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The level of cardiac troponin T and its possible influence factors in maintenance hemodialysis patients

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Abstract

We aimed to study level of cardiac troponin T(cTnT) and its possible influence factorsin maintenance hemodialysis (MHD) patients. Blood was obtained from 123 MHD patients before undergoing hemodialysis. Patients with cardiovascular disease (CVD) had higher cTnT levels than those without CVD (0.062 [0.044 - 0.083] ng/mL vs 0.031[0.020 - 0.046] ng/mL, P = 0.002). Patients with diabetes mellitus (DM) had higher cTnT levels than those non-DM (0.061[0.042 - 0.102] ng/mL vs 0.044[0.025 - 0.064] ng/mL, P = 0.003). We found that in all MHD patients, cTnT correlated positively with age(ρ = 0.309, P = 0.001), glycated albumin (ρ = 0.192, P = 0.040), amino-terminal pro-B-natriuretic peptide (NT-proBNP) (ρ = 0.448, P < 0.001), high-sensitive C reactive protein(hsCRP) (ρ = 0.335, P < 0.001), carotid artery intima-media thickness (ρ = 0.315, P = 0.004) and left ventricular mass index(ρ = 0.369, P < 0.001); negatively with pre-albumin(ρ = -0.280, P = 0.002), high density lipoprotein cholesterol(ρ = -0.201, P = 0.047). Age (β = 0.204, P = 0.043), NT-proBNP (β = 0.299, P = 0.010) and left ventricular mass index (β = 0.345, P = 0.003) were independently associated cTnT. Receiver operating characteristic (ROC) curves analysis showed the correlation between cTnT and CVD was more closely than NT-proBNP and hsCRP, the correlation between cTnT and left ventricular hypertrophy was lower than NT-proBNP, and higher than hsCRP. In conclusions, serum cTnT is markedly elevated in MHD patients; Serum cTnT is associated with advanced age, fluid overload, malnutrition, microinflammation, left ventricular hypertrophy and CVD in MHD patients.

Keywords: hemodialysis; cardiac troponin T; cardiovascular disease; left ventricular hypertrophy.

Practical Application: We explored the level of cardiac troponin T(cTnT) and its possible influence factorsin maintenance hemodialysis (MHD) patients. Serum cTnT is markedly elevated in MHD patients; Serum cTnT is associated with advanced age, fluid overload, malnutrition, microinflammation, left ventricular hypertrophy and CVD in MHD patients.

1 Introduction

Chronic kidney disease (CKD), increasing mortality as well as health care expenditure, affects 5-10% of the world's population, and renal replacement therapies, including maintenance hemodialysis (MHD) and peritoneal dialysis, are regarded as effective methods for patients with end-stage CKD (Plata et al., 1998; Eknoyan et al., 2004; Waziri et al., 2019). However, while prolonging survival, reducing morbidities, and improving patients' quality of life, renal replacement therapies also increase the chance of occurrence of cardiovascular disease (CVD) (cardiovascular disease), which accounts for almost 40-50% of all-cause mortality, a rate 10 to 30 fold higher than in the general population (Schocken et al., 2008; Moor et al., 2017). A cross-sectional study from Cameroon indicated that approximately 55% of population in the study presented a moderate or high risk of cardiovascular disease, and duration on dialysis, number of physical activity sessions per week, fasting serum glucose, serum triglycerides, and serum urea levels may impact our hemodialysis patients' risk of CVD(cardiovascular disease) (Moor et al., 2017). Therefore, early diagnosis and effective prevention and treatment of CVD are of great significance, especially for patients who underwent renal replacement therapies. Currently, troponin is recognized as the most sensitive and specific marker of myocardial injury, which generally increases 5-8 h after myocardial injury, reaches the peak value 12-24 h later, and the increase of cTnT lasts 10-14 days. In asymptomatic patients with end-stage renal disease, 16% - 94% of them showed increased troponin (Gupta & Lemos, 2007; Liesemer et al., 2012;). A considerable number of patients with MHD without acute coronary syndrome had elevated serum cTnT levels to varying degrees, and the exact mechanism and clinical significance of the elevated serum cTnT levels were controversial (Wang & Lai, 2008). In this study, serum cTnT levels of MHD patients were detected to explore their pathophysiological mechanism and clinical significance.

2 Materials and methods

2.1 Research object

In August 2019, there were 123 patients with MHD(maintenance hemodialysis) in the blood purification center of Shanghai Yangsi hospital and Pudong New Area Gongli hospital. This study was approved by the medical ethics committee of Shanghai Yangsi hospital and Pudong New Area Gongli hospital, and all subjects

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signed the informed consent. Inclusion criteria: patients who have maintained hemodialysis for more than 3 months, with over 18-year old and stable condition. Exclusion criteria: patients with severe heart failure, liver disease, severe infection, active tuberculosis, malignant tumor, taking immunosuppressant for active disease; patients with acute cardiovascular events in the past month; patients with peritoneal dialysis or kidney transplantation converted to hemodialysis; patients with recent surgery or blood transfusion history; patients who are unwilling to participate in the study. Dialysis strategy: the patients were all treated with Fresenius 4008B/S dialyzer from Germany and Nikkiso DBB from Japan. The dialyzer was disposable, and the membrane material was polysulfone membrane with an area of 1.4-1.6m2. The dialysis water is reverse osmosis water, standard bicarbonate dialysate, the dialysate flow is 500 mL/min, and the blood flow is 200-300 mL/min. Dialysis prescription is 3 times a week, 4 hours each time. Anticoagulation was performed with heparin or heparin with low molecular weight. The vascular access was autogenous arteriovenous fistula or central venous catheterization. Patients with primary diseases included 58 cases with chronic glomerulonephritis (47.2%), 25 cases with diabetic nephropathy (20.3%), 13 cases with hypertensive renal damage (10.6%), 8 cases with polycystic kidney (6.5%), 4 cases with obstructive nephropathy (3.3%), 4 cases with aristolochic acid nephropathy (3.3%), 3 cases with chronic pyelonephritis (2.4%), 3 cases with lupus nephritis (2.4%), and other 5 cases (4.1%). CVD(cardiovascular disease) refers to those who have been diagnosed with myocardial infarction, angor pectoris, heart failure, cerebral hemorrhage, cerebral infarction and other diseases or who have undergone vascular reconstruction (including cardiovascular and peripheral vascular).

2.2 Clinical data

Clinical data, including age, gender, erythropoietin dosage, smoking history, diabetes history, cardiovascular history and data related to dialysis were collected. Body mass index (BMI) (Body mass index) = body weight (kg) / [height (m)]^2. Single - compartment model spKt / V was used to evaluate dialysis adequacy.

2.3 Laboratory examination

Routine methods for hemoglobin (Hb) (hemoglobin), white blood cell count (WBC) (blood cell count), serum creatinine (Scr) (serum creatinine), blood urea nitrogen (BUN) (blood urea nitrogen), uric acid, calcium (Ca), phosphorus (P), intact PTH (iPTH) (intact PTH), albumin, prealbumin, triglyceride (TG) (triglyceride), total cholesterol (TCH)(total cholesterol), high-density lipoprotein cholesterol (HDL-C) (high-density lipoprotein cholesterol), low-density lipoprotein cholesterol (LDL-C) (low-density lipoprotein cholesterol), blood glucose, glycosylated albumin, glycosylated hemoglobin, β 2-microglobulin, transferrin, ferritin, homocysteine and high-sensitivity c-reactive protein (hsCRP). The amino terminal pro- B-natriuretic peptide (NT-proBNP) was detected by electrochemiluminescence (ECL) (electrochemiluminescence).

2.4 Determination of serum cTnT

2 mL fasting blood samples was collected from the patients before dialysis. Electrochemiluminescence method was used to determine it on Roche Elecsys 2010 analyzer, with the lower limit of 0.01 ng/mL. The myocardial injury was considered to exist in the patients with normal renal function when the value was greater than 0.03 ng/mL.

Measurement of carotid intima-media thickness (IMT) (intima-media thickness)

After hemodialysis, the IMT (intima-media thickness) was measured with Philips SD800 ultrasound, and the probe frequency was 7.5MHz. The patient was supine, and 1cm near proximal furcations of the distal common carotid artery, furcations and the posterior wall for 1cm above the starting part of the internal carotid artery was measured. The real-time two-dimensional images of the transverse and longitudinal axes of the common carotid artery and its branches were continuously observed from the root of the neck section by section, with a upward trend, and the end diastolic images were taken to measure the vertical distance from the inner surface of the lumen to the outer surface of the mesomembrane as the carotid IMT (intima-media thickness).

2.5 Echocardiography

All MHD (maintenance hemodialysis) patients underwent echocardiography within 2 hours after HD. It was performed by 2 experienced ultrasound doctors, using Phillips IE33 color Doppler echocardiography with a probe frequency of 3.5MHz. The subjects were lying on the left lateral position, with a standard long axis view of the left ventricle beside the sternum. The systolic and diastolic wall thickness, the change of left ventricular diameter and left ventricular ejection fraction (LVEF) (left ventricular ejection fraction) were measured by the method recommended by the American Society of echocardiography, and the data were measured for 3 cardiac cycles and averaged. The left ventricular mass (LVM) (left ventricular mass) was calculated by Devereux (Schocken et al., 2008) formula. LVM (left ventricular mass) (g) was 0.8×1.04 [(left ventricular end diastolic diameter + left ventricular posterior wall thickness + interventricular septum thickness) ^{3}-left ventricular end diastolic diameter ^{3}] + 0.6. Left ventricular mass index (LVMI) (Left ventricular mass index) = LVM(left ventricular mass) / height$^{2.7}$. The diagnosis of left ventricular hypertrophy (LVH) (left ventricular hypertrophy) was defined as: LVMI(Left ventricular mass index) in male > 50 g/m $^{2.7}$, female > 47 g/m $^{2.7}$.

2.6 Statistical analysis

SPSS19.0 software was used for data statistical analysis. The continuity variable is first tested for normality. The differences between the two groups were compared by non-parametric test, t-test or χ^2 test. The correlation between cTnT and each index was analyzed by Spearman correlation and linear regression. The correlation between cTnT, CVD(cardiovascular disease) and LVH(left ventricular hypertrophy) was analyzed by receiver operator characteristic curve (ROC)(receiver operator characteristic). All P values were two-sided test, $P < 0.05$ was statistically significant. All confidence intervals were 95%.

3 Results

3.1 General data of patients

There were 123 hemodialysis patients, including 65 males and 58 females, aged 63.0 (53.8 - 71.3) years. Among them, 60 cases (48.8%) were complicated with CVD(cardiovascular disease), including 10 cases with myocardial infarction (16.7%), 7 cases with angor pectoris (11.7%), 10 cases with heart failure (16.7%), 18 cases with cerebral infarction (30.0%), 11 cases with cerebral hemorrhage (18.3%), 4 cases with peripheral vascular disease (6.7%). Echocardiography showed left ventricular hypertrophy in 58 patients (47.2%). See Table 1 for clinical data and laboratory test results of patients.

3.2 Serum cTnT level

The median of Serum cTnT from all patients was 0.046 (0.029 - 0.066) ng/mL, which was higher than the normal reference value. The median of NT-proBNP was 4175.0 (1645.5 - 13105.5) pg/mL in male patients and 3541.0 (1749.0 - 10971.5) pg/mL in female patients. There was no significant difference between the two groups (P = 0.792). (phosphorus) The median NT-proBNP was 3861.5 (1972.5 - 10845.3) pg/mL in 22 patients aged ≥ 75 years. Among 108 patients < 75 years old, the median NT-proBNP was 3715.0 (1630.0 - 12033.0) pg/mL, with no significant difference between the two groups (P = 0.884) (phosphorus). Among them, the serum NT-proBNP level of patients complicated with CVD (cardiovascular disease) was significantly higher than that of patients without CVD (cardiovascular disease) (4649 [2920-14069] pg/mL vs 3006 [1457-7478] pg/mL, P=0.002).

Table 1. Analysis of factors related to serum NT-proBNP level.

	$\overline{x} \pm s$ or median	ρ	*P* value
Age (year)	63.0 (53.8 - 71.3)	0.309	0.001
BMI (kg/m^2)	21.9 ± 3.0	0.014	0.894
Dialysis age (month)	44.0 (19.8 - 88.3)	0.006	0.949
spKt/V	1.31 (1.15 - 1.57)	-0.145	0.135
EPO (U/week)	10000(5000 - 10000)	0.129	0.166
Diastolic pressure (mmHg)	136.1 ± 22.9	0.139	0.153
Systolic pressure (mmHg)	79.1 ± 13.2	0.032	0.745
Serum albumin (g/L)	39.7 ± 3.3	-0.168	0.066
prealbumin(g/L)	0.36 ± 0.08	-0.280	0.002
Scr (μmol/L)	967.3 ± 243.3	-0.064	0.491
BUN (mmol/L)	25.1 ± 6.3	0.156	0.192
Uric acid (μmol/L)	437.5 ± 90.8	0.052	0.578
Ca (mmol/L)	2.23 (2.12 - 2.39)	-0.046	0.623
P (mmol/L)	1.97 (1.59 - 2.50)	0.022	0.814
Ca × P (mmol^2/L^2)	4.35 (3.33 - 5.98)	0.016	0.863
Ipth (pg/mL)	310.4 (177.2 - 559.6)	0.003	0.974
Tch (mmol/L)	4.44 (3.78 - 5.05)	-0.082	0.419
TG (mmol/L)	1.41 (1.05 - 1.99)	0.050	0.623
HDL-C (mmol/L)	1.08 (0.93 - 1.32)	-0.201	0.047
LDL-C (mmol/L)	2.54 (1.90 - 3.01)	-0.032	0.754
β_2-microglobulin(mg/L)	30.7 (18.6 - 36.4)	0.150	0.104
BG (mmol/L)	6.2 (4.8 - 8.1)	0.168	0.068
Glycosylated hemoglobin(%)	5.3 (4.9 - 5.9)	0.152	0.105
Glycosylated albumin(%)	14.6 (13.2 - 16.6)	0.192	0.040
Hb (g/L)	112.5 (101.5 - 120.0)	-0.044	0.632
WBC (10^9/L)	5.86 (4.99 - 6.85)	-0.008	0.930
Transferrin(g/L)	1.87 (1.70 - 2.09)	0.015	0.876
Ferritin(ng/ml)	164.9 (80.3 - 321.2)	-0.026	0.783
Homocysteine(umol/L)	29.9 (26.2 - 38.0)	0.073	0.437
NT-proBNP (pg/ml)	3956 (1931 - 11757)	0.448	< 0.001
IMT (cm)	0.8 (0.7 - 0.8)	0.315	0.004
LVMI (g/m$^{2.7}$)	48.7 (39.2 - 59.9)	0.369	< 0.001
LVEF (%)	65(62-69)	-0.142	0.136
hsCRP (mg/L)	3.5(1.3-13.1)	0.335	<0.001

EPO, erythropoietin; BG, blood glucose; NT-proBNP, amino-terminal pro brain natriuretic peptide

3.3 Analysis of factors related to serum cTnT level

Spearman correlation analysis showed that serum cTnT was positively correlated with age, glycosylated albumin, NT-proBNP, hsCRP, IM and LVMI (Left ventricular mass index), negatively correlated with prealbumin and LDL-C (low-density lipoprotein cholesterol), and not correlated with dialysis age, spKt/V, weekly dose of erythropoietin, blood pressure, serum albumin, BUN (blood urea nitrogen), Scr (serum creatinine), Ca, P (phosphorus), iPTH (intact PTH), β 2-microglobulin, Hb (hemoglobin) and homocysteine. See Table 1.

3.4 Linear regression analysis of factors related to serum cTnT level

Multiple linear regression analysis showed that age, NT-proBNP and LVMI(Left ventricular mass index) were independently correlated with cTnT level (variables related to single variable analysis and cTnT level, cardiovascular history, diabetes history, smoking history and others were introduced into the regression equation as independent variables, and natural logarithm conversion was performed for skewed distribution data). See Table 2.

3.5 cTnT, NT-proBNP and hsCRP correlated with CVD and LVH

ROC(receiver operator characteristic) curve analysis for CVD(cardiovascular disease) showed that the area under the curve of cTnT was 0.813(95% CI 0.737 - 0.890, P < 0.001); the area under the curve of hsCRP was 0.722 (95% CI 0.631-0.813,P < 0.001); and the area under the curve of T-proBNP was 0.656 (95% CI 0.560 - 0.752, P = 0.003). See Figure 1A. ROC (receiver operator characteristic) curve analysis for LVH

Table 2. Linear regression analysis of factors related to serum cTnT level.

	Unnormalized regression coefficients	Normalized regression coefficients	*P* value
Age	0.005	0.204	0.043
NT-proBNP	0.179	0.209	0.010
LVMI	0.309	0.345	0.003

NT-proBNP = amino-terminal pro-B-natriuretic peptide; LVMI = left ventricular mass index.

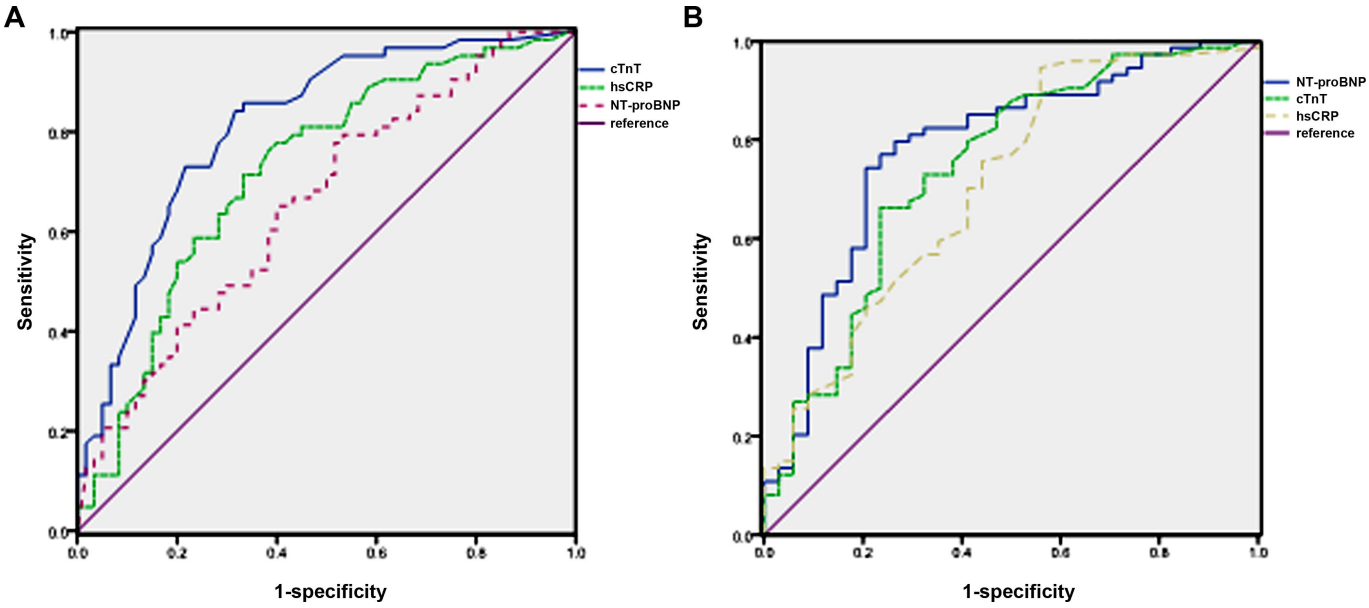

Figure 1. cTnT, NT-proBNP and hsCRP correlated with CVD and LVH. (A) cTnT, NT-proBNP and hsCRP correlated with CVD; (B) cTnT, NT-proBNP and hsCRP correlated with LVH.

(left ventricular hypertrophy) showed that the area under the curve of cTnT was 0.741 (95% CI 0.636 - 0.847, P < 0.001); the area under the curve of NT-proBNP was 0.783 (95% CI 0.685 - 0.880, P < 0.001); and the area under the curve of hsCRP was 0.709 (95% CI 0.600 - 0.817, P = 0.001). See Figure 1B.

4 Discussion

In MHD patients, the factors related to the increase of cTnT are reported abroad, including cardiac hypertrophy, cardiac insufficiency, volume load, myocardial stunning, diabetes mellitus, history of cardiovascular disease, age, chronic inflammation, malnutrition, oxidative stress, increase of dialysis time and others, and the increase of its level is significantly correlated with the increase of mortality (Sommerer et al., 2007; Jacobs et al., 2009; Kalaji & Albitar, 2012; Breidthardt et al., 2012). Therefore, the research interest of troponin in MHD patients has shifted from the diagnosis of suspected coronary syndrome to the application of disease risk stratification (Assa et al., 2013). Our results showed that 73.2% of MHD patients had increased cTnT, which confirmed that there was a considerable increase in serum cTnT level of MHD patients without acute coronary syndrome at different levels. Among them, cTnT of male, diabetic and CVD patients increased significantly, which was consistent with the literature (Park et al., 2009; Breidthardt et al., 2012; Pianta et al., 2012). ROC curve analysis showed that the correlation between cTnT and CVD was higher than that between NT-proBNP and hsCRP. It also suggested that the increase of cTnT was closely related to the occurrence of CVD (Liu & Li, 2021; Rehman et al., 2021; Yerlikaya et al., 2021). Hill et al. (2009) showed that the serum cTnT concentration in MHD patients without acute coronary syndrome was stable within 15 weeks, and the risk of death in MHD patients with increased cTnT was increased. Therefore, the serum cTnT should be detected regularly to establish the individual baseline value. The following reasons were considered for cTnT value variation: short-term variation considers the change of volume status, blood pressure fluctuation, and systemic status change, and long-term variation considers the loss of residual renal function or the change of cardiac status, such as the increase of LVMI. Individual variation should not be considered when cTnT value of patients is higher than 0.02 ng/mL or absolute value is higher than 0.06 ng/mL. Asymptomatic MHD patients should be evaluated every half a year or one year, ECG and cTnT should be examined for risk stratification, echocardiography and other non-invasive cardiac tests should be performed for high-risk patients, so that more patients can benefit from it (Kalaji & Albitar, 2012).

This study showed that serum cTnT was positively correlated with age, glycosylated albumin, NT-proBNP, hsCRP, IMT and LVMI, and negatively correlated with serum prealbumin and HDL-C. Multiple Linear Regression analysis showed that age, NT-proBNP and LVMI were independently correlated with Serum cTnT level, which was consistent with previous studies (Sommerer et al., 2007; Hallén et al., 2011; Kalaji & Albitar, 2012). cTnT related to age is believed to be associated with increased patients with diabetes mellitus and potential CVD with age (Hill et al., 2009). The secretion of NT-proBNP increases when the ventricular wall tension increases, which can be a marker of volume status in vivo, and its independent correlation with cTnT suggests that cTnT is affected by the long-term volume status. Volume overload can cause the increase of cTnT and play an important role in the occurrence and development of vascular and myocardial injury (Park et al., 2009; Antlanger et al., 2013). Long term volume overload can cause LVH, increase diffusion distance of oxygen and aggravate subclinical myocardial ischemia. Moreover, the increase of mechanical traction can also change the permeability of myocardial cell membrane, resulting in the leakage of cTnT. In this study, ROC curve analysis of showed that NT-proBNP and cTnT are closely related to LVH, which

supports the above viewpoint. In our study, cTnT was increased in patients with diabetes mellitus, and cTnT was positively correlated with glycosylated albumin. It may be related to the increased incidence of CVD caused by poor blood glucose control in patients with diabetes mellitus, and may also be related to the increased level of advanced glycation end-products in MHD patients with diabetes mellitus. Studies have shown that the risk of volume overload caused by hypotension during frequent dialysis is increased in patients with diabetes mellitus, resulting in the increase of cTnT (Park et al., 2009). There was a positive correlation between hsCRP and cTnT in this study, which indicated that myocardial injury could be caused by micro-inflammatory state. IMT is recognized as a subclinical atherosclerotic index, and cTnT is positively correlated with IMT, which support that cTnT elevation in MHD patients may be a marker of subclinical myocardial injury caused by various reasons. Recent studies have shown that standard hemodialysis with 3 times a week can induce myocardial perfusion reduction and regional ventricular wall motion abnormalities. Intermittent dialysis has a significant effect on hemodynamics of MHD patients, and 20% to 30% of patients will have hypotension during dialysis. High incidence of hemodynamic changes and LVH, increased arterial stiffness, left ventricular diastolic dysfunction and other causes increased vulnerability to rapid volume change. In the absence of coronary stenosis, the decrease of coronary flow reserve can significantly increase the risk of myocardial ischemia in MHD patients. It has been reported that compared with the stable dialysis process, if hypotension occurs during the previous dialysis process, the cTnT level of patients will be significantly increased before dialysis (Hung et al., 2004; Breidthardt & McIntyre, 2011; Assa et al., 2013). In this study, serum prealbumin and HDL-C were negatively correlated with cTnT, indicating that malnutrition and decrease of HDL-C were risk factors for CVD in MHD patients. Our results support that both traditional (such as male, advanced age, diabetes and HDL-C reduction and non-traditional risk factors (such as volume overload, micro-inflammatory state, malnutrition, etc.) play an important role in the occurrence and development of CVD in MHD patients.

5 Conclusion

In conclusion, the serum cTnT level in maintenance hemodialysis patients was significantly increased, which was associated with advanced age, volume load, malnutrition, micro-inflammatory state, left ventricular hypertrophy and concomitant cardiovascular disease. Patients with maintenance hemodialysis should be regularly tested for serum cTnT levels, and patients with highly variable cTnT levels should undergo careful cardiac status assessment even if they have no clinical symptoms, so as to identify high-risk populations in early stage, actively intervene and improve the prognosis of patients.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that they have no competing interest.

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