**Performance of a novel high sensitivity cardiac troponin I assay in asymptomatic hemodialysis patients – evidence for sex-specific differences**

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**Abstract**

Background

High sensitivity assays for the determination of cardiac troponin I (cTnI) are able to reliably measure cTnI far below the 99th percentile of healthy persons (hs-cTnI) and display sex-specific differences. There is uncertainty regarding the clinical utility of hs-cTnI in asymptomatic haemodialysis (HD) patients and if sex-specific differences also apply in this cohort.

Methods

In this multicenter study we measured hs-cTnI and sensitive cTnI (s-TnI) concentrations (both on Siemens Centaur) in 215 HD patients from a predialytic sample to determine the prevalence of elevated concentrations above the 99th percentile, the association with baseline characteristics, prognostic accuracy for death, and sex-specific differences.

Results

Hs-cTnI and s-cTnI concentrations were below the 99th percentile in 93% and 85% of patients with a median concentration of 12 ng/L (interquartile range 7 to 66) and 19 ng/L (12; 31, p<0.0001). Hs-cTnI and s-cTnI concentrations were independently associated with age (p<0.05) and ischemic cardiac disease (p<0.05), but not with residual renal function. Both hs-cTnI and s-cTnI were predictors of death after median follow-up of 2.6 years with an AUC of 0.733 and 0.744, respectively (both p<0.0001). Important sex-differences emerged for hs-cTnI, but not for s-cTnI: first, for hs-cTnI, women had significantly lower hs-cTnI concentrations than men (p=0.03); second, hs-cTnI had significantly higher prognostic accuracy for death in women than for men (AUC 0.824 vs. 0.674, p=0.04).

Conclusions

The majority of HD patients have (h)s-cTnI concentrations below the 99th percentile. High normal values are predictive of death. Hs-cTnI allows to elucidate important sex-differences in HD patients with lower concentrations and higher prognostic accuracy in women.

**Introduction**

The detection of cardiac troponins I or T (cTn) in the plasma is the gold standard of diagnosing any injury and damage to the heart, be it ischemic, haemodynamic or inflammatory in origin [1, 2]. In the most recently published 4th universal definition of myocardial infarction, any elevation of cardiac troponins above the 99th percentile define the newly coined umbrella term myocardial injury [3]. According to this concept, myocardial injury due to myocardial ischaemia represents myocardial infarction. Any acute myocardial injury such as acute myocardial infarction (AMI) is characterized by an increase or decrease in the plasma cTnI or cTnT concentrations, with one value over the 99th percentile [3]. By contrast, plasma cTn concentration can also be chronically elevated in some patients, indicating chronic myocardial injury in the setting of structural heart disease without acute ischemia [3-5]. In patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), chronic elevations of the plasma cTn concentration have been reported since the advent of troponin testing [6-8], and several longitudinal studies [9-11] and their meta-analyses [12, 13] consistently showed that elevated troponin concentrations in CKD patients are strong predictors of increased mortality. Although reduced clearance was accounted for in some of these results, particularly those with troponin T [10, 14], the current view is that an increase in cTn plasma concentration in CKD is primarily the result of increased release from the diseased myocardium due to chronic strain or injury in CKD [3, 15, 16].

To improve the accuracy and early diagnosis of AMI, cTn assays with increased sensitivity have been developed and successfully tested in patients with acute chest pain [17, 18]. These tests have heralded a new era in the diagnosis of AMI, enabling the rapid rule-in and rule-out within as little as 1–3 hours using well-defined and clinically evaluated algorithms [4]. A high sensitivity cTn assay can be defined by the ability to detect cTn in the plasma of at least 50% (ideally >95%) of a healthy population [19]. Recently, Siemens introduced the hs-cTnI-Centaur assay as an improvement to its sensitive cTnI Ultra assay (s-cTnI), and it is considered the third high-sensitivity cTn (hs-cTnI) assay to become available for clinical use. So far, this assay has been tested and validated in a single study involving patients with an acute coronary syndrome [20]. The authors found that the diagnostic performance was similar to that of the other two hs-cTn assays and that the area under the receiver operating characteristics curve (AUC) value of these assays reached more than 0.93. As a result of the improved precision and resolution, high-sensitive cTn assays demonstrate sex-specific differences so that they are now interpreted using sex-specific reference values [20-22]. In addition, high sensitive assays will be able to detect temporal changes in cTn concentrations more accurately.

In patients with ESRD on haemodialysis (HD), no studies have been conducted that used the hs-cTnI-Centaur assay. Gunsolus et al. analysed hs-cTnI in CKD patients using the cTnI assay from Abbott (Architect) [22] and reported that the specificity for diagnosing AMI using sex-specific reference values continuously decreased with increasing CKD stages to 15%–32% in ESRD patients, thereby reducing the rapid rule-out of AMI in CKD patients with chest pain. During follow-up, they again confirmed that a plasma hs-cTnI concentration greater than the 99th percentile was a strong predictor of long-term mortality.

In this study, we evaluated the Siemens hs-cTnI-Centaur assay in a previously characterized HD cohort [23] with regard to distribution, influencing factors and prognostic significance after 2.6 years of follow-up. We showed that the majority of HD patients had a hs-cTnI plasma concentration below the 99th percentile, which was still predictive of long-term mortality.

**Material and methods**

*Patients and cohort*

This prospective, multicentre study included stable prevalent HD patients from four outpatient dialysis centres in Southwest Germany (Tuebingen, Leonberg, Herrenberg and Sindelfingen) from July 2014 to August 2015. The objective of the study was to assess haemodynamic parameters using the Transonic HD03 monitor in an arteriovenous circuit excluding HD patients with a dialysis catheter [23]. In addition, blood samples were taken from each patient. Each patient provided a written informed consent. The study was in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University of Tuebingen (614/2014BO2).

*Laboratory assays and clinical data*

From each patient, one sample was taken at the beginning of the HD session in which haemodynamics was measured. The plasma concentrations of hs-cTnI and s-cTnI were measured on the ADVIA Centaur XPT automated chemiluminescent immunoassay system (Siemens Healthineers, Eschborn, Germany) in the central laboratory of the University hospital Tuebingen. The novel hs-cTnI assay (Siemens ADVIA Centaur TNIH) uses a preformed magnetic latex solid phase containing two monoclonal anti-cTnI antibodies for increased avidity and a recombinant anti-cTnI antibody Fab’ fragment attached to a BSA carrier with multiple trisulfopropyl-acridinium esters (TSPAE) for chemiluminescent detection, achieving an improvement in precision and functional sensitivity over the previous s-cTnI (TnI-Ultra) assay [24]. This results in a reduction of the Limit of Detection (LoD) from 6 to 2.21 ng/L, the Limit of Quantification form 17 to 2.5 ng/L and the 10 % CV value from 30 to 4.5 ng/L for the ADVIA Centaur TNIH compared with the TnI-Ultra assay, according to the manufacturer. The hs-cTnI assay has a 99th percentile concentration (both sexes) of 47 ng/L with a corresponding coefficient of variation (CV) of less than 5%. The 99th percentiles for men and women have been reported by the manufacturer to be 57 ng/L and 37 ng/L, respectively. The s-cTnI assay has a 99th percentile concentration (both sexes) of 40 ng/L with a CV of less than 5%. NT-pro-BNP was measured on the Siemens Immulite solid phase chemiluminescent immunoassay system. For each patient, data on the clinical or dialysis-related factors were extracted from the records.

*Haemodynamic variables*

Access flow (AF, L/min), cardiac output (CO, L/min), from which cardiac index (CI, L/min/m²) was derived, and central blood volume index (CBVI, mL/kg) were determined from each patient at the beginning of a single routine HD session (Table 1) using the Transonic HD03 monitor (Transonic, Ithaca, NY, USA). The correction of CO for AF (CO-AF) and indexing yielded the systemic cardiac index (SCI, L/min/m²), which reflects the CI that is available for whole-body perfusion. In addition, fluid status was determined using bioimpedance spectroscopy (body composition monitor, Fresenius Medical Care, Homburg, Germany). Overhydration (OH) was inferred from the body composition model, which divides the whole body into three compartments: normally hydrated lean tissue, normally hydrated adipose tissue and OH [25, 26]. OH was normalized to the body surface area [27]. Patient survival and adjudication was assessed by the treating nephrologists (FA and BF).

*Statistical analysis*

All continuous data were checked for a normal distribution using the Kolmogorov–Smirnov test. Two groups were compared using the non-parametric rank sum test (Fig. 2). The association of hs-cTnI or s-cTnI with clinical or dialysis-related factors was analysed using non-parametric correlation and multivariable linear regression (Table 3). All variables with a positive non-parametric correlation were entered into a multivariable linear regression model after log transformation. For survival analysis, follow-up was defined from the day of blood draw until April 30, 2017. Causes of death were classified according to the best knowledge of each particular case. Cardiovascular death was considered as sudden death (most probably circulatory or cardiac arrest) and death due to a cardiovascular event or disease (coronary artery disease, heart failure, stroke, or peripheral artery disease). Patients receiving a kidney graft were censored on the day of transplantation. The Kaplan–Meier curves were generated after stratification into tertiles of hs-cTnI and s-cTnI plasma concentration according to its distribution and compared using the log-rank test (Fig. 3). ROC curve analysis was performed with the end-point mortality and compared according to the method of DeLong [28] (Fig. 4). Cut-off values were derived from the Youden´s J statistic and correspond to the value at which maximum sensitivity and specificity is achieved. Crude and adjusted proportional hazards were calculated using the Cox regression analysis (Table 4). Statistical analyses were conducted with MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium), and the figures were created with JMP 11 (SAS Institute Inc., Cary, NC, USA) and Microsoft PowerPoint.

**Results**

*Study cohort*

Among the 235 patients who were treated with an arteriovenous (AV) fistula or graft in the participating centres, 215 were included in the study, 5 declined to participate and 15 were excluded because of stenosed access defined by recirculation. The characteristics of the study cohort are provided in Table 1. The participants had a median age of 73 years and had been dialysed for a median of 47 months using a native AV fistula (85%) and a high-flux membrane (98%). Online haemodiafiltration was used in n=144 (69%) with a high substitution volume (median 21 L). Cardiac comorbidities were present in a large proportion of the patients (80%). Valvular heart disease was the most frequent condition (47%). Systolic left ventricular (LV) dysfunction was found in 19% of the patients (Table 1). The baseline characteristics were similar for males and females, except for a lower weight in females and a slightly higher prevalence of normal systolic LV function (Table 1).

*Plasma hs-cTnI and s-cTnI concentrations in the cohort*

Both hs-cTnI and s-cTnI were above the LoD in 207 (96%) and in 204 (95%), respectively, out of the 215 enrolled patients (Table 2). The median hs-cTnI plasma concentration was 12 ng/L (interquartile range: 7; 66, Fig. 1) and was significantly lower than the median s-cTnI concentration (19 ng/L [12; 31], p < 0.0001). The plasma hs-cTnI and s-cTnI concentrations were strongly correlated with each other (r=0.76, p < 0.0001). Women had a significantly lower hs-cTnI concentration than men (11 [6; 18] vs. 13 [9; 20], p=0.0336, Fig. 2A), an outcome that was not seen with s-cTnI (p=0.2433). The sex-specific difference with higher values in males compared to females remained robust when analysis was restricted to those with normal systolic LV function (13 [8; 19] vs. 8 [5; 17], p=0.0246).

The histograms of the distribution of the hs-cTnI and s-cTnI concentrations are shown in Figure 1. The categorical distribution according to different analytical thresholds is shown in Table 2. Whereas the majority of the patients had a plasma hs-cTnI and s-cTnI concentration below the 99th percentile (93% and 85%, respectively), significantly more patients were above the 99th percentile using the s-cTnI assay (15% vs. 7%, p =0.0148). Using the hs-cTnI assay, significantly more patients had a value below the threshold for a CV less than 20% or 10%, indicating the improved precision of the new assay (Table 2). Using sex-specific 99th percentiles at 37 ng/L for women and 57 ng/L for men, significantly more women than men were above these thresholds (11% vs. 4%, p=0.0468).

*Factors influencing plasma hs-cTnI and s-cTnI concentrations*

To analyse the determinants of the plasma hs-cTnI and s-cTnI concentrations, correlation analyses and multivariable linear regression were performed. As shown in Table 3, hs-cTnI was significantly correlated with age, gender, presence of atrial fibrillation, history of revascularization, congestion (represented by central blood volume index [CBVI]) and overhydration (represented by [OH]). Cardiac function (represented by systemic cardiac index [SCI]) was inversely correlated with hs-cTnI, reflecting the release by the failing heart as shown previously [10]. S-cTnI was similarly correlated with these variables, but there was no correlation with gender. A moderate correlation of hs-cTnI and s-cTnI with NT-pro-BNP was found (r=0.399 and r=0.403, respectively, both p < 0.0001).

In the multivariable regression analysis with all of these parameters, age, history of revascularization, CBVI, OH and SCI remained to be correlated with the plasma hs-cTnI concentration. Body mass index emerged as significant predictor of both hs-cTnI and s-cTnI (Table 3). Overall, the adjusted r² of the model was 0.18, indicating that only 18% of the variability in plasma hs-cTnI concentrations could be explained by these factors. This value was similarly low for the model with s-cTnI reaching an adjusted r² of 0.22. Therefore, other unknown variables must account for the release and plasma concentrations of hs-cTnI and s-cTnI.

*Prognostic value*

After 2.6 years, 65 patients died (30%), 8 (4%) received kidney transplantation and 7 (3%) moved away or terminated HD. The mean follow-up time was 963 days (575; 983). Cardiovascular death, as defined by a composite of sudden death, coronary artery disease, stroke and peripheral artery disease, occurred in 25 patients (38% of all deaths). The remaining causes of death were malignancy (8 patients, 12%), infection (8 patients, 12%), gastrointestinal bleeding (4 patients, 6%), discontinuation (8 patients, 12%) and unknown (12 patients, 18%).

The median plasma hs-cTnI and s-cTnI concentrations were significantly (p < 0.0001) higher in patients who died during follow-up (19 [12;31] ng/L and 30 [20;42] ng/L, respectively) than in those who survived (11 [6;15] ng/L and 16 [9;28] ng/L, respectively, Fig. 2B). The survival curves stratified for the tertiles of plasma hs-cTnI and s-cTnI concentrations are shown in Figure 3. The tertiles had good separation and showed an incremental relative risk of mortality for hs-cTnI and s-cTnI (Fig. 3). When analysing the association with mortality using receiver–operator curves, hs-cTnI and s-cTnI showed almost similar AUC values (0.733 and 0.744, Fig. 4A). Sensitivity and specificity were 67% and 71% at the cut-off value of 14 ng/L for hs-cTnI and 79% and 60% at the cut-off value of 18 ng/L for s-cTnI, respectively. Interestingly, the performance of hs-cTnI was significantly (p=0.0426) improved in women, reaching the AUC value of 0.823 compared with 0.675 in men (Fig. 4B). As a result, the sensitivity and specificity in women increased to 90% and 67%, respectively, at the cut-off value of 11 ng/L. The sex-specific differences tended to be similar using s-cTnI but did not reach statistical significance (AUC of 0.817 in women vs. 0.706 in men, p=0.1023).

Table 4 shows the hazard ratios (HRs) calculated from the Cox regression analysis. In a crude model, the HRs for a standard deviation increase in the plasma hs-cTnI and s-cTnI concentrations were 1.23 (95% CI 1.06: 1.43) and 1.15 (1.02; 1.31), respectively. The HRs were robust after adjusting for other factors related to mortality in this cohort (Table 4). The HR of hs-cTnI for CV mortality was similar to that obtained for all-cause mortality and that of s-cTnI was less robust.

*Performance of a repeat hs-cTnI and s-cTnI after one year*

From n=151 patients, a second sample was drawn after a median of 364 days (351; 382). The median hs-cTnI plasma concentration tended to increase (from 12 ng/L to 15 ng/L [8; 27], p=0.0783), which was not paralleled by the s-cTnI concentration (from 19 [13; 32] to 17 ng/L [7; 29], p=0.005). The CV of the values was 19% (10; 38) for hs-cTnI and 39% (16; 32) for s-cTnI. The correlation of these time-dependent values was high (r=0.770, p < 0.0001 for hs-cTnI and r=0.604, p < 0.0001 for s-cTnI). Again, more patients were above the 99th percentile using the s-cTnI assay than when using the hs-cTnI assay (14% vs. 7%, p < 0.0001). The AUC for all-cause mortality from the repeat hs-cTnI and s-cTnI concentration was similar (0.745 and 0.761) to the initial value, indicating the robust association of these biomarkers with mortality. However, the change in hs-cTnI concentration calculated either as the difference or the ratio of the two values was not predictive of mortality (AUC values 0.572, p=0.251 and 0.541, p=0.478, respectively). This outcome was also true for s-cTnI.

**Discussion**

The study shows that this novel Siemens hs-cTnI assay has improved precision in asymptomatic HD patients compared with the sensitive cTnI Ultra assay from the same manufacturer and reveals sex-specific differences. This result is indicated by the finding that 96% of the hs-cTnI values were measured below the threshold of a CV less than 20% in contrast to 53% of the s-cTnI values. Strictly speaking, s-cTnI values with a CV greater than 20% cannot be taken for further clinical decision making. The improved precision resolved a sex-specific difference of only 2 ng/L higher hs-cTnI values in male patients. The sex-specific difference is a new and characteristic feature of high-sensitive cTn assays, and it is also observed with the hs-cTnT assay from Roche [10] and the hs-cTnI from Abbott [29]. The sex-specific difference is considered to reflect a higher cardiac mass in males and the differences in troponin turnover that lead to higher values for the 99th percentile in males [30-32]. This is also indicated by the association of hs-cTnI with BMI. However, the influence of sex was attenuated and almost lost in our multivariable model after adjustment for potential confounders which is often not done rigorously in other studies describing sex-differences in hs-cTnI.

A recent meta-analysis of studies with healthy persons demonstrated a lower 99th percentile of hs-cTnI (Abbott) and hs-cTnT (Roche) in females than in males [29]. In the hs-cTnI assay of the present study, the 99th percentile values are 37 ng/L and 57 ng/L for females and males, respectively, and 47 ng/L for both sexes. Applying the female-specific limit to our cohort led to a higher prevalence of women with an elevated hs-cTnI, enabling the improved detection of patients at risk. The use of sex-specific reference values for the interpretation of hs-cTn values in clinical practice is currently under investigation. In a study evaluating the performance of the hs-cTnI of this study in chest pain patients, sex-specific reference values led to a slightly higher sensitivity but a lower specificity in women and a slightly lower sensitivity but a higher specificity in men [20]. Independent from a sex-specific reference limit, we found an improved prediction of all-cause mortality in female patients in this study, reaching a sensitivity and specificity of 90% and 67%, respectively, at the cut-off value of 11 ng/L. Conversely, the prognostic value of hs-cTnI was worse in men. A higher scatter of hs-cTnI in males compared to females most likely explains this finding as the standard deviation was nearly double of that in females (40 vs. 22 ng/L). Therefore, this confounded the discrimination of the surviving patients from those who deceased in a dichotomous ROC analysis. Currently, we do not have any explanation for the higher scatter in males except for a higher variability in troponin turnover that could be related to a higher cardiac mass.

In contrast to the results with the hs-cTnI assay by Abott [22], the median hs-cTnI of our patients was well below the 99th percentile, and 93% of the patients had a normal hs-cTnI concentration. This finding implies that the specificity to diagnose AMI will not be hampered in these patients. The reason for the discrepancy of the different proportions of patients with an increased baseline hs-cTnI is most likely related to the differences in cardiac comorbidities and cardiac status of the studied cohorts. Accordingly, our cohort seemed to be less sick than that studied by Gunsolus et al. [22] as reflected by the higher annual mortality of 20% compared with that of 11% in our study. In sum, having a baseline hs-cTnI value from each CKD and particularly from ESRD patients prior to the development of symptoms suggestive of AMI would be desirable.

Age was an independent predictor of the plasma concentration of both hs-cTnI and s-cTnI with higher values in elder patients. In the general population, hs-cTnI similarly increased with age and lead to an increase of the 99th percentile in persons >60 years [31]. The increase of hs-cTnI with age suggests a higher prevalence of subclinical cardiac disease in the elderly. In contrast, residual renal function was not a predictor of the plasma concentration of both hs-cTnI and s-cTnI ruling out accumulation as an explanation for increased cTnI values. Therefore, any increase of the plasma cTnI concentration is always the result of release from the diseased heart.

Although hs-cTnI was in the normal range in the majority of the patients, high normal values in the second and third tertiles were associated with increased all-cause and cardiovascular mortality after 2.6 years of follow-up. The prediction was similarly good in a sample taken one year apart, and it was only slightly different from the initial value. The strong and continuous association of the cTn plasma concentration with mortality in asymptomatic ESRD patients is a robust finding of numerous studies. In a meta-analysis of 98 studies, a pooled HR of 3.3 (CI, 1.8–5.4) for increased cTnT and 4.2 (CI, 2.0–9.2) for increased cTnI was calculated [13]. Compared with other modern peptide biomarkers, cTn is highly predictive of all-cause mortality and tends to perform better than NT-pro-BNP, another cardiac biomarker that has a higher biological variability and also reflects different aspects of the heart [33, 34]. In this cohort, the AUC of NT-pro-BNP for all-cause mortality was 0.667 [23]. It is noteworthy that both troponin and natriuretic peptides are associated with haemodynamic variables and reflect systolic dysfunction, central venous congestion and overhydration as shown in table 3, which are all predictors of mortality [23].

The limitations of the study include the lack of data on hs-cTnT or hs-cTnI measured with a different assay and the lack of patients with suspected AMI or those dialyzed by a dialysis catheter who are expected to have higher morbidity and mortality.

In conclusion, this study shows that the novel Siemens hs-cTnI assay has improved precision in asymptomatic HD patients in comparison with the sensitive cTnI Ultra assay and reveals sex-specific differences. The vast majority of HD patients had an hs-cTnI concentration in the normal range below the 99th percentile, which was still predictive of mortality.

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**Competing interests:**

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**Figure 1: Distribution of hs-cTnI (A) and cTnI (B) in the cohort**

The majority of the HD patients had a plasma hs-cTnI or cTnI concentration below the 99th percentile indicated by the vertical line.

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Automatisch generierte Beschreibung**

**Figure 2. Plasma hs-cTnI concentration according to gender (A) and survival status (B).**

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**Figure 3. Survival curves for tertiles of hs-cTnI (A) and s-cTnI plasma concentration (B) and relative risk according to the tertiles**

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**Figure 4. ROC curves for the outcome all-cause mortality by hs-cTnI and s-cTnI (A) and influence of gender on ROC of hs-cTnI (B).**

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**Table 1: Baseline characteristics of the cohort (N=215).**

Values are shown as median and interquartile range for continuous variables and as percentages for categorical variables. Differences between male and female patients were tested for significance using the rank sum test and chi-squared-test.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | All (N=215) | men (N=140) | women (N=75) | p-value men vs. women |
| age, years | 73 (64;80) | 73 (62;79) | 75 (65;80) | 0.4326 |
| body weight, kg | 77 (69; 88) | 80 (74;90) | 70 (60;81) | <0.0001 |
| time on dialysis, months | 47 (20;83) | 48 (15;83) | 47 (26;96) | 0.2974 |
| dialysis access  native AV fistula  PTFE graft | 184 (85%)  31 (15%) | 123 (88%)  17 (12%) | 61 (82%)  14 (18%) | 0.1133 |
| underlying renal disease  diabetic nephropathy glomerulonephritis  hypertensive nephropathy  PKD  unknown | 43 (20%)  44 (20%)  15 (7%)  10 (5%)  103 (48%) | 32 (23%)  28 (19%)  12 (9%)  5 (4%)  63 (45%) | 11 (15%)  16 (21%)  3 (4%)  5 (7%)  40 (53%) | 0.3091 |
| residual excretion, L/24 h | 0.3 (0;1.2) | 0.46 (0;1.3) | 0.0 (0;0.9) | 0.1246 |
| ultrafiltration, mL/h/kg | 6.5 (3.8; 8.7) | 6.3 (3.8;8.7) | 6.7 (3.8;9.1) | 0.4966 |
| dialyzer  high flux  low flux | 210 (98%)  5 (2%) | 135 (96%)  5 (4%) | 75 (100%)  0 (0%) | 0.0977 |
| dialysis modality  double needle HD  online hemodiafiltration | 71 (31%)  144 (69%) | 41 (29%)  99 (71%) | 30 (40%)  45 (60%) | 0.1114 |
| blood pump, mL/min | 300 (280; 320) | 300 (300;320) | 300 (280;320) | 0.0214 |
| dialysis duration, h | 4 (4;4.25) | 4 (4;4.5) | 4 (4;4) | 0.0868 |
| spKt/V | 1.5 (1.3;1.7) | 1.42 (1.29;1.59) | 1.74 (1,58;2) | < 0.0001 |
| cardiac comorbidity  valvular disease  LV hypertrophy  CAD  PTCA  pulmonary hypertension pacemaker  atrial fibrillation  any of the above | 100 (47%)  92 (43%)  75 (35 %)  51 (24%)  48 (22%)  15 (7%)  83 (38%)  173 (80%) | 62 (45%)  61 (44%)  49 (35%)  35 (25%)  33 (24%)  11 (8%)  59 (42%)  113 (81%) | 38 (51%)  31 (41%)  26 (35%)  16 (21%)  15 (20%)  4 (5%)  24 (32%)  60 (80%) | 0.8998 |
| systolic LV function from echocardiography  normal  slightly impaired  moderately impaired  severely impaired  unknown | 135 (63%)  23 (11%)  13 (6%)  4 (2%)  40 (18%) | 79 (56%)  17 (12%)  12 (9%)  3 (2%)  29 (21%) | 56 (75%)  6 (8%)  1 (1%)  1 (1%)  11 (15%) | 0.0235 |

AV arteriovenous, PTFE polytetrafluorethylene, PKD polycystic kidney disease, spKt/V single-pool Kt/V, LV left ventricular, CAD coronary artery disease, PTCA percutaneous coronary angioplasty

**Table 2. Categorical distribution of the plasma hs-cTnI and s-cTnI concentration according to different analytical thresholds**

Proportions were tested for significance using the Fisher´s exact test.\* indicates numbers summing up to N=215 (100%).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | hs-cTnI | | s-cTnI | |  |
| cut-off | ng/L | N (%) | ng/L | N (%) | p |
| 99th percentile | >47.34 | 15 (7) | >40 | 33 (15) | 0.0148 |
| 10% CV | >4.46 | 189 (88) | >30 | 58 (27) | <0.0001 |
| 20% CV | >2.50 | 206 (96)\* | >17 | 113 (53)\* | <0.0001 |
| imprecise value (CV >20%) | ≤2.50 | 5 (2)\* | ≤17 | 98 (46)\* | <0.0001 |
| limit of detection | <2.21 | 4 (2) | <6 | 7 (3) | 1.000 |
| technical error |  | 4 (2)\* |  | 4 (2)\* | 1.000 |

**Table 3: Factors associated with plasma hs-cTnI and s-cTnI concentration**

Raw r-values from spearman rank correlation and adjusted r from multivariable regression with all variables entered. (N=209-211).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | hs-cTnI |  | s-cTnI |  |
| variable | raw | adjusted | raw | adjusted |
| gender (1=female, 2=male) | 0.147  *p=0.0333* | 0.070  p=0.3180 | 0.081  p=0.2442 | 0.0548  p=0.4398 |
| age | 0.303  *p<0.0001* | 0.1480  *p=0.0352* | 0.280  *p<0.0001* | 0.1035  *p=0.0144* |
| BMI | 0.061  p=0.3814 | 0.1970  *p=0.0051* | 0.080  p=0.2471 | 0.1970  *p=0.0050* |
| time on dialysis | 0.080  p=0.2502 | -0.0148  p=0.8348 | 0.164  *p=0.0171* | 0.0668  p=0.3461 |
| presence of AF (1=yes) | 0.242  *p=0.0004* | -0.0259  p=0.7151 | 0.317  *p<0.0001* | 0.0904  p=0.2020 |
| history of revascularization (1=yes) | 0.223  *p=0.0011* | 0.1450  *p=0.0399* | 0.301  *p<0.0001* | 0.2396  *p=0.0006* |
| SCI | -0.137  *p=0.0470* | -0.1982  *p=0.0048* | -0.148  *p=0.0321* | -0.1811  *p=0.0101* |
| CBVI | 0.173  *p=0.0118* | 0.2457  *p=0.0004* | 0.147  *p=0.0323* | 0.1866  *p=0.0080* |
| OH | 0.166  *p=0.0161* | 0.1454  *p=0.0394* | 0.189  *p=0.0058* | 0.1868  *p=0.0079* |

Abbreviations AF atrial fibrillation, SCI systemic cardiac index, CBVI central blood volume index, OH overhydration

**Table 4. Hazard ratios for all-cause and cardiovascular mortality from cox regression.**

All-cause mortality occurred in n=65 (30%) of the patients. n=150 alive patients were censored.

The hazard ratios with 95% CI are displayed for one standard deviation increase.

|  |  |  |
| --- | --- | --- |
|  | hs-cTnI | s-cTnI |
| standard deviation, ng/L | 34.5 | 35.2 |
| all-cause mortality |  |  |
| crude HR | 1.23 (1.06; 1.43)  p=0.0068 | 1.15 (1.02; 1.31)  p=0.0263 |
| adj HR 1 | 1.24 (1.02; 1.51)  p=0.0320 | 1.22 (1.04; 1.44)  p=0.0176 |
| CV mortality |  |  |
| crude HR | 1.30 (1.05; 1.60)  p=0.0149 | 1.15 (0.95; 1.39)  p=0.1355 |
| adj HR 1 | 1.31 (0.98; 1.75)  p=0.0667 | 1.27 (0.97; 1.66)  p=0.0788 |

1 adjusted for age and gender as well as other factors associated with increased mortality in this cohort such as time on dialysis, vascular access (fistula/graft), flux (low/high), plasma albumin and inorganic phosphorus concentration and presence of peripheral artery disease.

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