (2022 USD)			

Screening with AI algorithm	4.96	Uniform	NHIRD
Screening with TTE	62.50	Uniform	NHIRD
asymptomatic LVD evaluation (post-confirmatory testing)	209.26	Uniform	NHIRD
Annual costs of ACEi and BB treatment	172.82	Uniform	NHIRD
Cost of HF hospitalization	2,887 (1,444)	Gamma	Liao et al.[24]
Annual cost of outpatient HF management	5,400 (2,700)	Gamma	Liao et al.[24]
Discounting			
Costs	1.5%	Uniform	Assumption
Outcomes	1.5%	Uniform	Assumption

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AI, artificial intelligence; LVD, left ventricular dysfunction; BB, beta blocker; HF, heart failure; NHIRD, National Health Insurance Research Database of Taiwan; SOLVD, Studies of Left Ventricular Dysfunction; TTE, transthoracic echocardiogram

Table 2. Cost, Effect, and Incremental Cost-Effectiveness Ratio of Screening with Artificial Intelligence Algorithm Versus No Screen for Age of 65 and Other Age Groups

Strategy	Cost (USD)	Effect (QALYs)	ICER (USD)
No screening (base-case: age 65)			
All	487	14.636	reference
Man	826	13.844	reference
Woman	104	15.500	reference
Screening with AI-ECG (base-case: age 65, Strategy 1)			
All	443	14.642	-7,439, dominant
Man	735	13.854	-9,062, dominant
Woman	111	15.501	6,262
Screening with AI-ECG (base-case: age 65, Strategy 2)			
All	455	14.640	-8,081, dominant
Man	765	13.851	-9,000, dominant
Woman	103	15.500	-688, dominant
No screening (age 45)			
All	275	26.463	reference
Man	427	25.243	reference
Woman	111	27.806	reference
Screening with AI-ECG (age 45, Strategy 1)			
All	275	26.466	-1,051, dominant
Man	408	25.249	-3,317, dominant
Woman	122	27.808	77,738
Screening with AI-ECG (age 45, Strategy 2)			
All	268	26.465	-2,806, dominant
Man	411	25.247	-4,120, dominant
Woman	113	27.807	2,007
No screening (age 55)			
All	227	20.796	reference
Man	348	19.733	reference
Woman	92	21.963	reference
Screening with AI-ECG (age 55, Strategy 1)			
All	223	20.796	-1,263, dominant
Man	330	19.737	-3,392, dominant
Woman	104	21.965	9,592
Screening with AI-ECG (age 55, Strategy 2)			
All	220	20.798	-3,697, dominant
Man	332	19.736	-5,247, dominant
Woman	94	21.964	2,209
No screening (age 75)			

All	345	8.206	reference
Man	602	7.837	reference
Woman	59	8.604	reference
Screening with AI-ECG (age 75, Strategy 1)			
All	345	7.664	-7,149, dominant
Man	538	7.844	-9,579, dominant
Woman	73	8.605	20,104
Screening with AI-ECG (age 75, Strategy 2)			
All	323	8.209	-8,571, dominant
Man	557	7.841	-9,877, dominant
Woman	62	8.605	6,039

Abbreviations: AI, artificial intelligence; ICER, incremental cost-effectiveness ratio; USD, United States Dollar; QALY, quality-adjusted life years. Strategy 1, patients with medium risk or high risk of LVD stratified by AI-ECG receive echocardiograms. Strategy 2, patients with high risk of LVD stratified by AI-ECG receive echocardiograms.

Figure legends:

Figure 1. The structure of the decision analytic model. The first part follows a decision tree that represents the screening outcome. The second part consists of a Markov structure where patients' costs and effects are simulated for the analyzed horizon. The model was adopted from Tseng et al.[11] Abbreviations: AI, artificial intelligence; ALVD, asymptomatic left ventricular dysfunction; TTE, transthoracic echocardiography.

Figure 2. Flowchart depicting the enrollment process of patients who underwent artificial intelligence (AI)-ECG risk stratification followed by echocardiograms.

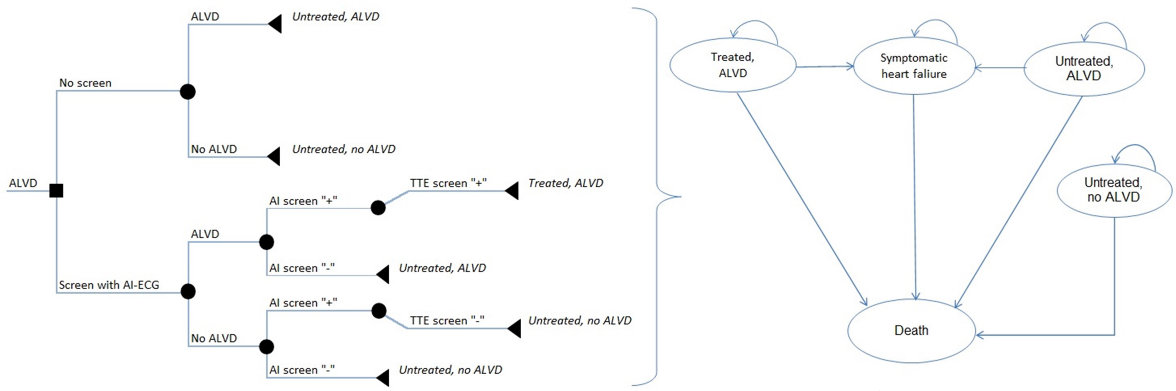
Figure 3. Timing, number and hazard ratio of patients who received echocardiograms after the index ECG in each risk group. The left side of the figure presents the proportions of patients who underwent echocardiograms in the internal and external validation sets, respectively. On the right side of the figure, the proportions of patients who did not undergo echocardiograms within 28 days but later had subsequent echocardiograms are depicted. Adj HR, adjusted hazard ratio; ECHO, echocardiogram.

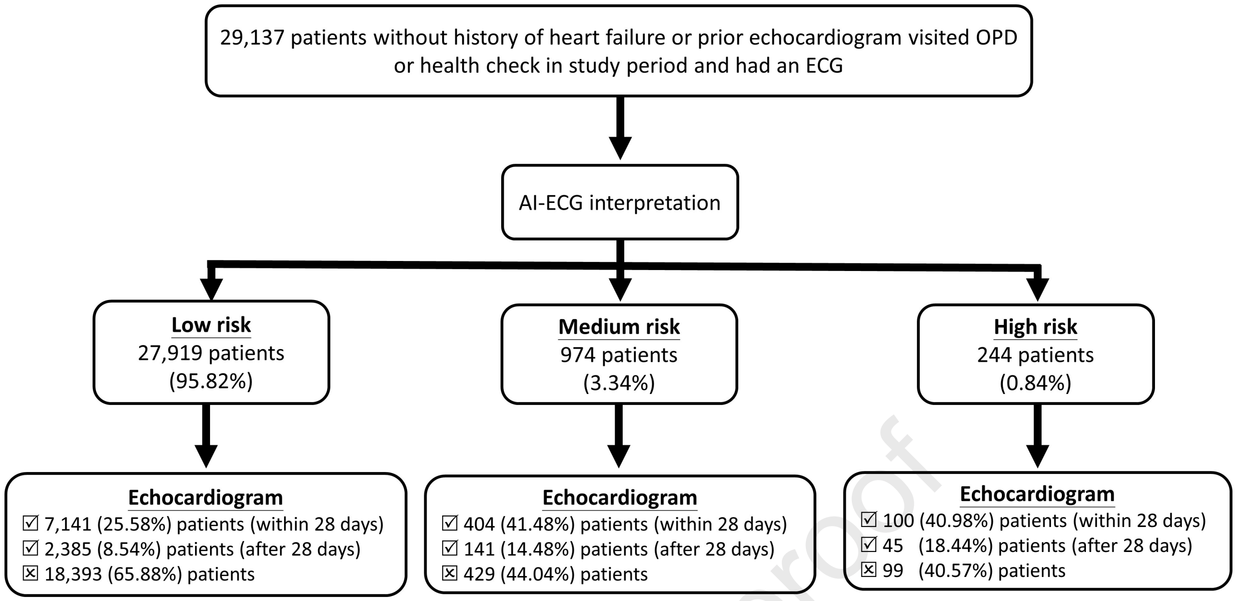
Figure 4. The area under the receiver operating characteristic (AUC) and area under the precision-recall curve (PRAUC) of DLMs predictions based on AI-S to detect LVEF. The LVEF is defined as an actual EF value ≤ 40%. The operating point for medium risk was selected using the maximum of Youden's index of AUC (the sum of sensitivity and specificity), while for high risk, it was selected using the maximum of Youden's index of PRAUC (the sum of positive predictive value and sensitivity) within the tuning set. The corresponding

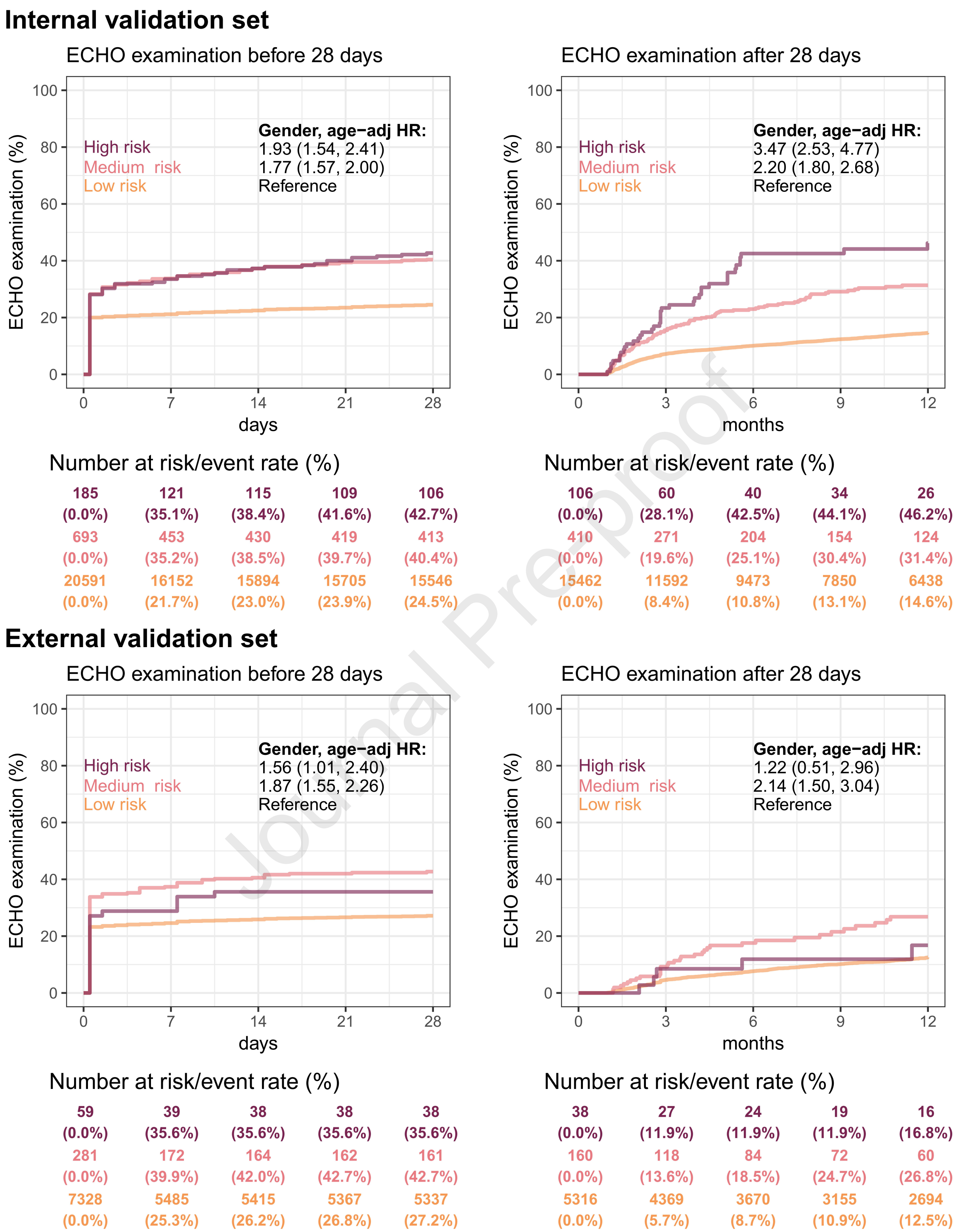
operating points are marked by circles, and associated metrics such as AUC, PRAUC, sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) are calculated accordingly. DLM, deep learning model.

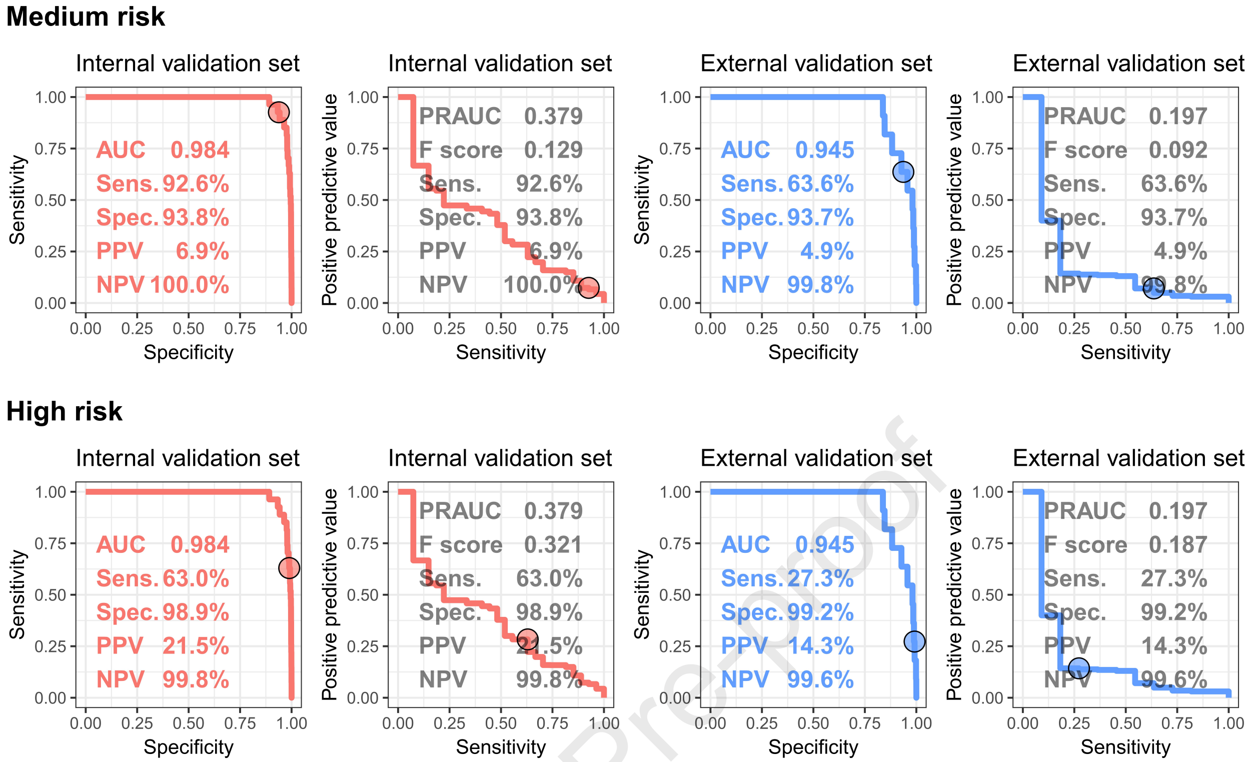
Figure 5. The timing, number, and hazard ratio of patients diagnosed with LVEF ≤40% after the index ECG in each risk group. Adj HR, adjusted hazard ratio; C-index, concordance index; LVEF, left ventricular ejection fraction.

Figure 6. Cost-effectiveness of AI-ECG screening vs. no screening for asymptomatic left ventricular dysfunction. (A) The incremental cost-effectiveness (ICE) scatterplot depicts the distribution of 5000 simulations, with dots colored red indicating non-cost-effective and those colored green indicating cost-effective. AI-ECG Screening for LVD was found to be cost-effective if willingness-to-pay is set to $30,000 in 90.9% of the simulations. AI-ECG Screening for LVD was dominant (QALY gained and cost saved) in 62.4% of the simulations. (B) The cost-effectiveness (CE) acceptability curve depicts the probability of AI-ECG screening being acceptable in terms of the cost-effectiveness depending on the willingness-to-pay threshold of a payer. The range of willingness-to-pay was expanded from 0 to USD 10,000 and did not considerably change beyond this threshold.

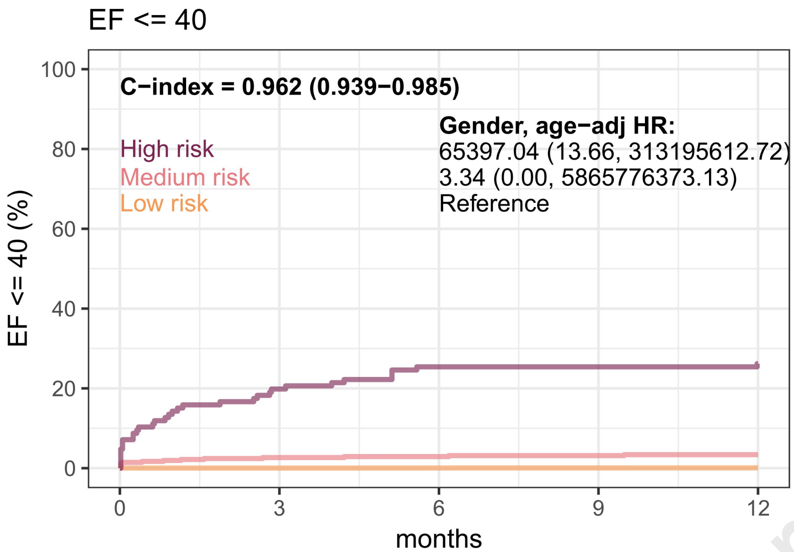

ALVD
No screen
ALVD
Untreated, ALVD
No ALVD
Untreated, no ALVD
Screen with AI-ECG
ALVD
AI screen "+"
TTE screen "+"
Treated, ALVD
AI screen "-"
Untreated, ALVD
No ALVD
AI screen "+"
TTE screen "-"
Untreated, no ALVD
AI screen "-"
Untreated, no ALVD
Treated, ALVD
Symptomatic heart faliure
Untreated, ALVD
Untreated, no ALVD
Death


29,137 patients without history of heart failure or prior echocardiogram visited OPD or health check in study period and had an ECG
AI-ECG interpretation
Low risk
27,919 patients
(95.82%)
Medium risk
974 patients
(3.34%)
High risk
244 patients
(0.84%)
Echocardiogram
☑ 7,141 (25.58%) patients (within 28 days)
☑ 2,385 (8.54%) patients (after 28 days)
☒ 18,393 (65.88%) patients
Echocardiogram
☑ 404 (41.48%) patients (within 28 days)
☑ 141 (14.48%) patients (after 28 days)
☒ 429 (44.04%) patients
Echocardiogram
☑ 100 (40.98%) patients (within 28 days)
☑ 45 (18.44%) patients (after 28 days)
☒ 99 (40.57%) patients


Internal validation set
ECHO examination before 28 days
ECHO examination (%)
100
80
60
40
20
0
High risk
Medium risk
Low risk
Gender, age−adj HR:
1.93 (1.54, 2.41)
1.77 (1.57, 2.00)
Reference
0 7 14 21 28
days
Number at risk/event rate (%)
185 (0.0%) 121 (35.1%) 115 (38.4%) 109 (41.6%) 106 (42.7%)
693 (0.0%) 453 (35.2%) 430 (38.5%) 419 (39.7%) 413 (40.4%)
20591 (0.0%) 16152 (21.7%) 15894 (23.0%) 15705 (23.9%) 15546 (24.5%)
ECHO examination after 28 days
ECHO examination (%)
High risk
Medium risk
Low risk
Gender, age−adj HR:
3.47 (2.53, 4.77)
2.20 (1.80, 2.68)
Reference
0 3 6 9 12
months
Number at risk/event rate (%)
106 (0.0%) 60 (28.1%) 40 (42.5%) 34 (44.1%) 26 (46.2%)
410 (0.0%) 271 (19.6%) 204 (25.1%) 154 (30.4%) 124 (31.4%)
15462 (0.0%) 11592 (8.4%) 9473 (10.8%) 7850 (13.1%) 6438 (14.6%)
External validation set
ECHO examination before 28 days
ECHO examination (%)
High risk
Medium risk
Low risk
Gender, age−adj HR:
1.56 (1.01, 2.40)
1.87 (1.55, 2.26)
Reference
0 7 14 21 28
days
Number at risk/event rate (%)
59 (0.0%) 39 (35.6%) 38 (35.6%) 38 (35.6%) 38 (35.6%)
281 (0.0%) 172 (39.9%) 164 (42.0%) 162 (42.7%) 161 (42.7%)
7328 (0.0%) 5485 (25.3%) 5415 (26.2%) 5367 (26.8%) 5337 (27.2%)
ECHO examination after 28 days
ECHO examination (%)
High risk
Medium risk
Low risk
Gender, age−adj HR:
1.22 (0.51, 2.96)
2.14 (1.50, 3.04)
Reference
0 3 6 9 12
months
Number at risk/event rate (%)
38 (0.0%) 27 (11.9%) 24 (11.9%) 19 (11.9%) 16 (16.8%)
160 (0.0%) 118 (13.6%) 84 (18.5%) 72 (24.7%) 60 (26.8%)
5316 (0.0%) 4369 (5.7%) 3670 (8.7%) 3155 (10.9%) 2694 (12.5%)


Medium risk
Internal validation set
AUC 0.984
Sens. 92.6%
Spec. 93.8%
PPV 6.9%
NPV 100.0%
Sensitivity
Specificity
Internal validation set
PRAUC 0.379
F score 0.129
Sens. 92.6%
Spec. 93.8%
PPV 6.9%
NPV 100.0%
Positive predictive value
Sensitivity
External validation set
AUC 0.945
Sens. 63.6%
Spec. 93.7%
PPV 4.9%
NPV 99.8%
Sensitivity
Specificity
External validation set
PRAUC 0.197
F score 0.092
Sens. 63.6%
Spec. 93.7%
PPV 4.9%
NPV 99.8%
Positive predictive value
Sensitivity
High risk
Internal validation set
AUC 0.984
Sens. 63.0%
Spec. 98.9%
PPV 21.5%
NPV 99.8%
Sensitivity
Specificity
Internal validation set
PRAUC 0.379
F score 0.321
Sens. 63.0%
Spec. 98.9%
PPV 21.5%
NPV 99.8%
Positive predictive value
Sensitivity
External validation set
AUC 0.945
Sens. 27.3%
Spec. 99.2%
PPV 14.3%
NPV 99.6%
Sensitivity
Specificity
External validation set
PRAUC 0.197
F score 0.187
Sens. 27.3%
Spec. 99.2%
PPV 14.3%
NPV 99.6%
Positive predictive value
Sensitivity

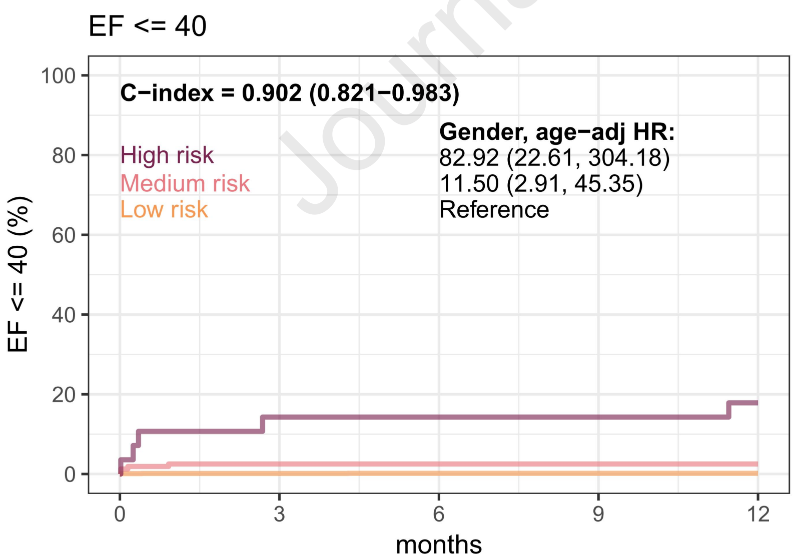
Internal validation set



Number at risk/event rate (%)

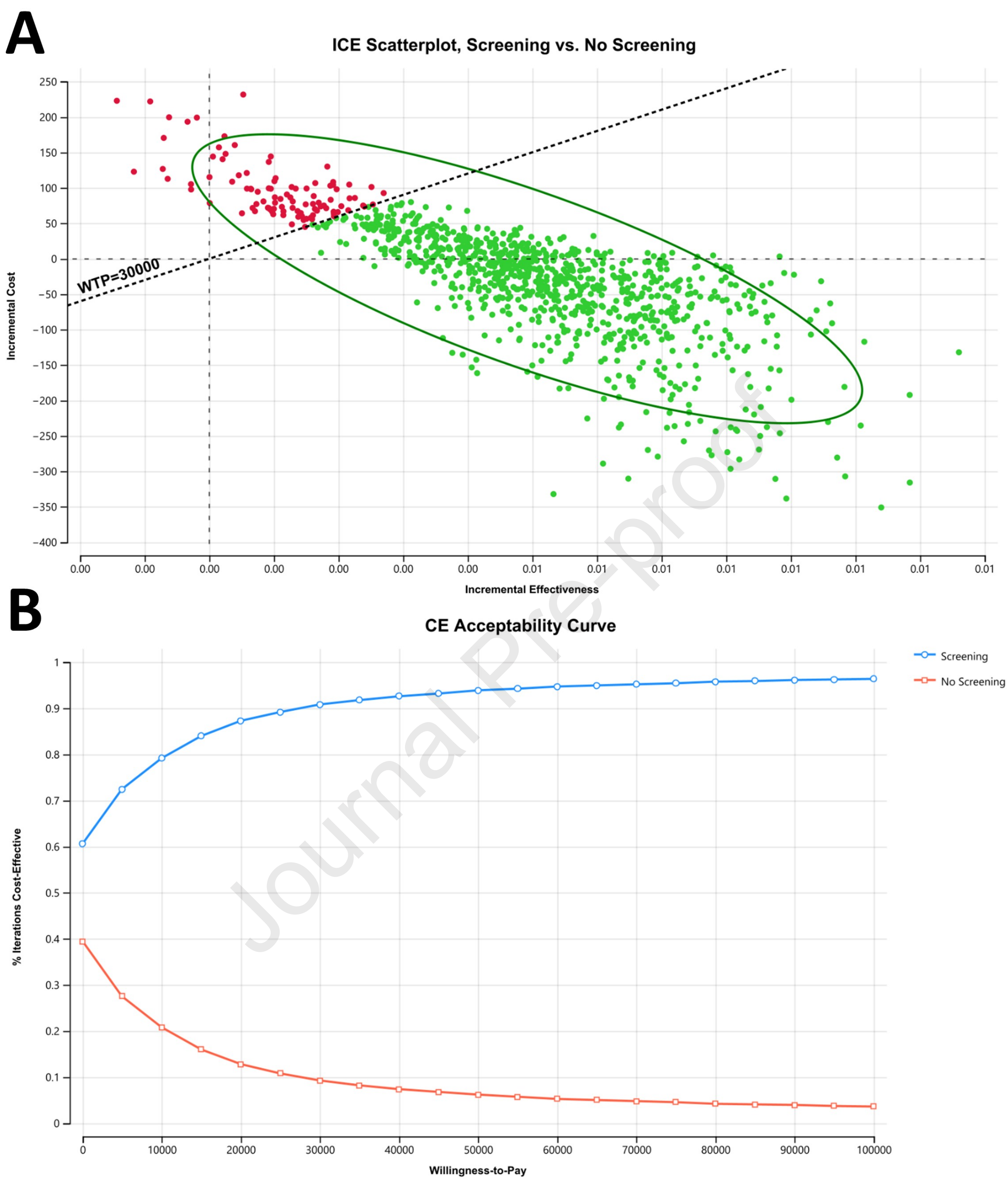
126 (0.0%)	99 (22.2%)	94 (26.2%)	94 (26.2%)	93 (26.2%)
413 (0.0%)	402 (2.9%)	400 (3.4%)	399 (3.4%)	399 (3.4%)
7498 (0.0%)	7496 (0.0%)	7493 (0.1%)	7492 (0.1%)	7491 (0.1%)

External validation set



Number at risk/event rate (%)

28 (0.0%)	24 (17.9%)	24 (17.9%)	24 (17.9%)	23 (17.9%)
159 (0.0%)	155 (2.5%)	155 (2.5%)	155 (2.5%)	155 (2.5%)
2821 (0.0%)	2817 (0.2%)	2816 (0.2%)	2816 (0.2%)	2816 (0.2%)


A
ICE Scatterplot, Screening vs. No Screening
WTP=30000
Incremental Cost
Incremental Effectiveness
B
CE Acceptability Curve
Screening
No Screening
% Iterations Cost-Effective
Willingness-to-Pay