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Original Article

Determination of Upper Reference Limit for High-Sensitivity Troponin T in Chronic Kidney Disease Patients

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ABSTRACT

Objective: To establish the 99th percentile of upper reference limit (URL) for high-sensitivity Troponin T (hs-Troponin T) in patients with Chronic Kidney Disease (CKD).

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology (AFIP), Rawalpindi Pakistan, from Jan to Jun 2025.

Methodology: A total of 300 males and 300 females were enrolled. Patients with CKD stages 3 to 5, based on estimated glomerular filtration rate (eGFR), between the ages of 18 and 80 years who had no self-reported history of cardiovascular disease were included.

Results: The study participants had a median (interquartile range) of eGFR of 26.62 (15.00 – 38.67) mL/min/1.73m². The data were not normally distributed. The median (IQR) of hs-Troponin T levels was 66 (35.40 – 100.00) ng/L in males and 76.20 (49.00 – 111.00) ng/L in females, with the 99th percentile URL at 402.9 ng/L for males and 264.9 ng/L for females. Therefore, the combined median hs-Troponin T value for both genders was 69.00 ng/L, with an IQR of 40 to 102.75 ng/L. The 99th percentile URL of hs-Troponin T was 394.74 ng/L. A moderate but statistically significant negative correlation, r = -0.4643 (95% CI), between eGFR and hs-Troponin T levels was identified.

Conclusion: The 99th percentile URL for hs-Troponin T in CKD patients was markedly elevated compared to that observed in the healthy population. These findings underscore the importance of establishing CKD-specific URL of hs- Troponin T to prevent the misclassification of myocardial infarction and enhance cardiovascular risk assessment in this patient group.

Keywords: Cardiac Biomarker, Cardiovascular Disease, Chronic Kidney Disease, Troponin T, Upper Reference Limit.

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INTRODUCTION

Chronic kidney disease (CKD) represents a pressing global medical issue. At least 10% individuals worldwide are currently diagnosed with CKD, an estimated disease burden in excess of 800 million. Its prevalence in the Pakistani population is 21.2%.[1] Additionally, over 17% of individuals with acute myocardial infarction also have clinically diagnosed CKD. hs- Troponin T levels are raised in patients with CKD even without myocardial infarction. This can complicate the interpretation of biomarkers and make it challenging to distinguish between renal dysfunction and acute cardiac events.[2]

The International Federation of Clinical Chemistry (IFCC) specifies two main criteria for an assay to be considered high-sensitivity: first, the coefficient of variation (CV) at the 99th percentile URL must be below 10%. Second, the assay should be able to detect measurable concentrations in more than 50% of healthy individuals, including both males and females, at or above its limit of detection (LOD).[3] Cardiac troponin T and I are generally regarded as equally useful, except in CKD patients, where hs-Troponin T tends to be higher.[4] Nearly 50 % of the patients with advanced stages of CKD ultimately succumb to cardiovascular complications.[5] Intra-cellularly, they are degraded by specific proteases and are removed via renal filtration.[6] The URL defines the highest value expected within a healthy population. For cardiac troponins, this corresponds to the 99th percentile and is used as the reference cut-off to support the diagnosis of acute myocardial infarction.[7]

Determining a CKD-specific 99th percentile URL is essential to distinguish acute pathology from chronic elevations, stratify cardiovascular risk, and refine diagnostic accuracy. This study aimed to establish the 99th percentile URL of hs-Troponin T in CKD patients without overt cardiovascular disease in a Pakistani cohort. No study has yet determined the 99th-percentile URL for hs-Troponin T in Pakistani

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CKD patients, highlighting an important local research gap.

METHODOLOGY

The cross-sectional analytical study was conducted at the Department of Chemical Pathology and Endocrinology, AFIP, Rawalpindi Pakistan, from January to June 2025, with prior Institutional Review Board approval (certificate number: IRB/24/3155 dated 28 Aug, 2024).

Inclusion Criteria: All patients of CKD stages 3 to 5 not undergoing renal replacement therapy (dialysis or renal transplant),[11] without any self-reported history of cardiovascular disease between the ages of 18 to 80 years, of both genders were included.

Exclusion Criteria: Patients diagnosed with acute kidney injury and eGFR change of >30% in the previous three months, history of cardiovascular disease, smoking, and Diabetes Mellitus were excluded.

The proposed study involved a detailed clinical history of the study participants, according to the above-mentioned inclusion and exclusion criteria.

The sample consisted of 600 subjects, equally divided between males and females (n=300 each). According to the International Federation for Clinical Chemistry Task Force recommendations and European Society of Cardiology guidelines, the minimum sample size for determination of the 99th percentile value with 95% confidence interval (CI) for hs- Troponin T is 300 for each gender.[8] The nonparametric 95% CI (n=300 per gender) for the 99th percentile is given by the values at ranks 293-300. This provides a sufficiently narrow CI with adequate precision for clinical use and aligns with IFCC recommendations for reference-limit studies.

A non-probability convenient sampling technique was employed to draw venous blood samples. A formal informed consent was taken from each participant before the initiation of the study. A pre-formulated data collection proforma was used to document all patient responses. Samples were analyzed on the Roche Cobas Pro C503 module and e801 by Roche Diagnostics using Total Lab Automation technology. Tri-level quality control was ensured, and eGFR was determined using the CKD EPI collaboration equation. CKD is defined as an eGFR of <60 mL/min/1.73 m^2 for a duration of 3 months. GFR categories are G1 with an eGFR of >90ml/min/1.73m^2, G2 with calculated eGFR between 60 - 89 ml/min/1.73m^2. G3 and G4 stage as eGFR of 30-59 mL/min/1 .^{73m2} and eGFR between 15-29mL /min/1.73m^2, respectively. G3 to G5 stages were included in the study, while G1 and G2 were excluded.[9]

Analytical performance specifications as claimed by the manufacturer for the hs-Troponin T assay's Limit of Blank is 2.5 ng/L, Limit of Detection is 3 ng/L, and Limit of Quantitation is 13 ng/L with an imprecision of <10%.[10] The assay in our lab showed a CV of 7.2% at the 99th percentile concentration (14 ng/L), compliant with the IFCC recommended precision criteria (Figure-1).

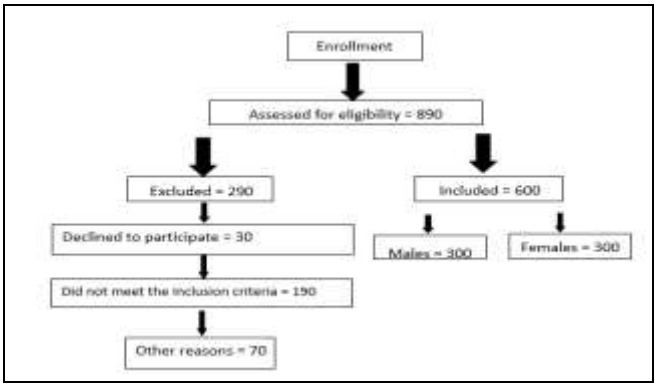

Figure-1: Patient Flow Diagram (n=600)

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 25. Data distribution was assessed with the Shapiro-Wilk test, and statistical methods were selected based on the data distribution and normality. The results were expressed as median and interquartile range (IQR), specifically for continuous variables such as age, serum creatinine levels, and eGFR stages. Qualitative variables (gender) were expressed as frequency and percentage. Pearson correlation coefficient was used to find the relationship between eGFR and hs- Troponin T and p value ≤ 0.05 was considered as significant. To determine the reference interval for hs-Troponin T, values were ranked in ascending order, and the 99th percentile was calculated for each stage of CKD after excluding outliers.

RESULTS

A total of 600 CKD patients (300 of each gender) were recruited for the study. The cohort demonstrated advanced kidney dysfunction with a median (IQR) eGFR of 26.62 (23.67) mL/min/1.73m^2, indicating predominantly CKD stages 3-5. The distribution of CKD patients on the basis of eGFR stages is illustrated

in Figure-2. The median (IQR) of hs-Troponin T was 69.00 (62.75) ng/L. The 99th percentile of hs trop T URL was determined to be 394.74 ng/L. The median (IQR) levels of hs troponin T in males and females were 66.00 (64.60) ng/L and 76.22 (62.00) ng/L, respectively, while the 99th percentile URL were 402.90 ng/L for males and 264.90 ng/L for females. Males show higher 99th percentile values, but females have slightly higher median levels. Out of 600 CKD patients, only 1 % of patients exceeded the URL of the 99th percentile threshold.

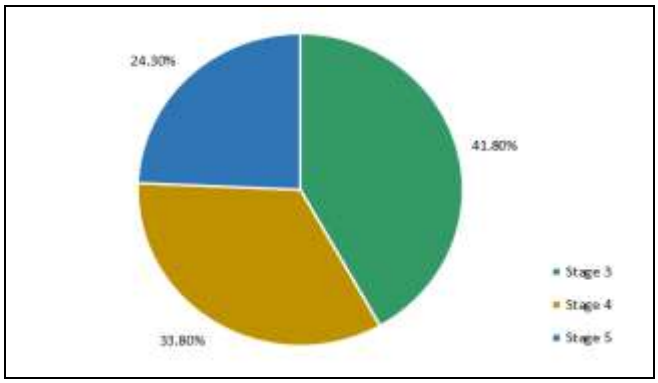

Figure-2: Distribution of Chronic Kidney Disease Patients by Estimated Glomerular Filtration Rate (eGFR), Stages

The analysis revealed a statistically significant moderate negative correlation, r = -0.4643; (p<0.05) at 95% CI (–0.53 to –0.40), between eGFR and hs-Troponin T levels. This indicates that as renal function deteriorates, levels of cardiac biomarkers tend to increase. 99th percentile URL for different eGFR stages is shown in Table.

Table: Median and 99th percentile Levels of hs-Troponin T (ng/L) according to Chronic Kidney Disease stages (n=600)

Parameters	Stage 3 Chronic Kidney Disease (251 patients)	Stage 4 Chronic Kidney Disease (203 patients)	Stage 5 Chronic Kidney Disease (146 patients)
Median (IQR) ng/L	50.00 (44.20)	80.00 (61.00)	114.00 (72.40)
99th Percentile URL	215.36 ng/L	462.72 ng/L	554.79 ng/L

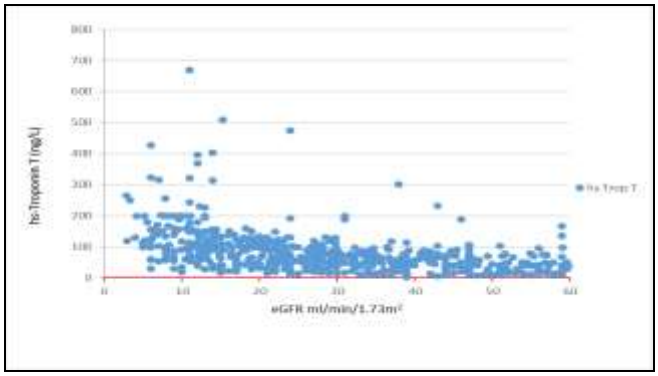

Figure-3: Correlation between Estimated Glomerular Filtration Rate (eGFR) and High-Sensitivity Troponin T (hs-Troponin T)

A stepwise increase is observed in hs-Troponin T values across CKD stages, with the median rising from 50 ng/L in Stage 3 to 115 ng/L in Stage 5. Moreover, stage 5 CKD patients demonstrated the greatest dispersion, with the highest standard deviation (SD: 88.45) and the high 99th percentile value (554.7 ng/L). A Moderate negative correlation (r = -0.464, p<0.05) is observed between eGFR and hs-Troponin T, explaining that deteriorating kidney function is associated with raised cardiac biomarkers, as illustrated in the scatter plot in Figure-3.

DISCUSSION

Electrocardiography findings are often abnormal and inconclusive in CKD patients due to the high incidence of electrolyte imbalance and underlying left ventricular hypertrophy. Moreover, there is a chronic elevation of troponin T levels and the non-specific nature of presenting symptoms. The presence of these symptoms complicates the interpretation and lowers the diagnostic specificity of hs-Troponin T for acute myocardial infarction.[12] The challenge is augmented by the utilization of hs-Troponin T assays, which, due to their improved analytical performance specifications, can detect elevated cardiac troponin levels above the 99th percentile in most CKD patients. Application of the conventional threshold may be misleading for assessment of acute coronary syndrome in these patients.[13] To address this, we conducted this study in a local clinical setting to determine the 99th percentile URL of hs-Troponin T in CKD patients.

According to a meta-analysis by Jan Kampmann et al., the hs-troponin T cutoff in CKD patients was identified as 48 ng/L, with substantially elevated thresholds noted in dialysis-dependent individuals, reaching as high as 239 ng/L.[14] In the present study, the median hs-Troponin T levels increased progressively with advancing CKD stage, with values of 50 ng/L in stage 3, 80 ng/L in stage 4, and 114 ng/L in stage 5. These results are consistent with previously published data and reflect the well-recognized impact of declining renal function on circulating troponin concentrations.

Bansal et al. observed that 68% of CKD patients had hs-Troponin T levels exceeding the conventional 99th percentile URL, with their cohort-specific 99th percentile established at 126 ng/L.[15] In the present study, the 99th percentile URL was comparatively higher for CKD stage 3 (215 ng/L) and stage 5 (554

ng/L), highlighting the importance of stage-specific interpretation. The relatively raised cutoffs observed in our population setting may be explained by chronic subclinical myocardial injury due to uremic and hemodynamic stress, reduced renal clearance of troponins, and dialysis-dependent factors in stage 5 patients. Additionally, the high prevalence of comorbidities such as hypertension, diabetes, and left ventricular hypertrophy in our cohort may have underlie the observed elevation in baseline values.

Another study by Bansal *et al.*, observed significant variations in the 99th percentile values of hs- Troponin T across all eGFR categories. Notably, among patients with advanced CKD 99th percentiles for hs-Troponin T were substantially raised to 219 ng/L as compared to the thresholds of 14 ng/L that are typically used to rule in disease in the healthy population.[16] This finding is also apparent in our CKD patients with preserved to moderately reduced renal function, where the 99th percentile values remained considerably raised compared to those defined for the healthy population.

In the present study, males exhibited raised 99th percentile values while females demonstrated slightly higher median values of hs-Troponin T, which may be attributed to biological differences between the genders. Males have slightly greater left myocardial volume and ventricular mass, resulting in higher baseline troponin release. The finding in the current study that females showed relatively higher median values is linked to the older age of the female subjects in our dataset. Further studies with a targeted age-specific population are warranted to minimize age-related effects.

The raised 99th percentile as compared to the global data studied likely results from demographic, genetic, and other contributing factors, like age at the time of diagnosis. Pakistan, being a developing country with economic constraints and limited healthcare infrastructure, has cases of CKD that are diagnosed late because of poor health literacy and poor compliance to treatment.

Our study builds upon existing literature by reviewing a broad spectrum of CKD patients of different stages and by proposing an alternative 99th percentile URL for hs-Troponin T of 394.74 ng/L based on ambulatory CKD patients without any self-reported previous cardiovascular disease history. This distribution holds clinical significance in defining CKD-specific URL for hs-Troponin T, which is essential given that conventional 99th percentile values based on healthy populations may not accurately reflect the levels observed in CKD patients.[17] The finding that 21.6% of the variance in hs-Troponin T is explained by eGFR suggests that while renal function plays a major role in troponin elevation among CKD patients, it is not the sole contributing factor, and other clinical variables may also influence troponin levels. This finding points to the need for further research to explore additional factors influencing hs-Troponin T levels in CKD patients and to better understand the complex interplay between cardiac and kidney function.[18]

LIMITATIONS OF STUDY

Being a cross-sectional and single-center study, these findings may not be generalizable and provide prognostic insights. Cardiovascular disease, medication, variability in sampling relative to dialysis sessions, inflammation and age are confounding factors that may have influenced our results. Moreover, the lack of correlation with clinical outcomes limits the direct applicability of the proposed URL.

CONCLUSION

Determination of the gender specific 99th percentile URL for hs-cardiac troponin T in CKD patients could substantially strengthen clinical interpretation. It would limit false detections of myocardial infarction and overtreatment. CKD patients have chronic elevation of cardiac troponin T levels unrelated to acute cardiac events.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SN & MQAK: Data acquisition, data analysis, critical review, approval of the final version to be published.

AH & SHK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SS & AUK: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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