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Prognostic Value of Cardiac Biomarkers in Hemodialysis Patients – which one to use?

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Abstract: *The high prevalence of cardiovascular mortality in the end-stage renal disease population is well established. The aim of this current study was to document the relative prognostic significance of established biomarkers high-sensitive cardiac troponin T (hs cTnT), cardiac troponin I (cTnI), and N-terminal proBNP (NT-proBNP) and high-sensitive CRP (hs CRP) in this population. A prospective cohort study of dialysis patients undertaken in a single centre in Bulgaria. The relation between mortality and cardiac biomarkers was evaluated in 140 hemodialysis patients. End-point of interest was cardiac mortality. Statistical analysis using Cox proportional hazards was used to study relationship between competing covariates and outcome. Patients was followed upor a median duration of 24 months. The mean concentrations (+/-SEM) of hs cTnT, cTnI, NT-proBNP and hs CRP were 0,07±0,01 µg/L, 0,03±0,01 µg/L, 14969±1125 pg/mL and 16,4±2,38 mg/L respectively. Thirty-six subjects died during the period of follow up. By univariate analysis, cardiac markers hs cTnT, cTnI and NT-proBNP were significantly associated with an increase mortality. On Cox proportional hazards analysis, hs cTnT showed a highest significant association with cardiac mortality, with hazard ratios of 2,46, 95% confidence interval (CI) 1,39-4,33, p<0,002, followed by cTnI- 1,82, 95% CI1,41-2,34, p<0,0001 and NT-proBNP - 1,78, 95% CI 1,28-2,48, p<0,001 respectively. In patients with end-stage renal failure on dialysis hs cTnT provides greater prognostic information compared with NT-proBNP and cTnI.*

Keywords: *cardiac biomarkers, hemodialysis, cardiac mortality*

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I. Introduction

Cardiovascular disease is the main cause of high mortality in hemodialysis patients. Elevations of cardiac troponins in asymptomatic hemodialysis patients are common and elevated cTnT has been associated with increased cardiac mortality in multiple studies [1-3]. The prevalence of elevated cTnI is lower compared with cTnT[4]. Cardiac troponins, which are released into the circulation and increased sharply if irreversible damage to the heart muscle exists [5]. There are other reasons for the presence of cTn. These are myocardial damage due to high pressure in the left ventricular wall in hypertrophy, acute or chronic volume overload, microvascular lesions, "quiet" subclinical myocardial ischemia fibrosis and necrosis. In hemodialysis patients, these conditions are very common [6]. N-terminal proBNP (NT-proBNP) is used as marker for congestive heart failure and is associated with left ventricular hypertrophy and systolic dysfunction in general population. B-type natriuretic peptide (BNP) is a hormone that is released in response to wall stretch of the cardiac ventricles. N-terminal proBNP (NT-proBNP) is an inactive fragment that is released along with BNP in a 1:1 ratio, cleared renally, and removed by hemodialysis (HD) to a very small extent [7]. The levels of both BNP and NT-proBNP are elevated in the ESRD population [7;8]. Elevation of this biomarker is high prevalent in dialysis population and is associated with increased mortality [9]. Elevated NT-proBNP in this population not only reflect wall stress, but also decreased renal clearance. The increased cardiovascular mortality is only partially explained by the presence of left ventricular hypertrophy and systolic dysfunction [10]. Moreover, there seems to be a complex interrelation with other biomarkers such as troponins and CRP. Elevations of hs CRP can be detected in this population such as in patients with chronic inflammation. Some studies report improved prognostic performance of these biomarkers when combined [11,12], whereas others do not [13]. The availability of these different biomarkers offers prognostic information that may be useful in various decision – making processes in hemodialysis patients, such as selecting patients for cardiovascular screening. The aim of this study was to investigate the performance of hs cTnT, cTnI, NT-proBNP and hs CRP to predict mortality in asymptomatic hemodialysis patients and interrelation between them.

II. Material and methods

We prospectively included 140 chronic hemodialysis patients between June 2014 and June 2015. They were followed 24 months. Patients were eligible for study inclusion if they were on chronic hemodialysis treatment for≥3 months. All patients used low-flux dialyzers with polysulfone membranes. Clinically they are hemodynamically stable, with no evidence of acute coronary syndrome or heart failure in the previous two months. Patients with a diagnosis of cancer, autoimmune diseases and signs of active inflammation were excluded. All patients were treated according to national quality guidelines, with frequency three times weekly duration of hemodialysis session of 4 hours. Patients characteristics, comorbidities, cause of end-stage renal disease and cause of death were collected from medical charts. The end-point was cardiovascular death. All patients were followed up prospectively for two years or until death. Cardiovascular death included sudden cardiac death and fatal cardiovascular events as defined below. Sudden cardiac death was defined as unexpected natural death within 1 h from the symptom onset and without any prior condition that would appear fatal. Fatal cardiovascular events included myocardial infarction, electrocardiographically documented arrhythmia, thromboembolic or hemorrhagic stroke (all defined using conventional clinical criteria) and sudden cardiac death.

Hs cTnT and NT-proBNP were analyzed with Elecsys 2010 immunoassay reagents of Roshe Diagnostics. NT-proBNP was reported in pg/mL. The above hs cTnT reference value is specified by the manufacturer through testing of 533 healthy subjects (99th percentile of healthy) and was 0,014 μg/L. Quantitative determination of serum cTnI levels was performed with the AIA-Pack ST AIA-Pack for the cTnI 3 generation of the Tosoh company. Reference limits for cTnI was <0,06 μg/L and 99th percentile – 0,04 μg/L. Hs CRP was investigated by biochemical analyzer Beckman Coulter AU 480 by immunoturbidimetric method with reagents Roshe Diagnostics and has an upper reference value of 1,0 mg/L.

Blood samples were taken immediately before the interim procedure for the week. Patients were divided into 4 subgroups for each biomarker. Hs cTnT cut-off values were: gr. 1≤0,014 μg/L; gr. 2 - 0,015-0,030 μg/L; gr. 3 - 0,031-0,099 μg/L; gr. 4≥0,099 μg/L. The first group is within the 99th percentile of healthy population; the value of 0,10 μg/L is the cut-off point for myocardial infarction. For cTnI cut-off values were: gr. 1≤0,020 μg/L; gr. 2 - 0,021-0,035 μg/L; gr. 3 - 0,036-0,040 μg/L; gr. 4 ≥0,040 μg/L. The first three groups are within the the 99th percentile of healthy population, the value of 0,040 μg/L is the cut-off point for myocardial infarction. NT-proBNP values >125 pg/mL may indicate cardiac dysfunction and are associated with an increased risk of cardiac complications. Elevated NT-proBNP values above the cut-off point for heart failure was present in all patients. For NT-proBNP cut-off values were: gr. 1≤3410 pg/mL; gr.2 – 3411-6567 pg/mL; gr.3 – 6568-10449 pg/mL; gr.4≥10500 pg/mL. These are values corresponding to 95th percentile in patients with heart failure NYHA class I to IV. hs CRP cut-off values were for gr. 1≤1,0 mg/L; for gr. 2 – 1,0-5,0 mg/L; for gr. 3 – 5,0-10,0 mg/L and for gr. 4≥10,0 mg/L.

To process the statistical data was used Statistical Package for Social Sciences (SPSS) version 20.0. Variables were expressed as mean±SEM. All parameters were tested for normal distribution using the test of Shapiro-Wilk. The relationship between performances was recorded using linear regression. One-way ANOVA test was used to determine the presence of a significant difference between the values of the biomarkers in the different subgroups. Survival analysis in different subgroups was done using Kaplan-Meier time-to-event curves, followed by a log-rank test. Cox proportional hazard modelswere used to calculate unadjusted HRs (HRs) and adjusted HRs (adj HRs) for outcome analyzing each biomarker as a continuous variable. In multivariable analysis, we adjusted for important clinical variables - age, gender and hemodialysis duration. Statistically significant difference was accepted at p≤0,05.

III. Results

The baseline characteristics of the study population and underlying renal disease are shown in Table 1. Mean age was 53,4±1,3 years, 83 patients (59,3%) were male. Cardiac comorbidities were present in a large proportion of the patients. Ischemic heart disease was the most frequent condition (35%). CAD was documented in 49 patients, 25 of which had a history of myocardial infarction and 36 had diabetes mellitus. Cardiovascular mortality was 25,7 % (36 of 140 patients) within the study period. The mean values of cardiac biomarkers in different subgroups are shown in Table 2.

Table 1 Patient characteristics

	n = 140
Age, years	53,4 ± 1,3
Male, %	83 (59,3%)
Hemodialysis duration, months	45,2 ± 3,8
Diabetes mellitus, %	36 (25,7%)

History of MI	25 (17,8%)
CAD	49 (35%)
Cause of end stage renal disease	
Glomerulonephritis	29 (20,7%)
Interstitial nephritis	49 (35%)
Diabetic nephropathy	26 (18,6%)
Hypertensive nephropathy	16 (11,4%)
Cystic kidney disease	15 (10,7%)
Others	5 (3,6%)

Cardiac mortality was assessed in patient groups, divided according to the mean concentration of cardiac biomarkers (Table 2). We found elevated hs cTnT above 99th percentile of healthy in almost all 140 patients (98,6%) and the mean value was 0,067±0,005 µg/L.

Table 2 Number and % of patients in particular subgroups

Biomarkers	n=140
hs cTnT all patients	
mean±SE mean / µg/L	0,067 ± 0,005
gr.1 </= 0,014 µg/L	2 (1,4%)
gr.2 0,015-0,030 µg/L	27 (19,3%)
gr.3 0,031-0,099 µg/L	93 (66,4%)
gr.4 > 0,1 µg/L	18 (12,9%)
cTnI all patients	
mean±SE mean / µg/L	0,027 ± 0,006
gr.1 </= 0,02 µg/L	97(69,2%)
gr.2 0,021-0,035 µg/L	18 (12,9%)
gr.3 0,036-0,040 µg/L	7 (5%)
gr.4 > 0,040 µg/L	18 (12,9%)
NT-pro BNP all patients	
mean±SE mean / pg/mL	14969 ± 1125
gr.1 </= 3410 pg/mL	37 (26,5%)
gr.2 3411-6567 pg/mL	26 (18,6%)
gr.3 6568-10449 pg/mL	11 (7,8%)
gr.4 > 10500 pg/mL	66 (47,1%)
hs CRP all patients	
mean±SE mean / mg/L	7,39 ± 2,38
gr.1 </= 1,0 mg/L	5 (3,6%)
gr.2 1,0-5,0 mg/L	47 (33,6%)
gr.3 0,5-10,0 mg/L	30 (21,4%)
gr.4 > 10,0 mg/L	58 (41,4%)

Patients with hs cTnT≤0,014 µg/L and 0,015–0,030 µg/L were combined as a group for analysis because there were only 2 patients with hs cTnT≤0,014 µg/L. There is a significant difference between mean values of hs cTnT in group of alive patients for the study period – 0,055±0,004 µg/L and these who died due to cardiovascular reasons – 0,096±0,016 µg/L, p<0,001. Cardiac mortality was 50% and significantly higher in gr.3 patients with hs cTnT>0,1 µg/L than patients in gr.1 – 10,3% and gr.2 – 25,8%, p<0,001(Fig.1A). Additionally, there is a significant difference in values of hs cTnT between gr. 2 (0,064±0,004 µg/L) and gr. 3 (0,209±0,13 µg/L), p<0,001.

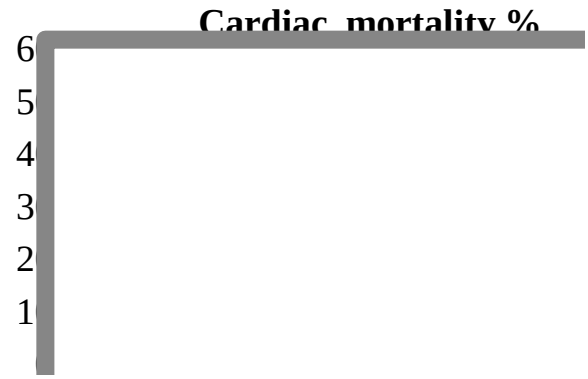

Fig.1A Cardiac mortality in groups, divided by mean hs cTnT

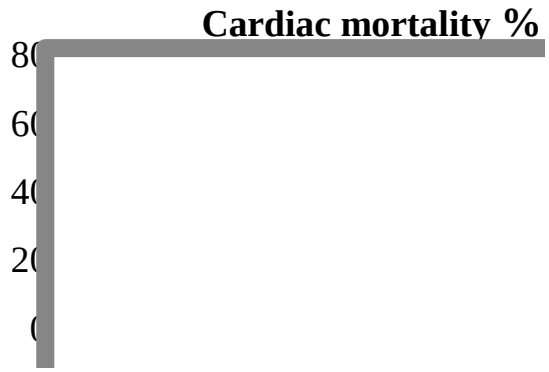

Fig.1B Cardiac mortality in groups, divided by mean cTnI

There is a significant difference between mean values of cTnI in group of alive patients for the study period – 0,015±0,002 μg/L and these who died due to cardiovascular reasons – 0,063±0,02 μg/L, p<0,001. cTnI above 0,040 μg/L was found at 18 of 140 patients (12,9%). In the divided 4 groups, for cTnI cut-off values for gr.1, 2 and 3 are within the the 99th percentile of healthy population, the value of 0,040 μg/L is the cut-off point for myocardial infarction. One-way ANOVA statistic shows a significant difference between groups, p<0,001. Cardiac mortality significantly increased from gr.1 to gr.4, respectively 17%, 22%, 28% and 72%, p=0,015 (Fig. 1B). There was not a significant difference between gr.2 and gr.3.

All patients have have elevated values of NT-proBNP. The one-way ANOVA statistical test shows a significant difference in the mean values between the groups, p<0,001.There is a significant difference between mean values of NT-proBNP in group of alive patients for the study period – 12368±1303 pg/mL in these who died due to cardiovascular reasons – 22738±2131 pg/mL, p<0,001. In gr.4 with highest value of NT-proBNP we have 66 patients and cardiovascular mortality is 42% of them. Patients in groups 1,2 and 3 had significantly lower mortality than those with higher NT-proBNP concentrations in group 4, p<0,001 (Fig. 1C). Patients in gr.2 did not differ significantly in cardiac mortality compared to those in gr.1 and 3.

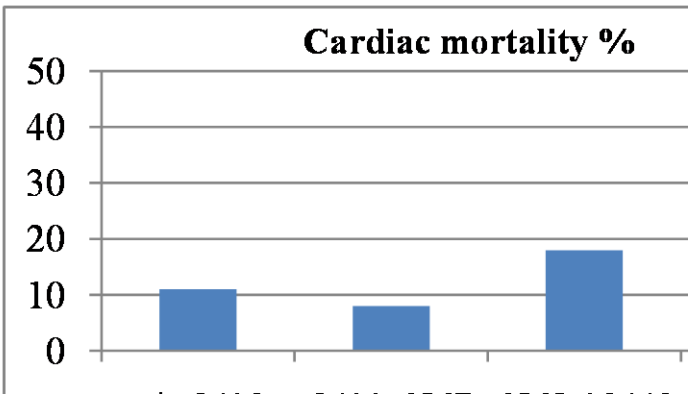

Fig.1C Cardiac mortality in groups, divided by mean NT-proBNP

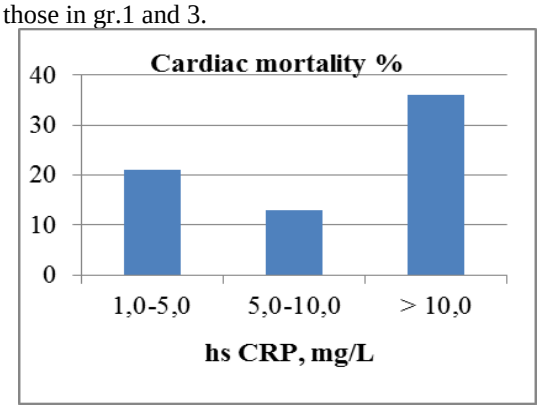

Fig.1D Cardiac mortality in groups, divided by mean hs CRP

Patients with normal hs CRP values in gr.1 was only 5 and they had 100% survival. Due to the small number they are not included in the statistical analysis. In 135 patients (96,4%) hs CRP values were above 1,0 mg/L as in 58 patients (41,4%) were above 10,0 mg/L. There is a significant difference between mean values of hs CRP in group of alive patients for the study period – 12,6±2,2 mg/L an these who died due to cardiovascular reasons – 24,8±6,8 mg/L, (p<0,05). Cardiovascular mortality increase to 36% in gr.4 of patients and we found significant difference between groups using ANOVA test (p=0,036).

Studied four cardiac biomarkers showed a strong relationship and positive correlation with each other. Table 3 detailed factors associated with hs cTnT in the multiple linear regression analysis. cTnI was most significantly associated with hs cTnT – r=0,74. Other significant factors (in descending order of significance) included NT-proBNP (r=0,37) and hs CRP (r=0,36). Male gender, age and HD duration were not significantly associated with hs cTnT.

Table 3 Multiple linear regression model for hs cTn T r – Pearson correlation; Adjusted $R^2$of the model =0,56

	r	p-value
Age	-0,01	0,49
Male gender	0,11	0,12
HD duration	-0,14	0,06
cTnI	0,74	0,001
NT-proBNP	0,37	0,001
hs CRP	0,36	0,001

Overall, the adjusted $R^2$of the model was 0,56, indicating that 56% of the variability in plasma TnT concentrations could be explained by these factors.

Table 4 Univariate correlation analysis between cardiac biomarkers; r – Pearson correlation

	hs cTnT	TnI	NT-proBNP	hs CRP
hs cTnT	-	r=0,74; p<0,001	r=0,37; p<0,001	r=0,36; p<0,001
cTnI	r=0,74; p<0,001	-	r=0,32; p<0,001	r=0,33; p<0,001
NT-proBNP	r=0,37; p<0,001	r=0,32; p<0,001	-	r=0,18; p<0,02
hs CRP	r=0,36; p<0,001	r=0,33; p<0,001	r=0,18; p<0,02	-

We are investigate the presence and strength of interrelation between four study biomarkers. The values of hs cTnT in all investigated patients showed strong positive correlation with cTnI (r = 0,74) and moderate correlation NT-proBNP (r = 0,37) and hs CRP (r = 0,36), p<0,001. The correlations of cTnI were in similar values (Table 4). NT-proBNP shows moderate correlation with hs cTnT and cTnI, but a weaker one with hs CRP (r = 0,18), all p-values<0,05.

Fig. 2 shows the Kaplan-Meier survival curves in relation to cardiovascular death across the different groups, divided by values of hs cTnT, TnI, NT-proBNP and hs CRP. With increasing of values of biomarkers the incidence of cardiac mortality also increase. Log-rank test showed significant difference between groups 1 to 4 for hs cTnT, TnI and NT-proBNP (p<0,005), but not between groups 1 to 4 for hs CRP (p= 0,10).

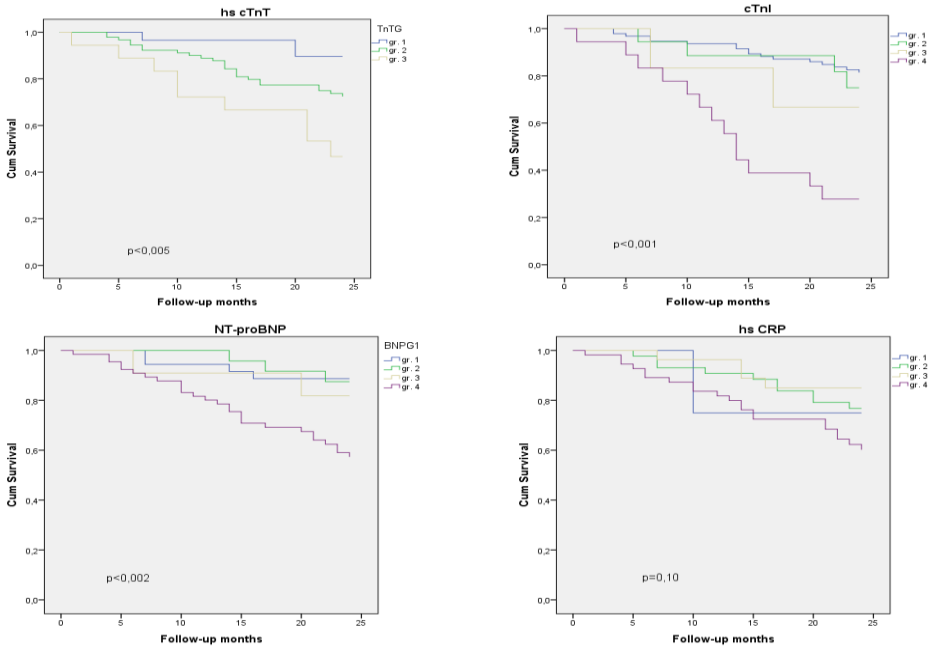

Fig. 2 Kaplan-Meier survival curve analysis across the subgroups of hs cTnT, cTn I, NT-proBNP and hs CRP in relation to cardiovascular death

For evaluation of the effect of cardiac biomarkers in predicting the time to cardiovascular mortality relative risks and 95% confidence intervals (CI) were calculated as hazard ratios (HR) derived from the Cox proportional hazards regression model.

Table 5 Hazard ratios for cardiac biomarkers and hazard ratios after adjustment for ade, gender and HD duration

Biomarker	HR	CI (95%)	p-value	Adj HR	CI (95%)	p-value
hs cTn T	2,46	1,39 – 4,33	0,002	2,35	1,28 – 4,22	0,02
cTn I	1,82	1,41 – 2,34	0,001	1,91	1,47 – 2,51	0,001
NT-proBNP	1,78	1,28 – 2,48	0,001	1,81	1,29 – 2,53	0,001
hs CRP	1,38	0,95 – 2,02	0,09	1,42	0,97 – 2,08	0,07

Univariate Cox regression analysis of the different biomarkers in relation to cardiovascular death is shown in Table 5. In the multivariable Cox regression model hs cTnT remained a most significant predictor of cardiovascular death after adjustment for age, sex and HD duration – HR 2,35, 95% CI 1,28-4,22, p=0,002, followed by cTnI - HR 1,91, 95% CI 1,47-2,51, p=0,001 and NT-proBNP - HR 1,81, 95% CI 1,29-2,53, p=0,001.

IV. Discussion

In this study, we investigated the short-term prognostic value of hs cTnT, cTnI, NT-proBNP and hs CRP in hemodialysis patients. We observed a significantly higher incidence of cardiovascular death in ESRD patients with a high baseline hs cTnT. Earlier studies that examined serum biomarkers in hemodialysis patients used the older cTnT assays (third and fourth generation) and confirmed that cTn T was one of the better markers for predicting adverse events[14]. Using high sensitive assay, we found a higher proportion of our dialysis population with hs-cTnT concentrations above the reference interval of the healthy population, results in agreement with previous studies [15-17]. This is a marked difference compared to previous studies, in which only 15% to 45% of patients on dialysis were found to have increased concentrations [18-20]. In line with our current data, hs cTnT also appears to be a better predictor of outcome than the older assays for patients on dialysis[21]. In our study, cTnT was elevated in nearly all of the patients (98,6%) compared to cTnI (12,9%). This is similar to the findings of Jacobs et al., who found elevations of cTnT measured with the high sensitive Roche assay in all of the patients studied whereas cTnI measured using a conventional assay was elevated in only 28% of the cases [22].

Cardiac mortality was significantly higher in gr.3 patients with hs cTnT> 0,1 µg/L than patients in gr.1 and gr.2. We found also a significant difference in values of hs cTnT between gr.2 and gr.3. We can assume that even mild elevations of hs cTnT are associated with increased cardiovascular mortality. Our findings clearly extend the usefulness of hs cTnT as a serum biomarker for short-term outcome prediction and cardiovascular risk stratification to ESRD patients receiving long-term hemodialysis. However, there should be caution when interpreting high cTnT values as more accumulation [23]. Elevated cTnT and cTnI concentrations are both strong predictors of mortality. Accumulation of cTnT can only occur following release after myocyte damage and should be regarded as a pathologic finding in any ESRD patients. Furthermore, accumulation can only occur when residual renal function declines, which is a strong predictor of survival in hemodialysis patients [24]. Therefore, plasma cTnT concentrations provide information about cardiac release and dialysis heritage, which might explain the improved prognostic value of cTnT compared to cTnI, as seen in our and other studies[25-27]. Our results shows that elevated hs cTnT, cTnI, NT-proBNP and hs CRP correlate with cardiovascular mortality. In this study, elevated NT-proBNP was seen in all patients. In spite of generally elevated levels NT-proBNP is still an independent predictor of cardiac mortality and might have prognostic value. In a multivariate proportional hazards model with age, sex and HD duration both troponins and NT-proBNP are independent predictors and are significantly associated with an increase in cardiovascular mortality, but hs cTnT remained the most powerful predictor of cardiovascular death.

V. Conclusion

Biomarkers that have a high predictive value for cardiovascular events may be helpful in deciding treatment strategy and determining prognosis in ESRD patients. Elevated hs cTnT, cTnI and NT-proBNP correlate with cardiovascular mortality. Using high-sensitivity assay almost all hemodialysis patients have elevations of hs cTnT. There is a positive, strong correlation between hs cTnT and cTnI and moderate correlation with NT-proBNP and hs CRP. Both hs cTnT and cTnI are strong predictors of mortality in the short-term and are useful markers to identify patients at risk, however, cTnT is more retained compared to cTnI. Hs cTnT was found to be the most powerful predictor of mortality in ESRD patients among other established cardiac biomarkers.

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