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RESEARCH ARTICLE

A Moderate Walking Test Predicts Survival in Women With Cardiovascular Disease

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Introduction: Cardiovascular disease (CVD) is the principal cause of death in U.S. women. Peak oxygen uptake is strongly related to mortality and CVD. This study aimed to investigate the association between estimated peak oxygen uptake, determined using a moderate 1-km walking test, and all-cause mortality in female patients with stable CVD.

Methods: Of the 482 women in our registry between 1997 and 2020, we included 430 participants in the analysis (aged 67 [34−88] years). A Cox proportional hazard model was used to determine the variables significantly associated with mortality. On the basis of the peak oxygen uptake estimated using the 1-km walking test, the sample was subdivided into tertiles, and mortality risk was calculated. The discriminatory accuracy of peak oxygen uptake in estimating survival was assessed by receiver operating characteristic curves. All results were adjusted for demographic and clinical covariates.

Results: A total of 135 deaths from any cause occurred over a median of 10.4 years (IQR=4.4−16.4), with an average annual mortality of 4.2%. Estimated peak oxygen uptake was a stronger predictor of all-cause mortality than demographic and clinical variables (c-statistic-0.767; 95% CI=0.72, 0.81; $p<0.0001$). The survival rate decreased from the highest tertile of fitness to the lowest. Compared with the lowest group, hazard ratios (95% CIs) for the second and third tertiles were 0.55 (0.37, 0.83) and 0.29 (0.16, 0.51), respectively (p for trend <0.0001).

Conclusions: Higher peak oxygen uptake levels were associated with a lower risk of all-cause mortality. The indirect estimation of peak oxygen uptake using the 1-km walking test is feasible and can be applied for risk stratification among female patients undergoing secondary prevention programs.

INTRODUCTION

According to the most recent annual mortality statistics, cardiovascular disease (CVD) is the leading cause of mortality in women, accounting for 420,812 deaths in the U.S. in 2019.[1] Despite major advances in the diagnosis and treatment of CVD in females,[2] women are still labeled as a special population in many guidelines related to CVD.[3] Today, the fact that conventional CVD risk factors impact women differently from the impact on men is well known.[2,4,5] In addition, there are female-specific and female-predominant risk modifiers that are considered in CVD risk assessment, such as pregnancy-related issues, menopause, or the presence of polycystic ovarian syndrome.[6] Moreover, women remain underrepresented in

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diagnostic and prognostic studies, and sex-based inequalities persist. For example, women are less likely to receive guideline-recommended diagnostic testing and therapies,[3] including participation in cardiac rehabilitation/secondary prevention (CR/SP) programs.[7,8]

Physical activity (PA) and cardiorespiratory fitness (CRF) are considered major markers of cardiovascular risk and core components of CR/SP programs.[9–11] Benefits of regular PA in the secondary prevention of CVD are well recognized both for men and women,[12] and CRF is strongly inversely associated with mortality risk and the incidence of many chronic diseases.[13,14] Despite the plethora of evidence related to the independent and powerful influence of PA and CRF on human health and despite the efforts of many health organizations to increase awareness of this evidence, physical inactivity and low cardiorespiratory fitness remain overlooked risk factors.[15] Directly measured peak oxygen consumption (VO_{2peak}) determined during maximal incremental cardiopulmonary exercise testing is the gold-standard objective measure of CRF.[16] The measurement of VO_{2peak} is used for evaluating disease severity, predicting prognosis among patients with CVD, and assessing the effectiveness of training for patients involved in CR/SP programs.[17] However, because of physical, financial, and time limitations, direct CRF determination is often not routinely assessed in clinical settings. Submaximal exercise testing can be a viable alternative to cardiopulmonary exercise testing, although less is known about the association between cardiorespiratory fitness assessed by submaximal exercise testing and clinical outcomes in patients with CVD. It has been shown that a moderate and self-paced 1,000-m (1-km treadmill walking test [1k-TWT]) treadmill or outdoor walking test is useful for estimating cardiorespiratory fitness.[18,19] The purpose of this study was to further analyze this relationship among 430 female patients enrolled in a secondary prevention program, quantify all-cause mortality, and investigate how cardiorespiratory fitness differences might explain variation in survival.

METHODS

Study Population

Data were extracted from the ITER (InTegrating exERcise into lifestyle of cardiac outpatients) study. ITER is a patient registry observational study coordinated by the Center of Sport and Exercise Science, University of Ferrara (Ferrara, Italy). The purpose of this registry is to evaluate the efficacy of an exercise-based secondary prevention program among male and female outpatients with stable CVD. The starting sample was composed of 482 women referred by cardiologists or general practitioners to the center between 1997 and 2020. *CVD history* was defined as follows: acute myocardial infarction (AMI), percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or heart valve repair or replacement. Specific diagnoses were identified according to the International Classification of Diseases, Ninth Revision, version 9, coding system. During each follow-up visit, patients received a clinical evaluation including medical history, fasting blood chemical analysis, and major cardiovascular risk factor control. BMI and blood pressure (BP) were measured at each visit. *Hypertension* was defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg.[20] The study was approved by the University of Ferrara Ethics Committee (Number 22-13). Written informed consent was obtained from all participants at the time of enrollment.

Measures

During each center-based session, all patients performed a submaximal, moderate, and perceptually-regulated 1k-TWT for the estimation of cardiorespiratory fitness.[18] Patients started the test at a walking speed (WS) of 2.0 km/h, with a subsequent increase of 0.3 km/h every 30 seconds up to a WS corresponding to a perceived exertion of 11–13 on the Borg 6–20 Rating of Perceived Exertion scale. During the entire duration of the test, participants were encouraged to maintain this intensity for up to 1,000-m if WS was ≥3.0 km/h. The Rating of Perceived Exertion was assessed approximately every 2 minutes, modifying WS to maintain the selected moderate perceived intensity. Heart rate was monitored continuously using a Polar RS 100 heart rate monitor (Polar Electro, Kempele, Finland). VO_{2peak} was estimated using a specific equation considering the distance, age, height, weight, heart rate, and β-blocker use[21] and specifically adapted for women.[22] Patients unable to complete the test at a WS ≥3.0 km/h performed the test over 500 m or 200 m, and the time to walk was multiplied for 2 or 4, respectively.[23–25] Participants were followed for all-cause mortality. Information on deaths was provided by the regional Health Service Registry of the Emilia-Romagna region or by contacting the subject's physician or relatives to determine vital status. Time from baseline to death was calculated in months.

Statistical Analysis

Patients were subdivided into tertiles on the basis of estimated VO_{2peak} (mL/kg/min). Normal distribution was verified through a Kolmogorov–Smirnov test. All-cause mortality was the endpoint for survival analysis. For each patient, the follow-up ended on the date of death or the end of follow-up (December 31, 2020). Differences in survival across the tertiles were evaluated using Kaplan–Meier curves. Cox proportional hazard models were performed, and all results are reported as hazard ratios (HRs) and 95% CIs. The lowest tertile was considered the reference group. Main analyses were adjusted for age, BMI, hemoglobin, triglycerides, and creatinine as continuous variables, and risk factors (hypertension, diabetes), medications (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, calcium antagonists, and diuretics), medical history (AMI, coronary artery bypass graft, heart valve replacement) were considered categorical variables. The proportional hazards assumption was verified by tests on the basis of Schoenfeld residuals. To reduce the potential influence of reverse causality, we performed a sensitivity analysis, excluding all participants who died in the first three years. The nonlinear association between cardiorespiratory fitness and mortality was investigated using penalized cubic splines fitted in Cox proportional hazard models. Penalized spline is a variation of basis spline that permits better estimation accuracy in nonlinear data than the commonly used restricted cubic spline.[26] Receiver operating characteristic curves were evaluated after fitting a logistic regression model, including mortality as the dependent variable and adjusting for confounders as independent variables. The level of statistical significance was set at $p<0.05$. Statistical analyses were performed using MedCalc Statistical Software, Version 20.110 (MedCalc Software Ltd, Ostend, Belgium), and Statistica for Windows, Version 13.3 (Stat Soft, Tulsa, OK).

RESULTS

Of the 482 participants, 430 women were included in this study. Fifty-two patients (11%) were excluded for the

Table 1. Baseline Characteristics of the 430 Patients Examined by Tertile of Estimated VO_{2peak}

Variable	All subjects (*n*=430)	I tertile (*n*=144)	II tertile (*n*=146)	III tertile (*n*=140)
Estimated VO_{2peak} (ml/kg/min)				
Mean (SD)	19.0 (5.7)	12.8 (2.8)	19.2 (1.5)	25.3 (3.3)
Range (min/max)	3.9−37.7	3.9−16.7	16.8−21.6	21.7−37.7
Demographics				
Age (year)	67 (10)	74 (7)	68 (8)	59 (9)
BMI (kg/m^2)	26.6 (4.4)	28.6 (5.0)	26.8 (3.9)	24.4 (3.1)
LV ejection fraction (%)	58 (9)	57 (8)	58 (9)	58 (11)
Marital status (married, %)	67.1	60.4	69.9	71.4
Risk factors				
Family history (%)	42.9	36.8	47.9	44.3
Hypertension (%)	65.7	75.7	67.1	54.3
Diabetes (%)	15.5	18.8	21.9	5.7
Current smoking (%)	14.8	13.9	14.4	16.4
Hemoglobin (mg/dL)	12.8 (1.4)	12.6 (1.4)	12.8 (1.5)	13.1 (1.2)
Total cholesterol (%)	201.2 (42.6)	202.7 (36.5)	203.6 (50.0)	197.3 (39.8)
HDL cholesterol (mg/dL)	58.4 (16.4)	60.9 (19.4)	55.6 (14.0)	59.0 (15.4)
Serum triglycerides (mg/dL)	122.3 (43.7)	126.3 (47.6)	126.1 (44.6)	114.3 (37.2)
Serum creatinine (mg/dL)	0.94 (0.31)	1.00 (0.31)	0.94 (0.38)	0.88 (0.21)
Medical history				
Myocardial infarction (%)	35.3	25.0	34.9	46.4
PTCA (%)	22.7	18.1	23.3	27.1
CABG (%)	32.5	38.2	36.3	22.9
Valvular replacement (%)	31.8	43.8	29.5	22.1
Other (%)	13.5	10.4	10.3	20.0
Medications				
ACE inhibitor or ARB (%)	53.4	61.8	56.2	42.1
Aspirin (%)	62.4	63.9	57.5	66.4
β-blocker (%)	64.7	44.4	80.8	69.3
Calcium antagonist (%)	17.4	23.6	17.8	10.7
Statin (%)	50.6	45.8	47.9	58.6
Diuretic (%)	31.6	50.0	29.5	15.0

Note: Values are presented as mean (SD) or percentage.
ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LV, left ventricular; PTCA, percutaneous transluminal coronary angioplasty; VO_{2peak}, peak oxygen consumption.

following reasons: (1) inability to complete the test, (2) heart failure classified as Class II or higher according to the New York Heart Association,[27] (3) other physical or psychological conditions that interfered with walking ability, or (4) missing data for measures or covariates considered in the analysis. The 1k-TWT was performed by all the patients without any major complication. The average VO_{2peak} estimated by the test was 19.0 ± 5.7 ml/kg/min. The median follow-up period was 10.4 years (IQR=4.4–16.4) during which a total of 135 subjects died of any cause, with an average annual mortality of 4.2%. Demographic and clinical characteristics of the patients stratified by fitness tertiles are given in Table 1. Individuals in the higher group were relatively younger than those in other quartiles, with a lower BMI and lower presence of risk factors. In terms of medical history, they presented a higher percentage of AMI diagnoses as well as a higher percentage of percutaneous transluminal coronary angioplasty. Finally, younger individuals had a lower overall percentage of medication use. Survival, represented by Kaplan–Meier curves, is reported in Figure 1. Survival was progressively lower as the estimated VO_{2peak} decreased. The percentage of survival was evaluated for each tertile at 10 and 20 years. In the lowest tertile, survival rates were 63.7% and 24.2%; in the middle tertile, survival rates were 85.9% and 42.4%, whereas in the highest tertile, survival rates were 91.8% and 67.8% for 10 and 20 years, respectively. Relative mortality risk across tertiles adjusted for confounders is described in Appendix Table 1 (available online). HRs of the second and third tertile were significantly lower than that of the referent group (HR=0.55 [95% CI=0.37, 0.83; p=0.004]; HR=0.29 [95% CI=0.16, 0.51; p<0.001], respectively). Thus, there was a significant trend for reduction in risk because VO_{2peak} was higher (p for trend<0.0001). Furthermore, considering the exposure as a continuous variable, each 1-mL/kg/min increment in average VO_{2peak} was associated with a 9% reduction in all-cause mortality (HR=0.91; 95% CI=0.87, 0.94). Sensitivity analysis, conducted by excluding the 34 participants who died in the first 3 years, showed similar results to those of the main analysis (Appendix Table 2, available online). The relationship between fitness and all-cause mortality is represented in Figure 2. It shows a linear inverse association for all-cause mortality. There is an important decrease in risk up to 25 ml/kg/min. Beyond this point, the association reached a plateau. Finally, the area under the receiver

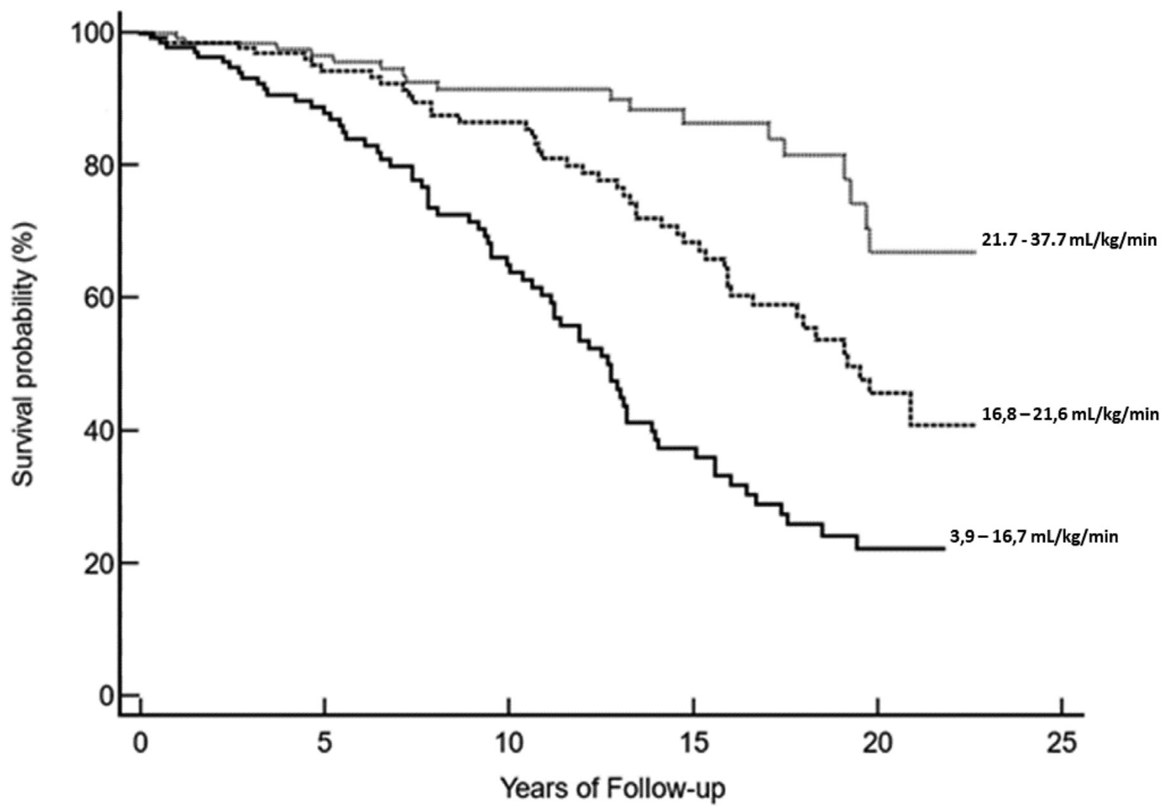
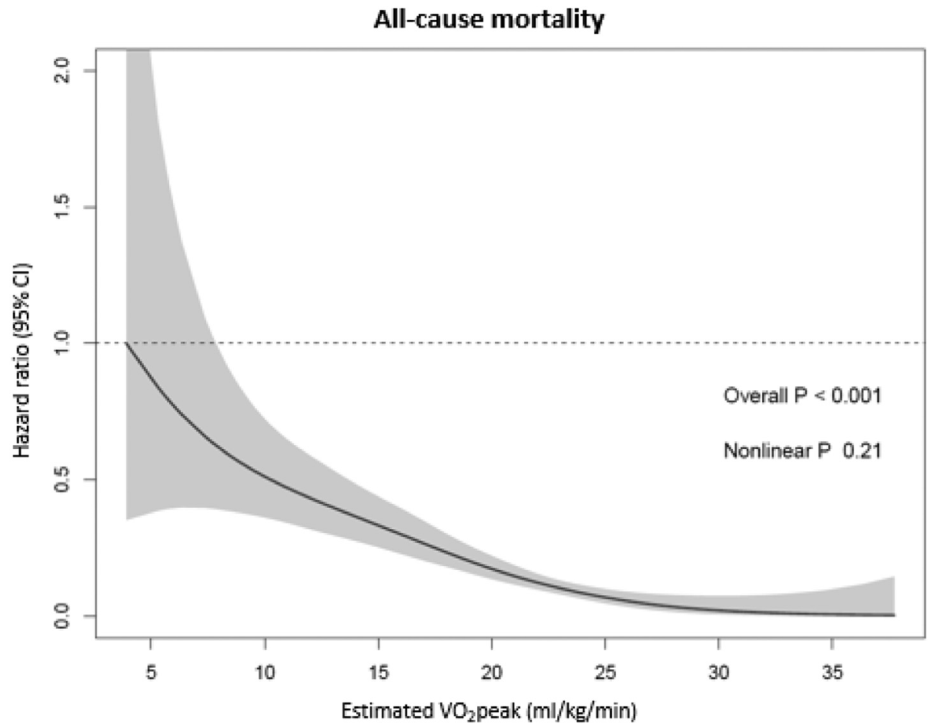


Figure 1. Survival curves stratified according to estimated VO_{2peak} by 1k-TWT.
1k-TWT, 1-km treadmill walking test; VO_{2peak}, peak oxygen consumption.



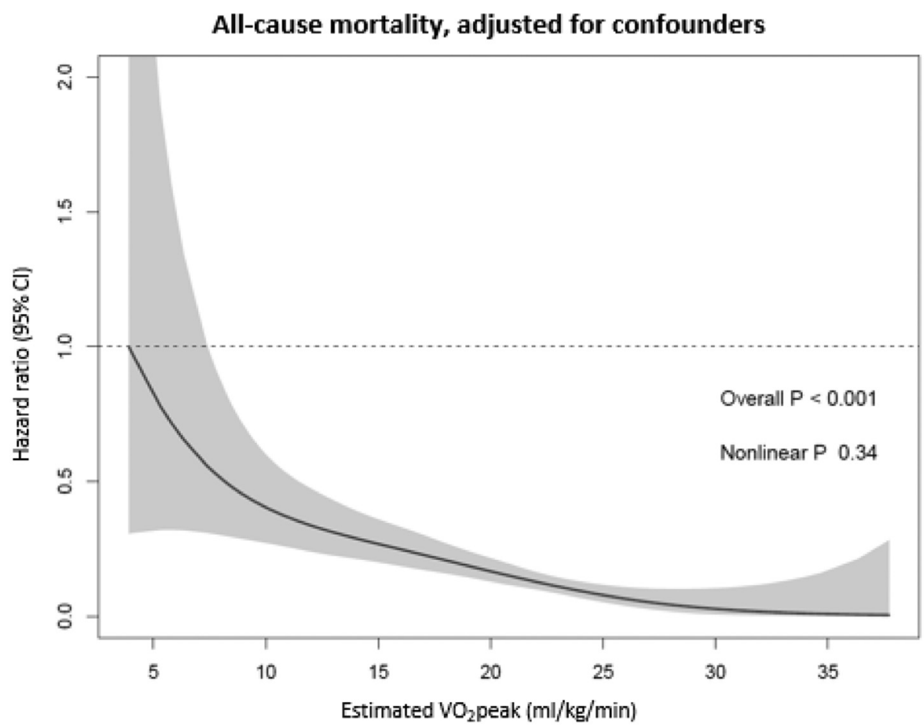


Figure 2. Linear association between estimated VO_{2peak} and all-cause mortality HR.
The model has been adjusted for age, BMI, hemoglobin, triglycerides, creatinine, hypertension, diabetes, ACE inhibitor or ARB, calcium antagonists, diuretics, acute myocardial infarction, coronary artery bypass graft, and valvular replacement. Overall P indicates a linear trend, whereas nonlinear P indicates deviation from linearity.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HR, hazard ratio; VO_{2peak}, peak oxygen consumption.

operating characteristic curve for VO_{2peak} in predicting all-cause mortality, adjusted for confounders, was 0.767 (95% CI=0.72, 0.81; $p<0.0001$) (Figure 3).

DISCUSSION

The main outcome of this study was the inverse association observed between all-cause mortality and estimated VO_{2peak} estimated by the 1k-TWT in a cohort of 430 women with stable CVD. The relation between survival and cardiorespiratory fitness illustrated by the Kaplan−Meier curves revealed a significant reduction in risk of all-cause death between the tertiles of VO_{2peak}. Participants in the highest fitness group, after adjusting for confounders, showed a 71% overall reduction in mortality risk compared with those in the lowest group, whereas an improvement in average VO_{2peak} of 1 mL/kg/min was associated with a reduction in all-cause mortality of 9%. Thus, the current findings are consistent with previous literature and provide further evidence regarding the protective effects of CRF. Among 3,141 participants in the Cooper Center Longitudinal Study, Shuval et al. described a similar analysis over 28 years of follow-up. They reported reduced mortality risks of 20% and 24% for intermediate and high fitness, respectively, versus those of low fitness groups.[28] Among 74,836 UK Biobank participants, fitness was inversely related to all-cause mortality; each 1 MET higher fitness was associated with a 4% lower risk of mortality (HR=0.96; 95% CI=0.95, 0.98; $p<0.0001$).[29] In terms of the utility of the 1k-TWT, its ability to predict survival has been previously shown in male patients with stable CVD[30,31] and is consistent with other scores, such as the Framingham risk score (c-statistic=0.74−0.77).[32] This study extends these findings by showing the value of the 1k-TWT protocol among women. Recent evidence has in fact underscored the importance of considering sex in clinical decision making, given the important differences between men and women related to diagnosis, therapy, exercise testing, and prescription.[33,34] Furthermore, the 1k-TWT is practical and simple to perform. In addition, because the test is carried out at a moderate effort, it is safer and more agreeable to patients than other common

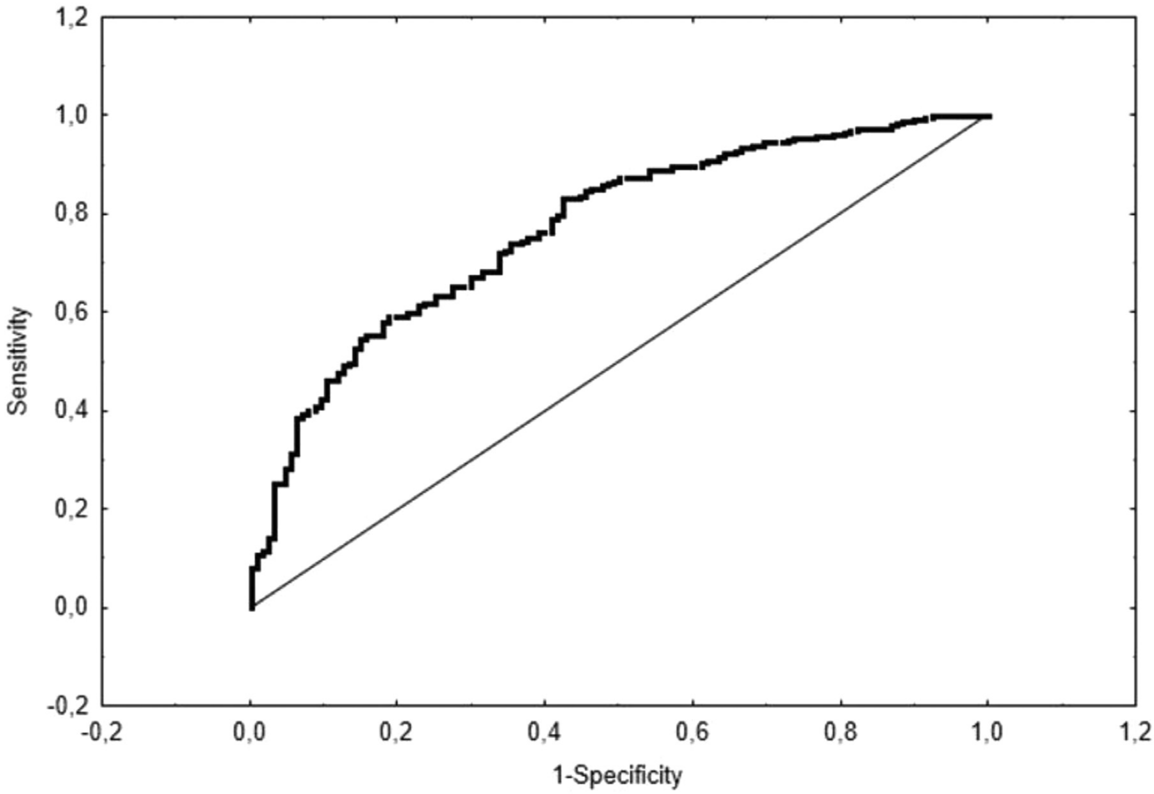


Figure 3. Receiver operating characteristics curves for estimating the risk of death from any cause by estimated VO_2peak, adjusted for confounders.

The model has been adjusted for age, BMI, hemoglobin, triglycerides, creatinine, hypertension, diabetes, ACE inhibitor or ARB, calcium antagonists, diuretics, acute myocardial infarction, coronary artery bypass graft, and valvular replacement.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; VO_{2peak}, peak oxygen consumption.

walking tests (that are frequently performed at a near-maximum exercise intensity) and can be applied to most outpatients. Therefore, these results extend previous evidence regarding the application of the 1k-TWT in an epidemiologic context as well as in CR/SP programs and support the concept that healthcare professionals should encourage patients to improve their fitness. Finally, the broad inclusion criteria used in this study are likely to reflect real-world clinical practice.

Limitations

This study has several limitations. First, the results were obtained from volunteers with an interest in participating in an exercise-based secondary prevention program. Therefore, external validation of our findings is not assured. Second, sex-specific risk factors for CVD such as hormone replacement therapy, early menarche, premature menopause, hypertensive disorders of pregnancy, or gestational diabetes were not examined. Third, other known risk factors such as alcohol consumption and previous smoking levels were not available nor were socioeconomic data; therefore, unmeasured confounders could have influenced our results. Fourth, the prognostic value of CRF may have been modified by behavioral or clinical intervention strategies occurring during the follow-up period, and we were not able to account for these factors.

CONCLUSIONS

Study results extend the evidence that VO_2peak, estimated from a moderate and perceptually-regulated treadmill walk test, predicts all-cause mortality among female patients with stable CVD. These findings have important implications for clinical practice because the 1k-TWT is simple to perform and provides potentially useful information on risk stratification for women with CVD. The test also has utility for assessing the efficacy of exercise prescription in addition to providing a basis for counseling on lifestyle changes. Further studies are needed to assess its serial value in CR/SP programs across the spectrum of patients participating in such programs.

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The study was an investigator-driven clinical trial conducted by the University of Ferrara (Ferrara, Italy). The datasets used and/or analyzed during this study will be available from the corresponding author upon reasonable request. The study protocol was approved by the institutional ethics committee (22−13) and was conducted in accordance with the principles of the Declaration of Helsinki. Patients were informed that their participation was voluntary, and all of them gave written informed consent.

All the authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. No financial disclosures were reported by the authors of this paper.

CREDIT AUTHOR STATEMENT

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2023.02.025.

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