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Research Letter

Comparisons of Percent-predicted Peak Oxygen Uptake Achieved on Cardiopulmonary Exercise Testing: Stratifying Mortality Risk by Wasserman, FRIEND, and Brazilian equations.

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Running head: predicted peak oxygen uptake and mortality risk.

Information about previous presentations

None of the paper's contents have been previously published. A partial analysis of the study will be presented at the ESC Preventive Cardiology Congress 2024.

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Cardiorespiratory fitness (CRF) is an important prognostic marker [1–3], and the direct measurement of peak oxygen uptake (VO2peak) by cardiopulmonary exercise testing (CPET) is considered the gold-standard method[1]. Measured VO2peak is the most studied variable for risk assessment[4]. However, the VO2peak achieved compared to the percentage of age-predicted values (%VO2peak) is commonly employed in daily practice[5], providing a more contextual understanding of individual CRF while considering variations due to age, sex, anthropometry, and nationality[6].

The %VO2peak is calculated using specific equations, one of the oldest and most widely used being the Wasserman algorithm[7]. Previous studies have proposed various prediction equations for %VO2peak, each tailored to specific populations and exercise modalities[8]. Recently, the Fitness Registry and the Importance of Exercise National Database (FRIEND) registry developed a prediction equation for both treadmill and cycle-ergometer[9]. In 2022, Milani et al.[6] conducted a pooled analysis of 26,661 assessments from three regions and generated a Brazilian prediction equation, representing a significant advancement given the diverse and region-specific characteristics of the population.

Regarding prognostic studies on %VO_2peak, Myers et al.[10] compared the Wasserman and FRIEND registry equations in a heart failure database. The FRIEND registry equation demonstrated similar or slightly better performance than the Wasserman equation[11]. In another study involving the indirect estimation of VO_2peak through a 1-km treadmill-walking test, the FRIEND registry equation outperformed the Wasserman equation. Despite the availability of Brazilian reference values[6], no prognostic studies have been conducted.

Hence, we aimed to assess the predictive capability for all-cause mortality in a Brazilian outpatient cohort using %VO_2peak values derived from various prediction equations.

A cohort of individuals (aged 20-80, both sexes) underwent cycle-ergometer CPET at a private center from January 2018 to January 2023, using an individualized ramp protocol. The %VO2peak was calculated using three prediction equations: Wasserman[7], FRIEND registry[10], and Brazilian[6].

All-cause mortality was determined by cross-referencing national registry numbers with official Brazilian records. Survival status was verified between April 1st and 30th, 2023. The study was approved by the Human Research Ethics Committee (CAAE: 35706720.4.0000.8093), and all patients provided informed consent.

Due to non-normal distribution, data were described using median and interquartile range (IQR). ROC curve analysis assessed the diagnostic performance of the equations. The Hanley-McNeil method calculated the standard error of AUC, and the DeLong approach compared differences in AUC—optimal %VO2peak thresholds balanced sensitivity and specificity for predicting mortality. Multivariate logistic regression models assessed the independent predictive ability of each equation for mortality, incorporating %VO2peak, age, and sex. A p-value <0.05 was considered statistically significant. Data analysis was conducted using SPSS version 29.0 and MedCalc version 22.013.

2,684 participants were included (62.4% males; mean age: 52.9 ± 14.5 years). The median follow-up was 451 days (IQR: 152, 575), and 31 deaths were recorded (1.2%). Non-survivors were significantly older than survivors [72 (IQR: 62, 76) *versus* 52 (IQR: 42, 65) years; $p < 0.001$] and exhibited markedly reduced values in both absolute [1.20 (0.91, 1.52) *versus* 1.98 (1.40, 2.72) L/min; $p < 0.001$] and relative VO_2peak [15.7 (12.2,

17.3) *versus* 25.6 (18.7, 34.3) ml/kg/min; $p < 0.001$]. The %VO_2peak was consistently lower in non-survivors; however, heterogeneous values were observed (Table 1), consistent with the international variations described for CRF[6].

In terms of prognosis, all three %VO_2peak equations were significant predictors of all-cause mortality (Figure 1A), with AUC values ranging from 0.753 (Brazilian) to 0.812 (Wasserman). The difference in AUC between the Wasserman and Brazilian equations was statistically significant ($p = 0.018$). The FRIEND equation presented an intermediate AUC value (0.796), and it was not statistically different from either the Wasserman ($p = 0.611$) or Brazilian ($p = 0.329$) equations. The optimal cut-off points for %VO_2peak were as follows: ≤ 84% for Wasserman (Sensitivity: 80.7%; Specificity: 69.4%), ≤ 82% for the FRIEND registry (Sensitivity: 77.4%; Specificity: 57.3%), and ≤ 76% for the Brazilian equation (Sensitivity: 80.7%; Specificity: 57.8%). The lower cut-off values for the Brazilian equation were most likely due to the ergometer specificity, as the equation was developed for a treadmill. This resulted in an overestimation of predicted VO_2peak in our sample, as higher values are expected on a treadmill compared to a cycle-ergometer[9].

The three equations showed similar results in multivariate logistic regression models, with %VO2peak independently associated with mortality after controlling for age and sex, underscoring its significance in evaluating mortality risk.

This study initially explores the Brazilian equation's prognostic properties. Developed for treadmill assessments, it performed comparably to the FRIEND equation and slightly inferior to the Wasserman equation. This highlights its potential clinical applicability. The AUC values for Wasserman and FRIEND were not statistically different, with similar cut-off values (84% vs. 82%), contrasting with previous studies showing slight superiority for the FRIEND equation[10,11].

This study is limited by the low number of events. We did not include a Cox proportional hazards analysis due to potential overfitting and multicollinearity. Physical activity data were not available, and comorbidities, although listed in Table 1, were not included in the model, potentially affecting the prognostic value of VO2. Future studies with more events will address these issues.

In conclusion, our study provides insights into the prognostic utility of various VO2peak prediction equations. Each equation, adjusted for age and sex, is independently associated with all-cause mortality, underscoring %VO2peak's significance as a clinical predictor. The results highlight the challenges in establishing universal VO2peak reference values due to international heterogeneity, emphasizing the need for tailored approaches to assess cardiorespiratory fitness. Different %VO2peak cut-offs may be necessary to evaluate mortality risk based on the reference equation.

Author's contributions

FB and MM contributed to the conception and design of the work. JM, MF, FD, JP, AM, GM, and BF contributed to data acquisition, analysis, or interpretation. FB and MM drafted the manuscript. JGPOM, DH, GCJ, JM, and RMR critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Data availability statement

The data supporting this study's findings are available from the corresponding author, [FB], upon reasonable request.

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1 **Table 1: Clinical and Physiological Characteristics of Study Participants by Vital Status**

Characteristics	Survivals (n = 2,653)	Non-survivals (n = 31)	p-value
Age, years	52 (42, 65)	72 (62, 76)	< 0.001
Male sex, n (%)	1,652 (62.3%)	24 (77.4%)	0.083
Weight, kg	77.0 (66.7, 87.7)	71.5 (63.4, 87.3)	0.490
Height, cm	172 (165, 179)	169 (163, 176)	0.302
BMI, kg/m^2	25.9 (23.4, 28.9)	25.8 (23.0, 30.5)	0.754
Comorbidities			
Hypertension, n (%)	861 (32.5%)	13 (41.9%)	0.263
Diabetes mellitus, n (%)	245 (9.2%)	8 (25.8%)	0.002
Dyslipidemia, n (%)	906 (34.2%)	7 (22.6%)	0.176
Obesity, n (%)	491 (18.6%)	8 (25.8%)	0.306
Smoker (actual or former), n (%)	582 (21.9%)	16 (51.6%)	< 0.001
Coronary artery disease, n (%)	329 (12.4%)	1 (3.2%)	0.122
Myocardial infarction, n (%)	105 (4%)	1 (3.2%)	0.835
Percutaneous angioplasty, n (%)	219 (8.7%)	1 (3.2%)	0.317
Coronary by-pass surgery, n (%)	57 (2.1%)	0 (0%)	0.409
Heart failure, n (%)	114 (4.3%)	3 (9.7%)	0.145
Stroke, n (%)	21 (0.8%)	1 (3.2%)	0.135
COPD, n (%)	136 (5.1%)	6 (19.4%)	< 0.001
Renal disease, n (%)	24 (0.9%)	1 (3.4%)	0.159
Cancer, n (%)	233 (8.8%)	15 (48.4%)	< 0.001
Cardiorespiratory fitness			

VO_2peak, L/min	1.98 (1.40, 2.72)	1.20 (0.91, 1.52)	< 0.001
VO_2peak, mL/kg/min	25.6 (18.7, 34.3)	15.7 (12.2, 17.3)	< 0.001
%VO_2peak			
Wasserman Equation[7], %	97 (80, 115)	67 (56, 84)	< 0.001
FRIEND equation[9], %	87 (72, 103)	63 (46, 77)	< 0.001
Brazilian Equation[6], %	81 (65, 100)	56 (44, 75)	< 0.001

Data expressed as median and interquartile range or absolute and relative frequency

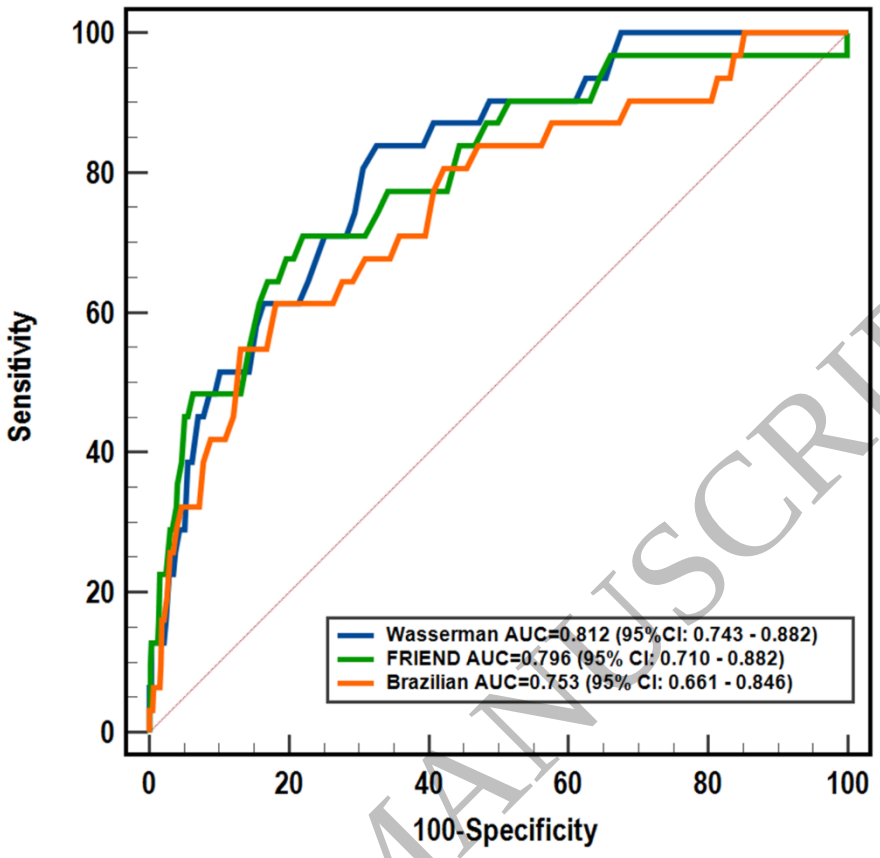
BMI, body mass index; COPD, chronic obstructive pulmonary disease; VO_2peak, peak oxygen uptake; %VO_2peak, percent-predicted peak oxygen uptake achieved.

Figure 1. All-cause mortality prediction using Wasserman, FRIEND registry, and Brazilian peak oxygen uptake predictive equations. A) Comparative analysis of ROC curves. B) Multivariable logistic regression analysis.

Statistical comparisons of the AUC: Wasserman vs. FRIEND: p = 0.611; Wasserman vs. Brazilian: p = 0.018; FRIEND vs. Brazilian: p = 0.329

AUC, area under the curve; ROC, receiver operating characteristic.

A



B

Multivariate Logistic Regression Analysis				
Prediction Equation	**Variable**	**β**	**p value**	**OR (95% CI)**
Wasserman[7]	**Sex**	**-0.721**	**0.102**	**0.486 (0.205 to 1.153)**
	Age	**0.067**	**0.000**	**1.069 (1.034 to 1.106)**
	%VO₂peak	**-0.048**	**0.000**	**0.953 (0.935 to 0.971)**
FRIEND registry[8]	**Sex**	**-0.452**	**0.315**	**0.636 (0.263 to 1.537)**
	Age	**0.073**	**0.000**	**1.075 (1.039 to 1.112)**
	%VO₂peak	**-0.033**	**0.001**	**0.967 (0.949 to 0.986)**
Brazilian[6]	**Sex**	**-0.689**	**0.117**	**0.502 (0.212 to 1.188)**
	Age	**0.085**	**0.000**	**1.088 (1.050 to 1.128)**
	%VO₂peak	**-0.042**	**0.000**	**0.959 (0.939 to 0.979)**

Figure 1
126x200 mm (x DPI)