EMCREG International
EMERGENCY MEDICINE CARDIAC RESEARCH AND EDUCATION GROUP
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Interpretation of Cardiac Troponins in Patients with Chronic Kidney Disease and Suspected Acute Coronary Syndrome in the Emergency Setting

A SUMMARY FOR EMERGENCY PHYSICIANS

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Dear Colleagues,

Patients with chronic kidney disease are at very high risk for acute coronary syndrome and often suffer cardiovascular death. Disease processes such as diabetes mellitus and hypertension commonly cause chronic kidney disease. These same diseases also serve as risk factors for acute coronary syndrome.

Detecting acute coronary syndrome in a patient with chronic kidney disease is a significant challenge for any physician caring for these patients acutely. Cardiac biomarkers such as Troponin T or I are sensitive and specific indicators of acute myocardial necrosis. In some patients with chronic kidney disease, the troponins may show slight elevation above the typical laboratory cut off value, making the evaluation of these patients problematic.

Dr. Jin Han, Assistant Professor of Emergency Medicine at the University of Cincinnati, provides a detailed discussion of the interpretation of elevated values in patients with chronic kidney disease and acute coronary syndrome for this EMCREG-International newsletter. It is our hope that the readers of this newsletter will find their evaluation of patients with chronic kidney disease and acute coronary syndrome more effective, resulting in improved patient care.

Sincerely,

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W. Brian Gibler, MD
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Introduction

Patients with chronic kidney disease (CKD) are at high risk for acute coronary syndrome (ACS) including acute myocardial infarction (AMI) and cardiovascular death, as they are predisposed to accelerated atherosclerosis compared to the general population.[1-3] An AMI is often a lethal event in patients with CKD; two-year post-myocardial infarction mortality rates have reported to be up to 73% in patients with end stage renal disease.[4] Cardiac biomarkers of necrosis such as creatine-kinase MB,[5] myoglobin,[6] and cardiac troponins[7] are difficult to interpret in patients with CKD because they may be elevated in the absence of AMI.

For patients with normal renal function, the development of cardiac troponin T and I have helped revolutionize the diagnosis and treatment of AMI. Because of their near absolute myocardial tissue specificity, as well as their ability to detect microinfarctions despite normal creatine kinase-MB levels, cardiac troponin T and I have become the preferred cardiac biomarker for the diagnosis of AMI.[8,9] Cardiac troponin T and I have the additional prognostic ability to predict adverse cardiovascular outcomes.[10]

The diagnostic ability and prognostic value of cardiac troponin T and I in patients with CKD are uncertain in the emergency setting. Elevations in both cardiac troponin T and I have been reported in asymptomatic patients with CKD.[7] As a result, these elevations have often been described as non-specific for myocardial injury[11] and disregarded by clinicians. Understanding the clinical significance of elevated cardiac troponin T and I in this patient population is extremely important as individuals with CKD have a higher pretest likelihood for having ACS.[2] The purpose of this summary is to briefly review the current literature concerning the interpretation of cardiac troponin T and I results in patients with CKD within the emergency setting.

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Cardiac Troponin T

Source of Cardiac Troponin T Elevations

Over the past decade, the role of cardiac troponin T (cTnT) in patients with CKD has been studied extensively. When cTnT was first introduced, elevations were observed in up to 70% of asymptomatic dialysis patients.[12] The source of these elevations was thought to be secondary to uremic myopathy,[13] which led to re-expression of cTnT isoforms in regenerating skeletal muscle.[14,15]

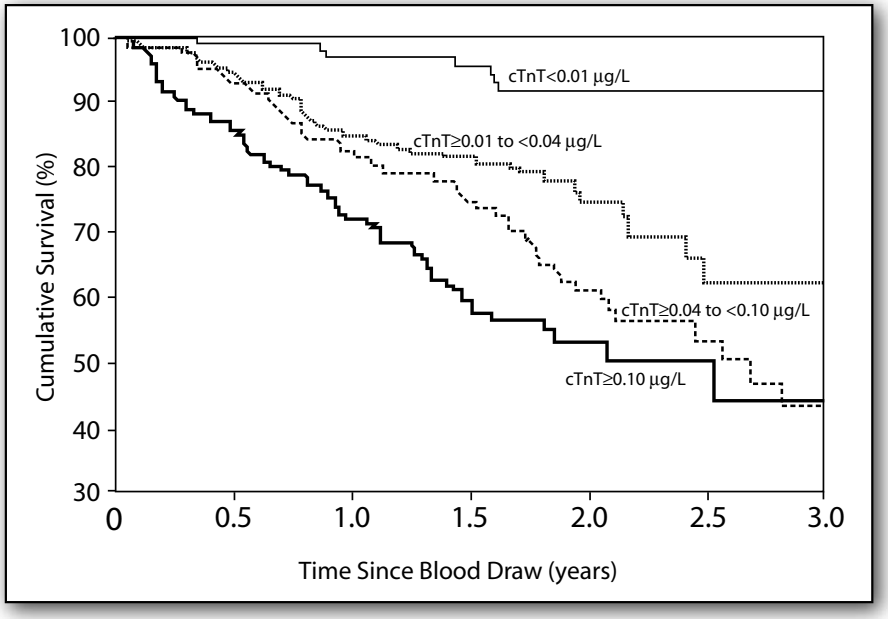
Currently, cross-reaction with the skeletal muscle cTnT isoforms is no longer found with more specific second- and third-generation cTnT immunoassays.[14] Serum cTnT elevations above 0.10 ng/ml, however, are still observed in up to 20% of asymptomatic dialysis patients[7] suggesting that elevated cTnT is cardiac specific in patients with CKD. In dialysis patients, elevated cTnT is associated with multi-vessel coronary artery disease.[16] Even in the absence of coronary artery disease, elevations in cTnT may represent clinically occult, minor myocardial injury exacerbated by uremia.[17] Proposed mechanisms of cTnT level elevation in patients receiving hemodialysis have included silent ischemic injury and an apoptotic process.[16]

Cardiac Troponin T in Asymptomatic Patients with CKD

Recently, there have been numerous published reports observing an association between elevated cTnT and mortality in patients with CKD. Most of these studies have been performed with asymptomatic dialysis patients. There is strong evidence to support the ability of cTnT to predict long-term all-cause mortality. Apple and colleagues performed the largest study to date consisting of 733 asymptomatic dialysis patients using a third-generation cTnT immunoassay.[7] They found that elevated serum cTnT levels ere associated with worsening all-cause mortality rates, even with elevations as little as 0.01 ng/ml **(Figure 1)**.[7] Subjects with cTnT elevations above the 0.01 ng/ml, 0.04 ng/ml, and 0.10 ng/ml cutoffs had increased risk of death, with adjusted relative risks of 4.3, 2.1, and 2.2, respectively.[7] Additionally, elevated cTnT was also associated with cardiovascular mortality **(Figure 2)**.[19] Dierkes and colleagues studied 102 dialysis patients and found that cTnT elevations above 0.05 ng/ml were associated with a 7-fold increase in risk of cardiac death.[20] These findings have been

"Even in the absence of coronary artery disease, elevations in cTnT may represent clinically occult, minor myocardial injury exacerbated by uremia."

Figure 1. Kaplan-Meier survival curves for all-cause mortality based upon the different cTnT cut-offs in asymptomatic hemodialysis patients. Higher cTnT is associated with worsening prognosis. Reprinted with permission from Apple et al. Circulation 2002;106:2944.

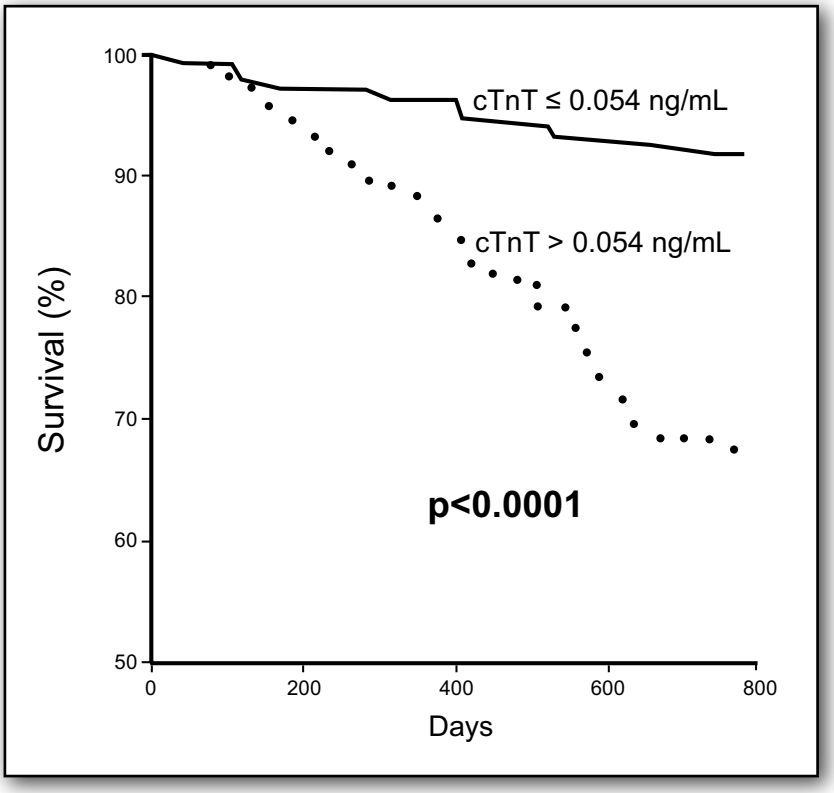


replicated by numerous other studies and suggest that cTnT may have a possible role for risk assessment in asymptomatic patients with CKD. [16,21-23]

Cardiac Troponin T in Patients with CKD and Possible ACS

Interpretation of cTnT levels in patients with CKD and suspected ACS in the emergency setting remains difficult. Because most studies have been performed in asymptomatic patients on dialysis, it may be difficult to extrapolate these results to a symptomatic ED population, across the entire spectrum of renal dysfunction. However, it would be reasonable to assume that an elevated cTnT in patients with CKD and suspected ACS portends a high risk for adverse cardiovascular events.

Figure 2. Kaplan-Meier survival curves for cardiovascular mortality in asymptomatic hemodialysis patients using cTnT cut-off of 0.054 ng/ml. Reprinted with permission from Hocher et al. J Am Soc Nephrol 2003; 14:2333.

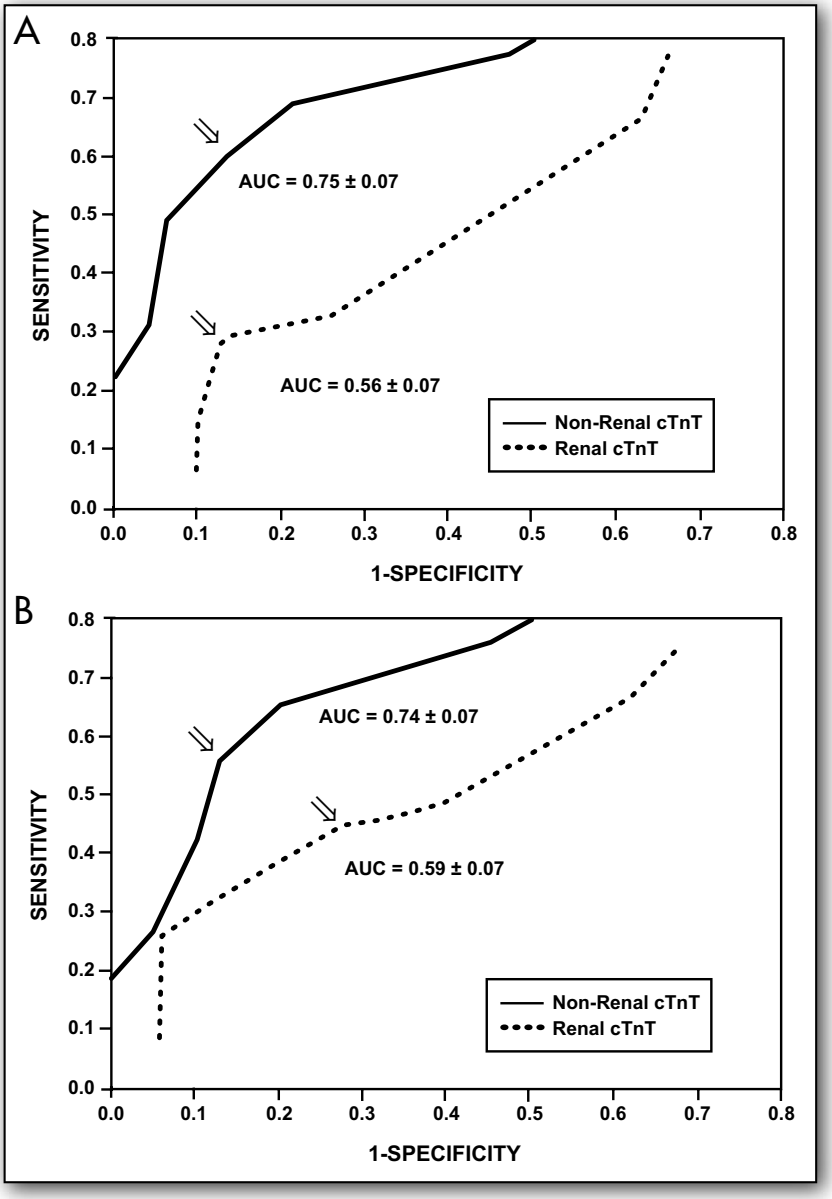


Aviles and colleagues studied over 7000 patients with suspected ACS, and found that elevated baseline cTnT measurements were strongly predictive of death and AMI.[24] They found that those patients with creatinine clearances less than 58 ml/minute and a serum cTnT level > 0.10 ng/ml had a 2.5 fold increase in the odds of 30-day death and AMI.[24] However, only odds ratios were reported and these have limited utility at the bedside. The specificity of an elevated baseline cTnT measurement in this high risk population has been questioned. Van Lente prospectively studied 51 patients with CKD matched by 102 patients with normal renal function. Using a composite endpoint of death, coronary surgery, recurrent ischemia, reinfarction, congestive heart failure, and positive cardiac catheterization with or without percutaneous coronary intervention, found a decrease in test performance of cTnT in patients with CKD compared to patients with normal renal function **(Figure 3)**.[25] The authors also found that raising the cut-off from 0.10 ng/mL to 0.50 ng/mL improved specificity from 63% to 87% while decreasing sensitivity from 43% to 29%.[25]

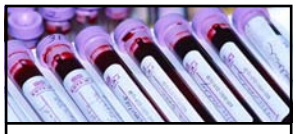
"However, it would be reasonable to assume that an elevated cTnT in patients with CKD and suspected ACS portends a high risk for adverse cardiovascular events."

Measuring changes in cTnT improves diagnostic specificity in the emergency setting. Acutely, serum cTnT levels as a result of AMI in CKD patients should have typical elevation and release kinetics, regardless of the patient's creatinine clearance.[9] A retrospective cohort study of 66 patients with serum creatinines greater than 2.0 mg/dl, suspected ACS, and an initial cTnT value of 0.10 ng/mL indicated that an increase in serum cTnT of as little as 0.10 ng/mL over a period of several hours increased the likelihood of adverse cardiac events at hospitalization, 30-days, and 6-months.[26] Adverse cardiac events in this study were defined as ACS, revascularization, cardiac dysrhythmias, all-cause death, or congestive heart failure.[26]

Figure 3. Receiver operating characteristic curves for cTnT in patients with and without CKD. An area under the curve (AUC) closer to 1 indicates better test performance. (A) represents in-hospital events and (B) represents 6-month events. Reprinted from Van Lente et al. J Am Coll Cardiol 1999;33:475,477 with permission from American College of Cardiology Foundation.



When comparing cTnT between ED visits, an increase in cTnT may be associated with acute myocardial injury secondary to atherosclerotic plaque rupture. However, the number of studies evaluating this phenomenon is limited. In asymptomatic dialysis patients, Ooi and colleagues reported a relative risk of 2.0 for all-cause mortality when cTnT rose greater than 60% from serum drawn at least a year apart.[27] Within the ED setting, one study evaluated 105 patients with CKD in patients having multiple ED visits for suspected ACS.[28] For individual patients, an ED visit with an in-hospital adverse cardiac event was associated with higher serum cTnT levels when compared to cTnT levels drawn during ED visits not associated with an adverse cardiac event.[28] Additional prospective studies are needed to clarify the significance of long term increases in cTnT within the emergency setting.



"Measuring changes in cTnT improves diagnostic specificity in the emergency setting."

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Cardiac Troponin I

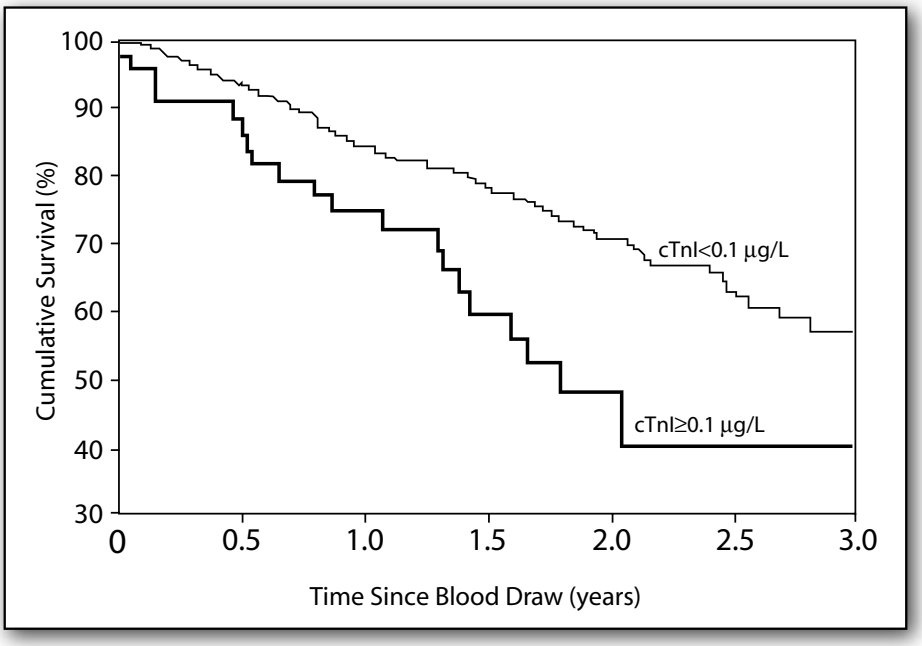
Cardiac Troponin I Elevations in Asymptomatic Patients

In asymptomatic dialysis patients, elevations above the diagnostic cutoff for AMI are only observed in 0.4% of the patients using cTnI compared to 20% for cTnT.[7] Instead, minor elevations are more prevalent, but their clinical significance is unclear.[29] Theoretically, these elevations are from the myocardial tissue, as cTnI is not found in the skeletal muscle of patients with CKD.[30] These elevations are likely to be clinically significant; for the general population with suspected ACS, minor elevations in cTnI below the AMI cutoff level have been associated with poor outcomes.[31] There is a lack of precision in assays for cTnI at the lower range of cTnI elevations and these minor elevations may represent artifacts caused by analytical interference.[32]

There have been discordant results, perhaps due to this assay imprecision, for multiple studies evaluating the ability of cTnI to predict mortality in asymptomatic patients with CKD. Khan and colleagues found no association with serum cTnI levels greater than the lower detection limit (0.03 ng/ml) and all-cause or cardiac mortality.[33] To the contrary, others have found that small elevations of cTnI appear to predict mortality **(Figure 4)**.[7] Boulier and colleagues studied 191 hemodialysis patients and found that elevations in cTnI above the 99th percentile value (0.04 ng/ml) were associated with a four-fold increased risk of all-cause mortality, after adjusting for patient demographics and history.[34]

Interpretation of the results of these studies is difficult, as multiple immunoassays for cTnI exist. Apple and colleagues compared two cTnI assays in asymptomatic dialysis patients and found elevations above the lower detection limit in 19% and 4% of the enrolled patients.[35,36] This disparity may be due to the improved ability of certain immunoassays to detect lower levels of cTnI.[37]

Figure 4. Kaplan-Meier survival curves for all-cause mortality in asymptomatic hemodialysis patients based upon the different 99th percentile cutoff for cTnI. Reprinted with permission from Apple et al. Circulation 2002;106:2944.



"Elevations above the diagnostic cutoff for AMI are only observed in 0.4% of the patients using cTnI compared to 20% for cTnT."

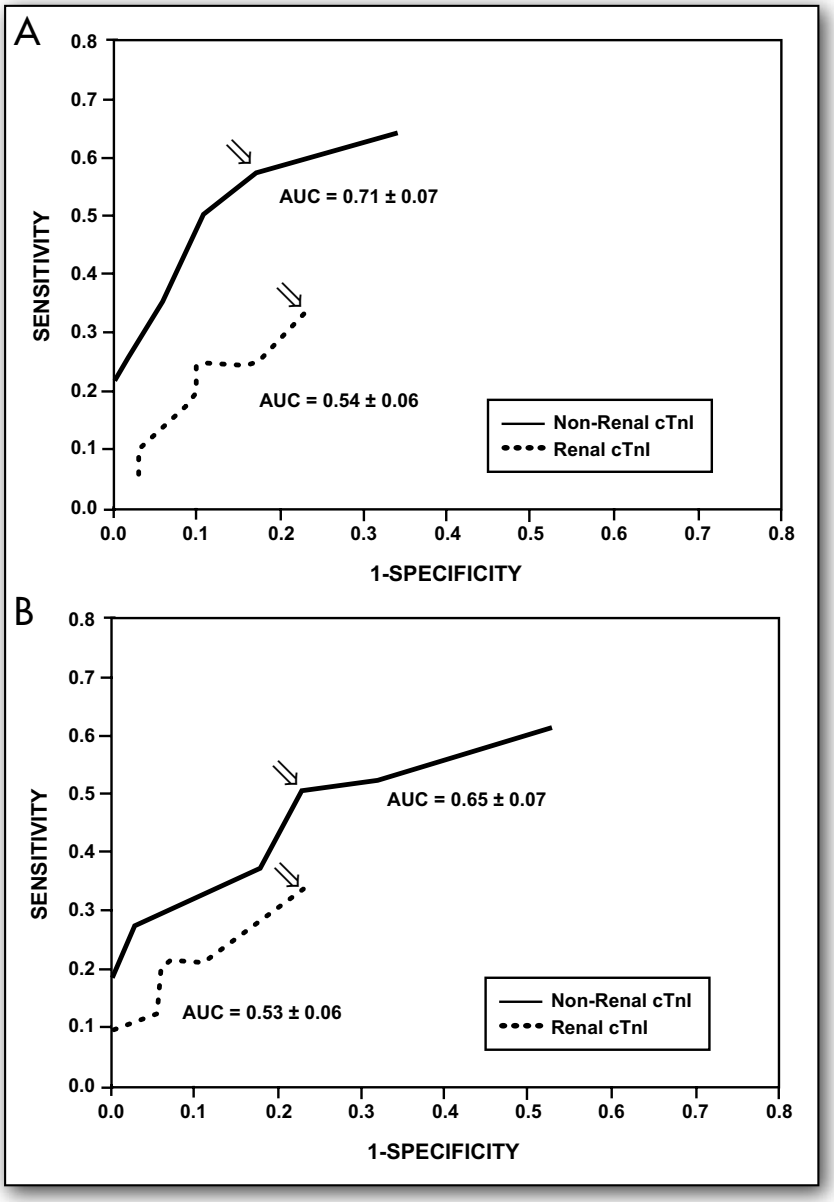
Troponin I in Symptomatic ED Patients

As noted previously, serum levels of cTnI above the diagnostic cutoff for AMI are rarely seen in patients with CKD not having symptoms. Martin and colleagues studied 56 patients admitted for ACS evaluation with CKD and acute renal failure. They found that elevated cTnI values were 100% specific and 94% sensitive for AMI.[38] McCullough and colleagues studied 808 patients and found that cTnI test performance was consistent throughout various degrees of renal impairment.[6] Van Lente, however, found that cTnI did not have the same diagnostic power for the diagnosis of adverse cardiac events in patients with chronic kidney disease compared to patients with normal renal function **(Figure 5)**.[25]

There are a number of limitations with cTnI immunoassays. Unlike cTnT, where there is a single immunoassay manufacturer, there are multiple cTnI immunoassays in existence, each possessing different diagnostic cutoffs for AMI. There is no standardization between cTnI immunoassays; each assay uses different reference materials to calibrate the assay and different antibodies are used to detect specific portions of the cTnI molecule. As a result, measurement of cTnI between different cTnI immunoassays for identical specimens may vary up to a hundred-fold.[39] Caution must be exercised by the clinician when extrapolating results from one cTnI immunoassay to another. Currently, efforts to standardize the cTnI immunoassay are in progress.[40]

"Caution must be exercised by the clinician when extrapolating results from one cTnI immunoassay to another."

Figure 5. Receiver operating characteristic curves for cTnI in patients with and without CKD. An area under the curve (AUC) closer to 1 indicates better test performance. (A) represents in-hospital events and (B) represents 6-month events. Reprinted from Van Lente et al. J Am Coll Cardiol 1999;33:475,477 with permission from American College of Cardiology Foundation.



Comparing Cardiac Troponin T versus Cardiac Troponin I

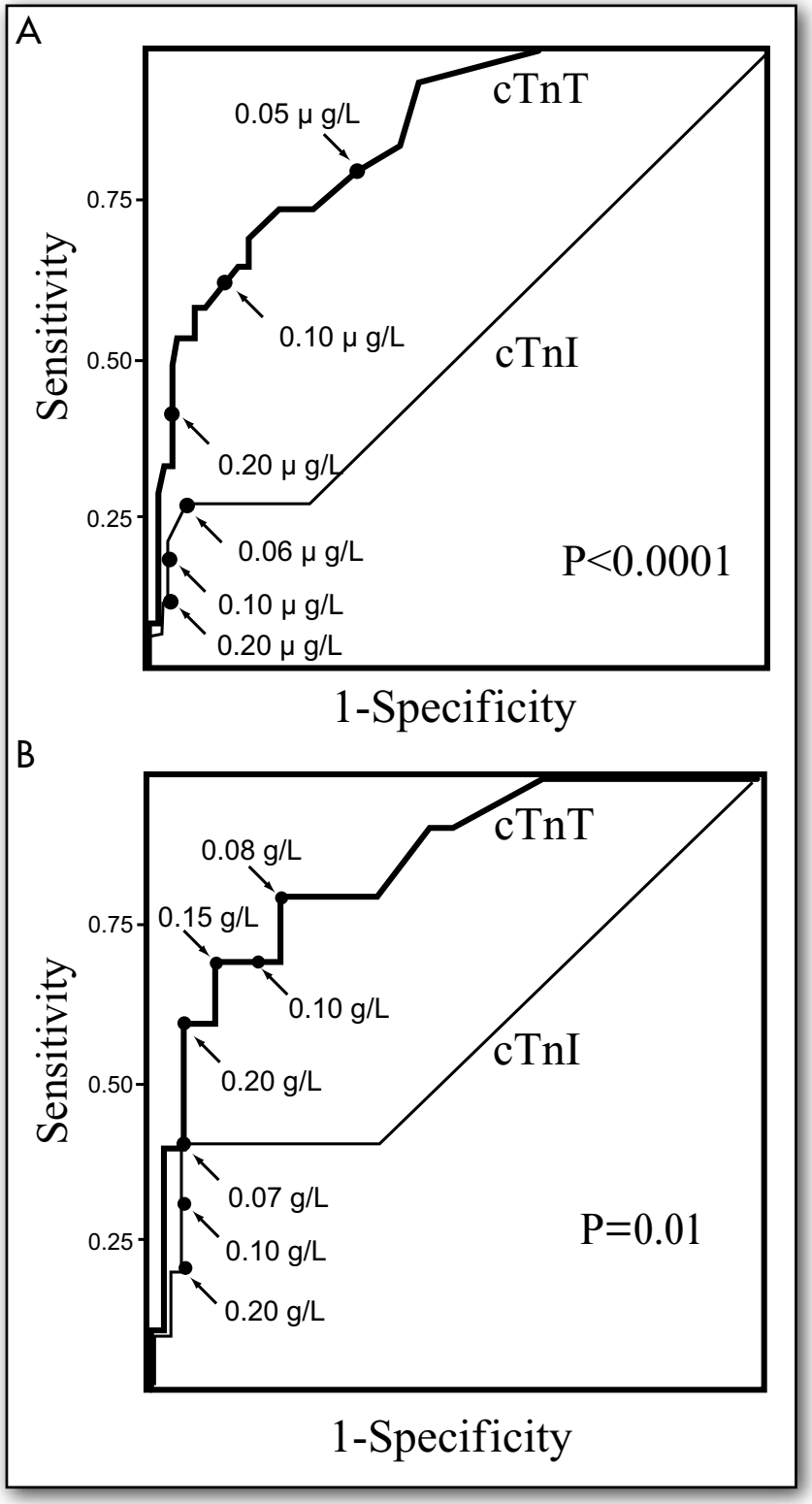
In the asymptomatic dialysis patient, cTnT elevations above the AMI cutoff are observed more often than cTnI elevations.[7] The mechanisms for this are speculative and require additional study. There is evidence to suggest that cTnT may be a superior marker to cTnI in predicting adverse outcomes in asymptomatic dialysis patients. Ishii and colleagues compared receiver-operating characteristic curves between these two markers, and found that cTnT had significantly greater area under the curve than cTnI for all-cause and cardiac mortality **(Figure 6)**.[22]

In the emergency setting, some authors have suggested that cTnI is a superior marker,[38] because elevations above the diagnostic cutoff for AMI are rarely observed in asymptomatic patients.[7] However, the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction has advocated using the 99th percentile value of the assay as the cutoff level for AMI.[9] A significantly higher proportion of asymptomatic dialysis patients will have cTnI elevations above this lower cutoff value.[7] As previously discussed, interpretation of such elevations is problematic because of imprecision at the lower values of cTnI.[32]

Cardiac Troponin T and I Directed ACS Therapy in CKD

In patients with normal renal function and non-ST segment elevation ACS, elevated cardiac troponin T and I levels have allowed clinicians to identify those who would most benefit from early invasive management,[31] low-molecular weight heparin,[41] and glycoprotein IIb-IIIa inhibitor therapy.[42] Sub-analyses of large trials have been performed suggesting

Figure 6. Receiver operating characteristic curves for cTnT and cTnI in asymptomatic dialysis patients. (A) represents all-cause mortality and (B) represents cardiac mortality. Reprinted from Ishii et al. Clin Chimica Acta. 2002;312:69-79, with permission from Elsevier.



benefit in using glycoprotein IIb-IIIa inhibitors[43] and low-molecular-weight heparin[44] for patients with CKD though these patients have not been specifically studied. These studies have typically excluded patients with moderate to severe CKD so the value of troponin measurement in such patients must be extrapolated. The benefits of such therapies in the presence of elevated cardiac troponin T and I for patients with severe CKD thus requires further evaluation.

Conclusions

Interpretation of cardiac troponin T and I in patients with CKD remains a difficult task in the emergency setting. Patients with CKD already have a higher pretest likelihood of ACS than the general population. In asymptomatic patients with CKD, elevations in cardiac troponin T and I have been associated with worsening all-cause and cardiovascular mortality. Though it may be difficult to extrapolate these results to a symptomatic ED population with CKD, those patients having elevated cardiac troponin T and I are likely at higher risk for poor outcomes and should be evaluated carefully. Observing a typical rise in serum cardiac troponin T and I levels should further increase the clinician's suspicion for ACS with myocardial necrosis. Using cardiac troponin T and I levels to guide therapy in this patient population requires further study.

Recommendations for Cardiac Troponin Interpretation in Patients with CKD in the ED

- Elevations in cTnT or cTnI likely represent myocardial injury, and should not be considered non-specific increases due to CKD.
- Patients with elevated cTnT or cTnI levels, no matter how minor, are at higher risk for all-cause and cardiovascular mortality.
- Though all myocardial damage and elevated troponin levels may not be secondary to coronary artery disease, patients with CKD are at higher risk for ACS. Any elevation in cardiac troponin levels should warrant further cardiac evaluation.
- Measuring a typical rise in cTnT and cTnI over a period of several hours improves diagnostic accuracy for acute myocardial injury in patients with CKD having chronic low level elevations in cTnT in the blood.

DISCLOSURES:

Dr. Han has no disclosures to report.

CME ACCREDITATION

The University of Cincinnati College of Medicine designates this educational activity for a maximum of one (1) Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits he/she actually spent in the educational activity. The University of Cincinnati College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Application has been made to the American College of Emergency Physicians for ACEP Category 1 credit.

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CME Post-Test Answer Form and Evaluation Questionnaire

CME Post Test

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question.

(Please circle answers below)

1) Using third-generation immunoassays, cardiac troponin T elevations above the AMI cutoff are seen in what percentage of asymptomatic dialysis patients:
a. Less than 1%
b. 5%
c. 20%
d. 50%
e. Greater than 70%

2) Cardiac troponin I elevations above the AMI cutoff are seen in what percentage of asymptomatic dialysis patients:
a. Less than 1%
b. 5%
c. 20%
d. 50%
e. Greater than 70%

3) In asymptomatic dialysis patients, elevated cardiac troponin I and T most likely reflect:
a. cross reaction skeletal muscle cardiac troponin
b. myocardial damage
c. inability of the kidney to remove whole cardiac troponin molecules
d. dialysis
e. none of the above

4) In the emergency setting, elevated cardiac troponin T has been associated with _____ in patients with chronic kidney disease and suspected ACS:
a. 30-day death
b. 30-day AMI
c. Both A and B
d. Neither A or B

5) Is the following statement true or false? In the emergency setting, improved specificity for an elevated cardiac troponin T and cardiac troponin I for the diagnosis of ACS may be improved by observing a typical rise and gradual fall in patients with CKD.
a) True
b) False

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