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Original article

Higher event rate in patients with high-risk Duke Treadmill Score despite normal exercise-gated myocardial perfusion imaging

ABSTRACT

This prospective study was carried out to find the negative predictive value of various Duke Treadmill Scores (DTSs) in patients with normal myocardial perfusion imaging (MPI). This study was conducted from August 2012 to July 2015, and 603 patients having normal exercise MPIs were included. Patients were followed for 2 years for fatal myocardial infarction (FMI) and nonfatal myocardial infarction (NFMI). Follow-up was not available in 23 patients, leaving a cohort of 583 participants. DTS was low risk (≥5) in 286, intermediate risk (between 4 and − 10) in 211, and high risk (≤−11) in 86 patients. Patients with high- and intermediate-risk DTS were significantly elder than low-risk DTS cohort. Patients with high-risk DTS had significantly higher body mass index with male preponderance compared to other groups. No significant difference was found among three groups regarding modifiable or nonmodifiable risk factors and left ventricular ejection fraction. On follow-up, single FMI was observed in high-risk DTS group (log-rank test value = 5.779, $P = 0.056$). Five NFMI events were observed in high-risk DTS (94.2% survival; log-rank test value = 19.398, $P = 0.0001$; significant) as compared to two events each in low- and intermediate-risk DTS (nonsignificant). We conclude that patients with normal exercise MPI and low-to-intermediate risk DTS have significantly low NFMI. High-risk DTS despite normal exercise MPI had high NFMI. Further, validation studies to find the predictive value of symptomatic and asymptomatic ST deviation resulting in high-risk DTS in patients with normal exercise MPI are warranted.

Keywords: Duke Treadmill Score, exercise testing, myocardial perfusion imaging, nonfatal cardiac event, prognosis

INTRODUCTION

Dynamic exercise using treadmill for the evaluation of coronary artery disease (CAD) is used in about 47% of all myocardial perfusion imaging (MPI) in Europe.[1] It is considered as a preferred and more physiological mode of stress in patients with adequate functional capacity. The annualize event rate in patients having a normal exercise-gated MPI is 0.45%.[2] The Duke Treadmill Score (DTS) is a weighted index combining treadmill exercise time using standard Bruce protocol, maximum net ST segment deviation (depression or elevation), and exercise-induced angina. DTS classifies patients into low- (DTS ≥5 with 99% survival at 4 years), moderate- (DTS between −10 and 4 with 95% survival at 4 years), and high-risk (DTS ≤−11 with 79% survival at 4 years) mortality categories.[3] Patients with high-risk DTS and moderate-to-severe abnormal MPI findings are considered candidates for coronary angiography (CA).[3] However, it is not uncommon to have patients with high-risk DTS and normal MPI, and data are limited about the prognosis in such clinical scenarios.

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The aim of this study was to determine the clinical outcomes in patients with different DTS and normal exercise MPI.

MATERIALS AND METHODS

Study population

This was a prospective study conducted from August 2012 to July 2015 at Nuclear Cardiology Department of Karachi Institute of Heart Disease, Karachi, Pakistan. This study was approved by the Ethical Review Committee, and informed consents were obtained from all the participants. Patients who underwent exercise MPI for the evaluation of known or suspected CAD during the study period and had a normal MPI with valid DTS were included in the study. Patients having noninterpretable electrocardiogram (ECG) due to conduction abnormalities such as left bundle branch block, paced rhythm, or preexcitation syndrome were excluded from the study. Six-hundred and three patients qualified the inclusion criteria and they were followed for 2 years for fatal myocardial infarction (FMI) and nonfatal myocardial infarction (NFMI). Follow-up was not available in 23 patients, leaving a cohort of 583 participants.

Treadmill exercise protocol

All patients underwent a standardized symptom-limited treadmill exercise test to the endpoints as defined by the American Heart Association.[4] Heart rate, blood pressure, and 12-lead ECG were recorded in resting, during exercise, and recovery periods. Stress-induced maximal ST changes were defined as ST-segment deviation as horizontal or downsloping ST-segment deviation (at 80 ms after the J point when horizontal and at the J point when downsloping). A standard Bruce protocol was used in majority of patients. For patients who underwent modified Bruce protocol, a conversion factor was used to equate for duration with standard Bruce protocol based on metabolic equivalents (METs). Radiotracer (259–370 MBq of Technetium-99 m Methoxy Isobutyl Isonitrile; ^{99m}Tc-MIBI) was injected at peak exercise and after 60–90 s, treadmill was switched to the recovery phase. The DTS was calculated as follows: exercise time in minutes − (5 × maximum ST segment deviation in mm) − (4 × angina index). Angina index was defined as a value of 0 if no angina, 1 if nonlimiting angina, and 2 if typical limiting angina occurred. Patients were classified as low risk (DTS ≥ 5), intermediate risk (DTS between −10 and 4), and high risk (DTS ≤−11).[3]

Image acquisition and interpretation

At least 30 min after exercise, all patients underwent acquisition of gated single-photon emission computed tomography (SPECT) MPI using dual-head dedicated cardiac gamma cameras (Cardio MD, Philips) fitted with low energy all-purpose collimator. Resting SPECT images were acquired on the same day using 592–925 MBq of ^{99m}Tc-MIBI. For both sets of images, no attenuation or scatter correction was used. Image reconstruction and left ventricular functional parameters such as ejection fraction (left ventricular ejection fraction [LVEF]), end-diastolic volume, end-systolic volume, wall motion, and transient ischemic dilatation (TID) were contemplated using commercially available Astonish® and Autoquan® software packages (Acacialaan, Ostend, Belgium), respectively. A gated myocardial perfusion imaging (GMPI) with sum stress score (SSS), sum rest score, sum difference score >2, and TID >1.22 was considered abnormal. For the purpose of extent SSS and for severity percentage, sum thickness score was used. Each study was interpreted by two experienced, board-certified nuclear cardiologists having at least 10 years' experience.

Follow-up

All patients (or a family member in case patient has expired) were interviewed on telephone (12–24 months after GMPI) regarding major acute cardiac events such as FMI or NFMI. Patients who could not be contacted (23 patients) were excluded from the study population.

Statistical analysis

Data were analyzed using commercially available packages the MedCalc® statistical software version 17.4.4 and Statistical Package for the Social Sciences (Version 17®, Armonk, New York, United States). Comparisons between patient groups were performed using Student's t-test for continuous variables and Chi-square test for categorical variables. Continuous variables were described by mean ± standard deviation. Kaplan–Meier plot for event-free survival and for the purpose of comparison of survival curves log-rank test was applied for patients with low, moderate, and high-risk DTS. For all values of $P < 0.05$ were considered as statistically significant.

RESULTS

This study included 583 patients with a mean age of 50 ± 10 years, and patients with moderate- and high-risk DTS were significantly, albeit marginally elder than low-risk DTS cohort. Patients in high-risk DTS cohort were significantly obese (higher body mass index) with male dominance than low- and moderate-risk DTS groups. Mean ST segment deviation (both elevation and depression) was significantly high in high-risk DTS score group (03 mm ± 03; P significant). Significantly, high angina score was observed in high-risk DTS score 10% and 12% for score 2 and 1, respectively [Figure 1]. As expected, the mean METs were significantly lower in high-risk DTS group. No significant difference was seen in three groups regarding hypertension, diabetes mellitus, dyslipidemia, smoking, family history for CAD, and measured LVEF [Table 1].

Follow-up data showed single fatal MI in high-risk DTS group (FMI event rate/2 year = 1.1%; nonsignificant *P* value). Totally nine NFMIs were seen in follow-up; two each in low- and moderate-risk DTS (NFMI event rate/2 year = 0.7% and 0.9%, respectively; nonsignificant *P* value) and five in high-risk DTS (NFMI event rate/2 year = 5.8%; significant *P* value). Kaplan–Meier survival plot for FMI showed event-free survival of 100% in low- and moderate-risk DTS and 98.8% in high-risk DTS group (nonsignificant log rank value) [Figure 2]. Kaplan–Meier survival plot for NFMI showed event-free survival of 99.30% and 99.05% in low- and moderate-risk DTS, respectively, but 94.2% in high-risk DTS group (significant log-rank value) [Figure 3].

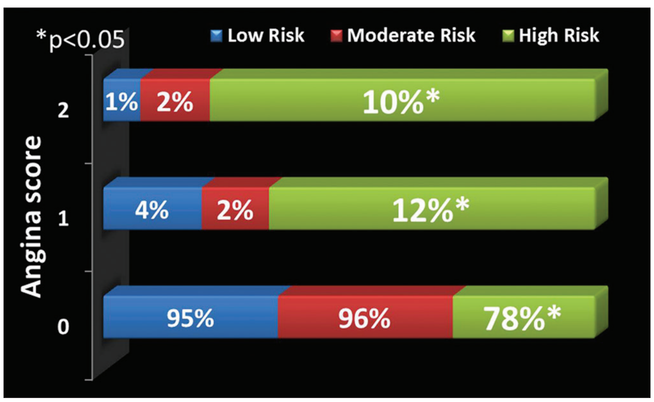

Figure 1: Angina score percentage distribution in low-, moderate-, and high-risk Dukes Treadmill Score groups with normal myocardial perfusion imaging results

DISCUSSION

Exercise stress testing in conjunction with ECG has been established as one of the focal points in the diagnosis and prognosis of CAD. For risk stratification of patients having ECG-based exercise test, the DTS is a well-validated tool[5], and patients with high-risk DTS are considered candidates for CA. Similarly, patients with a normal exercise-gated MPI have a high net present value (NPV) and <1% annual event rate and generally do not require CA.[6] However, about 19% of patients are found to have normal exercise MPI with a high DTS[7], and this poses a management dilemma for treating physicians. The aim of this prospective study was to find out the clinical outcomes in patients with a normal exercise-gated MPI with different DTS risk scores.

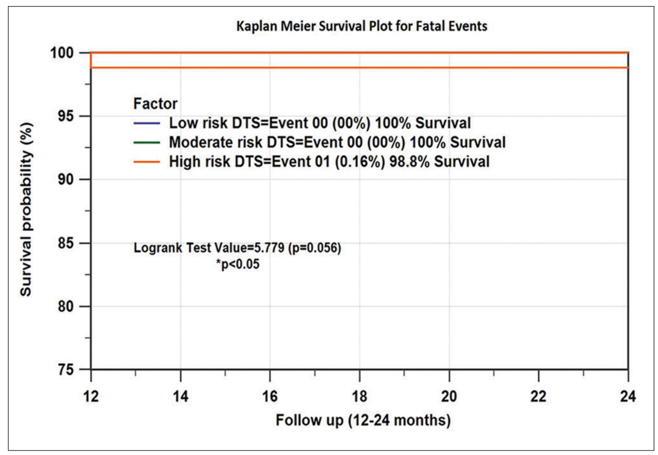

Figure 2: Kaplan–Meier survival curves for fatal myocardial events in low-, moderate-, and high-risk Dukes Treadmill Score groups with normal myocardial perfusion imaging results

Table 1: Patients' demographics

Variables	Total (*n*=583)	Low-risk DTS (≥5) (*n*=286)	Moderate-risk (4-−10) DTS (*n*=211)	High-risk DTS (≤−11) (*n*=86)
Age (years), mean±SD	50±10	49±10	51±10*	52±10*
Male:Female	265:318 (45%:55%)	130:156 (45%:55%)	85:126 (40%:60%)	50*:36 (58%:42%)
BMI (kg/m^2), mean±SD	25.814±4.788	25.214±4.463	25.942±4.939	26.842±5.403*
MPHR, mean±SD	87±09	88±09	87±10	86±09
DTS median (range)	4.0±7.7 (−16-15.5)	7.8±2.1 (5 till 15.5)	0.5±3.6* (−10-4)	−12±1.4* (−16-−11)
ST segment deviation (mm), mean±SD	2±2	2±2	2±2	3±3*
METs, mean±SD	7.6±2.2	8.5±2.2	7.38±1.99	5.01±1.6*
Hypertension (%)	383 (66)	183 (64)	141 (67)	59 (69)
Diabetes mellitus (%)	185 (32)	87 (30)	65 (31)	33 (38)
Dyslipidemia (%)	176 (30)	90 (31)	60 (28)	26 (33)
Family history for CAD (%)	250 (43)	127 (44)	86 (41)	37 (43)
Smoking (%)	79 (14)	37 (13)	27 (13)	15 (17)
%LVEF, mean±SD	69±8	69±7	69±8	69±7
Fatal event rate (24 months)	0.17% (1)	0% (0)	0% (0)	1.1% (1)
Nonfatal event rate (24 months)	1.5% (9)	0.7% (2)	0.9% (2)	5.8% (5)*

*$P<0.05$. SD: Standard deviation; BMI: Body mass index; MPHR: Maximum predicted heart rate; DTS: Dukes Treadmill Score; METs: Metabolic equivalents; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction

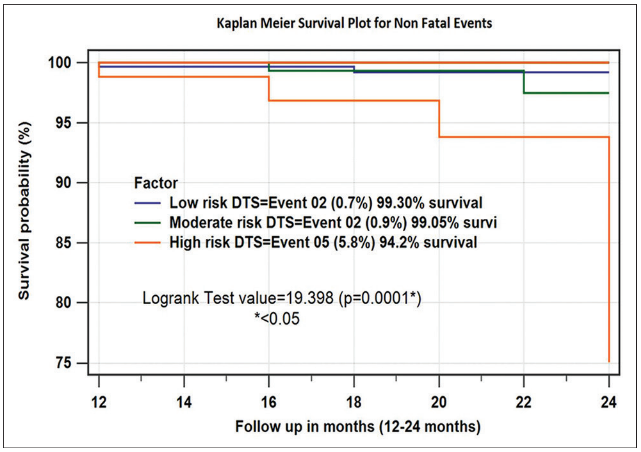

Figure 3: Kaplan–Meier survival curves for nonfatal myocardial events (hospitalization/ischemic attacks) in low-, moderate-, and high-risk Dukes Treadmill Score groups with normal myocardial perfusion imaging results

In our study, only 15% of participants with normal exercise-gated MPI had high-risk DTS which reflects the referral of majority of this population to CA and comparable with the published data as stated above.[7] However, in a recently published study, 29% of participants were found to have normal MPI with high-risk DTS which could be explained by elder age and higher incidence of hypertension (resulting in false positive ST changes) in their participants than the present study.[8] In the present study, patients with low- and moderate-risk DTS had no FMI and <1% NFMI/2 year. These findings are in complete concordance with large body of data favoring exceedingly high NPV of normal MPI (>99%),[2,6,9,10] low-risk DTS (99%), and moderate-risk DTS (97%).[11] In cohort with high-risk DTS and normal exercise MPI, the FMI event rate/2 year was 1.1% (nonsignificant), and NFMI event rate/2 year was 5.8% (significant *P* value). The FMI rate/2 year in cohort with high-risk DTS is very low (nonsignificant as well) as compared to the Mark *et al*.[11] study which reported a mean annual mortality rate of 5%, and this discrepancy could be due to a shorter follow-up in the present study and difference in patients' characteristics. The higher NFMI, rate/2 year in high-risk DTS group in this study, is in contradiction to a general understanding that a normal MPI even in patients with known CAD has a high NPV.[2,12-14] The plausible explanations could be that these patients were significantly older with male predominance and had significantly lower METs as compared to low- and moderate-risk DTS cohorts. However, according to a study published by our group revealed higher event rates (both FMI and NFMI) in patients with known CAD and normal MPI.[15] A recently published study by Vítola *et al*.[8] reported an annual FMI and NFMI 0 and 1.1%, respectively, in patients with high-risk DTS and normal-gated MPI. The authors explained a high ST deviation without chest pain resulting in high-risk DTS in their patients despite having good effort tolerance. Hence, we strongly feel that in clinical scenario of high-risk DTS and normal MPI, it is important to look for all three components of DTS calculation as asymptomatic ST deviation could be the real game changer. Patients with high-risk DTS due to asymptomatic ST deviation may be managed conservatively as published data favors good prognosis in these patients.[13] While patients with symptomatic ST deviation, high-risk DTS and normal MPI may be considered for aggressive management. In this study, we did not subclassify high-risk cohort on basis of angina index and ST deviation due to smaller sample size in each subcohorts. However, we have planned to continue this study as validation study to find the predictive value of symptomatic and asymptomatic ST deviations resulting in high-risk DTS patients with normal exercise MPIs.

Our study has limitations such as (1) female dominance in low and moderate risk and vice versa in high-risk DTS cohorts; (2) shorter follow-up and in view of high incidence of diabetes (38% in high-risk DTS group) possibility of a further higher event rate after 2 years cannot be ascertained; and (3) possibility of balanced three vessel disease which is an established limitation of MPI was not assessed as CA could not be justified.

CONCLUSION

Patients with normal exercise MPI and low-to-intermediate DTS have significantly low NFMI. High-risk DTS despite normal exercise MPI was found to be associated with high NFMI. We feel that further validation studies to find the predictive value of symptomatic and asymptomatic ST deviations resulting in high-risk DTS in patients with normal exercise MPI are warranted.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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