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Poor Exercise Capacity and Elevated N-Terminal Prohormone of Brain Natriuretic Peptide in the Prediction of Long-Term Cardiovascular Events and Mortality in Advanced Chronic Kidney Disease: The CADKID Study

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Keywords
Chronic kidney disease · Exercise capacity · Cardiac biomarkers · Mortality · Major adverse cardiovascular and cerebrovascular events

Abstract

Introduction: Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease and mortality. However, data on the prediction of long-term adverse outcomes in advanced predialysis CKD patients are lacking. ***Methods:*** We studied the factors associated with mortality and major adverse cardiovascular and cerebrovascular events (MACCEs, including cardiovascular death, myocardial infarction, stroke, and coronary revascularization) in a cohort of 210 patients with non-dialysis CKD stages 4–5 during a 5-year follow-up. The participants underwent stress ergometry testing to study maximal exercise capacity (Wmax%), a plain lateral abdominal radiograph to study abdominal aortic calcification score (AAC) and laboratory tests including cardiac troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (ProBNP). Furthermore, a dichotomous composite covariate was created and explored by combining ProBNP and Wmax% using the cut-offs determined with the Youden index. The associations between covariates of interest and study outcomes were explored using multivariable Cox proportional hazards models adjusted with age, sex, coronary artery disease (CAD), and incident kidney transplantation (KTx). ***Results:*** Median age at baseline was 65 (52–73) years and eGFR 12 (10–15) mL/min/1.73 m^2, 34.8% were female, and 44.8% had diabetes. Altogether 67 (31.9%) patients died during follow-up, and 65 (31.0%) were observed with a MACCE. In separate multivariable Cox proportional hazards models adjusted for age, gender, CAD, and KTx, Wmax% (HR 0.983 [95% CI: 0.968–0.999], $p = 0.019$), TnT (HR 1.004 [95% CI: 1.002–1.005], $p < 0.001$),

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and ProBNP (HR 1.036 per 1,000 ng/L [95% CI: 1.014–1.059], $p = 0.002$) were independently associated with mortality. In similarly adjusted multivariable Cox models, Wmax% (HR 0.977 [95% CI: 0.962–0.992], $p = 0.003$), TnT (HR 1.004 [95% CI: 1.002–1.005], $p < 0.001$), and ProBNP (HR 1.034 per 1,000 ng/L [95% CI: 1.010–1.058], $p = 0.006$) were independently associated with the occurrence of MACCE during follow-up. AAC was associated with the risk of an incident MACCE (HR 1.080 [95% CI: 1.028–1.135], $p = 0.002$) but, surprisingly, not with mortality (HR 1.046 [95% CI: 0.994–1.101], $p = 0.083$). Finally, in participants with Wmax ≤50% and ProBNP ≥1,270 ng/L, the risk of mortality (HR 8.760 [95% CI: 4.730–16.222], $p < 0.001$) and MACCE (HR 3.293 [95% CI: 1.850–5.862], $p < 0.001$) was significantly greater than those with Wmax >50% and/or ProBNP <1,270 ng/L. ***Conclusion:*** Wmax% and ProBNP separately and together as a composite risk factor may serve as important predictors of long-term all-cause mortality and MACCE in patients with CKD stages 4–5 not undergoing dialysis at baseline.

Introduction

Chronic kidney disease (CKD) affects more than 800 million individuals across the world, increases the risk of cardiovascular disease (CVD), and is one of the leading causes of death globally [1]. The risk of death increases with the progression of CKD toward end-stage kidney disease (ESKD). The majority of deaths in the CKD population can be attributed to the effects of CVD [2]. Kidney transplantation (KTx) is the most effective treatment for ESKD and can substantially improve the prognosis and quality of life in these patients [3, 4]. However, despite the fact that only every fourth ESKD patient is eligible for a kidney transplant, the need for KTx is growing faster globally than the number of available kidney grafts [5, 6]. Thus, effective risk assessment for long-term adverse outcomes is mandatory in potential kidney transplant candidates for optimal graft allocation as well as those not eligible for one.

CKD patients often lead a sedentary lifestyle and have poor physical condition. Previously, our group showed an association between poor exercise capacity (EC) assessed with an ergometry stress test and mortality in predialysis CKD stage 4–5 patients in a short-term follow-up [7]. Troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (ProBNP), diagnostic biomarkers for the screening of myocardial infarction and heart failure, as well as abdominal aortic calcification score (AAC), a tool for detecting subclinical vascular calcification with a simple lateral abdominal radiograph, have also been shown to be associated with mortality and poor EC in the short term [7, 8]. Furthermore, previous studies have shown the prognostic value of natriuretic peptides in high-risk populations such as acute coronary syndrome or ESKD [9, 10]. However, existing evidence on the value of ProBNP in dialysis-dependent ESKD or post-acute coronary syndrome populations may not directly translate to predialysis CKD patients. The performance of these measures in the prediction of mortality and cardiovascular adverse outcomes in a long-term follow-up is yet to be determined and of high clinical interest as risk projection for a period of several years into the future in CKD stage 4–5 patients at the threshold of kidney replacement therapy (KRT) would be of great help in the planning of optimized care.

In the prospective Chronic Arterial Disease, Quality of Life and Mortality in Advanced Chronic Kidney Disease (CADKID) study, we have previously reported the cardiovascular risk factors for mortality in a short-term 2 years of follow-up. In this prespecified report of the CADKID study, we explored the risk factors for mortality and a composite cardiovascular outcome in the long term of 5-year follow-up in a cohort of CKD stage 4–5 patients not undergoing dialysis at baseline.

Methods

CADKID is a prospective follow-up study assessing CVD, mortality, and quality of life and associated risk factors in predialysis patients with CKD stages 4–5 (http://www.ClinicalTrials.gov, NCT04223726). The CADKID study recruitment began in August 2013 in the predialysis outpatient clinic in the Turku University Hospital Kidney Centre with the aim of recruiting at least 200 participants. Inclusion criteria were age >18 years and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. Study recruitment was completed in September 2017 with the successful enrollment of 210 participants. None of the participants received dialysis at baseline. Individual medical history was manually gathered from the hospital electronic medical records by the researchers.

Stress Ergometry Test

Maximal EC testing was performed at the Department of Clinical Physiology of Turku University Hospital as an incremental, symptom-limited ergometry exercise stress test. The primary test workload and workload increment

per minute for each participant were chosen according to an estimated maximum workload (data derived from the Mini Suomi study [11]) and a targeted symptom limitation within 6–10 min as per standard clinical protocol in the research hospital. The target speed of 60 rpm was reached during a 30-s warm-up phase. The ergometry software was programmed to increase the workload automatically by 10–20 W per minute. The study patients were instructed to continue cycling at 60 rpm until exhaustion. The mean proportional workload of the last 4 min of age, sex, and body size predicted value of maximal workload capacity (Wmax%) was collected and used in the analyses.

Assessment of AAC

A lateral abdominal radiograph in a standing position was used to calculate AAC using a previously validated system [12]. Two researchers analyzed the radiographs independently, and the mean of the resulting two scores was used in the analyses. AAC is calculated as a sum of anterior and posterior calcifications of the aorta in the level of the four most cranial lumbar vertebrae (L1–L4). Calcifications in each of the four anterior and four posterior segments of the aorta are graded 0–3 (0 = no calcific deposits, 1 = small scattered calcific deposits filling less than one-third of the longitudinal aortic wall, 2 = one-third to two-thirds of the longitudinal aortic wall calcified, 3 = at least two-thirds of the longitudinal aortic wall calcified), giving a total AAC of 0–24.

Biochemical Parameters

Blood samples were obtained at baseline and analyzed by Turku University Hospital Laboratory Division (Tykslab). Laboratory variables analyzed included blood hemoglobin (Hb), leukocytes, thrombocytes, glycated hemoglobin, pH, bicarbonate and base excess, plasma C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), glucose, alanine aminotransferase, alkaline phosphatase, creatinine, urea, albumin, sodium, potassium, phosphorus, total and ionized calcium and parathyroid hormone, TnT, and ProBNP. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13].

Outcomes

Primary outcomes of the study were all-cause mortality and major adverse cardiovascular and cerebrovascular event (MACCE), consisting of cardiovascular death, acute myocardial infarction, ischemic or hemorrhagic stroke, and coronary revascularization, during the 5-year follow-up. All deaths were ascertained from the Digital and Population Data Services of Finland, and the data regarding incidence of MACCE were manually gathered by the researchers from the electronic medical record system used in all public hospitals in the area of Southwest Finland.

Statistical Methods

The results were presented as mean ± standard deviation or median (interquartile range) for normally distributed or nonparametric continuous variables, respectively. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normality assumption in continuous covariates. The normally distributed continuous covariates were compared using Student's T test, and Mann-Whitney U test was used for skewed covariates. Categorical variables were reported as absolute and relative (percentage) frequencies and compared using the Fisher's exact or Pearson χ^2 test.

In preliminary analyses, the associations between variables of interest and mortality or MACCE within 5 years of follow-up were examined separately using univariate Cox proportional hazards models. The covariates with a $p < 0.05$-level association with the outcome were entered into separate respective multivariable Cox models. The multivariable Cox survival models were adjusted by including age, gender, coronary artery disease (CAD), and KTx within follow-up as covariates along with a single covariate of interest (e.g., TnT or ProBNP or Wmax%, etc.) into each respective analysis. The censoring in the survival analyses was set to occur at the time of incident MACCE (in the analyses studying the associations with MACCE as the dependent variable), death, or end of the 5-year follow-up. Due to the limited sample size, number of events, and risk of overfitting and multicollinearity, adjusted multivariable analyses including several covariates of interest or more comprehensive adjustment could not be performed.

For the statistical analyses including ProBNP as an independent variable, ProBNP was entered as a quotient of 1/1,000. To address missingness (34 [16.2%] patients for Wmax%, 7 [3.3%] patients for TnT, 13 [6.2%] patients for ProBNP, and 11 [5.2%] patients for AAC), we repeated the adjusted multivariable Cox proportional hazards analyses after multiple imputation. Multiple imputation was performed with 100 iterations to eliminate missingness in the dataset, and the results of the pooled adjusted multivariable Cox models were reported to complement the original analyses.

As the focus of the present study was the relationship between subclinical cardiovascular biomarkers and physical EC and mortality and MACCE, we further

examined the association between mortality or MACCE within 5-year follow-up and TnT, ProBNP, and Wmax% as dichotomous covariates. The optimal cut-offs for transforming the continuous variables into categorical ones were determined (42 ng/L for TnT, 1,270 ng/L for ProBNP, and 50% for Wmax%) using the Youden index. The generated dichotomous covariates were then separately entered into univariate Cox models to test for the association with mortality and MACCE during follow-up. The analyses regarding TnT, ProBNP, and Wmax% as dichotomous variables were then repeated using pooled analyses after multiple imputation to exclude the effect of missingness, illustrated using Kaplan-Meier plots, and further tested with the log-rank test.

Interaction term testing between Wmax% and ProBNP was performed by entering Wmax%, ProBNP, and their interaction variable as continuous covariates in multivariable Cox models for 5-year mortality and MACCE in separate analyses. To demonstrate the magnitude of the association between the explored subclinical biomarkers and 5-year mortality and MACCE, a composite dichotomous variable was generated by combining ProBNP and Wmax% using the cut-offs determined with the Youden index, resulting in a categorical variable (Wmax% >50% and/or ProBNP <1,270 ng/L vs. Wmax% ≤50% and ProBNP ≥1,270 ng/L). ProBNP and Wmax% were chosen due to having the strongest associations and hazard ratios (HRs) with mortality in the adjusted multivariable Cox models. The relationship between mortality or MACCE and the categorical composite variable was similarly tested and illustrated using a univariate Cox model, a Kaplan-Meier plot, and log-rank testing, and the analyses were repeated after multiple imputation. As a sensitivity analysis, the association between the composite dichotomous variable of Wmax% and ProBNP and mortality or MACCE within the 5-year follow-up was tested in separate univariate Cox analyses in patients that received a kidney transplant during follow-up and those that did not.

All analyses were two-sided, and significance was set at $p < 0.05$. IBM SPSS Statistics software version 29.0 and SAS version 9.3 were used to perform all analyses as appropriate.

Results

Baseline Characteristics

Altogether 210 patients were recruited for the CADKID study. The median age of participants was 65 (52–73) years, 73 (34.8%) were female, and 94 (44.8%) had diabetes. The median baseline eGFR was 12 (10–15) mL/min/1.73 m^2. TnT and ProBNP were available in 203 (96.7%) and 197 (93.8%) patients, respectively. A total of 199 (94.8%) patients underwent a plain lateral lumbar radiograph to study AAC, and 176 (83.8%) patients underwent the bicycle ergometry stress test. During the 5-year follow-up, 176 (83.8%) initiated dialysis and 79 (37.6%) received a kidney transplant.

Risk Factors Independently Associated with 5-Year All-Cause Mortality

A total of 67 (31.9%) patients died (7.62 deaths per 100 patient years) during the 5-year follow-up. The most common cause of death (25 deaths, 37.3%) was CVD. Other causes of death included infection (15 deaths, 22.4%), malignancy (10 deaths, 14.9%), renal causes (3 deaths, 4.5%), trauma/poisoning (3 deaths, 4.5%), gastrointestinal (3 deaths, 4.5%), musculoskeletal (2 deaths, 3.0%), and one death (1.5%) was caused by pulmonary, neurological, and endocrinological causes, each. Moreover, 3 deaths (4.5%) were of miscellaneous causes.

Table 1 shows the baseline clinical and laboratory characteristics, examinations, and outcomes of the patients by their survival status at 5-year follow-up. Deceased patients had significantly higher ProBNP, TnT, CRP, urea, ESR, and AAC. Plasma albumin, eGFR, and Wmax% were significantly higher in those who survived. Those who died during follow-up had significantly more cardiovascular comorbidities and received fewer kidney transplants.

Separate univariate Cox proportional hazards models were used to preliminarily assess the associations between baseline covariates and mortality at 5-year follow-up. The results are presented in Table 2. In separate multivariable Cox proportional hazards models adjusted for age, sex, CAD, and KTx during follow-up, a significant association between mortality at 5-year follow-up and Wmax% (HR 0.983 [95% CI: 0.968–0.999], $p = 0.019$), ProBNP (HR 1.036 per increment of 1,000 ng/L [95% CI: 1.014–1.059], $p = 0.002$), TnT (HR 1.004 [95% CI: 1.002–1.005], $p < 0.001$), ESR (HR 1.013 [95% CI: 1.003–1.023], $p = 0.008$), Hb (HR 0.961 [95% CI: 0.939–0.984], $p < 0.001$), high-density lipoprotein cholesterol (HR 0.416 [95% CI: 0.185–0.936], $p = 0.034$), urea (HR 1.077 [95% CI: 1.041–1.114], $p < 0.001$), albumin (HR 0.943 [95% CI: 0.891–0.997], $p = 0.040$), and prior stroke (HR 2.099 [95% CI: 1.137–3.873], $p = 0.018$) were observed. AAC, however, was not associated with all-cause mortality during the 5-year follow-up in the

Table 1. Baseline characteristics, examinations, and outcomes of the deceased and alive patients at 5 years of follow-up

	Deceased (N = 67)	Alive (n = 143)	p value
Age median (IQR), years	72 (65–77)	61 (48–70)	<0.001
Female	19 (28.4)	54 (37.8)	0.215
Body mass index	27.3 (23.2–29.5)	27.8 (24.5–31.6)	0.117
History of smoking	28 (43.7)	64 (44.8)	0.380
Hypertension	66 (98.5)	139 (97.2)	1.000
Diabetes	37 (55.2)	57 (39.9)	0.039
CAD	24 (35.8)	11 (7.7)	<0.001
Prior myocardial infarction	15 (22.4)	8 (5.6)	<0.001
History of heart failure	27 (40.3)	21 (14.7)	<0.001
History of atrial fibrillation	25 (37.3)	16 (11.2)	<0.001
Peripheral artery disease	22 (32.8)	15 (10.5)	<0.001
Prior stroke	13 (19.4)	10 (7.0)	0.016
Laboratory measurements			
Hb, g/L	111 (102–119)	114 (108–123)	0.016
eGFR, mL/min/1.73m^2	12 (10–14)	13 (11–15)	0.025
Urea, mmol/L	24.4 (19.9–29.5)	21.5 (17.9–26.0)	0.004
CRP, mg/L	3 (1–7)	2 (1–4)	0.016
ESR, mm/h	38 (26–53)	28 (16–44)	0.006
Albumin, g/L	33.7 (30.8–36.2)	35.6 (32.9–38.2)	0.005
TnT (n = 203), ng/L	63 (40–97)	29 (18–48)	<0.001
ProPNB (n = 197), ng/L	2,490 (1,475–7,780)	801 (386–2,085)	<0.001
Imaging studies			
AAC (n = 199)	10 (6–14)	4 (0–9)	<0.001
Ergometry			
Wlast4 (W) (n = 176)	60 (46–77)	88 (64–112)	<0.001
Wmax% (n = 176)	44 (±17)	60 (±21)	<0.001
Outcomes within 5 years of follow-up			
Dialysis initiation	50 (74.6)	126 (88.1)	0.017
Transplantation	5 (7.5)	74 (51.7)	<0.001

IQR, interquartile range; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; ProBNP, N-terminal pro-B-type natriuretic peptide; AAC abdominal aortic calcification score; Wlast4, mean workload of the last 4 min of maximal stress; Wmax%, mean proportional workload of the last 4 min of predicted value of maximal stress.

adjusted multivariable Cox survival model (HR 1.046 [95% CI: 0.994–1.101], p = 0.083). After imputation for missing data, the findings in the multivariable Cox survival models remained similar (Table 3) and the association between AAC and mortality at 5-year follow-up remained nonsignificant.

We further analyzed the relationship between TnT (HR 4.955 [95% CI: 2.805–8.752], p < 0.001), ProBNP (HR 6.798 [95% CI: 3.446–13.412], p < 0.001), and Wmax% (HR 5.601 [95% CI: 2.841–11.043], p < 0.001) as dichotomous variables and mortality using separate univariate Cox proportional hazards models, and each association was significant. The results remained similar in repeated analyses after multiple imputation to address missingness in the data (Table 3). The relationships between TnT, ProBNP, and Wmax% as dichotomous variables and mortality after multiple imputation are illustrated with Kaplan-Meier plots in Figure 1. Finally, we combined the two dichotomous covariates, ProBNP and Wmax%. The composite covariate of ProBNP and Wmax% was significantly associated with mortality at 5-year follow-up in a

Table 2. Univariate Cox proportional hazard analyses of the associations between selected variables and 5-year all-cause mortality and MACCE

	Mortality			MACCE		
Covariate	HR	CI (95%)	*p* value	HR	CI (95%)	*p* value
Age	1.067	1.043–1.093	<0.001	1.033	1.013–1.053	<0.001
Sex	1.401	0.824–2.384	0.213	1.220	0.720–2.065	0.460
Body mass index	0.963	0.918–1.009	0.112	1.009	0.965–1.054	0.701
Smoking	1.092	0.768–1.555	0.624	1.313	0.938–1.837	0.113
Hypertension	1.611	0.224–1.606	0.636	1.627	0.226–11.732	0.629
Diabetes	1.724	1.065–2.792	0.027	2.797	1.686–4.640	<0.001
History of heart failure	3.028	1.856–4.940	<0.001	3.024	1.828–5.003	<0.001
Prior stroke	2.638	1.438–4.839	0.002	1.572	0.748–3.303	0.233
CAD	4.028	2.437–6.658	<0.001	3.861	2.262–6.592	<0.001
Prior myocardial infarction	3.312	1.860–5.896	<0.001	3.223	1.745–5.951	<0.001
Peripheral artery disease	2.971	1.783–4.953	<0.001	5.325	3.227–8.788	<0.001
History of atrial fibrillation	3.097	1.884–5.091	<0.001	1.601	0.910–2.817	0.103
Hb	0.974	0.955–0.994	0.012	0.964	0.944–0.984	<0.001
CRP	1.005	0.987–1.024	0.591	1.002	0.982–1.022	0.869
ESR	1.013	1.004–1.021	0.004	1.008	0.999–1.018	0.087
Urea	1.074	1.038–1.112	<0.001	1.078	1.040–1.117	<0.001
Albumin	0.941	0.895–0.989	0.017	0.943	0.896–0.992	0.022
Ionized calcium	0.021	0.001–0.484	0.016	0.015	0.001–0.346	0.009
Phosphate	1.159	0.538–2.495	0.706	1.483	0.698–3.150	0.306
PTH	0.998	0.997–1.000	0.066	1.001	0.999–1.002	0.416
HbA1c	0.978	0.799–1.197	0.830	1.269	1.072–1.503	0.006
TnT	1.005	1.003–1.006	<0.001	1.004	1.002–1.005	<0.001
ProBNP (per 1,000 ng/L)	1.060	1.040–1.080	<0.001	1.055	1.033–1.077	<0.001
Total cholesterol	0.729	0.577–0.922	<0.001	0.838	0.672–1.046	0.118
HDL cholesterol	0.377	0.185–0.770	0.007	0.912	0.513–1.622	0.754
LDL cholesterol	0.724	0.547–0.957	0.024	0.759	0.577–0.997	0.047
Triglycerides	0.997	0.772–1.287	0.982	1.126	0.856–1.481	0.395
Wlast4 (W)	0.980	0.970–0.989	<0.001	0.981	0.972–0.989	<0.001
Wmax%	0.967	0.953–0.982	<0.001	0.968	0.955–0.981	<0.001
AAC	1.106	1.062–1.151	<0.001	1.102	1.059–1.146	<0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, glycosylated hemoglobin; TnT, Troponin T; ProBNP, N-terminal pro-B-type natriuretic peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Wlast4, mean workload of the last 4 min of maximal stress; Wmax%, mean proportional workload of the last 4 min of predicted value of maximal stress; AAC, abdominal aortic calcification score; PTH, parathyroid hormone.

Table 3. Adjusted (age, sex, CAD, and transplantation) multivariable Cox proportional hazards analyses of selected covariates (upper section) and univariate Cox proportional hazards analyses of the created dichotomous covariates (lower section) with significant associations with 5-year all-cause mortality or MACCE in the imputed cohort (n = 210) with multiple imputation performed as required

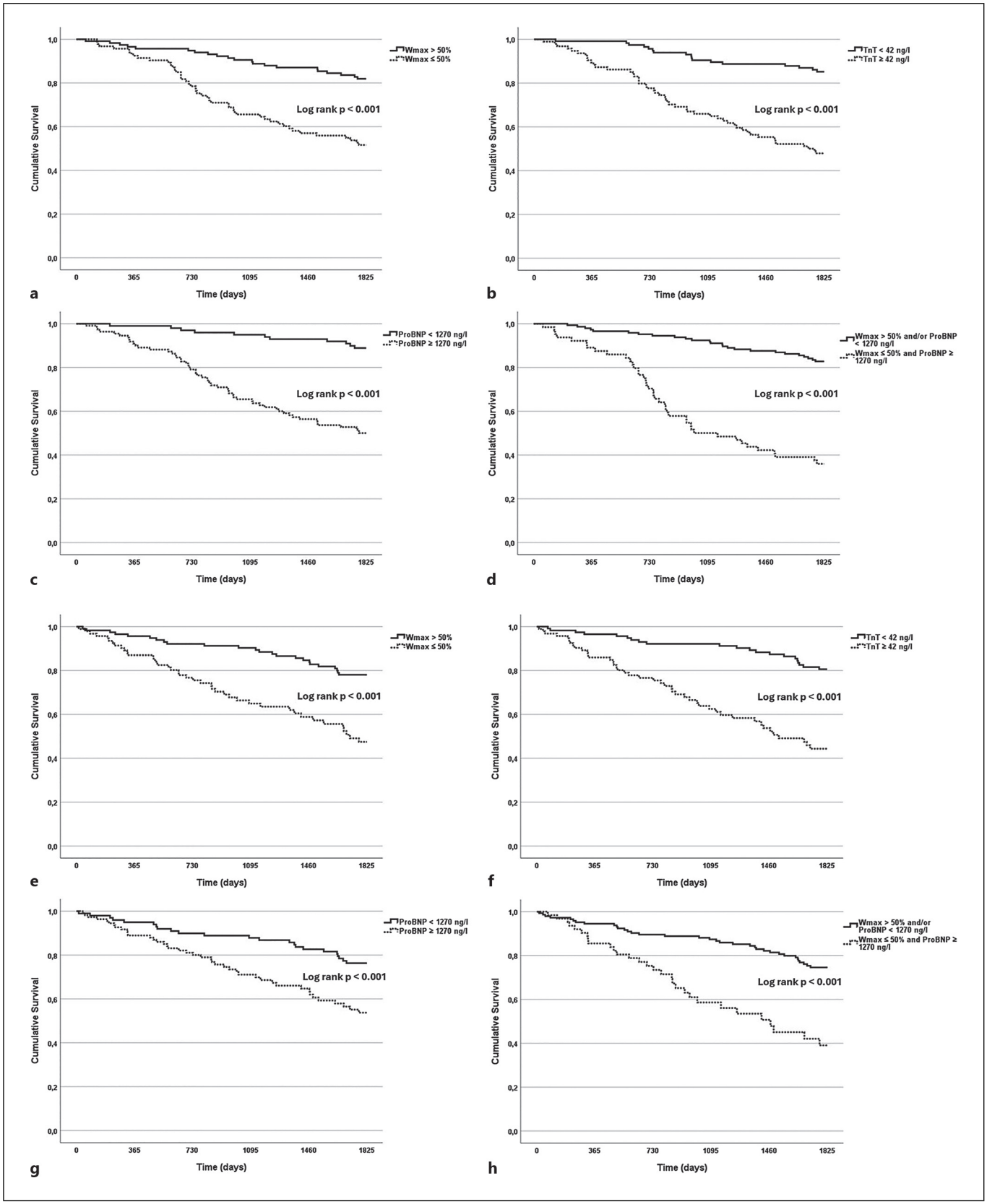
Multivariable analyses	Mortality			MACCE		
covariate	HR	95% CI	p value	HR	95% CI	p value
Wmax%[a]	0.983	0.968–0.999	0.034	0.978	0.963–0.992	0.003
Hb	0.961	0.939–0.984	0.001	0.954	0.931–0.977	<0.001
Urea	1.077	1.041–1.114	<0.001	1.076	1.039–1.114	<0.001
TnT[b]	1.004	1.002–1.005	<0.001	1.004	1.002–1.005	<0.001
ProBNP[c] (per 1,000 ng/L)	1.036	1.013–1.060	0.002	1.034	1.010–1.058	0.006
AAC[d]	1.037	0.987–1.090	0.149	1.071	1.020–1.124	0.006
Univariate analyses						
Wmax%[a] – dichotomous	4.118	2.236–7.584	<0.001	3.422	1.967–5.951	<0.001
TnT[b] – dichotomous	4.742	2.692–8.355	<0.001	3.923	2.318–6.639	<0.001
ProBNP[c] – dichotomous	6.430	3.272–12.633	<0.001	2.451	1.458–4.122	<0.001
Wmax% and ProBNP – composite dichotomous	6.202	3.538–10.871	<0.001	3.042	1.774–5.218	<0.001

Wmax%, mean proportional workload of the last 4 min of predicted value of maximal stress; TnT, troponin T; ProBNP, N-terminal pro-B-type natriuretic peptide. [a]Data missing in 34 (16.2%) patients and multiple imputation performed for the imputed cohort to nullify missingness. [b]Data missing in 7 (3.3%) patients and multiple imputation performed for the imputed cohort to nullify missingness. [c]Data missing in 13 (6.2%) patients and multiple imputation performed for the imputed cohort to nullify missingness. [d]Data missing in 11 (5.2%) patients and multiple imputation performed for the imputed cohort to nullify missingness. The dichotomous cut-offs for TnT (42 ng/L), ProBNP (1,270 ng/L), and Wmax% (50%) were determined with the Youden index.

univariate Cox model (HR 8.760 [95% CI: 4.730–16.222], $p < 0.001$), and the association remained significant after multiple imputation (Table 3). The results did not change in sensitivity analyses restricted to patients that received a kidney transplant during the study (n = 79, HR 10.750 [95% CI: 1.793–64.475], $p = 0.009$) or those that did not (n = 131, HR 5.153 [95% CI: 2.642–10.053], $p < 0.001$). The magnitude of the association between mortality at 5-year follow-up and ProBNP and Wmax% is further depicted in Figure 2. The risk of death was 65.9% vs. 12.0% ($p < 0.001$) in patients with ProBNP ≥1,270 ng/L and Wmax% ≤50% of expected EC compared to those with lower ProBNP and higher Wmax%. Only 5 (6.3%) patients out of the 79 who received a kidney transplant had ProBNP ≥1,270 ng/L and Wmax % ≤50%, and 2 of these patients died during the study.

Risk Factors Independently Associated with MACCE within the 5-Year Follow-Up

An incident MACCE was observed in 65 (31.0%) patients (7.39 MACCEs per 100 patient years) within the 5-year follow-up. The associations between explored covariates and MACCE in separate univariate Cox survival analyses are summarized in Table 2. In separate and similarly adjusted (as those for 5-year mortality) multivariable Cox proportional hazards models, Wmax% (HR 0.977 [95% CI: 0.962–0.992], p = 0.003), AAC (HR 1.080 [95% CI: 1.028–1.135], p = 0.002), diabetes (HR 2.246 [95% CI: 1.315–3.837], p = 0.003), history of heart failure (HR 1.889 [95% CI: 1.066–3.348], p = 0.029), peripheral artery disease (HR 3.482 [95% CI: 1.969–6.158], p = 0.003), ProBNP (HR 1.034 per increment of 1,000 ng/L [95% CI: 1.010–1.058], p = 0.006), TnT (HR 1.004 [95% CI: 1.002–1.005], $p < 0.001$), Hb (HR 0.954 [95% CI: 0.931–0.977], $p < 0.001$), urea (HR 1.076 [95% CI: 1.039–1.114], $p < 0.001$), ionized calcium (HR 0.032 [95% CI: 0.001–0.743], p = 0.032), and glycated hemoglobin (HR 1.252 [95% CI: 1.033–1.518], p = 0.022) were independently associated with MACCE at 5-year follow-up. The repeated separate multivariable Cox models in the imputed cohort are summarized in Table 3. Plasma albumin (HR 0.954 [95% CI: 0.903–1.009], p = 0.097) was not associated with incident MACCE at 5-year follow-up in the adjusted multivariable Cox model.



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Similar to the analyses regarding 5-year mortality, dichotomous variables for TnT (HR 4.068 [95% CI: 2.401–6.893], $p < 0.001$), ProBNP (HR 2.434 [95% CI: 1.433–4.132], $p < 0.001$), and Wmax% (HR 3.847 [95% CI: 2.161–6.849], $p < 0.001$) were created using the same cut-offs determined with the Youden index and entered in separate univariate Cox proportional hazards models to test the associations with the occurrence of MACCE within 5-year follow-up. The results remained unchanged in repeated analyses after multiple imputation (Table 3). The association between MACCE at 5-year follow-up and the composite dichotomous covariate of ProBNP and Wmax% was tested in a univariate Cox model (HR 3.293 [95% CI: 1.850–5.862], $p < 0.001$), and the association remained significant after multiple imputation to address missingness (Table 3). The results did not change in a sensitivity analyses performed in patients that received a kidney transplant during the study ($n = 79$, HR 9.992 [95% CI: 2.965–33.678], $p < 0.001$). However, the association between the dichotomous composite covariate and MACCE during 5-year follow-up was not significant when the analysis was repeated in patients that did not receive a kidney transplant ($n = 131$, HR 1.743 [95% CI: 0.907–3.350], $p = 0.096$). The association between MACCE at 5-year follow-up and ProBNP and Wmax% is illustrated in Figure 3. In the interaction term testing analyses, the interaction variable was not significantly associated with the risk of 5-year mortality or MACCE, while both Wmax% ($p < 0.001$ for both analyses) and ProBNP ($p < 0.023$ for both analyses) were, when the interaction variable was excluded, suggesting no significant interaction between Wmax% and ProBNP.

Discussion

The present study shows that simple inexpensive repeatable biomarkers, such as baseline EC measured with an ergometry stress test, TnT, and ProBNP, were strongly and independently associated with all-cause mortality and MACCE within a long term of 5 years of follow-up in CKD stage 4–5 patients not receiving dialysis at baseline. Strikingly, almost two-thirds of the patients with a Wmax% less than half of the expected EC and coincident high ProBNP died, and nearly half were observed with a MACCE within 5 years of follow-up. Moreover, only a fraction of patients who received a kidney transplant during this time period were observed with the same two risk factors. These risk factors appear to have potential in the prediction of long-term adverse outcomes in CKD stage 4–5 patients at the threshold of KRT suggesting clinical implications in the assessment of KTx eligibility.

In line with our previous work in the CADKID cohort demonstrating a link between EC and mortality during a brief 2-year follow-up period, we observed an independent association between poor EC and mortality in a long-term 5-year follow-up. Moreover, poor EC was independently associated with the occurrence of MACCE in similarly adjusted multivariable models. Our results underline the importance of assessing EC in CKD stages 4–5 when assessing eligibility for KRT, as poor EC was associated with adverse outcomes despite adjustment for CAD and KTx. The impact of measuring EC in terms of adverse outcome prediction in these patients appears to be profound, as KTx, the most effective treatment for ESKD, did not diminish the association with mortality or MACCE in the adjusted multivariable models. Furthermore, the coexistence of moderately elevated ProBNP and Wmax% below 50% of the expected EC was associated with very high mortality regardless of incident KTx and substantial risk of incident MACCE. In the sensitivity analyses, however, the association between incident MACCE and the dichotomous composite covariate was not significant in patients who did not receive a kidney transplant during the study. This is probably explained by patient selection as patients who do not receive a kidney transplant often have poor prognosis and high disease burden which may "drown" the effect of the covariate of interest in risk assessment. Nevertheless, our findings suggest that EC assessment with a common ergometry test along with the measurement of ProBNP may help identify predialysis CKD stage 4–5 patients at high risk for adverse

Fig. 1. Kaplan-Meier plots depicting the association between mortality within 5-year follow-up and the dichotomous variables of Wmax% (**a**), TnT (**b**), ProBNP (**c**), and the composite covariate of Wmax% and ProBNP (**d**), and the association between the risk of MACCE within 5-year follow-up and the dichotomous variables of Wmax% (**e**), TnT (**f**), ProBNP (**g**), and the composite covariate of Wmax% and ProBNP (**h**). Wmax%, mean proportional workload of the last 4 min of predicted value of maximal stress; TnT, troponin T; ProBNP, N-terminal pro-B-type natriuretic peptide; MACCE, major adverse cardiovascular or cerebrovascular event.

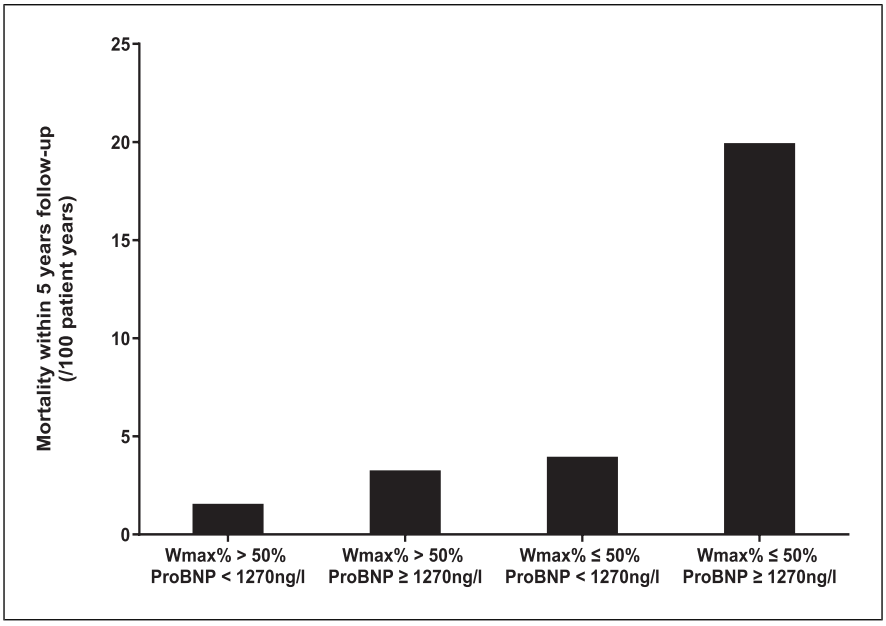

Fig. 2. Cumulative effect of Wmax% and ProBNP as dichotomous variables on the risk of mortality at 5-year follow-up. Wmax %, mean proportional workload of the last 4 min of predicted value of maximal stress; ProBNP, N-terminal pro-B-type natriuretic peptide.

outcomes and aid in the decision-making of choosing optimal care. Importantly, only a handful of patients observed with both of these risk factors received a kidney transplant and almost half of them died regardless during the study follow-up. Thus, our study suggests that patients with reduced EC and elevated ProBNP may require closer risk stratification and individualized assessment when considering KTx. However, definite conclusions cannot be drawn from these data and further research to establish causality is naturally required.

The traditional indication for ergometry stress testing in predialysis CKD stage 4–5 patients during kidney transplant evaluation has been the screening of clinically relevant CAD. However, the clinical benefit of screening for CAD in this setting has been called to question as most patients are often asymptomatic and coronary revascularization, a typical sequelae related to coronary angiography after an ischemic finding suggestive of CAD during ergometry testing regardless of symptoms, has not been found to be superior to optimal medical therapy [14, 15]. We hypothesize that the measuring of EC during ergometry stress testing may be actually more clinically relevant as a screening measure for frailty, that is, aging-related attenuation of physical, mental, psychological, and cognitive performance, than the screening of CAD in these patients. The notion is intuitive as poor EC is associated with frailty, common in CKD, and strongly associated with adverse outcomes in ESKD patients as well as in kidney transplant recipients [16, 17]. Poor EC was effectively associated with poor prognosis and MACCE regardless of the presence of CAD or KTx in our study.

According to our current findings, EC presents a novel modifiable risk factor for risk reduction of CKD-associated mortality and MACCEs. A recent systematic review and meta-analysis comparing EC between less severe and more advanced CKD stages showed a gradual decrease in cardiorespiratory capacity with progressive loss of kidney function [18]. Given the poor prognosis in patients with advanced CKD, the effect of improving the physical fitness of these patients should be addressed. The KDIGO guidelines recommend physical activity in patients with CKD [19]. Exercise training programs have been shown to result in significant improvements in the functional capacity, measures of lower extremity performance, EC, and cardiorespiratory fitness in CKD patients [20–22]. However, data on whether improved physical condition in CKD translates to better survival remain so far inconsistent [23].

Cardiac biomarkers TnT and ProBNP are readily available and widely used tools in daily clinical practice. The prognostic value of TnT and ProBNP has been demonstrated in dialysis and non-dialysis CKD populations as well as in cohorts with increased cardiovascular risk and normal kidney function in previous literature as well as in our previous work [7, 9, 10, 24, 25]. In line with our previous observations within a

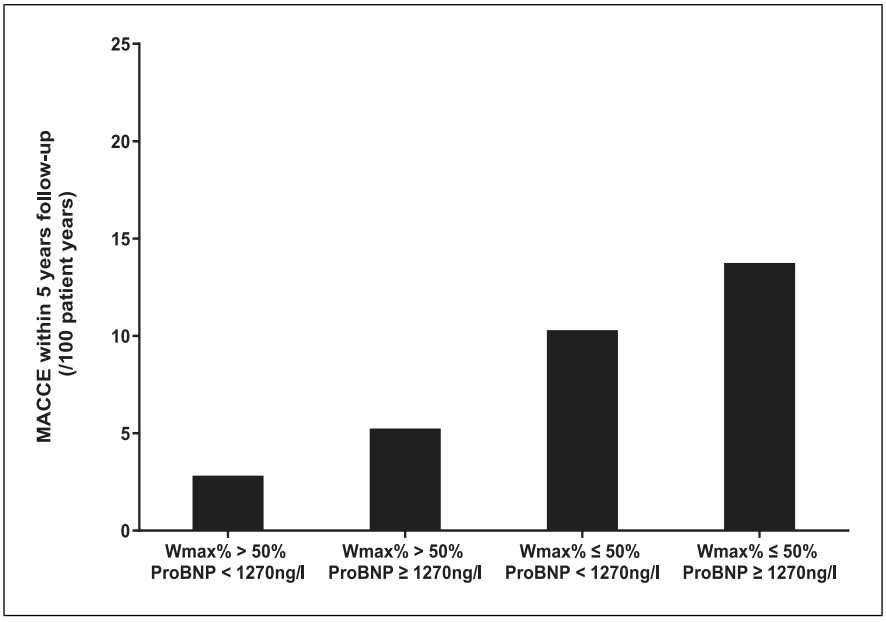

Fig. 3. Cumulative effect of Wmax% and ProBNP as dichotomous variables on the risk of MACCE within 5-year follow-up. Wmax%, mean proportional workload of the last 4 min of predicted value of maximal stress; ProBNP, N-terminal pro-B-type natriuretic peptide; MACCE, major adverse cardiovascular or cerebrovascular event.

short-term follow-up of 2 years, we observed independent associations between TnT and ProBNP, and mortality as well as MACCE in a 5-year follow-up after adjusting for age, sex, CAD, and KTx in the present study. Plasma albumin is a well-studied prognostic marker in CKD and among the strongest predictors of survival in these patients, especially those receiving KRT [26]. In our study, lower plasma albumin was associated with all-cause mortality but not with incident MACCE during the 5-year follow-up. A similar observation was made in a prior study investigating the relationship between serum albumin and all-cause and cardiovascular mortality in patients with CKD stages 3–4. In line with our findings, serum albumin was associated with all-cause mortality, whereas no association with cardiovascular mortality could be detected [27]. Hypoalbuminemia is common in advanced CKD and associated with increased risk of infections and fractures which may partly explain the significant association between lower circulatory albumin and all-cause mortality in previous literature and our work [28–30]. However, the relationship between hypoalbuminemia and CAD among CKD patients is less clear especially in the lower levels of circulatory albumin and this might in part explain the lack of association between albumin and MACCE in our study [31].

Contrary to our prior findings, AAC was significantly associated with mortality only in the univariate Cox analysis, but lost significance in the adjusted multivariable models. Then again, AAC was independently associated with MACCE in the adjusted multivariable Cox analysis. In fact, recent literature on the link between AAC and all-cause mortality has shown conflicting results while that of MACCE has been more consistent. In a study investigating all-cause mortality during 5-year follow-up in CKD stage 1–4 patients, AAC was not significantly associated with all-cause mortality after adjusting for age, sex, and eGFR [32]. Furthermore, a link between AAC and cardiovascular mortality but not with all-cause mortality has been observed in studies on patients undergoing hemodialysis or peritoneal dialysis [33, 34]. Thus, it could be hypothesized that AAC, primarily a biomarker for cardiovascular morbidity and mortality, may not be optimal for assessing the risk of all-cause mortality in the long term in advanced CKD as non-cardiovascular conditions such as infections and malignancies account for substantial mortality in these patients [7]. In line with this reasoning, ergometry stress testing with or without cardiac biomarkers like TnT or ProBNP was consistently associated with all-cause mortality and MACCE in a long-term follow-up while AAC was not.

The limitations of the current study include those of an observational study, the relatively small sample size limiting the power of the study, single-center design, and homogeneous patient ethnicity. The observational nature of the study limits interpretations of causality. However,

the patients were extensively examined by the same clinicians and the quality of the data is high. Furthermore, all study patients resided in the hospital district of the research tertiary hospital minimizing the risk of missed outcome. Moreover, the patient record database of the research hospital is linked to the national population information system ensuring the completeness of the mortality data in our study. The multivariable Cox models could not be adjusted for all relevant covariates due to limited sample size and number of events due to the risk of overfitting, and no data of suitability for KTx at baseline were collected. However, the multivariable Cox analyses were adjusted for age and sex as well as CAD and KTx, four well-established factors known to be associated with CKD-specific outcomes. There was some missingness in the data pertaining to the main variables of interest. However, missingness of the data was addressed with multiple imputation, a strategy that has been shown to produce valid statistical inference, and the results remained unchanged. The use of ergometry stress testing for the assessment of EC may have led to some selection bias as the most comorbid patients often are unable to perform the test. However, ergometry stress testing was standard protocol for the screening of CAD at the time of the study at our center. To combat the potential inability of patients in poor condition to perform a stress ergometry test, we have launched a new study (http://www.ClinicalTrials.gov, NCT06935786) that includes both spiroergometry and 6-min walking test for EC assessment. Despite these limitations, we believe that our findings have shed light on the connection between poor EC and common cardiovascular biomarkers and cardiovascular morbidity and mortality in patients with CKD stages 4–5 at the threshold of KRT and help guide future research on the optimal care of these patients.

Conclusion

The results of the current study show single measurements of maximal EC, TnT, and ProBNP taken prior to KRT dependence may be used to assess cardiovascular morbidity and mortality of advanced CKD patients even in the long term.

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Statement of Ethics

Medical Ethics Committee of the Hospital District of Southwest Finland approved the study design (Reference No. T05/024/20). All procedures were in accordance with the Declaration of Helsinki. All patients signed written informed consent before entering the study.

Conflict of Interest Statement

Noora Manni has received support for congress attendance from AstraZeneca. Markus Hakamäki has received consulting, lecturing, and authoring fees from MSD and Bayer and support for congress attendance from AstraZeneca and Otsuka. Niilo Liuhto, Roosa Lankinen, Jussi Pärkkä, and Mikko J. Järvisalo have no conflict of interest. Jonna Virtanen has received support for congress attendance from Otsuka Pharma. Tomi Toukola has received consulting, lecturing, and authoring fees from Boehringer Ingelheim and support for congress attendance from AstraZeneca and CSL Vifor; and also holds a position of board member and fund manager (unpaid) in the Finnish Society of Nephrology. Kaj Metsärinne has received funding from Finska Läkaresällskapet and the Perklen Foundation. Tapio Hellman has received consulting, lecturing, and authoring fees from Astellas, AstraZeneca, GSK, MSD, and Boehringer Ingelheim, and support for congress attendance from AstraZeneca.

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Author Contributions

N.M. and M.H.: data collection, data curation, original draft, formal analysis, visualization, review, and editing; N.L., R.L., J.V., T.T., and J.P.P.: data collection, data curation, review, and editing; K.M.: funding, supervision, review, and editing; M.J.J.: data collection, data curation, supervision, resources, project administration, review, and editing; T.H.: conceptualization, data collection, data curation, supervision, project administration, formal analysis, visualization, review, and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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