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A pilot study to assess the utility of five established variables to standardize exercise treadmill test reporting☆

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ABSTRACT

Background: The prognostic utility of 5 established variables (functional capacity, Duke treadmill score, chronotropic response to exercise, heart rate recovery, and premature ventricular contractions) together after routine exercise treadmill testing (ETT) has not been determined.
Methods: We assessed the combined prognostic ability of 5 established variables for the primary outcome (myocardial infarction [MI], coronary revascularization [CR] or all-cause mortality) and the secondary outcome of unnecessary downstream testing (defined as receipt of further noninvasive imaging without CR, MI, or death) compared with standard methods. Using a retrospective study design, 1857 consecutive patients were enrolled in the year 2014 and followed until December 31, 2015. Optimal discrimination and global fit statistics were assessed from logistic regression models. Classification and regression tree (CART) methodology was used for the final model.
Results: The mean [SD] age was 56.0 [12.5] years; median comorbidities (2, IQR 2) with 26% having an equivocal report. Compared to other models, a model with age, sex, and the 5 established variables showed an improvement in discrimination for the primary [c-statistic 0.85 versus (0.69–0.79)] and secondary [c-statistic 0.73 versus (0.65–0.71)] outcomes with substantial improvement in global fit. The final, optimal, 10-fold cross-validated CART model had a c-statistic of 0.78.
Conclusions: The utility of the 5-established variables, based on the current study, resides in its ability to decrease unnecessary downstream testing and improve cardiovascular event prognostication. This is accomplished by removing the subjective interpretation of currently used ETT variables that can lead to an equivocal report.

1. Introduction

A routine exercise treadmill test (ETT) is known to have a lower sensitivity and specificity when compared to ETT accompanied by a concomitant imaging modality (myocardial perfusion or echocardiography). As a result of this lower diagnostic accuracy, ETT reports are often deemed equivocal. This frequently results in additional, often unnecessary, noninvasive imaging. The reasons for the equivocal reports are most likely related to the variability in the interpretation of commonly used ETT variables with an unnecessary focus on the ST-segment [1–2]; a possible reason for the low utilization of routine ETT in the United States [3].

The assessment of functional capacity, Duke treadmill score, chronotropic response to exercise, heart rate recovery, and premature ventricular contraction (PVC) burden are individually well-established as diagnostic and prognostic markers after ETT [2]. However, little is known of their prognostic ability when used together. Therefore, we conducted the retrospective, observational Triage after EXercise Treadmill (TEXT) study. The primary aim of the TEXT study was to assess whether the combined use of these 5-established variables could maximize prediction of cardiovascular outcomes while also decreasing unnecessary downstream testing. The primary hypothesis was that a model with the 5-established variables would have a higher

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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discriminative ability for the primary and secondary outcome than currently used methods.

2. Materials and methods

2.1. Exercise treadmill testing

Patients were referred and scheduled for ETT using the Kaiser Permanente Northern California (KPNC) electronic health records. The 3-minute BRUCE protocol is the standard protocol used in the treadmill laboratory [1]. A trained registered nurse and/or staff routinely reminds scheduled patients to have appropriate footwear as well as to stop any medications on the day of the procedure that may decrease the sensitivity of the test. Patients are further screened prior to the test to ensure no significant contraindications are present [1].

2.2. Population

Our source population included members of KPNC, a large, integrated health-care delivery system that provides comprehensive care to more than 3.8 million members across Northern California. Our target population were consecutive adult members who underwent ETT between January 1, 2014 and December 31, 2014, at the Kaiser Permanente San Jose medical center. Subjects were identified at the time of the treadmill test. The inclusion criteria for entry into the study were age ≥ 18 years old and a referral for ETT by a physician or physician extender. Patients were excluded from the study if the ETT was part of a stress imaging protocol (nuclear stress imaging or stress echocardiogram) or part of a cardiac rehabilitation program. The Northern California Kaiser Foundation Research Institute's Institutional Review Board approved the study. A waiver of informed consent was obtained due to the observational nature of the study.

2.3. Clinical outcomes

The primary outcome was the occurrence of myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or death during follow-up, which continued until December 31, 2015. The secondary outcome was unnecessary downstream testing which was defined as the receipt of additional noninvasive imaging (stress nuclear myocardial perfusion imaging, stress echocardiography, or cardiac computed tomography) after the index ETT without a coronary revascularization procedure, myocardial infarction, or death. We initially identified the receipt of further downstream noninvasive imaging tests, coronary revascularization procedures, and all-cause mortality through International Classification of Diseases, Ninth edition (ICD-9) codes, and procedure codes. This was subsequently confirmed by individual chart review.

2.4. Predictor variables

The primary exposure variable is a group of predictor variables that will be henceforth called established variables. This group of established variables include observed/expected functional capacity, Duke treadmill score, heart rate recovery at 2 min, chronotropic response to exercise and number of PVCs.

2.5. Collection of covariates

Experienced physicians in treadmill testing blinded to downstream outcomes were given abstraction forms along with the actual treadmill tracings, and data (including medical record numbers) were abstracted from the ETT tracings. The unique medical record number was used to obtain information on baseline patient demographics, physician reported patient symptoms, comorbidities, medications, laboratory data, health care utilization, and downstream outcomes from Health plan clinical and administrative databases.

The ETT variables abstracted directly from the treadmill tracings output were heart rate (baseline, peak, 2 min into recovery), ST-segment depression (baseline, peak), observed functional capacity, total number of minutes exercised, and number of PVCs during recovery; all as continuous variables. In concordance with the 2013 scientific statement the ST-segment depression at baseline and exercise was coded as 0 if there was no ST-segment depression 60–80 ms after the J point or if only J-point depression was observed. If the ST-segment depression was horizontal, or downsloping the exact magnitude of the ST-depression was coded as a continuous variable. In cases of upsloping ST-segment depression or equivocal ST-segment depression, we allowed the experienced physician abstracters to use their individual judgement and code the magnitude of ST-segment depression as 0 or a continuous variable >0 [1]. The presence or absence of chest pain during the treadmill test was abstracted from the ETT report. The calculated variables include change in ST-segment (peak –baseline), expected functional capacity (men: 14.7 – [0.1 × age], women: 14.7-[0.13 × age]), observed/expected functional capacity, chronotropic response to exercise ([peak heart rate – resting heart rate]/[220 – age – resting heart rate]), heart rate recovery at 2 min (difference between heart rate at peak exercise and at 2 min into recovery), Duke treadmill score [2] (total minutes on treadmill – [5 × ST-segment change] – [4 × angina score]). Standard normative values for predicted functional capacity (abnormal if <85% of predicted), chronotropic response (abnormal if ≤80%), heart rate recovery (abnormal if ≤22 beats per minute 2 min into recovery), ventricular ectopy during recovery (>7 beats per minute, couplets, bigeminy, trigeminy, ventricular tachycardia, or fibrillation), Duke treadmill score (low risk if ≥5, intermediate between −10 and 4, high risk if lower than −10) were used [1–2]. The ETT report was obtained from the electronic health records, and data were abstracted by a research associate blinded to the clinical scenario and downstream outcomes. The ETT report was determined to be equivocal if any of the following were found in the final official report: words such as inconclusive, suboptimal, indeterminate, borderline. The covariates collected were baseline patient demographics, indications for ETT, comorbidities, medications, laboratory data, health care utilization, ETT variables, and ETT report variables (as shown in Tables 1 and 2).

2.6. Statistical analysis

Statistical analyses were performed using STATA version 13 (StataCorp, College Station, TX). We presented descriptive statistics using means and standard deviations [SD] for continuous variables and proportions for dichotomous variables and reported extent of missing variables. Categorical characteristics were compared using χ^2 tests. We used multivariable logistic regression analysis to obtain odds ratios (OR) and 95% confidence intervals (CI). An area under the receive operator characteristics curve (c-statistic) and measures of global fit (Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC] and log-likelihood test) were obtained for each model. The lowest values for AIC, BIC, and log-likelihood were considered the most appropriate global fit along with the highest c-statistic for optimal discrimination. A priori interactions between age and Duke treadmill score and between sex and Duke treadmill score were tested individually as well as being included within the full model. The model with the most appropriate discrimination statistics and global fit was then used to develop the optimal classification and regression tree (CART). CART methodology was performed using CART® Pro SPM version 8.0 Computer Software (Salford Systems, San Diego, CA). The final CART analyses (model statistics, variable importance, receiver operator characteristic curves) shown are from the test model after tree pruning and 10-fold cross validation.

3. Results

3.1. Baseline characteristics

The initial cohort sample size was 2004. After removal of duplicates and index treadmill tests that were part of a stress imaging protocol, the final sample size was 1857. Baseline characteristics are shown in Table 1. The mean age in this cohort was 56.0 [12.5] years, with 56.2% being men, and 43.7% white. The mean body mass index was 28.9 [6.3] and the neighborhood level income was $100,195 [$39,834]. Most patients were KPNC members with an average duration of membership of 10 years. The median number of baseline comorbidities was 2 (IQR 2) and the mean baseline number of medications was 1.3 [1.5]. Participants in the study had overall well-controlled laboratory values as well as low health care use in the year before the index ETT.

3.2. Index treadmill test and downstream testing

The mean Duke treadmill score was 7.2 [3.9], with an above average observed/expected functional capacity, normal chronotropic response, and heart rate recovery with an overall low number of PVCs in the recovery phase. ETT results and the proportion of patients with an equivocal treadmill test report (26.4%) are shown in Supplement Table 1. The prevalence of low, intermediate and high risk Duke treadmill scores were 78.2%, 21.6%, and 0.22% respectively. Fig. 1a, schematically demonstrates the flow of patients in the current study. After an index ETT, 9.6% underwent nuclear stress imaging, 2.6% underwent cardiac computed tomographic angiography, and < 1% underwent both nuclear stress imaging and cardiac computed tomography. Of the total cohort 87.2%, did not undergo any further testing. A significantly higher proportion of patients were referred directly for coronary revascularization (32/1857, 1.72%) than after a second imaging test (16/1857.0.86%; $p < 0.0001$).

3.3. Outcomes

The presence of an equivocal report significantly varied across Duke treadmill score categories ($p < 0.0001$) with no equivocal report found in the high-risk Duke treadmill score category (Fig. 1b). An equivocal report was found less frequently in those with the primary outcome of coronary revascularization, MI or death (42.0% versus 57.9%, $p < 0.0001$) and more frequently in those with the secondary outcome of unnecessary downstream tests (51.6% vs 48.4%, $p < 0.0001$)