High-sensitivity cardiac troponin T in detecting obstructive coronary artery disease in hemodialysis patients listed for kidney transplantation

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ABSTRACT

Background: Cardiovascular diseases are the leading cause of morbidity and mortality in patients with end-stage renal disease.

Aims: This study aimed to assess the prognostic value of high-sensitivity cardiac troponin T (hs-cTnT) in identifying patients with obstructive coronary artery disease (CAD) among patients on hemodialysis listed for kidney transplantation.

Methods: The study prospectively enrolled consecutive adult hemodialysis patients listed for kidney transplantation. They underwent laboratory tests and a standardized set of imaging and functional tests, including coronary angiography, according to patient characteristics.

Results: The study included 100 consecutive patients (72 men)at a median age of 56.5 years. Ultimately, 48% of the patients were diagnosed with obstructive CAD. Age and plasma hs-cTnT levels predicted the diagnosis of obstructive CAD (OR, 1.13; 95% CI, 1.08–1.20; P <0.001 and OR, 1.03l 95% CI, 1.01–1.05; P = 0.001, respectively). The calculated cut-off value for age was 53 years, which showed sensitivity of 87.5% and specificity of 76.9% for obstructive CAD diagnosis. The calculated value for hs-cTnT was 0.067 ng/ml, which showed sensitivity of 61.4% and specificity of 82.2% for the detection of obstructive CAD. In patients aged >52 years, 79.2% were diagnosed with obstructive CAD. However, in the group of patients ≤52 years and with hs-cTnT >0.069 ng/ml, the incidence of obstructive CAD was significantly higher than in the group with hs-cTnT level ≤0.069 ng/ml.

Conclusions: Baseline hs-cTnT level is a useful prognostic biomarker in the diagnosis of obstructive CAD in hemodialysis patients listed for kidney transplantation.

Key words: cardiovascular diseases, end-stage renal disease, hemodialysis, high-sensitivity cardiac troponin T, obstructive coronary artery disease

INTRODUCTION

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality in patients with end-stage renal disease (ESRD) who are treated with hemodialysis. Among them, chronic coronary syndrome (CCS), acute coronary syndrome, and sudden cardiac death are the major causes of death [1]. The reported 3-year all-cause mortality in ESRD patients or hemodialysis patients is approximately 27.5% [1]. Despite such high cardiovascular mortality when compared to subjects with normal kidney function, they are less likely to receive optimal medical treatment and less frequently undergo cardiovascular interventions. Notably, this group is less likely to present with typical cardiovascular symptoms [1], which makes CVD diagnosis more difficult.

WHAT'S NEW?

Cardiovascular diseases are the leading cause of death in patients with end-stage renal disease. So far, there are no specific guidelines defining what cardiac assessment should be performed in patients qualified for kidney transplantation. This study prospectively enrolled 100 consecutive adult hemodialysis patients listed for kidney transplantation who underwent broad cardiac assessment including high-sensitivity cardiac troponin T (hs-cTnT) and coronary angiography. This approach adds novel information to current knowledge by identifying patients with high risk of obstructive coronary artery disease. Studies indicate that patients below 52 years of age and plasma hs-cTnT <0.069 ng/ml may not need to undergo diagnostic workup for obstructive coronary artery disease or revascularization before kidney transplantation. On the other hand, hs-cTnT >0.069 ng/ml and age above 52 years in this subgroup should raise suspicion of obstructive coronary artery disease and warrant diagnostic workup, and selected patients may need coronary artery revascularization.

Patients listed for kidney transplantation (KTx) are often at high risk of adverse cardiovascular events, including acute coronary syndrome and CCS [2–8]. To prevent cardiovascular events in hemodialysis patients listed for KTx, diagnostic markers for cardiovascular complications are being sought. Troponins, especially high-sensitivity cardiac troponin T (hs-cTnT), are very sensitive and specific markers of cardiomyocyte injury. The European Society of Cardiology guidelines point out that elevated hs-cTnT levels in patients with chronic kidney disease (CKD) should not be attributed to impaired renal clearance and, consequently, considered harmless [9]. It has been shown that in patients with CKD in the pre-dialysis period, the hs-cTnT level rises, even if myocardial cells have not been damaged. However, the etiology of this phenomenon is not fully understood [10]. It should be noted that hs-cTnT is considered a marker for CCS, especially multivessel CCS, left ventricular hypertrophy (LVH), dysfunction of the left ventricle (LV), and, eventually, a mortality predictor in patients with CKD [11–13]. This prospective study aimed to assess the diagnostic value and define the cut-off point of hs-cTnT for detecting CCS in hemodialyzed patients listed for KTx.

METHODS

We initially considered 485 consecutive patients with CKD who underwent renal replacement therapy in the Department of Internal Medicine and Nephrology, Medical University of Warsaw, and tertiary dialysis centers. Based on the following exclusion and inclusion criteria, finally, a group of 100 consecutive adult hemodialysis patients who were hospitalized in the Department of Internal Medicine and Cardiology, Medical University of Warsaw and listed for KTx were enrolled from 2014 until 2017 for CVD assessment (Table 1). The exclusion criteria were as follows: lack of consent to participate in the study, life expectancy <12 months, advanced cancers, pregnancy, severe coronary artery disease, and addiction to psychoactive substances. All of the included patients underwent detailed clinical evaluation that included blood tests (hs-cTnT level), standard 12-lead electrocardiography, transthoracic echocardiography focused on LV morphology and function, exercise electrocardiogram tests, and exercise perfusion heart scintigraphy (SPECT). Subsequently, all subjects with LV wall motion abnormalities on echocardiography or abnormal exercise test or SPECT (at least 5% of LV mass-induced ischemia) underwent coronary angiography. If the patient did not meet the above criteria, further diagnostics workup of obstructive CCS was not performed, and the patient was treated with optimal medical therapy for comorbidities.

Table 1. Characteristics of the study group

Patients (n = 100)	
Male gender, n (%)	72 (72)
Age, years	56.5 (24–81; IQR 22.25)
Time of dialysis, months	24 (1–228; IQR 50.25)
Weight, kg	77.1 (46.3–110; IQR 24.625)
Height, m	1.705 (1.52–1.9; IQR 0.15)
BMI, kg/m^2	24.91 (17.21–35.51; IQR 7.02)
Hs-cTnT, ng/ml	0.05 (0.016–0.32; IQR 0.055)
EF, %	64 (20–68; IQR 5)
PW, mm	12 (9–15; IQR 1)
IVS, mm	12 (9–18; IQR 2)
Contractility disorder, n (%)	16 (16)
LVH, n (%)	75 (75)
Cause of ESRD	
Glomerulonephritis, n (%)	34 (34)
DM, n (%)	29 (29)
Polycystic kidney disease, n (%)	16 (16)
Postrenal failure, n (%)	5 (5)
HT, n (%)	3 (3)
Other, n (%)	6 (6)
Unknown cause, n (%)	7 (7)
Comorbidities	
HT	95 (95)
Hyperlipidemia	70 (70)
DM	35 (35)
CHF	23 (23)
AF	10 (10)
Stroke	5 (5)
Smoking	50 (50)
VA	69 (69)

Data are shown as numbers (%) or medians (min–max; IQR)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHF, chronic heart failure; DM, diabetes mellitus; ESRD, end stage renal disease; hs-cTnT, high-sensitivity cardiac troponin T; HT, hypertension; IQR, interquartile range; IVS, interventricular septum thickness; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; PW, posterior wall thickness; VA, ventricular arrhythmias

Chronic coronary syndrome

Obstructive CAD was diagnosed when at least 50% narrowing of the epicardial coronary artery was detected on angiography. During coronary angiography (Allura FD 40, Philips, Amsterdam, the Netherlands), atherosclerotic lesions in the coronary arteries were assessed, and in cases of borderline lesions (40%–90% stenosis), fractional flow reserve was assessed to verify their hemodynamic significance. Lesions equal to or over 90% of the diameter stenosis of the coronary artery were deemed significant. All the significant lesions were treated with percutaneous coronary angioplasty [14].

Troponin T assay

Peripheral blood for the hs-cTnT assay was drawn from every patient on a day after hemodialysis (HD) and was analyzed with Roche's Elecsys Troponin T-high sensitive test. The cut-off point for a positive result was 0.014 ng/ml.

Ethics

This study protocol was reviewed and approved by the Bioethics Committee of the Medical University of Warsaw, approval number (KB/58/2014). The study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant before participation in the study.

Statistical analysis

Nominal variables were described as frequencies with their percentage share in the studied group. Quantitative variables were described using median, minimum, maximum, and IQR. The chi-square test (with Yates' correction) or Fisher's exact test (depending on the distribution of expected frequencies) were used to assess the relationship between qualitative variables. The Mann-Whitney U test was applied for comparisons of quantitative variables in subgroups. Multivariable logistic regression was used to predict obstructive CAD. The overall quality of the models was reported as Tjur's R^2 [14], and the area under the curve (AUC). Additionally, receiver operating characteristic (ROC) curves were constructed to assess the diagnostic value of the selected parameters and determine optimal cut-off points. The cut-off point was determined based on Youden's criterion, optimizing both the sensitivity and specificity of the classifier. Besides the cut-off point, each ROC curve reported sensitivity, specificity, positive and negative predictive values, and AUC, along with 95% confidence intervals (95% CI) and *P*-values. Results were considered statistically significant when two-sided $P < 0.05$. The conditional inference decision tree method was utilized to create a classification algorithm for obstructive CAD detection. This algorithm implements a decision tree by conducting statistical tests at each step to identify the best split based on predictor variables, aiming to improve the homogeneity of the resulting nodes (in our case, the required *P*-value at each split was <0.10). The analysis used implementation from rpart package [15]. Data analysis was performed using the R statistical package (version 4.0.2 R Core Team, 2020).

RESULTS

The study included 100 patients (72 men and 28 women) at a median age of 56.5 years (21–85 years). The median time of treatment with dialysis was 24 months (1–228 months). Ultimately, obstructive CAD was angiographically diagnosed in 48 patients. Among 48 patients with obstructive coronary disease, 34 had revascularization. None of the patients qualified for coronary artery bypass graft. The characteristics of the patients diagnosed with obstructive CAD are shown in Table 2. Patients diagnosed with obstructive CAD were older, presented with lower left ventricular ejection fractions (LVEF), and had higher plasma hs-cTnT values. Notably, no differences in CKD etiology and duration of hemodialysis with respect to obstructive CAD diagnosis were found.

ROC curves for obstructive CAD diagnosis

The area under the ROC curve for age as a predictor of obstructive CAD in the study population amounted to 0.86 (95% CI, 0.78–0.93; $P < 0.001$). The calculated cut-off value for age was 53 years, showing sensitivity of 87.5% and specificity of 76.9% for the diagnosis of obstructive CAD (Figure 1). The area under the ROC curve for hs-cTnT as a predictor of obstructive CAD in the study population amounted to 0.75 (95% CI, 0.65–0.85; $P < 0.001$). The calculated value for hs-cTnT was 0.067 ng/ml showing sensitivity of 61.4% and specificity of 82.2% for obstructive CAD (Figure 2 and Table 3). The aforementioned cut-off value for age significantly predicted the diagnosis of obstructive CAD: for age (odds ratio [OR], 1.132; 95% CI, 1.077–1.204; $P < 0.001$) and for hs-cTnT concentration (OR, 1.026; 95% CI, 1.009–1.048; $P = 0.001$)

Multivariable regression analysis

Multivariable regression analysis was used to understand better the unique contribution of the hs-cTnT level in the context of key covariates, namely age and duration of hemodialysis. The model's Tjur was $R^2 = 0.482$ and AUC = 0.90 (95% CI, 0.83–0.96). Only age and hs-cTnT level were determined to be significant (results of simple and multivariable analyses are reported in Table 4). Moreover, despite the significant univariate relationship between LVEF and CAD (OR, 0.88; $P = 0.006$), the multivariate model was not significantly improved by its addition ($P = 0.32$)

Classification algorithm — conditional inference trees

To create a more interpretable diagnostic algorithm integrating information from both predictors of obstructive CAD that were identified in the multivariable regression model (age and hs-cTnT), the method of conditional inference trees was used. This allowed for the building of a staged diagnostic approach. In the group of patients aged

Table 2. Comparison of variables between obstructive CAD (–) and obstructive CAD (+)

	Obstructive CAD (–) n = 52	Obstructive CAD (+) n = 48	*P*-value
Age	44.5 (24–70; IQR 16.25)	63.5 (34–81; IQR 12)	<0.001
Time of dialysis, months	21 (1–191; IQR 46.5)	31.5 (1–228; IQR 45)	0.07
Weight, kg	77.25 (46.3–110; IQR 29.125)	76.85 (53–107; IQR 21.125)	0.55
Height, m	1.7 (1.58–1.9; IQR 0.145)	1.71 (1.52–1.88; IQR 0.155)	0.66
BMI, kg/m^2	24.5 (17–35; IQR 7.6)	25.6 (19.5–34.5; IQR 6.38)	0.25
LVEF, %	65 (45–68; IQR 2.75)	60 (20–68; IQR 5.5)	<0.001
PW, mm	11 (9–15; IQR 3)	12 (10–15; IQR 1)	0.06
IVS, mm	12 (9–16; IQR 2.25)	13 (10–18; IQR 1)	0.01
hs-cTnT, ng/ml	0,039 (0.016–0.152; IQR 0.033)	0.082 (0.021–0.32; IQR 0.06)	<0.001
Total cholesterol, mg/dl	173 (111–200; IQR 37)	145 (87–300; IQR 55.5)	0.003
LDL-cholesterol, mg/dl	103 (43–218; IQR 41)	74 (30–240; IQR 49)	0.001
Contractility disorder, n (%)	3 (5.8)	13 (27.1)	0.008
Cause of ESRD			
Glomerulonephritis, n (%)	20 (38.5)	14 (29.2)	0.03
DM, n (%)	8 (15.4)	21 (43.8)	
Polycystic kidney disease, n (%)	8 (15.4)	8 (16.7)	
Postrenal failure, n (%)	4 (7.7)	1 (2.1)	
HT, n (%)	2 (3.8)	1 (2.1)	
Other, n (%)	4 (7.7)	2 (4.2)	
Unknown cause, n (%)	6 (11.5)	1 (2.1)	
Comorbidities			
HT	47 (90.4)	48 (100)	0.06
Hyperlipidemia	27 (51.9)	43 (89.6)	<0.001
DM	11 (21.1)	24 (50.0)	0.005
CHF	6 (11.5)	17 (35.4)	0.009
AF	4 (7.7)	6 (12.5)	0.51
Stroke	2 (3.8)	3 (6.3)	0.69
Smoking	26 (50.0)	24 (50.0)	1
LVH	35 (67.3)	40 (83.3)	0.11
VA	35 (67.3)	34 (70.8)	0.87

Data are shown as numbers (%) or medians (min–max; IQR)

Abbreviations: see Table 1

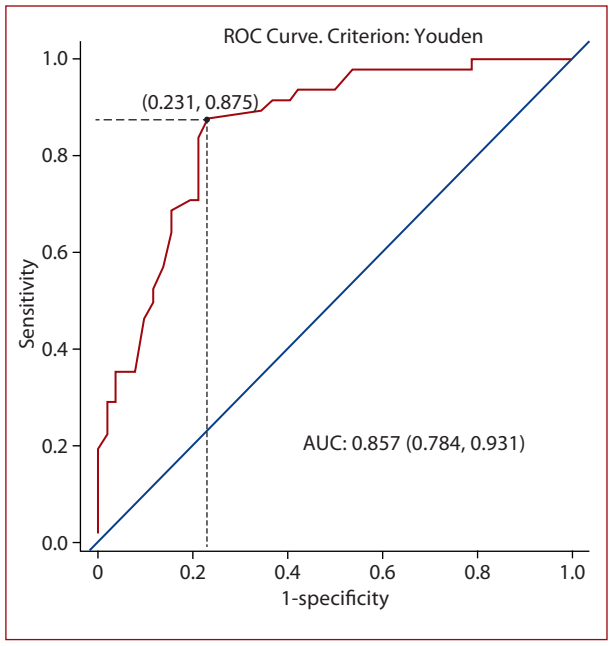

Figure 1. Receiver operating characteristic (ROC) curve for age in predicting obstructive coronary artery disease

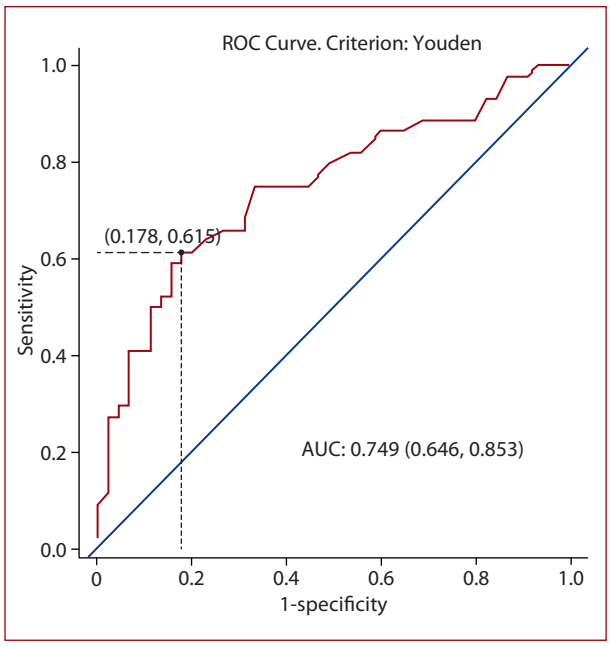

Figure 2. Receiver operating characteristic (ROC) curve for high-sensitivity cardiac troponin T level in predicting obstructive coronary artery disease

Table 3. Optimal cut off points and characteristics of classifiers for parameters significant in predicting obstructive coronary artery disease

	Obstructive coronary artery disease						
	AUC	95% CI	Cut-off point	Sensitivity	Specificity	PPV	NPV
Age, years	0.86	0.78–0.93	53	87.5%	76.9%	77.8%	87.0%
Hs-cTnT, ng/ml	0.75	0.65–0.85	0.067	61.4%	82.2%	77.1%	68.5%

Abbreviations: AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval; other — see Table 1

Table 4. Significant predictors of obstructive coronary artery disease in logistic regression model

Predictor	Simple logistic regression			Multivariable logistic regression		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, years	1.14	1.09–1.21	<0.001	1.13	1.08–1.20	<0.001
Time of dialysis, months	1.01	1.00–1.02	0.21	1.00	0.99–1.01	0.78
Hs-cTnT, ng/ml	1.03	1.01–1.04	<0.001	1.03	1.01–1.05	0.001

Abbreviations: NS, non-significant; OR, odds ratio; other — see Tables 1 and 3

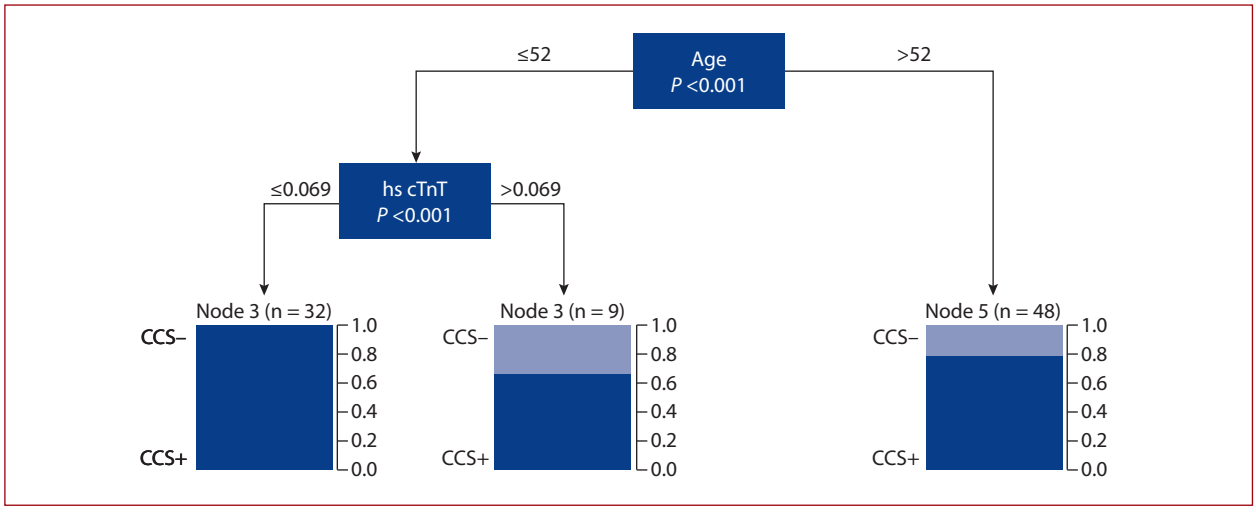

Figure 3. Algorithm of classification of patients, including age and high-sensitivity cardiac troponin T (hs-cTnT) level, used to diagnose obstructive coronary artery disease in hemodialyzed patients

>52 years, obstructive CAD was diagnosed in 80%. Plasma hs-cTnT levels >0.069 ng/ml were useful for the detection of obstructive CAD in this subgroup. Thus, the incidence of obstructive CAD in patients <52 years of age presenting with hs-cTnT levels >0.069 ng/ml was 66.6%, while in subjects younger than 52 years with lower hs-cTnT levels, no obstructive CAD was observed (Figure 3).

Kidney transplantation (KTx)

Among the study group, 28 patients had kidney transplantation, however, 3 transplantations did not succeed due to postoperative failure of the transplanted organ. Importantly, none of the transplanted patients experienced cardiac complications after the surgery.

DISCUSSION

This study revealed a high prevalence of angiographically confirmed obstructive CAD (48% of patients) in hemodialyzed patients listed for KTx. This high rate of obstructive CAD in the study group can be attributed to a high rate of diabetes (29% of patients) and hypertension (95% of patients), which are usually complicated by LVH. Moreover, 70% of the studied patients had hyperlipidemia. Age and baseline hs-cTnT plasma levels were significant predictors of obstructive CAD diagnosis.

Higher levels of hs-cTnT in hemodialyzed patients have been reported to be associated with a higher rate of CVD, comorbidities, and a higher mortality rate during follow-up [9, 16, 17]. In our study group, it was found that age and hs-cTnT concentration significantly predicted a diagnosis of obstructive CAD, while ESRD etiology and duration of hemodialysis did not. In this study group, the median hs-cTnT level was 0.05 ng/ml (0.016–0.32; IQR, 0.055). Some authors associate elevated hs-cTnT levels with impaired kidney function. Dubin et al. [18] analyzed a group of 2464 CKD patients who had an eGFR ≥20 ml/min/1.73 m^2 Modification of Diet in Renal Disease, without declared CVD, and determined that the most important predictor in this group was reduced eGFR. Importantly, the European Society of Cardiology guidelines underline that elevated hs-cTnT levels in CKD patients should not be attributed to impaired renal clearance and that every patient with

elevated hs-cTnT concentration should undergo cardiological screening [9]. However, Dubin et al. [18] also point out that other factors, such as age, male sex, black race, LVH, uncontrolled hypertension, and diabetes mellitus, were associated with increased concentrations of hs-cTnT.

A significantly higher concentration of hs-cTnT was observed in ESRD patients diagnosed with obstructive CAD compared to the group of patients with ESRD without significant diseases or alterations in the coronary arteries (0.0815 vs. 0.039 ng/ml; P <0.001). The multivariable analysis showed that only age and hs-cTnT concentration predicted obstructive CAD diagnosis (OR, 1.13; 95% CI, 1.08–1.20; P <0.001 and OR, 1.03; 95% CI, 1.01–1.05; P = 0.001, respectively). These observations correspond with data reported by Kamińska et al. [13], who found that hs-cTnT in CKD patients is a marker for CCS, especially its multivessel form, and is a predictor of mortality in this group of patients. Moreover, Sommerer et al. [11] conducted a study of 134 hemodialysis patients and showed that the hs-cTnT concentration was elevated in 40% of asymptomatic patients, which had a strong association with the occurrence of long-term cardiovascular events. Mongeon et al. [19] indicated that an initially elevated hs-cTnT concentration was associated with the presence of stable CCS but did not show such a relationship in the case of diabetes mellitus. Since hs-cTnT is significantly elevated in hemodialyzed patients with coexisting cardiovascular diseases compared to dialyzed patients without cardiovascular diseases, it has been shown that hs-cTnT is a good prognostic marker for cardiac complications. In this study group, a cut-off point of 0.067 ng/ml of hs-cTnT was determined for predicting obstructive CAD. It was characterized by high sensitivity and specificity (61.4% and 82.2%, respectively). The authors of this study proposed a staged diagnostic approach integrating age and hs-cTnT level. In the group of patients >52 years of age, obstructive CAD was diagnosed in 80%. However, in the group of patients aged ≤52 years with hs-cTnT concentration >0.069 ng/ml, the occurrence of obstructive CAD was significantly more frequent than in the group with hs-cTnT concentration ≤0.069 ng/ml.

To our knowledge, there are limited studies in the available literature that would show in such a detailed way the relationship between hs-cTnT concentration and obstructive CAD. [20] Based on analysis of data from 174 hemodialyzed patients, Niizuma et al. [21] demonstrated that elevated hs-cTnT concentration is associated with risk of congestive heart failure and peripheral arterial disease, independently of each other. They did not show a relationship with the occurrence of CCS. However, they did not provide a specific cut-off point for hs-cTnT, at which an elevated risk of these diseases can be expected. Hassan et al. [22] showed that higher hs-cTnT concentrations (by quartile) were associated with the occurrence of myocardial infarction in both peritoneal dialysis and hemodialysis patients, while in the hemodialysis group, they were also associated with an increase in mortality. An attempt to determine a specific cut-off point was made by Fernández-Reyes et al. [23] in a group of 58 hemodialysis patients. The authors assessed the concentration of hs-cTnT 3 times: at the beginning of the study and after 6 and 18 months. Based on these values, they classified patients into one of four groups depending on their hs-cTnT concentration: I — hs-cTnT <0.04 ng/ml; II — hs-cTnT 0.04–0.1 ng/ml; III — hs-cTnT >0.1 ng/ml; IV — an increase in hs-cTnT concentration during observation. They showed that patients in groups III and IV had a higher risk of developing CCS.

It should be emphasized that the limitations of this study are that it was a single-center study, and the number of participants was relatively small.

Age and baseline hs-cTnT concentration are useful diagnostic markers of obstructive CAD in chronically hemodialyzed patients who have been qualified for KTx. The data in this study indicate that patients below 52 years of age and plasma hs-cTnT <0.069 ng/ml may not need a diagnostic workup for obstructive CAD or revascularization before KTx, whereas hs-cTnT >0.069 ng/ml in this subgroup and age above 52 years should raise suspicion of obstructive CAD and warrant a diagnostic workup for obstructive CAD and possibly revascularization in selected patients. These data require further validation in multicenter studies and may constitute an introduction to the development of an algorithm for use in the cardiological qualification of patients being prepared for KTx surgery.

Article information

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