Normal Range of Serum Highly-Sensitive Troponin-T in Patients with Chronic Kidney Disease Stage 3-5

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Background: *Serum troponin-T concentrations are commonly increased in chronic kidney disease (CKD) without acute coronary syndrome. Highly-sensitive troponin-T, the new tool that helpful for diagnosis of acute coronary syndrome, provides few data about normal value in patients with chronic kidney disease.*
Material and Method: *The authors studied 89 patients with CKD stage 3-5: 40 had CKD stage 3, 26 had CKD stage 4 and 23 had CKD stage 5. Serum samples were collected for the analysis of highly-sensitive troponin-T levels. The values of highly-sensitive troponin-T of the total group and each CKD stage were presented.*
Results: *The level of highly-sensitive troponin-T in patients with CKD stage 3-5 was 0.044 ± 0.076 ng/ml. For CKD stages 3, 4 and 5 levels were 0.015 ± 0.016, 0.043 ± 0.056, 0.098 ± 0.121 ng/ml, respectively. 95th percentile of the total group was 0.139 ng/ml. 95th percentile for stage 3, 4 and 5 were 0.052, 0.136, 0.297 ng/ml, respectively.*
Conclusion: *95th percentile for highly-sensitive troponin-T of patients with CKD stage 3-5 was 0.139 ng/ml. This number may be considered as the cut-off value for diagnosis of acute myocardial infarction.*

Keywords: *Troponin-T, Chronic kidney disease, Acute coronary syndrome, High sensitive*

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Acute coronary syndrome (ACS) is the common cause of death in patients with chronic kidney disease (CKD). According to Unstable Angina (UA) and Non-ST-Elevation Myocardial Infarction (NSTEMI) guideline[1], tools used for diagnosis include electrocardiography and cardiac biomarkers integrated with clinical presentation. The most common used cardiac biomarker is cardiac troponin, because of its specificity and sensitivity. However, there are many conditions that cause elevated troponin level, *e.g.* CKD, sepsis, pulmonary embolism, pulmonary hypertension, respiratory failure, burn, heart failure, myocarditis, pericarditis, tachyarrthythmias, chemotherapy and neurological diseases. High value of troponin in the patient with CKD is the common problematic in patients with suspected ACS[2-4].

When renal function (estimated by creatinine clearance or glomerular filtration rate) decreased to less than 60 ml/min, troponin level will increase; dialysis also causes increasing troponin level[4]. There have been many studies which indicated that increased troponin in CKD patients cause poor outcome[2,4].

There has now been a novel tool developed for increasing sensitivity of troponin for diagnosis of myocardial infarction that is highly-sensitive troponin-T. This tool can be a positive aid in the patients with myocardial infarction with negative traditional troponin test[5].

There has been concern whether highly-sensitive troponin-T could be rising in CKD patients without myocardial infarction the same as traditional generation troponin. If so, it should be problematic for using this new cut-off value to determine the CKD patients that are diagnosed with myocardial infarction. The present study is to determine the normal range of highly-sensitive troponin-T in CKD patients stage 3-5 by overall group and also divided by each stage of the disease.

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Material and Method

Study population

Between February 2009 and February 2010, 89 patients with CKD without history of myocardial infarction within 14 days who came to the out-patient

department for follow-up were recruited to the present study. Exclusion criteria included patients with history of myocardial infarction within 14 days, history of angina pectoris or heart failure that may be angina equivalences, burn, acute neurological disease such as cerebral infarction or intracranial hemorrhage, severe sepsis, acute pulmonary embolism, pulmonary hypertension, myocarditis, pericarditis, tachyarrhythmias, receiving chemotherapy or chest trauma within 14 days. The study had ethics approval from the Ethics Committee of Siriraj Hospital. All patients gave written informed consent.

A detailed clinical history was recorded, including age, sex, body weight, comorbidity (diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, and cerebrovascular disease).

Estimated glomerular filtration rate (GFR) was calculated by Crockcroft-Gault formula[6]. Patients were stratified into stage 3 CKD (GFR = 30-59 ml/min per 1.73 m^2 body surface area), stage 4 (GFR = 15-29 ml/min per 1.73 m^2 body surface area) and stage 5 (GFR < 15 ml/min per 1.73 m^2 body surface area) according to guidelines. Additional analysis was performed on the estimation of GFR according to the Modification of Diet in Renal Disease (MDRD) formula[7].

Analytical methods

Blood samples were collected in non-fasting stage. Analysis included creatinine and highly-sensitive troponin-T within 24 hours. Highly-sensitive troponin-T was measured with electrochemiluminescent immunoassay (ECLIA) on Elecsys and cobase immunoassay analyzers (Roche Diagnostics Ltd.). The minimal value of detection = 0.003 ng/ml.

Data analysis

Data were analyzed with SPSS 16.0 and Medcal computer programs. Categorical data was presented by percent. Numerical data were described by mean and standard deviation. Value of highly-sensitive troponin-T was presented by mean $\pm$ SD, normal range was presented by 5^{th}-95^{th} percentile, by overall CKD patients and divided by stage of CKD. Main results were based on calculation of GFR by Crockcroft-Gault formula. Results based on calculation of GFR by MDRD formula were also reported. A p-value < 0.05 was considered significant.

Comparisons between the CKD groups were based on either 1-way ANOVA (Normality) or Kruskal-Wallis (Non-normality) for continuous variables, as appropriate, with further testing between CKD groups being undertaken with either the Tamhane comparison or Dunn multiple-comparisons test when indicated. For categorical variables, the Chi-square test was used. Comparison between creatinine groups (divided to creatinine $\leq$ 1.5 mg/dl and creatinine > 1.5 mg/dl) were base on Independent t-test or Mann-Whitney U test.

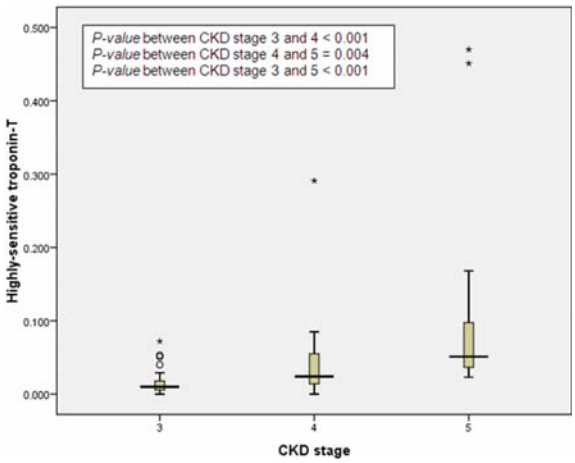

Fig. 1 Range of highly-sensitive troponin-T of each stage of CKD

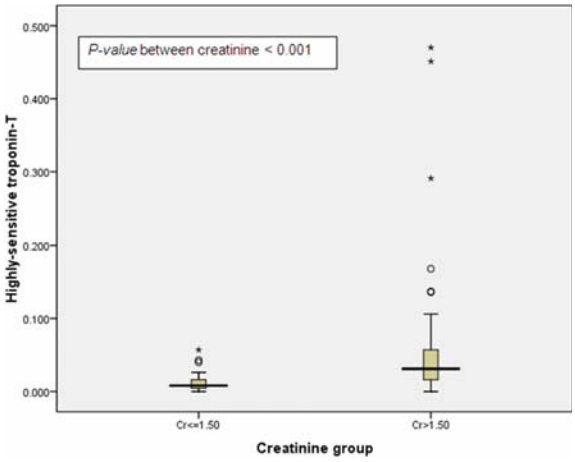

Fig. 2 Range of highly-sensitive troponin-T divided by creatinine group

Results

Patient characteristics for whole study population and by CKD stage are given in Table 1. There was significant difference of baseline age, sex, body weight and serum creatinine. Average highly-sensitive troponin-T was increased with advance stage of CKD. There was significant in difference of highly-sensitive troponin-T between CKD stages. Comparison

Table 1. Baseline characteristic for the whole group and of each group of CKD stage 3-5

	CKD stage 3-5	CKD stage 3	CKD stage 4	CKD stage 5	p-value
Numbers	89	40	26	23	
Age (years)	67.15 ± 12.02	65.25 ± 8.75	73.27 ± 10.91	63.52 ± 15.57	0.006
Male (%)	58 (65.2)	37 (92.5)	12 (46.2)	9 (39.1)	< 0.001
Body weight (kg)	61.65 ± 11.79	65.60 ± 9.22	57.38 ± 10.32	59.61 ± 15.16	0.012
Diabetes mellitus (%)	44 (49.4)	17 (42.5)	15 (57.7)	12 (52.2)	0.461
Hypertension (%)	57 (64.0)	24 (60.0)	17 (65.4)	16 (69.6)	0.738
Dyslipidemia (%)	29 (32.6)	14 (35.0)	10 (38.5)	5 (21.7)	0.418
CAD (%)	22 (24.7)	12 (30.0)	8 (30.8)	2 (8.7)	0.117
CVD (%)	6 (6.7)	3 (7.5)	1 (3.8)	2 (8.7)	0.770
Creatinine (mg/dl)	3.46 ± 4.29	1.56 ± 0.26	2.26 ± 0.72	8.11 ± 6.49	< 0.001
Median (IQR)	1.9 (1.9)	1.5 (0.4)	2.2 (0.77)	6.3 (5.8)	
hs-Tn-T (ng/ml)	0.044 ± 0.076	0.015 ± 0.016	0.043 ± 0.056	0.098 ± 0.121	< 0.001*
Median (IQR)	0.021 (0.041)	0.010 (0.014)	0.024 (0.042)	0.051 (0.074)	

Data are presented as mean ± SD or median (IQR) or number (%)
*Comparison of hs-Tn-T levels of each stage of CKD was performed by Kruskal-Wallis test

Table 2. Hs-Tn-T levels of the whole group and of each group of CKD stage 3-5 based on GFR calculated by MDRD formula

	CKD stage 3-5	CKD stage 3	CKD stage 4	CKD stage 5	p-value
Numbers	89	52	15	22	
hs-Tn-T (ng/ml)	0.044 ± 0.076	0.018 ± 0.019	0.082 ± 0.123	0.081 ± 0.096	< 0.001*
Median (IQR)	0.021 (0.041)	0.012 (0.014)	0.044 (0.057)	0.050 (0.062)	

Data are presented as mean ± SD or median (IQR) or number (%)
*Comparison of hs-Tn-T levels of each stage of CKD was performed by Kruskal-Wallis test

Table 3. Normal range of highly-sensitive troponin-T for the whole group and each stage of CKD

CKD stage	Highly-sensitive troponin-T (ng/ml)	
	Median	5^{th}-95^{th} percentile
3	0.010	0.000-0.052
4	0.024	0.000-0.136
5	0.051	0.000-0.297
3-5	0.021	0.000-0.139

of highly-sensitive troponin-T among different CKD stages classified by MDRD formula is shown in Table 2. Table 3 presented normal range of highly-sensitive troponin-T by the whole group and divided by stage of CKD. Fig. 1 presented the range of value of highly-sensitive troponin-T divided by each stage of CKD, there was significant difference of highly-sensitive troponin-T level between CKD stage 3 and CKD stage 5.

Baseline characteristics and highly-sensitive troponin-T divided by creatinine groups (creatinine ≤ 1.5 mg/dl and creatinine > 1.5 mg/dl) were presented in Table 4. Range of highly-sensitive troponin-T value divided by creatinine groups was presented in Fig. 2. There was significant difference of highly-sensitive troponin-T between creatinine groups. Increased highly-sensitive troponin-T (≥ 0.016 ng/ml) was demonstrated in 59 patients (60.67%).

If divided patient group by creatinine level, first group had creatinine ≤ 1.5 mg/dl and the second group had creatinine > 1.5 mg/dl, there was 46/61 (75.41%) had highly-sensitive troponin-T level more than 99^{th} percentile.

Discussion

The results of the present study showed that 95^{th} percentile of patients with CKD stage 3-5 without evidence of ACS was 0.139 ng/ml. 95^{th} percentile for

Table 4. Baseline characteristics divided by creatinine group

	All	Cr ≤ 1.5 mg/dl	Cr > 1.5 mg/dl	p-value
Numbers	89	28	61	
Age (years)	67.15 ± 12.02	66.64 ± 12.35	67.38 ± 11.97	0.741
Male (%)	58 (65.2)	21 (75.0)	37 (60.7)	0.187
Body weight (kg)	61.65 ± 11.79	62.04 ± 9.64	61.93 ± 12.72	0.131
Diabetes mellitus (%)	44 (49.4)	9 (32.1)	35 (57.4)	0.027
Hypertension (%)	57 (64.0)	15 (53.6)	42 (68.9)	0.163
Dyslipidemia (%)	29 (32.6)	7 (25.0)	22 (36.1)	0.301
CAD (%)	22 (24.7)	5 (17.9)	17 (27.9)	0.309
CVD (%)	6 (6.7)	1 (3.6)	5 (8.2)	0.394
hs-Tn-T (ng/ml)	0.044 ± 0.076	0.013 ± 0.014	0.058 ± 0.088	< 0.001
Median (IQR)	0.021 (0.41)	0.008 (0.012)	0.032 (0.042)	

Data are presented as mean ± SD or number (%)

stage 3, 4 and 5 were 0.052, 0.136, 0.297 ng/ml respectively.

Troponin-T is widely used for the diagnosis of acute myocardial infarction[8]. Cut off level of troponin-T is based on 99th percentile of upper reference limit[9]. There are many causes of falsely elevated troponin-T[10]. Common causes of false positive test[11] were heart failure[12] and renal insufficiency[2,13]. High level of troponin-T in conditions without ACS indicates a poor prognostic marker[9,14]. Pattern of troponin-T elevation may help to diagnose ACS in patients with renal insufficiency[15]. Abbas et al noted troponin-T in CKD patients were increased over 99th percentile for 43%[2]. Goicoechea et al[3] noted a lower proportion (16%) of CKD patients had troponin-T ≥ 0.01 ng/ml. High sensitive troponin has been developed with the aim for the early diagnosis of acute myocardial infarction[5]. Validation of high sensitive troponin-T has been reported[16] including serum from marathon runner[17]. When compared the present study with this value, there was 61% of patients with CKD stage 3-5 had highly-sensitive troponin-T above 99th percentile. This implied that highly-sensitive troponin-T may be less specificity than traditional troponin-T for detection of myocardial infarction in patients with CKD stage 3-5. The level highly-sensitive troponin-T was increased when the stage of CKD increased. This finding was consistent with previous reports on troponin-T[2].

Mechanism of increased troponin-T in CKD patients with CKD is unknown. It could be multifactorial such as delayed excretion of troponin-T, skeletal myopathy or increased myocardial wall stress[9]. It has been shown that increased traditional troponin-T in CKD patients without acute coronary syndrome was related to adverse events[18]. This finding may be caused by silent myocardial ischemia or cardiac remodeling process in the development of left ventricular hypertrophy[2,19].

The limitation of the present study was a relatively small sample size to determine upper limit of normal range at 99th percentile, so we used 95th instead of 99th percentile to determine upper normal limit.

In summary, the present study presented data of increased highly-sensitive troponin-T in patients with CKD stage 3-5 and it increased more in advanced stages of the disease. The 95th percentile of highly-sensitive troponin-T of patients with CKD stage 3-5 was 0.139 ng/ml. This number may be considered as the cut-off value for diagnosis of acute myocardial infarction.

Potential conflicts of interest

None.

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การหาค่าปกติของระดับโทรโปนินทีชนิดความไวสูงในผู้ป่วยโรคไตวายเรื้อรังระยะ 3-5

ธัญนพ โชติวนาวรรณ, รุ่งโรจน์ กฤตยพงษ์

***ภูมิหลัง**: โทรโปนินทีในเลือดมีระดับสูงกว่าปกติได้ในผู้ป่วยโรคไตวายเรื้อรังที่ไม่มีกล้ามเนื้อหัวใจตาย ปัจจุบันมีการพัฒนาโทรโปนินทีชนิดความไวสูง ซึ่งทำให้สามารถวินิจฉัยภาวะกล้ามเนื้อหัวใจตายได้เร็วขึ้น แต่ข้อมูลเกี่ยวกับค่าปกติในผู้ป่วยโรคไตวายเรื้อรังยังมีไม่มาก*

***วัสดุและวิธีการ**: ผู้ป่วยโรคไตวายเรื้อรัง 89 ราย เป็นระยะที่ 3 จำนวน 40 ราย ระยะที่ 4 จำนวน 26 ราย และระยะที่ 5 จำนวน 23 ราย ได้รับการส่งเลือดตรวจหาค่าระดับโทรโปนินทีชนิดความไวสูง แล้วนำข้อมูลที่ได้มาหาค่าเฉลี่ยและค่าปกติโดยรวมของผู้ป่วยโรคไตวายเรื้อรัง และแยกเป็นแต่ละระยะของโรคไตวายเรื้อรัง*

***ผลการศึกษา**: ระดับโทรโปนินทีชนิดความไวสูงเฉลี่ยในผู้ป่วยโรคไตวายเรื้อรังทั้ง 3 ระยะเท่ากับ 0.044 $\pm$ 0.076 นาโนกรัมต่อมิลลิลิตร สำหรับค่าเฉลี่ยในแต่ละระยะของโรคไตวายเรื้อรังเท่ากับ 0.015 $\pm$ 0.016, 0.043 $\pm$ 0.056, 0.098 $\pm$ 0.121 นาโนกรัมต่อมิลลิลิตรในระยะที่ 3, 4 และ 5 ตามลำดับ สำหรับค่าขอบบนของค่าปกติ (ค่าเปอร์เซ็นไทล์ที่ 95) เท่ากับ 0.139 นาโนกรัมต่อมิลลิลิตรในกลุ่มผู้ป่วยโรคไตทั้ง 3 ระยะ และเท่ากับ 0.052, 0.136, 0.297 นาโนกรัมต่อมิลลิลิตรในระยะที่ 3, 4 และ 5 ตามลำดับ*

***สรุป**: ค่าขอบบนของค่าปกติของโทรโปนินทีชนิดความไวสูงในผู้ป่วยโรคไตวายเรื้อรังระยะ 3-5 เท่ากับ 0.139 นาโนกรัมต่อมิลลิลิตร ซึ่งค่านี้อาจนำมาใช้เป็นค่าอ้างอิงสำหรับใช้ในการวินิจฉัยภาวะกล้ามเนื้อหัวใจตายเฉียบพลันในผู้ป่วยโรคไตวายเรื้อรังระยะ 3-5*