***The impact of co-morbidities on peak troponin levels and mortality in acute myocardial infarction: A population based, nationwide study***

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***Word count:*** 3691

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**Key questions**

**What is already known on this topic?**

* Previous studies have suggested that peak cardiac troponin levels are higher in patients with acute myocardial infarction(AMI) and chronic kidney disease(CKD) compared to those without CKD. However, the magnitude of troponin increase has not been evaluated.
* Patients with prior coronary artery disease(CAD), congestive heart failure(CHF) or chronic obstructive pulmonary disease(COPD) presenting with AMI reportedly have lower peak troponin levels compared to patients without the respective co-morbidities; however, these studies had not adjusted for age, sex and other relevant co-morbidities.

**What this study adds?**

* In this study, we show for the first time the magnitude and directionality of troponin change in common co-morbidities and the impact of the severity of co-morbidities (e.g., severity of CKD) on peak troponin levels in 330,000 patients with AMI.
* In contrast to widely held assumptions, in AMI, comorbid illness is a more important predictor of mortality than peak troponin levels.

**How might this impact on clinical practice?**

* Clinicians should refrain from being reassured by lower peak troponin levels in patients with NSTEMI and concomitant HF, COPD, or prior CAD. Conversely, a higher peak troponin level may be less informative in the setting of CKD where up to 40% of the elevation may relate to the presence of CKD alone.

**ABSTRACT**

**Objectives:** To characterize peak cardiac troponin levels, in patients presenting with acute myocardial infarction (AMI), according to their comorbid condition and determine the influence of peak troponin (cTn) levels on mortality.

**Methods:** We included patients with the first admission for AMI in the United Kingdom. We used linear regression to estimate the association between eight common co-morbidities {diabetes mellitus(DM), previous angina, peripheral arterial disease(PAD), previous myocardial infarction(MI), chronic kidney disease(CKD), cerebrovascular disease(CVD), chronic heart failure(CHF), and chronic obstructive pulmonary disease(COPD)} and peak cTn. Peak cTn levels were adjusted for age, sex, smoking status and co-morbidities. Logistic regression and restricted cubic spline models were employed to investigate the association between peak cTn and 180-day mortality for each co-morbidity.

**Results**: 330,367 patients with AMI were identified. Adjusted peak cTn levels were significantly higher in patients with CKD[adjusted % difference in peak cTnT for CKD=42%, 95%CI 13.1 to 78.4] and significantly lower for patients with COPD, previous angina, previous MI and CHF when compared to patients without the respective co-morbidities (reference group) [cTnI;COPD=-21.7%,95%CI -29.1 to -13.4;previous angina=-24.2%, 95%CI -29.6 to -8.3;previous MI=-13.5%, 95%CI -20.6 to -5.9;CHF=-28% 95%CI -37.2 to -17.6]. Risk of 180-day mortality in most of the co-morbidities did not change substantially after adjusting for peak cTn. In general, cTnI had a stronger association with mortality than cTnT.

**Conclusions:** In this nationwide analyses of patients presenting with acute myocardial infarction, co-morbidities substantially influenced systemic concentrations of peak cTn. Comorbid illness is a significant predictor of mortality regardless of peak cTn levels and should be taken into consideration while interpreting cTn both as a diagnostic and prognostic biomarker.

**Funding:** This work was funded by an MRC Population Health Scientist Fellowship held by JKQ [G0902135]

**Keywords:** troponin I, troponin T, hsTnT, Acute Myocardial Infarction, Non -ST elevation MI, STEMI, mortality, co-morbidities

**INTRODUCTION**

Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) isoforms, are regulatory proteins within the myocardium that are released into the circulation following myocardial injury, regardless of the underlying etiology.2,3 The use of cTnT and cTnI as protein markers of acute myocardial infarction (AMI) was first recommended two decades ago and is now the cornerstone for establishing a diagnosis of AMI.4,5 Following AMI, systemic blood concentrations of cardiac troponin (cTn) rise and their peak levels strongly correlate with the infarct size of the myocardium and thus cTn has excellent prognostic value; with higher levels associated with a worse prognosis. 6

Patients presenting with an AMI, particularly non-ST elevation myocardial infarction (NSTEMI), frequently have multiple co-morbidities which may affect systemic concentrations of both cTnT and cTnI. 7, 8 Previous studies have suggested that cTn levels are higher in patients with AMI and chronic kidney disease (CKD) compared to those without, though the magnitude of cTn increase and the impact of severity of CKD on peak cTn levels have not been systematically evaluated. 9–12 Conversely, patients with prior coronary artery disease (CAD), congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD) presenting with AMI reportedly have lower peak cTn levels compared to patients without the respective co-morbidities, albeit these studies did not adjust for age, smoking status, medications, and other relevant co-morbidities; moreover, the relevance of lower peak troponin levels in these patients have not been studied.13–16 Indeed, the influence of common co-morbidities on peak cTn levels in patients presenting with AMI has not been systematically evaluated and the quantum of change in cTn caused by such co-morbidities needs further investigation. This has important clinical implications, particularly in the context of NSTEMI, the most common type of AMI, where implementation of guideline-recommended therapies in real world rely heavily on the degree of cTn elevation,17 and in older patients with multiple co-morbidities where the interpretation of cTn could be marred due to a complex interplay of age, sex, co-morbidities, type of cTn assay and AMI [i.e. STEMI versus NSTEMI]. 18–25

Previous studies have demonstrated a linear and graded relationship of peak cTn and mortality in patients presenting with AMI.26 However, this linear relationship between peak cTn and mortality could vary based on the baseline co-morbidities and the type of cTn assay (cTnT vs cTnI). To characterize peak cTn levels in common co-morbid conditions and determine the impact of these varying cTn levels on mortality in AMI, we carried out this large population based study across the United Kingdom.

**METHODS**

***Study Population***

We included all patients with hospitalisation for acute coronary syndrome (ACS) between January 2003 and June 2013 from the Myocardial Infarction National Audit (MINAP), which is contributed to by all 230 National Health Service (NHS) trusts in England and Wales. MINAP was linked to the Office of National Statistics (ONS), providing mortality data at 180 days post discharge. Records were excluded if they did not have a measurement for either cTnI or cTnT, were missing a patient unique identifier, or ONS mortality data. Patients with prior coronary artery bypass graft surgery (CABG) were excluded from the analysis, as coronary bypass grafts can significantly influence peak levels of cTn and infarct size. 16, 17 The details of data collection in MINAP and completeness of the data are outlined in the Supplementary Appendix.

***Identification of co-morbidities***

Co-morbid conditions were pre-defined by MINAP (Supplementary Appendix Table S1). According to common practice when analysing MINAP data, missing clinical variables were assumed to be absent.

***Troponin values***

The peak cTn levels in MINAP where entered by the physician as part of the audit. We primarily used cTnT and cTnI for this analysis. The European Society of Cardiology Study Group on Biomarkers in Cardiology recommended the routine use of High sensitivity troponin as a diagnostic biomarker for AMI in 2012; hence in the UK, high sensitivity troponin was seldom measured prior to 2012. 30 Despite the paucity of data, we were able to perform a subgroup analysis of patients with high sensitivity troponin T (hsTnT) (grouping together STEMI and NSTEMI) to investigate the trends in peak hsTnT stratified by co-morbidities.

***Statistical analysis***

For the primary analysis (difference in peak cTn), we log transformed peak cTn levels and used linear regression to compare peak cTn values between patients with and without specific co-morbidities of interest, stratified by the type of MI (included STEMI and NSTEMI). We exponentiated linear regression coefficients to obtain a ratio of geometric means, adjusting for age, sex, smoking status, and co-morbidities. We performed additional analysis stratified by severity of CKD, to ascertain the impact of the degree of CKD on cTn elevation.

To evaluate the relationship between comorbidity, peak cTn and mortality, we restricted the analysis to patients with NSTEMI, as peak cTn levels have greater therapeutic implications in the management of this group as compared with a STEMI where primary percutaneous coronary intervention (PCI) is the standard of care regardless of cTn value. Three sets of analysis were performed for the outcome of 180-day all-cause mortality; 1) To investigate whether any differences in peak cTn associated with a specific comorbidity had an impact on the risk of death, we used logistic regression models to investigate the risk of death associated with the specific comorbidity – before and after adjustment for peak cTn level. We used likelihood ratio tests to test for statistical evidence (p<0.05) that peak cTn modified the association between each comorbidity and mortality at 180 days. 2) Peak cTn was further categorized into quartiles for each specific co-morbidity (i.e. 180-day mortality in CKD patients with <25th percentile of troponin elevation among all CKD patients etc.) and adjusted mortality was estimated for each category. 3) We used restricted cubic splines with three knots {0.8, 3.82 and 22.57 for cTnI and 0.09, 0.38 and 2.15 for cTnT for the overall analysis in NSTEMI (Supplementary Appendix Figure S1) to evaluate the non-linear association between peak cTn level and risk of death at 180 days for each of the co-morbidities in our study. The knots differed when spline analysis was performed for each co-morbidity (Supplementary Appendix Table S2-S3). Troponin was used as a continuous variable for the spline analyses.

Data for 180-day all-cause mortality were presented as adjusted OR [adjusting for age, sex, smoking status, co-morbidities: peripheral arterial disease (PAD), cerebrovascular disease (CVD), COPD, CKD, CHF, hypertension (HTN), previous myocardial infarction (MI), diabetes mellitus (DM), previous angina; location of infarct (anterior vs non- anterior), medications (antiplatelet therapy, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta-blockers and statins) and revascularization and maximally adjusted OR (adjusting for peak cTn for each co-morbidity). We did not perform multiple imputation as previous studies have shown that imputation analyses on the MINAP registry did not significantly alter effect sizes, suggesting that missingness in MINAP is at random. Additionally, the level of missingness of data in MINAP did not affect the mortality ratios.

**Results**

657,376 patients with ACS were identified in MINAP database between January 2003 and June 2013. The baseline characteristics of patients with missing data on peak troponin data were largely similar to those with the available data (Supplementary appendix Table S4). Among the patients admitted, 32% (128,960) of the patients presented with STEMI, 49.9% (201,407) with non-STEMI and 18.1% (72,664) had unstable angina (UA) (Figure 1). As expected, patients with NSTEMI were older and had a higher comorbidity burden than patients with STEMI (Table 1).

***Peak troponin levels stratified by co-morbidities following NSTEMI***

In patients with NSTEMI, those with COPD (-21.7%, 95%CI -29.1 to -13.4%), previous angina (-24.2%, 95%CI -29.6 to -18.3 %), previous MI (-13.5%, 95% CI -20.6 to -5.9%), CVD (-16%, 95% CI -24.2 to -7.0%) and CHF (-28.0%, 95%CI -37.2 to -17.6%) had significantly lower adjusted difference in peak cTnI, (Figure 2A & Table 2). There were no significant differences in adjusted peak cTnI levels in patients with DM, PAD and CKD compared to those without the respective co-morbidity. Similarly, in patients whose cTnT was measured, a similar association was seen for COPD (-14.3%, CI -18.7 to -9.7%), and CHF (-9.1%, 95%CI -30.4 to -18.7%), although patients with CKD had a substantially higher adjusted difference in peak cTnT (+42%, CI +13.1 to +78.4%) (Table 2) (Figure 2A)

***Peak troponin levels stratified by co-morbidities following STEMI***

In patients presenting with STEMI, after adjustment for age, sex, smoking status, MI location (anterior or non-anterior), and other co-morbidities, a similar pattern was observed. Peak cTnI was lower for patients with previous angina (-20.4%, 95% CI -29.7 to - 17.1%), previous MI (-20.4 % 95%CI -27.2 to -13.0 %), and CHF (-26.7% 95%CI -40.0 to -10.6%) compared to patients with STEMI without the respective co-morbidity (Figure 2B & Table 3). In the case of cTnT, peak levels were found to be lower for previous angina (-13.2 % 95% CI -21.5 to -4.1 %), previous MI (-18.6% 95% CI -26.9 to -8.0 %), CHF (-24.8% 95% CI-40.9 to -4.2%) and with COPD (-14.7% 95CI -23.8 to -4.6 %). There were no significant differences in adjusted peak cTnI and cTnT levels in patients with DM, PAD and CVD (Table 3). There was a trend towards lower peak cTnI in patients with COPD and higher cTnT in patients with CKD but this was not statistically significant, most likely due to small sample sizes within these groups (Figure 2B & Table 3)

***Peak hsTnT following AMI***

The trends in adjusted peak hsTnT values in patients with COPD, CKD, CHF, previous MI and previous angina were quite similar to the groups with cTnT (Figure 3). However, the trends in peak values did not reach statistical significance in certain groups (CKD and CHF), probably due to small sample size (Table 4).

***Risk of 180-day all-cause mortality with each comorbidity before and after adjustment of peak troponin***

In patients with NSTEMI, almost all co-morbidities were associated with increased risk of death at 180-days after adjustment for age, sex, smoking status and other co-morbidities. After adjusting for peak cTn level, odds ratios (OR) for risk of death for each comorbidity at 180-days did not change substantially for all the co-morbidities (Table 2). In patients with STEMI, a similar pattern was observed (Table 3). Additional analysis performed by categorizing peak cTn into quartiles for each co-morbidity did not reveal a clear relationship between increasing quartiles of peak cTn and mortality in most of the co-morbidities (in NSTEMI and STEMI), with the exception of DM (Supplementary Appendix Tables S5-S8). The joint association between increased cTn and comorbidity on the risk of 180-day mortality following NSTEMI and STEMI are presented in (Supplementary Appendix Table S9-S10).

***Relationship between peak troponin and mortality stratified by co-morbidities in patients with NSTEMI; results of spline analysis***

In patients with NSTEMI, the results of spline regression indicated that mortality increased with rising peak cTnI up to at least 50ng/mL (Supplementary Appendix Figure S1). However, there appeared to be a ceiling effect on the association between peak cTnT and mortality following NSTEMI after around 1.5ng/mL, after which rising peak cTn was not associated with increased mortality (Supplementary Appendix Figure S2). Splitting this analysis by co-morbidity produced associations with broadly similar shapes. There was a clear positive association between peak cTnI and 180 day-mortality for most of the co-morbidities (Figure 4). No such relationship was observed for cTnT (Figure 5).

***Subgroup analysis in CKD***

We included 277,071 patients with serum creatinine values for this analysis (Supplementary Appendix Figure S3). GFR was calculated using CKD-epi cohort equation. In patients with AMI (both STEMI and NSTEMI), adjusted percentage difference in peak troponin was significantly higher in CKD stages 3b, 4 and 5{Stage 3b: 8.6% 95% CI: 0.8- 16.9%; Stage 4: 27.2% 95% CI: 15.4-40.2%; Stage 5: 30.8% 95% CI: 9-53.2%} when compared to patients with CKD stage 1. The adjusted odds ratio for mortality increased with increasing severity of CKD (Figure 6A and 6B). There was no evidence of interaction between CKD severity and peak troponin (p >0.05) for the outcome of 180-day mortality

**Discussion:**

This nationwide study of patients presenting with AMI, revealed that co-morbidities substantially influenced systemic concentrations of cTn; however the presence of comorbidity alone, irrespective of peak cTn, was the major determinant of mortality.

***Major findings***

The major findings of our study could be summarized as follows – 1) In patients presenting with AMI and COPD, previous angina, previous MI or CHF, peak cTn levels were significantly lower compared to patients without the respective co-morbidity, with similar trends regardless of cTn assays (i.e. peak cTnT and cTnI) or AMI presentation (STEMI and NSTEMI). Results for hsTnT, although limited by the small sample size, revealed similar trends. 2) Among the comorbidities analysed, the quantum of change in cTnT was highest for patients with CKD (42% higher) as compared to those without CKD. 3) There was a significant impact of CKD severity (GFR<45ml/min/1.73m2) on the degree of cTn elevation. 4) All co-morbidities were associated with an increased risk of mortality in AMI, which was not altered after adjusting for peak cTn with the exception of DM. 5) CTnI had a stronger association with mortality than cTnT for most of the co-morbidities analysed.

**i) Chronic kidney disease**

The interpretation of cTn in the setting of CKD can be challenging, as patients with CKD can have elevated cTn levels even in the absence of ischemia.9, 17 The AMI cut-off based on a healthy general population has been shown to be significantly lower than the receiver operating curve optimal cut-off for patients with CKD.36 Twerenbold et al showed that while the European Society of Cardiology (ESC) 0/1-hour algorithm (using hsTnT and hsTnI) had high sensitivity in patients with CKD, the specificity of rule-in and the overall efficacy of the ESC algorithm was substantially reduced.11

Multiple mechanisms have been postulated for the elevation of cTn and contrary to common belief, decreased renal clearance seems to be an implausible explanation, as cardiac troponins are high molecular weight compounds (37kDa), unlikely to be cleared by the kidneys.37,38 Some of the other possible explanations are the presence of, increased left ventricular (LV) mass, left ventricular systolic dysfunction or subclinical CAD, resulting in increased membrane permeability and cTn leaks. 39,40 To our knowledge, our study is the first to report the quantum of cTn elevation in patients with CKD, impact of severity of CKD on cTn elevation and its prognostic relevance after accounting for important confounders including HF and type of MI.

**ii) Chronic Heart Failure**

Our analysis demonstrated that while patients with HF had substantially lower adjusted peak cTn levels than those without HF, the presence of HF was associated with a higher mortality. This was corroborated with the spline analysis, which revealed a ceiling effect in prognostic value for both cTnT and cTnI in patients with CHF (Figures 4C and 5C). The lower peak cTn and high mortality in this group could be due to a multitude of reasons including the possibility that patients ischemic cardiomyopathy may have reduced viable myocardium.41,42 Poor myocardial reserve in this group of patients might therefore help explain high mortality with smaller infarct size based on lower peak cTn. Endogenous protective mechanisms following ischemia/reperfusion injury could be attenuated in patients with ventricular remodelling or clinical HF.43 Morphological and biological alterations in HF can impact the signal transduction cascade of pre and post–conditioning cardio protection, resulting in increased mortality despite smaller initial infarct size. 35 Finally in ischemic cardiomyopathy, even minor infarcts could result in ventricular premature contractions.44

**iii) COPD, Previous MI and previous angina**

In patients with COPD and heightened cardiovascular risk, plasma cTnI concentrations have been shown to be a major predictor of future cardiovascular events and cardiovascular death;45 however, the diagnostic and prognostic accuracy of cTn in COPD patients with AMI have not been established. We observed lower peak cTn levels in patients with COPD, angina and previous MI after adjusting for important confounders including smoking, age, CHF, HTN, DM, area of infarct and renal impairment.The lower peak cTn level among these patients may have arisen due to myriad reasons. Patients with prior CAD are more likely have been prescribed drugs for secondary prevention such as antiplatelet therapy, statins and angiotensin converting enzyme inhibitors which could have influenced the infarct size. The phenomenon of ischemic pre-conditioning may be an innate protective physiological mechanism for lower cTn peak among COPD, previous MI and angina co-morbidities.46 47 The chronic hypoxic state in patients with COPD may pre-condition the myocardium to become more resistant to future infarcts.48,49 This may explain why COPD patients do not have an equivalent high peak cTn level as compared to patients without COPD. Ischemic pre-conditioning still remains a topic for considerable future research on its role in MI amongst COPD patients and its potential use in clinical practice.

***Clinical implications***

The results of this study has important clinical implications.It is well established that in patients with NSTEMI, implementation of guideline-recommended treatment in real world depends on the extent of cTn elevation i.e., patients with intermediate to major elevations are more likely to receive guideline directed therapy as compared to those with minor cTn elevations.17 In contrast to generally held assumptions, our findings suggest that, AMI patients with specific co-morbidities and lower peak cTn levels may still have a poor prognosis. Clinicians should refrain from being reassured by lower peak cTn levels in patients with AMI (particularly NSTEMI) and concomitant HF, COPD, angina, or a previous MI. Conversely, a higher peak cTnT level may be less informative in the setting of CKD (Stage 3b and higher) where up to 40% of the elevation in cTnT may relate to the presence of CKD alone (or due to increased LV mass, subclinical CAD or subclinical LV systolic dysfunction), irrespective of AMI type or other relevant confounders.

***Limitations***

The diagnosis of acute coronary syndrome in the MINAP registry was made by the physician treating the patient using standard investigations, including clinical history, electrocardiogram and troponin. In a study performed by Herrett et al, only 50% of myocardial infarction’s reported in hospital episode statistics (nationwide in-hospital records in the UK) and Clinical Practice Research Registry- CPRD (Primary care records in the UK) were found to be included in the MINAP registry. Moreover, patients with AMI recorded in CPRD had about half the hazard of mortality (at 30 days) of patients with AMI recorded in the MINAP, indicating differences in case ascertainment between the registry, hospital admissions and primary care databases. We were not able to determine the impact of different combinations of comorbidities (multi-morbidity) on peak cTn using the data available, and further studies on comorbidity-to-comorbidity interactions are needed. The MINAP database did not have all the information we would have ideally included in the analysis such as socioeconomic status, results of structural imaging such as echocardiogram and timing of revascularisation. We were not able to conduct a complete analysis with the hsTnT assay alone due to small sample size (n=10,064). However, our analysis of hsTnT revealed that the magnitude and directionality of change in important co-morbidities such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) were similar to those of less sensitive cTnT (e.g., 40 to 50 % increase in adjusted peak values of hsTnT and regular cTnT in CKD, ~ 25% decrease in both hsTnT and cTnT in COPD, ~10-15% decrease in CHF). This is because the ratio of peak troponin for each comorbidity to those without the comorbidity is likely to be the same for both highly sensitive and less sensitive troponins.

**Conclusion**

In this large nationwide analyses of patients presenting with AMI in the UK suggests that co-morbidities significantly affect peak cTn. Co-morbidities should be taken in to consideration while interpreting cTn in the setting of AMI, as the prognostication varies based on patient’s pre-existing co-morbid illness.

**Acknowledgements**

The extract from the MINAP database was provided through the MINAP Academic Group following peer review of our research proposal. We acknowledge all the hospitals in England and Wales for their contribution of data to MINAP. There are no competing interests and the authors have nothing to declare.

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