9-9-2021

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Recommended Citation

Chu DJ, Ahmed AM, Qureshi WT, Brawner CA, Keteyian SJ, Nasir K, Blumenthal RS, Blaha MJ, Ehrman JK, Cainzos-Achirica M, Patel KV, Rifai MA, and Al-Mallah MH. Prognostic Value of Cardiorespiratory Fitness in Patients with Chronic Kidney Disease: The FIT (Henry Ford Exercise Testing) Project. Am J Med 2021.

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CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Prognostic Value of Cardiorespiratory Fitness in Patients with Chronic Kidney Disease: The FIT (Henry Ford Exercise Testing) Project

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ABSTRACT

PURPOSE: We conducted this study to investigate the association of cardiorespiratory fitness and all-cause mortality among patients with chronic kidney disease.

METHODS: We studied a retrospective cohort of patients from the Henry Ford Health System who underwent clinically indicated exercise stress testing with baseline cardiorespiratory fitness and estimated glomerular filtration rate measurement. Cardiorespiratory fitness was expressed as metabolic equivalents of task, and kidney function was categorized into stages according to estimated glomerular filtration rate. Multivariable-adjusted Cox proportional hazard models were used to examine the association between metabolic equivalents of task and all-cause mortality among patients with chronic kidney disease stages 3-5. Discrimination of mortality was assessed using receiver operating characteristic curves, while reclassification was evaluated using net reclassification index (NRI).

RESULTS: Among 50,121 participants, the mean age was 55 ± 12.6 years; 47.5% were women, 64.5% were white, and 6877 (13.7%) participants had chronic kidney disease stage 3-5. Over a median follow-up of 6.7 years, 6308 participants died (12.6%). Each 1-unit higher metabolic equivalents of task was associated with a significant 15% reduction in all-cause mortality (hazard ratio 0.85; 95% confidence interval [CI], 0.84-0.87). Metabolic equivalents of task improved discriminatory ability of mortality prediction when added to traditional risk factors and estimated glomerular filtration rate (area under the curve 0.7996; 95% CI, 0.789-0.810 vs 0.759; 95% CI, 0.748-0.770, respectively; $P < .001$). The addition of metabolic equivalents of task to traditional risk factors resulted in significant reclassification (6% for events, 5% for non-events: NRI = 0.13, $P < .001$).

CONCLUSIONS: Cardiorespiratory fitness improves mortality risk prediction among patients with chronic kidney disease. Cardiorespiratory fitness provides incremental prognostic information when added to traditional risk factors and may help guide treatment options among patients with renal dysfunction.

 • The American Journal of Medicine (2021) 000:1–9

KEYWORDS: Cardiorespiratory fitness; Chronic kidney disease

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing the manuscript.

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0002-9343/
https://doi.org/10.1016/j.amjmed.2021.07.042

INTRODUCTION

Chronic kidney disease, which affects 10%-13% of the US population, is universally regarded as a major contributor to health care costs through significant effects on morbidity and mortality.[1,2] Renal dysfunction predisposes patients to adverse cardiovascular disease outcomes through multiple pathophysiologic pathways. However, widely used cardiovascular disease risk calculators may not be well calibrated in this patient population, as individuals with chronic kidney disease were not well represented in the derivation cohorts used to construct these risk calculators. The addition of estimated glomerular filtration rate and albumin-to-creatinine ratio to traditional cardiovascular disease risk factors in patients with chronic kidney disease has been shown to improve the predictive accuracy of cardiovascular disease events.[3,4] Therefore, additional efforts are needed to identify novel risk factors to refine prognostication in this patient population.

CLINICAL SIGNIFICANCE

- Higher cardiorespiratory fitness is associated with a lower adjusted risk of all-cause mortality across the spectrum of chronic kidney disease stages.
- Cardiorespiratory fitness improves mortality risk discrimination and reclassification when added to traditional cardiovascular risk factors.
- Cardiorespiratory fitness may provide important prognostic information among patients with chronic kidney disease.

Cardiorespiratory fitness is an objective physiologic measure that describes the capacity of an individual's circulatory and respiratory systems to transport and utilize oxygen in the metabolically active skeletal muscle during exercise. Importantly, it is an integrative measure influenced by several factors including physical activity habits, obesity, genetics, and traditional risk factors. Over the past 4 decades, numerous studies have demonstrated a favorable effect of cardiorespiratory fitness on long-term adverse outcomes.[5-12] Higher cardiorespiratory fitness is associated with a reduction in cardiovascular disease risk factors, major adverse cardiac events, and overall mortality.[13,14]

Prior studies have shown that exercise leads to improved functioning in patients with chronic kidney disease.[15-18] Poor cardiorespiratory fitness among patients with renal dysfunction is independently associated with a high burden of cardiovascular risk factors in addition to increased aortic stiffness, increased left ventricle afterload, and poor left ventricular function, providing a milieu of increased overall cardiovascular risk.[19]

To date, little is known about the prognostic significance of cardiorespiratory fitness in patients with chronic kidney disease. We aimed to evaluate the prognostic value of cardiorespiratory fitness for predicting mortality among patients with renal dysfunction. We hypothesized that cardiorespiratory fitness would provide incremental value to traditional risk factors in predicting mortality in this high-risk patient population. As chronotropic incompetence may contribute to low cardiorespiratory fitness, we also examined the interrelationship between chronotropic incompetence and cardiorespiratory fitness among patients with chronic kidney disease.

METHODS

Study Cohort

The Henry Ford Exercise Testing Project (FIT Project) is a retrospective cohort study that examined the long-term prognostic implications of cardiorespiratory fitness in an ethnically diverse cohort. The FIT Project consists of 69,885 patients who underwent physician-referred treadmill stress testing between 1991 and 2009. Study details have been previously described.[20] The FIT project was approved by the Henry Ford Hospital Institutional Review Board.

Exclusion Criteria

Patients were excluded if they were <18 years old or if the testing protocol was not the standard Bruce protocol. We further excluded patients who had a history of heart failure (defined as prior clinical diagnosis of systolic or diastolic heart failure; n = 1579) and patients missing relevant covariate data, including creatinine (n = 17,434) or metabolic equivalents of task (n = 751).

Assessment of Outcomes

The primary end point of our analysis was all-cause mortality, which was verified through the Social Security Death Index master file using each patient's social security number, first name, last name, and date of birth. The annualized mortality rate for each group was calculated by dividing the observed mortality rate during the follow-up duration by the mean follow-up time for the group. Secondary outcomes included major adverse cardiac events (defined as myocardial infarction or revascularization), which were ascertained through June 2010 using administrative claims files from services delivered by the affiliated group practice or reimbursed by the health plan. Linkage was performed using relevant International Statistical Classification of Diseases and Related Health Problems, ninth revision (410.xx). To minimize bias from loss to follow-up, patients were censored at their last contact with the Henry Ford Health System when ongoing coverage with the health plan could no longer be confirmed.

Treadmill Stress Testing and Metabolic Equivalents of Task

All patients underwent clinically indicated, symptom-limited maximal treadmill stress testing following the standard Bruce protocol and administered by clinical exercise physiologists or registered nurses. For individuals with repeat stress testing during the data collection period, only the

results of the first test were included. Patients undergoing pharmacological stress testing, modified Bruce, and other non-Bruce protocol tests were excluded. In accordance with American Heart Association and American College of Cardiology guidelines, tests were terminated at the discretion of the supervising clinician for potentially life-threatening reasons (significant arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, exercise-limiting symptoms such as chest pain or shortness of breath) or if the patient was unable to continue.

Cardiorespiratory fitness was estimated using metabolic equivalents of task based on the workload derived from the maximal speed and grade achieved during the treadmill time. Metabolic equivalents of task were categorized as <6, 6 to 10, 10 to 12, and >12 because these cut-off points best represent the distribution of cardiorespiratory fitness in the FIT database and have been shown in prior studies to be associated with incident adverse outcomes.[8,21,22] Failure to achieve target heart rate was defined as not achieving ≥85% of maximum predicted heart rate.

Assessment of Renal Function

Creatinine measurements were collected from the electronic medical record and laboratory databases. For each patient, the test conducted closest to the date of the stress test was selected for inclusion. The median time difference between stress testing and creatinine measurement was 22 days (interquartile range 5-71 days). Estimated glomerular filtration rate was calculated using the Levey Modification of Diet in Renal Disease formula: estimated glomerular filtration rate = 175 * standardized serum creatinine − 1.154 * age − 0.203 * 1.212 (if black) * 0.742 (if female). The calculated glomerular filtration rate values were categorized as ≥90 mL/min per 1.73 m^2 (stage 1), 60 to 89 mL/min per 1.73 m^2 (stage 2), 30 to 59 mL/min per 1.73 m^2 (chronic kidney disease stage 3), and <30 mL/min per 1.73 m^2 (stage 4/5), based on the Kidney Disease Outcomes Quality Initiative classification of kidney function.[23] Renal insufficiency was defined as chronic kidney disease stage 3 or greater.

Assessment of Covariates

Details on medical history including age, sex, race, anthropomorphic data, cardiovascular risk factors, past medical history, and active medication use were obtained by nurses or exercise physiologists immediately prior to stress testing. Diabetes mellitus was defined as a previous diagnosis of diabetes, use of hypoglycemic medications, or a database-verified diagnosis of diabetes. Dyslipidemia was defined by a previous diagnosis of any major lipid abnormality, use of lipid-lowering medications, or a database-verified diagnosis of dyslipidemia. History of coronary artery disease was defined as previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or previous documented obstructive coronary heart disease by angiogram. Body mass index was calculated as weight in kilograms divided by height in meters squared and categorized as <18.5, 18.5-24.9, 25-29.0, and >30 kg/m^2.

Statistical Analysis

Baseline characteristics were stratified by chronic kidney disease stage. Categorical data were presented as percent frequencies and compared between groups by chi-squared testing. Continuous variables were presented as mean ± standard deviation and compared using Student's t test. Non-normally distributed variables were presented as median and 25th to 75th interquartile rages and were compared using nonparametric test (Mann-Whitney test).

Kaplan-Meier curves were constructed to graphically demonstrate the cumulative survival all-cause mortality and major adverse cardiovascular events, stratified by chronic kidney disease stages and achieving target heart rate. After confirming the proportionality assumption using Schoenfeld residuals, multivariable-adjusted Cox proportional hazard adjusted models were used to study the association between metabolic equivalents of task (modeled as categorical or continuous) and all-cause mortality. Model 1 was adjusted for age, sex, and race. Model 2 was additionally adjusted for hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, aspirin use, beta-blocker use, failure to achieve target heart rate, and estimated glomerular filtration rate.

Improvement in risk discrimination of incident outcomes was assessed using area under receiving operating characteristic curves (AUC) based on Cox models. The base model (Model 1) was adjusted for age, sex, race, hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, and aspirin use. Model 2 was additionally adjusted for estimated glomerular filtration rate and Model 3 was additionally adjusted for metabolic equivalents of task. We calculated the P value comparing Model 1 and 2 C-statistics and comparing Model 1 and 3 C-statistics. Improvement in reclassification was assessed using the net reclassification index (NRI) for the addition of metabolic equivalents of task to age, sex, race, hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, and aspirin use.

Additional sensitivity analyses were conducted to determine the robustness of our results. 1) We expanded our definition of chronic kidney disease to include stages 2 to 5. 2) We evaluated the association between metabolic equivalents of task and all-cause mortality stratified by each chronic kidney disease stage and performed multiplicative interaction testing between metabolic equivalents of task and chronic kidney disease stages to assess for effect modification. 3) We evaluated the association between failure to achieve target heart rate and all-cause survival adjusting for age, sex, race, hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease,

history of smoking, statin use, aspirin use, beta-blocker use, glomerular filtration rate, and metabolic equivalents of task.

A P value $< .05$ was considered statistically significant. Statistical analyses were performed using SPSS (version 21.0; IBM Inc., Chicago, III) and STATA (IC Version 16; StataCorp, College Station, Texas). The analyzing software considered the correlated estimates of the model performance, given that the same dataset was used for comparison of the concordance statistics and in calculating the AUC. Of note, AUC for time-dependent receiver operating characteristic analysis has also been utilized successfully in several other publications.[24]

RESULTS

Baseline Characteristics

A total of 50,121 patients (mean age 55 ± 13 years, 48% female, and 29% black) were included in the analysis. Baseline characteristics of the study cohort are summarized in Table 1. Patients in higher chronic kidney disease stages were more often women, white, and a had a high burden of cardiovascular risk factors including diabetes mellitus, hypertension, hyperlipidemia, and prior myocardial infarction ($P < .001$). The prevalence of cardioprotective medication use including cholesterol-lowering agents, beta-blockers, aspirin, diuretics, angiotensin-converting enzyme inhibitors, and aldosterone receptor blockers was higher among patients with higher chronic kidney disease stages ($P < .001$) (Table 2).

Outcomes

Over a median follow-up period of 6.7 years (25th to 75th percentiles; 3.9 to 10 years), 6308 patients (12.6%) died. The rate of death increased with worsening renal function, with the highest percentage seen in those with advanced renal disease (annualized death rate = 1.4%, 1.6%, 3.7%, and 9.8% for chronic kidney disease stage 1, 2, 3, and 4/5, respectively, $P < .001$).

Table 1 Baseline Characteristics of the Study Cohort According to Chronic Kidney Disease Stages

	Chronic Kidney Disease				
	Total	Stage 1 CKD eGFR ≥90 mL/min/1.73 m^2	Stage 2 CKD eGFR 60-89 mL/min/1.73 m^2	Stage 3 CKD eGFR 30-59 mL/min/1.73 m^2	Stage 4/5 CKD eGFR < 30 mL/min/1.73 m^2
	50,121	12,990 (25.9)	30,254 (60.4)	6449 (12.9)	428 (0.9)
Age (years)	54 (46, 64)	50 (41, 56)	55 (48, 64)	65 (55, 73)	62 (51, 72)
Female sex	23,790 (47.5)	6189 (47.6)	13,993 (46.3)	3418 (53)	190 (44.4)
Race					
White	32,342 (64.5)	6049 (46.6)	21,225 (70.2)	4875 (75.6)	193 (45.1)
Black	14,329 (28.6)	5899 (45.4)	6968 (23)	1243 (19.3)	219 (51.2)
Other	3450 (6.9)	1042 (8)	2061 (6.8)	331 (5.1)	16 (3.7)
BMI (Kg/m^2)	28.7 (25, 33)	29.3 (26, 34)	28.6 (25, 32)	28.2 (25, 32)	28.3 (24, 33)
Resting heart rate (beats per minute)	73 ± 12.6	74 (± 12.7)	72 (± 12.5)	71 (± 12.7)	73 (± 14.3)
Peak systolic blood pressure (mm Hg)	178 (± 27)	177 (± 27.3)	179 (± 26.5)	176 (± 27.8)	177 (± 33.7)
Medical history					
Diabetes	10,766 (21.5)	2837 (21.8)	5891 (19.5)	1810 (28.1)	228 (53.3)
Hypertension	33,844 (67.5)	8115 (62.5)	19,977 (66)	5332 (82.7)	420 (98.1)
Hyperlipidemia	24,202 (48.3)	5110 (39.3)	15,126 (50)	3765 (58.4)	201 (47)
History of smoking	21,325 (42.5)	6064 (46.7)	12,544 (41.5)	2534 (39.3)	183 (42.8)
Prior myocardial infarction	5092 (10.2)	1243 (9.6)	2744 (9.1)	983 (15.2)	122 (28.5)
Prior coronary artery disease	6422 (12.8)	1486 (11.4)	3485 (11.5)	1305 (20.2)	146 (34.1)
Prior coronary artery angioplasty	2288 (4.6)	510 (3.9)	1265 (4.2)	486 (7.5)	27 (6.3)
Prior CABG	1632 (3.3)	309 (2.4)	852 (2.8)	432 (6.7)	39 (9.1)
Metabolic equivalents of task achieved:					
METs <6	7851 (15.7)	1595 (12.3)	4119 (13.6)	1895 (29.4)	242 (56.5)
METs 6-<10	14,457 (28.8)	3652 (28.1)	8452 (27.9)	2229 (34.6)	124 (29)
METs 10-<12	17,931 (35.8)	4937 (38)	11220 (37.1)	1718 (26.6)	56 (13.1)
METs ≥12	9882 (19.7)	2806 (21.6)	6463 (21.4)	607 (9.4)	6 (1.4)

BMI = body mass index; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; METs = metabolic equivalents of task.

All categorical data presented as total number (%), and continuous data presented as mean (standard deviation) or median (25th, 75th), as appropriate.

Table 2 Medication Use Across Chronic Kidney Disease Stages

	Total	Stage 1 CKD eGFR ≥90 mL/min/ 1.73 m^2	Stage 2 CKD eGFR 60-89 mL/min/ 1.73 m^2	Stage 3 CKD eGFR 30-59 mL/min/ 1.73 m^2	Stage 4/5 CKD eGFR <30 mL/min/ 1.73 m^2	*P* Value
	50,121	12,990 (25.9)	30,254 (60.4)	6449 (12.9)	428 (0.9)	—
Medications:						
β-blocker	11,260 (22.5)	2549 (19.6)	6351 (21)	2193 (34)	167 (39)	< .001
Ca channel blocker	6903 (13.8)	1494 (11.5)	3843 (12.7)	1370 (21.2)	196 (45.8)	< .001
ACE inhibitor	10,235 (20.4)	2262 (17.4)	5877 (19.4)	1945 (30.2)	151 (35.5)	< .001
ARBs	1659 (3.3)	308 (2.4)	923 (3.1)	386 (6)	42 (9.8)	< .001
Diuretics	10,698 (21.3)	2123 (16.3)	6000 (19.8)	2387 (37)	188 (43.9)	< .001
Aspirin	10,529 (21)	2499 (19.2)	6117 (20.2)	1779 (27.6)	134 (31.3)	< .001
Cholesterol-lowering agents	13,111 (26.2)	2549 (19.6)	7997 (26.4)	2418 (37.5)	147 (34.3)	< .001
Insulin	1957 (3.9)	523 (4)	924 (3.1)	419 (6.5)	91 (21.3)	< .001

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; Ca = calcium; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

All data are categorical and they presented as total number (%).

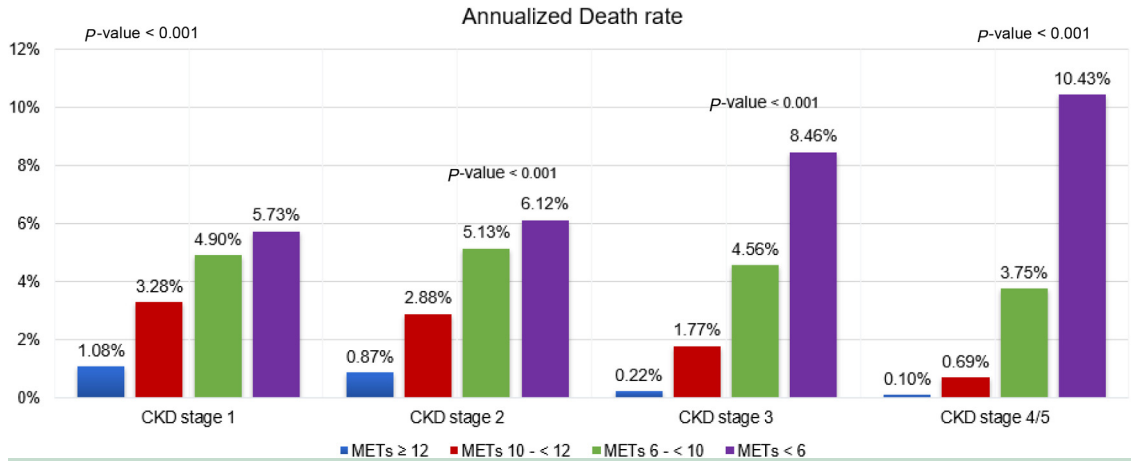

Figure 1 Annualized mortality incidence rates (%) for the association of estimated glomerular filtration rates (GFR) and mortality stratified by cardiorespiratory fitness assessed using metabolic equivalents of task (Metabolic equivalents of task; unadjusted data).
CKD = chronic kidney disease; METs = metabolic equivalents of task.

There was an incrementally higher risk of mortality with lower metabolic equivalents of task achieved across each chronic kidney disease category. For example, the annualized death rate was 10.4% vs 0.1% for metabolic equivalents of task <6 vs ≥12 among patients with chronic kidney disease stage 4/5; $P < .001$ (Figure 1). The cumulative risk of mortality and major adverse cardiovascular events was higher among patients with chronic kidney disease stage 3 and greater, and also higher among those who did not achieve 85% of predicted target heart rate. Patients with at least chronic kidney disease stage 3 who did not achieve target heart rate had the worst survival for these outcomes (Figure 2).

Multivariate Survival Analysis

There was a significantly lower risk of overall adjusted mortality with higher metabolic equivalents of task achieved among patients with chronic kidney disease (Table 3). For example, the adjusted hazard ratio (HR) (95% confidence interval [CI]) among those who attained ≥12 metabolic equivalents of task, compared with those who attained <6, was 0.18 (0.12-0.28). Each 1 unit higher metabolic equivalents of task was associated with a significant 15% reduction in all-cause mortality (HR 0.85; 95% CI, 0.84-0.87).

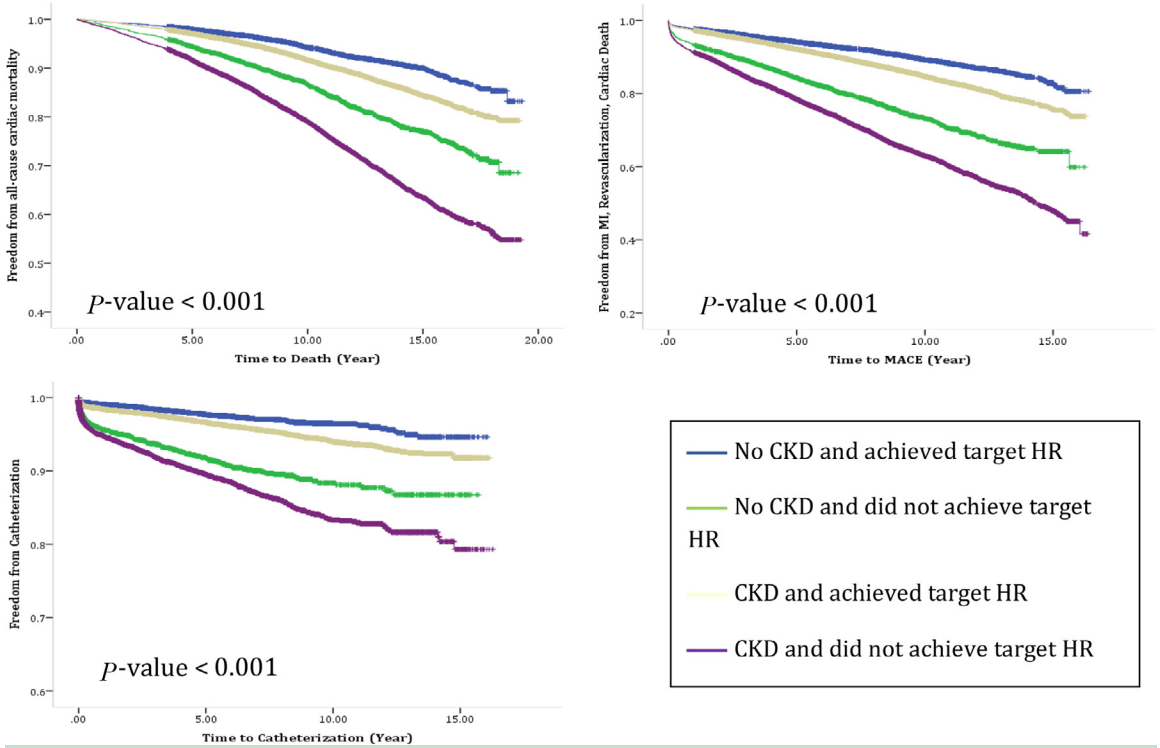

Figure 2 Kaplan-Meier curves for the interplay of renal insufficiency (chronic kidney disease stage 3 to 5) and achieving target heart rate with the outcomes of (**A**) cardiac mortality and (**B**) myocardial infarction, or cardiac mortality.
CKD = chronic kidney disease; HR = heart rate; MACE = major adverse cardiovascular events.

Mortality Risk Discrimination and Reclassification

Metabolic equivalents of task improved the discriminatory ability for mortality prediction when added to traditional risk factors and estimated glomerular filtration rate (AUC 0.7996; 95% CI, 0.789-0.810 vs 0.759; 95% CI, 0.748-0.770, respectively, $P < .001$). The addition of metabolic equivalents of task to traditional risk factors resulted in significant reclassification of mortality (6% for events, 5% for non-events: NRI = 0.13, $P < .001$).

Sensitivity Analyses

The inclusion of stage 2 in our definition of chronic kidney disease demonstrated similar results with a graded inversed association between higher metabolic equivalents of task and lower risk of all-cause mortality (Supplementary Table 1). In general, we found a consistent association between metabolic equivalents of task and all-cause mortality in all chronic kidney disease stages, with no evidence of effect modification (P for interaction = .49) (Supplementary Table 2). Failure to achieve target heart rate was associated with lower survival in the adjusted model (HR 0.79; 95% CI, 0.71-0.88).

Table 3 Association Between Metabolic Equivalents of Task Achieved and All-Cause Mortality in Patients with Chronic Kidney Disease Stage 3-5: Hazard Ratio (95% Confidence Interval)

	Model 1	Model 2
Cardiorespiratory fitness categories		
<6 METs	1.00 (ref)	1.00 (ref)
6-<10 METs	0.46 (0.42-0.51)	0.60 (0.54-0.67)
10-<12 METs	0.25 (0.21-0.29)	0.39 (0.33-0.46)
≥12 METs	0.09 (0.06-0.14)	0.18 (0.12-0.28)
P trend across categories as ordinal variable	< .001	< .001
METs per 1 unit	0.79 (0.77-0.80)	0.85 (0.84-0.87)
P value	< .001	< .001

METs = metabolic equivalents of task.
Model 1 adjusted for age, sex, and race.
Model 2 adjusted for model 1 and hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, aspirin use, beta-blocker use, failure to achieve target heart rate, and estimated glomerular filtration rate.

DISCUSSION

In a large (n = 50,121) and diverse retrospective cohort of patients who completed a clinically indicated stress test, we found that cardiorespiratory fitness was independently and

inversely associated with mortality across the spectrum of chronic kidney disease stages. We also showed that cardiorespiratory fitness improves risk discrimination and reclassification of mortality events.

Our findings are consistent with prior studies showing that cardiorespiratory fitness predicts mortality and adverse events among patients with chronic kidney disease.[25,26] Gulati et al[27] found that cardiorespiratory fitness improves mortality risk prediction among patients with chronic kidney disease, although the analysis included only women, whereas our large study cohort included both men and women and was ethnically diverse. In a separate study, Howden et al[19] noted that patients with chronic kidney disease and low cardiorespiratory fitness, as measured by peak maximal oxygen intake, had increased aortic stiffness, left ventricular afterload, and overall cardiovascular risk burden. In addition, the study found that chronic kidney disease was associated with lower levels of fitness. However, the cohort in the analysis was small, with only 136 patients with chronic kidney disease stage 3 or 4, and did not have follow-up for long-term outcomes.

We found that patients with renal dysfunction who had not achieved target heart rate had the worst survival. Previous studies have demonstrated an association between autonomic imbalance, adverse cardiovascular outcomes, and incidence of chronic kidney disease.[28] Largely determined by sympathetic and parasympathetic activity, heart rate is the biggest driver of VO_2 increase during exercise, along with maximal stroke volume and maximal arteriovenous oxygen difference.[29] Chronic kidney disease leads to muscle catabolism through means of anorexia, uremia, and inflammation, and worsening renal function may lead to further inactivity and risk factor accumulation.[30] Improved cardiorespiratory fitness may exert a survival advantage by not only attenuating traditional risk factors, but also through beneficial impact on the hematologic, vascular, and immune systems.[31-35]

Future research should assess the effect of interventions aimed at improving cardiorespiratory fitness among patients with chronic kidney disease by examining change in cardiovascular risk factor profile, renal function, VO_2 max and oxygen consumption, lean body mass, markers of inflammation, endocardial dysfunction, myocardial injury, and subclinical atherosclerosis. Such prospective studies could identify mechanisms by which cardiorespiratory fitness can affect survival among patients with chronic kidney disease. Additional research should examine the utility of incorporating cardiorespiratory fitness, if available, into clinical scoring models by validating our findings in other datasets.[36,37]

Our results have important clinical implications. Because physical activity is the main lifestyle factor that can modify cardiorespiratory fitness, participating in at least 30 minutes per day of moderate-intensity exercise may carry a significant benefit to overall health and mortality.[38,39] Improved cardiorespiratory fitness may exert a protective effect on reducing burden of cardiovascular risk factors and is associated with a lower incidence of coronary heart disease, stroke, cancer, and mortality.[5,20] One metabolic equivalent of task is approximately equivalent to the resting metabolic rate, or the energy spent while sitting quietly. An additional metabolic equivalent is a multiple of this, and at the low end of the spectrum could be making your bed or folding, compared with sitting quietly or washing your car. At the higher end of the spectrum, it is the difference between running at a pace of an 8-minute mile and a 7-minute mile. It is important to counsel the most sedentary patients to perform at least moderate activities (>6 metabolic equivalents of task) such as biking, running, swimming, or participation in sports. Our results add to the already robust body of evidence related to the benefits of physical activity and reinforce the 2016 American Heart Association Statement on cardiorespiratory fitness as a clinical vital sign.

Our results should be interpreted in the setting of several key limitations:

1) The FIT Project is a retrospective cohort of patients who were recruited at a single health system with distinct practice norms, which may limit generalizability to other health care systems.
2) Temporal changes in risk factors and medication use may hinder generalizability of our results to modern-day populations.
3) Patients included in the current analysis underwent a clinically indicated stress test to rule out coronary artery disease. This raises the potential of selection bias and could attenuate the clinical impact of our results.
4) Furthermore, those with preexisting electrocardiogram abnormalities or significant functional limitations, prevalent in patients with advanced chronic kidney disease, likely underwent diagnostic tests other than exercise stress testing to rule out coronary ischemia. As patients who underwent pharmacological stress testing or other imaging modalities were excluded from the dataset, we could not compare our results with this group.
5) We only measured cardiorespiratory fitness and estimated glomerular filtration rate at a single point in time, but changes in fitness or renal impairment over time are also significant.
6) While chronic kidney disease guidelines both mandate use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitor regardless of diabetes, a relatively small proportion of the cohort was compliant with these medications due to a significant portion of the study cohort preceding modern guidelines.
7) Estimated glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation as opposed to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which may be more accurate.

8) We could not determine whether patients were on dialysis in those with chronic kidney disease stage 4/5, as this information was not available in the FIT database.
9) Our chronic kidney disease population was mostly stage 3, as opposed to 4/5, which may limit generalizability of results to patients with more advanced renal dysfunction. However, our results stratifying by chronic kidney disease stage showed consistent results for improved survival with cardiorespiratory fitness regardless of renal function.
10) Lastly, many but not all chronic kidney disease-related factors contributing to cardiovascular risk were included, which could result in residual confounding. For example, calcium phosphorus product, which becomes more relevant in later stages of chronic kidney disease, was not included.
11) We could not evaluate mechanistic pathways underlying the association between cardiorespiratory fitness and all-cause mortality given the observational nature of this study.

In conclusion, we observed that higher cardiorespiratory fitness is inversely and independently associated with all-cause mortality in patients with chronic kidney disease. Cardiorespiratory fitness may help reclassify the risk of mortality and may inform treatment decisions in this high-risk group.

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Supplementary Table 1 Association Between Metabolic Equivalents of Task Achieved and All-Cause Mortality in Patients with Chronic Kidney Disease Stages 2-5: Hazard Ratio (95% Confidence Interval)

	Model 1	Model 2
Cardiorespiratory fitness categories		
<6 METs	1.00 (ref)	1.00 (ref)
6-<10 METs	0.49 (0.46-0.52)	0.61 (0.57-0.65)
10-<12 METs	0.26 (0.23-0.28)	0.38 (0.35-0.41)
≥12 METs	0.14 (0.12-0.16)	0.23 (0.19-0.27)
P trend across categories as ordinal variable	< .001	< .001

METs = metabolic equivalents of tasks.
Model 1 adjusted for age, sex, and race.
Model 2 adjusted for model 1 and hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, aspirin use, beta blocker use, failure to achieve target heart rate, and estimated glomerular filtration rate

Supplementary Table 2 Association Between Metabolic Equivalents of Task Achieved and All-Cause Mortality Stratifying by Chronic Kidney Disease Stage: Hazard Ratio (95% Confidence Interval)

	Stage 1 CKD eGFR ≥90 mL/min/1.73 m^2	Stage 2 CKD eGFR 60-89 mL/min/1.73 m^2	Stage 3 CKD eGFR 30-59 mL/min/1.73 m^2	Stage 4/5 CKD eGFR <30 mL/min/1.73 m^2
Cardiorespiratory fitness categories				
<6 METs	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
6-<10 METs	0.57 (0.50-0.66)	0.63 (0.58-0.69)	0.61 (0.54-0.68)	0.62 (0.46-0.83)
10-<12 METs	0.40 (0.34-0.48)	0.39 (0.35-0.44)	0.40 (0.34-0.48)	0.29 (0.16-0.52)
≥12 METs	0.27 (0.20-0.35)	0.26 (0.22-0.31)	0.18 (0.12-0.28)	0.65 (0.15-2.83)
P trend across categories as ordinal variable	< .001	< .001	< .001	< .001
P for interaction = .27				
METs per 1 unit	0.86 (0.84-0.88)	0.86 (0.85-0.88)	0.86 (0.84-0.87)	0.86 (0.81-0.91)
P value	< .001	< .001	< .001	< .001
P for interaction = .49				

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; METs = metabolic equivalents of task.
Model 1 adjusted for age, sex, and race.
Model 2 adjusted for model 1 and hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, aspirin use, beta-blocker use, failure to achieve target heart rate, and estimated glomerular filtration rate.