Ischemic Electrocardiographic Abnormalities and Prognosis in Decompensated Heart Failure

Douglas Greig, MD, MSc; Peter C. Austin, PhD; Limei Zhou, PhD; Jack V. Tu, MD, PhD; Peter S. Pang, MD; Heather J. Ross, MD, MSc; Douglas S. Lee, MD, PhD

Background—Identification of coronary ischemia may enable targeted diagnostic and therapeutic strategies for acute heart failure. We determined the risk of 30-day mortality associated with ischemic ECG abnormalities in patients with acute heart failure.

Methods and Results—Among 8772 patients (53.4% women, median 78 years [Q1, Q3: 68,84]) presenting with acute heart failure to 86 hospital emergency departments in Ontario, Canada, Q-waves, T-wave inversion, or ST-depression were present in 51.8% of subjects. However, presence of ST-depression was the only finding associated with 30-day mortality with adjusted odds ratio 1.24 (95% confidence interval [CI], 1.02–1.50). Using continuous net reclassification improvement, addition of ST-depression to the Emergency Heart failure Mortality Risk Grade model reclassified 16.9% of patients overall, and 29.3% of those with a history of ischemic heart disease (both $P<0.001$). By adding ST-depression to the model, the Emergency Heart failure Mortality Risk Grade was extended to predict 30-day death with high discrimination (*c*-statistic 0.801), with 0.57% mortality rate in the lowest risk decile. Adjusted odds ratios for 30-day mortality were 2.81 (95% CI, 1.48–5.31; $P=0.002$) in quintile 2, 7.41 (95% CI, 4.13–13.30; $P<0.001$) in quintile 3, and 14.47 (95% CI, 8.20–25.54; $P<0.001$) in quintile 4 compared with the lowest risk quintile. When the highest risk quintile was subdivided into 2 equally sized risk strata (deciles 9 and 10), the adjusted odds ratios for 30-day mortality were 27.20 (95% CI, 15.33–48.27; $P<0.001$) in decile 9 and 58.96 (95% CI, 33.54–103.65; $P<0.001$) in highest risk decile 10.

Conclusions—Presence of ST-depression on the ECG reclassified risk of 30-day mortality in patients with acute heart failure, identifying both high- and low-risk subsets. **(*Circ Heart Fail*. 2014;7:986-993.)**

Key Words: electrocardiography ■ heart failure ■ mortality ■ prognosis

Acute heart failure is characterized clinically by the development of new or worsening symptoms of heart failure that require urgent care. Heart failure is a major public health issue because of its high mortality, with 1 in every 9 deaths including heart failure as a contributing cause.[1] It is a leading cause of hospitalizations and readmissions, which contributes substantially to the high healthcare costs of this condition.[2] Frequently, patients with acute heart failure (AHF) are evaluated in the emergency department (ED), where there are potential limitations or errors in intuitive clinical decisions made by physicians.[3] Ideally, clinical decisions should be guided by prognostic information; however, safe and efficient instruments to aid decision making in the ED are required.[3]

Clinical Perspective on p 993

Decision making can be improved by the use of risk stratification methods, such as the Emergency Heart failure Mortality Risk Grade (EHMRG), which was designed for prediction of 7-day mortality in the broad group of patients with AHF presenting to the ED.[4] In the EHMRG risk stratification model and in other studies, the importance of even mild troponin elevation was underscored, suggesting the potential importance of cardiac injury or ischemia as a mechanism of adverse outcomes.[5,6] In patients with acute coronary syndromes, the ECG is a potentially useful tool in both diagnosis and prognosis. However, the prognostic importance of the ECG in AHF has not been well defined.

In this study, we examined the prognostic importance of ECG abnormalities and the net reclassification improvement (NRI) afforded by ischemic changes on 30-day mortality. Based on our prior work, we hypothesized that the presence of ST-depression or T-wave inversion on the resting 12-lead ECG would be associated with a significantly increased risk of mortality in a broad cohort of patients presenting to the ED with AHF.

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From the Division of Cardiology, Peter Munk Cardiac Centre (D.G., H.J.R., D.S.L.) and Joint Department of Medical Imaging (D.S.L.), University Health Network, Toronto, Canada; University of Toronto, Toronto, Canada (D.G., P.C.A., J.V.T., H.J.R., D.S.L.); Division of Cardiovascular Diseases, School of Medicine, P. Universidad Católica de Chile, Santiago, Chile (D.G.); Institute for Clinical Evaluative Sciences, Toronto, Canada (P.C.A., L.Z., J.V.T., D.S.L.); Institute of Health Policy, Management, and Evaluation, Toronto, Canada (P.C.A., J.V.T., D.S.L.); Division of Cardiology, Sunnybrook Schulich Heart Centre, Toronto, Canada (J.V.T.); and Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis (P.S.P.).

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Correspondence to Douglas S. Lee, MD, PhD, University of Toronto, Room G-106, 2075 Bayview Ave, Toronto, ON, M4N 3M5, Canada. E-mail dlee@ices.on.ca

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Methods

Cohort and Sampling Methods

In this population-based retrospective cohort study, we studied the data of 8772 patients aged ≥18 years who were residents of Ontario, Canada, and visited an ED for AHF from April 1, 2004, to March 31, 2007. We examined those who were either discharged or hospitalized after the ED visit. In those with multiple visits during the study period, the first episode was selected as the index visit. The patients in the study were required to meet the Framingham criteria for heart failure and also have a final discharge diagnosis of heart failure using the *International Classification of Diseases, 10th revision* (*ICD-10-CA*) code I50 in the discharge abstract.[7,8] We examined the primary diagnoses in the Canadian Institute for Health Information Discharge Abstract Database for hospitalized and the National Ambulatory Care Reporting System database for nonhospitalized patients. All patients were required to have undergone a standard 12-lead ECG at 25 mm/s performed on presentation to ED. Research ethics approval was obtained from Sunnybrook Health Sciences Center.

Patient information was obtained from the EHMRG Study database for those patients who were discharged home, and the Enhanced Feedback for Effective Cardiac Treatment phase II study database (EFFECT) that contains the information on patients who were hospitalized for heart failure, which have been detailed previously.[4,9] Briefly, patients in both databases were randomly selected using stratified cluster sampling according to the type of hospital in the province (small, large, and teaching hospital) and combined into 1 database for the purposes of this study. Patients with ST-elevation suggestive of transmural infarction were excluded because this acute ECG finding will directly influence the care pathway. Those with complete bundle branch block or electronically paced rhythm were also excluded because these conditions preclude the evaluation of ST-segment and T-wave changes for evidence of myocardial ischemia. Finally, patients with do not resuscitate orders before ED arrival and those who were dialysis dependent were excluded.

Clinical Data Abstraction and ECG Interpretation

Clinical and ECG information were abstracted by highly trained nurses using validated methods described elsewhere.[9] Nurse abstractors were required to demonstrate high reliability on standardized chart abstractions before field deployment. The ECG characteristics were analyzed according to international standards criteria and definitions,[10] and ST-segment abnormalities indicative of ischemia were defined as flat or downsloping segment depression with ST-J depression of ≥1.0 mm in ≥2 adjacent leads. T-wave abnormalities indicative of ischemia were defined as any negative or biphasic T-wave in ≥2 contiguous leads while significant Q-waves were ≥40 ms and >1/3 the height of the R wave. Ischemic ECG abnormalities included ST-segment depression, T-wave abnormalities, or Q-waves as described above. For descriptive purposes, ECG abnormalities were grouped according to location of the abnormality as anterior (leads V1–V4), anterolateral (leads V5–V6), lateral (leads I, aVL), or inferior (leads II, III, aVF).

Outcomes and Definitions

Mortality was determined by linking the clinical data abstracted from the EFFECT phase II and EHMRG studies to the Registered Persons Database for all deaths, using the patients' unique, encrypted health card number. Unlike the EHMRG model (which focussed on 7-day mortality), the primary outcome in this study was death within 30 days of the date of initial presentation to the ED with AHF. Patients were classified to be of ischemic pathogenesis if there was a prior myocardial infarction, documented history of coronary artery disease, or prior coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery. All remaining patients were considered nonischemic and were subclassified as hypertensive, valvular, or other, as described previously.[11]

Statistical Analysis

Continuous variables were expressed as medians (25th, 75th percentiles) and compared using the Wilcoxon rank-sum test. The distribution of categorical variables was compared between groups using the χ^2 statistic. A random sample of 220 ECGs (2.5%) was independently read by a cardiologist (D.S.L.) and tested for inter-rater reliability using the κ statistic.[12] The odds of 30-day mortality was evaluated using univariate and multivariable logistic regression models adjusting for the variables contained in a validated clinical risk model derived from a similar population and setting, the EHMRG risk score.[4] The variables included were the following: age, presentation via emergency medical services, systolic blood pressure, heart rate, oxygen saturation, serum creatinine and potassium concentration, active cancer, use of metolazone at home, and troponin elevation exceeding the upper limit of normal.

We expanded the original EHMRG model that was initially designed for predicting 7-day mortality for use as our base model for predicting 30-day mortality (https://ehmrg.ices.on.ca). We initially used 2 different methods to evaluate the incremental benefit of adding specific ECG abnormalities to the base model: (1) using a likelihood ratio test for comparing differences in the −2 log likelihood statistic because of the inclusion of ECG variables; (2) examining the change in the area under the receiver operating characteristic curve for 30-day mortality. We explored the impact of the ECG abnormalities and combinations of these abnormalities on 30-day death using univariate and multivariable logistic regression analysis. These ECG abnormalities included ST-depression, T-wave abnormality, or Q-wave in any anatomic wall location, and combinations of these abnormalities (ie, ST-depression or T-wave abnormality, ST-depression or Q-wave, T-wave abnormality or Q-wave, or presence of any of these abnormalities). To examine whether the ECG abnormalities prognosticated differently in those with known ischemic or nonischemic pathogenesis, we tested for interactions between ECG abnormalities and ischemic versus nonischemic pathogenesis.

Net Reclassification Improvement

We examined the ability of prognostically significant ECG abnormalities to reclassify risk compared with the EHMRG risk model by examining NRI. After calculating the predicted probability of 30-day death using the disaggregated EHMRG risk model covariates, we determined both categorical and continuous NRI as described by Pencina et al.[13,14] For categorical estimates, we subdivided the study sample into 3 risk groups by collapsing the lowest 2 risk quintiles into a low-risk group, the middle 2 risk quintiles into an intermediate group, and the highest risk quintile as a standalone high-risk group. Continuous NRI or NRI(>0) is equal to the sum of the differences in the probability of net upward reclassification for events (death) and probability of net downward reclassification for nonevents (nondeath). We defined a minimally important change in net reclassification of the predicted probability death to be 0.1% because of the severity of the outcome. All analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC) for UNIX environments.

Results

Description of the Cohort

A total of 14 123 subjects were identified from the EFFECT II and the EHMRG cohorts who fulfilled the Framingham criteria, had an ECG performed in the ED, and did not have a do not resuscitate order before presentation. After applying exclusion criteria, the final cohort consisted of 8772 patients comprised of 4685 (53.4%) women (Figure 1). The median age of the study cohort was 78 years (Q1, Q3: 69,84), and 4616 (52.6%) had heart failure deemed to be of ischemic pathogenesis based on clinical criteria. Electrocardiographic manifestations of ischemic heart disease were present in 4545 (51.8%) patients. κ statistics were 0.915 for ST-depression, 0.800 for T-wave abnormality, and 0.817 for Q-waves, indicating excellent inter-rater reliability. Overall, 2352 (26.8%) patients were discharged home from the ED. The mortality rate at 30 days was 8.3% in the overall cohort.

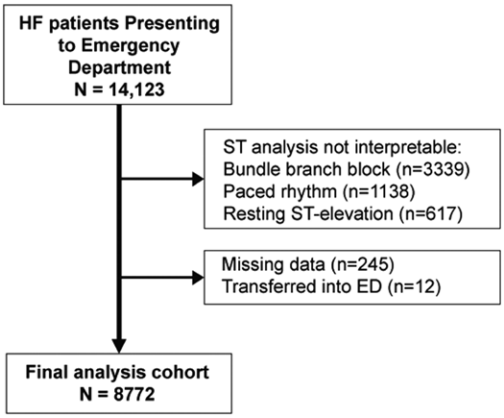

Figure 1. Study flow diagram. ED indicates emergency department; and HF, heart failure.

Table 1 shows baseline characteristics of the patients according to presence or absence of ischemic ECG abnormalities. Patients with ischemic ECG abnormalities were predominantly men and had higher prevalence of coronary heart disease, smoking, and diabetes mellitus. The use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-adrenoreceptor antagonists, loop diuretics, and aldosterone receptor antagonists was more frequent in patients with ischemic ECG abnormalities. Table 2 shows the clinical presentation and laboratory test results performed in the ED. Patients with ischemic ECG abnormalities presented with more severe clinical manifestations including lower systolic blood pressure. Although the majority of patients did not demonstrate troponin elevation, patients with ischemic ECG abnormalities more frequently exhibited values that exceeded the upper limit of normal. There were only minor differences in serum creatinine and glucose concentrations, and no differences in pulmonary congestion or other signs of volume overload. The baseline and clinical characteristics according to the presence or absence of ST-depression are presented in Appendix Tables A and B in the Data Supplement.

ECG Characteristics and Predictors of Mortality

There were no differences in the prevalence of sinus rhythm (63.9% versus 63.4%; *P*=0.617) or atrial fibrillation/flutter (34.4% versus 34.7%; *P*=0.774) between patients with ischemic ECG abnormalities present or absent, respectively. Among patients with ischemic ECG abnormalities, the most frequent finding was T-wave inversion, which was more evident in the lateral (34.1%) and anterolateral (30.6%) leads.

Figure 2 shows the unadjusted odds ratios of the ECG variables for prediction of 30-day mortality compared to those without ischemia-related abnormalities. Whether in isolation or in combination, all ECG features were associated with a significant increase in the unadjusted odds of 30-day mortality, with the exception of isolated Q-waves or T-wave abnormalities. However, after covariate adjustment, the only ECG finding associated with a significant increase in 30-day mortality was the presence of ST-segment depression with an adjusted odds ratio of 1.24 (95% confidence interval [CI]; 1.02–1.50). The combination of ST-depression with either Q-waves or T-wave inversion was not significantly associated with 30-day mortality compared to those without the specified abnormality (Figure 3).

Table 1. Baseline Characteristics

	Any Ischemic ECG Abnormality	No Ischemic ECG	*P* Value
N	4545	4227	
Demographics			
Age (y), median (Q1, Q3)	78 (70, 84)	78 (69, 84)	0.473
Men, n (%)	2219 (48.8%)	1868 (44.2%)	<0.001
Pathogenesis, n (%)			
Ischemic	2830 (62.3%)	1786 (42.3%)	<0.001
Hypertensive	1069 (23.5%)	1528 (36.1%)	
Valvular	140 (3.1%)	154 (3.6%)	
Other	506 (11.1%)	759 (18.0%)	
Comorbidities, n (%)			
Current smoker	538 (14.1%)	435 (12.2%)	0.014
Diabetes mellitus	1826 (40.6%)	1515 (35.9%)	<0.001
Myocardial infarction	2012 (45.5%)	1073 (25.9%)	<0.001
CABG/PCI	1053 (23.4%)	587 (13.9%)	<0.001
Valve disease	842 (19.0%)	664 (15.9%)	<0.001
Cerebrovascular disease	856 (19.2%)	688 (16.4%)	<0.001
Peripheral vascular disease	609 (13.7%)	447 (10.7%)	<0.001
Any cancer	512 (11.5%)	549 (13.0%)	0.023
COPD/asthma	1284 (28.7%)	1260 (30.0%)	0.196
LV ejection fraction, n (%)			
>50%	917 (20.2%)	1115 (26.4%)	<0.001
31% to 50%	864 (19.0%)	573 (13.6%)	
≤30%	572 (12.6%)	336 (7.9%)	
Medications, n (%)			
Aspirin	1955 (43.4%)	1497 (35.7%)	<0.001
ACE inhibitor or ARB	2620 (58.1%)	2253 (53.7%)	<0.001
β-Adrenoreceptor antagonist	2210 (49.0%)	1785 (42.5%)	<0.001
Calcium antagonist	1456 (32.3%)	1403 (33.4%)	0.265
Clopidogrel	528 (11.7%)	321 (7.6%)	<0.001
Warfarin	1255 (27.8%)	1106 (26.4%)	0.117
Digoxin	901 (20.0%)	591 (14.1%)	<0.001
Loop diuretics	2285 (50.7%)	1994 (47.5%)	0.003
Thiazide diuretics	449 (10.0%)	493 (11.7%)	0.007
Aldosterone receptor antagonist	346 (7.7%)	251 (6.0%)	0.002
Oral nitrates	1120 (24.9%)	816 (19.4%)	<0.001
Lipid-lowering agent	2000 (44.4%)	1500 (35.7%)	<0.001
Anti-arrhythmics	304 (6.7%)	279 (6.6%)	0.856

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; Q1, Q3: 25th, 75th percentiles; and PCI, percutaneous coronary intervention.

Extension of the EHMRG AHF Risk Model to Include ST-Depression

The multivariable model for 30-day mortality included the presence of ST-depression along with the covariates comprising the original EHMRG 7-day mortality model as shown in Table 3. Because the presence of ST-depression was the only

Table 2. Clinical Characteristics of Patients With Ischemic and Nonischemic ECG

	Any Ischemic ECG Abnormality	No Ischemic ECG	*P* Value
Clinical presentation, median (Q1, Q3)*			
Systolic blood pressure, mm Hg	144 (126, 167)	147 (129, 170)	<0.001
Diastolic blood pressure, mm Hg	78 (67, 91)	78 (67, 90)	0.570
Heart rate, beats/min	89 (74, 106)	88 (72, 107)	0.443
Respiratory rate, breaths/min	22 (20, 28)	22 (20, 28)	0.804
Rales >50% of lung field, n (%)	569 (12.7%)	467 (11.2%)	0.078
Bilateral ankle edema, n (%)	2804 (63.3%)	2764 (66.9%)	<0.001
Neck vein distension, n (%)	2311 (56.5%)	2119 (56.4%)	0.979
Hepatojugular reflux positive, n (%)	245 (6.0%)	209 (5.5%)	0.280
Third heart sound (S3), n (%)	191 (4.4%)	207 (5.1%)	0.117
Radiographic features			
Cardiomegaly, n (%)	2263 (53.1%)	1795 (45.8%)	<0.001
Pleural effusion, n (%)	2125 (49.4%)	1811 (45.3%)	<0.001
Laboratory tests, median (Q1, Q3)*			
Hemoglobin, g/dL	12.3 (10.9, 13.7)	12.2 (10.9, 13.6)	0.703
White blood cell, $\times 10^9$/L	8.8 (7.0, 11.2)	8.6 (6.9, 11.0)	0.031
Serum sodium, mmol/L	139 (136, 141)	139 (136, 142)	0.170
Serum potassium, mmol/L	4.2 (3.8, 4.6)	4.2 (3.8, 4.6)	0.431
Creatinine, mg/dL	1.20 (0.95, 1.62)	1.13 (0.89, 1.50)	<0.001
Troponin >ULN, n (%)	812 (17.9%)	391 (9.3%)	<0.001
Glucose, mg/dL	132 (108, 184)	124 (105, 166)	<0.001

Q1,Q3 indicates 25th, 75th percentiles; and ULN, upper limit of normal.
*Values are median (Q1, Q3) unless otherwise indicated.

significant ECG abnormality in adjusted analyses, it was the sole electrocardiographic covariate entered into the 30-day mortality model. The EHMRG and ST-depression model for 30-day mortality (EHMRG30-ST) exhibited high discrimination with *c*-statistic 0.801 (95% CI, 0.785–0.817), with no lack of model fit (Hosmer–Lemeshow χ^2 statistic=12.1,

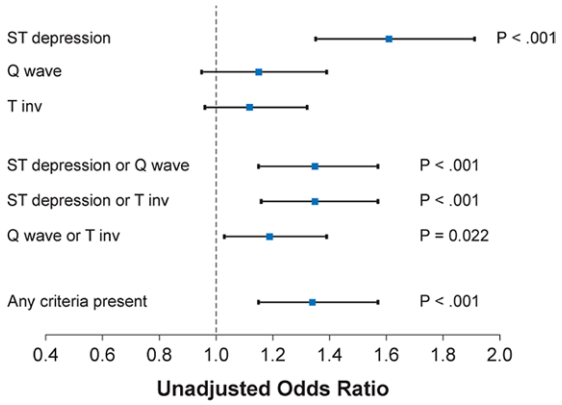

Figure 2. Unadjusted odds ratios and 95% confidence intervals for 30-day mortality by different ECG characteristics. T inv indicates T-wave inversion.

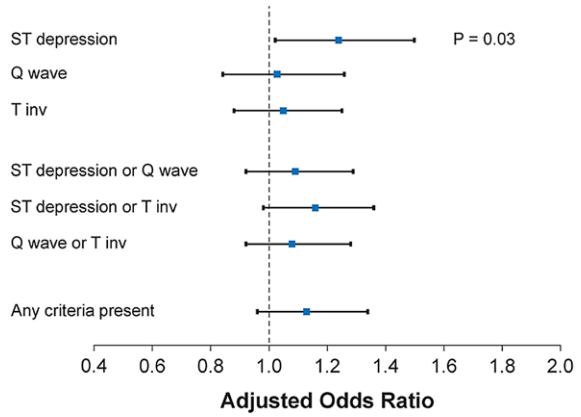

Figure 3. Adjusted odds ratios and 95% confidence intervals for 30-day mortality by different ECG characteristics. T inv indicates T-wave inversion.

P=0.148). In a subgroup of patients with continuous measurements of PR interval and QRS duration (n=2495), there was no significant association between these 2 covariates and 30-day mortality when the covariates were added to the EHMRG30-ST model. Adjusted odds ratios for 30-day mortality were 0.99 (95% CI, 0.95–1.04) per 10 ms increase in PR interval and 0.98 (95% CI, 0.89–1.07) per 10 ms increment in QRS duration.

The 30-day mortality rates and odds ratios for death based on the predicted probability risk quintiles and deciles from the EHMRG30-ST model are shown in Table 4. The 30-day mortality rate in the lowest quintile was 0.74%, whereas there was a high risk in the highest quintile: 27-fold increase in risk in decile 9 and ≈59-fold increase in risk in decile 10 (both *P*<0.001 versus quintile 1). When stratified into predicted risk deciles based on the EHMRG30-ST model, there was a gradient in predicted 30-day mortality that was similar to the observed mortality rates in the respective categories as shown in Figure 4. The observed mortality rate was 0.57% (95% CI, 0.19–1.33) in the lowest and 30.56% (95% CI, 27.01–34.45) in the highest predicted risk deciles based on the EHMRG30-ST model.

Net Reclassification of Risk and Measures of Model Performance

The addition of ST-depression to the EHMRG model reclassified 16.9% of patients (*P*<0.001) when using continuous NRI(>0). However, ST-depression did not significantly reclassify risk using categories (Appendix Table in the Data Supplement), reclassifying only 0.6% of patients into low-, intermediate-, or high-risk groups (*P*=0.396). The addition of ST-depression improved model fit, significantly reducing the -2 log likelihood statistic to 4160.4 from 4165.0 in the base EHMRG model (*P*=0.032). However, the *c*-statistic of the EHMRG30-ST model was not significantly different from that of the base EHMRG model alone, with *c*-statistics of 0.801 (95% CI, 0.785–0.817) in both models (*P*=0.694). As shown in the predictiveness curve (Figure 5), 25.7% of patients exhibited high predicted mortality risk ≥10%, 23.1% were low predicted risk (≤2%, equivalent to the average 7-day mortality rate), and 7.3% had a predicted probability of 30-day death

Table 3. ST-Depression Modified EHMRG Model for 30-Day Mortality: EHMRG30-ST Model

Variable	Model β-Coefficient	Odds Ratio Units	Odds Ratio (95% CI)	*P* Value
Age	0.459	10 y increase	1.58 (1.45–1.72)	<0.001
Transport by EMS	0.935		2.55 (2.12–3.06)	<0.001
Systolic BP	–0.518	20 mm Hg increase*	0.60 (0.55–0.64)	<0.001
Heart rate	0.157	10 bpm increase†	1.17 (1.11–1.23)	<0.001
Oxygen saturation	–0.136	5% increase‡	0.87 (0.82–0.93)	<0.001
Creatinine	0.220	1 mg/dL increase§	1.25 (1.17–1.32)	<0.001
Potassium		4.0–4.5 mEq/L	Referent	NA
	0.470	≥4.6 mEq/L	1.60 (1.32–1.95)	<0.001
	0.107	≤3.9 mEq/L	1.11 (0.90–1.37)	0.314
Troponin elevated‖	0.645		1.91 (1.57–2.31)	<0.001
Active cancer	0.787		2.20 (1.74–2.77)	<0.001
Metolazone at home	0.375		1.45 (0.81–2.61)	0.210
ST-depression		Absent	Referent	NA
	0.212	Present	1.24 (1.02–1.50)	0.030

BP indicates blood pressure; bpm, beats per minute; CI, confidence interval; EHMRG, Emergency Heart failure Mortality Risk Grade; EMS, emergency medical services; and NA, not applicable.

*Initial/triage systolic blood pressure, maximum 160 mm Hg.

†Initial/triage heart rate, minimum of 80 beats/min and maximum of 120 beats/min.

‡Lowest initial/triage oxygen saturation, maximum of 92%.

§1 mg/dL=88.4 μmol/L.

‖Greater than the upper limit of normal.

<1%. Therefore, the middle 51.2% of patients were not classified as high- or low-predicted 30-day mortality risk using the EHMRG30-ST model.

Subgroup Analyses

There was a significant interaction between the presence of ST-depression alone and ischemic pathogenesis in the unadjusted and adjusted analyses (both *P* interaction <0.001). In patients with ischemic disease and ST-depression, the adjusted odds ratio for 30-day death was 1.63 (95% CI, 1.27–2.09), reclassifying 29.3% (*P*<0.001) of the patients when using NRI(>0). In patients with nonischemic pathogenesis, ST-depression was not associated with mortality, with adjusted odds ratio 0.86 (95% CI, 0.63–1.19).

Table 4. EHMRG30-ST Risk Quintiles and 30-Day Mortality

Risk Category	Observed 30-Day Mortality Rate (95% CI)	*P* Value*	Odds Ratio (95% CI)	*P* Value*
Quintile 1	0.74 (0.39, 1.27)	Reference	Reference	Reference
Quintile 2	2.05 (1.44, 2.84)	<0.001	2.81 (1.48, 5.31)	0.002
Quintile 3	5.24 (4.23, 6.43)	<0.001	7.41 (4.13, 13.30)	<0.001
Quintile 4	9.75 (8.34, 11.32)	<0.001	14.47 (8.20, 25.54)	<0.001
Decile 9	16.88 (14.27, 19.82)	<0.001	27.20 (15.33, 48.27)	<0.001
Decile 10	30.56 (27.01, 34.44)	<0.001	58.96 (33.54, 103.65)	<0.001
Overall	8.30 (7.71, 8.92)	NA		

CI indicates confidence interval; EHMRG, Emergency Heart failure Mortality Risk Grade; and NA, not applicable.

*Vs quintile 1.

Discussion

The 12-lead ECG is a simple, low-cost diagnostic test that is widely available; however, its usefulness in patients with primary AHF has not been delineated. In this study, we found that presence of ST-segment depression was a significant predictor of 30-day mortality, which improved net reclassification of risk beyond that of the EHMRG risk covariates. Other ECG indicators of ischemia or infarction, specifically the presence of Q-waves or T-wave abnormalities, were not significantly associated with mortality in patients with AHF. Interestingly, nearly all of the 7-day mortality predictors comprising the EHMRG risk score (except metolazone use) were predictive of 30-day mortality when ST-depression was included in the multivariable model. Another important observation was that inclusion of ST-depression improved reclassification using continuous NRI(>0), suggesting that this ECG marker may assist in refining risk estimation beyond that of a validated mortality risk model.

Prior studies have examined the prognostic implications of the ECG in persons without cardiovascular disease; however, few studies have examined its utility in those with AHF. In NHANES III (Third National Health and Nutrition Examination Survey), which examined a healthy free-living population in the United States, the presence of combined nonspecific ST-segment and T-wave abnormalities was associated with an increased risk of overall mortality, using an ECG classification system similar to that used in our study.[15] Furthermore, in both the Women's Health Initiative and a cohort study of 46 950 healthy men, the presence of ST-segment depression, T-wave abnormalities, and minor Q-waves was associated with higher risk of death compared with those without electrocardiographic abnormalities.[16,17] Although there are many AHF risk prediction models, few have included electrocardiographic variables indicative of ischemia in the model, due in part, to the complexity and wide range of potential features to consider. The time-insensitive predictive instrument did include flattened T-waves as a predictor of in-hospital mortality but did not systemically evaluate multiple electrocardiographic indices of ischemia and did not examine reclassification of risk compared with validated predictors of death.[18] A small, prospective cohort of 208 clinically stable ischemic heart failure patients with left ventricular ejection fraction ≤40% and documented nonsustained ventricular tachycardia reported that the presence of ST-segment depression in V5 or V6 without left ventricular hypertrophy was associated with >2.8-fold mortality at 3 years.[19] However, this study did not evaluate the presence of ST-segment depression in other leads or other concomitant ECG abnormalities.

Although the ECG has been widely available, the paucity of studies in the literature suggests that it has been a challenge to ascertain its prognostic value in the setting of AHF. The preponderance of studies examining the prognostic value of the ECG has focused on QRS width or bundle branch block.[20,21] In addition, previous registries reporting on the importance of the

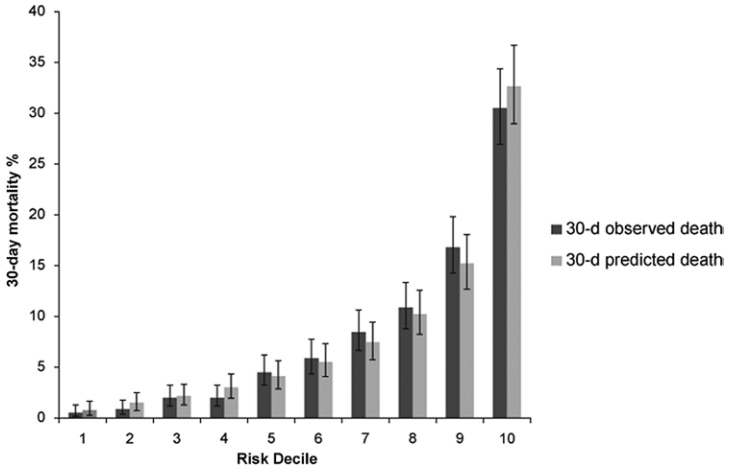

Figure 4. Predicted vs observed 30-day mortality rates according to risk deciles of Emergency Heart failure Mortality Risk Grade ST-depression (EHMRG30-ST) model.

ECG in patients with AHF have focused on parameters other than ischemic ECG characteristics.[22] Prior studies demonstrating that troponin elevation is prognostically important in AHF have also not examined electrocardiographic features.[5,23] The novelty of our findings is underscored by the demonstration that ST-depression was associated with 30-day mortality even after accounting for the presence of elevated troponin at presentation, a covariate in the EHMRG risk model.

The mechanisms by which minor electrocardiographic alterations, such as ST-depression, confer increased risk of mortality remain poorly understood. In the Cardiovascular Health Study, the association between minor nonspecific ST-segment or T-wave abnormalities and cardiovascular mortality was attributed to an increased risk of arrhythmias.[24] The mechanisms involved in the failing heart, however, are likely more complex. In a study of 11 327 patients with chronic heart failure, isolated electrocardiographic abnormalities, including ST-T abnormalities and presence of Q-waves, were not associated with major structural disease or significant left ventricular dysfunction.[25] In this study, we found that the mortality risk of patients with ST-depression was significant primarily among patients with ischemic heart failure, suggesting that the effect of this electrocardiographic feature is linked with but not fully explained by the presence of underlying coronary artery disease.

Our study has implications for both clinicians and researchers. From a clinical standpoint, the presence of ST-segment depression is prognostically important and adds incremental value to known predictors of early death in AHF. Inclusion of ST-segment depression in the EHMRG30-ST model resulted in additional stratification of risk for patients with the same predicted probability of 7-day death as shown in Figure 6. Our study lends further support to the hypothesis that improving outcomes of AHF may necessitate enhanced strategies for identification and early therapy of myocardial ischemia as a precipitant. This is a challenge in the context of AHF, where troponin elevation has demonstrated limitations as an indicator of ischemic heart disease.[26,27] Our study also demonstrated implications for the use of NRI, which is a measure for assessing the clinical utility of a novel risk marker. The NRI

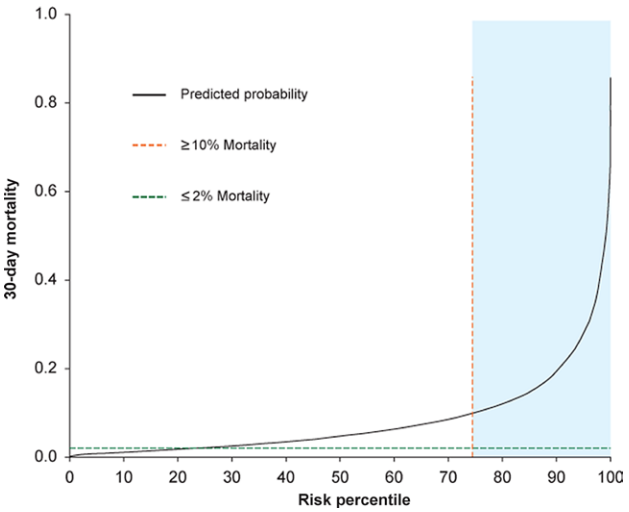

Figure 5. Predictiveness curve for 30-day mortality based on Emergency Heart failure Mortality Risk Grade ST-depression (EHMRG30-ST) model.

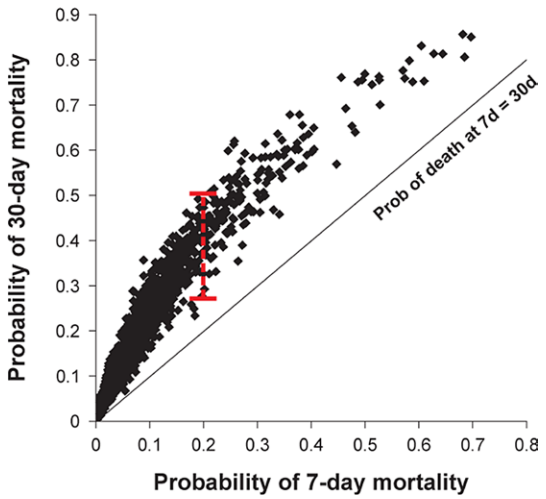

Figure 6. Scatterplot of predicted 7-day mortality using Emergency Heart failure Mortality Risk Grade (EHMRG) and 30-day mortality using EHMRG30-ST model. Dashed vertical line shows range of predicted 30-day mortality for a fixed 20% probability of 7-day death.

allows clinicians to understand if the addition of a biomarker (eg, ECG characteristic) to a previously defined risk model provides a useful change of the risk category and which categories are reclassified predominantly. We found that continuous but not categorical NRI was altered by the inclusion of ST-segment depression on the ECG. Furthermore, a statistically significant impact on continuous NRI was observed, despite no significant change in the *c*-statistic. Future studies should consider examination of continuous NRI in cases where there are adverse outcomes with severe consequences, and small changes in predicted probabilities of events may be important.

Our research study was limited by the lack of repeat ECGs performed in the ED. Potentially, the changes between a series of ECGs could provide prognostically important information or greater sensitivity for the detection of myocardial ischemia occurring in the duration of the hospital stay. Our study did not consider left ventricular ejection fraction or brain natriuretic peptide; however, the former is often not available in the ED and the latter, despite its prognostic significance, has not been shown to impact on outcomes in the acute care setting.[28,29]

Conclusions

In conclusion, we found that the presence of ST-depression on the 12-lead ECG performed at admission in the ED independently predicted mortality at 30 days in patients with AHF. The combination of ST-depression on the ECG and the EHMRG covariates extended the prediction of mortality to 30 days after AHF presentation. Greater awareness of the prognostic importance of electrocardiographic characteristics will assist in the identification of patients who are at high risk of death and may benefit from more intensive evaluation of ischemic heart disease.

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Disclosures

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CLINICAL PERSPECTIVE

Improving outcomes in patients with acute heart failure is a challenge. In this population-based cohort of 8772 patients, we show that the presence of ST-depression on the ECG of patients with acute heart failure presenting to the emergency department, independently predicted 30-day mortality (adjusted odds ratio of 1.24 [95% confidence interval, 1.02–1.50]). Furthermore, using net reclassification improvement, we show that the addition of ST-depression to a previously validated risk model (Emergency Heart Failure Mortality Risk Grade) reclassified risk in ≈17% of patients. The use of the ECG in the emergency department may assist clinicians in better identifying patients with acute heart failure who are at high risk of death within 30 days of acute presentation. Our findings add to the growing evidence that myocardial ischemia is an important, potentially modifiable precipitant of acute heart failure.

Ischemic Electrocardiographic Abnormalities and Prognosis in Decompensated Heart Failure

Douglas Greig, Peter C. Austin, Limei Zhou, Jack V. Tu, Peter S. Pang, Heather J. Ross and Douglas S. Lee

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SUPPLEMENTAL MATERIAL

Appendix Table A. Baseline characteristics of patients with vs. without ST-segment depression

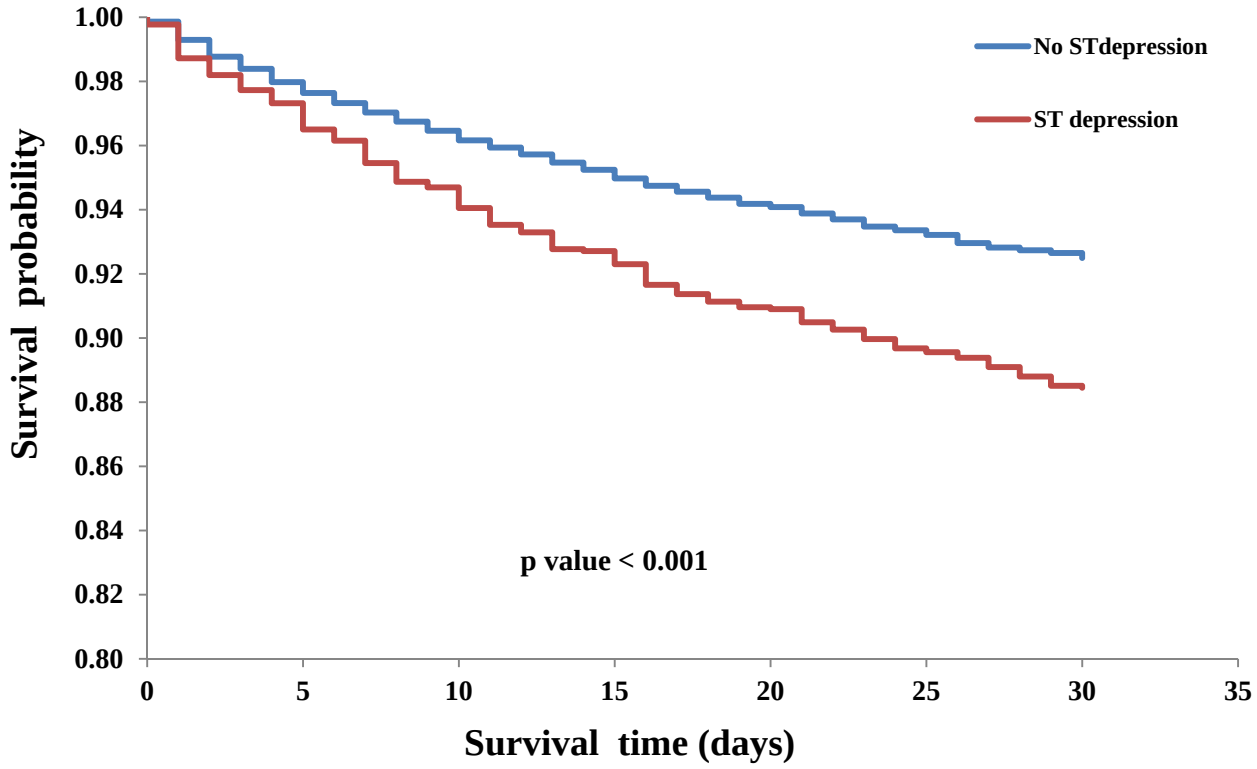
	ST-segment Depression	**No ST-segment Depression**	**p-value**
N	1714	7058	
Demographics			
Age (years), median (Q1,Q3)	79 (72,85)	77 (69,84)	<0.001
Men, n (%)	786 (45.9%)	3301 (46.8%)	0.497
Etiology, n (%)			
Ischemic	1070 (62.4%)	3546 (50.2%)	<0.001
Hypertensive	398 (23.2%)	2199 (31.2%)	
Valvular	62 (3.6%)	232 (3.3%)	
Other	184 (10.7%)	1081 (15.3%)	
Comorbidities, n (%)			
Current smoker	161 (11.1%)	812 (13.7%)	0.008
Diabetes mellitus	708 (41.9%)	2633 (37.5%)	<0.001
Myocardial infarction	719 (43.2%)	2366 (34.3%)	<0.001
CABG / PCI	347 (20.6%)	1293 (18.4%)	0.04
Any valve disease	337 (20.2%)	1169 (16.8%)	0.001
Cerebrovascular disease	346 (20.7%)	1198 (17.2%)	<0.001
Peripheral vascular disease	222 (13.3%)	834 (11.9%)	0.124
Any cancer	186 (11.1%)	875 (12.5%)	0.112
COPD / Asthma	520 (30.9%)	2024 (28.9%)	0.105
LV ejection fraction, n (%)			
> 50%	300 (17.5%)	1137 (16.1%)	0.005
31-50%	358 (20.9%)	1674 (23.7%)	
≤ 30%	207 (12.1%)	701 (9.9%)	
Medications, n (%)			
Aspirin	750 (44.1%)	2702 (38.6%)	<0.001
ACE inhibitor or ARB	979 (57.6%)	3894 (55.6%)	0.138
β-adrenoreceptor antagonist	855 (50.3%)	3140 (44.8%)	<0.001
Calcium antagonist	600 (35.3%)	2259 (32.3%)	0.017
Clopidogrel	203 (11.9%)	646 (9.2%)	<0.001
Warfarin	524 (30.8%)	1837 (26.2%)	<0.001
Digoxin	456 (26.8%)	1036 (14.8%)	<0.001
Loop diuretics	922 (54.2%)	3357 (47.9%)	<0.001

Thiazide diuretics	147 (8.6%)	795 (11.4%)	0.001
Aldosterone receptor antagonist	125 (7.4%)	472 (6.7%)	0.369
Oral Nitrates	465 (27.4%)	1471 (21.0%)	<0.001
Lipid-lowering Agent	762 (44.8%)	2738 (39.1%)	<0.001
Anti-arrhythmics	117 (6.9%)	466 (6.7%)	0.735

Appendix Table B. Clinical characteristics of patients with vs. without ST-segment depression

	ST-segment Depression	No ST-segment Depression	p-value
Clinical presentation, median (Q1,Q3)*			
Systolic blood pressure, (mmHg)	145 (126,167)	146 (127,169)	0.383
Diastolic blood pressure, (mmHg)	78 (66,91)	78 (67,90)	0.966
Heart rate, (beats/min)	92 (76,110)	88 (72,106)	<0.001
Respiratory Rate, (breaths/min)	24 (20,28)	22 (20,28)	<0.001
Rales >50% of lung field, n(%)	245 (14.5%)	791 (11.4%)	<0.001
Bilateral ankle edema, n(%)	1008 (60.6%)	4560 (66.1%)	<0.001
Neck vein distension, n(%)	868 (56.4%)	3562 (56.5%)	0.931
Hepatojugular reflux positive, n(%)	74 (4.8%)	380 (6.0%)	0.067
Third heart sound (S3), n(%)	63 (3.8%)	335 (5.0%)	0.049
Radiographic features			
Cardiomegaly, n(%)	859 (52.9%)	3199 (48.8%)	0.003
Pleural effusion, n(%)	787 (48.3%)	3149 (47.2%)	0.447
Laboratory tests, median (Q1,Q3)*			
Hemoglobin, (g/dL)	12.1 (10.8,13.5)	12.3 (10.9,13.7)	0.036
White blood cell, (x 10^9 /L)	9.2 (7.3,11.8)	8.6 (6.9,10.9)	<0.001
Serum sodium, (mmol/L)	139 (136,141)	139 (136,142)	0.231
Serum potassium, (mmol/L)	4.2 (3.8,4.6)	4.2 (3.9,4.6)	0.078
Creatinine, (mg/dL)	1.20 (0.95,1.64)	1.17 (0.92,1.54)	<0.001
Troponin >ULN, n(%)	424 (24.7%)	779 (11.0%)	<0.001
Glucose, (mg/dL)	140 (110,202)	126 (104,167)	<0.001

Appendix Figure A. Kaplan-Meier curve comparing patients with and without ST-depression



Appendix Figure B. Adjusted survival curves comparing patients with and without ST-depression