Describing suspected non ST-elevation acute coronary syndrome using troponin at a regional, public South African emergency centre with the Roche cardiac reader

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ABSTRACT

Background: There are few data available regarding acute coronary syndrome presenting to emergency centres in sub-Saharan Africa compared to the rest of the world. The aim of this study was to describe the acute coronary syndrome diagnosis and its outcome in an undifferentiated chest pain population when using a troponin assay that predates current reference standards at a public, Cape Town emergency centre.
Methods: A retrospective, cross-sectional design was used. Comparisons were made between the diagnosis, outcome and troponin result (using the Roche cardiac reader). Findings were descriptively presented. Troponin results were qualitatively described in relation to a non ST-elevation acute coronary syndrome diagnosis. Associations were tested using the Chi2-test.
Results: Nine hundred and sixty-nine patients were included in the study, of which 40 patients (4%) were excluded due to poor clinical record keeping. Acute coronary syndrome was diagnosed in 256 patients (28%), from which 54 (21%) were troponin positive which differed to troponin negative acute coronary syndrome (p <0.001). Unstable angina was diagnosed in 197 (77%) of acute coronary syndrome patients.
Conclusions: Unsurprisingly, a high proportion of chest pain patients did not have acute coronary syndrome. Unstable angina numbers were much higher than described elsewhere. Although it is not possible to relate this finding to the assay's lower accuracy using only a descriptive design, a higher sensitivity assay would likely benefit the diagnostic process as it does elsewhere. Further research is required to explore safe, local diagnostic strategies that can strike a balance between patient safety and cost effectiveness.
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INTRODUCTION

The global burden of disease is shifting from communicable to non-communicable disease. Without intervention, the morbidity due to cardiovascular diseases will likely supersede human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) come 2030.[1-3] More than 80% of cardiovascular-related deaths are estimated to occur in low- to middle-income countries (LMICs) despite a dearth of cardiovascular disease knowledge in sub-Saharan Africa.[1-5]

Acute coronary syndrome (ACS) is the most common cause of death and disability among cardiovascular diseases.[3,5,6] Aggressive prevention strategies and treatment of ACS in high-income countries have yielded positive results with the resulting treatment reference standards having also been considered in LMICs.[5] However, the epidemiology, precise patterns and outcomes of ACS management in Africa remain poorly documented.[2,7,8] In LMICs – South Africa included – an increase of ACS appears to be largely due to transformational economic and lifestyle changes.[5,8,9] The INTERHEART study, one of the larger African studies on ischaemic heart disease, showed that risk factors in patients with ACS were similar to what had been documented in more developed settings, and smaller studies have replicated these findings.[4,7-11] However, these studies have also shown a trend towards a younger mortality cohort.[4,10,12] More importantly though, addressing cardiovascular disease locally has not matched its growth. Viable solutions remain elusive, mainly due to poor availability and/or quality of the resources required for diagnosis and care.[5,10,13]

Using the current definition, ACS includes ST-elevation myocardial infarction (STEMI) and non ST-elevation ACS (NSTE-ACS), with the latter including unstable angina and non ST-elevation myocardial infarction (NSTEMI).[14,15] Besides the clinical and electrocardiogram (ECG) findings, the use of high

sensitivity cardiac troponins has become the reference standard for the diagnosis of myocardial infarction, alongside risk stratification for ACS.[14-17] Troponin assays use monoclonal antibodies to specifically detect either the troponin T or I. The accepted reference standard for the upper reference limit of a troponin assay is currently considered at the 99th percentile with a coefficient of variability of less than 10%.[14-16,18-20] Importantly, as newer troponin assays (or high sensitivity troponin assays) continue to become more and more sensitive (and thus able to detect lower and lower levels of biomarker), the diagnosis of NSTEMI increases, with that of unstable angina becoming less common; perhaps only about 5% - 10% of ACS cases are currently described as unstable angina as a result of high sensitivity troponin assays.[21-23] In contrast, the Thrombolysis in Myocardial Infarction-3 study showed that 25% of unstable angina patients diagnosed using a negative CK-MB (as part of the older definition of myocardial infarction), turned out to have a positive troponin.[22] This is a notable point, as compared to unstable angina, NSTEMI is associated with an increased risk of mortality and adverse cardiac outcomes.[18] Unfortunately, the downside of a more sensitive assay includes an increase in falsely elevated troponins, i.e. raised troponin for non-ACS related pathology (or a false positive finding). To ensure the correct diagnosis is made, current reference guidance recommends serial troponin testing to reduce the proportion of false positives.[15,19,24,25] A significant change in troponin level of equal to, or more than, 20% from the baseline over a specified timeframe confirms an infarct.[15]

Although very little is known about the use of troponin testing in LMICs, many local emergency centres still make use of troponin assays that do not adhere to current reference standards. Sadly, this fact remains anecdotal as the specific type of assay used at various LMIC emergency centres is poorly documented. It is unclear how the use of less sensitive troponin assays with a wider coefficient of variability stack up to an acceptably, safe diagnosis, or how these assays would function within clinical decision rules that require more sensitive results – both over and under-diagnosis of ACS will carry at least some risk of harm.[13,17,24] The site where this study took place makes use of such an assay, as does many centres throughout South Africa. Understanding how this diagnostic test relates to the diagnostic work-up and outcome of suspected ACS is therefore an important quality consideration locally.

The aim of this study was to describe the troponin result on first assessment in undifferentiated chest pain patients that attended a district, public emergency centre with suspected NSTE-ACS, and to compare this with whether NSTE-ACS was subsequently diagnosed (or not), as well as the outcome (admission or discharge to/from the hospital locally, transfer to tertiary centre, or death at the hospital locally).

MATERIALS AND METHODS

The study was performed using a retrospective, cross-sectional design. It was conducted at Mitchells Plain Hospital emergency centre, Cape Town, South Africa. The Mitchells Plain catchment area includes a low- to middle-income suburban area within Cape Town. It houses around a third of a million people, mainly of mixed race (91%).[26] About 10% of the Mitchells Plain population has no income and 40.5% has an annual income equivalent to between US$ 2 700 and 11 000. [26] The emergency centre treats around 3 800 patients per month. Although exact figures are unknown, NSTE-ACS is perceived to have an above average prevalence in this area. It is important to note that the hospital does not have a cardiology service or angiography suite, and access to cardiology services, including angiography, is through Groote Schuur Hospital, a tertiary, referral hospital 23km away. Even so, primary coronary intervention is not consistently available, even at Groote Schuur Hospital. The standard treatment guidance for NSTE-ACS is described in the local, provincial emergency care guidance.[27]

The troponin assay used by Mitchell's Plain hospital's laboratory is the Roche CARDIAC® T Quantitative assay, or Cardiac Reader. We used the National Health Laboratory Service (NHLS) guidance to interpret the assay's results as follow: a result above 50ng/L is considered positive. This assay reports a definite positive result if the troponin T level is above 100ng/L and definitive negative result if below 50ng/L. The assay only provides a range for a level between 50 and 100ng/L. Where a range is reported, local emergency care guidance recommends a repeat test performed at 6 - 12 hours after the first. If the repeat troponin T assay remains between 50 and 100ng/L, the result is considered negative and if it rises above 100ng/L it is considered positive (thus dichotomising this finding).[27] Although a point of care assay, the test itself was performed in the laboratory by technicians and clinical staff were not involved in the testing or quality control process.

For the purpose of this study we were particularly interested in the NSTE-ACS cohort (NSTEMI and unstable angina), although instances of STEMI were also reported. It was assumed that STEMI data would be incomplete given the search strategy (STEMI is largely an ECG diagnosis in a particular clinical setting), hence the focus away from the STEMI cohort. As per local emergency centre guidance, patients suspected of NSTE-ACS are required to have a troponin test performed as part of their diagnostic workup.[27] We could therefore reliably identify study participants suspected of NSTE-ACS via the hospital laboratory for having had troponin T testing requested from the emergency centre. This allowed the study team to track clinical records retrospectively through the folder numbers obtained from the laboratory records. Data were sampled over a 4-month

period between 1 July 2015 and 31 October 2015. Information obtained from the clinical record included: age, gender, exit diagnosis (ACS [and type] or not ACS) and outcome (discharge from the local emergency centre, admission to Mitchells Plain Hospital, transfer from Mitchells Plain Hospital to Groote Schuur Hospital, or death during admission at Mitchells Plain hospital/EC). The following risk factors were also collected from the clinical record: hypercholesterolaemia, hypertension, diabetes mellitus, smoking, positive family history and obesity. The exit diagnosis was taken from the clinical record and were described on death, discharge, or transfer from the emergency centre or hospital. Either a specialist physician or emergency physician would have been involved in deriving the exit diagnosis. Resources did not allow for the ECG to be specifically evaluated as part of the study protocol. This is further discussed in the limitations section. For the purposes of this study, where multiple troponin T tests were performed during a single admission, the first troponin T result taken 6 - 12 hours after symptom onset (or admission in case symptom onset was not adequately described) was used to describe the result. Repeat troponins are encouraged in the local emergency care guidance, although non-consistently practiced.[27] Exclusions from the sample were for missing diagnosis and outcome variables. Patients were not excluded for missing risk factor variables, and instead calculations were adapted to accommodate for missing variables.

A sample size of 384 consecutive subjects meeting the inclusion criteria was required. The sample size calculation assumed a 50% proportion of positive clinical diagnosis of ACS (with

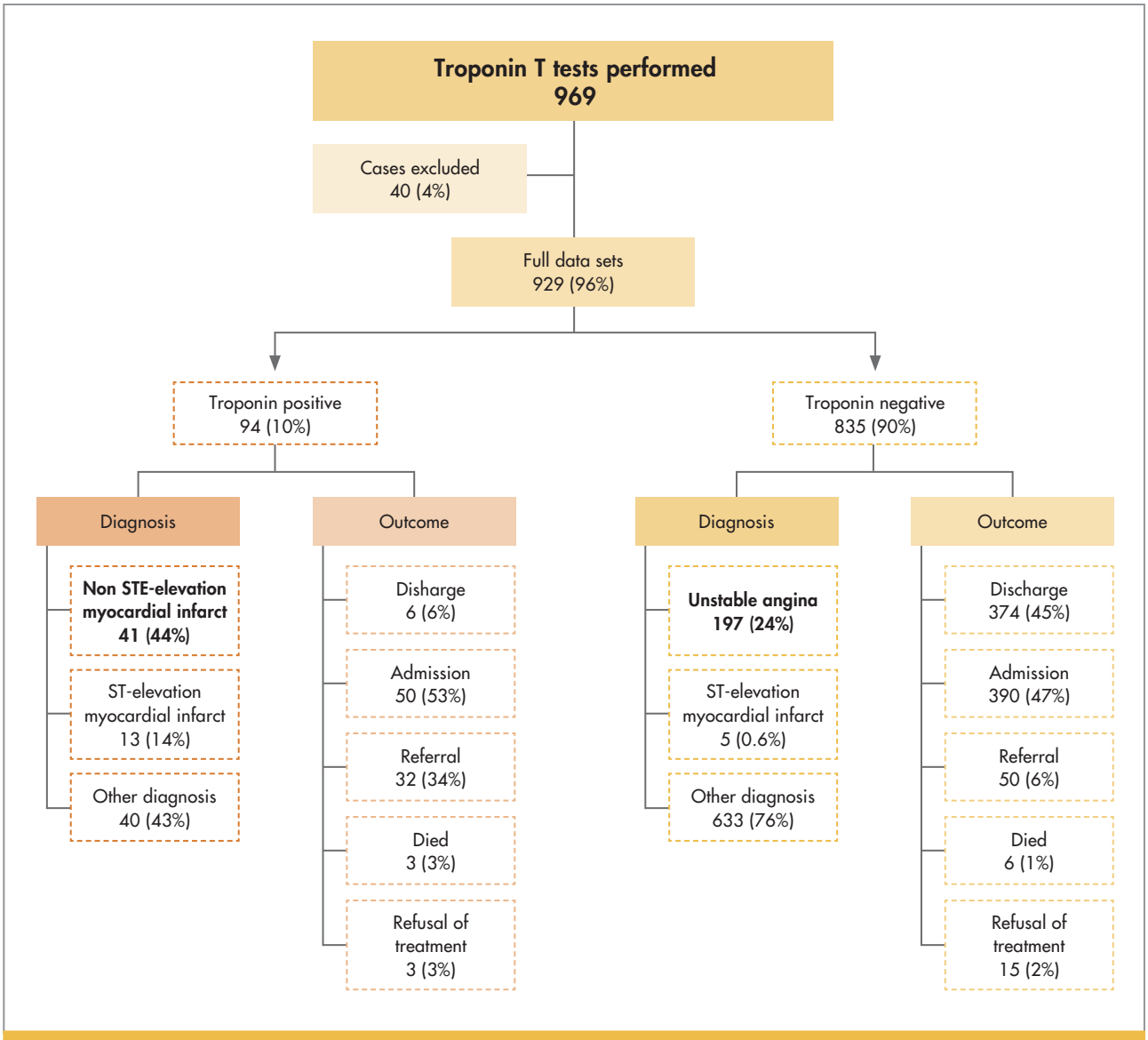

FIGURE 1: Summary of the study's main findings. Non ST-elevation acute coronary syndromes indicated in bold.

α=0.05 and ß=0.8). Microsoft Excel (Microsoft Office, Redmond, USA) and SPSS (IBM, Armonk, USA) were used for analysis. Numerical data (e.g. age) were expressed as mean and standard deviation (SD). Categorical data (troponin T results, disposition, diagnosis at disposition and risk factors) were expressed as frequencies. The Chi^2-test were used to compare troponin T results (positive/negative) to either the disposition diagnosis (ACS [and type] or not ACS), or the outcome (survival to discharge from local EC, survival to admission to Mitchells Plain Hospital ward, survival to transfer to Groote Schuur hospital, and death during admission at Mitchells Plain Hospital/EC). A p-value of less than 0.05 was considered statistically significant. To compare the disposition diagnosis (ACS, or not ACS) to ACS risk factors and troponin result, odds ratios were calculated using univariate logistic regression. Ninety five percent confidence intervals are presented, where appropriate, as a further measure of precision. The study received ethical approval from the Health Research Ethics Committee at Stellenbosch University (Reference: S16/02/029).

RESULTS

A sample of 969 datasets were collected of which 40 were excluded due to insufficient clinical information. The mean age was 58 years (SD ± 14) and there were 420 (45.2%) men in the sample. Figure 1 provides a summary of the study's main findings. Outcome observations included 911 datasets as 18 patients were discharged after refusing further hospital treatment.

A diagnosis of ACS was significantly associated with a positive troponin (Chi^2=22.1, p<0.001). Similarly, a diagnosis other than ACS was significantly associated with a negative troponin (Chi^2=8.9, p<0.01). Unstable angina was diagnosed in 197 (76.9%) ACS patients and represented 82.8% (197 patients out 238) of all NSTE-ACS patients. Significantly, more patients were discharged following a negative troponin assay result vs. a positive result (Chi^2=27.9, p<0.001), whilst significantly more patients were referred following a positive result (Chi^2=57.7, p<0.001). Admission to a ward and mortality showed no statistical difference, irrespective of whether the troponin result was positive or negative (p=0.54 and p=0.06, respectively).

Table I describes the number and proportion of comorbidities for the study population and Table II describes the odds ratios from the univariate logistic regression analysis.

DISCUSSION

As far as we are aware this is the first observational study on this topic described in a South African, public sector, emergency centre population. The study showed that ACS was diagnosed in about a quarter of all patients included in the study population. But even though ACS was significantly associated with a positive troponin T result, there were a substantial number of patients with NSTE-ACS with a negative troponin T result; in other words, unstable angina. This proportion was much higher than the 5% - 10% described by Lim, et al., in fact, unstable angina represented 4 out of every 5 patients diagnosed with NSTE-ACS.[21,22] It is possible that a reliance on risk factors and ECG findings may explain the high number of unstable angina diagnoses. As the Roche CARDIAC® T Quantitative assay is not a high sensitivity troponin assay, this possibly contributed as well. It would be interesting to know how many of the unstable angina patients would have converted to NSTEMI if a higher sensitivity assay was used. Interestingly, Roche recommends that results from the Roche CARDIAC® T Quantitative assay be confirmed by formal troponin testing. Although this might provide a safety net of sorts, this practice will also result in the delay of definitive diagnostic decisions and hence acute care. Point of care assays, such as the Roche CARDIAC® T Quantitative assay, are often less sensitive than assays that require to be performed in a central laboratory,

TABLE I: Summary records of risk factors among study participants. Proportions are a function of all cases included in the sample (n=929).

Risk factor	Risk factor documented as present n (%)	Risk factor not documented n (%)
Hypercholesterolaemia	346 (37.2)	452 (48.7)
Hypertension	709 (76.3)	2 (0.2)
Diabetes mellitus	365 (39.3)	5 (0.5)
Smoking	401 (43.2)	270 (29.0)
Family history	62 (6.7)	859 (92.4)
Obesity	75 (8.1)	844 (90.8)

TABLE II: Logistic regression to evaluate association of a positive troponin T assay and the risk factor variables with an ACS diagnosis.

Variable	Odds ratio (OR)	95% Confidence interval	p-value
Troponin T positive	4.24	2.73 - 6.57	<0.001
Hypercholesterolaemia	1.92	1.63 - 2.26	<0.001
Hypertension	1.92	1.32 - 2.78	<0.001
Smoking	1.25	1.05 - 1.49	0.01
Diabetes mellitus	1.11	0.83 - 1.48	0.47

especially in the first 6 hours post-onset of chest pain. Additionally, point of care assays often do not have the required less than 10% coefficient of variability for accurate diagnosing of NSTEMI. The assay may also be influenced by pre-analytical factors, such as haemolysis which may cause a false negative result. Hence, a troponin result from a point of care assay should ideally not be used in isolation to diagnose NSTE-ACS a repeat test needs to be performed to examine the kinetics to either confirm or reject an ACS diagnosis. During the study, repeat tests were not commonly applied outside the local guidance, or where requested by a specialist. In any event, it is unlikely that the repeat test would have been sent to a central laboratory for a high sensitivity test as recommended by Roche, unless this was specifically requested. This seems unlikely seeing that this approach is not recommended on the NHLS results report.

Admittedly the present study was not designed to assess the accuracy of the assay, however, the large unstable angina cohort presented here cannot simply be ignored either. As explained earlier, NSTEMI has a less favourable cardiac adverse event outlook compared to unstable angina; more sensitive troponin testing has allowed us to describe both appropriately.[18,22] Unfavourable outcomes, of course, would occur whether NSTEMI is occult or not. Although it was not our intention to collect data on STEMI patients, some were invariably included in the study as part of the data collection strategy. Of note is the troponin negative STEMI cohort. There could be many reasons why STEMI patients would be associated with a negative troponin: early presentation, misdiagnosis and use of a less sensitive assay, to name but a few. A number of patients that presented with an elevated troponin were due to non-ACS causes. The study design did not describe these diagnoses in detail, however, there are a number of conditions described in the literature that can result in a troponin rise that is not considered ACS.[17-19] It would be interesting to describe this cohort in more detail in future research.

Given the significant associations with a number of reported risk factors, it is likely that the NSTE-ACS diagnosis relied substantially on an interpretation of risk factors and ECG findings in addition to troponin findings. The current study did not specifically evaluate ECG patterns commonly associated with ACS due to limited study resources, but rather relied on the exit diagnosis which usually involves either a specialist physician or an emergency physician. The findings from this study re-enforce those of the INTERHEART study as both show an association of NSTE-ACS to a number of known risk factors.[14] It was interesting to note that diabetes was equally common among ACS and non-ACS patients and this finding may need further review in future research. It is disappointing that documentation of risk factors was so poor. Risk factors are particularly important in this study setting given the concern about the accuracy of the troponin assay.

From a high-income country perspective, the current value of troponin testing in the emergency centre rests in its ability to rule-out NSTE-ACS, since the vast majority of patients presenting with a suspected diagnosis of ACS turn out to not have the disease. What is concerning is that local clinicians' interpretations of troponin results are likely based on, and influenced by, international reference standards and risk assessment scores (such as the HEART score) that would not apply given a less sensitive troponin assay.[25,27] Hypothetically, patients that are diagnosed as non-ACS on the basis of a false negative troponin result may come to harm from under-diagnosis. Likewise, over-diagnosis of ACS due to compensation for a flawed troponin assay will also be associated with an increased risk of harm (e.g. anticoagulation, missed alternative diagnosis, etc.). A further disadvantage of the assay is the presentation of a range for a finding that should really be more easily dichotomised – using a range as wide as presented by the Cardiac Reader renders serial testing flawed as clinically important changes in troponin level may occur without detection.[14,19] It is vital that clinicians are familiar with the assay in use within their local setting when making clinical decisions for suspected ACS in the emergency centre. Although this study was not designed to differentiate between the clinical and diagnostic factors that contributed to the diagnosis, it is clear that there are at least some concerns with the Roche CARDIAC® T Quantitative assay that may invalidate its use. It is our understanding that the NHLS are already considering these.

Although the study findings were anticipated, the extent of the findings were unexpected. It opened up questions regarding the limitations of the diagnostic process within the study setting, the accuracy of the test used, and how these findings may impact on local NSTE-ACS care. As a retrospective study, it relied heavily on the quality of data collected from patient files, some of which (as reported) were omitted from the clinical records. The troponin interpretation protocol applied also had limitations, specifically as regards serial investigations surrounding a result provided as a range. Other limitations of this study include: non-randomisation of the study sample, non-reporting of ECG findings and non-reporting of the 30-day major adverse cardiovascular event rate. Randomisation should be considered in future studies to improve the strength of the findings. Similarly, including an ECG evaluation in the study protocol would have improved the strength of the findings, but this would have required an independent review to be of value. The study team did not have the resources to include independent ECG evaluation and therefore used the exit clinical

diagnosis as a proxy to define whether ACS existed or not. An attempt should be made to include ECG findings in future research. Inclusion of the 30-day major adverse cardiac event rate would also improve the strength of the findings. This may, however, be more challenging to execute for 2 reasons: local electronic records are not as robust as in high-income settings and discharged patients are difficult to track as many do not have any formal contact details. Regarding the test itself, we did not report on the assay in depth. As the assay were performed by laboratory staff, issues surrounding quality control and lot to lot variation were not corrected for. Haemolysis may have been reported in the results, although we did not individually report these. Finally, the various non-ACS diagnoses and drugs that can affect troponin measurements were not controlled for.

CONCLUSION

Unstable angina made up a large proportion of NSTE-ACS in our study sample. It is possible that a more sensitive troponin assay would have resulted in a higher proportion of NSTEMI diagnosis and that that may have resulted in different down-stream care. Despite internationally accepted reference standards, many LMIC facilities continue to make use of troponin assays that are unable to accurately and reliably detect troponin rises. Emergency care providers working in these settings are reminded of the importance of diligent clinical record keeping; the value of a thorough history and physical examination when ACS is suspected; that a negative troponin should only be considered truly negative after close evaluation of a patient's symptoms, the history and ECG findings and that serial troponin testing is not necessarily a panacea when a range is presented instead of an absolute value. Evaluation of the diagnostic process in a multi-centre emergency care setting, particularly focusing on the contribution of ECG findings and the 30-day major adverse cardiac event rate, should be encouraged in order to strengthen a case for better diagnostic tools for LMIC emergency centres.

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