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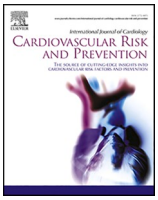

Cardiorespiratory fitness estimations and their ability to predict all-cause mortality in patients with cardiovascular disease

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ABSTRACT

Background: In cardiac rehabilitation programs, cardiorespiratory fitness is commonly estimated (eCRF) from the maximum workload achieved on a graded exercise test. This study compared four well-established eCRF equations in their ability to predict mortality in patients with cardiovascular disease (CVD).
Methods: A total of 7269 individuals with CVD were studied (81% male; age 59.4 ± 10.3yr). eCRF was calculated using equations from the American College of Sports Medicine, Bruce et al., the Fitness Registry and the Importance of Exercise International Database, and McConnell and Clark. The eCRF from each equation was compared with a RMANOVA. Cox proportional hazard models assessed the relationship between the eCRF equations and mortality risk. The predictive ability of the models was compared using the concordance index.
Results: There were 284 deaths (85% male) over a follow-up period of 5.8 ± 2.8yr. Although differences in eCRF were observed between each equation ($P < 0.05$), the eCRF from each of the four equations was predictive of mortality ($P < 0.05$). The concordance index values for each of the models were the same (0.77) indicating similar predictive performance.
Conclusions: The four well-established eCRF equations did not differ in their ability to predict mortality in patients with CVD, indicating any could be used for this purpose. However, the differences in eCRF from each of the equations suggest potential differences in their ability to guide clinical care and should be the focus of future research.

1. Introduction

Cardiorespiratory fitness (CRF) is a singular measure of whole-body physiological function that is associated with health and quality of life. In patients with cardiovascular disease (CVD), lower CRF is associated with greater risk for mortality, future CVD events, and higher healthcare costs [1–5]. Accordingly, recommendations suggest CRF should be assessed to stratify patient risk and guide clinical care [6–8]. The most accurate determination of CRF involves exercise testing with direct measurement of ventilatory expired gas (i.e., cardiopulmonary exercise testing) [4]. In cardiac rehabilitation (CR) programs, though, if CRF is assessed, it is commonly indirectly estimated (eCRF) from the peak workload or total test time of a graded exercise stress test.

Previous research has demonstrated that eCRF is predictive of mortality risk [9–11]. However, the equations used to determine eCRF differ in their accuracy compared to direct assessment of CRF [12]. These sources of error are due to a variety of factors that can subsequently influence risk classification and treatment plans. Equations from the American College of Sports Medicine (ACSM) [13] assume individuals are exercising at a steady state, yet this assumption is not met at the end of a maximal exercise stress test, leading to overestimations of CRF and inaccurate classifications of risk [12]. Other eCRF equations utilizing

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total test duration, such as the Bruce equation [14], can have errors as they do not account for the potential plateau in oxygen uptake at maximal intensity.

While differences exist in the accuracy of eCRF equations, whether these differences also lead to different predictions of health outcomes (e.g., mortality) still needs to be examined. This is particularly important in patients with CVD since estimating CRF from an exercise stress test is common in CR. Thus, the aim of this study was to compare four well-established CRF equations in their ability to predict all-cause mortality in patients with CVD participating in CR. We hypothesized that eCRF would be predictive of all-cause mortality, yet significant differences would be observed in the predictive ability of the different eCRF equations.

2. Methods

2.1. Study design and cohort

This study was a secondary analysis of data from a retrospective cohort. The cohort consisted of adults aged 20–90yr with CVD who were referred to CR through TotalCardiology™ Rehabilitation in Calgary, Alberta between January 1, 2009 and December 31, 2019. Additional inclusion criteria included performing a symptom-limited Bruce treadmill stress test protocol upon intake to CR, having an exercise stress test duration >1min, data available in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database, and ≥1yr of follow-up from intake. The protocol for this study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Conjoint Health Research Ethics Board of the University of Calgary.

2.2. Assessment of eCRF

Each patient performed a symptom-limited Bruce treadmill protocol. The eCRF for each patient was then calculated using equations from the ACSM [13], Bruce et al. [14], the Fitness Registry and the Importance of Exercise International Database (FRIEND) [15], and McConnell and Clark [16]. Variables within the eCRF equations included the following: sex, peak treadmill speed and grade, and/or test duration (Table 1). The two equations from the ACSM were designed to be used during walking (<3.7mph [6.0 km/hr]) or running (>5.0mph [8.0 km/hr]). However, the Bruce protocol involves stages at 4.2mph (6.8 km/hr) and 5.0mph (8.0 km/hr). Since the walk/run transition was not known for each patient, and with the goal of maximizing the study sample size, the walking equation was used when test duration was ≤11.5min (30sec left of the stage at 4.2mph [6.8 km/hr]) and the running equation was used for a test duration >11.5min. Lastly, each equation estimated relative CRF (mL/kg/min), which was then converted to metabolic equivalents (METs) by dividing by 3.5 [13].

Table 1
Summary of the equations used for estimating CRF[a].

Authors	Equation
ACSM Walk Equation [13]	0.1(speed; m/min) + 1.8(speed; m/min)(fractional grade) + 3.5
ACSM Run Equation [13]	0.2(speed; m/min) + 0.9(speed; m/min)(fractional grade) + 3.5
Bruce et al. 1973 [14]	6.70–2.82(sex; M = 1, F = 2) + 0.056(test duration; seconds)
FRIEND Equation [15]	(speed; m/min)(0.17 + 0.79(fractional grade)) + 3.5
McConnell and Clark 1987 [16]	2.587(test duration; minutes) + 6.004

[a] The equations determine relative CRF (mL/kg/min) but were converted to metabolic equivalents (METs) for the present study.

2.3. Assessment of clinical risk factors

Clinical risk factors were obtained from medical records at the time of intake to CR [17]. Patients were categorized as a current smoker if they used cigarettes within the past month and former smoker if they quit smoking greater than one month prior to admission. Diabetes status was determined based on a fasting plasma glucose ≥7.0 mmol/L [18], diagnosis by a physician, or taking medication to treat diabetes. Patients were classified as having hypertension if they had a resting blood pressure ≥140/90 mmHg [19], were diagnosed by a physician, or were taking a medication to treat hypertension. Dyslipidemia was classified based on fasting total cholesterol/HDL cholesterol ratio ≥4, triglycerides ≥2 mmol/L, LDL cholesterol ≥2.5 mmol/L [20], physician diagnosis, or taking a medication to treat dyslipidemia.

2.4. Outcomes and follow-up

All participants were followed from the date of their initial exercise test until the date of death or through January 1, 2021. All-cause mortality status was collected from Alberta Vital Statistics.

2.5. Statistical analysis

Analyses were performed in Python version 3.9.12. Differences between mortality-based subgroups (i.e., survivor vs. deceased) were assessed with independent samples *t*-tests and Chi-square tests. A RMANOVA with Tukey post-hoc was used to compare eCRF from each equation. Cox proportional hazard models were performed to assess the relationship between the eCRF equations and mortality risk. Models were adjusted for clinical risk factors (sex, age, body mass index, current smoking status, former smoking status, hypertension, dyslipidemia, diabetes, kidney disease, dialysis, liver disease, peripheral artery disease, cerebrovascular disease, heart failure, presence of malignancy, prior coronary artery bypass grafting, prior myocardial infarction, prior percutaneous coronary intervention, and severity of coronary artery disease [Duke Jeopardy score]). The predictive ability of the models was compared using the concordance index. Statistical significance was set at $P < 0.05$, two-tailed. Data are presented as mean ± SD.

3. Results

Descriptive characteristics of the cohort are provided in Table 2. The cohort consisted of 7269 individuals with CVD (81% male; age 59.4 ± 10.3yr; 66% referred for myocardial infarction) and there were 284 deaths (85% male) over a follow-up period of 5.8 ± 2.8yr. Differences in eCRF were observed between each equation with the ACSM equation resulting in the highest eCRF (9.6 ± 2.7 peak METs) and the McConnell and Clark equation resulting in the lowest eCRF (7.6 ± 1.9 peak METs) ($P < 0.05$). Regardless of the equation used, the eCRF was higher in participants identified as living compared to deceased at the time of follow-up ($P < 0.05$).

The Cox models indicated that the eCRF from each of the four equations was predictive of mortality ($P < 0.05$); each one-point increase in peak METs was associated with a 16–24% reduction in risk of death (Table 3). The concordance index values for the models were the same (0.77) suggesting similar predictive performance between each of the models.

4. Discussion

The present study compared four well-established eCRF equations within a cohort of patients with CVD. Significant differences in eCRF were observed between the equations similar to previous research on apparently healthy individuals [12]. As hypothesized, eCRF from each equation was predictive of all-cause mortality in patients with CVD. However, despite the differences in eCRF between the equations and

Table 2
Descriptive characteristics of the survivors and deceased participants within the cohort.

	All n = 7269	Alive n = 6985	Deceased n = 284
Age, yr	59.4 ± 10.3	59.1 ± 10.2	66.8 ± 11.0[a]
BMI, kg/m^2	28.3 ± 4.8	28.3 ± 4.8	27.3 ± 4.8[a]
Current Smoking Status, n (%)	2148 (30)	2051 (29)	97 (34)
Former Smoking Status, n (%)	2358 (32)	2238 (32)	120 (42)[a]
Hypertension, n (%)	2990 (41)	2861 (41)	129 (45)
Dyslipidemia, n (%)	3565 (49)	3415 (49)	150 (53)
Diabetes, n (%)	1327 (18)	1253 (18)	74 (26)[a]
Kidney Disease, n (%)	44 (1)	43 (1)	1 (0)
Dialysis, n (%)	4 (0)	3 (0)	1 (0)
Liver Disease, n (%)	40 (1)	34 (0)	6 (2)[a]
Peripheral Artery Disease, n (%)	51 (1)	40 (1)	11 (4)[a]
Cerebrovascular Disease, n (%)	89 (1)	76 (1)	13 (5)[a]
Heart Failure, n (%)	70 (1)	64 (1)	6 (2)
Presence of Malignancy, n (%)	163 (2)	142 (2)	21 (7)[a]
Prior Coronary Artery Bypass Grafting, n (%)	31 (0)	24 (0)	7 (2)[a]
Prior Myocardial Infarction, n (%)	54 (1)	52 (1)	2 (1)
Prior Percutaneous Coronary Intervention, n (%)	280 (4)	269 (4)	11 (4)
Duke Jeopardy Score	3.4 ± 2.6	3.4 ± 2.6	4.3 ± 3.0[a]
eCRF – ACSM, peak METs [13]	9.6 ± 2.7	9.7 ± 2.7	7.9 ± 2.4[a]
eCRF – Bruce, peak METs [14]	8.7 ± 2.8	8.8 ± 2.8	7.0 ± 2.5[a]
eCRF – FRIEND, peak METs [15]	8.0 ± 2.2	8.1 ± 2.2	6.7 ± 1.8[a]
eCRF – McConnell and Clark, peak METs [16]	7.6 ± 1.9	7.7 ± 1.8	6.4 ± 1.7[a]
Follow-Up Time, yr	5.8 ± 2.8	5.8 ± 2.9	4.6 ± 2.3[a]

Data are presented as mean ± SD or n (%).
Abbreviations: ACSM, American College of Sports Medicine; BMI, body mass index; eCRF, estimated cardiorespiratory fitness; FRIEND, Fitness Registry and the Importance of Exercise National Database; METs, metabolic equivalents.
[a] Significantly different from survivors ($P < 0.05$).

Table 3
Hazard ratios for all-cause mortality according to the different predictions of CRF.

	Hazard Ratio (95% CI)	Concordance Index
eCRF – ACSM [13]	0.84 (0.79–0.88)[a]	0.77
eCRF – Bruce [14]	0.82 (0.78–0.87)[a]	0.77
eCRF – FRIEND [15]	0.79 (0.73–0.85)[a]	0.77
eCRF – McConnell and Clark [16]	0.76 (0.70–0.83)[a]	0.77

Abbreviations: ACSM, American College of Sports Medicine; eCRF, estimated cardiorespiratory fitness; FRIEND, Fitness Registry and the Importance of Exercise National Database.
[a] Significant relationship ($P < 0.05$).

contrary to our hypothesis, each equation had a similar ability to predict mortality, indicating any could be used for this purpose.

As expected, the McConnell and Clark [16] equation resulted in the lowest eCRF since this equation is designed for individuals using handrail support and the ACSM equation [13] resulted in the highest eCRF since this equation assumes an individual is exercising at a steady state. These trends are similar to those observed in a cohort of apparently healthy individuals [12]. Considering an improvement in CRF as low as 1 peak MET significantly reduces mortality [4,6,8,21], the average difference of 2 peak METs between the ACSM and McConnell and Clark equations suggests potential for clinically meaningful impacts depending on which equation is used with a patient. Thus, regardless of the similar ability to predict all-cause mortality, these differences in eCRF equations suggest potential differences in their ability to guide clinical care.

The present study determined eCRF from an exercise stress test, although there are other techniques to estimate CRF. Non-exercise prediction equations are an easy and inexpensive method for estimating CRF because exercise is not required, and the needed information is typically available in electronic medical records. A non-exercise prediction equation has even been developed specifically for individuals with CVD [22]. The eCRF from these non-exercise prediction equations is associated with mortality [21,23–25] but have errors in accuracy [12,26,27], are less predictive of mortality compared to direct assessments of CRF [21], and do not allow for the collection of other metrics assessed during exercise testing that have clinical utility (e.g. exercising electrocardiogram and blood pressure). Nonetheless, exercise testing is not always feasible and future research should compare the predictive ability of the different determinations of CRF in a population of individuals with CVD.

The strengths of the present study include the cohort of males and females with CVD and a diversity of clinical risk factors. There were, however, some limitations that should be noted. The directly-measured CRF of the patients is not known and as a result it is not possible to determine which eCRF equation is most accurate in this cohort. Further, only 4% of the cohort was deceased by the end of a relatively short follow-up period (5.8 ± 2.8yr). A longer follow-up period could help to better distinguish predictive differences between eCRF equations.

In conclusion, eCRF from any of the four studied equations can similarly identify all-cause mortality risk in patients with CVD. These findings support recommendations that eCRF be calculated to improve patient risk stratification when the direct assessment of CRF using cardiopulmonary measures is not feasible [6]. However, the significant differences in eCRF values from each equation suggest potential differences in their ability to guide clinical treatment plans and should be the focus of future prospective research.

Author contribution

James Peterman: Conceptualization, Methodology, Writing – original draft. **Codie Rouleau**: Conceptualization, Methodology, Writing – review & editing. **Ross Arena**: Conceptualization, Methodology, Writing – review & editing. **Sandeep Aggarwal**: Investigation, Writing – review & editing. **Stephen Wilton**: Investigation, Writing – review & editing. **Trina Hauer**: Project administration, Writing – review & editing. **Matthew MacDonald**: Formal analysis, Data curation, Writing – review & editing. **Leonard Kaminsky**: Conceptualization, Methodology, Writing – review & editing.

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References

[1] M. Guazzi, R. Arena, J. Myers, Comparison of the prognostic value of cardiopulmonary exercise testing between male and female patients with heart failure, Int. J. Cardiol. 113 (3) (2006) 395–400.
[2] L. Vanhees, R. Fagard, L. Thijs, J. Staessen, A. Amery, Prognostic significance of peak exercise capacity in patients with coronary artery disease, J. Am. Coll. Cardiol. 23 (2) (1994) 358–363.
[3] J. Myers, R. Doom, R. King, et al., Association between cardiorespiratory fitness and health care costs: the Veterans Exercise Testing Study, Mayo Clin. Proc. 93 (1) (2018) 48–55.
[4] J. Lavie Carl, F. Sanchis-Gomar, C. Ozemek, Fit is it for longevity across populations, J. Am. Coll. Cardiol. 80 (6) (2022) 610–612.

[5] A. Tutor, C.J. Lavie, S. Kachur, H. Dinshaw, R.V. Milani, Impact of cardiorespiratory fitness on outcomes in cardiac rehabilitation, Prog. Cardiovasc. Dis. 70 (2022) 2–7.
[6] R. Ross, S.N. Blair, R. Arena, et al., Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a Scientific Statement from the American Heart Association, Circulation 134 (24) (2016) e653–e699.
[7] M. Guazzi, V. Adams, V. Conraads, et al., EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations, Circulation 126 (18) (2012) 2261–2274.
[8] J.A. Laukkanen, N.M. Isiozor, S.K. Kunutsor, Objectively assessed cardiorespiratory fitness and all-cause mortality risk: an updated meta-analysis of 37 cohort studies involving 2,258,029 participants, Mayo Clin. Proc. 97 (6) (2022) 1054–1073.
[9] P. Kokkinos, J. Myers, C. Faselis, et al., Exercise capacity and mortality in older men, Circulation 122 (8) (2010) 790–797.
[10] C.J. Lavie, R. Arena, L.A. Kaminsky, Making the case to measure and improve cardiorespiratory fitness in routine clinical practice, Mayo Clin. Proc. 97 (6) (2022) 1038–1040.
[11] P. Kokkinos, C. Faselis, I. Samuel, et al., Cardiorespiratory fitness and mortality risk across the spectra of age, race, and sex, J. Am. Coll. Cardiol. 80 (6) (2022) 598–609.
[12] J.E. Peterman, M.P. Harber, M.T. Imboden, et al., Accuracy of exercise-based equations for estimating cardiorespiratory fitness, Med. Sci. Sports Exerc. 53 (1) (2021) 74–82.
[13] G. Liguori, Y. Feito, C. Fountaine, B.A. Roy, ACSM's Guidelines for Exercise Testing and Prescription, eleventh ed., Wolters Kluwer, 2021.
[14] R.A. Bruce, F. Kusumi, D. Hosmer, Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease, Am. Heart J. 85 (4) (1973) 546–562.
[15] P. Kokkinos, L.A. Kaminsky, R. Arena, J. Zhang, J. Myers, New generalized equation for predicting maximal oxygen uptake (from the fitness registry and the importance of exercise national database), Am. J. Cardiol. 120 (4) (2017) 688–692.
[16] T.R. McConnell, B.A. Clark, Prediction of maximal oxygen consumption during handrail-supported treadmill exercise, J Cardiopulm Rehabil 7 (1987) 324–331.
[17] D.A. Southern, C.M. Norris, H. Quan, et al., An administrative data merging solution for dealing with missing data in a clinical registry: adaptation from ICD-9 to ICD-10, BMC Med. Res. Methodol. 8 (2008) 1.
[18] S. Meltzer, L. Leiter, D. Daneman, et al., Clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association, CMAJ (Can. Med. Assoc. J.) 159 (Suppl 8) (1998) S1–S29.
[19] R.D. Feldman, N. Campbell, P. Larochelle, et al., Canadian recommendations for the management of hypertension. Task force for the development of the 1999 Canadian recommendations for the management of hypertension, CMAJ (Can. Med. Assoc. J.) 161 (12) (1999) S1–S17.
[20] J.G. Fodor, J.J. Frohlich, J.J. Genest Jr., P.R. McPherson, Recommendations for the management and treatment of dyslipidemia. Report of the working group on hypercholesterolemia and other dyslipidemias, CMAJ (Can. Med. Assoc. J.) 162 (10) (2000) 1441–1447.
[21] M.T. Imboden, M.P. Harber, M.H. Whaley, W.H. Finch, D.L. Bishop, L.A. Kaminsky, Cardiorespiratory fitness and mortality in healthy men and women, J. Am. Coll. Cardiol. 72 (19) (2018) 2283–2292.
[22] J.E. Peterman, R. Arena, J. Myers, et al. A nonexercise prediction of peak oxygen uptake for patients with cardiovascular disease: data from the Fitness Registry and the Importance of Exercise International Database (FRIEND). J Cardiopulm Rehabil Prev. Online ahead of print. doi: 10.1097/HCR.0000000000000722.
[23] E.G. Artero, A.S. Jackson, X. Sui, et al., Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality, J. Am. Coll. Cardiol. 63 (21) (2014) 2289–2296.
[24] B.M. Nes, L.J. Vatten, J. Nauman, I. Janszky, U. Wisloff, A simple nonexercise model of cardiorespiratory fitness predicts long-term mortality, Med. Sci. Sports Exerc. 46 (6) (2014) 1159–1165.
[25] Y. Wang, S. Chen, J. Zhang, et al., Nonexercise estimated cardiorespiratory fitness and all-cancer mortality: the NHANES III Study, Mayo Clin. Proc. 93 (7) (2018) 848–856.
[26] J.E. Peterman, M.P. Harber, M.T. Imboden, et al., Accuracy of nonexercise prediction equations for assessing longitudinal changes to cardiorespiratory fitness in apparently healthy adults: BALL ST Cohort, J. Am. Heart Assoc. 9 (11) (2020), e015117.
[27] J.E. Peterman, M.H. Whaley, M.P. Harber, et al., Comparison of non-exercise cardiorespiratory fitness prediction equations in apparently healthy adults, Eur J Prev Cardiol 28 (2) (2021) 142–148.