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ORIGINAL ARTICLE

High-sensitivity troponins in dialysis patients: variation and prognostic value

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ABSTRACT

Background. Dialysis patients have a high prevalence of cardiovascular mortality but also elevated cardiac troponins (cTns) even without signs of cardiac ischaemia. The study aims to assess variation and prognostic value of high-sensitivity cTnI and cTnT in prevalent dialysis patients.

Methods. In 198 prevalent haemodialysis (HD) and 78 peritoneal dialysis (PD) patients, 4-monthly serum troponin I and T measurements were obtained. Reference change values (RCVs) were used for variability assessment and competing-risk regression models for survival analyses; maximal follow-up was 50 months.

Results. HD and PD patients had similar troponin levels [median (interquartile range) troponin I: 25 ng/L (14–43) versus 21 ng/L (11–37), troponin T: 70 ng/L (44–129) versus 67 ng/L (43–123)]. Of troponin I and T levels, 42% versus 98% were above the decision level of myocardial infarction. RCVs were +68/−41% (troponin I) and +29/−23% (troponin T). Increased variability of troponins related to higher age, male sex, protein-energy wasting and congestive heart failure, but not ischaemic heart disease or dialysis form. Elevated troponin T, but not troponin I, predicted death after adjusting for confounders.

Conclusions. A large proportion of prevalent dialysis patients without current established or ongoing cardiac events have elevated levels of high-sensitivity cTns. Mortality risk was doubled in patients with persistently high troponin T levels. The large intraindividual variation of cTns suggests that serial measurements and reference change levels may be used to improve diagnostic utility. However, evidence-based recommendations require more data from large studies of dialysis patients with cardiac events.

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Keywords: dialysis, high-sensitivity troponins, survival, variability

INTRODUCTION

Cardiac troponins (cTns) are sensitive markers of myocardial injury and play an important role in diagnosing cardiac ischaemia in the acute setting [1]. With the use of new and high-sensitivity troponin (hs-cTn) assays, the early diagnosis of acute myocardial infarction (MI) has improved in the non-renal population, with higher sensitivity at the cost of specificity [2, 3]. Hs-cTn assays have been shown to maintain high diagnostic accuracy in patients with chronic kidney disease (CKD) [4]. However, interpretation of hs-cTn levels in end-stage renal disease (ESRD) patients becomes particularly challenging, as ESRD patients without overt cardiac symptoms often have levels above the MI decision level [5, 6]. There are no reference values for hs-cTn in dialysis patients, making the interpretation of elevated troponin levels difficult. Possible causes of elevated troponin concentrations in dialysis patients are both cardiac and non-cardiac, such as left ventricular systolic dysfunction, left ventricular hypertrophy, myocardial stunning, volume overload and decreased clearance [6–10]. Additionally, the long-term variability of troponins, associated factors and prognostic value are largely unknown in ESRD patients. hs-cTn concentrations have been scarcely studied in haemodialysis (HD) patients and even less in peritoneal dialysis (PD) patients. Only when the normal variability of the hs-cTns in dialysis patients is established can a reference value for these patients be determined.

The aim of this study was to assess the variation of hs-cTnI and hs-cTnT in unselected, prevalent dialysis patients without currently established or ongoing acute coronary events, and the relation between variation and underlying factors. We also evaluated the prognostic value of serial hs-cTnI and hs-cTnT measurements. The second aim was to investigate if reference change values (RCVs) of hs-cTns would improve the diagnostic utility of hs-cTns in acute coronary syndromes (ACSs).

MATERIALS AND METHODS

Study population

The study was based on two cohorts of unselected, prevalent HD and PD patients in Stockholm, Sweden from the Mapping of Inflammatory Markers in Chronic Kidney disease (MIMICK) study, that have been described previously [11, 12]. A total of 198 HD and 78 PD patients were included (Supplementary Material). Inclusion criteria were age ≥18 years and dialysis treatment for ≥3 months. Exclusion criteria were: an acute MI 3 months prior to or during the study period, or contagious infections. The study duration was 3 months, blood samples were collected once per month for serum hs-cTnI and hs-cTnT analyses. Patients were followed for a median time of 36 months regarding survival. Baseline data were collected on comorbidity [ischaemic heart disease (IHD); angina pectoris, MI and/or coronary intervention], congestive heart failure (CHF; based on clinical history, chest X-ray and/or echocardiography findings), peripheral/cerebral vascular disease (PVD) and diabetes mellitus (DM), current medication and protein-energy wasting (PEW). Subjective Global Assessment (SGA) was used for PEW, which was defined as SGA >1 [13]. The Ethics Committee of Karolinska Institutet, Stockholm, Sweden, approved the study protocol. Written, informed consent was obtained from each patient.

Dialysis treatment

One hundred and seventy-nine patients (90%) were treated with HD three times a week, 13 (7%) two times a week and 4 (2%) four or six times a week (data missing $n = 2$). One hundred and forty-three patients (72%) were treated with low-flux and the remaining 54 (27%) with high-flux membranes (data missing $n = 1$). Among PD patients, 60 (77%) were treated with continuous ambulatory PD and 18 (23%) with automated PD. Information on urine volume was available in 58 PD patients; median volume 925 mL/24 h [interquartile range (IQR) = 500–1300].

Laboratory measurements

Monthly blood samples were collected in vacuum tubes without additives; the HD patients had blood drawn from their accesses before dialysis sessions and PD patients had peripheral venous blood drawn. The samples were kept frozen at −70°C. Hs-cTnI and hs-cTnT were measured from serum at 0, 4, 8 and 12 weeks. Hs-cTnI was analysed using an Abbott Diagnostics Architect i4000SR analyser [14] and hs-cTnT with the Roche Diagnostics Cobas E 411 analyser [15]. The limit of detection is 2 ng/L for hs-cTnI and 5 ng/L for hs-cTnT, and the analytical coefficient of variation is 8 and 4% for hs-cTnI and hs-cTnT, respectively. The clinical decision level for MI in a non-renal population is ≥27 ng/L for hs-cTnI and ≥14 ng/L for hs-cTnT [16]. Troponin levels were analysed at Aleris Medilab, Täby, Sweden. Routine biochemistry was analysed at the local laboratory of each dialysis unit.

Statistics

Categorical data are reported as frequency/percentage, continuous data are presented as median values and IQR. Non-parametric tests were used to compare data between HD and PD populations. The P-value was set at <0.05. The correlation between hs-cTnI and hs-cTnT was analysed with Pearson's test. Troponin variation is described with individual coefficient of variation [coefficient of variation by individual (CV_i)] for intra-individual variation and grouped CV [coefficient of variation by group (CV_g)] for inter-individual variation. The relation between intra and inter-individual variations is expressed by an index of individuality (II). For estimation of changes exceeding the observed variation, RCVs are used [17]. The CV_i is calculated from the median CV for each patient (CV_t) and the analytical CV (CV_a), CV_g are the mean of 4-monthly CVs based on troponins from all patients. For further details on the II and the RCV rise and fall, see Supplementary Material. Outliers were determined using a Box–Cox transformation as done by Horn *et al.* [18] The associations between baseline factors and cTn variability were analysed with a multivariate mixed model accounting for repeated measurements and fixed factors adjusting for confounders (age, sex, dialysis modality, time on dialysis, IHD, CHF, PVD, DM and PEW). Intra-class correlation (ICC) was determined from the model showing the ratio between intra- and inter-individual variability.

Levels of cTns were divided into tertiles at baseline. Mortality was analysed according to groups of patients with monthly troponins in the same tertile throughout the study (groups named low, middle or high) or moving between tertiles (groups named low–middle, middle–high or low–middle–high).

We adjusted the cumulative incidence curves by competing risk analysis. The outcomes death and renal transplantation were included in the competing risk regression model [19]. Risk estimates for patients were expressed as sub-hazard ratios (sHRs) for the different groups mentioned above where the patient group with repeatedly low levels served as reference. We used Fine and Gray models and these were adjusted for confounders [20]. Statistical analyses were performed with SAS version 9.4 (SAS, Cary, NC, USA) and R version 3.3.2.

RESULTS

The two cohorts of prevalent HD and PD patients did not differ with regard to comorbidity, age, sex or nutritional status (Table 1). N-terminal pro B-type natriuretic peptide (NT-proBNP) was significantly higher in HD patients. Baseline hs-cTnI and hs-cTnT were not statistically different in the two cohorts. In a combined cohort of 276 HD and PD patients, hs-cTnI and hs-cTnT increased in patients with CHF, IHD and PVD (Table 2). Hs-cTnT was increased in patients with higher SGA score and DM, whereas hs-cTnI was not. Baseline troponins were increased in men compared with women in PD, but not HD patients (Table 3).

Hs-cTn variation

During the 3 months that hs-cTns were measured repeatedly with a total of four measurements in each patient, hs-cTnI was above the decision level of MI (27 ng/L) 42% of the time while hs-cTnT was above the decision level of 14 ng/L 98% of the time. Based on the cut-off value of 8.7 ng/L for hs-cTnI as presented by Wildi *et al.* [21], 91% of the patients had elevated levels. Median levels of hs-cTnI and hs-cTnT did not differ between cohorts (Table 3). There were no significant differences in the mean ranks between the baseline study visit and the following three visits (data not shown). Only 0.4% of all hs-cTnI and 0.2% of all hs-cTnT measurements were below the limit of detection of the assays. The Pearson's correlation between log values of hs-cTnI and hs-cTnT was $r = 0.62$ [95% confidence interval (CI) 0.58–0.65] (Supplementary Material).

Table 1. Clinical characteristics and biomarkers at baseline in HD and PD patients without suspected acute myocardial ischaemia

Variables	HD, $n = 198$	PD, $n = 78$	P-value
Age, years	66 (51–74)	64 (56–77)	0.59
Sex, men, *n* (%)	57 (112)	67 (52)	0.10
BMI, kg/m^2	24 (21–27)	25 (23–28)	0.05
Smoking, no/yes, *n* (%)[a]	81/19 (153/36)	79/21 (62/16)	0.78
PEW (SGA > 1), *n* (%)[b]	45 (87)	39 (30)	0.42
Time on dialysis, months	28 (15–54)	11 (6–29)	<0.001
Comorbidity, low/medium/high, *n* (%)	18/57/25 (35/114/49)	27/56/17 (21/44/13)	0.31
IHD, *n* (%)	30 (60)	31 (24)	0.90
CHF, *n* (%)	22 (43)	15 (12)	0.23
DM, *n* (%)	25 (49)	23 (18)	0.78
PVD, *n* (%)	30 (59)	28 (22)	0.88
Albumin, g/L	35 (33–38)	32 (28–35)	<0.001
Hs-CRP, mg/L	6.2 (2.5–19)	4.7 (1.5–11)	0.05
NT-proBNP, ng/L	9724 (2969–26571)	3045 (1173–8615)	<0.001
Hs-cTnI, ng/L	25 (14–43)	21 (11–37)	0.16
Hs-cTnT, ng/L	70 (44–129)	67 (43–123)	0.41
Antihypertensive medication, *n* (%)			
β-blockers	49 (98)	72 (56)	<0.001
Calcium channel blockers	24 (48)	32 (25)	0.19
ACEi/ARB	32 (63)	55 (43)	<0.001
Statins	33 (66)	49 (38)	0.02
Acetylsalicylic acid	30 (60)	41 (32)	0.09
Aetiology of underlying kidney disease, *n* (%)			–
Chronic glomerulonephritis	19 (37)	15 (12)	–
Diabetic nephropathy	17 (33)	12 (9)	–
Vascular disease/ nephrosclerosis	16 (31)	10 (8)	–
Interstitial nephritis	12 (23)	8 (6)	–
Polycystic kidney disease	12 (25)	8 (6)	–
Miscellaneous/unknown causes	20 (42)	46 (36)	–
Systemic inflammatory disease	4 (7)	1 (1)	–

Data expressed as median (IQR) values or *n* (%).
BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.
[a]Data missing; nine HD.
[b]Data missing; four HD, two PD.

There was a wide intra- and inter-individual variation in levels of both hs-cTnI and hs-cTnT (Figure 1). The overall CV_i was 19% for hs-cTnI and 8% for hs-cTnT with little difference between dialysis cohorts (Table 3). CV_g was also higher for hs-cTnI than hs-cTnT (304% versus 127%). Excluding outliers, CV_i was 16% versus 8% and CV_g 125% versus 94% for hs-cTnI versus hs-cTnT, respectively.

The overall rise and fall of RCV was larger in hs-cTnI than hs-cTnT, +68/−41% of hs-cTnI and +29/−23% of hs-cTnT. A high CV_g compared with CV_i is expressed with a low II. Patients with overall levels outside the RCVs of hs-cTnI and hs-cTnT (both in a positive and negative direction) were more likely to have PEW, lower serum albumin and higher interleukin-6 than patients with levels within the RCVs. In the case of hs-cTnT these patients also had higher high-sensitivity C-reactive protein (hs-CRP; see tables in Supplementary Material).

Table 2. Hs-cTnI and hs-cTnT by comorbidities in 276 dialysis patients

	Hs-cTnI (ng/L)			Hs-cTnT (ng/L)		
Variables	Yes	No	P-value	Yes	No	P-value
CHF	40 (29–74)	19 (11–33)	<0.001	135 (65–184)	67 (42–117)	<0.001
IHD	33 (20–57)	19 (11–33)	<0.001	101 (59–152)	67 (42–119)	0.001
PVD	28 (17–53)	20 (12–35)	0.005	110 (57–158)	66 (42–115)	<0.001
DM	23 (14–41)	22 (13–41)	0.41	110 (57–170)	67 (42–121)	<0.001
PEW	23 (13–52)	23 (13–34)	0.08	84 (51–155)	63 (42–117)	0.009

Based on each patient median hs-cTnI and hs-cTnT. Data expressed as median (IQR) values.

Association of comorbidities with hs-cTn 3-month variation

The troponin variation over 3 months was significantly increased with age, male sex, PEW and CHF. This applied to both hs-cTnI and hs-cTnT. Elevated estimates represent increased association between cTns and patient factors when adjusted for possible confounders [age, sex, dialysis vintage (time on dialysis), dialysis modality, IHD, CHF, PVD, DM and SGA] (Table 4). Troponin variation did not associate with IHD, PVD, DM, dialysis modality or vintage. These associations did not change significantly when in a stepwise manner adding comorbidities and then PEW. The overall troponin variability during the study period was caused by changes in levels within and between patients. An ICC model (Table 4) showed that the largest proportion of troponin variability was associated with differences between patients (74% for hs-cTnI and 87% for hs-cTnT), rather than within patients (26% for hs-cTnI and 13% hs-cTnT).

Troponin variability and survival

To assess variability further and its relation to outcome, hs-cTnI and hs-cTnT were divided into tertiles based on their concentrations in nanogram per litre at baseline hs-cTnI tertiles: <2–15 (low), 16–32 (middle) and 33–2615 (high) and hs-cTnT tertiles: 12–51 (low), 52–107 (middle) and 108–1175 (high). For hs-cTnI measurements, 61% ($n = 167$) patients had a stable pattern on repeated monthly measures during 3 months (within the low, middle or high tertiles), and 39% ($n = 109$) had a varying pattern (within two or three tertiles). Similarly, for hs-cTnT, 71% ($n = 196$) of patients had a stable pattern and 29% ($n = 80$) had a varying pattern. In the univariate analyses, both hs-cTnI and hs-cTnT were associated with survival. The highest mortality

Table 3. Hs-cTnI and hs-cTnT variation in HD and PD patients

Variables	HD ($n = 198$)	PD ($n = 78$)	All ($n = 276$)	P-value
Hs-cTnI				
Median (IQR), ng/L	24 (14–41)	21 (11–45)	23 (13–41)	0.26
Range, ng/L	Less than 2–4057	2–1764	Less than 2–4057	
Men versus women,	24 (14–42)	24 (13–46)	24 (14–42)	0.7[a]
median (IQR), ng/L	28 (14–50)	16 (6–25)	20 (11–39)	0.009[b]
Proportion above MI decision level (≥27 ng/L), %	44	35	42	–
Limit of 99th percentile, ng/L	495	946	661	–
CV_i, %	17	18	19	–
CV_g, %	312	248	304	–
Reference change value, %	+67/−40	+70/−41	+68/−41	–
Index of individuality	0.06	0.08	0.07	–
Hs-cTnT				–
Median (IQR), ng/L	70 (45–130)	71 (42–138)	70 (45–132)	0.66
Range, ng/L	<5–1961	12–1008	<5–1961	
Men versus women, median	74 (48–138)	71 (51–133)	81 (50–141)	0.31/0.02
(IQR) ng/L	66 (42–120)	48 (24–112)	63 (40–118)	
Proportion above MI decision level (≥14 ng/L), %	98	96	98	–
Limit of 99th percentile, ng/L	901	829	900	–
CV_i, %	9	6	8	–
CV_g, %	146	123	127	–
Reference change value, %	+30/−23	+23/−19	+29/−23	–
Index of individuality	0.06	0.06	0.07	–

Data expressed as median (IQR) values or percentage based on 4-monthly measurements.
[a]Men versus women on HD.
[b]Men versus women on PD.

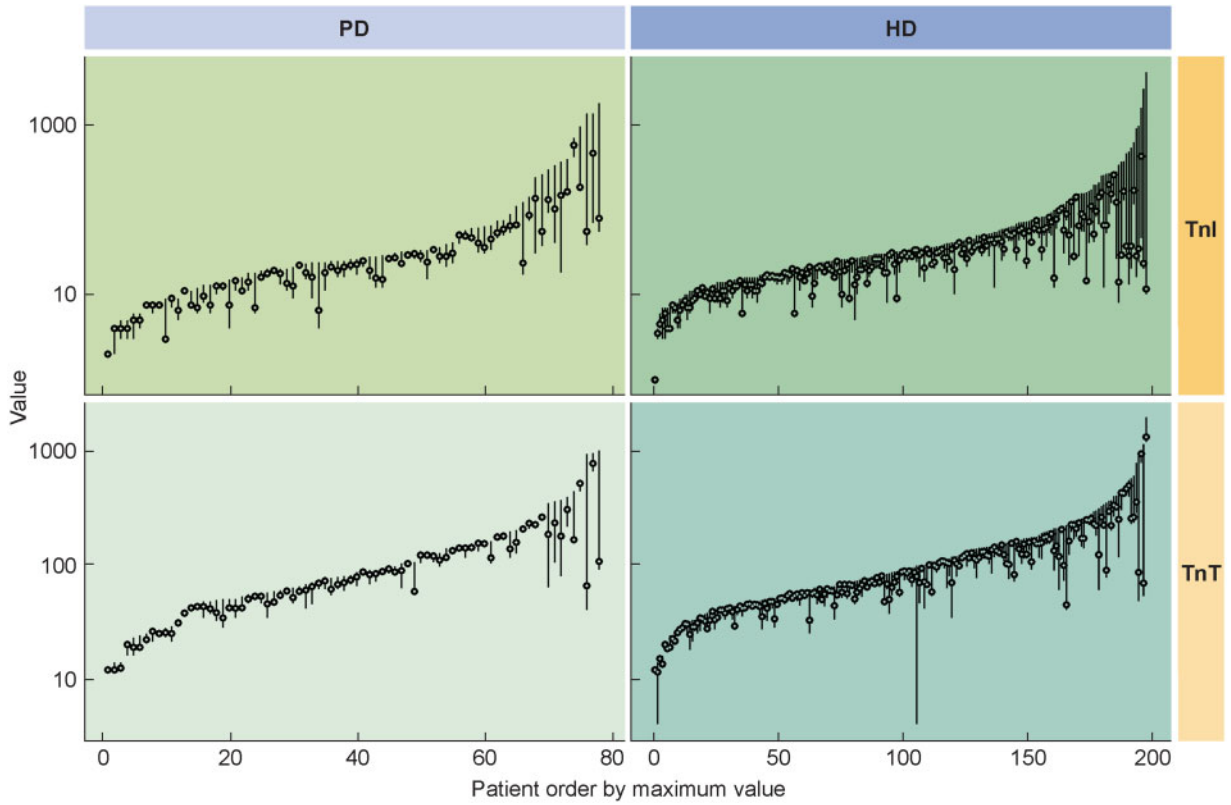

FIGURE 1: Serum hs-cTns in PD and HD patients.

was observed in the group of patients with persistently high cTn levels. In multivariate analyses, after adjusting for age, sex, vintage, modality, IHD, PVD, CHF, diabetes, PEW, hs-CRP, hs-cTnI did not predict outcome. Mortality analyses were also done using hs-cTnI and hs-cTnT as continuous variables adjusting for the same factors as well as medication and NT-proBNP. These results also show hs-cTnT, but not hs-cTnI, related to outcome (see Supplementary Material).

In contrast, hs-cTnT within the middle, middle–high, low–middle–high and high tertiles predicted poorer survival compared with low tertile levels after adjusting for the same confounders (Table 5, Figure 2).

DISCUSSION

The four main findings of this study are the large variability of hs-cTnI and hs-cTnT on repeated measurements, the difference in variability between hs-cTnI and hs-cTnT, the insight into which factors predict cTn variability in dialysis patients and the prognostic value for survival of hs-cTnT but not hs-cTnI.

The large inter-individual differences in cTn levels limit the diagnostic utility of fixed cut-off levels for dialysis patients. However, serial regular measurements, as in our study, can be used to determine an individual basal interval, which together with the dynamic change in cTn levels over the first hours in patients presenting with suspected ACS might be the preferred diagnostic method. The RCVs, i.e. the monthly rise and fall of cTn, a way to assess dynamic changes, were higher for hs-cTnI than hs-cTnT, confirming findings reported by Aakre *et al.* [22] from a small group of HD patients and healthy individuals. Others have reported that CV_i differed little by dialysis modality [10]. The large variation in cTns between patients shown by a high CV_g and a low index of individuality supports the conclusion by others [23, 24] that a population-based reference interval for dialysis patients is not useful for diagnostic purposes. An expert panel recently highlighted the added information provided by serial testing of cTns and the potential benefit of relying on RCV in ACS, in particular when troponin levels are high [25]. The RCV may help in the interpretation of serial hs-cTn measurements in ESRD. A patient with a change in hs-cTns smaller than the RCV may be classified as stable and ACS is unlikely, whereas a patient showing a rise or fall of hs-cTn greater than the RCV may have a cardiac or severe non-cardiac event with altered hs-cTn release. Others have shown the safety of ruling out ACS when changes in hs-cTns are small in patients with renal dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m^2 but ESRD patients on dialysis excluded) [26]. As of yet, cTns for diagnosing MI are scarcely studied in dialysis patients. All the same, these results together with previously shown low RCV of hs-cTn in 90 min in stable dialysis patients [22] support the use of samples at 0 and 1 h in assessing for ACS. Our findings that troponin levels are high, very different between patients, and variable in elderly patients and those with CHF, support the use of RCV when assessing dialysis patients for acute cardiac events. Sandoval *et al.* have shown, in a large HD patient cohort measuring hs-cTns twice in 3 months, that hs-cTn above versus below RCV relates to an increased 2-year mortality, supporting the use of RCV even further. Their findings included lower RCVs than in our study (+37/−30% for hs-cTnI versus +25/−20% for hs-cTnT) explained by the exclusion of troponin levels outside each assay's respective 99th percentile upper reference limit [27]. Including all troponin levels in

Table 4. Factors related to hs-cTn variation

	hs-cTnI						hs-cTnT					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
Variables	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value
Age, ≤45/46–65/>65 years	0.54 (0.17) 0.89 (0.17)	<0.001	0.49 (0.17) 0.82 (0.17)	<0.001	0.45 (0.17) 0.74 (0.17)	<0.001	0.44 (0.15) 0.68 (0.14)	<0.001	0.4 (0.14) 0.62 (0.14)	<0.001	0.34 (0.14) 0.56 (0.14)	<0.001
Sex, women versus men	0.27 (0.1)	0.02	0.27 (0.11)	0.01	0.31 (0.11)	0.005	0.3 (0.09)	0.002	0.32 (0.09)	<0.001	0.38 (0.09)	<0.001
Modality, PD versus HD	0.15 (0.13)	0.23	0.12 (0.12)	0.34	0.14 (0.12)	0.25	0.11 (0.11)	0.29	0.08 (0.1)	0.44	0.09 (0.10)	0.39
Dialysis vintage, <24 versus ≥24 months	<0.01 (0.01)	0.98	<0.01 (<0.01)	0.94	<0.01 (<0.01)	0.8	<0.01 (<0.01)	0.86	<0.01 (<0.01)	0.93	<0.01 (<0.01)	0.84
IHD	–	–	<0.01 (0.13)	0.97	0.03 (0.13)	0.82	–	–	−0.09 (0.11)	0.4	−0.05 (0.1)	0.6
PVD	–	–	−0.03 (0.12)	0.8	−0.02 (0.12)	0.83	–	–	−0.06 (0.1)	0.57	−0.05 (0.1)	0.64
CHF	–	–	0.50 (0.15)	<0.001	0.45 (0.15)	0.002	–	–	0.51 (0.12)	<0.001	0.46 (0.12)	<0.001
DM	–	–	0.09 (0.13)	0.46	0.1 (0.13)	0.42	–	–	0.14 (0.11)	0.19	0.14 (0.1)	0.17
PEW, (SGA > 1)	–	–	–	–	0.25 (0.11)	0.02	–	–	–	–	0.28 (0.09)	0.002
ICC	0.73	–	0.72	–	0.74	–	0.88	–	0.87	–	0.87	

Three models with stepwise adjustments for listed factors.
SE, standard error.

Table 5. Risk estimates for mortality expressed as sHRs

Hs-cTnI	sHR	sHR (95% CI)	P-value
Low, $n = 64$ (23%)	1	–	–
Low–middle, $n = 49$ (18%)	0.73	0.35–1.50	0.39
Middle, $n = 36$ (13%)	0.63	0.30–1.54	0.36
Middle–high and low–middle–high, $n = 60$ (22%)	1.19	0.61–2.29	0.60
High, $n = 67$ (24%)	1.39	0.71–2.71	0.32
Hs-cTnT	**sHR**	**sHR (95% CI)**	**P-value**
Low, $n = 72$ (26%)	1	–	–
Low–middle, $n = 40$ (15%)	1.76	0.78–3.93	0.16
Middle, $n = 49$ (18%)	2.11	1.05–4.22	0.03
Middle–high and low–middle–high, $n = 40$ (14%)	2.21	1.04–4.69	0.04
High, $n = 75$ (27%)	2.38	1.19–4.73	0.01

Adjusted for age, sex, vintage, modality, IHD, PVD, CHF and diabetes, PEW and hs-CRP at baseline.

prevalent dialysis patients represents RCV as it could be in the everyday clinical situation. Repeated measurements of troponins in dialysis patients without overt cardiac symptoms (e.g. a few times a year) may be helpful to support interpretation of troponins when acute events arise. A reassessment might be wise when the cardiac status of a patient has changed. To further assess the RCV to be used for these patients, a large, prospective trial would need to be undertaken, including enough patients to have a substantial amount of acute coronary events.

Troponin levels were similar in HD and PD cohorts, confirming Hassan *et al.* [28], who reported that dialysis modality did not relate to short-term troponin variability.

This study showed that whereas patients with CHF had more fluctuations in monthly troponins, IHD and DM were not associated with variation in the mixed-model analysis. cTnT has been shown to correlate well with left ventricular mass and systolic dysfunction in HD patients [29, 30]. The Dallas Heart Study showed increased left ventricular mass and chamber dilation but not coronary artery calcium score to be independent determinants of detectable hs-cTnT [31]. Some cross-sectional studies on clinically stable HD and PD patients have found hs-cTnI to be more strongly correlated to left ventricular dysfunction and hs-cTnT to coronary artery disease based on a single troponin value [32]. Other conditions that may lead to troponin release are subclinical IHD anaemia, arrhythmias, hypertension, angina [33], physical exertion [34], myocardial stunning [35] and intradialytic hypotension [36]. PEW, which is a common feature of the uraemic phenotype [37], has also been related to higher troponin levels. This could be explained to some extent by the fact that PEW is related to fluid overload in dialysis patients [38]. The dry weight, towards which a patient's dialysis prescription is aimed, can be wrongly determined in the presence of PEW, which leads to chronic fluid overload, myocardial stretch and troponin release. A positive relation between fluid overload and cTnT has been observed in a previous study [7]. Clinically, it is therefore important to assess patients' fluid and nutritional status when fluctuations in troponins are found without signs of acute cardiac events.

Based on our findings that hs-cTnT had lower intra-individual variation and was a better predictor of mortality than hs-cTnI, it might be that hs-cTnT is preferable to determine basal hs-cTn levels in dialysis patients. Previous studies have reported that hs-cTnT is superior to hs-cTnI in ruling out MI in

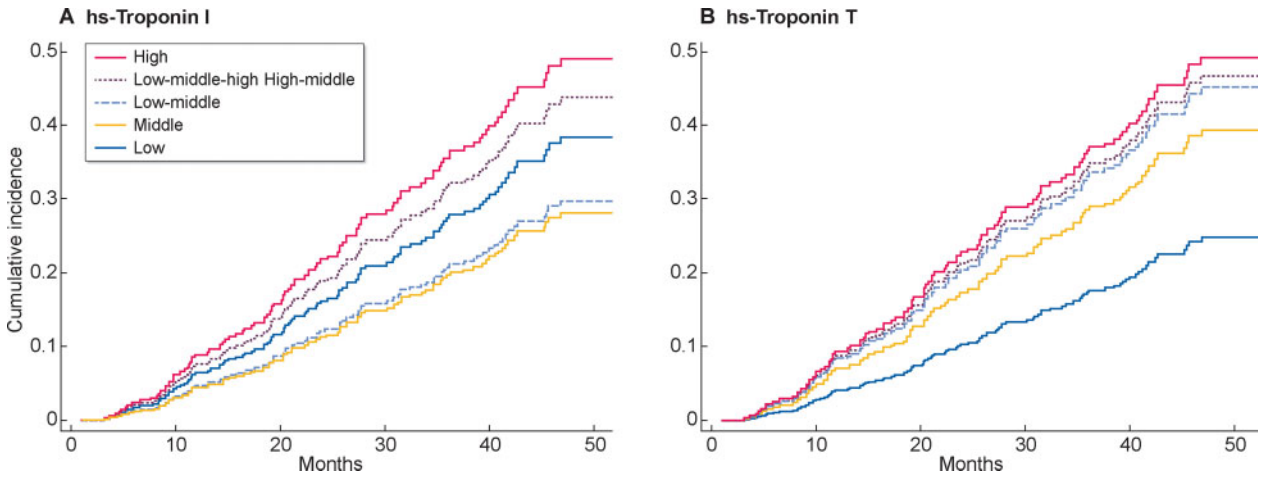

FIGURE 2: (**A**) Cumulative incidence (%) curves of 60-month mortality in relation to hs-cTnI after adjusting for confounders. Adjustments for confounders included age, sex, vintage, modality, IHD, PVD, CHF and diabetes, PEW and hs-CRP at baseline. The group of patients with low served as a reference. (**B**) Cumulative incidence (%) curves of 60-month mortality in relation to hs-cTnT after adjusting for confounders. Adjustments for confounders included age, sex, vintage, modality IHD, PVD, CHF and diabetes, PEW and hs-CRP at baseline. The group of patients with low served as a reference.

ESRD [22]. Others yet have shown hs-cTnT to better predict all-cause and cardiovascular death than hs-cTnI based on single cTn measurements using both older and hs-cTn assays in ESRD and in CHF patients [39–41]. More recent findings are that a single measurement of hs-cTnT, but not hs-cTnI, predicts 5-year survival in HD and PD patients [42]. Sandoval *et al.* presented a large cohort (677 stable HD outpatients) where higher RCV for hs-cTnI was a stronger predictor for mortality than for RCV hs-cTnT (although both predicted death). In their study, adjustments for outcome were done for sex, age, race and dialysis vintage [27]. Our study contributes more in-depth information by being able to adjust for comorbidities and nutritional status, important factors to consider in the dialysis population.

The correlation between hs-cTnI and hs-cTnT levels was moderate, possibly explained by differences in half-life and stability in the circulation, renal and dialysis clearance [43, 44], ratio of free cytoplasmic cTn [29] or in kinetics [45, 46]. In CKD, hs-cTnT correlates inversely with estimated glomerular filtration rate to a greater extent than hs-cTnI [47–49].

Some caveats of this study should be considered when data are interpreted. At first, although patients were clinically stable in the aspect of not having an MI during or shortly before the study period, dialysis patients are prone to several mechanisms for troponin elevation, which may not be quantified or excluded, such as asymptomatic heart failure episodes and interdialytic volume overload. Care was taken to ensure stability during the sample collection for 12 weeks, excluding ACS. However, patients could have had an episode shortly before the collection, which was not captured in the data, and which potentially could have affected the troponin level during the 12-week period.

Moreover, since samples were taken at monthly intervals, the study does not provide any information on variation over shorter times (days–hours) and hence cannot propose a diagnostic utility of hs-cTn assays for dialysis patients presenting with chest pain or dyspnoea in the emergency room. Data on mortality are based on overall mortality, not on specific causes of death. Thirty percent of the PD patients denied participation in the study, mainly due to it being too cumbersome. It is possible that these patients suffered from more comorbidities than the study participants, which could affect the results of the study. It should be noted that the RCVs calculated in this study do not describe the biological variations of hs-cTn but the estimated variations of hs-cTn in non-ACS ESRD patients, which are higher than the biological variations.

In conclusion, the majority of hs-cTnT and nearly half of hs-cTnI levels are elevated with significant monthly variability in prevalent, unselected dialysis patients. Large differences in hs-cTns between dialysis patients suggest that serial measurements and the use of reference change levels may improve diagnostic accuracy to detect acute cardiac events. Temporarily increased levels of hs-cTnI and hs-cTnT are associated with CHF, PEW, age and male sex. Constantly high levels of hs-cTnT predict a doubled risk of death over 4 years of follow-up, and hs-cTnT is a better predictor of survival than hs-cTnI in this patient group.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format.

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