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**Original Article**

# Estimation of Cardiac Troponin I and T in Patients with Clinically Stable Chronic Kidney Disease

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## Abstract

**Background:** Patients with chronic kidney disease (CKD) have an increased prevalence of cardiovascular disease with declining renal function. However, the concentration of cardiac troponins is increased among CKD patients in the absence of clinical evidence of acute myocardial infarction. In this study cardiac troponin I and cardiac troponin T concentrations were studied in patients with CKD.
**Objective:** To determine cardiac troponin I and T levels in patients with clinically stable chronic kidney disease presenting to a tertiary care hospital in Rahim Yar Khan.
**Methods:** This cross-sectional study was conducted in the Department of Chemical Pathology, Sheikh Zayed Hospital, Rahim Yar Khan from January to September 2024. A total of 222 individuals with CKD without any known cardiac diseases were included. Serum cTnI and cTnT were measured on chemiluminescence immunoassay analyzer. Mann-Whitney U test and Kruskal-Wallis H test followed by post-hoc analysis were used for the analysis of significance. Spearman rank was used to evaluate correlation of eGFR with cTnT and cTnI.
**Results** A total of 222 patients, 142 males (64%) and 80 females (36%), with CKD were included. There was a statistically significant difference between stages of CKD and cTnT levels, *p* value <0.001 but not between stages of CKD and cTnI levels, *p* value =0.114. The eGFR showed a negative correlation to cTnT (r = -0.456) but had a negligible negative correlation (r =-0.140) with cTnI.
**Conclusion:** The level of cTnT increases across CKD stages however the concentration of cTnI appears to be stable.
**Key words:** Cardiac troponin I (cTnI), cardiac troponin T (cTnT), chronic kidney disease (CKD).

## Introduction

Chronic kidney disease (CKD) imposes substantial medical and economic burdens on healthcare systems, with a proposed frequency of more than 13% globally.[1] CKD lessens the lifetime of an individual by escalating the mortality risk from cardiovascular complications and its advancement to ESRD (end-stage renal disease).[2] People suffering from CKD have an higher risks of cardiovascular diseases [3] and an elevated mortality risk from complications of the cardiovascular system as the renal dysfunction increases.[4] Consequently, patients have an increased probability of dying from the complexities of the cardiovascular disease than progressing to end-stage renal failure if they have CKD.[5]

Diagnosis of acute myocardial infarction (AMI) is made by observing an increasing and/or decreasing trend in the levels of troponin; this signifies myocardial injury, with one or more measures above the upper 99th percentile of a healthy population taken as reference and proof of myocardial ischemia denoted by characteristic patterns of ECG and symptoms characteristic of myocardial infarction. Raised cardiac troponin (cTn) levels crossing the 99th percentile URL (upper limit of reference) indicate injury to the myocardium. The insult to the myocardium is categorized as acute when troponin values demonstrate a characteristic increasing and/or decreasing pattern.[6]

Cardiac troponins (cTn) I and T are essential proteins of myocardial cells for their regulation, facilitating the interaction between actin

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**Authors Contribution**

MM & SSH conceptualized the project. MM, MA & TI did the data collection. MM, SSH, MA, TI & ZG did the literature search. MM, SSH, MA & SS performed the statistical analysis. Drafting, revision & writing of manuscript were done by MM, SSH, MA, TI & SS

and myosin through calcium-mediated processes and playing a crucial role in cardiomyocyte contraction. The troponin complex comprises three constituents: Tropomyosin binding Troponin T (TnT), Troponin C (TnC) binds to calcium ions (Ca2+), and Troponin I (TnI): inhibitory subunit.[6] Isoforms of cTnI and cTnT are cardiac-specific. At the same time, the TnC isoform present in the cardiac fibers also exists in the skeletal fibers of the slow-twitch type, rendering it non-specific for cardiac tissue. Therefore, troponin C is not employed in assays for diagnosing cardiac damage.[7]

CKD patients usually have circulating amounts of cardiac troponins exceeding the 99th percentile, even when there is no evidence of a myocardial infarction. Furthermore, reaching the diagnosis of infarction in the myocardium with certainty in individuals with diagnosed CKD is difficult as the characteristic ischaemic symptoms and signs are absent in these individuals.[6] The factors considered risk of cardiovascular disorder are persistent in CKD patients; their involvement in atherosclerosis of vasculature is remarkable, especially in the initial stages of kidney disease.[8,9] Among CKD patients, increased serum cardiac troponins are observed without clinical evidence of AMI.[10] In 2012, the KDIGO (Kidney Disease Improving Global Outcome) guidelines recommended classifying CKD based on the value of eGFR, in mL/min/1.73m2, into five groups: Stage 1 (more than or equal to 90), Stage 2 (between 60 and 89), Stage 3 (between 30 and 59), Stage 4 (between 15 and 29) and Stage 5 (less than 15).[11] The rate of filtration by the glomeruli (GFR) is measured in ml/min, at which blood substances are filtered through the glomeruli. Estimated from serum creatinine (S.Cr) using MDRD equation for creatinine (mg/dl): eGFR = 186 * (S.Cr)-1.154 * Age - 0.203 * (1.212 if African ethnicity) * (0.741 for the female gender). The reference interval for S.Cr is 0.670 - 1.170 for men and 0.560-0.960 mg/dl for women. The most advanced stage of CKD (eGFR at or below 15) is autonomously associated with a rapid amplification in troponin T levels, indicating worsening cardiac damage.[12]

The kidney's role in processing cardiac biomarkers makes their interpretation in AKI complicated, where dynamic changes in glomerular filtration occur. Furthermore, CKD and ESKD patients display constantly elevated concentrations of biomarkers, so caution is needed for interpretation.[13] The clinical utility of hs-cTnI and hs-cTnT in individuals with kidney deterioration is alarming as the biomarker amounts are persistently raised in CKD whilst AMI is absent.[14] The 99th percentile for cardiac troponins is set up using the healthy population; this study was conducted to estimate the baseline levels of cardiac troponins using high-sensitivity troponin assays in patients at various stages of CKD without ACS.

## Methods

This cross-sectional study was carried out during January to September 2024 in the section of Department of Chemical Pathology, Sheikh Zayed Hospital (SZMC/H), Rahim Yar Khan

The eligibility criteria were all individuals present in or presenting to the in-patients and out-patients Department of Nephrology SZMC/H, both genders, aged between 18-80 years with clinically stable CKD (Stages 1-5) based on 2012 KDIGO guidelines. Clinically stable CKD referred to patients without acute kidney injury or recent deterioration in renal function. eGFR was estimated from the level of serum creatinine using the modification of diet in renal disease (MDRD) equation. Patients with stable chronic diabetes mellitus, hypertension, and anemia associated with CKD were included. The exclusion criteria were acute metabolic complications of diabetes mellitus, hypertensive emergency, acute severe anemia due to blood loss or requiring transfusion, malignant conditions, and medical conditions that alter cTn levels, like coronary artery diseases and ACS. Individuals with a history of kidney transplant, cognitive impairment, and amputation were also excluded, as well as pregnant and lactating women. These criteria were assessed based on patients' histories and medical records.

Sample size (n) was calculated by taking a 95% confidence interval and margin of error (e) 5%, z score value (z) is 1.96, and population proportion (p) was taken as 17%, which is the proportion of Patients of CKD known to have increased cTnI level.[15] Calculated sample size was 218, which was increased to 222. Eligible subjects with clinically stable CKD, filtered through the criteria set for exclusion and inclusion, were registered in the study. After obtaining consent, socio-demographic data like address, contact number, residential status, gender, and age were collected. Height (m) and weight (kg) were measured to estimate the body mass index (BMI) with the formula: Weight (kg)/length ($m^2$) for each subject. The specimens were collected using standard venipuncture procedures in serum separator gel tubes. After collection, samples were centrifuged within 20 mins and analyzed for hs-cTnI and hs- cTnT on an immunoassay analyzer by electrochemiluminescence immunoassay.

SPSS (version 23) was utilized for the entry and analysis of data. Categorical data like gender, residential status, educational status, and increased

cTnI and cTnT levels were computed as frequency and percentages. cTnI and cTnT were analyzed as continuous variables and also categorized according to standard clinical cut-off values, as mentioned in Table-1. The distribution of quantitative data was ascertained by the Shapiro-Wilks test. As the data for quantitative variables was non-gaussian; cTnI (W: 0.810, *p*-value <0.001), cTnT (W: 0.774, *p*-value <0.001) and eGFR (W: 0.860, *p*-value <0.001), it was described as median and interquartile range (IQR). We addressed the effect modifiers like age, gender, BMI, and the stage of CKD through stratification. Post-stratification, Mann-Whitney U, and Kruskal-Wallis H, succeeded by post-hoc analysis, were used to study significance. *p*-values ≤0.05 were considered to be significant. Spearman rank coefficient (r) was employed to evaluate correlations among eGFR with cTnT and cTnI.

## Results

Among 222 study participants, 142 (64%) were males and 80 (36%) were females. The median (IQR) age was 33(14) with a 95% confidence interval of 33.03-36.04, with 126 (56.8%) subjects below the age of 35. The distribution of subjects concerning quantitative and qualitative variables is given in Table-1.

Only 2 (0.9%) study subjects had cTnI levels above the cut-off (manufacturer's limit) of 30 ng/L; both had stage-5 CKD. A total of 37 (16.7%) subjects had cTnT level above the cut-off manufacturer's upper reference limit; URL) of 25 ng/L, among which 4 (10.8%) were of stage-3 CKD, 13 (35.1%) were of stage-4 CKD and 20 (54.1%)

**Table 1: Characteristics and distribution of study subjects.**

| *Variable* | *Median (95% CI) - IQR* | *Subgroup* | *Frequency (%)* |
|---|---|---|---|
| Gender | | Male | 142 (64) |
| | | Female | 80 (36) |
| Age (years) | 33 (33.02-36.04) - 14 | ≤ 35 years | 126 (56.8) |
| | | > 35 years | 96 (43.2) |
| Residence | | Urban | 52 (23.4) |
| | | Rural | 170 (76.6) |
| BMI (kg/m$^2$) | 20 (20.86-21.97) - 6 | Underweight | 60 (27) |
| | | Healthy | 120 (54) |
| | | Overweight | 30 (13.5) |
| | | Obese | 12 (5.4) |
| eGFR (ml/min/1.73m$^2$) | 38 (48.45-59.12) - 71 | | |
| Stage of CKD | | Stage 1 | 54 (24.3) |
| | | Stage 2 | 34 (15.3) |
| | | Stage 3 | 32 (14.4) |
| | | Stage 4 | 56 (25.2) |
| | | Stage 5 | 46 (20.7) |
| cTnI (ng/L) | 10 (9.94-11.43) - 4 | ≤ 30 ng/L | 220 (99.1) |
| | | > 30 ng/L | 2 (0.9) |
| cTnT (ng/L) | 10 (13.35-16.23) - 12 | ≤ 25 ng/L | 185 (83.3) |
| | | > 25 ng/L | 37 (16.7) |

**Table 2: Comparison of cTnT (cardiac troponin T) level in study subjects with respect to variables.**

| *Variable of interest* | | *cTnT ng/L Median (95% CI) - IQR* | *p value* |
|---|---|---|---|
| Stage of CKD | Stage 1 | 9.0 (7.65-9.35) - 4 | 0.000* |
| | Stage 2 | 10.0 (9.98-13.85) - 10 | |
| | Stage 3 | 10.0 (10.78-16.06) - 11 | |
| | Stage 4 | 10.0 (13.01-18.53) - 10 | |
| | Stage 5 | 20.5 (19.36-28.42) - 25 | |
| Residential Status | Urban | 10.0 (11.78-17.95) - 10 | 0.287$^+$ |
| | Rural | 10.0 (13.13-16.41) - 13 | |
| Gender | Male | 10.0 (14.53-18.48) - 11 | 0.003$^+$ |
| | Female | 10.0 (9.97-13.53) - 3 | |
| Age | ≤ 35 years | 10.0 (10.12-13.23) - 3 | 0.000$^+$ |
| | > 35 years | 18.0 (16.46-21.31) - 16 | |
| BMI | Underweight | 10.0 (9.28-14.76) - 3 | 0.000* |
| | Healthy | 10.0 (12.25-16.05) - 11 | |
| | Overweight | 19.0 (14.54-21.79) - 16 | |
| | Obese | 27.0 (20.16-33.17) – 15 | |

**Table 3. Comparison of cTnI (cardiac troponin I) level in study subjects with respect to variables.**

| *Variable of interest* | | *cTnI ng/L Median (95% CI) - IQR* | *p value* |
|---|---|---|---|
| Stage of CKD | Stage 1 | 8.0 (7.73-9.05) - 3 | 0.144* |
| | Stage 2 | 10.0 (9.24-13.34) - 10 | |
| | Stage 3 | 10.0 (9.29-14.58) - 12 | |
| | Stage 4 | 10.0 (9.77-12.48) - 7 | |
| | Stage 5 | 8.5 (9.48-13.56) - 8 | |
| Residential Status | Urban | 10.0 (9.76-13.13) - 2 | 0.180+ |
| | Rural | 10.0 (9.62-11.29) - 4 | |
| Gender | Male | 10.0 (9.99-11.86) - 5 | 0.224+ |
| | Female | 9.5 (9.00-11.53) - 3 | |
| Age | ≤ 35 years | 8.0 (8.19-9.76) - 4 | 0.000+ |
| | > 35 years | 10.0 (11.66-14.19) - 10 | |
| BMI | Underweight | 7.0 (7.82-10.64) - 4 | 0.000* |
| | Healthy | 10.0 (9.56-11.39) - 3 | |
| | Overweight | 19.0 (9.37-13.37) - 9 | |
| | Obese | 20.0 (13.77-22.89) – 10 | |

were of stage-5 CKD. A significant difference between cTnT levels among the subjects at different CKD stages, geneder age and BMI was observed (*p*-value <0.001); Table-2. In the posthoc analysis for pair-wise comparison between categories of CKD concerning cTnT levels, there was a statistically significant difference among the first two stages (*p*-value =0.034), stage 1 and stage 4 (*p*-value <0.002), stage 1 and stage 5 (*p*-value <0.002), stage 2 and stage 5 (*p*-value =0.005), stage 3 and the last stage (*p*-value =0.034). However, the difference between cTnI levels among the subjects at various stages of CKD was not statistically significant (*p*-value 0.114) as described in Table-3.

A statistically significant difference between cTnT and cTnI levels among various categories of BMI, Gender and residential status of the study participants were compared and presented in Table-2 and Table-3. The cTnT and cTnI levels were positively related, with the correlation coefficient (r) being 0.659. The eGFR and cTnT levels were negatively correlated (r =- 0.456), while the correlation of eGFR with cTnI, yet negative, indicated a negligible relationship (r =- 0.140).

## Discussion

Our study exhibited a noteworthy difference between the two age divisions (≤35 &>35 years) for both cTnT and cTnI levels with a *p*-value of less than 0.001, Table-3. In a cohort study conducted at the five centers of acute care in the United Kingdom, among a total of 257,948 patients with a median (IQR) of 65 (50-79), 180,239 subjects had troponin results below the URL with median (IQR) age of 60 (46-75) while 77,709 subjects had troponin result above the URL with median (IQR) age of 74 (62-84); *p*-value <0.001. This study also indicated that the troponin levels increased almost linearly from 20 years of age to 60. Each decade after that, the troponin level increased exponentially with age.[16]

Another study on age-related hs-cTnI concentration difference in disease-free adults conducted by Peter EH et al. demonstrated that the subjects aged less than 65 had lower concentrations of troponin than those more than or equal to 65 years. These findings reinforce that the concentration of troponins increases as age increases.[17]

A pronounced difference among the different categories of BMI for both cTnI and cTnT levels was also noted. Furthermore, the difference lies between underweight-overweight, underweight-obese, and healthy obese for cTnT (*p*-value: 0.002, 0.000 & 0.002 respectively), while for cTnI, the difference was between underweight-obese, healthy-obese, and overweight-obese groups (*p*-value: 0.000, 0.002 & 0.026 respectively). The study conducted by Huang J et al. demonstrated a higher hs-cTnT level in the obese group (*p*-value: <0.001) and concluded that obesity is associated independently to elevated amounts of circulating TnT and throughout the BMI categories, the positive correlation with TnT was evident; spearman r = 0.209, *p*-value <0.0001.[18]

The difference between cTnT levels and gender was statistically significant (*p*-value <0.004), but there was an insignificant difference between gender and cTnI levels (*p*-value = 0.224). In a study done by Kaura A et al., 60.7% of the study participants with troponin levels above the URL were males, while only 53% of the subjects who died were male (*p*-value < 0.001).[17]

Chung JZ et al. examined more than seventeen thousand paired cTnT and creatinine values from around ten thousand hospitalized patients, and dynamic changes in cTnT levels were observed. Within a brief period (median 15 hours), cTnT concentrations rose and fell in tandem with improving (>120 ml/min)and worsening kidney function (5 ml/min), implying renal clearance as the primary reason for the observed fluctuations.[20] In a study conducted in Abbottabad, Pakistan, elevated Troponin T was observed in 45 (38.5%) patients with chronic renal failure.[21] A study from Karachi, Pakistan reported an asymptomatic rise in cTnI in 20.5% of hemodialysis patients, indicating elevated troponin levels in CKD dialysis patients.[22]

As the persistent elevation of cardiac troponin in CKD patients complicates diagnosis using traditional cut-offs, a common workaround is to look for a change of >20% between two values of cTn in the same patient over several hours, this strategy is still unsupported by convincing evidence and may lead to under-diagnosis of myocardial events, highlighting the need for CKD-specific diagnostic recommendations.[23]

This study had certain limitations. Patients from a single center were included, so the findings may not apply to other populations or settings. Although stratification and non-parametric tests were applied to explore associations, no multivariable regression analysis was done; therefore, the independent effect of age and CKD stage on troponin levels could not be determined and residual confounding cannot be excluded. The cause-and-effect relationship must be clarified, as a cross-sectional study cannot establish the temporal precedence.

## Conclusion

In conclusion, cTnT levels tend to increase with advancing CKD stages, while cTnI levels appear relatively stable. These findings suggest that cTnT may require cautious interpretation in advanced CKD, whereas cTnI may serve as a more stable marker across CKD stages for clinical assessment.

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**Availability of Data:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethical Approval:** The Institutional Review Board of Sheikh Zayed Medical College/ Hospital, Rahim Yar Khan approved the study via letter no. 680/IRB/SZMC/SZH, dated 06/04/2023.

**Conflict of Interest:** None declared.

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