Incorporation of Serial 12-Lead Electrocardiogram with Machine Learning to Augment the Out-of-Hospital Diagnosis of Non-ST Elevation Acute Coronary Syndrome

Zeineb Bouzid, MS; Ziad Faramand, MD; Christian Martin-Gill, MD; Susan M. Sereika, PhD; Clifton W. Callaway, MD, PhD; Samir Saba, MD; Richard Gregg, MS; Fabio Badilini, PhD; Ervin Sejdic, PhD; Salah S. Al-Zaiti, RN, PhD, FAHA*

*Corresponding Author. E-mail: ssa33@pitt.edu.

Study objective: Ischemic electrocardiogram (ECG) changes are subtle and transient in patients with suspected non-ST-segment elevation (NSTE)-acute coronary syndrome. However, the out-of-hospital ECG is not routinely used during subsequent evaluation at the emergency department. Therefore, we sought to compare the diagnostic performance of out-of-hospital and ED ECG and evaluate the incremental gain of artificial intelligence-augmented ECG analysis.

Methods: This prospective observational cohort study recruited patients with out-of-hospital chest pain. We retrieved out-of-hospital-ECG obtained by paramedics in the field and the first ED ECG obtained by nurses during inhospital evaluation. Two independent and blinded reviewers interpreted ECG dyads in mixed order per practice recommendations. Using 179 morphological ECG features, we trained, cross-validated, and tested a random forest classifier to augment non ST-elevation acute coronary syndrome (NSTE-ACS) diagnosis.

Results: Our sample included 2,122 patients (age 59 [16]; 53% women; 44% Black, 13.5% confirmed acute coronary syndrome). The rate of diagnostic ST elevation and ST depression were 5.9% and 16.2% on out-of-hospital-ECG and 6.1% and 12.4% on ED ECG, with ~40% of changes seen on out-of-hospital-ECG persisting and ~60% resolving. Using expert interpretation of out-of-hospital-ECG alone gave poor baseline performance with area under the receiver operating characteristic (AUC), sensitivity, and negative predictive values of 0.69, 0.50, and 0.92. Using expert interpretation of serial ECG changes enhanced this performance (AUC 0.80, sensitivity 0.61, and specificity 0.93). Interestingly, augmenting the out-of-hospital-ECG alone with artificial intelligence algorithms boosted its performance (AUC 0.83, sensitivity 0.75, and specificity 0.95), yielding a net reclassification improvement of 29.5% against expert ECG interpretation.

Conclusion: In this study, 60% of diagnostic ST changes resolved prior to hospital arrival, making the ED ECG suboptimal for the inhospital evaluation of NSTE-ACS. Using serial ECG changes or incorporating artificial intelligence-augmented analyses would allow correctly reclassifying one in 4 patients with suspected NSTE-ACS. [Ann Emerg Med. 2022;■:1-13.]

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INTRODUCTION

The 12-lead electrocardiogram (ECG) remains the initial diagnostic test for evaluating the 7 million Americans presenting annually to an emergency department for a chief complaint of nontraumatic chest pain.[1] To expeditiously identify acute coronary syndrome, guidelines now recommend the acquisition of a 12-lead ECG in the out-of-hospital setting (ie, during transport by emergency medical services) and transmitting it to the receiving hospital.[2] The practice of acquiring and transmitting an out-of-hospital-ECG in patients with a high pretest probability of disease has been shown to dramatically improve outcomes in patients with ST elevation (STE)-acute coronary syndrome.[3-5] However, the clinical impact of this practice is mostly confined to reducing first medical contact-to-intervention time through early catheterization laboratory activation for those with STE-acute coronary syndrome.[6,7] In the absence of ST-segment elevation, out-of-hospital personnel frequently do not transmit the out-of-hospital-ECG, and ED clinicians primarily rely on initial findings seen on ED ECG in conjunction with guideline-recommended biomarker-driven evaluations. Thus, the

Editor's Capsule Summary

What is already known on this topic

Out-of-hospital ECGs may contain valuable information that may be lost in the transition to the hospital.

What question this study addressed

Does the incorporation of the out-of-hospital EKG into the initial emergency department (ED) evaluation of those with chest pain enhance diagnosis of NSTEMI?

Does adding an artificial intelligence analysis of the ECG improve diagnosis of NSTEMI?

What this study adds to our knowledge

Artificial intelligence techniques improved the appreciation of subtle ST depression and elevation in the out-of-hospital and first ED ECGs.

How this is relevant to clinical practice

Attention to the out-of-hospital ECG and use of artificial intelligence aided analysis may improve diagnosis of acute myocardial ischemia.

out-of-hospital-ECG is not routinely used as an informative data point in the comprehensive inhospital evaluation of all patients with the suspected acute coronary syndrome. Although the practice of out-of-hospital-ECG implementation and integration into systems originated over a decade ago, a lack of systematic inclusion of out-of-hospital-ECG into the diagnostic workup beyond STE-acute coronary syndrome remains.[8] This lack of inclusion is further aggravated by the variability of out-of-hospital ECG acquisition practices and the poor integration of out-of-hospital and inhospital electronic health records, which often leaves the out-of-hospital-ECG unavailable to ED clinicians during the initial patient evaluation.[9,10]

Nearly two-thirds of acute coronary syndrome cases are considered non-STE acute coronary syndrome (NSTE-acute coronary syndrome).[11] Due to the heterogeneity of findings when compared to STE-acute coronary syndrome,[12] the diagnostic workup of NSTE-acute coronary syndrome often involves a lengthy monitoring and assessment process, including frequent examinations, serial cardiac biomarker assays, and repeated ECG evaluation during their ED and hospital stay.[2] This is further complicated by the fact that the ST elevation myocardial infarction (STEMI) versus not-a-STEMI diagnostic paradigm has its limitations when deciding the optimal treatment strategy.[13] Nearly 40% of STEMI-ECGs have no total coronary occlusions, and 25% of those with not-a-STEMI-ECG have a total coronary occlusion requiring intervention.[14] Integrating the out-of-hospital-ECG into this paradigm of inhospital evaluation of NSTE-acute coronary syndrome is not yet established due to the dearth of data regarding its potential incremental value in identifying NSTE-acute coronary syndrome. However, it is known that around 20% of diagnostic ST-segment elevations seen on out-of-hospital-ECG resolve by the time the first ED ECG is acquired, which has important implications in STE-acute coronary syndrome detection.[15-17] Furthermore, the pathogenesis of NSTE-acute coronary syndrome suggests that coronary occlusions are more likely to be transient and/or unstable, especially when first-line antiischemic therapies (eg, aspirin and nitroglycerin) are administered by out-of-hospital personnel; hence it is plausible that the out-of-hospital-ECG might play an even bigger role in NSTE-acute coronary syndrome detection.[18] Unfortunately, data on such a diagnostic potential are scarce.

Another challenge posed by ECG detection of NSTE-acute coronary syndrome is that 12-lead ECG changes are subtle and multidimensional, requiring advanced algorithms to identify changes that cannot be detected otherwise.[19] Subtle ECG changes are also dynamic over time, and their evolution prior to hospital arrival might provide further diagnostic value for detecting NSTE-acute coronary syndrome. Harvesting subtle and significant ischemia ECG patterns other than ST amplitude has significantly improved the diagnosis of occlusion MI, especially when initial ECG findings do not meet STEMI criteria.[20] Thus, the recent incorporation of explainable artificial intelligence algorithms for cardiac ischemia detection from 12-lead ECG data can provide a powerful tool to help identify cases of NSTE-acute coronary syndrome that clinicians can otherwise miss.[21] The role of artificial intelligence-augmented ECG diagnosis of NSTE-acute coronary syndrome is yet to be explored.

Herein, we report findings from a large out-of-hospital-ECG database of patients calling 9-1-1 for chest pain in the United States. The specific aims of this analysis were to (1) examine whether incorporating the out-of-hospital-ECG in serial ECG analysis (ie, classical interpretation of ST amplitude) results in an increase in diagnostic gain of NSTE- acute coronary syndrome; and (2) given the out-of-hospital-ECG is more likely to capture transient subtle ischemic patterns, does the use of artificial intelligence-ECG (ie, mining for important ischemic patterns other than ST amplitude) improve the diagnostic gain of NSTE-acute coronary syndrome.

MATERIALS AND METHODS

Study Design and Setting

Subjects for this subanalysis were obtained from the EMPIRE study (ECG Methods for the Prompt Identification of Coronary Events).[19] Study methods are described in detail elsewhere and are published on ClinicalTrials.gov (NCT04237688). Briefly, the study was a prospective, observational study of nontraumatic chest pain patients who called 9-1-1 for a chief complaint of chest pain or other atypical, suspicious symptoms (eg, shortness of breath, epigastric pain, and syncope) requiring ECG evaluation. Between 2013 to 2018, we prospectively enrolled consecutive patients who called 9-1-1 in the City of Pittsburgh and were transported by Pittsburgh Emergency Medical Services to 3 separate University of Pittsburgh Medical Center (UPMC) hospitals: UPMC Shadyside, UPMC Presbyterian, and UPMC Mercy. As part of routine care for patients with symptoms suspicious of the acute coronary syndrome, all enrolled patients had their 12-lead ECG transmitted to the UPMC Medical Command Center for further evaluation by a physician. For this subanalysis, we included patients who had both an out-of-hospital ECG and an ED ECG. We excluded patients with out-of-hospital catheterization laboratory activation for suspected STE-acute coronary syndrome identified in the field by paramedics, ventricular fibrillation/tachycardia, or with secondary repolarization changes confounding ischemia evaluation (eg, ventricular pacing, bundle branch block, or left ventricular hypertrophy with strain pattern). The patients were recruited for the study under a waiver of informed consent, and the University of Pittsburgh institutional review board approved this study.

Clinical Data and Outcome Adjudication

Independent reviewers manually abstracted the key inhospital data elements from the electronic health records as recommended by the American College of Cardiology for measuring the management and outcomes of patients with acute coronary syndrome, including[22]: demographics, past medical history, home medications, clinical presentation, and course of hospitalization, laboratory tests, imaging studies, cardiac catheterization, treatments, and inhospital complications.

The primary outcome of the study was the diagnosis of acute coronary syndrome any time during the indexed admission, which included unstable angina, NSTE-acute coronary syndrome, and STE-acute coronary syndrome. Two independent physician reviewers adjudicated the primary outcome of acute coronary syndrome as per the following universal definition of MI criteria[12]: (1) rise and fall in cardiac troponin I (≥99th percentile according to location criteria); (2) diagnostic STE or ST depression (STD) in 2 contiguous ECG leads[12]; (3) echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormalities; or (4) coronary angiographic or nuclear imaging demonstrating greater than 70% stenosis of a major coronary artery with or without treatment.[23] Patients were considered to have a confirmed acute coronary syndrome diagnosis if they displayed any or all of these criteria.

ECG Signal Processing

All ECGs were obtained as part of routine medical care. The out-of-hospital ECG was obtained by paramedics in the field using HeartStart MRX monitors (Philips Healthcare, Cambridge, MA). We obtained the digital raw XML files transmitted to our medical command center and stored them for offline analysis. The ED ECG was obtained by ED staff using MAC VUE360 Resting ECG devices (GE Healthcare, Milwaukee, WI). We obtained the digital vectorized PDF files stored in the inhospital electronic health record system and stored them for offline analysis. For the purpose of serial ECG analyses, we selected the patients' first out-of-hospital ECG and first ED ECG as the corresponding study ECGs.

Out-of-hospital ECGs were processed by manufacturer-specific software (Advanced Algorithm Research Center, Philips Healthcare, Andover, MA), whereas ED ECGs were processed by CALECG software (AMPS LLC, New York, NY). First, noise, artifact, and ectopic beats were removed, and time-synchronized median beats were calculated per ECG lead. Next, a total of 179 ECG features were calculated from each ECG, including (1) multilead global ECG intervals (k=8); (2) frontal-plane axes (k=3); (3) lead-specific amplitude, duration, and/or area of P wave, Q wave, R/R` wave, S/S` wave, QRS complex, ST80 segment, and T wave (k=144); and (4) lead-specific PR interval and QT interval (k=24).

Expert ECG Interpretation

Each ECG was reviewed by 2 independent physicians who were blinded to the study outcome. Expert interpretation aimed to capture physicians' performance in reviewing ECG and adjudicating for cardiac ischemia when patients are presenting with symptoms suggestive of acute coronary syndrome. The performance of these independent reviewers was given the title "reference standard." First, the independent physicians adjudicated the presence of diagnostic territorial STE or ST depression (STD) as per

the Universal Definition of MI recommendation as 2 contiguous leads with[12]: (1) STE $\geq$2 mm in V2–V3 in men $\geq$40 years, $\geq$2.5 mm in men <40 years, or $\geq$1.5 mm in women; or STE $\geq$1 mm in other leads; or (2) new horizontal or downsloping STD $\geq$0.5 mm in any lead with or without T-wave inversion >1 mm in leads with prominent R wave or R/S ratio >1. Any disagreements between the reviewers were resolved by review by a board-certified cardiologist. ST changes on the out-of-hospital-ECG or ED ECG were documented per patient in the anterior, lateral, or inferior myocardial walls as either no changes (0), STD (1), or STE (2). This coding scheme yielded an ordinal scale variable with a range of 0 to 6, which was used in a logistic regression model to generate the predicted probability of acute coronary syndrome and for area under receiver operative curve analysis. Next, temporal changes between out-of-hospital-ECG and ED ECG were also documented in the anterior, lateral, and inferior myocardial walls as either no changes (0); resolution of changes seen on out-of-hospital-ECG (1); evolution of new changes not seen on out-of-hospital-ECG (2); and persistence of changes at the ED as seen on the out-of-hospital-ECG (3). This coding scheme yielded an ordinal scale variable with a range of 0 to 9, which was also used in a logistic regression model to generate the predicted probability of acute coronary syndrome and for area under receiver operative curve analysis.

Artificial Intelligence-Augmented ECG Analysis

We divided our dataset of out-of-hospital-ECG and ED ECG dyads into 80% training and 20% testing subsets. The training and testing subsets were each preprocessed using imputation of missing values with the mean or mode of the corresponding feature for continuous or categorical variables, respectively, and normalization with the L2 norm. We ran a 10-fold cross-validation to obtain results for the training subset, then used the remaining unseen data set for testing.

Next, we used a random forest classifier to build our artificial intelligence models for predicting confirmed acute coronary syndrome cases. Besides its robustness to outliers, data skewness, missingness, and unbalanced outcome distribution,[24] we have previously shown that the random forest classifier is well suited to handle the multidimensionality observed in 12-lead ECG data. The random forest classifier was implemented with 1,000 trees with a fixed criterion to measure the quality of a split using "entropy" (for information gain). The "balanced subsample" mode was selected where weights were computed for the output values automatically and inversely proportional to class frequencies in the bootstrap sample for every tree. These parameters were tuned during the 10-fold cross-validation training stage. An unseen hold-out set of patients was then used to assess model's generalizability during the testing stage. For model explainability, we used the algorithm agonist approach based on feature importance. The traditional feature importance based on a mean decrease in impurity shows bias toward high cardinality features, even if they are random and unrelated to the outcome, so it tends to overfit using these features. Therefore, we used the permutation importance method and plotted the importance ranking using the test set, which would reflect the usefulness of the features in making generalizable predictions instead of reflecting an overfitting model.

Using the modeling approach described above, we built 4 random forest classifiers: (1) artificial intelligence-out-of-hospital-ECG, (2) artificial intelligence-ED ECG, (3) artificial intelligence-Serial-ECG, and (4) artificial intelligence-ECG-Clinical. We used the 179 features from the out-of-hospital ECG to build the first classifier and used the 179 features from the ED ECG to build the second classifier. For the third classifier, we used the 179 features from out-of-hospital ECG (baseline) and the delta change in each value between the out-of-hospital ECG and the ED ECG dyads. The final classifier included the 179 features from out-of-hospital ECG, the 179 corresponding delta changes in features between the 2 ECG dyad, and the clinical data available at triage. The clinical data elements from the latter included age, sex, race, comorbidities (hypertension, diabetes, smoking, dyslipidemia, heart failure, known coronary artery disease (CAD), old MI, chronic obstructive pulmonary disease, and prior catheterization), and out-of-hospital interventions (morphine, oxygen, nitroglycerin, and aspirin).

Statistical Analysis

Variables were reported as mean (standard deviation) or count (%). Groups were compared using Chi-square for categorical variables or independent samples *t* test for continuous variables. Trend evolution between out-of-hospital and ED ECG was compared between groups using repeated-measures ANOVA. The diagnostic performance of STE and STD were seen on out-of-hospital-ECG and ED ECG, or their dynamic changes between the 2 timepoints were evaluated for predicting confirmed acute coronary syndrome using multivariate logistic regression. Predicted probabilities were used to evaluate classification performance using the area under the receiver operating characteristic (AUROC) curve. The presence of at least 1

wall with diagnostic STE or STD was used to build the confusion matrix and calculate sensitivity, specificity, positive predictive value, and negative predictive value. We used McNemar's test to compare the reclassification performance between different classifiers.

For artificial intelligence algorithms, the training results of random forest classifier on 10-fold cross-validation were reported as mean (standard error). We generated binary predictions using the Youden index on the receiver operating characteristic curves. The mean of thresholds resulting from training was used to produce the confusion matrices for the testing sets. We then computed the performance metrics described above along with the F1 score and net reclassification improvement index as compared to a reference standard. In addition, the comparison between the performance of the models was rigorously tested using the Wilcoxon's signed rank test on the 2 groups of AUROC values formed, each, by the results of the 10-folds. Each group corresponds to the model having one of these sets of input variables: out-of-hospital-ECG and ED ECG variables. To compare the 2 paired groups of values, this method was chosen because it is the nonparametric alternative to the paired *t* test since we are dealing with data that does not necessarily satisfy the assumptions of the *t* test. For testing, we used bootstrapping on the test set to generate a group of 10 AUROC values for each model and compared them using the Wilcoxon signed-rank test. Statistical analyses were completed using SPSS statistical software (version 24.0; SPSS Inc, Chicago, IL), and artificial intelligence models were implemented using Python version 3.7. The significance level was set at α=0.05 for 2-tailed hypothesis testing.

Table. Demographics and Clinical Characteristics.

Clinical Characteristics	All Patients (n=2,122)
Demographic	
Age (y)	58 (16)
Female sex	1001 (47%)
Race	
White	1216 (58%)
Black	859 (40%)
Other	47 (2%)
Ethnicity	
Hispanic or Latino	15 (0.7%)
Not Hispanic or Latino	1973 (93%)
Unspecified	134 (6.3%)
Past Medical History	
Hypertension	1469 (69%)
Ever smoked	1293 (68%)
Hyperlipidemia	833 (39%)
Known CAD	715 (38%)
Previous PCI or CABG	668 (31%)
Diabetes mellitus	593 (28%)
Heart failure	337 (16%)
Diagnostics	
Positive initial troponin	166 (8%)
Positive serial troponin	253 (12%)
Stress test with SPECT scan	278 (13.1%)
Focal evidence of ischemia	29 (1.4%)
Outcomes and Course of Hospitalization	
Confirmed acute coronary syndrome	288 (13.6%)
Final discharge diagnosis of NSTE-ACS	179 (8%)
Subsequent inhospital evolution of STE-ACS	109 (5%)
Treatment with PCI or CABG	197 (9%)
30-day complication or adverse events	256 (12%)

CABG, coronary artery bypass grafting; CAD, coronary artery disease; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography; STE-ACS, ST elevation acute coronary syndrome.

RESULTS

The study enrolled 2,400 patients in total. For the purposes of this study, we excluded 89 patients with out-of-hospital catheterization laboratory activation for STE-acute coronary syndrome identified in the field by paramedics, 22 patients with ventricular fibrillation/tachycardia, and 154 patients with secondary repolarization changes confounding ischemia evaluation, and 13 patients with either missing inhospital or out-of-hospital ECG. The final population for this study included 2,122 patients with suspected NSTE-acute coronary syndrome (age 59 [16]; 53% women; 44% Black). Approximately 69% of our population had hypertension, 38% had a known history of coronary artery disease, and 28% had diabetes mellitus. The demographic and clinical characteristics of the population are summarized in Table. There were 288 (13.6%) cases of confirmed acute coronary syndrome during inhospital evaluation. Among those with confirmed inhospital acute coronary syndrome, 37% had subsequent evolution of STE-acute coronary syndrome that was not apparent during the initial evaluation. The interrater agreement between the reviewers ranged from Kappa 0.86 to 0.91.

Most patients (89.4%) were in normal sinus rhythm, and 10.6% were in atrial fibrillation. Figure 1 shows the initial ischemic findings on out-of-hospital- and ED ECGs

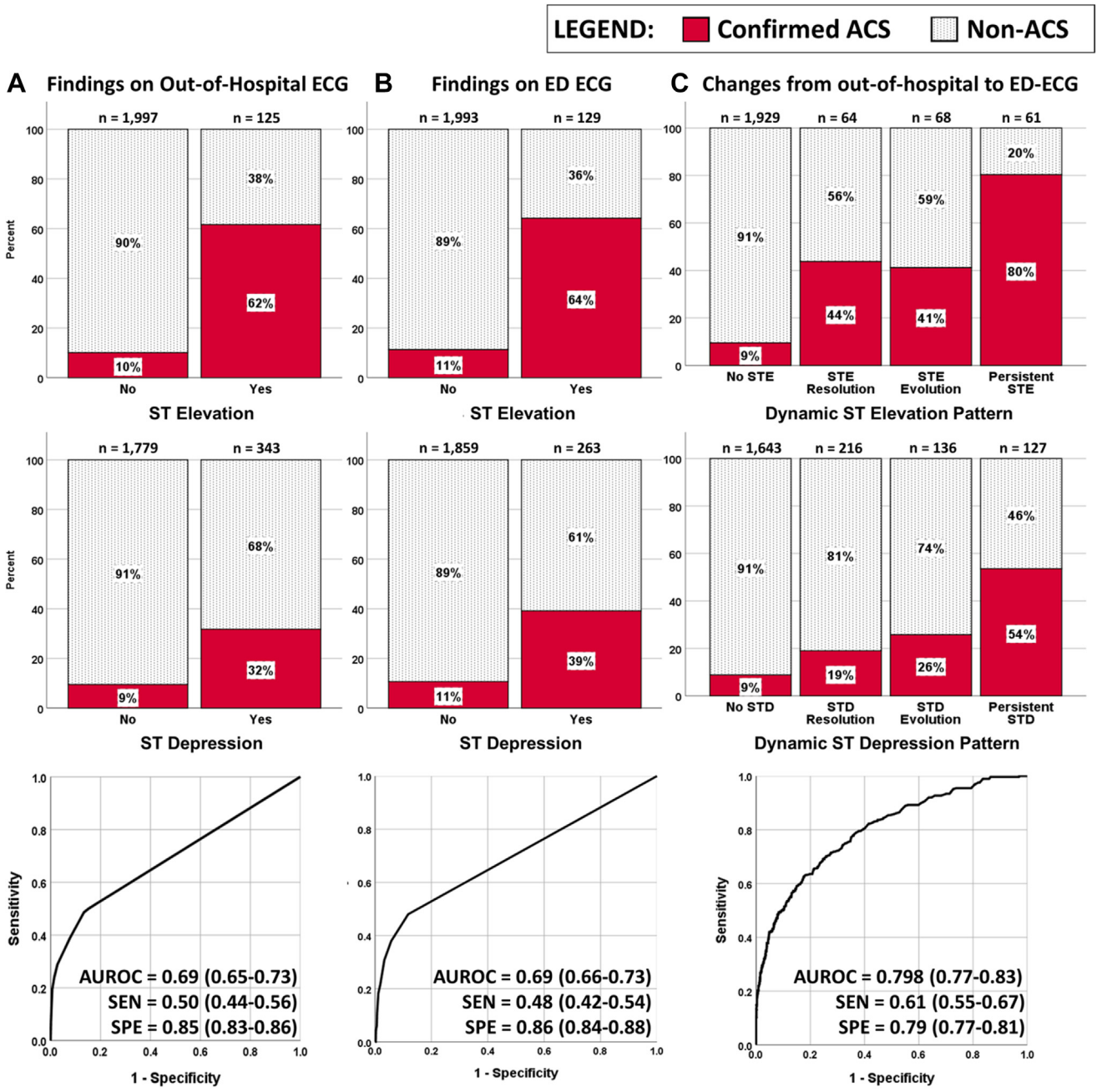
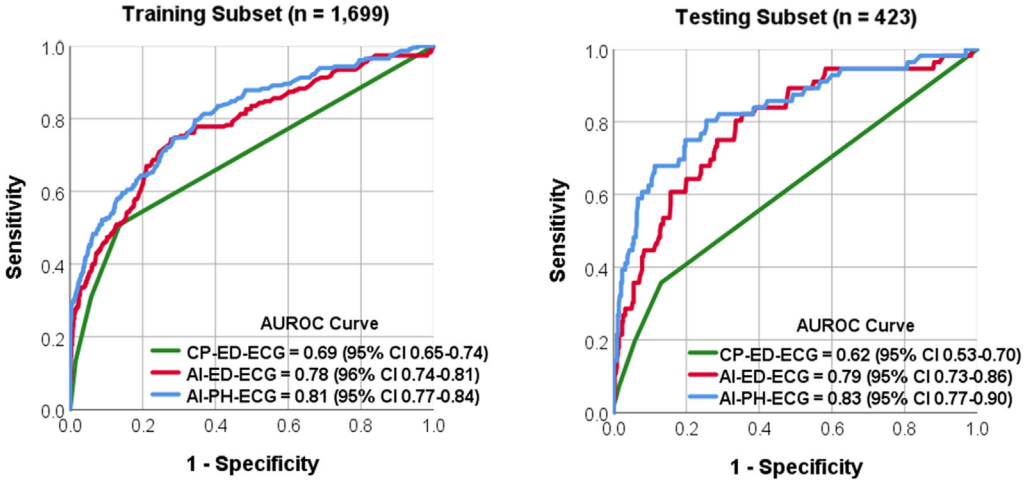


Figure 1. The relationship between ischemic electrocardiogram (ECG) findings and acute coronary syndrome. This figure shows how diagnostic ST changes correlated with acute coronary syndrome on the *A*, Out-of-hospital-ECG, *B*, Emergency department (ED)-ECG, and C, Serial dynamic changes between both ECGs. ECG changes included diagnostic ST elevation (STE) or STD interpreted retrospectively by independent reviewers as per the 4th universal definition of myocardial infarction guidelines.[12] We excluded from these analysis patients with out-of-hospital catheterization laboratory activation for suspected STE-acute coronary syndrome identified in the field by paramedics. The area under the receiver operating characteristic (AUROC) curves are based on a logistic regression classifier using the ST changes seen on each ECG or their dynamic patterns. AUROC, SEN, and SPE are reported as values (95% CI). AUROC, area under the receiver operating characteristic; CI, confidence interval; SEN, sensitivity; SPE, specificity; STD, ST depression.

for the entire cohort (n=2,122 patients). On out-of-hospital-ECG, 125 patients (5.9%) had diagnostic STE and 343 (16.2%) had diagnostic STD, with the rate of confirmed acute coronary syndrome in these subgroups of 62% and 32%, respectively (Figure 1A). Similarly, there were 129 (6.1%) and 263 (12.4%) diagnostic STE, and

STD on ED ECG, with the rate of the confirmed acute coronary syndrome of 64% and 39%, respectively (Figure 1B). These ischemic findings on the out-of-hospital- and ED ECG had poor classification performance of acute coronary syndrome events with AUROC of 0.692 (0.65 to 0.73) and 0.693 (0.66 to 0.73), sensitivity of 0.50 (0.44 to 0.56) and 0.479 (0.42 to 0.54), and specificity of 0.845 (0.83 to 0.86) and 0.864 (0.84 to 0.88), respectively. More interestingly, considering both ECGs together shows that only 49% and 37% of diagnostic STE and STD were seen on out-of-hospital-ECG persisted until ED ECG, with 51% and 63% of out-of-hospital diagnostic changes resolving prior to ED arrival. Figure 1C shows the rate of confirmed acute coronary syndrome in those who had resolving, new, or persistent diagnostic STE or STD. An approach based on the presence of dynamic ECG changes between out-of-hospital and ED timepoints achieved a very good classification performance of confirmed acute coronary syndrome (AUROC 0.798 [0.77 to 0.83]).

Next, we explored the value of artificial intelligence-augmenting analysis of out-of-hospital- and ED ECG. Figure 2 shows the results of algorithm performance on the training subset (n=1,699, 14% confirmed acute coronary syndrome) and testing subset (n=423, 13% confirmed acute coronary syndrome) as compared to the baseline classification performance of diagnostic findings on ED ECG. During algorithm testing, both artificial intelligence-out-of-hospital-ECG and artificial intelligence-ED ECG algorithms had significantly higher performance compared to the reference standard (AUROC 0.83 [0.77 to 0.90] and 0.79 [0.73 to 0.86] versus 0.62 [0.53 to 0.70], respectively). The artificial intelligence-out-of-hospital-ECG algorithm outperformed the reference standard with sensitivity, specificity, positive, and negative predictive values of 0.75 (0.62 to 0.86), 0.76 (0.71 to 0.80), 0.32 (0.29 to 0.39), and 0.95 (0.92 to 0.97) versus 0.36 (0.23 to 0.50), 0.86 (0.82 to 0.89), 0.28 (0.21 to 0.39), and 0.90 (0.87 to 0.90) for expert ECG interpretation, respectively. This significant gain in performance translates into net reclassification improvement index of 29.5% (P <.001). We then investigated the incremental gain in classification performance of artificial intelligence-out-of-hospital-ECG when supplemented by serial temporal ECG changes (model 3: Artificial intelligence-serial-ECG) and the



	CP-ED-ECG	AI-ED-ECG	AI-PH-ECG
Sensitivity	0.509	0.703	0.707
Specificity	0.863	0.758	0.744
PPV	0.373	0.315	0.304
NPV	0.918	0.942	0.941
NRI Index	Ref	8.9%	7.9%

	CP-ED-ECG	AI-ED-ECG	AI-PH-ECG
Sensitivity	0.357	0.714	0.750
Specificity	0.858	0.736	0.760
PPV	0.278	0.292	0.323
NPV	0.897	0.944	0.952
NRI	Ref	23.5%	29.5%

Figure 2. Classification performance of non-ST elevation acute coronary syndrome using artificial intelligence-augmented electrocardiogram (ECG) analysis. The figure shows random forest classification performance using features from out-of-hospital ECG (artificial intelligence-out-of-hospital-ECG) or the emergency department (artificial intelligence-ED ECG) as compared to clinical practice based on ED evaluation (CP-ED ECG) on both training subset (left) and testing subset (right). The tables show the diagnostic accuracy measures and the net reclassification performance index as compared to CP-ED ECG as a reference standard (Reference). AUROC, area under the receiver operating characteristic.

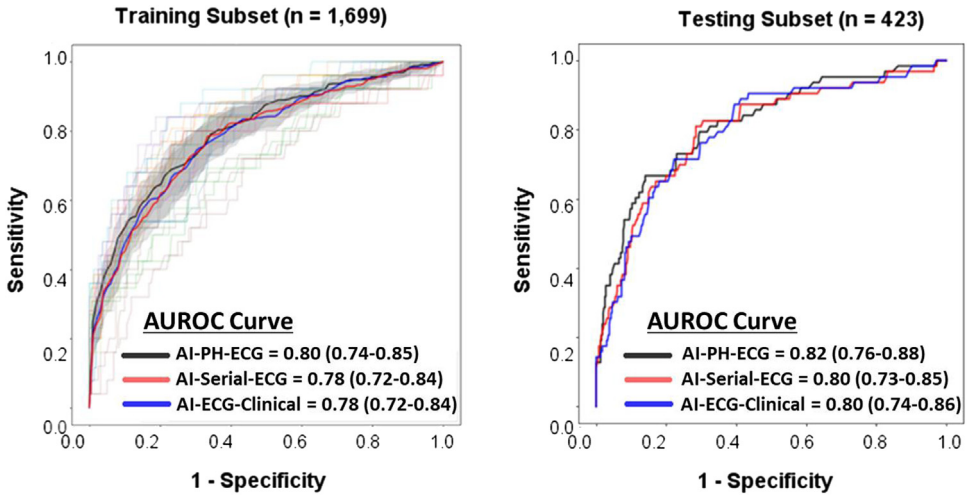


Figure 3. Classification performance of artificial intelligence-augmented electrocardiogram (ECG) analysis supplemented by serial ECG and clinical data. The figure shows the baseline classification performance of the random forest model using features from out-of-hospital ECG (artificial intelligence-out-of-hospital-ECG), both out-of-hospital and emergency department ECGs (artificial intelligence-serial-ECG), and serial ECG plus clinical data typically available during triage (artificial intelligence-ECG-clinical) on both training subset (left) and testing subset (right). This figure demonstrates that artificial intelligence-augmented ECG analysis reaches its classification performance plateau with out-of-hospital-ECG alone, with no additional gain in performance when adding serial ECG or any other clinical data elements. In the training set, the lighter lines correspond to the results obtained for the individual folds during the 10-fold cross-validation, whereas the thicker lines correspond to the mean results for each model. The shaded areas highlight the space englobing all curves within 2 standard errors around the mean curves. AUROC, area under the receiver operating characteristic.

addition of clinical data elements available during triage (model 4: Artificial intelligence-ECG-clinical). Figure 3 shows there was no significant gain in AUROC for either of the 2 latter models during training and testing, with peak classification performance achieved by out-of-hospital-ECG alone, plateauing at AUROC of 0.82 (0.76 to 0.88).

Finally, we used random forest permutation importance ranking to add explainability to the observed gain in the net reclassification improvement index using the artificial intelligence-out-of-hospital-ECG model. Among the 179 features used in that model, the most important classical features were ST amplitude in leads aVL, I, III, V2, aVR, V4, V3, and V6; T amplitude in leads aVL, V2, III, V3, and I; and T area in leads aVL, III, V2, and I. The most important novel features were global T_{peak} to T_{end} interval (rank #3), mean QRS−T angle (rank #8); spatial T axis (rank #15), and relative T to R amplitude ratio on RMS signal (Root Mean Square) (rank #12). Figure 4A shows the mean group differences in global T_{peak} to T_{end} interval and QRS−T angle on out-of-hospital- and ED ECGs. Patients with the confirmed acute coronary syndrome had significantly longer global T_{peak} to T_{end} interval and wider QRS−T angle compared to their counterparts, with more pronounced dispersion on out-of-hospital-ECG. To understand the multidimensional complexity of the 12 lead ECG, Figure 4B shows the 3-dimensional scatterplot of the 3 most important features in random forest classification delineating a nonlinear hyperplane of acute coronary syndrome cases characterized by prolonged global T_{peak} to T_{end} interval, STE in the lead III, and distorted ST-segment in lead aVL (STE or STD).

LIMITATIONS

Our study has a few limitations that should be considered when interpreting our findings. First, patients with secondary repolarization abnormalities (ie, pacing, bundle branch block, left ventricular hypertrophy, or ventricular rhythm) were excluded from the study. These patients have a different course and are usually sicker; therefore, our results are not generalizable to this population. Second, the findings of our study are based on a single health care system; therefore, it is difficult to generalize our results to a different system. Testing our artificial intelligence models on an independent system is necessary before establishing clinical utility. Finally, the out-of-hospital-ECG and the ED ECG were processed by different manufacturer-specific software. A classical review paper previously looked at the systematic differences among automated ECG interval measurements by 7 widely used computer-based ECG interpretation algorithms, including AMPS and Philips (the 2 we used). The paper indicated the measurements' differences are clinically negligible (eg, the

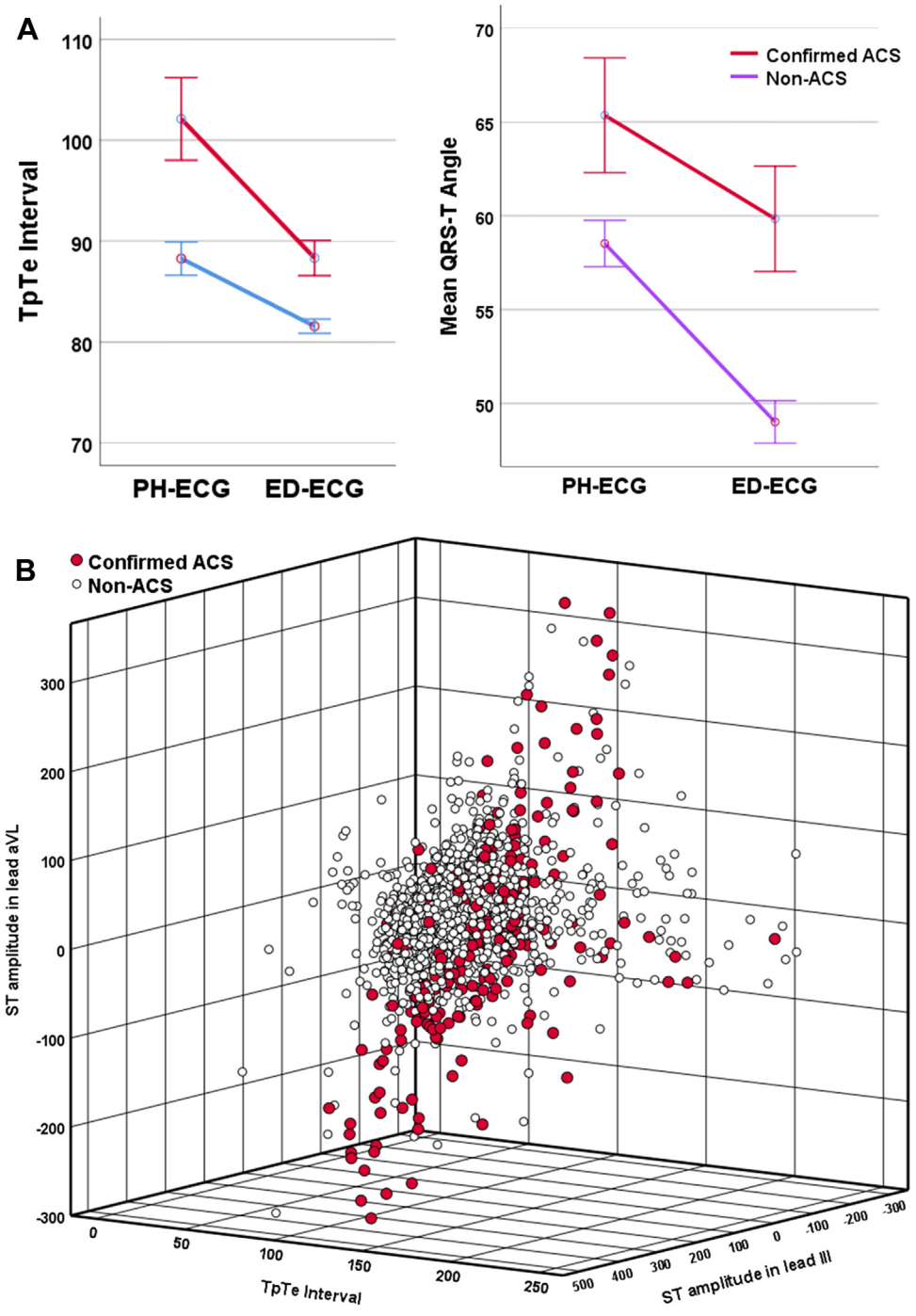


Figure 4. Correlation between the most important electrocardiogram (ECG) features in diagnosing acute coronary syndrome. Plot A shows mean group differences in T_{peak} to T_{end} interval (left) and QRS−T angle (right) on out-of-hospital-ECG and emergency department (ED)-ECG in those with or without the acute coronary syndrome. Plot B shows the 3-dimensional scatterplot of the 3 most important features in the random forest delineating a nonlinear hyperplane of acute coronary syndrome cases characterized by prolonged global T_{peak} to T_{end} interval, ST elevation in the lead III, and distorted ST-segment (elevation or depression) in lead aVL. ACS, acute coronary syndrome.

difference in QRS duration between AMPS and Philips is 4 milliseconds on average).[25] Thus, the differences captured in the delta values are likely physiological rather than technical in nature.

DISCUSSION

In this study, we compared the diagnostic value of out-of-hospital- and ED ECG for classifying patients with suspected acute coronary syndrome and evaluated the

diagnostic gain using artificial intelligence-augmented analysis of 12-lead ECG data. We found that more than one half of diagnostic STE and STD resolve prior to ED arrival. Furthermore, we demonstrated that using these temporal dynamic changes between out-of-hospital- and ED ECG yields very good classification performance (AUROC∼0.80), which far exceeds the diagnostic value of the ECG at each timepoint separately. However, using artificial intelligence-augmented analysis of the 12-lead ECG yields a net reclassification improvement index of ∼24% to 30% compared to the current expert overread of ECG data during ED evaluation, a gain that can be achieved by using only the out-of-hospital-ECG without the need for serial ECG changes or other clinical data elements. This gain in performance is based on subtle multidimensional changes in the STT waveform and other novel markers of ventricular repolarization dispersion. These findings support the notion that the out-of-hospital-ECG should be systematically considered as an important predictive data point in the diagnostic workup of suspected NSTE- acute coronary syndrome, especially when augmented by powerful artificial intelligence tools.

This study demonstrates that exclusively relying on the ED ECG during inhospital evaluation comes with poor classification performance (AUROC<0.70), significantly limiting providers' ability to rule in or out acute coronary syndrome. It is known that ischemic ECG changes are often transient in nature. Acquiring an ECG during acute symptoms when patients are undergoing ischemic distress is more likely to elicit important prognostic information. We show that more than half the ischemic changes seen on out-of-hospital-ECG resolve prior to ED arrival. The reason for this possibly reflects the timing the out-of-hospital-ECG is acquired in the continuum of care, including the acquisition prior to initiating any antiischemic therapies. Such interventions could transiently improve the underlying cardiac ischemia and blunt ECG findings by the time the ECG is acquired in the ED.[26,27] It is also well established that acute coronary syndrome has an unstable course, meaning ischemic ECG findings could spontaneously resolve by the time patients are evaluated in ED.[16]

Clinical practice guidelines emphasize the importance of out-of-hospital-ECG use for clinical decisionmaking and advocate for its systematic incorporation in systems of care as a class I recommendation.[4,28] Moreover, it is well established that detecting transient ischemic ECG changes in acute coronary syndrome, including those detected in the out-of-hospital setting, can help identify patients with a higher risk for adverse events.[29,30] Yet, in clinical practice, the primary emphasis remains focused on identifying STE requiring catheterization lab activation, and few studies have previously analyzed the diagnostic value of out-of-hospital-ECG in suspected NSTE-acute coronary syndrome. Some studies report that subtle changes in out-of-hospital-ECG are associated with adverse outcomes in this population, demonstrating a positive impact on care processes, including early disposition, timely interventions, and improved survival rate.[31-33] Our study supports the notion that significant information gets lost by excluding the out-of-hospital-ECG during inhospital decisionmaking when evaluating NSTE-acute coronary syndrome. This has important clinical implications, as often no permanent record is kept of out-of-hospital-ECGs in the inhospital electronic health records, hence losing a valuable diagnostic data point in the lengthy process of patient evaluation. We demonstrate that using temporal dynamic patterns of STE and STD between out-of-hospital- and ED ECG yields very good classification performance compared to using either one separately, which aligns well with current literature.[34-36]

It is well established that ECG findings in NSTE-acute coronary syndrome are not always grossly evident and often require novel identification methods.[19] There are numerous reasons for these shortcomings; the infarct might be relatively small, the location of the infarct might be in a location only weakly sensed by the lead fields of the standard 12-lead ECG, or the infarct is slowly developing.[37] Intriguingly, myocardial ischemia affects the configuration of the QRS complex and ST-T waveform. Thus, an evolving infarct would translate into progressive regional changes in ST amplitude and slope, T-wave amplitude and morphology, and QRS duration and configuration. These subtle and interrelated changes in ECG features, as measured from the different 12 leads of the ECG, open an important opportunity for artificial intelligence-augmented analysis of ECG data to learn multidimensional patterns in these features that humans would otherwise miss. This explains the superior performance of artificial intelligence-augmented analysis of ECG when compared to expert ECG interpretation, allowing clinicians to correctly reclassify at least 1 in 4 patients with the suspected acute coronary syndrome in our study. Interestingly, such artificial intelligence-based pattern recognition of subtle ECG changes achieved the maximum gain in diagnostic performance using only the out-of-hospital-ECG, without serial ECG changes or other clinical data elements. This again emphasizes the value of systematically incorporating the out-of-hospital-ECG into care systems while evaluating patients with suspected NSTE-acute coronary syndrome. This still does not undermine the value of serial ECG in NSTE-acute

coronary syndrome, given the complexity of temporality and the specific characteristics of these subtle changes.[35,36]

It is worth noting that many novel ECG features can globally quantify the subtle changes in QRS and ST-T waveform morphologies, greatly improving the sensitivity of the ECG for ischemia as well as drastically reducing the time required to diagnose NSTE-acute coronary syndrome.[37] For instance, T_{peak} to T_{end} interval indicates global repolarization dispersion, and the QRS-T angle is a general toolkit for identifying abnormalities in conduction and repolarization.[38] Enriching our artificial intelligence models with such features might have played a significant role in the observed diagnostic gain as compared to expert ECG interpretation based on practice recommendations. Nevertheless, elucidating novel ECG features beyond STE versus NSTE clinical practice paradigm can dramatically change care at the bedside.

This study has important clinical implications. First, in the absence of STE on presenting ECG, ED providers still need to consider abnormalities seen on the out-of-hospital-ECG and their dynamic changes in the overall diagnostic workup of patients with suspected NSTE-acute coronary syndrome. This requires hospitals and systems of care to develop new tools or adopt existing ones to systematically incorporate the out-of-hospital-ECG into the inhospital electronic health record. Second, deploying artificial intelligence-based automated ECG interpretation algorithms on out-of-hospital-ECG can provide real-time decision support for out-of-hospital and ED providers, which has important implications for improving patient safety (infarct size and adverse events), nursing surveillance and care (frequency of monitoring, caseload mixture, and staff allocation), and care delivery systems (ED overcrowding, regionalization of care, resource utilization, admission unit availability, higher cost versus lower cost bed allocation, catheterization lab activation). Moreover, the implementation of an artificial intelligence-based automated ECG interpretation can offer a way to identify acute coronary syndrome cases that do not display criteria fulfilling STEMI criteria, such as occlusion MI.[20] This can help identify occlusion MI patients early, particularly since they often display only subtle changes and consequently face treatment delays.

In conclusion, in 3 hospitals with coordinated emergency medical service care, we found that more than one half of diagnostic STE and STD changes on an out-of-hospital ECG resolve prior to ED arrival. Exclusively relying on ED ECG during inhospital evaluation of NSTE-acute coronary syndrome comes with poor classification performance, which can be overcome by evaluating the temporal dynamic changes between out-of-hospital- and ED ECG in response to out-of-hospital interventions. These findings come with a number of clear takeaways: (1) serial negative ECGs do not significantly increase the negative predictive value of ECG, (2) serial positive ECGs do increase positive predictive value, and (3) a single positive ECG (ie, positive out-of-hospital-ECG and negative ED ECG, or vice versa) has an intermediate predictive value. This pattern seems to hold true for STE and STD on the 12-lead ECG. Moreover, this study demonstrates that artificial intelligence-based analytics on a single ECG obtained during ongoing ischemia (ie, out-of-hospital-ECG) can capture subtle patterns indicative of NSTE-acute coronary syndrome without the need for serial ECG has important and immediate clinical implications for ED practice. This enhanced interpretability may lead to the reclassification of 1 in 4 patients with suspected NSTE-acute coronary syndrome. This suggests a need for hospitals to develop tools to incorporate out-of-hospital-ECG into systems of care as informative data points in the inhospital evaluation of patients with the suspected acute coronary syndrome. In addition, these findings require future validation in other emergency medical services systems.

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Author affiliations: From the University of Pittsburgh, (Bouzid, Martin-Gill, Sereika, Callaway, Saba, Al-Zaiti), Pittsburgh, PA; Northeast Georgia Health Systems (Faramand), Gainesville, GA; University of Pittsburgh Medical Center (Martin-Gill, Callaway, Saba), Pittsburgh, PA; Advanced Algorithm Research Center, Philips Healthcare, Cambridge, MA (Gregg); University of California San Francisco, San Francisco, CA (Badilini); University of Toronto, Toronto, Ontario, Canada (Sejdic).

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REFERENCES

1. Niska R, Bhuiya F, Xu J. National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. *Natl Health Stat Report*. 2010;26:1-31.
2. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;144:e368-e454.
3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362-e425.
4. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177.
5. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. 2006;355:2308-2320.
6. Adams GL, Campbell PT, Adams JM, et al. Effectiveness of prehospital wireless transmission of electrocardiograms to a cardiologist via hand-held device for patients with acute myocardial infarction (from the Timely Intervention in myocardial Emergency, NorthEast Experience [TIME-NE]). *Am J Cardiol*. 2006;98:1160-1164.
7. Diercks DB, Kontos MC, Chen AY, et al. Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. *J Am Coll Cardiol*. 2009;53:161-166.
8. Ting HH, Krumholz HM, Bradley EH, et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. *Circulation*. 2008;118:1066-1079.
9. Al-Zaiti SS, Shusterman V, Carey MG. Novel technical solutions for wireless ECG transmission and analysis in the age of the Internet cloud. *J Electrocardiol*. 2013;46:540-545.
10. Zègre-Hemsey JK, Asafu-Adjei J, Fernandez A, et al. Characteristics of prehospital electrocardiogram use in north Carolina using a novel linkage of emergency medical services and emergency department data. *Prehosp Emerg Care*. 2019;23:772-779.
11. Meyers HP, Bracey A, Lee D, et al. Comparison of the ST-elevation myocardial infarction (STEMI) vs. NSTEMI and occlusion MI (OMI) vs. NOMI paradigms of acute MI. *J Emerg Med*. 2021;60:273-284.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231-2264.
13. Birnbaum Y, Bayés de Luna AB, Fiol M, et al. Common pitfalls in the interpretation of electrocardiograms from patients with acute coronary syndromes with narrow QRS: a consensus report. *J Electrocardiol*. 2012;45:463-475.
14. Al-Zaiti SS, Macleod MR, Van Dam PM, Smith SW, Birnbaum Y. Emerging ECG methods for acute coronary syndrome detection: recommendations and future opportunities. *J Electrocardiol*. 2022;75:65-72.
15. Bouwmeester S, van Hellemond IE, Maynard C, et al. The stability of the ST segment estimation of myocardial area at risk between the prehospital and hospital electrocardiograms in patients with ST elevation myocardial infarction. *J Electrocardiol*. 2011;44:363-369.
16. Ownbey M, Suffoletto B, Frisch A, et al. Prevalence and interventional outcomes of patients with resolution of ST-segment elevation between prehospital and in-hospital ECG. *Prehosp Emerg Care*. 2014;18:174-179.
17. Badings EA, Remkes WS, The SHK, et al. Early or late intervention in patients with transient ST-segment elevation acute coronary syndrome: subgroup analysis of the ELISA-3 trial. *Catheter Cardiovasc Interv*. 2016;88:755-764.
18. Al-Zaiti SS, Callaway CW, Kozik TM, et al. Clinical utility of ventricular repolarization dispersion for real-time detection of non-ST elevation myocardial infarction in emergency departments. *J Am Heart Assoc*. 2015;4:e002057-e002058.
19. Al-Zaiti SS, Martin-Gill C, Sejdić E, et al. Rationale, development, and implementation of the electrocardiographic Methods for the Prehospital Identification of non-ST Elevation myocardial infarction Events (EMPIRE). *J Electrocardiol*. 2015;48:921-926.
20. Pendell Meyers H, Bracey A, Lee D, et al. Accuracy of OMI ECG findings versus STEMI criteria for diagnosis of acute coronary occlusion myocardial infarction. *Int J Cardiol Heart Vasc*. 2021;33:100767-100768.
21. Al-Zaiti SS, Besomi L, Bouzid Z, et al. Machine learning-based prediction of acute coronary syndrome using only the pre-hospital 12-lead electrocardiogram. *Nat Commun*. 2020;11:3966-3967.
22. Cannon CP, Brindis RG, Chaitman BR, et al. 2013 ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on clinical data

standards (writing committee to develop acute coronary syndromes and coronary artery disease clinical data standards). *J Am Coll Cardiol*. 2013;61:992-1025.

23. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145:e18-e114.
24. Hastie T, Tibshirani R, Friedman J, et al. The elements of statistical learning: data mining, inference, and prediction. *Springer series in statistics*. New York: Springer; 2009:587-604.
25. Kligfield P, Badilini F, Denjoy I, et al. Comparison of automated interval measurements by widely used algorithms in digital electrocardiographs. *Am Heart J*. 2018;200:1-10.
26. Awan NA, Amsterdam EA, Vera Z, et al. Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction. *Circulation*. 1976;54:761-765.
27. Beltrame JF, Stewart S, Leslie S, et al. Resolution of ST-segment elevation following intravenous administration of nitroglycerin and verapamil. *Am J Cardiol*. 2002;89:452-455.
28. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;78:2218-2261.
29. Pelter MM, Adams MG, Drew BJ. Transient myocardial ischemia is an independent predictor of adverse in-hospital outcomes in patients with acute coronary syndromes treated in the telemetry unit. *Heart Lung*. 2003;32:71-78.
30. Zègre Hemsey JK, Dracup K, Fleischmann KE, et al. Prehospital electrocardiographic manifestations of acute myocardial ischemia independently predict adverse hospital outcomes. *J Emerg Med*. 2013;44:955-961.
31. Quinn T, Johnsen S, Gale CP, et al. Effects of prehospital 12-lead ECG on processes of care and mortality in acute coronary syndrome: a linked cohort study from the Myocardial Ischaemia National Audit Project. *Heart*. 2014;100:944-950.
32. Ravn-Fischer A, Karlsson T, Johanson P, et al. Prehospital ECG signs of acute coronary occlusion are associated with reduced one-year mortality. *Int J Cardiol*. 2013;168:3594-3598.
33. Zègre Hemsey JKZ, Drew BJ. Prehospital electrocardiography: a review of the literature. *J Emerg Nurs*. 2012;38:9-14.
34. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267-315.
35. Lehmacher J, Neumann JT, Sörensen NA, et al. Predictive value of serial ECGs in patients with suspected myocardial infarction. *J Clin Med*. 2020;9:2303-2304.
36. Sarak B, Goodman SG, Yan RT, et al. Prognostic value of dynamic electrocardiographic T wave changes in non-ST elevation acute coronary syndrome. *Heart*. 2016;102:1396-1402.
37. Lux RL. Non-ST-segment elevation myocardial infarction: A novel and robust approach for early detection of patients at risk. *J Am Heart Assoc*. 2015;4:e002279-e002279.
38. Lux RL. Basis and ECG measurement of global ventricular repolarization. *J Electrocardiol*. 2017;50:792-797.