

Evaluation of Serum High Sensitive Cardiac Troponin-T as a Significant Biomarker of Left Ventricular Diastolic Dysfunction in Subjects with Non-Diabetic Chronic Kidney Disease

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Abstract: Objectives: This study was done to evaluate possible correlation between serum high sensitive cardiac troponin-T and left ventricular diastolic dysfunction in subjects with non-diabetic chronic kidney disease (non-dialysis patients). Background: Chronic kidney disease (CKD) is one of several chronic diseases affecting mostly older people and leading to a substantially increased risk of cardiovascular disease. since individuals with CKD are more likely to die of cardiovascular disease than to develop kidney failure, indeed, the term cardiorenal syndrome has been increasingly used. Even in the absence of clinical heart failure, left ventricular diastolic dysfunction (LVDD) is associated with increased rates of future hospitalizations, development of heart failure, and all-cause mortality. Worsening stages of LVDD with advanced CKD stages are associated with an increase risk of development of clinical heart failure. In patients with renal failure, conventionally assessed cTnT levels may be elevated simply owing to delayed cTnT clearance. A highly sensitive (hs) assay for cardiac troponin T (cTnT) has recently been developed, which determines concentrations that are lower by a factor of 10 than those measurable with conventional assays and higher levels correlate strongly with increased cardiovascular mortality. Methods: Samples were obtained from 80 persons who were classified into 2 groups 60 patients as case group (CKD stages II, III and IV) and 20 healthy individuals will serve as the control group. The level of serum high sensitive cardiac troponin T (hs-cTnT), complete blood count, complete urine analysis, kidney function tests (urea & Creatinine), estimated creatinine clearance (eCCr) using Cockcroft-Gault, lipid profile (including total cholesterol and triglycerides), erythrocyte sedimentation rate & C-reactive protein, fasting and 2h-post prandial blood were obtained. Echocardiography was done to all subject Results: Subjects were categorized into two groups, 60 CKD patients on conservative therapy serve as case group and 20 age-sex matched healthy individuals will serve as the control group. Case group further divided into stages (II, III and IV) CKD depending on their estimated GFR using Cockcroft-Gault formula, and divided into grades (I, II, III, IV) LVDD depending on echocardiography finding. There was a significant statistical positive correlation between the hs-cTnT and LVDD grade in patients group also there is a significant statistical positive correlation between the hs-cTnT and CKD grade in patients group. Conclusion: from this study we concluded that there is a possible significant statistical positive correlation between high sensitive cardiac troponin-T and left ventricular diastolic dysfunction grade in CKD patients group (Non –Heamodialysis patients).

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Key words: hs-cTnT; LVDD; CKD.

1. Introduction:

Chronic kidney disease is one of several chronic diseases affecting mostly older people and leading to a substantially increased risk of cardiovascular disease. The increased prevalence of kidney failure and early stages of chronic kidney disease, and the high costs and poor outcomes of treatment constitute a worldwide public health threat. Costs for dialysis and transplantation are increasing alongside costs for other chronic diseases.¹

The Kidney Disease Improving Global Outcomes of the National Kidney Foundation (KIDGO/NKF) define CKD as abnormalities of

kidney structure or function, present for more than 3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).²

Diastolic dysfunction is defined as functional abnormalities that exist during LV relaxation and filling. When such abnormalities cause or contribute to the clinical syndrome of heart failure with a normal LV ejection fraction, it is appropriate to describe the condition as diastolic heart failure.³

Left ventricular (LV) diastolic dysfunction, as occurs in patients with hypertension, diabetes mellitus, and/or aging, carries a substantial risk of the

subsequent development of heart failure and reduced survival, even when it is asymptomatic or "preclinical."⁴

In general, when doctors use the terms diastolic dysfunction and diastolic heart failure, they are referring to isolated diastolic abnormalities - there is diastolic dysfunction without any evidence of systolic dysfunction. "Systolic dysfunction" is just another name for a weakening of the heart muscle, which occurs in the more typical forms of heart failure. Still, it is now thought that almost half the patients who come to emergency rooms with episodes of acute heart failure actually have diastolic heart failure.⁵

This diagnosis carries a mortality rate that is similar to that seen in systolic failure, approaching 15% per year in patients older than 65 years.³

The prevalence of asymptomatic LV systolic or diastolic dysfunction ranges from 6% to 21% and increases with age.⁶

Diagnostic echocardiographic and Doppler techniques have improved, and criteria for the diagnosis of diastolic heart failure have been developed, but the evolution of therapeutic strategies has not kept pace with this growing public health problem.⁷

In the Left Ventricular Dysfunction Prevention study, participants with untreated asymptomatic LV dysfunction had a 10% risk for developing HF symptoms and an 8% risk of death or HF hospitalization annually.⁶

Cardiac troponin (cTn) has established itself firmly as the "gold standard" in the diagnosis of acute coronary syndrome (ACS) so cTn should be measured in all patients presenting with symptoms suggestive of ACS, in conjunction with physical examination and ECG. Because of the specificity of cTn for myocardial damage, a single cTn above the decision limit, along with clinical evidence, is indicative of myocardial injury. However, serial testing can be useful, depending on clinical presentation and onset of symptoms.⁸

A highly sensitive (hs) assay for cardiac troponin T (cTnT) has recently been developed, which determines concentrations that are lower by a factor of 10 than those measurable with conventional assays. In patients with chronic heart failure and chronic coronary artery disease (CAD) circulating cTnT is detectable in almost all individuals with the highly sensitive assay, and higher levels correlate strongly with increased cardiovascular mortality.⁹

In patients with renal failure, conventionally assessed cTnT levels may be elevated simply owing to delayed cTnT clearance.¹⁰

Numerous studies have shown the strong prognostic significance of elevated troponin levels in patients with CKD.^{11,12}

In patients with heart failure with a normal EF, concentric hypertrophy or remodeling can be observed. In addition, several studies have demonstrated an independent association between troponin levels and the presence of LVH in non-dialysis CKD patients.¹³

Patients and methods

The study was conducted at nephrology unit, internal medicine department, Menoufia University Hospital and internal medicine department, Karmouz insurance hospital in the period from January 2014 to July 2014.

The study was conducted on 80 person classified into 2 groups:

1-Group I (cases)

Included sixty CKD patients stages (II, III and IV) patients (25 males and 35 females) with mean age of (56.03 ± 5.79).

2-Group II (control)

Included twenty patients (10 males and 10 females) with mean age of (55.65 ± 7.28).

• Inclusion criteria:

Non-diabetic chronic kidney disease patients (stages II-III and stage V) before starting renal replacement therapy.

The following patients were excluded from this study:

1. Patients have cardiogenic shock and congestive heart failure.
2. Patients have Malignancy.
3. Patients with diabetic nephropathy.
4. Patients on haemodialysis. (renal replacement therapy).

After approval of the local ethical committee and informed consent from each one, patients who were selected scheduled to undergo a sheet was taken to all patients subjected and were conducted to the following:

1-Full history taking:

Age, sex, height, duration of disease, history of any previous renal disease, history of any previous cardiac disease.

2-Clinical examination:

Stressing on blood pressure, neurological and cardiac examination.

3- Radiological:

Echocardiography was performed using a cardiac ultrasound unit with a 2- to 3.5-MHz transducer.

Samples

Venous blood samples were taken after fasting for 10-12 hours and 2h post prandial, 2 ml of venous blood were transferred to EDTA tubes for complete blood picture measured by Sysmex KX-21 automated hematology analyzer (Sysmex Corporation, Japan)

The rest of venous blood was transferred slowly

into a plain tube, allowed to clot, and then centrifuged for ten minutes. The clear supernatant was separated in several aliquots, kept frozen at -20°C, till analysis of fasting and post prandial blood sugar, serum cholesterol and triglycerides, blood urea and serum creatinine using the open system auto analyzer synchron CX5 (Beckman, USA), quantitative measurement of high sensitive cardiac troponin-T in (ng/L) determined by the Elecsys®/cobas e™ cTnT 4th-generation assay (Roche Diagnostics) on the (Elecsys 2010/cobas e411), according to the instructions of the manufacturer. The lower limit of detection of the hs-cTnT assay was 3.00 ng/L.

Principles of hs-cTnT measurement method:

- Sandwich principle. Total duration of assay: 18 minutes.
- 1st incubation: 50 µL of sample, a biotinylated monoclonal cardiac troponin T-specific antibody, and a monoclonal cardiac troponin T-specific antibody labeled with a ruthenium complexa react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve (5-point calibration) provided via the reagent barcode

- The analyzer automatically calculates the analyte concentration of each sample (either in pg/mL, ng/L or optional in µg/L).

Statistical analysis of the collected data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. The quantitative data were expressed as mean and standard deviation (Mean ±SD). The qualitative data were expressed as number and percentage and analyzed by the chi-square test (χ^2) and the student's t test for the normally distributed variables and for the none normally distributed variables. The student t-test for comparison between two means. All these tests were used as tests of significance at $p < 0.05$ level.

3. Results

This study included 80 persons, 60 of them were chronic kidney disease (CKD) on conservative therapy, there were 25 males and 35 females and 20 of them were healthy control; they were 10 males and 10 females, the cases group classified according to CKD stage into: 24(40%) patients were stage (II), 23 (38%) patients were stage (III) and 13(21.7%) patient were stage (IV) and classified according to LVDD grade, the cases group were 60 patients classified into: 14 (23.3%) patient were grade (I), 26(43.3%) patients were grade (II), 13(21.7%) were grade (III) and 7(11.7%) were grade (IV). Statistical analysis of the data of these groups showed the following results:

Table (1): Comparison between the studied groups according to demographic data

	Cases (n = 60)		Control 0(n = 20)		Test of sig.	p
	No.	%	No.	%		
Sex						
Male	25	41.7	10	50.0	$\chi^2=0.423$	0.515
Female	35	58.3	10	50.0		
Age						
Min. – Max.	45.0 – 63.0		45.0 – 65.0		t=0.240	0.811
Mean ± SD.	56.03 ± 5.79		55.65 ± 7.28			
Median	56.0		56.50			

There is no significant statistical difference between patients with CKD & control group regarding the gender (P -value =0.515) and age. (P -value =0.811).

Table (2): Comparison between cases and control according to High sensitive cardiac troponin-T (Hs-cTnT)

	Cases (n = 60)	Control (n = 20)	Z	p
Hs-cTnT (ng/L)				
Min. – Max.	20.4 – 600.0	3.0 – 13.90	6.668*	<0.001*
Mean ± SD.	163.60 ± 156.40	7.48 ± 3.53		
Median	107.0	7.15		

Table (3): Relation between LVDD grade and Hs-cTnT in patients group

	LVDD grade				kw	p
	I (n = 14)	II (n = 26)	III (n = 13)	IV (n = 7)		
Hs-cTnT (ng/L)						
Min. – Max.	20.40 – 70.20	31.70 – 438.0	116.0 – 530.0	438.0 – 600.0	45.795	<0.001***
Mean ± SD	39.25 ± 16.28	115.60 ± 80.01	218.52 ± 129.41	488.57 ± 63.22		
Median	32.30	101.0	154.90	452.0		
Sig. bet. grades	I-II***, I-III***, I-IV***, II-III***, II-IV***, III-IV**					

Table (4): Agreement (sensitivity, specificity and accuracy) for Hs-cTnT for diagnosing grade I and grade II (LVDD)

LVDD grade		Grade I	Grade II	Sensitivity	Specificity	PPV	NPV	Accuracy
Hs-cTnT	≤70.2	14	4					
	>70.2	0	22					

With cutoff (70.2 ng/L), Hs-cTnT can differentiate between grade I and grade II with sensitivity (84.62 %) and specificity (100.0 %) and accuracy (90.0%).

Table (5): Relation between CKD stage and Hs-cTnT in patients group

	CKD grade			kw	p
	II (n = 24)	III (n = 23)	IV (n = 13)		
Hs-cTnT (ng/L)					
Min. – Max.	20.40 – 154.90	44.0 – 530.0	107.0 – 600.0	30.337	<0.001***
Mean ± SD	64.10 ± 40.03	176.34 ± 144.19	324.75 ± 175.60		
Median	42.30	112.0	245.0		
Sig. bet. grades	II-III***, II-IV***, III-IV**				

Table (6): Correlation between High Sensitive Cardiac Troponin-T (Hs-cTnT) with different parameters in patients group

	Hs-cTnT	
	r _s	p
LVDD	0.880*	<0.001
CKD	0.717*	<0.001
S. cholesterol	0.256*	0.049
S.TG	0.175	0.180

There is a significant statistical positive correlation between the hs-cTnT and LVDD grade, CKD stage and s.cholesterol in patients group. (*P* value <0.001) but there is no significant statistical positive correlation between the hs-cTnT and serum triglyceride level in patients group. (*P* value <0.180)

4. Discussion

Persistently elevated cardiac troponin is frequently observed among patients with end-stage renal disease¹⁴. The prevalence of increased troponin values among patients with chronic renal failure in the absence of clinically suspected ischemia may be the result of small areas of clinically silent myocardial necrosis. However, other causes, such as

increased LVM and impaired renal troponin excretion, have also been proposed.¹⁵

Cardiovascular disease is frequently associated with CKD, which is important, since individuals with CKD are more likely to die of cardiovascular disease than to develop kidney failure. Indeed, the term cardiorenal syndrome has been increasingly used, and a new classification was proposed because a large

proportion of patients admitted to the hospital have various degrees of heart and kidney dysfunction.¹⁶

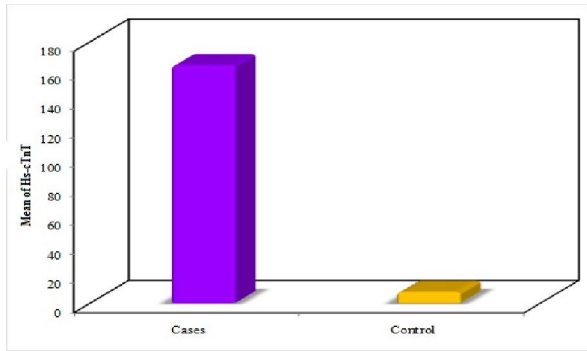


Figure (1): Comparison between cases and control according to Hs-cTnT

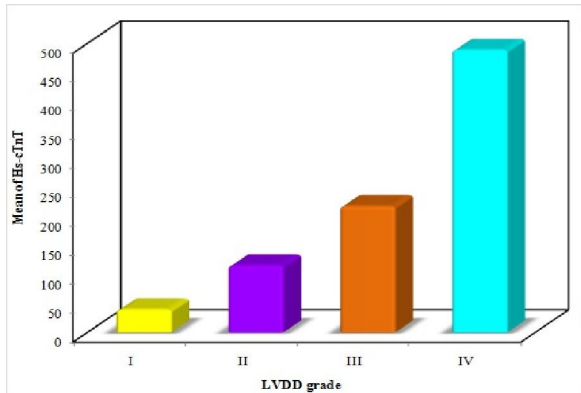


Figure (2): Relation between LVDD grade and Hs-cTnT in patients group

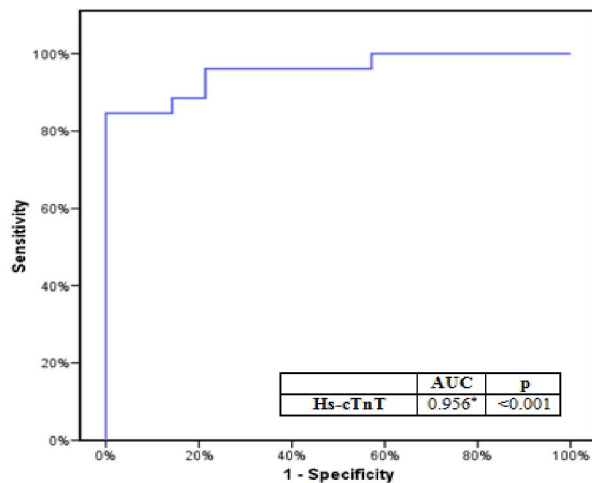


Figure (3): ROC curve for Hs-cTnT for diagnosing grade I and grade II (LVDD)

Left ventricular (LV) diastolic dysfunction, as occurs in patients with hypertension, diabetes mellitus, and/or aging, carries a substantial risk of the subsequent development of heart failure and reduced

survival, even when it is asymptomatic or “preclinical.”⁴

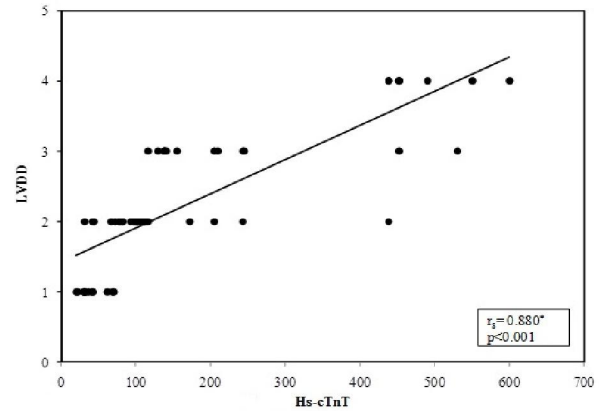


Figure (4): Correlation between Hs-cTnT with LVDD grade in patients group

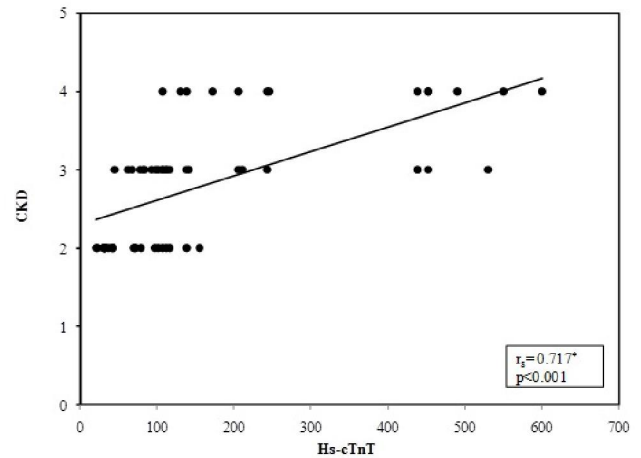


Figure (5): Correlation between Hs-cTnT with CKD stage in patients group

In patients with heart failure with a normal EF, concentric hypertrophy or remodeling can be observed. In addition, several studies have demonstrated an independent association between troponin levels and the presence of LVH in non-dialysis CKD patients.¹³

In this study, we observe the relation between high sensitive cardiac troponin-T(Hs-cTnT) and left ventricular diastolic dysfunction (LVDD) grade in non-diabetic chronic kidney disease(CKD) grades (II, III and IV) before starting renal replacement therapy.

In the present study, there is no significant statistical difference between patients with CKD & control group regarding the gender and age. The high sensitive cardiac troponinT (Hs-cTnT) detected in nearly 97% of cases group, about 90% of detected Hs-cTnT is above the 99 centile of the normal healthy population (14 ng/L). and detected in nearly

90% of control group, but none of detected Hs-cTnT is above the 99 centile of the normal healthy population. (14ng/L). According to serum Hs-cTnT level, cases group ranged from (20.4 – 600.0 ng/L) with mean (\pm SD is 163.60 ± 156.40) and median (107.0) while in control group ranged from (3.0 – 13.90 ng/L), with mean (\pm SD is 7.48 ± 3.53) and median (7.15).

In comparison with **Mishra et al., study**,¹⁷ on Chronic Renal Insufficiency Cohort (CRIC; N= 3,243), hs-cTnT was detectable in 2,735 (84%) persons; the median was 13.3 (IQR, 7.7–23.8) ng/L. Compared with undetectable cTnT (<3.0 ng/L), the highest quartile (23.9 – 738.7 ng/L) was associated with approximately two times as likely to experience LV hypertrophy in the fully adjusted model.

In **Wolley et al., study**,¹² they found that hs-cTnT levels are elevated in almost all patients with ESRF (293patients). Variation in hsT over 1 month was <50% in most patients. Greater variation may indicate an acute coronary syndrome or worsening cardiac disease.

Dubin et al.,¹¹ found that Hs-TnT was detectable in 81% of subjects, and the median (IQR) hs-TnT was 9.4 ng/L (4.3-18.3), adjusting for renal and non-renal factors. After adjustment, lower eGFR was associated with higher expected hs-TnT; participants with eGFR < 30 ml/min/1.73m² had 3-fold higher expected hs-TnT compared to subjects with eGFR > 60. Older age, male gender, black race, LV mass, diabetes and higher blood pressure all had strong, independent associations with higher expected hs-cTnT.

The presence of cardiac troponin in blood indicated that cardiac injury had occurred. The high-sensitivity assays remarkably increased sensitivity and increased early detection of myocardial necrosis, but this was associated with decreased specificity.¹⁸ Despite the nearly absolute specificity of cTn for myocardial tissue, the greater sensitivity of the cTnT assay was confusing.¹⁹

In the present study, we observed in our study that the serum level of high sensitive troponin-T in Egyptian people higher than other population as it ranged from (20.4 – 600.0 ng/L) with mean (\pm SD is 163.60 ± 156.40) and median (107.0 ng/L) and our explanation is may due high prevalence of D.M, obesity, hyperlipidemia, smoking, cardiovascular diseases and delayed diagnoses of CKD dt lack of seeking medical advice among Egyptian people. Also we noticed that There is a significant statistical positive correlation between the hs-cTnT and serum cholesterol level in patients group (P value <0.049), which confirm that hypercholesterolemia may be a contributing risk factor for elevated hs-cTnT among CKD patients in Egyptian people.

In our study, There is a significant statistical positive correlation between the hs-cTnT and CKD stage in patients group. (P value <0.001). Similar result in **Dubin et al., study**,¹¹ they conclude that in the absence of CVD, the most important renal predictor of higher hs-TnT in the CRIC cohort is lower eGFRcys. Non-renal predictors include age, male gender, black race, diabetes, and higher systolic blood pressure

In **Christopher deFilippi et al., study**,²⁰ they suggests that prevalent ongoing subclinical myocyte cell death (in the form of oncosis, apoptosis, or autophagy) is present among patients with stage 3–4 CKD. The independent association of both hs cardiac troponin assays with eGFR and Urinary Albumin/Creatinine ratio (UACR) in this study identifies potential renal-specific mechanisms of cardiac injury that are not identified by cardiac imaging.

In contrast, **Fahie-Wilson et al.**,²¹ and **Bates et al.**,²² reported that the form of cTnT observed in the serum of patients with kidney failure is predominantly the free intact form, and there is no evidence of cTnT fragments existing in the circulation. Their data are consistent with the view that circulating cTnT in renal failure patients reflects cardiac injury.

In the present study, There is a significant statistical positive correlation between the hs-cTnT and LVDD grade in patients group. Also there is a significant statistical positive correlation between the hs-cTnT and serum cholesterol level in patients group. (P value <0.049).

This agree with **Mishra et al.**,¹⁷ study as In large CKD cohort without heart failure, detectable cTnT had a strong association with left ventricular hypertrophy, a more modest association with LV systolic dysfunction, and no association with diastolic dysfunction. These findings indicate that circulating cTnT levels in CKD are predominantly an indicator of pathological LV hypertrophy.

In contrary, another study of 222 participants with CKD by **Abbas et al.**,²³ there was no independent association between cTnT, measured with the standard assay, and LVH, detected by echocardiography.

In the present study, we found a high prevalence of LVH in our population and confirmed the independent association of cTnT with LVDD and prevalence of LVH, increasing incrementally from undetectable across categories of detectable cTnT. Differences between our findings and those previously reported may be related to high prevalence of cardiovascular diseases and presence of hypercholesterolemia as a contributing risk factor for elevated hs-cTnT among CKD patients in Egyptian

people. Also use of high sensitivity assay and detection of very low levels of troponin T may play role in confirmed the independent association of cTnT with LVDD.

Wolley *et al.*¹² conclude that, hsT levels correlate strongly with CV mortality and are above the 99th centile value for normal subjects in almost all stable haemodialysis patients. In 95% of clinically stable patients, hsT varied by <54% over 1 month by <24% over dialysis. These observations are relevant to the use of hsT for diagnosis of acute myocardial infarction, As **The National Academy of Clinical Biochemistry**²⁴ has defined a clear change in troponin values in patients with renal failure, based on analytical considerations, of 20% to define a rising pattern and therefore acute cardiac injury.

In the present study, we exclude diabetic patients as **Wolley *et al.***¹² conclude that higher troponin T levels were strongly associated with the presence of diabetes and predicted CV mortality during 6 months follow-up. The association between diabetes and increased hsT suggests that troponin T may be a sensitive measure of diabetic cardiomyopathy.

In the present study, there is significant statistical positive correlation between LVDD grade and CKD stage in patient group. (P value <0.001)

Similar result in **Hayashi *et al.***, study,²⁵ as they conclude that in CKD, diastolic dysfunction is common and its severity is correlated with the degree of Decreased kidney function. Moreover, in patients with HF, CKD-associated mortality may be worse in those with diastolic HF than in those with systolic HF.

In this study, we investigated the relationship between hs-cTnT values and LVDD in CKD patients without clinically apparent heart failure as diagnosing LVDD could possibly lead to improved treatments and may have substantial health care implications, from both clinical and resource utilization perspectives.

In our study, usin ROC analysis, we found that the performance test of hs-cTnT to differentiate between grade I (asymptomatic) and grade II (symptomatic) left ventricular diastolic dysfunction is significant. (AUC=0.956) (P <0.001)

With cutoff (70.2 ng/L), we can differentiate between grade I and grade II with sensitivity (84.62 %) and specificity (100.0 %) and accuracy (90.0 %).

In this study, our explanation for increasing LVDD grade with increased CKD stage in our patients is considered to be multifactorial, hypertension, alterations in fluid and electrolyte balance, and anemia, hyperlipidemia, and delayed onset of LVDD symptoms. So they are identified as

the major determinants of LV growth in our CKD patients.

Conclusion

Results of the present study revealed that there is a significant statistical positive correlation between high sensitive cardiac troponin-T and Left ventricular diastolic dysfunction grade in CKD patients group (non –heamodialysis patients).

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