Diagnostic Utility of Creatine Kinase in Patients Presenting to the Emergency Department with Chest Pain

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ABSTRACT

Introduction: Creatine Kinase (CK) is routinely performed in some emergency departments (ED) for Non-ST-elevation myocardial infarction (NSTEMI) workup. Its diagnostic utility is not well understood. The objectives of this study were to assess the value of CK in NSTEMI diagnosis in the troponin era and the association between the highest CK/Troponin values and ejection fraction (EF) during NSTEMI follow-up.

Methods: A prospective cohort study conducted at the two EDs of The Ottawa Hospital from March 2014 to March 2016 enrolled adults (≥18 years) for whom troponin I (TnI) and CK were ordered for NSTEMI symptoms. We excluded those with ST-Elevation Myocardial Infarction (STEMI). The primary outcome was a NSTEMI within 30 days. We used descriptive statistics and report test diagnostic characteristics with 95% confidence intervals (CI). We compared the highest median CK/Troponin values using Wilcoxon test.

Results: Of the 2,153 patients enrolled, 99 (4.6%) suffered a NSTEMI. The sensitivity and specificity were: CK (cutoff >250U/L) 31.3% (95%CI 22.2, 40.5) and 91.1% (95%CI 89.9, 92.4) respectively; TnI (cutoff >0.045µg/L) 98.0% (95%CI 95.2, 100) and 86.2% (95%CI 84.7, 87.7) respectively. The median CK values were not significantly different between those with normal (n=267) and abnormal EF (n=55) on follow-up (107 U/L and 118 U/L respectively; p=0.31), whereas the median TnI values were significantly different (0.02 µg/L and 0.1 µg/L respectively; p<0.0001).

Conclusions: CK measurements do not provide any value in the ED work-up of NSTEMI and is not associated with EF on follow-up. Discontinuing routine CK measurements would improve resource utilization.

RÉSUMÉ

Introduction: Le dosage de la créatine kinase (CK) est couramment effectué dans certains services d'urgence pour le bilan de l'infarctus du myocarde sans sus-décalage du segment ST (NSTEMI). Son utilité diagnostique n'est pas bien comprise. Les objectifs de cette étude étaient d'évaluer la valeur de la CK dans le diagnostic de l'infarctus du myocarde sans sus-décalage du segment ST à l'ère de la troponine et l'association entre les valeurs les plus élevées de CK/Troponine et la fraction d'éjection (FE) pendant le suivi de l'infarctus du myocarde sans sus-décalage du segment ST.

Méthodes: Une étude de cohorte prospective menée dans les deux urgences de l'Hôpital d'Ottawa de mars 2014 à mars 2016 a recruté des adultes (≥18 ans) pour lesquels la troponine I (TnI) et la CK ont été prescrites pour des symptômes de NSTEMI. Nous avons exclu les personnes présentant un infarctus du myocarde avec surélévation du segment ST (STEMI). Le résultat primaire était un NSTEMI dans les 30 jours. Nous avons utilisé des statistiques descriptives et rapporté les caractéristiques diagnostiques des tests avec des intervalles de confiance (IC) à 95%. Nous avons comparé les valeurs médianes les plus élevées de CK/Troponine en utilisant le test de Wilcoxon.

Résultats: Sur les 2153 patients recrutés, 99 (4,6 %) ont souffert d'un NSTEMI. La sensibilité et la spécificité étaient : CK (seuil >250U/L) 31,3% (95%CI 22,2, 40,5) et 91,1% (95%CI 89,9, 92,4) respectivement ; TnI (seuil >0,045µg/L) 98,0% (95%CI 95,2, 100) et 86,2% (95%CI 84,7, 87,7) respectivement. Les valeurs médianes de CK n'étaient pas significativement différentes entre ceux qui avaient une FE normale (n=267) et anormale (n=55) lors du suivi (107 U/L et 118 U/L respectivement ; p=0,31), alors que les valeurs médianes de TnI étaient significativement différentes (0,02 µg/L et 0,1 µg/L respectivement ; p<0,0001).

Conclusions: La mesure de la CK n'est d'aucune utilité dans l'évaluation de la NSTEMI aux urgences et n'est pas associée à la FE lors du suivi. L'abandon de la mesure systématique de la CK améliorerait l'utilisation des ressources.

Keywords: Chest Pain, Creatine Kinase, Non-ST Elevated Myocardial Infarction

INTRODUCTION

Chest pain is the second most common emergency department (ED) presenting complaint with an estimated 600,000 patients presenting annually across Canada.1 The etiology of chest pain varies from musculoskeletal to cardiac causes such as acute coronary syndrome (ACS). ACS encompasses unstable angina (UA), Non-ST Elevated Myocardial Infarction (NSTEMI), and ST- Elevated Myocardial Infarction (STEMI).2 STEMI is diagnosed by electrocardiogram (ECG) and UA is diagnosed clinically in absence of elevated cardiac biomarkers. NSTEMI is defined as a rise and/or fall in cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit with clinical symptoms of ischemia such as chest pain or shortness of breath.2 As STEMI and UA constitute only 30% of patients with ACS, it is patients with a suspected NSTEMI that take up a significant proportion of ED resources.3 Currently, cTn is considered the standard biomarker for NSTEMI diagnosis.4 However, CK (creatine kinase) is also released into the blood stream as myocardial cells become infarcted and is one of the first cardiac biomarkers available in history to assess for NSTEMI.5 Hence, clinicians in several centers have been measuring serial CK levels in addition to cTn to rule-out NSTEMI. Additionally, in our center, patients hospitalized with NSTEMI have serial CK measurements performed and the peak CK levels documented on discharge.

The primary objective of this study was to assess the value of CK in NSTEMI diagnosis among ED patients with MI symptoms in the troponin era. The secondary objective was to evaluate the association between the highest CK or troponin I (TnI) values and ejection fraction (EF) on follow-up after NSTEMI hospitalization.

METHODS

We conducted a prospective cohort study at two EDs of The Ottawa Hospital (Civic and General Campuses) from March 2014 to March 2016 with the primary objective of developing a pathway for optimal use of the conventional troponin assay. The secondary objective of this prospective study is to assess the role of CK in NSTEMI diagnosis. We enrolled adults (age ≥ 18) for whom cTn and CK tests were ordered for NSTEMI symptoms within the past 24 hours. We excluded patients with STEMI. The study was approved by the Ottawa Health Science Network Research Ethics Board. Emergency physicians obtained consent and enrolled patients into the study. We collected patient demographics, medical history, cTn and CK values, disposition, final ED diagnosis, and EF on follow-up echocardiogram among patients hospitalized with an NSTEMI. The EF was reported as intervals, >65%, 55%-65%, 45%-54%, 30%-44%, and <30%. EF ≥45 was considered normal while EF <45 was classified as abnormal.6 Both ED academic centers use a conventional Siemens Vista TnI assay.

The primary outcome was an NSTEMI within 30 days of the index ED visit. The outcomes were assessed by an adjudication committee comprised of two physicians who were blinded to the study data. A third physician adjudicated the outcome if there were any disagreements.

Data analysis

We described our patient population using mean with standard deviation (SD), or median with interquartile range (IQR) for continuous variables based on the distribution, and frequency with proportion for categorical variables respectively. We used 250U/L, the upper reference range limit for CK and 0.045 μg/L, the 99th percentile for the normal population for TnI as the cut-point thresholds. We report sensitivity and specificity for the two biomarkers for NSTEMI diagnosis. We report 95% confidence intervals (CI) for the point estimates using either the large sample approximation or the exact binomial distribution where appropriate. We compared the median CK and TnI values between patients in the EF categories (normal vs abnormal) using the Wilcoxon test. We used SAS (version 9.4) software for data analysis. As the primary objective was to develop a troponin pathway, the sample size was guided by this primary objective.

RESULTS

During the study period, of the 2,319 patients enrolled, 25 (1.1%) patients did not have CK measured and we were unable to achieve 30-day follow-up among 141 (6.1%) patients. The remaining 2,153 patients were included in the final analysis. *Table 1* shows the baseline characteristics, medical history, ED management and outcomes among study patients. Ninety-nine or 4.6% (95% CI 3.8% to 5.6%) of patients suffered a NSTEMI during the 30-day follow up period. Ninety patients were diagnosed with NSTEMI in the ED and nine patients after ED disposition.

Table 1. Patient characteristics and outcomes.

Variables	No. (%) of patients N = 2,153
Age (yrs)	
Mean ± SD	62.9 (15.7)
Sex	
Male	1,175 (54.6)
Medical History	
Coronary artery disease	667 (31.0)
Congestive heart failure	180 (8.4)
Hypertension	1,026 (47.7)
Diabetes	391 (18.2)
Hyperlipidemia/Dyslipidemia	757 (35.2)
Transient ischemic attack and cerebrovascular accident	170 (7.9)
History of percutaneous coronary interventions and coronary artery bypass gr aft	548(25.5)
Family history of coronary artery disease	316 (14.7)
Previous cardiac arrest	7 (0.3)
Current smoker	237 (11.0)
ED Management & 30-Day Outcomes	
NSTEMI within 30-days	99 (4.6)
Hospitalized	270 (12.6)

NSTEMI: Non-ST Elevation Myocardial Infarction

There were 213 patients (9.9%) who had CK levels >250U/L and 31 of them were diagnosed with NSTEMI (Appendix 1). Conversely, 68 patients diagnosed with NSTEMI had a normal CK level. **Table 2** shows the diagnostic characteristics of CK and TnI. The sensitivity and specificity of CK for NSTEMI diagnosis was 31.3% (95%CI 22.2% to 40.5%) and 91.1% (95%CI 89.9% to 92.4%) respectively. Of the 99 patients with NSTEMI, TnI was elevated TnI among 97 patients. The sensitivity and specificity of TnI was 97.9% (95%CI 95.2% to 100%) and 86.2% (95%CI 84.7% to 87.7%). The paired agreement for CK and TnI for NSTEMI diagnosis was 0.07 (95% CI 0.03 to 0.12).

Table 2. Diagnostic characteristics of CK and TnI

Diagnostic Characteristics of CK and TnI	Sensitivity (95% CI)	Specificity (95% CI)
CK	31.3% (95% CI 22.2%-40.5%)	91.1% (95% CI 89.9%-92.4%)
TnI	97.9% (95% CI 95.2%-100%)	86.2% (95% CI 84.7%-87.7%)

CK: Creatine Kinase; CI: Confidence Interval; TnI: Troponin I

324 patients had an echocardiography performed within a mean of 22(±25.6) days after hospitalization. **Table 3** shows the relationship between EF and highest median CK/TnI values. Patients with normal EF had a median CK value of 107 U/L (IQR 71 to 166) and those with abnormal EF had a median value of 118 U/L (IQR 72 to 195; p=0.31). For TnI, patients with normal EF had a median TnI value of 0.02 μg/L (IQR 0.02 to 0.13) and those with abnormal EF had a median value of 0.1 μg/L (IQR 0.03 to 0.65; p<0.0001).

Table 3. EF versus highest median CK/TnI

Post-Admission EF Versus Highest Median CK/ TnI	Highest Median CK (IQR) (U/L)	Highest Median TnI (IQR) (μg/L)
Normal EF (≥45)	107 (71-166)	0.02 (0.02-0.13)
Abnormal EF (<45)	118 (72-195)	0.1 (0.03-0.65)

CK: Creatine Kinase; EF: Ejection Fraction; IQR: Interquartile Range; TnI: Troponin I

Limitations

We compared CK to a conventional TnI assay. However, if compared to high-sensitive troponin assays such as Abbott ARCHITECT, Beckman ACCESS assays, the results may be more significant. Our study enrolled a random sample of patients and hence, selection bias is plausible.

DISCUSSION

While most centers have abandoned the routine CK measurements for evaluation of patients with NSTEMI symptoms, there are still a significant number of healthcare facilities that continue the practice of CK measurements in addition to cTn for chest pain.[7,8] However, our study shows evidence that CK is not useful in NSTEMI diagnosis when another cardiac enzyme assay such as TnI provides both a high sensitivity and specificity.

While the specificity of CK and TnI were similar, TnI has a markedly higher sensitivity. Due to TnI's high sensitivity and specificity compared to CK, TnI should be the only measurement used in patients with a suspected NSTEMI. Among 2 patients that were diagnosed with NSTEMI with TnI values below the cut-off, CK was also within normal limits and hence, had no diagnostic value.

Our study also shows that there is no statistically significant

difference of the median CK value between normal and abnormal EF. Although EF may seem associated with CK, the CK median values do not go above the cutoff (>250U/L) meaning these values would not be considered to be abnormally elevated. Furthermore, as the TnI values show an association for future low EF, there is no added benefit from CK measurements, and it is a waste of healthcare resources.

CONCLUSION

In conclusion, our study shows that CK adds no diagnostic value in the workup of a NSTEMI among patients with negative TnI and hence should be discontinued. Our study shows no apparent association between highest median CK values and EF on follow-up echocardiogram. In contrast, TnI shows better association with lower EF. Discontinuing CK measurements will decrease costs and improve resource utilization.

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