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Improving the diagnostic performance of troponin assays for acute myocardial infarction in renal impairment

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ABSTRACT

Background Serum troponin measurement forms a cornerstone of acute myocardial infarction (AMI) diagnosis. A major challenge is interpretation of an elevated first troponin in patients with impaired renal function. We aimed to (1) evaluate the relationship between estimated glomerular filtration rate (eGFR) and first troponin, (2) characterise the performance of different troponin assays for diagnosing AMI and (3) derive eGFR-specific thresholds for potential clinical use.

Methods We analysed the distribution of troponin values stratified by eGFR and AMI. Diagnostic performance was analysed using the C-statistic. Test detection rate, false positive rate and positive predictive value were calculated for different cut-offs.

Results We included 221 175 patients between 2010 and 2017 from four acute tertiary care hospitals in London, UK, with a median age of 65 years (IQR 49–79). eGFR was<60 mL/min/1.73 m^2 in 20.6% of patients and 6.4% of patients had a diagnosis of AMI. In patients without AMI, we observed an inverse log-linear relationship between eGFR and troponin. Diagnostic performance for AMI was best in patients with eGFR>90 (C-statistic 0.93) and worst in eGFR<15 (C-statistic 0.81). For high-sensitive troponin T, using the conventional cut-off of 14 ng/L, false positive rates ranged from 68–93% for eGFRs between 15 and 60 mL/min/1.73 m^2. Restricting the false positive rate to 15% yields eGFR specific cut-offs of 73, 112 and 184 ng/L, with detection rates of 73%, 70% and 68% in patients with an eGFR of 45–60, 30–45 or 15–30 mL/min/1.73 m^2.

Conclusions The diagnostic performance of an unadjusted troponin cut-off for AMI falls with worsening renal function. We propose consideration of eGFR specific cut-offs to support more effective triage and early management of suspected AMI in patients with renal impairment.

Trial registration number NCT03507309.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Serum troponin measurement forms a cornerstone of acute myocardial infarction (AMI) diagnosis.
⇒ A major challenge is interpretation of an elevated troponin among individuals with impaired renal function as values can often be evaluated in patients without AMI.
⇒ Current guidelines recommend the use of serial troponin measurements, but there is a paucity of data on the interpretation of single or first troponin measurements in patients with chronic kidney disease.

WHAT THIS STUDY ADDS

⇒ There was an inverse log-linear relation between estimated glomerular filtration rate (eGFR) and troponin in a real-world cohort of 222 175 patients.
⇒ Higher troponin cut-offs were required to maintain the same false positive rate for AMI diagnosis in patients with decreased eGFR.
⇒ The application of adjusted cut-offs to initial troponin values may help clinicians on the front line with *early* clinical decision-making including triage, keeping patients in acute care settings, need for additional or repeat investigations and initiation of treatment before serial troponin levels are available.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The impact of renal function on troponin performance must be considered when using the test to diagnose AMI.
⇒ The proposed eGFR specific cut-offs could support more appropriate early triage of patients with suspected AMI and renal impairment before serial measurements are available.

INTRODUCTION

Patients with chronic kidney disease (CKD) are at increased risk of cardiovascular and coronary disease.[1 2] Troponin is used as a biomarker that forms part of the universal definition of acute myocardial infarction (AMI).[3] Although AMI risk increases with worsening renal function, making a diagnosis of AMI is complicated in such patients as renal clearance of troponin is impaired causing chronically elevated blood levels of troponin introducing clinical uncertainty.[4]

A previous systematic review of troponin levels in patients with CKD and suspected AMI used older troponin assays, small sample sizes and heterogeneous adjudication methods limiting its conclusions.[5] In a multicentre randomised controlled trial setting, troponin assay performance according to renal function was hampered by modest sample sizes.[6 7] Current guidelines and consensus documents point to the value of serial measurements and evaluating the 'delta', as a way to counter the high baseline troponin values.[8 9] However, serial measurements are not always feasible and initial decisions often need to be made to facilitate rapid triage and determine the need for admission, monitoring or repeat measurements in patients with renal impairment. This challenge is growing as more patients are living with CKD and are at increased risk of coronary disease.[10]

In this study, we used routinely recorded National Health Service (NHS) clinical data from UK hospitals participating in the National Institute for Health Research Health Informatics Collaborative.[11–13] We included data between 2010 and 2017 from all admissions where a troponin test was completed for any clinical reason and where there was a measure of renal function and a coded outcome diagnosis. We aimed to describe (1) the distribution of troponin levels in patients with and without a diagnosis of AMI according to estimated glomerular filtration rate (eGFR), (2) evaluate the test performance of different troponin assays for AMI in renal impairment and (3) derive adjusted and eGFR-specific cut-offs for the diagnosis of AMI.

METHODS

Study population

Data were obtained from four collaborating hospitals (Imperial College Healthcare Trust, University College London Hospitals NHS Foundation Trust, Oxford University Hospitals Trust and Guy's and St Thomas' Hospital Trust), which are all tertiary centres with emergency departments. We defined the target cohort as patients who had a troponin measured for any reason during the study period between 2010 and 2017 (2008–2017 for University College London Hospital) and from which a serum creatinine value was available within a 72-hour period. Only the first episode of hospital care with a troponin measurement was eligible for inclusion.

Study parameters

The definition of AMI was based on the diagnosis codes assigned by clinical coding staff after patient discharge. Diagnoses were coded using International Classification of Diseases 10th edition (ICD-10) codes. AMI included non-ST elevation myocardial infarction (NSTEMI), ST elevation MI (STEMI) and subsequent myocardial infarction (MI) (online supplemental table 1). Admitted patients without a discharge diagnosis were excluded. Patients who were not admitted were classified as not having had an AMI. Data on cardiovascular and clinical comorbidities were derived from the coded discharge diagnoses and were only available in admitted patients. Renal function was determined as eGFR using the 2021 revised Chronic Kidney Disease Epidemiology Collaboration equation.[14] Patients were stratified according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria based on eGFR in mL/min/1.73 m^2 at presentation (≤15, 15–30, 30–45, 45–60, 60–90, >90).[15] Patients with an eGFR<3 or >150 were excluded. To estimate the percentage of acute kidney injury (AKI), we calculated the change in creatinine at baseline compared with lab values measured between a year before and 7 days prior to inclusion or 90 days and 1 year after inclusion. AKI was defined based on the KDIGO criteria as a relative increase of >50% or absolute increase of >26.5 µmol/L.[15] Full details on laboratory methods and details on how troponin data were collected from electronic health records and subsequently pooled have been reported in detail previously.[13] All troponin values were measured on clinical indication, an overview of the included assays is given in table 1. Troponin values were additionally expressed as a ratio with respect to their upper limit of normal (ULN) as specified by the manufacturer, in order to pool measurements of different troponin assays, in keeping with previously published methods.[13] For high-sensitive troponin I (hs-TnI), all analyses were performed stratified by sex as a sex-specific ULN is recommended, while for high-sensitive troponin T (hs-TnT) the sexes were combined in the analysis as the same ULN for both sexes is provided by the manufacturer. Serial troponin values were analysed if patients had two troponin measurements within 24 hours.

Table 1 Overview of the different assays

Assay overview	N (%)	N (%)	Cut-off (ng/L)
High sensitive	92 644 (41.7)		
Roche Elecys hs-cTnT		69 452 (31.3)	14
Abott iSTAT hs-cTnI		23 192 (10.4)	34 (men)/15 (women)
Contemporary	129 531 (58.3)		
Abott Architect cTnI		71 604 (32.2)	40
Abott cTnI		48 587 (21.9)	32
Roche Elecys cTnT		8373 (3.8)	30
Roche CardiacReader cTnT		967 (0.4)	50

hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity crdiac troponin T.

Statistical analyses

Descriptive analyses of baseline characteristics including age, sex, ethnicity and cardiovascular risk factors were performed for patients with and without an ultimate diagnosis of AMI and were compared between groups. Continuous variables were assessed for normality by visual inspection of histograms; given non-normal distributions for age and eGFR, groups were compared using the Wilcoxon rank-sum test, while categorical variables were compared using χ^2 tests.

The relation between the first troponin value and eGFR was analysed by determining percentile scores for the 1st, 10th, 25th, 50th, 75th, 90th and 99th troponin values in patients with and without AMI for each eGFR stratum. Results were visualised by depicting the density curve of the distribution of the log-transformed troponin values. The diagnostic performance of the first troponin value for a final diagnosis of AMI was evaluated through receiver operator curves (ROC) and corresponding C-statistic by eGFR strata for each assay and for

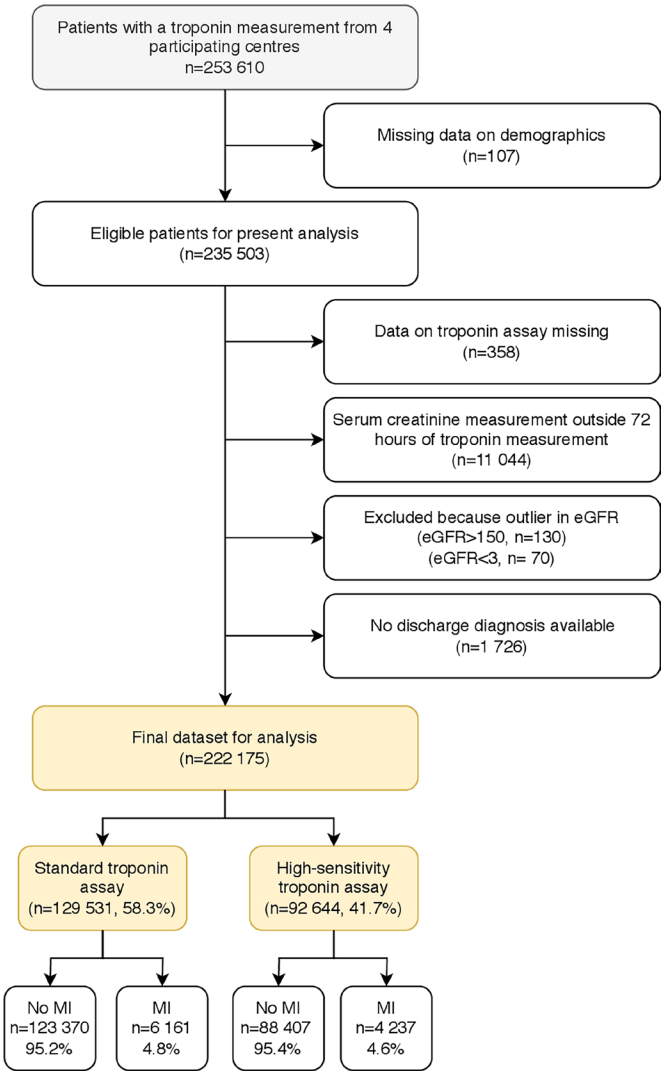

Figure 1 Flowchart of this study. eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

the complete cohort using normalised troponin values. A sensitivity analysis was performed to examine the test performance separately in patients with STEMI, where the diagnosis of AMI was more certain, or other types of MI (NSTEMI or subsequent MI) after excluding all STEMI cases. For high-sensitivity troponin assays, the data were split randomly into an 80% derivation and 20% validation set. We calculated sensitivity (detection rate), specificity (1−false positive rate) and positive predictive value for the conventional test threshold as specified by the manufacturer in the derivation subset. We then sought to derive eGFR specific cut points (1) using the median troponin value in patients without AMI and (2) that would preserve the same false positive rate (or specificity) as observed in patients with an eGFR>90 when using the conventional cut-off. We first derived the cut-offs and evaluated the test performance in the 80% derivation set. The adjusted cut-offs were then validated in the 20% validation set. For comparison, we performed the same analysis using the complete dataset for contemporary assays. A descriptive analysis of the absolute differences in troponin value between first and second troponin according to renal function and MI diagnosis was also conducted. All analyses were performed using R V.4.0.0.

Patient and public involvement

This study used existing routine care data and did not include specific patients as study participants. No patients or public were involved in the design, conducting and reporting of the results of this study.

RESULTS

Study population

Figure 1 shows 235 610 patients had a troponin measurement during the study period. After exclusion of records without diagnostic data and where serum creatinine was missing or assessed >72 hours before or after troponin value, 221 175 patients were included in the final dataset. In the final dataset, the median age of patients was 65 years (IQR 49–79), 55% were men and 74% Caucasian. The median eGFR was 87.8 mL/min/1.73 m^2 and 21.6% of the patients had an eGFR<60 mL/min/1.73 m^2 (table 2). A quarter (25.4%) of admitted patients had an eGFR<60 mL/min/1.73 m^2, although only 4.9% of admitted patients had an ICD-10 diagnosis code for CKD. Creatinine data were available in the 12 months prior or after index admission in 88 603 (39.5%) of the patients. among those, percentage of AKI was 11.6%. In 41.7% of all patients, a high-sensitivity troponin assay was used (table 1). A total of 10 398 (4.7%) patients had a discharge diagnosis of AMI.

Distribution of troponin values by renal function

Figure 2 shows the distribution of hs-TnT and hs-TnI values in patients with and without AMI according to eGFR strata. In patients without AMI, we observed an inverse log-linear relationship between troponin and eGFR: median hs-TnT and TnI were higher (4 vs 81 ng/L and 2 vs 35 ng/L, respectively) in patients with higher versus lower eGFR (>90 vs <15 mL/min/1.73 m^2, respectively). In patients with AMI there was no consistent relation between troponin and eGFR with median values ranging between 292 and 755 ng/L and 295–919 ng/L for hs-TnT and hs-TnI among the different eGFR strata. The proportion of patients with a troponin above the conventional threshold for hs-TnT and hs-TnI among patients with and without MI increased from 18% and 11% in patients with eGFR>90 mL/min/1.73 m^2 to 97% and 65% for patients with an eGFR<15 mL/min/1.73 m^2. In patients who had a troponin value measured using a non-high sensitivity troponin assay, the inverse relationship between troponin and eGFR was only observed in patients with an eGFR<30 mL/min/1.73 m^2 or for 75th percentile and higher of troponin values. The distribution of troponin values using contemporary assays is given in online supplemental table 2B.

Diagnostic performance

In the ROC analysis of the complete cohort, the overall C-statistic was 0.90 for troponin measurement in the diagnosis of AMI. The C-statistic was 0.93 in patients with eGFR>90 mL/min/1.73 m^2 and ranged from 0.84 to 0.89 in patients with eGFR 15–60 mL/min/1.73 m^2 and 0.81 in patients with an eGFR<15 mL/min/1.73 m^2 (figure 3 and table 3). High-sensitivity assays had a better test performance (C-statistic 0.91) compared with contemporary assays (C-statistic 0.70–0.90, (online supplemental table 3). The relationship between test performance and eGFR was consistent across all assays (online supplemental figure 2). In the additional analysis using STEMI as a more certain discharge diagnosis of AMI, we observed a similar overall

Table 2 Baseline characteristics of the patients included in the present analysis, stratified by discharge diagnosis of myocardial infarction

	Overall	No MI	MI	P value
n	222 175	211 777	10 398	
Age	65.0 (49.0, 79.0)	64.0 (49.0, 79.0)	70.0 (59.0, 80.0)	<0.01
Ethnicity*				<0.01
Caucasian	138 584 (74.2)	132 249 (74.2)	6335 (75.0)	
Black	16 823 (9.0)	16 480 (9.2)	343 (4.1)	
Asian	14 226 (7.6)	13 091 (7.3)	1135 (13.4)	
Other	17 035 (9.1)	16 398 (9.2)	637 (7.5)	
Men	122 731 (55.2)	115 405 (54.5)	7326 (70.5)	<0.01
eGFR (mL/min/1.73 m^2)	87.8 (65.7, 102.7)	88.1 (66.1, 103.1)	81.1 (58.3, 96.0)	<0.01
eGFR category				<0.01
<15	4755 (2.1)	4474 (2.1)	281 (2.7)	
15–30	7738 (3.5)	7230 (3.4)	508 (4.9)	
30–45	13 333 (6.0)	12 553 (5.9)	780 (7.5)	
45–60	20 029 (9.0)	18 845 (8.9)	1184 (11.4)	
60–90	73 247 (33.0)	69 319 (32.7)	3928 (37.8)	
>90	103 073 (46.4)	99 356 (46.9)	3717 (35.7)	
Diagnosis of MI	10 398 (4.7)			
NSTEMI (%)	5743 (2.6)	0 (0.0)	5743 (55.2)	
STEMI (%)	4358 (2.0)	0 (0.0)	4358 (41.9)	
Subsequent MI (%)†	297 (0.1)	0 (0.0)	297 (2.9)	
Unstable angina (%)	2253 (1.0)	2253 (1.1)	0 (0.0)	
Other acute ischaemic heart disease (%)	1551 (0.7)	1551 (0.7)	0 (0.0)	
Admitted patients‡	129 305 (58.2)	118 907 (56.1)	10 398 (100.0)	<0.01
Hypertension (%)	45 460 (35.2)	40 289 (33.9)	5171 (49.7)	<0.01
Diabetes	23 828 (18.4)	21 268 (17.9)	2560 (24.6)	<0.01
Hypercholesterolaemia (%)	23 168 (17.9)	19 617 (16.5)	3551 (34.2)	<0.01
Previous MI (%)	9810 (7.6)	7078 (6.0)	2732 (26.3)	<0.01
History of CKD (%)	6358 (4.9)	5749 (4.8)	609 (5.9)	<0.01

MI classification was based solely on discharge diagnosis, assuming that all patients with MI were admitted.
*Ethnicity data were missing for 35 507 patients.
†Defined as: infarction of any myocardial site, occurring within 4 weeks (28 days) from onset of a previous infarction.
‡Data for comorbidities were only available for admitted patients.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; (N)STEMI, (non)-ST segment MI.

C-statistic 0.91, although test performance was less affected by eGFR decline with a C-statistic of 0.87 in eGFR<15 compared with 0.93 in eGFR>90 mL/min/1.73 m^2. The test performance after excluding those with STEMI was slightly lower (overall C-statistic 0.89), with a similar pattern across eGFR strata (online supplemental table 4 and online supplemental figure 3).

Strategies to improve diagnostic performance

The decline in test performance with worsening renal function is further illustrated by assessment of false positive and detection rates for diagnosis of AMI. Table 4 shows these test performance metrics for an initial hs-TnT measurement using both conventional and new eGFR adjusted cut-offs for the diagnosis of AMI. For hs-TnT, a conventional cut-off of 14 ng/L, in patients with an eGFR between 15 and 60 mL/min/1.73 m^2, yielded a high detection rate of 94–100% but at the expense of a significantly high false positive rate of between 68–93%, compared to just 15% for those with an eGFR >90 mL/min/1.73 m^2. Using the median high sensitivity troponin T values of 22, 34 or 55 ng/L in patients with eGFR 45–60, 30–45 and 15–30 mL/min/1.73 m^2, respectively, and without MI, improved the false positive rate down to ~50%, while the detection rate was maintained between 89% and 93%. We then manually adjusted the cut-off thresholds to match the false positive rate of the reference group with eGFR>90 mL/min/1.73 m^2, while accounting for different strata of renal function. To maintain the same low false positive rate of 15% (corresponding to a specificity of 0.85), higher hs-TnT cut-offs, of 73, 112 and 184 ng/L were required in patients with an eGFR of 45–60, 30–45 or 15–30 mL/min/1.73 m^2, respectively, and gave corresponding detection rates of 73%, 70% and 68%. These new cut points resulted in an overall improvement in the PPV of the hs-TnT test in all patients, from 0.11 to 0.19. In the validation subset, applying these adjusted cut-offs led to a similar increase in PPV from 0.10 to 0.18 (see online supplemental table 5).

We observed a similar pattern for hs-TnI; however, overall detection rate was marginally lower than for hs-TnT (81% in men and 91% in women vs 93% combined) and false positive rate was higher for women (15% in men and 20% in women vs 33%). The use of adjusted cut-offs to reach the same false positive rate (8% for hs-TnI) increased PPV in men from 0.30 to 0.42 and in women from 0.15 to 0.27, with similar results in the validation subset (table 5). The sensitivity and specificity for contemporary troponin assays using different cut-offs are available in online supplemental table 6.

Repeat troponin measures

In a subset of 58 445 (26.3%) patients, a second troponin measurement was available within 24 hours, of which 44%

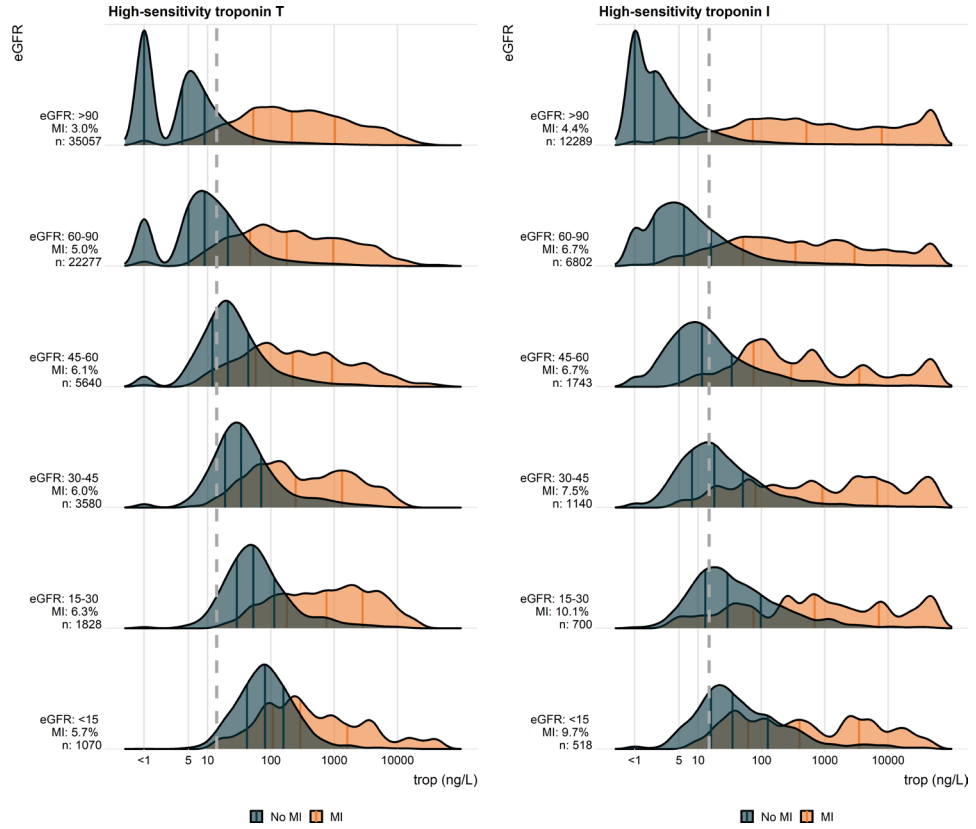

Figure 2 Distribution of troponin values according to renal function in patients with (red) and without (blue) myocardial infarction, illustrating the log-linear relation between eGFR and troponin in patients without acute MI. X-axis shows troponin values, Y-axis the relative density of distribution of troponin values, vertical lines within distribution depict quantiles. Dotted vertical line depicts conventional cut-off of each assay (respectively 14 and 15 ng/L). eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

utilised a high-sensitivity assay. In this subset, the prevalence of AMI on discharge diagnosis was higher (12.0% vs 4.68%). The distribution of absolute changes (delta) in troponin was similar across eGFR strata in patients with and without AMI (figure 4). An overview of the median change and other percentiles is given in online supplemental table 7 and 8.

DISCUSSION

To our knowledge, we present the largest observational study of unselected, hospitalised patients in whom a troponin and creatinine were measured, exploring the relationship between the *initial* troponin value and a final diagnosis of AMI. Our key findings were that among those without AMI, there is an inverse near exponential relationship between troponin and worsening renal function, which was associated with severe degradation of test performance, for all assays, increasing false positive diagnoses, when using conventional cut-off values. However, by fixing the false positive rate to match that found in individuals with normal renal function, higher troponin cut-offs can be established by eGFR strata, resulting in improved test performance. We propose eGFR specific cut points that could be used to support the initial triage and clinical risk assessment, where only a single troponin value is available, for the diagnosis of AMI in patients with impaired renal function.

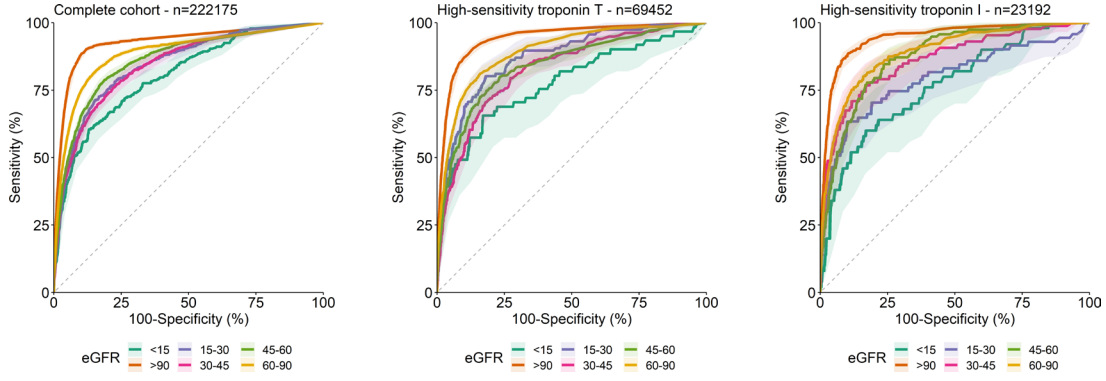

Figure 3 Diagnostic performance of first troponin for diagnosis of myocardial infarction stratified by eGFR at presentation, showing the decrease in test performance when renal function decreases. Colours depict different eGFR strata, bands indicate 95% CIs. eGFR, estimated glomerular filtration rate.

Table 3 C-statistic of test performance of first troponin value for discharge diagnosis of myocardial infarction, for complete cohort, high sensitive cardiac troponin T (hs-cTnT) and troponin I (hs-cTnI)

	Complete cohort						hs-cTnT						hs-cTnI					
eGFR	n	Cases	Prev	AUC	95% CI		n	Cases	Prev	AUC	95% CI		n	Cases	Prev	AUC	95% CI	
All	222 175	10 398	4.68	0.90	0.89	0.90	69 452	2919	4.20	0.91	0.90	0.91	23 192	1318	5.68	0.91	0.91	0.92
>90	103 073	3717	3.61	0.93	0.92	0.93	35 057	1064	3.04	0.94	0.94	0.95	12 289	539	4.39	0.95	0.94	0.96
60–90	73 247	3928	5.36	0.89	0.88	0.89	22 277	1122	5.04	0.89	0.88	0.9	6802	455	6.69	0.89	0.87	0.91
45–60	20 029	1184	5.91	0.86	0.85	0.87	5640	342	6.06	0.84	0.82	0.87	1743	117	6.71	0.88	0.84	0.91
30–45	13 333	780	5.85	0.84	0.83	0.86	3580	214	5.98	0.83	0.80	0.86	1140	86	7.54	0.86	0.82	0.91
15–30	7738	508	6.57	0.85	0.83	0.87	1828	116	6.35	0.87	0.84	0.91	700	71	10.14	0.80	0.73	0.86
≤15	4755	281	5.91	0.81	0.78	0.83	1070	61	5.7	0.78	0.71	0.85	518	50	9.65	0.77	0.69	0.84

AUC, area under the curve; eGFR, estimated glomerular filtration rate; Prev, prevalence.

Multiple observational studies have examined the relationship between troponin values and renal impairment, including routine monitoring of patients with CKD and inpatient and outpatient clinical encounters.[16 17] The relationship between CKD and peak troponin levels of patients with acute coronary syndrome (ACS) was additionally analysed in a previous synthesis of UK national audit data for MI between 2003 and 2013.[18] In 330 367 patients, the adjusted peak cTn levels were 42% higher in patients with CKD; however, this cohort only included patients with confirmed ACS and >95% of troponin values were not measured using a high sensitivity troponin assay. Our findings are consistent with an inverse relationship between troponin values and renal impairment in an unselected population, more closely mirroring real-world clinical practice.

The High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) trial was the largest trial that evaluated an undifferentiated patient population with high sensitivity troponin assays.[19] The overall proportion of patients with renal impairment was lower than observed in our study and the population was predominantly Caucasian (93%).[6] In pre-specified secondary analysis, renal impairment (eGFR<60 mL/min/1.73 m^2) was associated with a threefold increase in the proportion of troponin measurements above the 99th centile, along with an increased incidence of the primary outcome (HR 1.53, 95% CI 1.31 to 1.78).[20] We extend these results by including the full range of eGFR thresholds and using a larger number of patients with renal impairment in a more generalisable and unselected population.

To address the clinical challenge, we sought to identify an optimal threshold for troponin assays, for clinicians to use when interpreting a raised first troponin for any given eGFR value. While similar studies have examined adjusted thresholds for use in renal impairment, these have been limited because of their inclusion of only one troponin assay or smaller sample size.[21 22] Our study has the largest number of patients identified for such analyses and has included both traditional and high sensitivity troponin assays. For all assays, our analyses demonstrated that significantly higher absolute troponin values are required in patients with impaired renal function to achieve the same false positive rate for the diagnosis of AMI using a single troponin. Importantly, where repeat troponin values within 24 hours were available, we found that the value of the troponin change did not depend on renal function or troponin assay, for either patients with or without MI. This confirms that the absolute values of delta troponin are a helpful discriminatory feature independent of renal function, in keeping with other studies[7] and recent European Society of Cardiology (ESC) guidelines.[8 9] In this context, eGFR specific thresholds could have a complementary role in interpreting an initial troponin value, guiding differential diagnoses or risk assessments and supporting triage decisions while awaiting repeat troponins to inform diagnosis and patient disposition (online supplemental figure 4). These should be interpreted as pragmatic real-world thresholds to support early decision-making in unplanned hospital admissions, rather than fully adjudicated biological cut-offs for diagnosing MI because of an atherothrombotic event (type 1 MI).

Limitations

The primary limitation of this study was that it was a retrospective observational analysis and we were unable to adjudicate MI diagnoses independently. However, in a sensitivity analysis using

Table 4 Sensitivity/specificity for hs-cTnT using conventional cut-offs, cut-offs based on 50th of troponin distribution in patients without MI according to eGFR strata and eGFR adjusted cut-offs to match the specificity of the reference group (eGFR >90) in 80% derivation set

Roche Elecys hs-cTnT														
			Conventional cut-off for Troponin				50th centile				Adjusted cut-off to match specificity of reference group			
eGFR	n	Prev	ng/L	Sens	Spec	PPV	ng/L	Sens	Spec	PPV	ng/L	Sens	Spec	PPV
All	55 561	4.3		0.93	0.67	0.11		0.95	0.51	0.08		0.82	0.85	0.19
>90	28 000	3.1	14	0.92	0.85	0.16	4	0.98	0.51	0.06	14	0.92	0.85	0.16
60–90	17 866	5.2	14	0.92	0.64	0.12	9	0.95	0.5	0.09	33	0.80	0.85	0.22
45–60	4513	6.2	14	0.94	0.32	0.08	22	0.89	0.52	0.11	73	0.69	0.85	0.23
30–45	2856	6	14	0.98	0.17	0.07	34	0.88	0.51	0.10	112	0.67	0.85	0.22
15–30	1464	6.4	14	1.00	0.07	0.07	55	0.93	0.5	0.11	184	0.74	0.85	0.25
≤15	862	5.9	14	1.00	0.03	0.06	81	0.80	0.51	0.09	226	0.63	0.85	0.21

eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity crdiac troponin T; MI, myocardial infarction; PPV, positive predictive value; Prev, prevalence; Sens, sensitivity; Spec, specificity.

Table 5 Sensitivity/specificity for hs-TnI using conventional cut-offs, cut-offs based on 50th of troponin distribution in patients without MI according to eGFR strata, and eGFR adjusted cut-offs to match the specificity of the reference group (eGFR >90) in 80% derivation set.

Abott iSTAT hs-cTnI, men														
			Conventional cut-off for Troponin				**50th centile**				**Adjusted cut-off to match specificity of reference group**			
eGFR	**n**	**Prev**	**ng/L**	**Sens**	**Spec**	**PPV**	**ng/L**	**Sens**	**Spec**	**PPV**	**ng/L**	**Sens**	**Spec**	**PPV**
All	10012	7.33		0.81	0.85	0.30		0.95	0.51	0.13		0.69	0.92	0.42
>90	5590	6.23	34	0.83	0.92	0.42	2	0.99	0.5	0.12	34	0.83	0.92	0.42
60–90	2656	8.96	34	0.76	0.84	0.32	7	0.94	0.53	0.17	99	0.61	0.92	0.44
45–60	730	7.26	34	0.81	0.73	0.19	13	0.94	0.52	0.13	295	0.47	0.92	0.33
30–45	491	8.35	34	0.85	0.66	0.19	19	0.93	0.5	0.15	357	0.61	0.92	0.42
15–30	314	11.15	34	0.86	0.52	0.18	33	0.86	0.51	0.18	1042	0.46	0.92	0.43
≤15	231	8.23	34	0.79	0.45	0.11	40	0.74	0.5	0.12	435	0.37	0.92	0.30
Abott iSTAT hs-cTnI, women														
			Conventional cut-off for Troponin				**50th centile**				**Adjusted cut-off to match specificity of reference group**			
eGFR	**n**	**Prev**	**ng/L**	**Sens**	**Spec**	**PPV**	**ng/L**	**Sens**	**Spec**	**PPV**	**ng/L**	**Sens**	**Spec**	**PPV**
All	10677	3.7		0.91	0.80	0.15		0.95	0.52	0.07		0.73	0.92	0.27
>90	8541	3.66		0.90	0.80	0.15	1	0.97	0.51	0.04	15	0.86	0.92	0.17
60–90	4241	1.79	15	0.86	0.92	0.17	5	0.95	0.54	0.09	84	0.75	0.92	0.33
45–60	2796	4.83	15	0.90	0.77	0.17	10	0.97	0.5	0.11	166	0.58	0.92	0.32
30–45	660	5.76	15	0.92	0.61	0.13	16	0.93	0.51	0.11	203	0.67	0.92	0.37
15–30	438	6.16	15	0.93	0.49	0.11	22	0.96	0.5	0.17	394	0.65	0.92	0.48
≤15	233	9.87	15	0.96	0.34	0.14	33	0.86	0.51	0.13	1213	0.43	0.92	0.33

eGFR, estimated glomerular filtration rate; hs-cTnI, high-sensitivity cardiac troponin I; hs-TnI, high-sensitive troponin I; MI, myocardial infarction; PPV, positive predictive value; Prev, prevalence; Sens, sensitivity; Spec, specificity.

only patients with STEMI, for whom diagnostic certainty is high and which is diagnosed independently from troponin values, the overall test performance was very similar, providing some degree of confidence in the results. Similarly, we found a slightly lower C-statistic but a similar relation with eGFR after in the sensitivity analysis of mainly patients with NSTEMI. Nonetheless, we acknowledge limitations working with coded datasets. For example, type 2 MI caused by a mismatch between oxygen supply and demand was not available as a specific ICD-10 code in the dataset and no case note review of free-text, imaging or other relevant data was undertaken to determine the reason for troponin measurement or to adjudicate clinical outcomes.[23] Accordingly, some cases classified as AMI may have included patients with type 2 MI which is particularly relevant in patients with renal impairment, where misclassification may have influenced the derived eGFR-specific thresholds. The proposed thresholds are derived from real-world coded diagnoses, intended to support triage and early risk assessment, rather than definitive biological cut-offs for type 1 MI.

A further limitation was the relatively modest number of admissions with more than one troponin and creatinine value. This precluded the ability to conduct serial analyses or time-sensitive analyses of creatinine and troponin values and the proportion of AKI compared with established CKD in our cohort is an approximation based on only a subset of the whole cohort. However the overall percentage of AKI (11.6%) was small and the use of eGFR measured at the same time as troponin values in the present analysis resembles clinical practice in which previous serum creatinine measurements from the outpatient clinic are not always available for decision-making. Importantly, the proposed cut-offs are based on presentation eGFR and should not be interpreted as thresholds specific for stable CKD. In routine acute care, reduced renal function noted at presentation may reflect background CKD, AKI or both, and as such the proposed thresholds are intended for use in this unselected real-world setting. In addition, the proposed cut points should be applied with particular caution in the eGFR<15 subgroup, where the absolute number of positive cases was relatively small (91 in the high sensitive subgroup, 281 overall), reducing diagnostic performance and increasing heterogeneity. In this group serial troponin and clinical context should take priority over the single threshold based approach. For the delta troponin, we included all troponin measurements which were measured within 24 hours, however the exact timing of the measurement was not available. Finally, we did not examine medication use and the potential harms of inappropriate dual antiplatelet therapy[24] or additional downstream decision-making including invasive management, where recent trial data have shown inconclusive outcomes in patients with ischaemia and CKD.[25]

Clinical implications and application to routine clinical practice

We observed that in over a quarter of all patients presenting to hospital, in whom troponin was measured, there was significant renal impairment (eGFR<60 mL/min/1.73 m^2) highlighting the burden of this clinical problem. Since the basis for measuring troponin can vary, including routine order sets for chest pain irrespective of pretest likelihood,[26] for most practising clinicians, the consult of 'what does this troponin value mean for my patient?' is a commonly encountered clinical scenario that is represented in this study cohort. The diagnostic challenge increases in the presence of renal impairment, where MI can present atypically.[4] Although recent data from two US centres has highlighted the possible role for including an adjusted delta in the second troponin based on renal function, we contend that the clinical challenge is largest when handling interpretation of single troponin values, and that the potential added benefit of

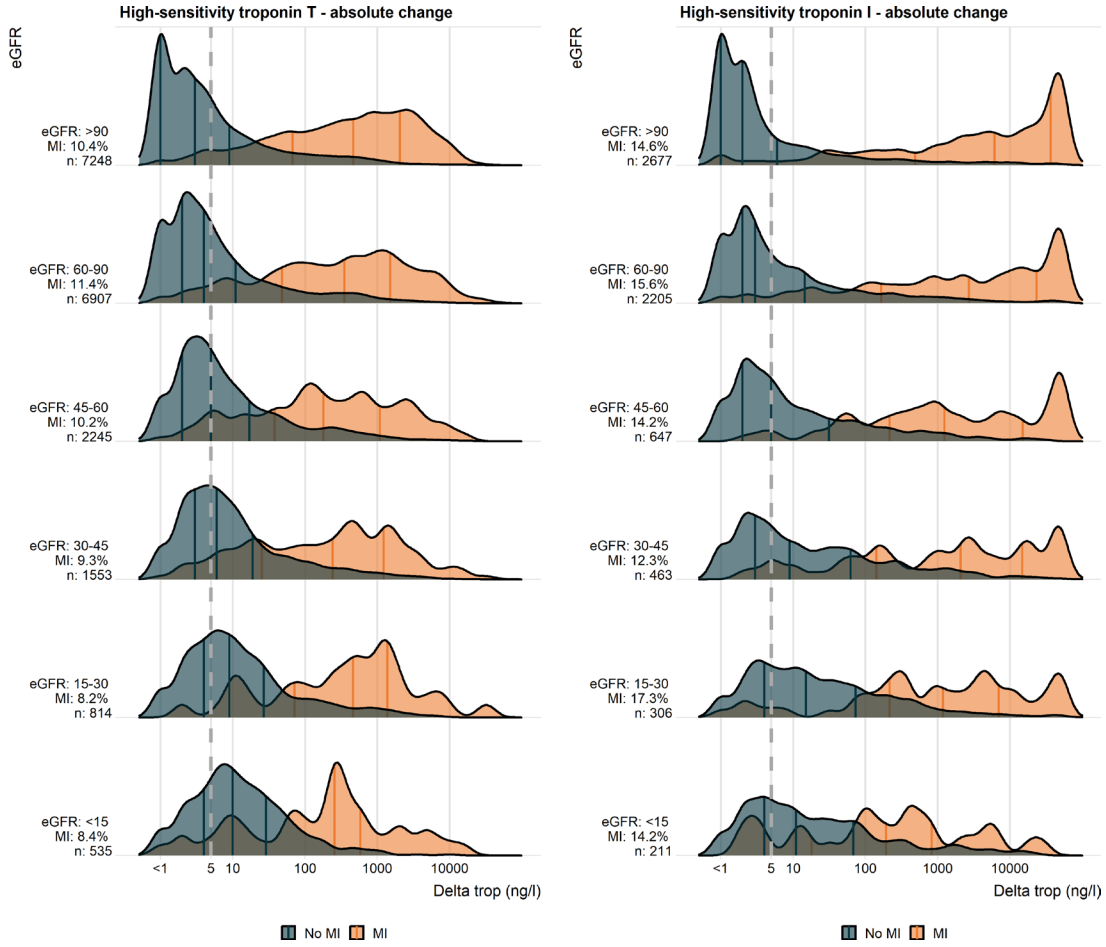

Figure 4 Subgroup analysis of participants in which second troponin was measured. Curves indicate distribution of absolute difference between first and second troponin measurement. Dotted line depicts conventional cut-off (5 ng/L for delta). eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

adjustment to the delta may be diluted by other parameters such as dynamic changes in ECG or clinical signs and symptoms.[27]

In addition, adherence to recent professional guidance and rule out algorithms based on 1-hour troponins have shown mixed results, with poor reporting of the proportion of patients with renal impairment and an inability to safely rule out 30-day cardiac death or MI in patients with known coronary artery disease.[28] The use of adjusted eGFR thresholds for initial troponin values as aids to support provisional 'rule in' and 'rule out' decisions for patients with impaired renal function may therefore serve as a useful adjunct to clinicians faced with acute decisions about safe triage and patient disposition before a second troponin or additional clinical information becomes available (online supplemental figure 4) to make a formal diagnosis. The two approaches should be considered complementary in the acute care context. Further validation in external cohorts is warranted before clinical adoption of the proposed eGFR specific cut points.

CONCLUSION

In the largest real-world study, to date, of unselected patients in whom a troponin was measured acutely, we demonstrate that more than half had some degree of renal impairment and confirm the inverse association between troponin and eGFR. Test performance steadily deteriorates with falling eGFR but importantly, we observed that performance can be optimised by using eGFR specific cut-points. We propose these additional cut points could be used in the initial assessment of patients with renal impairment, guiding triage and acute care decisions while awaiting serial troponins for a more definitive diagnosis or when there is clinical uncertainty for interpretation of a single raised troponin value.

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