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Association of Longitudinal High-Sensitivity Troponin T With Mortality in Patients With Chronic Kidney Disease

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ABSTRACT

BACKGROUND Cardiac troponin T (cTnT) is associated with mortality in chronic kidney disease (CKD). However, the association between longitudinal cTnT measurements and survival has not previously been assessed.

OBJECTIVES This study determined whether various parameterizations of longitudinal cTnT measurements were associated with patient survival in the older population with advanced CKD.

METHODS The EQUAL (European QUALity) study is an observational prospective cohort study that includes subjects with stage 4-5 CKD aged ≥65 years and not on dialysis. The study includes 176 participants in Sweden, where longitudinal information of cTnT was collected. The study uses joint models for longitudinal and time-to-event data to assess the longitudinal association between cTnT and survival.

RESULTS There were 927 cTnT measurements (median 6 per patient) collected over a median follow-up of 2.4 years. The overall 5-year survival was 57% (95% CI: 46%-69%). Longitudinally measured cTnT was associated with mortality risk, with every SD increase in cTnT, at any time point, associated with a 3.3-fold increase in mortality risk (HR: 3.3; 95% CI: 2.5-4.6). The slope of the cTnT trajectory was also associated with increased mortality risk (HR: 3.2; 95% CI: 2.0-6.0), as was the area under the cTnT trajectory (HR: 4.2; 95% CI: 2.6-7.2), which reflected the cumulative cTnT exposure.

CONCLUSIONS Longitudinally measured cTnT is independently associated with mortality risk in older patients with stage 4 and 5 CKD, which suggests that monitoring patients with cTnT could be a valuable tool for the identification of subjects with a high mortality risk. (J Am Coll Cardiol 2022;79:327–336) © 2022 by the American College of Cardiology Foundation.

The global burden of chronic kidney disease (CKD) is high, affecting approximately 10% of the world's adult population.[1] Patients who have CKD have a considerably higher risk of mortality compared with the general population, particularly because of cardiovascular causes and especially those in the advanced stages of CKD.[2]

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

cTnT = cardiac troponin T

eGFR = estimated glomerular filtration rate

ERA-EDTA = European Renal Association-European Dialysis and Transplantation Association

The cardiac biomarker troponin T (cTnT), part of the troponin complex, plays a role in the regulation of myocyte contractions.[3] Following myocardial injury, cTnT is released into circulation and can be measured using high-sensitivity assays.[4] Elevated cTnT levels have also been observed in patients with CKD without significant acute myocardial necrosis, which may complicate the assessment of those with CKD and an atypical clinical presentation of myocardial injury.[5] The evaluation of cTnT in patients with CKD becomes even more challenging because the cTnT upper reference limits were originally derived from a healthy general population. There have been attempts to define the optimal cutoffs, specifically for patients with CKD. One study in patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 reported that an initial cTnT >2.5-fold higher than the 99th percentile was a predictor of acute myocardial infarction. However, this threshold resulted in an unacceptable loss of sensitivity.[6] If patients with CKD present late after the onset of chest pain, it may also be difficult to observe an increase and/or decrease in the cTnT values in the short term, particularly when the baseline value is elevated.[7]

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The elevation of cTn levels among patients with CKD is not spurious but foreshadows a worse prognosis. Previous studies established an association between baseline cTnT and mortality in dialysis-dependent[8] and nondependent CKD populations.[9-11] Longitudinal measurements of cTnT may provide additional information on the trajectory of the biomarker, which may better reflect the underlying physiology of (sub)clinical cardiovascular disease compared with a single measurement. As an example, a lower eGFR in patients with CKD was linked to more rapidly increasing cTnT.[12] However, beyond the cTnT level at the time of measurement, it remains unknown whether the speed of change in cTnT or the cumulative exposure to cTnT (reflecting patient history) provides clinically relevant information. Such information could help improve the identification and surveillance of subjects with a high mortality risk. Because the association between longitudinal cTnT measurements and mortality risk has not previously been explored we aimed to determine if: 1) longitudinal cTnT measurements; 2) the slope of cTnT over time; and 3) the cumulative cTnT exposure are associated with patient survival in the older population with advanced CKD.

METHODS

STUDY DESIGN AND POPULATION. The EQUAL (European QUALity) study is an ongoing observational multicenter prospective cohort study in patients with stage 4-5 CKD who are not on dialysis and who are receiving routine medical care in Germany, Italy, the Netherlands, Poland, Sweden, and the United Kingdom. Patients age 65 years and older were included consecutively from 2012 onward, with an incident eGFR of <20 mL/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease equation. Patients were excluded if the drop in eGFR resulted from an acute event or if they had previously received dialysis or a kidney transplant. Approval was obtained from the medical ethical committees in each country, and written informed consent was obtained from all patients. A full description of the study was published elsewhere.[13]

In the EQUAL study, the investigators in each participating country were able to outline ancillary substudies outside the core research question as add-ons to the study protocol. In Sweden, it was decided to add routine high-sensitivity cTnT to the study protocol to study changes over time and its association with renal function and various outcomes. Five nephrology clinics decided to participate in the extended study protocol and data collection. Therefore, the EQUAL cohort used for the purpose of this study included 176 patients recruited by 5 nephology clinics across Sweden (Huddinge, Solna, Danderyd, Eskilstuna, and Linköping), between April 2012 and December 2018.

EXPOSURE AND OUTCOME. High-sensitivity cTnT was analyzed at 3 different laboratories using instruments from Roche Diagnostics (Cobas e601/602, e411, or Modular E). The limit of detection was 5 ng/L with an upper limit of 10,000 ng/L, and the coefficient of variation was between 4% and 7%. Over the follow-up period, the assays, limit of detection, and coefficient of variation did not change in the respective laboratories. However, the instrument changed from Roche Modular E to Roche Cobas e602 in 1 of the laboratories where 3 of the clinics in Stockholm analyzed their samples. In addition, the cTnT method in the Eskilstuna center was not introduced until February 2013. Therefore, we included only data collected after this date for this center. Study visits and laboratory measurements were scheduled during routine follow-up at 6-month intervals, with additional visits at the initiation of dialysis, as per protocol. Patients were asymptomatic coincident with assessment of cTnT. Patients were followed until kidney transplantation (n = 4), death (n = 60), refusal

for further participation (n = 4), loss to follow-up (n = 3), or end of follow-up (n = 105). The primary outcome, all-cause mortality, was collected as part of the study protocol and validated through linkages with the Swedish national population register. Causes of death were coded in accordance with the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) coding system.

STUDY VARIABLES. Clinical data were collected through an online case record form on patient demographics, primary kidney disease, laboratory data, and cardiovascular risk factors (smoking status, body mass index, hemoglobin, blood pressure, cholesterol, and diabetes mellitus). Data on the following pre-existing cardiovascular comorbid conditions, confirmed by investigation, were also collected (definitions provided in the Appendix); cerebrovascular disease, peripheral vascular disease, myocardial infarction, angina pectoris, congestive heart failure, left ventricular hypertrophy, hypertension, and cardiac arrhythmias. Although the MDRD (Modification of Diet in Renal Disease Study) equation was used for recruitment purposes, eGFRs of the patients were calculated from serum creatinine level standardized to isotope-dilution mass spectrometry using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation for the analyses, because it was deemed more accurate than the MDRD equation.[14] Albumin-to-creatinine ratio was determined following routine 24-h urine collection. The cause of kidney disease was classified using the ERA-EDTA codes and grouped as glomerulonephritis, diabetes mellitus, tubulointerstitial disease, hypertension, and miscellaneous kidney diseases. All laboratory tests were performed according to local protocols and procedures; units of measurements were then standardized centrally.

STATISTICAL ANALYSES. Patient characteristics were reported by cTnT tertile at baseline as mean ± SD for normally distributed continuous variables, as medians with IQRs for skewed continuous variables, and as proportions for categorical variables. The evolution of cTnT over time was modeled using a linear mixed effects model. cTnT was log-transformed to improve normality. Random intercepts and random slopes for time were introduced to accommodate the variation in cTnT baseline value and cTnT trajectory between patients. Because of the nonlinear trajectory of TnT over time as observed in the data, the random effect for time was modeled using a natural cubic spline with 2 equally spaced knots positioned between the minimum and maximum of follow-up time. Cox proportional hazards regression and Kaplan-Meier curves were used to study the association between the baseline cTnT measurement and all-cause mortality. Patients were censored at kidney transplantation, discharge from nephrology clinic to primary care, withdrawal from the study, when lost to follow-up, and at the end of follow-up. All analyses were sequentially adjusted for patient sex, age, primary kidney disease, eGFR, albumin-to-creatinine ratio (log-transformed), comorbidities (diabetes, chronic heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease, angina pectoris, left ventricular hypertrophy, atrial fibrillation, hypertension), and blood chemistry (phosphate, albumin, potassium, cholesterol, calcium).

Joint models formed a powerful method for estimating the association between longitudinal measurements and survival.[15-17] We applied joint models for longitudinal and time-to-event data to assess the relationship between longitudinally measured cTnT and mortality risk in our population. The joint model linked the mixed-effects model, capturing the longitudinal cTnT measurements, to the survival model, which allowed for the estimation of the association between longitudinal cTnT and mortality risk.[18] We explored this relationship using 3 parameterizations of longitudinal cTnT. First, we estimated the association between a patient's current level of cTnT at time *t* and mortality risk at the same time point. Second, we estimated the association between the slope, which reflected the speed and direction of the cTnT trajectory, at time *t* and mortality risk at the same time point. Last, we estimated the association between the area under the longitudinal trajectory up to time *t*, as a summary measure for the cumulative cTnT exposure, and the hazard of mortality up to the same time point.[19] The R-package JMBayes was used to fit the joint models.[20] Imputation was applied to deal with missing values in covariates. All analyses were performed in R version 3.4.1 (R Foundation).

RESULTS

PATIENT BASELINE CHARACTERISTICS. Table 1 describes the baseline characteristics of 176 patients by cTnT tertile. We included 927 cTnT measurements (median of 6 per patient; IQR: 2-8) collected over a median follow-up of 2.4 years (IQR: 0.7-3.5 years). The median cTnT level at baseline was 36 ng/L (IQR: 24-56 ng/L) and was similar across all 5 nephology clinics (data not presented). On average, patients were 75 years old at inclusion, two-thirds were men, and the eGFR at baseline was 17.6 ml/min/1.73 m^2. Patients with pre-existing diabetes, atrial fibrillation,

TABLE 1 Baseline Patient Characteristics by Troponin T Tertiles

	Overall (N = 176)	cTnT Range 10-28 (n = 60)	cTnT Range 28-47 (n = 59)	cTnT Range 47-379 (n = 57)	*P* Value
Demographics					
Age, y	75.4 ± 6.4	74.6 ± 6.5	75.9 ± 6.3	75.5 ± 6.5	0.52
Male	119 (67.6)	33 (55.0)	43 (72.9)	43 (75.4)	0.04
Primary kidney disease					
Glomerular disease	24 (13.6)	7 (11.7)	6 (10.2)	11 (19.3)	0.06
Diabetes	40 (22.7)	8 (13.3)	16 (27.1)	16 (28.1)	
Hypertension	79 (44.9)	27 (45.0)	29 (49.2)	23 (40.4)	
Miscellaneous renal disorders	33 (18.8)	18 (30.0)	8 (13.6)	7 (12.3)	
Weight, kg	80.5 ± 17.8	78.4 ± 19.2	82.0 ± 14.6	81.0 ± 19.4	0.54
Height, cm	170.9 ± 10.1	168.7 ± 11.5	172.2 ± 8.7	171.8 ± 9.7	0.11
BMI, kg/m^2	27.5 ± 5.5	27.5 ± 5.9	27.6 ± 4.1	27.5 ± 6.4	0.99
Cardiovascular					
Systolic blood pressure, mm Hg	145.8 ± 21.8	143.5 ± 20.8	154.0 ± 21.8	139.7 ± 20.5	<0.001
Diastolic blood pressure, mm Hg	76.3 ± 12.2	74.9 ± 11.8	80.1 ± 11.8	73.8 ± 12.3	0.01
Hb, g/dL	7.3 ± 1.0	7.4 ± 1.0	7.5 ± 1.1	7.1 ± 1.1	0.18
Smoking status					
Current smoker	14 (8.0)	3 (5.0)	5 (8.5)	6 (10.5)	0.78
Ex-smoker	86 (48.9)	30 (50.0)	27 (45.8)	29 (50.9)	
Never	76 (43.2)	27 (45.0)	27 (45.8)	22 (38.6)	
Blood chemistry					
Albumin, g/dL	34.9 ± 4.2	36.0 ± 3.6	35.5 ± 3.8	33.1 ± 4.6	<0.001
Calcium, mmol/L	2.3 ± 0.2	2.3 ± 0.1	2.3 ± 0.2	2.3 ± 0.2	0.94
Cholesterol, mmol/L	4.6 ± 1.3	4.7 ± 1.1	4.6 ± 1.3	4.5 ± 1.5	0.65
PO4, mmol/L	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.5 ± 0.5	<0.001
Potassium, mmol/L	4.3 ± 0.6	4.4 ± 0.5	4.3 ± 0.5	4.2 ± 0.6	0.26
Renal function					
eGFR, mL/min/1.73 m^2	17.6 ± 7.1	18.6 ± 6.1	18.3 ± 7.4	15.8 ± 7.5	0.07
ACR	51.9 (12.7-172.5)	34.5 (3.6-170.0)	58.9 (16.4-162.1)	109.4 (17.2-291.4)	0.05
Comorbidities					
Diabetes	66 (37.5)	14 (23.3)	25 (42.4)	27 (47.4)	0.02
Chronic heart failure	30 (17.0)	4 (6.7)	8 (13.6)	18 (31.6)	<0.001
Cerebrovascular disease	28 (15.9)	6 (10.0)	11 (18.6)	11 (19.3)	0.30
Peripheral vascular disease	25 (14.2)	5 (8.3)	9 (15.3)	11 (19.3)	0.23
Myocardial infarction	24 (13.6)	4 (6.7)	11 (18.6)	9 (15.8)	0.14
Angina pectoris	26 (14.8)	6 (10.0)	9 (15.3)	11 (19.3)	0.36
Left ventricular hypertrophy	26 (14.8)	7 (11.7)	11 (18.6)	8 (14.0)	0.55
Atrial fibrillation	29 (16.5)	5 (8.3)	10 (16.9)	14 (24.6)	0.06
Hypertension	162 (92.0)	53 (88.3)	53 (89.8)	56 (98.2)	0.10

Values are mean ± SD, n (%), or median (IQR).

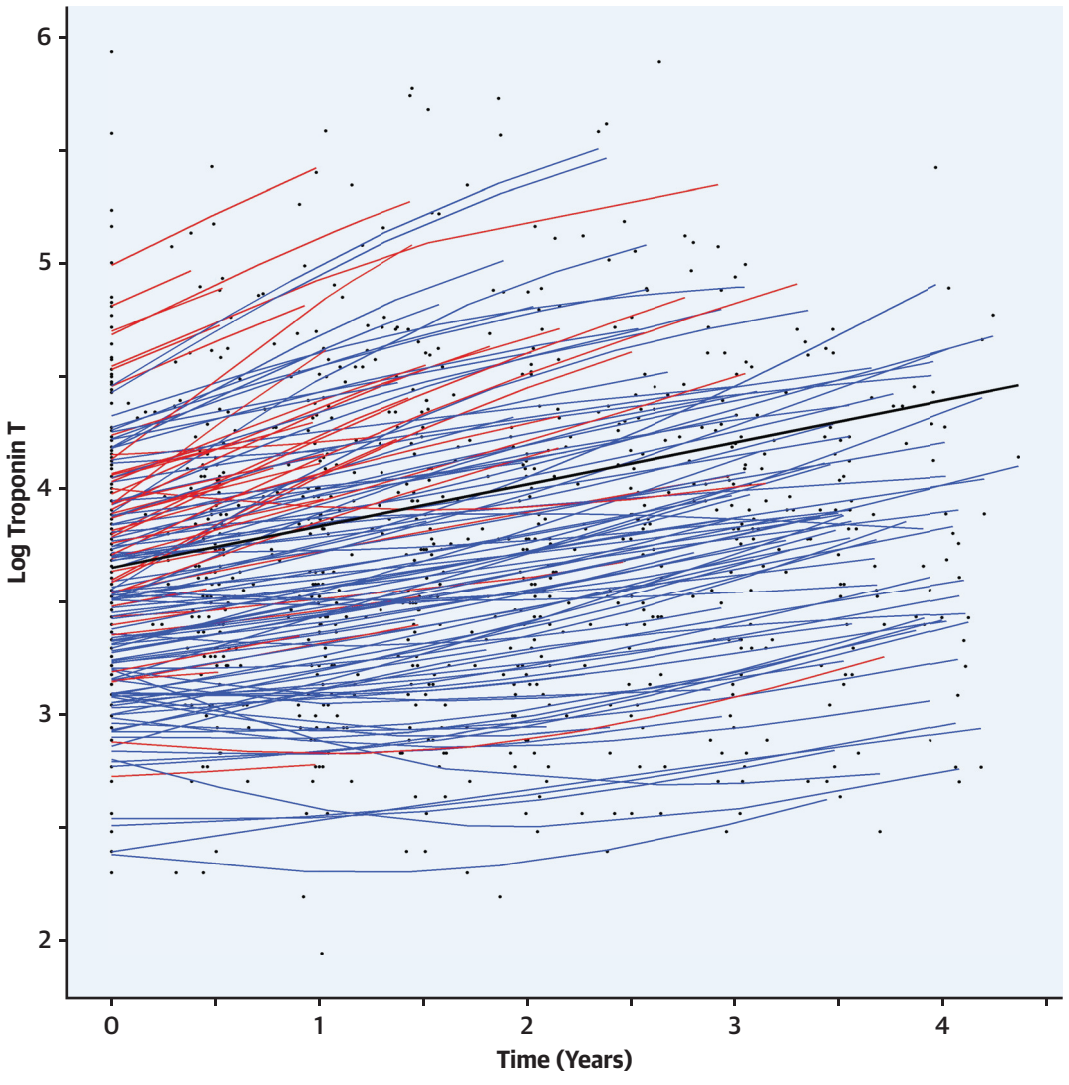
ACR = albumin-to-creatinine ratio; BMI = body mass index; cTnT = cardiac troponin T; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; PO4 = serum phosphate.

and chronic heart failure more often presented with higher baseline levels of cTnT. Individual cTnT measurements, individual cTnT trajectories (color coded by vital status), and the population average trajectory are presented in Figure 1.

PATIENT SURVIVAL AND BASELINE cTnT. During a total of 483 years of follow-up, 60 deaths occurred, 15 of which occurred while the patients were on dialysis. The distribution of cause of death is provided in Supplemental Table 1. Sixty patients initiated dialysis during follow-up. The overall 5-year survival was 57% (95% CI: 46%-69%) and was inversely correlated with baseline cTnT tertile (P <0.0001) (Figure 2). Patients in the highest cTnT tertile had a 9.1× (95% CI: 4.1-20.0) higher risk of death compared with those in the lowest cTnT tertile. Treated continuously, every SD increase in baseline cTnT was associated with a 3.2-fold increase in mortality risk (HR: 3.2; 95% CI: 2.4-4.3). Adjusting sequentially for important confounders had no meaningful impact on the risk estimates (Table 2).

PATIENT SURVIVAL AND LONGITUDINAL cTnT. Similar to the baseline effect of cTnT, longitudinally measured cTnT was associated with mortality risk

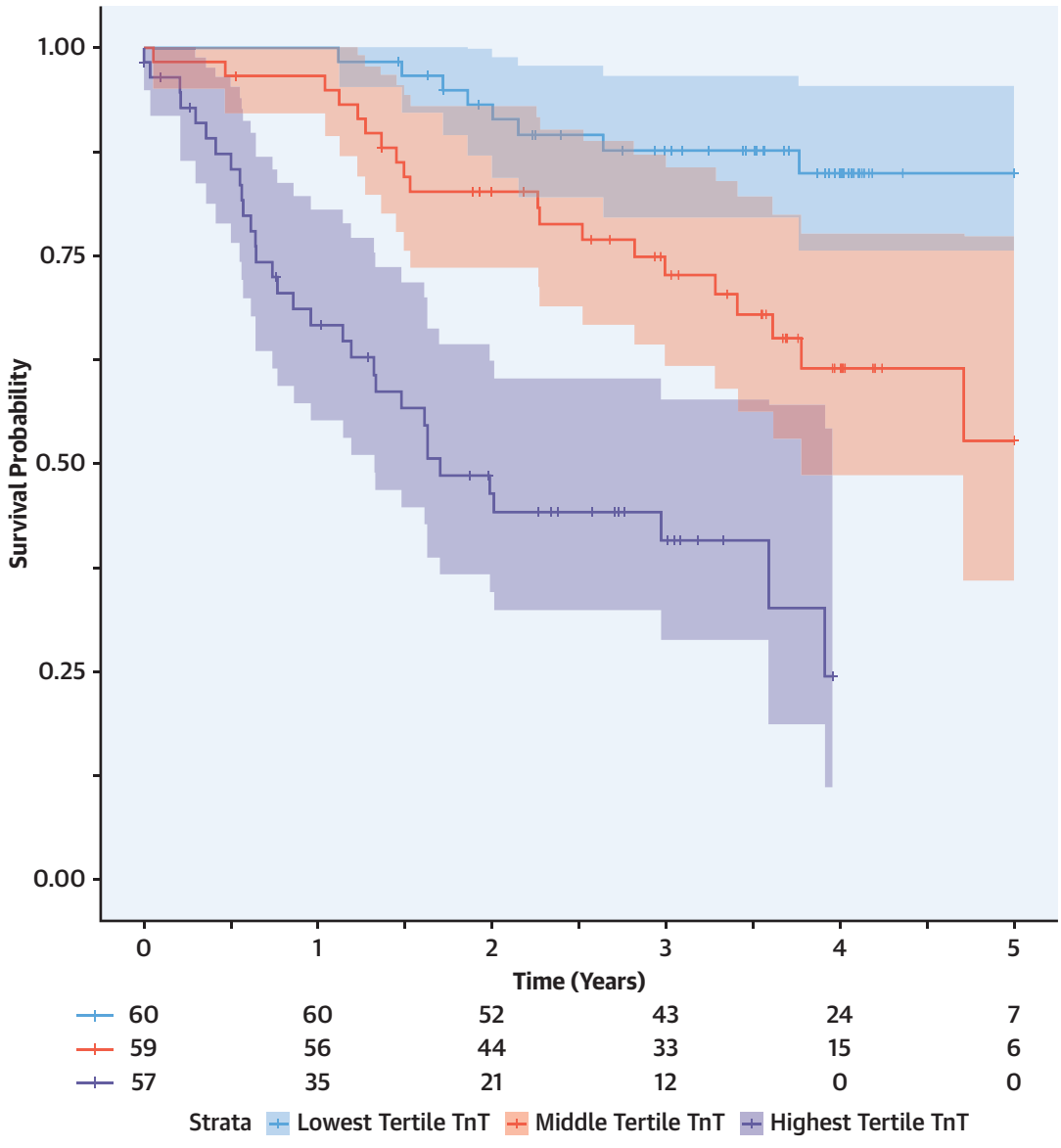
FIGURE 1 Individual and Population-Average Trajectories of cTnT



Individual cardiac troponin T (cTnT) measurements **(dots)**, individual cTnT trajectories **(lines)**, and the population average cTnT trajectory **(black lines)**. Individual cTnT trajectories are color coded by vital status (**red**: dead; **blue**: alive). Visual assessment suggests that patients with higher cTnT values and steeper cTnT slopes have a higher mortality risk.

(Table 2). The Central Illustration depicts how the cTnT level at the time of measurement, the cumulative exposure to cTnT (reflecting patient history), and the speed of change in cTnT can provide clinically relevant information on mortality risk. Every SD increase in cTnT, at any time point, was associated with a 3.3-fold increase in mortality risk (HR: 3.3; 95% CI: 2.5-4.6). The slope of the cTnT trajectory was also associated with increased mortality risk; if the cTnT slope increased by 1 SD, mortality risk would increase >3-fold (HR: 3.2; 95% CI: 2.0-6.0). As a summary measure for the patient history of cTnT levels, which accounts for both previous and current measurements, a 1 SD increase in the area under the cTnT trajectory was associated with a 4.2-fold increase (HR: 4.2; 95% CI: 2.6-7.2) in mortality risk. Effect estimates remained largely unchanged after adjustment for confounders. In a sensitivity analysis, we adjusted for time-updated confounders, including dialysis treatment, using a time-dependent Cox model, which had no meaningful impact on the HRs (Supplemental Table 2).

FIGURE 2 Patient Survival by cTnT tertile at Baseline



Patient survival and number at risk by cTnT tertile at baseline. The overall 5-year survival was 57% (95% CI: 46%-69%), and survival was inversely correlated with baseline cTnT tertile (P <0.0001). Patients in the highest cTnT tertile had a 9.1× (95% CI: 4.1-20.0) higher risk of death compared with those in the lowest cTnT tertile. Abbreviation as in Figure 1.

DISCUSSION

In the present study, using all available longitudinal cTnT measurements to assess the association with mortality risk in older patients with stage 4 and 5 CKD, we demonstrated that both cTnT at baseline and longitudinal cTnT measurements were independently associated with all-cause mortality, which supported the use of longitudinal cTnT measurements for the identification and surveillance of subjects with a high mortality risk.

Previous meta-analyses established that elevated baseline cTnT was independently associated with an approximately 3-fold increased mortality risk in both dialysis and nondialysis CKD populations,[8,21,22] which was in line with our own findings. The novelty of our

TABLE 2 The Association Between cTnT and Mortality

Model	Baseline cTnT	*P* Value	Longitudinal cTnT	*P* Value	Slope of TnT	*P* Value	Area Under Slope for TnT	*P* Value
Unadjusted	3.2 (2.4-4.3)	<0.0001	3.3 (2.5-4.6)	<0.0001	3.2 (2.0-6.0)	<0.0001	4.2 (2.6-7.2)	<0.0001
Sex, age	3.2 (2.4-4.3)	<0.0001	3.4 (2.5-4.5)	<0.0001	2.8 (1.7-5.1)	<0.0001	4.7 (2.8-8.1)	<0.0001
Primary kidney disease	3.2 (2.4-4.3)	<0.0001	3.4 (2.6-4.6)	<0.0001	3.6 (2.1-7.0)	<0.0001	4.1 (2.6-7.1)	<0.0001
eGFR, ACR	3.4 (2.5-4.5)	<0.0001	3.7 (2.7-5.1)	<0.0001	2.5 (1.6-4.0)	<0.0001	4.8 (2.8-8.5)	<0.0001
Comorbidities	3.0 (2.2-4.1)	<0.0001	4.0 (2.7-5.9)	<0.0001	3.4 (2-7.4.0)	<0.0001	4.8 (2.7-8.5)	<0.0001
Lab chemistry	2.8 (2.0-4.0)	<0.0001	3.7 (2.5-5.6)	<0.0001	2.1 (1.2-3.7)	<0.0001	3.8 (2.3-6.7)	<0.0001

HRs and 95% CIs for the effect of a SD increase in cTnT on mortality, adjusted sequentially for confounders. The unit for baseline cTnT is a SD increase in cTnT. The unit for longitudinal cTnT is a SD increase in the present value of cTnT. The unit for the cTnT slope is a SD increase in slope (cTnT/year). The unit for area under the trajectory for cTnT is a SD increase in the area under the cTnT trajectory. All analyses are based on log-transformed cTnT. Analyses were sequentially adjusted for patient sex, age, primary kidney disease, estimated glomerular filtration rate (eGFR), ACR (log-transformed), comorbidities (diabetes, chronic heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease, angina pectoris, left ventricular hypertrophy, atrial fibrillation, hypertension), and blood chemistry (phosphate, albumin, potassium, cholesterol, calcium) at baseline.

Abbreviations as in Table 1.

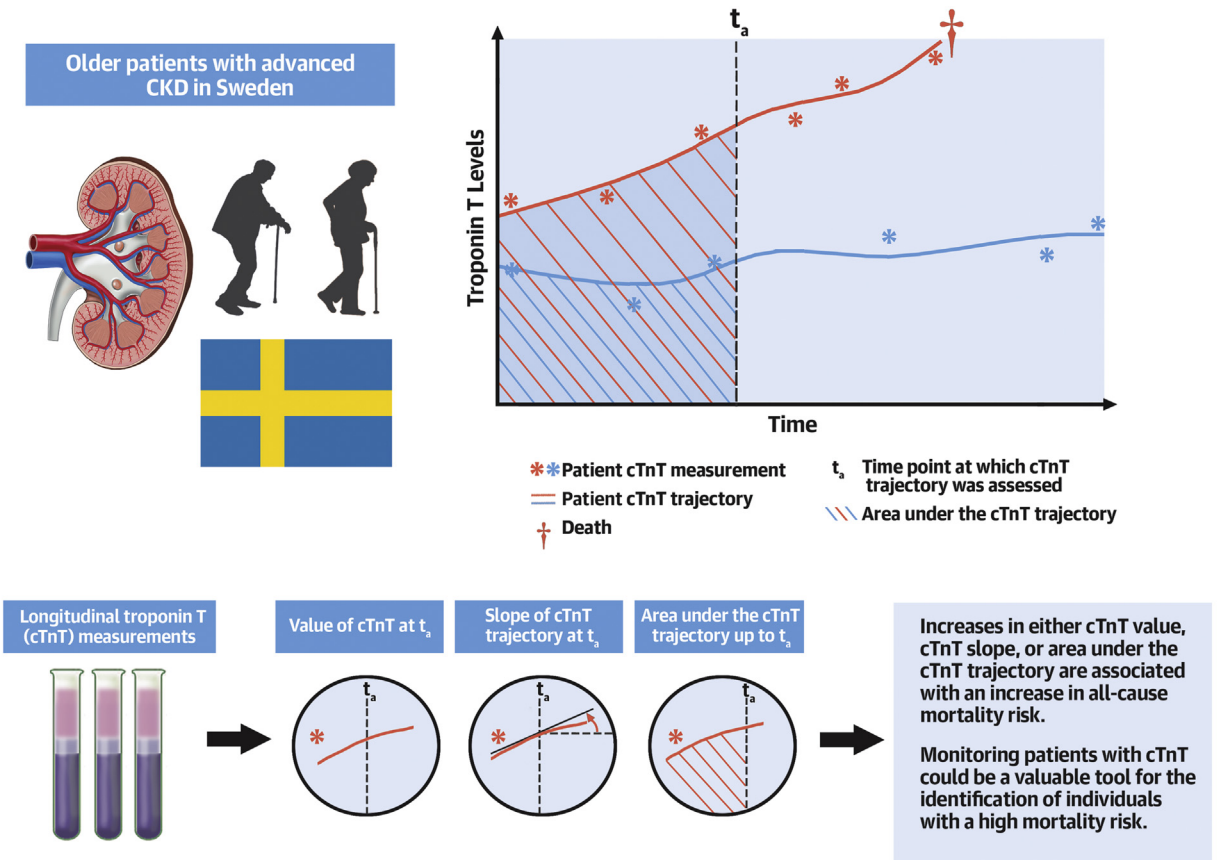
study was the assessment of regularly measured longitudinal cTnT over the course of several years in nondialysis patients with CKD and its association with mortality. Although some previous studies investigated the association between serial troponin measurements over a shorter time frame, studies on cTnT measured over longer periods of time and mortality risk are lacking. In our present study, we demonstrated that the longitudinally measured cTnT (current value, slope, and cumulative history) was strongly associated with mortality risk, which suggested that this type of information might have added clinical value, and that individual changes in the evolution of cTnT over time were likely to be physiologically and clinically relevant to a patient's prognosis.

Several studies conducted in dialysis populations supported our findings. In hemodialysis patients with serial measurements of cTnT collected 3 months apart over a median of 23 months follow-up, Sandoval et al[23] demonstrated that changes in cTnT identified patients at greater risk of all-cause mortality. In a cohort of asymptomatic hemodialysis patients, Roberts et al[24] assayed cTnT 5 times over the course of a year and found that the frequency of abnormal measurements was associated with mortality. Recently, Mavrakanas et al[25] measured TnI every 3 months over a year in another cohort of hemodialysis patients, finding that either persistently elevated or fluctuating TnI values were associated with a higher mortality risk. Moreover, the investigators demonstrated that serial TnI measurements conveyed a higher sensitivity and higher negative predictive value for all-cause mortality compared with a single measurement.[25] The ability to monitor changes using serial cTnT measurements to improve the identification of vulnerable patients was also demonstrated in other populations. For example, in patients with chronic heart failure with serial cTnT measurements, elevations in cTnT detected during follow-up were strongly associated with an increased risk of adverse clinical events, especially in those with frequent or persistent cTnT elevations.[26-30]

A unique strength of our study was that cTnT was measured prospectively throughout follow-up using high-sensitivity fifth-generation TnT assays, which were shown to be superior to conventional assays, especially at low levels of high-sensitivity TnT.[31] An additional strength of our study was that patients were prospectively included when their eGFR dropped below the predefined level, thus minimizing the selection of healthier survivors in our cohort. Finally, we leveraged the ability of joint models to associate a longitudinal biomarker with a survival outcome using various parametrizations.[20] We first assessed the association between longitudinal cTnT at any given point during follow-up and mortality risk, which we subsequently complemented by assessing whether the cTnT slope and a summary measure of cTnT history provided additional clinically relevant information. In the context of prediction modelling, joint models are capable of updating individual survival probabilities as additional measurements become available, thus providing opportunities for dynamic and individualized predictions of survival during follow-up.[20]

STUDY LIMITATIONS. First, because of the observational nature of our study, we were unable to infer causality to our findings. We lacked data on waitlist status, which would have provided an indication of patient risk, although because of the older age of patients and the low incidence of transplantation in our population, we expected a low percentage of patients to be on the waitlist for a transplant. Second,

CENTRAL ILLUSTRATION **Longitudinal Troponin T Is Associated With Mortality in Advanced Chronic Kidney Disease**



Chesnaye, N.C. et al. J Am Coll Cardiol. 2022;79(4):327–336.

In older patients with advanced chronic kidney disease (CKD), increases in longitudinally measured high-sensitivity troponin T are associated with mortality risk. The cardiac troponin T (cTnT) level at the time of measurement, the cumulative exposure to cTnT (reflecting patient history), and the speed of change in cTnT provides clinically relevant information that could help improve the identification and surveillance of subjects with a high mortality risk.

cTnT was measured at different laboratories, although similar instruments were used with equal limits of detection and coefficients of variation. Third, we were unable to directly compare the effect size of various cTnT parametrizations, precluding any statistical comparisons of the strength of these associations. Furthermore, because most patients were Caucasian, and our population was limited to CKD stages 4 and 5, our results might not be generalizable to other populations. In addition, our older study population (mean age of 75 years) was representative of referred patients with CKD in Sweden; therefore, this might not be the case for other regions. Consequently, further research on the association between cTnT and mortality risk is required in a larger and more diverse population to confirm our findings.

CONCLUSIONS

Both cTnT levels at baseline and longitudinally measured cTnT were independently associated with mortality risk in older patients with stage 4 and 5 CKD, which suggested that this information might provide nephrologists with a valuable tool for the identification and surveillance of subjects with a high

mortality risk, which, in turn, may guide decision making and a more targeted approach to the clinical management of older patients in stage 4 and 5 CKD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with CKD, blood levels of cTnT are associated with mortality. Compared with a single measurement, longitudinal measurements of cTnT better reflect subclinical cardiovascular disease in this population.

TRANSLATIONAL OUTLOOK: Additional research is needed to determine the optimal frequency and cost-effectiveness of cTnT measurements for risk assessment and surveillance in patients with CKD.

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KEY WORDS chronic kidney disease, joint model, survival, troponin T

APPENDIX For supplemental tables, please see the online version of this paper.