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Association of long cardiac troponin T forms with adverse long-term outcomes in patients with advanced chronic kidney disease

Selma Salonen[1], Emilia Kaipainen[1], Markus Hakamäki[2], Niilo Liuhto[2], Noora Manni[2], Tomi Toukola[3], Jonna Virtanen[2], Roosa Lankinen[2], Kaj Metsärinne[2], Tuija Vasankari[4], K. E. Juhani Airaksinen[4], Mikko J. Järvisalo[5], Saara Wittfooth[1†] and Tapio Hellman[2*†]

Abstract

Background Commercial high-sensitivity cardiac troponin T (hs-cTnT) assays measure both intact and degraded cTnT forms (i.e. total cTnT) and values are often elevated in chronic kidney disease (CKD) patients. The measurement of long cTnT forms has recently shown improved specificity for acute myocardial infarction compared to total cTnT. However, the associations between long cTnT and adverse long-term outcomes in CKD are unknown.

Methods Altogether, 136 CKD stage 4–5 patients not on dialysis were included in this prospective cohort study. Long cTnT and total cTnT levels before dialysis initiation were measured using investigational in-house immunoassays. The associations between cTnT measurements and all-cause mortality, incident major adverse cardiovascular or cerebrovascular events (MACCE), new-onset atrial fibrillation (NOAF) and a composite adverse outcome (all-cause mortality or MACCE) were assessed.

Results Mean age was 61 (±13) years, 47 (34.6%) were female and median values for long cTnT and total cTnT were 1.9 (1.3–3.0) ng/L and 37 (23–66) ng/L, respectively. After a median follow-up of 6.2 (4.6–7.7) years, 62 (45.6%) patients had died, 36 (26.5%) had experienced MACCE, 28 (23.3%) NOAF and 76 (55.9%) a composite adverse outcome. In multivariable Cox models adjusted for age, sex and coronary artery disease (CAD), long cTnT and total cTnT were independently associated with all-cause mortality, NOAF and the composite adverse outcome, while only total cTnT was associated with MACCE. Replacing the adjustment for CAD with kidney transplantation in the multivariable models weakened the significance of the associations.

Conclusions We describe for the first time associations between long cTnT and long-term cardiovascular adverse outcomes and all-cause mortality in a prospective cohort of CKD stage 4–5 patients.

Trial registration https://www.ClinicalTrials.gov NCT04223726. Retrospectively registered in December 10, 2019.

Keywords Chronic kidney disease, Cardiovascular, Atrial fibrillation, Biomarkers, Cardiac troponin T, Survival analysis

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[†] Saara Wittfooth and Tapio Hellman contributed equally to this work.

*Correspondence:
Tapio Hellman
tapio.hellman@varha.fi
[1] Biotechnology Unit, Department of Life Technologies, University of Turku, Turku, Finland
[2] Kidney Center, Turku University Hospital and University of Turku, Turku, Finland
[3] Department of Nephrology, Vaasa Central Hospital, Vaasa, Finland
[4] Heart Center, Turku University Hospital and University of Turku, Turku, Finland
[5] Department of Internal Medicine, The Wellbeing Services County of Satakunta, Pori, Finland

Background

Cardiac troponins (cTn) are the gold standard biomarkers for the detection of myocardial injury and diagnosis of acute myocardial infarction (AMI) [1]. Persistently elevated high-sensitivity cardiac troponin T (hs-cTnT) levels are common in patients with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, which potentially reflects both increased myocardial stress and reduced renal elimination of cTnT [2–6].

The current hs-cTnT assays detect intact cTnT as well as mildly and heavily degraded cTnT forms (i.e. total cTnT). Importantly, intact cTnT and only mildly degraded cTnT fragments (i.e. long cTnT forms) seem to be most prominent components of troponin release in the blood of early-presenting AMI patients, while small heavily degraded cTnT fragments become the predominant form later after AMI [7–9]. Small cTnT fragments also seem to prevail in other conditions associated with hs-cTnT elevations, such as end-stage kidney disease (ESKD), Takotsubo syndrome and following strenuous exercise, which may indicate different release mechanisms of cTnT [10–14]. Recently, a novel highly sensitive immunoassay was developed for the detection of long cTnT forms showing increased specificity for AMI by effectively discriminating between cTnT elevations in non-ST elevation myocardial infarction (NSTEMI) and ESKD patients undergoing hemodialysis [15].

Constantly elevated total cTnT measured with the commercial hs-cTnT assay has been associated with adverse long-term outcomes in CKD including ESKD patients receiving maintenance dialysis as well as in the general population [2, 16–19]. We recently described an independent association between total cTnT and all-cause mortality as well as new-onset atrial fibrillation (NOAF) in patients with CKD stage 4–5 not on dialysis [20, 21]. However, cTnT fragmentation has not yet been studied in the setting of CKD stage 4–5 prior to dialysis initiation and no data exist on the association between long cTnT forms and long-term adverse outcomes. The aim of the present study was to analyze long cTnT concentrations in patients with CKD stage 4–5 using a novel highly sensitive long cTnT assay and to examine the associations between long cTnT forms and all-cause mortality, incident major adverse cardiovascular or cerebrovascular events (MACCE) and incident NOAF.

Methods

Patients

The Chronic Arterial Disease, quality of life and mortality in chronic KIDney injury (CADKID) study (ClinicalTrials.gov, NCT04223726, retrospectively registered in December 10, 2019) is an ongoing, prospective follow-up study assessing arterial disease, quality of life, and mortality in patients with CKD stage 4–5. Altogether, 210 consecutive patients referred to the predialysis outpatient clinic of Turku University Hospital were recruited to the CADKID study between August 2013 and September 2017.

In total, 58 patients were excluded from the study as Li-heparin plasma samples were not available. Furthermore, 7 patients with samples collected over one year after recruitment to the CADKID study, 7 patients initiating dialysis prior to or at the day of sampling and 1 patient with a missing sampling date were excluded from the present analysis. Thus, a cohort of 137 patients entered the analyses for the study. The Li-heparin plasma samples were stored at −70 °C until long cTnT and total cTnT analyses.

Outcomes

The study outcomes included all-cause mortality, MACCE, NOAF and a composite adverse outcome (for definitions see Supplementary Methods). All study outcomes as well as dialysis initiations and kidney transplantations (KTx) were manually collected by the researchers from the electronic patient records of the research hospital. All study outcomes were confirmed by the attending clinician – NOAFs with ECGs or pacemaker logs, acute myocardial infarctions with ECGs and standard commercial hs-cTnT assays and strokes with standard imaging techniques. No independent adjudication was performed. The follow-up period lasted from the time of recruitment to the end of the year 2022. All patients resided in the catchment area of the study hospital throughout the follow-up period in terms of diagnosis and care of study outcomes. All mortality data are recorded into the patient archives of the research hospital via a data link with the national Digital and Population Data Services Agency.

Ethics

The study protocol (reference No. T05/024/20) was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the study was conducted in accordance with the Declaration of Helsinki. All participants provided a written informed consent before entering the study.

Analytical methods

Long cTnT concentrations were measured with a novel highly sensitive upconversion luminescence (UCL)-based sandwich-type immunoassay [15]. The anti-cTnT monoclonal antibodies (mAb) and human cardiac troponin ITC-complex used as the calibrator were obtained from HyTest (Finland). The capture antibody (7E7 mAb) and tracer antibody (1C11 mAb) target amino acid residues (aar) 223–242 and 171–190, respectively. Thus, the assay detects cTnT forms that are not degraded at the major

C-terminal cleavage site at aar 189–223. The limit of detection and quantitation of the assay are 0.4 ng/L and 1.8 ng/L, respectively [15].

Total cTnT was also analyzed using a non-commercial UCL-based in-house immunoassay. The selected capture antibody (300 mAb, HyTest) and tracer antibody (406 mAb, HyTest) bind to aar 119–138 and 132–151, respectively, resembling the setup of the widely used commercial hs-cTnT immunoassay (Elecsys hs-cTnT, Roche Diagnostics GmbH, binding sites aar 125–131 and 136–147). As the total cTnT assay targets the stable central region of the cTnT molecule, it can detect intact as well as mildly and heavily degraded forms of cTnT. Except for the different antibody combination and the supplementation of the tracer antibody dilution buffer with 0.1 M NaCl, the total cTnT assay was performed similarly to the previously published long cTnT assay protocol [15]. Comparison of the developed UCL total cTnT assay with the commercial hs-cTnT assay (Elecsys hs-cTnT, Roche Diagnostics GmbH, Mannheim, Germany) was performed by analyzing 20 patient samples from the TropoFragm study (ClinicalTrials.gov NCT04465591) resulting in a Pearson's correlation coefficient of 0.86 and mean relative bias of 9% (SD 26%). When two outliers were removed, the correlation became stronger (Pearson's r=0.97) and mean relative bias decreased to 2% (SD 16%) (Supplementary Fig. S1). The developed total cTnT assay was able to reach the analytical detection limit (zero calibrator + 3 × standard deviation, n=40) of 0.5 ng/L.

All samples were analyzed in duplicates in both long cTnT and total cTnT analyses. The troponin ratio was calculated by dividing the long cTnT result by the total cTnT result.

Statistical analysis

The results are presented as mean (SD) and median (25th– 75th percentiles) for normally distributed variables and skewed variables, respectively. Normality in continuous variables was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests.

The associations between cTnT values (long cTnT, total cTnT and troponin ratio) and outcomes (all-cause mortality, MACCE, NOAF or the composite adverse outcome) were studied using univariate and multivariable Cox proportional hazard models as well as Kaplan-Meier survival analysis and the log-rank test. The multivariable Cox models were adjusted for age, sex, and coronary artery disease (CAD) or KTx separately (i.e. two distinct multivariable models adjusted for age, sex and CAD or age, sex and KTx) to avoid the risk of overfitting. The optimal cut-off values of long cTnT and total cTnT for predicting all-cause mortality and the composite adverse outcome were defined using the Youden Index.

Separate univariate linear regression analyses were used to identify factors significantly associated with long cTnT and total cTnT values (both log transformed). Multivariable linear regression analyses adjusted for age, sex and eGFR were performed for each covariate with significant univariate association at $p < 0.05$ level with the dependent variable.

All tests were two-sided and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software version 29.0.

Results

Patient characteristics and study outcomes

A total of 136 patients with CKD stage 4–5 were included in the final study cohort; one patient was excluded as an outlier due to highly deviant total cTnT and long cTnT values that were inconsistent with the clinical presentation of the patient. Serial dilutions of the plasma sample showed non-linearity indicating the presence of interference in the sample. The included patients were slightly younger and had a lower prevalence of cardiovascular comorbidities compared to the excluded patients, while no difference in terms of study outcomes was observed between the groups (Supplementary Table S1). The baseline characteristics, cTnT measurements and study outcomes of the included patients are shown in Table 1. Mean age of the patients was 61 (±13) years, 47 (34.6%) patients were female and median eGFR was 12 (11–15) mL/min/1.73 m^2. Median values for total cTnT and long cTnT were 37 (23–66) ng/L and 1.9 (1.3–3.0) ng/L, respectively. Median troponin ratio was 0.05 (0.03–0.07).

After a median follow-up of 6.2 (4.6–7.7) years, 62 (45.6%) patients had died, 36 (26.5%) patients had experienced an incident MACCE and 28 (23.3%) a NOAF. Altogether 76 (55.9%) patients either died or experienced a MACCE i.e. the composite adverse outcome during follow-up. At the end of follow-up, 59 (43.4%) patients had started dialysis treatment, and 16 (11.8%) patients had not. Moreover, 61 (44.9%) patients had received a KTx (after dialysis) and the median time to KTx was 2.3 (1.5–3.8) years. Out of the 61 KTx recipients, 10 (16.4%) died during follow-up. Correspondingly, 52 (69.3%) patients died out of the 75 that did not receive a KTx during the study.

Associations between cTnT measurements and all-cause mortality

All the univariate and multivariable Cox proportional hazards analyses exploring the associations between total cTnT, long cTnT or the troponin ratio and study outcomes are summarized in Table 2.

Total cTnT and long cTnT were associated with all-cause mortality both in the univariate Cox proportional hazards analyses and multivariable Cox proportional

Table 1 Baseline characteristics and study outcomes

	Study cohort (*N* = 136)
Age (years)	61 (±13)
Female	47 (34.6%)
eGFR (mL/min/1.73 m^2)	12 (11–15)
Body mass index (kg/m^2)	27.9 (24.5–30.8)
History of smoking	57 (42.2%)
Hypertension	132 (97.1%)
Diabetes	62 (45.6%)
Coronary artery disease	17 (12.5%)
Prior myocardial infarction	11 (8.1%)
History of heart failure	23 (16.9%)
History of atrial fibrillation	16 (11.8%)
Peripheral artery disease	20 (14.7%)
Prior stroke	14 (10.3%)
Laboratory measurements	
Total cTnT (ng/L)	37 (23–66)
Long cTnT (ng/L)	1.9 (1.3–3.0)
Troponin ratio	0.05 (0.03–0.07)
Outcomes	
Total follow-up (years)	6.2 (4.6–7.7)
All-cause mortality	62 (45.6%)
MACCE	36 (26.5%)
NOAF[a]	28 (23.3%)
Composite adverse outcome	76 (55.9%)

Values are presented as counts (percentages) for categorical variables, and as means (standard deviations) for normally distributed continuous variables, or medians (25th percentile–75th percentile) for non-normally distributed continuous variables. eGFR, estimated glomerular filtration rate; cTnT, cardiac troponin T; MACCE, major adverse cardiovascular or cerebrovascular event; NOAF, new-onset atrial fibrillation.

[a] *N* = 120

hazards models adjusted for age, sex, and CAD (Table 2). However, the associations between all-cause mortality and total cTnT or long cTnT became nonsignificant when KTx was included as a covariate in the multivariable models instead of CAD. The binary cut-off values for total cTnT and long cTnT were determined at 38 ng/l and 1.89 ng/L, respectively, and both of the resulting binary cTnT variables were associated with all-cause mortality in the univariate Cox models ($p < 0.001$ for both comparisons). The Kaplan-Meier survival curves for all-cause mortality according to total cTnT and long cTnT are shown in Fig. 1.

Associations between cTnT measurements and other adverse outcomes

The association between total cTnT and MACCE, but not between long cTnT and MACCE, was significant after adjusting for age, sex and CAD or KTx (Table 2). Regarding incident NOAF, a significant association with long cTnT after adjusting for age, sex and CAD or KTx was observed while the associations between NOAF and total cTnT were less consistent in the multivariable analyses (Table 2).

The association between the composite adverse outcome and total cTnT was significant in both of the adjusted multivariable Cox analyses (Table 2). The association between the composite adverse outcome and long cTnT was weaker in the multivariable Cox model adjusted for age, sex and CAD and non-significant in the model adjusted for age, sex and KTx. The binary cut-off variables of total cTnT and long cTnT were also associated with the composite adverse outcome in the univariate Cox models ($p < 0.001$ for both comparisons). The Kaplan-Meier survival curves illustrating the associations between the composite adverse outcome and total cTnT and long cTnT are shown in Fig. 2.

Finally, the troponin ratio was not associated with any of the studied adverse outcomes in the univariate Cox proportional hazards analyses (Table 2).

Associations between baseline characteristics and cTnT measurements

In separate univariate linear regression models, diabetes, CAD and peripheral artery disease (PAD) were found to be associated with total cTnT and long cTnT levels, whereas older age and male sex were only associated with total cTnT levels. In separate multivariable linear regression analyses adjusted for age, sex and eGFR, the associations of total cTnT and long cTnT with diabetes, CAD and PAD remained significant (Supplementary Table S2).

Discussion

Long cTnT forms have been predominantly detected in the blood of early-presenting AMI patients and thus, the measurement of long cTnT shows promise for higher specificity for AMI compared to the current commercial hs-cTnT measurement. The present study demonstrated for the first time that long cTnT forms measured with our novel highly sensitive long cTnT assay were independently associated with all-cause mortality, NOAF and the composite adverse outcome in patients with CKD stage 4–5 not receiving dialysis at baseline in the multivariable Cox models adjusted for age, sex and CAD. Risk prediction in KTx recipients appears to be more difficult, however, as none of the associations between long cTnT and mortality or MACCE or the composite adverse outcome remained significant in the multivariable Cox models adjusted for age, sex and KTx.

KTx is strongly associated with improved quality of life and increased long-term survival in CKD patients and the most important treatment modality for improving long-term survival in maintenance dialysis patients [22, 23]. Thus, it was not surprising that most of the associations between long cTnT or total cTnT and adverse outcomes related to long-term survival lost their significance

Table 2 Univariate and multivariable Cox models exploring the associations between total cTnT, long TnT or troponin ratio and the study outcomes

Outcome	**Total cTnT**		**Long cTnT**		**Troponin ratio**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Univariate Cox models						
All-cause mortality	1.008 (1.004–1.011)	<0.001	1.019 (1.005–1.033)	0.007	1.598 (0.240–10.644)	0.628
MACCE	1.008 (1.004–1.012)	<0.001	1.015 (0.998–1.033)	0.088	2.171 (0.258–18.281)	0.476
NOAF	1.007 (1.002–1.012)	0.005	1.023 (1.008–1.039)	0.003	2.605 (0.312–21.771)	0.377
Composite adverse outcome	1.008 (1.005–1.011)	<0.001	1.015 (1.002–1.028)	0.021	1.491 (0.260–8.568)	0.654
Multivariable Cox models adjusted for age, sex and CAD						
All-cause mortality	1.006 (1.003–1.010)	<0.001	1.019 (1.005–1.033)	0.007	-	-
MACCE	1.008 (1.004–1.012)	<0.001	1.015 (0.997–1.033)	0.099	-	-
NOAF	1.007 (1.001–1.012)	0.014	1.024 (1.008–1.040)	0.003	-	-
Composite adverse outcome	1.007 (1.004–1.010)	<0.001	1.015 (1.002–1.028)	0.027	-	-
Multivariable Cox models adjusted for age, sex and KTx						
All-cause mortality	1.004 (1.000–1.008)	0.056	1.013 (0.999–1.027)	0.069	-	-
MACCE	1.005 (1.001–1.010)	0.026	1.009 (0.991–1.027)	0.310	-	-
NOAF	1.005 (0.999–1.011)	0.109	1.020 (1.004–1.037)	0.012	-	-
Composite adverse outcome	1.005 (1.001–1.008)	0.007	1.009 (0.996–1.022)	0.177	-	-

cTnT, cardiac troponin T; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiovascular or cerebrovascular event; NOAF, new-onset atrial fibrillation; KTx, kidney transplantation

in the context of KTx. The difference in the number of significant associations between cTnT measurements and outcomes in multivariable Cox models adjusted for CAD or KTx may be related to the presence of uremic inflammation. Notably, low intensity inflammation is an established risk factor for the instability of coronary plaques in CAD and, consequently, cardiovascular events and mortality [24] and total cTnT has been linked to the release of inflammatory biomarkers during non-cardiac diseases [25]. Furthermore, high prevalence of oxidative stress and inflammation are common in patients with advanced CKD and, in fact, a decline in various inflammatory biomarkers has been shown to occur after KTx [26]. In line with these data, the predictive effect of long cTnT and total cTnT for future adverse outcomes related to inflammation and subsequent mortality in advanced CKD may be dampened by the profound anti-inflammatory effect of KTx.

Nevertheless, the independent associations between long cTnT and the measured adverse outcomes apart from MACCE adjusted for age, sex and CAD were highly significant and the hazard ratios comparable to those of total cTnT. While further research is required, these results suggest that long cTnT that represented only 5% of the total cTnT may carry a substantial part of the prognostic weight related to cTnT in the prediction of long-term adverse outcomes in predialysis CKD stage 4–5 patients that are not eligible for KTx. This patient population is substantial in size as only every fifth dialysis patient was wait-listed in the United States in a recent national survey [27] and, as such, long cTnT may have potential in the risk assessment of future adverse outcomes in the majority of ESKD patients. However, the fact that total cTnT had more significant associations with adverse outcomes of interest apart from NOAF in our study compared to long cTnT suggests that total cTnT may currently be more useful in the prediction of long-term survival and cardiovascular outcomes in patients with advanced CKD. Ultimately, the differences in the prognostic values of long and total cTnT in the prediction of long-term outcomes require further research.

Long cTnT is released in large quantities into the circulation through acute myocardial necrosis especially during AMI and has demonstrated remarkable capacity in distinguishing cTnT elevations related to AMI from those of ESKD [15]. Long cTnT is suspected to be

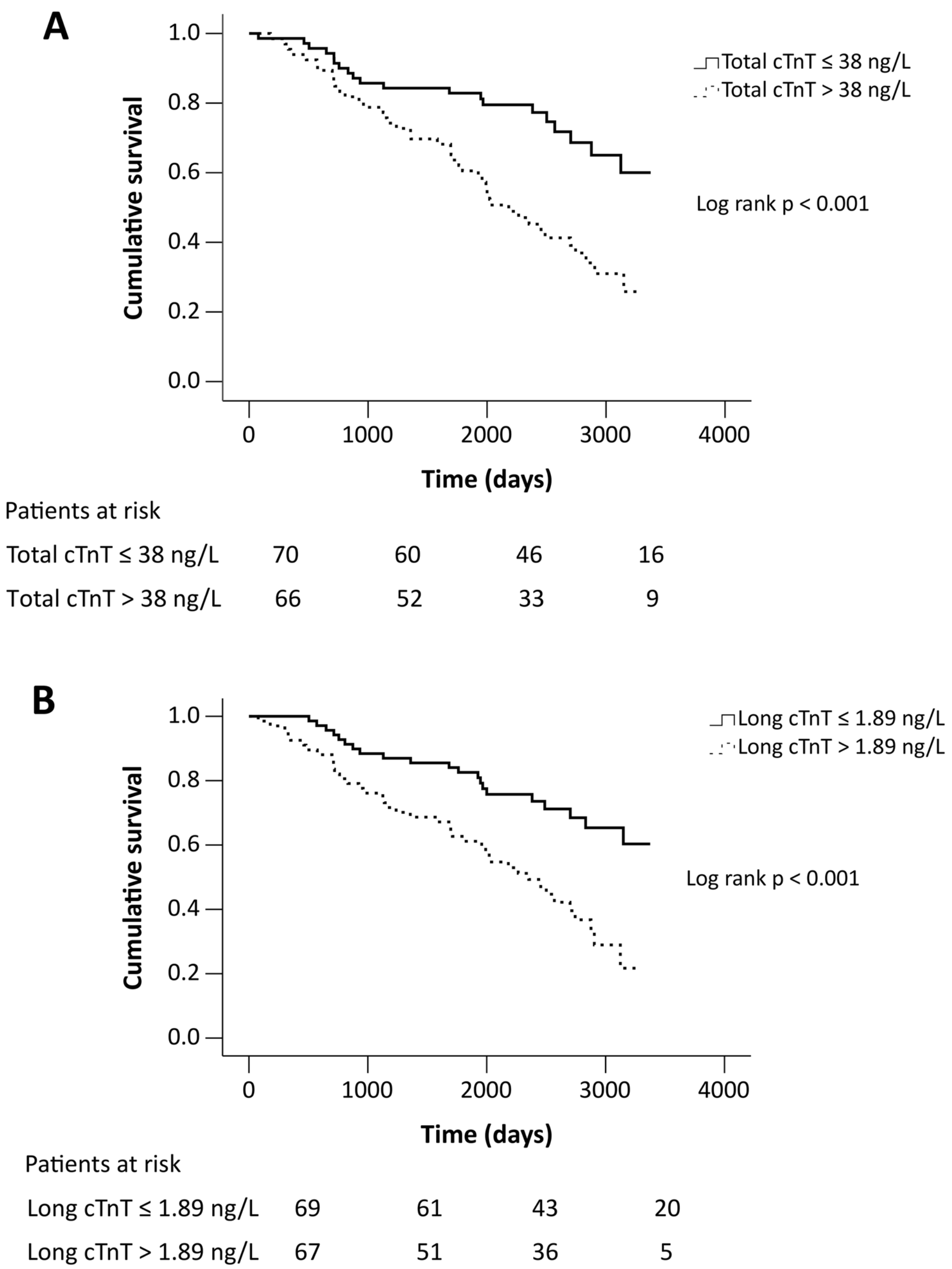
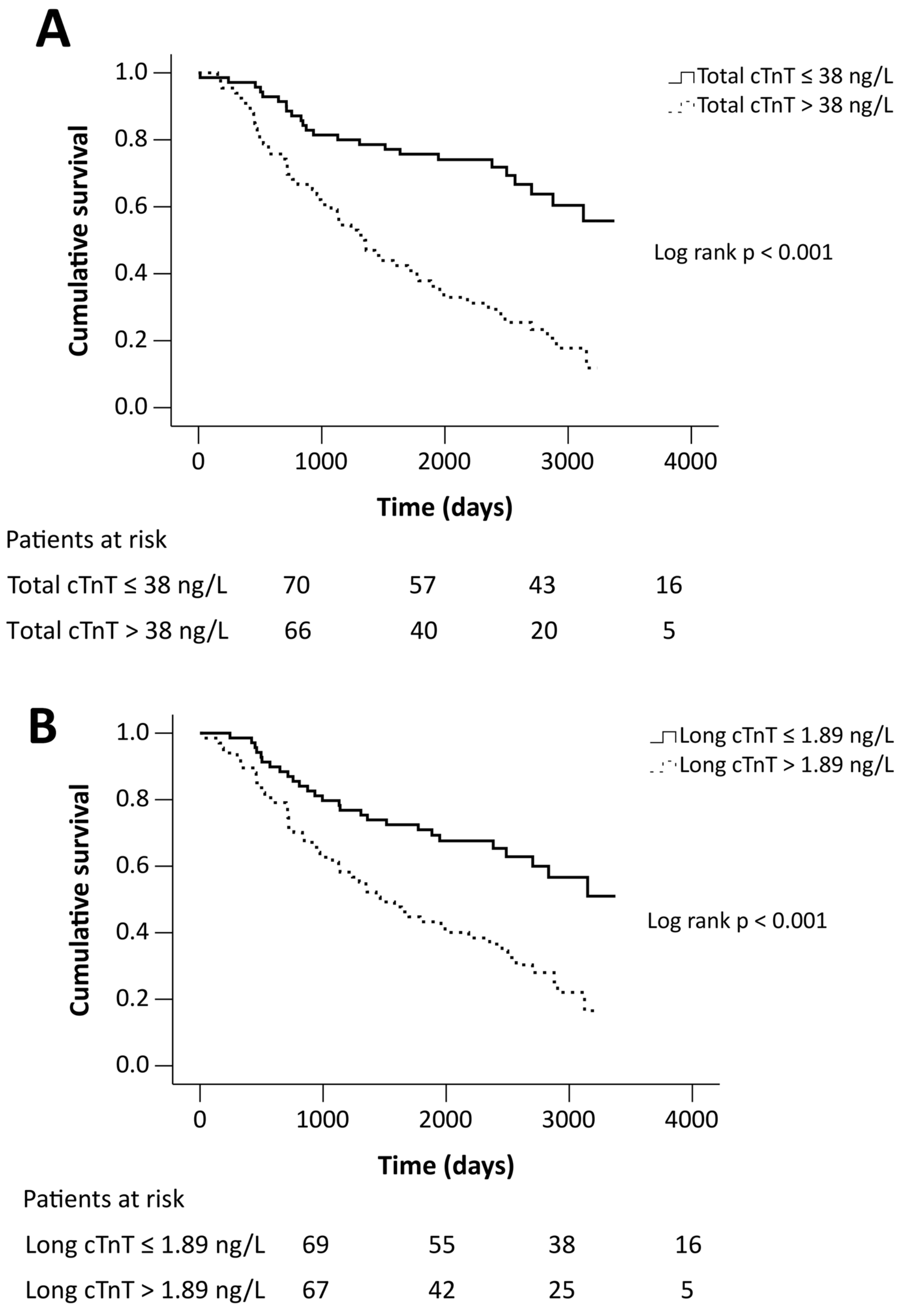


Fig. 1 Kaplan-Meier curves for all-cause mortality according to total cTnT (**A**) and long cTnT (**B**). cTnT, cardiac troponin T

a more specific marker for acute myocardial necrosis compared to total cTnT and has potential especially in improving the diagnostic accuracy of AMI in the setting of emergency care [11]. Smaller cTnT fragments seem to be released in reversible and/or more chronic myocardial injury patterns through other mechanisms that, for example, increase cell membrane permeability in the myocardial cells [28]. As long cTnT is observed only in low quantities in the circulation during stable clinical conditions, it is possible that the more abundant smaller cTnT fragments (that comprise most of the total cTnT outside acute myocardial damage) better represent reversible myocardial injury, the severity of cardiovascular burden and uremic inflammation in CKD patients. Nevertheless, both cTnT measurements were associated with the same cardiovascular comorbidities at baseline in the adjusted multivariable linear regression models in these patients suggesting that long cTnT levels are affected by the cardiovascular burden also in the non-acute setting.

Unsurprisingly, troponin ratio, a measure representing the extent of the prompt fragmentation process of cTnT from larger and longer to shorter and smaller forms at a given time point, was not associated with any of the



Patients at risk

Total cTnT ≤ 38 ng/L	70	57	43	16
Total cTnT > 38 ng/L	66	40	20	5

Patients at risk

Long cTnT ≤ 1.89 ng/L	69	55	38	16
Long cTnT > 1.89 ng/L	67	42	25	5

Fig. 2 Kaplan-meier curves for the composite adverse outcome (all-cause mortality or MACCE) according to total cTnT (**A**) and long cTnT (**B**). cTnT, cardiac troponin T; MACCE, major adverse cardiovascular or cerebrovascular event

studied long-term adverse outcomes. Troponin ratio essentially yields cross-sectional measures of troponin fragmentation, a high velocity time-dependent metabolic process, and the expected clinical implications reside in the diagnostics and care of conditions associated with explosive release of vast amounts of cTnT [11, 15].

Interestingly, long cTnT was independently associated with the occurrence of incident NOAF even after adjusting for age, sex and KTx whereas total cTnT was not. In previous literature, commercial hs-cTnT has been linked to the risk of incident NOAF in patients with and without CKD [21, 29] and the association between ongoing myocardial ischemia and development of NOAF has been comprehensively established in animal models [30]. While long cTnT appears to be a more specific indicator of acute myocardial damage compared to total cTnT, the more unspecific marker for cardiovascular comorbidity and inflammation in the presence of progressed CKD [11], it is possible that long cTnT may be more strongly associated with the risk of NOAF than total cTnT in these patients. In fact, the long cTnT values in this study on patients with advanced CKD resided roughly in the recently published reference range for healthy subjects [31] highlighting the magnitude of the association between long cTnT and NOAF although the mechanisms for this observation are likely multifactorial and presently remain obscure. It could be speculated that elevated long cTnT levels may be linked to the structural degeneration of the atria (atrial cardiomyopathy) which is a known condition to predispose to the later incidence of AF [32]. While a link between inflammation and the development of AF has also been observed in previous literature [33], the differences in the relationships between inflammation and the occurrence of NOAF or other cardiovascular outcomes are not known. Thus, the reasons for the inconsistencies in the associations between cTnT measurements and study outcomes remain ultimately unclear and require further research.

The major limitations of this study are related to the post hoc and retrospective nature of the study and, thus, definite conclusions cannot be drawn. The relatively small sample size and limited number of adverse events prevented optimal adjustment regarding the multivariable analyses and necessitated the testing of two separate multivariable Cox models adjusted for age, sex and CAD or KTx to mitigate the risk of overfitting and may have led to reduced statistical power. No independent adjudication was performed in terms of outcome measurement. However, all patients were extensively studied and resided in the catchment area of the research hospital throughout the study period minimizing the risk of missed outcome events. All outcome data were consistently collected by the same researchers. Furthermore, the included patients of the present study were similar in terms of the measured outcomes compared to the excluded patients and, thus, considered a well representative cohort of the total sample of the CADKID study. The distribution of long cTnT values in this study was narrow, which may also affect the findings in the study. Finally, the release and clearance mechanisms of cTnT still remain incompletely understood [28]. Improved knowledge of these mechanisms is required to better understand the associations between different cTnT forms and adverse long-term outcomes. Despite these limitations, we described the relationship between a novel long cTnT measurement and long-term adverse cardiovascular outcomes for the first time and demonstrated intuitive results. Thus, we believe our findings contribute to and assist in creating further study hypotheses for future cTnT research.

Conclusions

In the present study we describe for the first time associations between a novel highly sensitive long cTnT assay and long-term cardiovascular adverse outcomes and all-cause mortality in a prospective cohort of CKD stage 4–5 patients.

Abbreviations

cTn	Cardiac troponin
AMI	Acute myocardial infarction
hs-cTnT	High-sensitivity cardiac troponin T
ESKD	End-stage kidney disease
NSTEMI	Non-ST elevation myocardial infarction
NOAF	New-onset atrial fibrillation
MACCE	Major adverse cardiovascular or cerebrovascular event
KTx	Kidney transplantation
UCL	Upconversion luminescence
mAb	Monoclonal antibody
aar	Amino acid residue
PAD	Peripheral artery disease.

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-026-04803-6.

Supplementary Material 1

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Author contributions

SS, TV, KEJA, MJJ, SW and TH designed the study and NM, MH, NL, RL, KM, MJJ, TH were responsible for the data collection. JV and TT took part in data collection. SS and TH performed the statistical analyses. SS, EK and SW were responsible for the biochemical analyses. SS drafted the manuscript. KM, KEJA and SW acquired funding for the study and KM, TV, KEJA, MJJ, SW and TH supervised the study. SS, EK, MH, NL, NM, TT, JV, RL, KM, TV, KEJA, MJJ, SW and TH revised the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol (reference No. T05/024/20) was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the study was conducted in accordance with the Declaration of Helsinki. All participants provided a written informed consent before entering the study.

Consent for publication

Not applicable.

Competing interests

SS has received support from the Doctoral Programme in Clinical Research of the University of Turku, grants from the Turku University Foundation, the Varsinais-Suomi Regional Fund of the Finnish Cultural Foundation, and the Laboratoriolääketieteen edistämissäätiö sr, and the 3rd prize in NFKK Young Researcher Award 2024 competition. She also has a pending patent application WO2023187258 (A1)—ASSAY FOR LONG FORMS OF CARDIAC TROPONIN T. MH has received consulting, lecturing and authoring fees from MSD and Bayer and support for congress attendance from AstraZeneca and Otsuka. NM has received support for congress attendance from AstraZeneca. TT has received consulting, lecturing and authoring fees from Boehringer-Ingelheim and support for congress attendance from AstraZeneca and CSL Vifor. He also holds a position of board member and fund manager (unpaid) in the Finnish Society of Nephrology. KM has received funding from Finska Läkaresällskapet and the Perklen foundation. TV has a pending patent application WO2023187258 (A1)—ASSAY FOR LONG FORMS OF CARDIAC TROPONIN T. KEJA has received funding from the Finnish Foundation for Cardiovascular Research and consulting, lecturing and authoring fees from Bayer, Pfizer and Boehringer-Ingelheim. He also has a pending patent application WO2023187258 (A1)—ASSAY FOR LONG FORMS OF CARDIAC TROPONIN T. SW has received grants or travel grants from the International Federation of Clinical Chemistry and Laboratory Medicine, Finnish Society of Clinical Chemistry, the Varsinais-Suomi Regional Fund of the Finnish Cultural Foundation, Turku University Foundation and the Finnish Foundation for Cardiovascular Research and research funding from Business Finland and the EFLM Cardiac Marker Award 2024. She also has a pending patent application WO2023187258 (A1)—ASSAY FOR LONG FORMS OF CARDIAC TROPONIN T. TH has received consulting, lecturing and authoring fees from Astellas, AstraZeneca, GSK, MSD, Boehringer-Ingelheim and support for congress attendance from AstraZeneca. He also has a pending patent application WO2023187258 (A1)—ASSAY FOR LONG FORMS OF CARDIAC TROPONIN T.

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