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The Prognostic Value of CK-MB in Acute Myocardial Infarction in Developing Countries: A Descriptive Study

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Abstract

Background: Acute myocardial infarction is a common condition among developing countries with access-to-care issues. However, scarce information is available on the association between prognostic markers and patient outcomes in areas around the globe with scarcere sources.

Aim: To evaluate the association between creatine phosphokinase myocardial band (CK-MB) and outcomes measured up to six months after the infarction.

Methods: This is a longitudinal cohort study evaluating patients with a diagnosis of myocardial infarction up to six months after the ischemic event. Patients underwent catheterization up to 12 hours after the first symptoms. The primary predicting variable was CK-MB level, with outcome variables including re-infarction, death, and functional level status at 30 days and 6 months after infarction.

Results: The average time of arrival was seven hours after the start of pain. When combining all adverse outcomes, 13.7% presented with either a myocardial re-infarction or death. When evaluating the association between serial CK-MB measurements and various outcomes of interest, there was usually no significant association with re-infarction, death or functional class at the 30-day and six-month follow-up evaluations. However, increased CK-MB measurements at admission, 18 and 72 hours continued to be significantly associated with increased length of hospital stay after adjusting for age and gender. CK-MB levels greater than 124 mg/dl after 18 hours after first symptoms were significant predictors of all combined adverse outcomes.

Conclusion: CK-MB represents an alternative when it comes to prognostic predictors of combined outcomes including myocardial re-infarction, re-intervention or death.

Keywords: Creatine kinase; Myocardial infarction; Prognosis; Developing countries

Introduction

Acute Myocardial Infarction (AMI) is a common disease with high morbidity, mortality and cost to society [1,2], being the leading cause of mortality worldwide [3]. These adverse outcomes can be reduced through timely diagnosis, treatment and stratification of patients according to their prognoses. While biomarkers for myocardial injury have greatly assisted in the early diagnosis [2], the evaluation of CK-MB in relation to patients' prognoses in developing countries has not been extensively explored.

Many myocardial biomarkers have played a significant role in relation to AMI diagnosis. For example, the high sensitivity cardiac troponin has been recommended for use in the diagnosis of AMI because of its high accuracy in the detection of myocardial infarction [4]. Also, the heart-type fatty acid binding protein (H-FABP) [5] is increasingly being considered for its ability to distinguish between patients with and without ischemic heart conditions [5]. Despite their importance in the context of diagnosis, the role of these biomarkers in relation to patients' prognoses is still limited. For instance, although both biomarkers might be associated with the prediction of outcomes such as mortality and re-infarction following AMI, their association with risk stratification is still not entirely clear, in part due to a lack of assay standardization in relation to procedures and nomenclature [6]. Moreover, more modern biomarkers are costly and less readily available in resource-limited settings [7].

Creatine kinase (CK) is an enzyme expressed in high amounts in muscle tissues, with three isoenzymes: CK-MM (creatine phosphokinase skeletal muscle), CK-BB (creatine phosphokinase brain band), CK-MB (creatine phosphokinase myocardial band) [8]. CK-BB is found in brain tissue, CK-MM in skeletal tissue, while CK-MB is specific to myocardial cells although it is also found in skeletal muscle [8]. CK-MB levels increase with myocardial cell damage, being detectable within four to eight hours from the onset of chest pain, peaking at 18-24 hours and returning to baseline within 24 to 48 hrs [8]. Elevated CK-MB levels have high specificity for myocardial infarction, early clearance helping in the detection of re-infarction [8]. Creatine kinase myocardial band (CK-MB) is widely available and used in resource-limited areas around the globe. Elevated levels of CK-MB have been associated with higher mortality rates in AMI patients [9], this biomarker also potentially having a better prognostic

performance than cardiac troponin I [10]. Furthermore, in patients undergoing percutaneous coronary interventions (PCI), elevated CK-MB levels continue to be associated with increased mortality at the three-month, six-month and one-year follow-up [11,12]. Notwithstanding, the advent of cardiac markers with better diagnostic performance have shadowed further exploration of the prognostic value of CK-MB in developing countries, where it is most used given its lower cost.

Faced with this gap in the literature, our goal was to describe the association between CK-MB and AMI outcomes including re-infarction, mortality and functional classification in two referral hospitals in Brazil.

Methods

Study design

We designed a prospective cohort study to evaluate the prognostic value of CK-MB in patients with acute myocardial infarction treated at two referral hospitals in Brazil. Our study was described in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [13].

Ethics

Our study was approved by the Institutional Review Board of the Federal University of Goiás. Informed consent was obtained by all participants prior to the implementation of any study protocol.

Setting

Data were collected at the Clinical Hospital of the Federal University of Goiás and the Mount Sinai Hospital in Goiânia-GO, both serving patients coming from surrounding areas and primary health care facilities in the area. Participant accrual occurred between 2012 and 2014, with the end of follow-up occurring in August of 2014.

Participants

Our participants were selected from a total of 835 patients diagnosed with acute myocardial infarction at the participating hospitals. We included all patients above 18 years of age, presenting with an AMI with an ST-segment elevation or new/presumably new complete left bundle branch block, pain for less than 12 hours, as well as those having results from serial CK-MB measurements, electrocardiogram, and an angioplasty report. We excluded patients arriving within more than 12 hours after the onset of pain (94%), those without an elevated ST-segment or left bundle branch block, and those without results from serial CK-MB measurements or a documented angioplasty procedure. Participants were characterized according to Killip classification into the following classes: (I) no clinical signs of heart failure, (II) rales or crackles in the lungs, an S3, and elevated jugular venous pressure, (III) acute pulmonary edema and (IV) cardiogenic shock and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating). Treatment provided to patients included cardiac catheterization followed by angioplasty. We used the 12-hour cut-off for selection of our participants since procedures performed within this time were likely to have the best outcomes [14,15].

Treatment protocol

Initial treatment included oxygen, aspirin 200 mg per oral, clopidogrel 600 mg per oral, morphine 2 mg intra venous, sublingual nitrate depending on systemic blood pressure and infarction location, and vasoactive drugs in presence of hemodynamic instability. Glycoprotein IIb/IIIa was only used in situations where clopidogrel was not used. Coronary angiography and left ventriculography were performed through a femoral or radial access, with the intervention involving both left and right coronary arteries. Finally, the angiography was followed by a pre-dilation balloon, manual thrombus aspiration, and then by a coronary stent with a post-procedure angiography. Additional dilations were performed for residual lesions with greater than 70% stenosis or coronary dissection. Thrombolysis in myocardial infarction (TIMI) flow grade and myocardial blush grades (MBH) were used to access the myocardial tissue-level perfusion after angioplasty. TIMI was graded as 0 (no perfusion), 1 (penetration without perfusion), 2 (partial reperfusion), 3 (normal flow). Myocardial blush grades (MBH) was defined as 0 (no myocardial blush or contrast density), 1 (minimal myocardial blush or contrast density), 2 (moderate myocardial blush or contrast density less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery) and 3 (normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery).

Outcome variables

Outcomes of interest were any acute myocardial re-infarction, death, or re-intervention during in-hospital stay and at the six-month follow-up after discharge. In addition, we measured number of days between the intervention and any of the complications up to the six-month follow-up; functional class at admission, 30 days and six months after admission; and length of hospital stay. We defined a combined outcome variable as the presence of acute myocardial re-infarction or death or re-intervention. We used the third universal definition of myocardial infarction [16].

Predictor variables

Our main predictor was CK-MB level (mg/dl) measured at admission and every six hours in the first 24, 48, 72 and 96 hours after admission.

Potential confounding variables

Potential confounders were selected based on evidence from previous literature combined with clinical judgment [17]. Specifically, we selected age and gender as our main confounders of the association between CK-MB levels and outcomes of interest.

Statistical methods

We started our analysis by exploring the distributions, frequencies and percentages for each of the numeric and categorical variables. Categorical variables were evaluated for near-zero variation [18] while numeric variables were evaluated for non-normal distribution. Extensive graphical displays were further used for both univariate analysis and bivariate associations, followed by broader tests such as the Maximal Information Coefficient [19] and Nonnegative Matrix Factorization [20] algorithms for numeric variables. Missing data were explored using a combination of graphical displays involving

univariate, bivariate and multivariate methods, and imputation was performed using a k-nearest neighbors algorithm (n=5) [21].

We used a series of generalized linear models with a binomial family (logistic regression) to model the associations between CK-MB and acute myocardial infarction, death, re-infarction and functional class adjusted for age and gender. Each outcome is provided using 95% confidence intervals. Models were only reported where the sample size had adequate statistical power to test for associations between variables. We then performed a recursive partition model using unsupervised trees of hierarchical clustering (tree regression models) [22] to identify the most common associations and hierarchical patterns among the serial CK-MB measurements of patients for our combined outcomes. Tree regression models split predictor levels depending on their direct association with the combined outcome.

All analyses were performed using the R language [23] and the following packages: ggplot2 [24], rmarkdown [25].

Results

Participants

A total of 51 patients with an average age of 56 years old were included in this analysis, ultimately comprising 6.1% of the initial 834 sample. Most participants (67%) were males and most of them (70%) presented with chronic hypertension. The average time between start of pain and hospital arrival was seven hours. When combining all adverse outcomes, 13.7% presented with either a myocardial re-infarction or death. Anterior infarction was the most common location (45.1%), followed by inferior infarction (41.2%). The average ST-segment elevation in patients at admission was 5 millimeters, this measure dropping by 56% one hour after admission. Most patients presented TIMI grade III (54.9%) and a blush grade 2 (51%). Sixty four percent arrived with functional class I, and the average length of hospital stay was six days (Table 1).

Variable	Total (51)	Females (17)	Males (34)	p value
Age	56.43 (±13.01)	62.59 (±12.63)	53.35 (±12.24)	0.018
Chronic hypertension	38 (74.5%)	14 (82.4%)	24 (70.6%)	0.059
Diabetes	14 (27.5%)	8 (47.1%)	6 (17.6%)	0.059
Dyslipidemia	18 (35.3%)	8 (47.1%)	10 (29.4%)	0.351
Smoking	14 (27.5%)	4 (23.5%)	10 (29.4%)	0.912
Duration of chest pain (hours)	7.06 (±2.45)	7.53 (±3)	6.82 (±2.14)	0.395
Heart rate	93.14 (±21.37)	85.24 (±24.77)	97.09 (±18.61)	0.094
Systolic Blood Pressure	132.55 (±21.71)	130 (±28.06)	133.82 (±18.09)	0.614
Diastolic Blood Pressure	80.14 (±14.03)	75.29 (±17.72)	82.56 (±11.32)	0.137
Mean Arterial Blood Pressure	97.61 (±15.42)	93.53 (±20.33)	99.65 (±12.12)	0.265
Anterior Infarction	23 (45.1%)	7 (41.2%)	16 (47.1%)	0.921
Inferior Infarction	21 (41.2%)	8 (47.1%)	13 (38.2%)	0.763
Lateral Infarction	7 (13.7%)	2 (11.8%)	5 (14.7%)	1
ST-Segment Elevation on admission	5.02 (±1.24)	5.29 (±1.31)	4.88 (±1.2)	0.286
ST-Segment Elevation at one hour after admission				0.745
- 0	1 (2%)	0 (0%)	1 (2.9%)	
- 1	14 (27.5%)	4 (23.5%)	10 (29.4%)	
- 2	18 (35.3%)	6 (35.3%)	12 (35.3%)	
- 3	9 (17.6%)	3 (17.6%)	6 (17.6%)	
- 4	8 (15.7%)	3 (17.6%)	5 (14.7%)	
- 5	1 (2%)	1 (5.9%)	0 (0%)	
ST-Segment drop at one hour after admission	56.65 (±17.46)	54.64 (±16.14)	57.66 (±18.23)	0.551
TIMI Grade				0.274
- I	8 (15.7%)	2 (11.8%)	6 (17.6%)	
- II	15 (29.4%)	3 (17.6%)	12 (35.3%)	

- III	28 (54.9%)	12 (70.6%)	16 (47.1%)	
Blush Grade				0.426
- 1	10 (19.6%)	4 (23.5%)	6 (17.6%)	
- 2	26 (51%)	10 (58.8%)	16 (47.1%)	
- 3	15 (29.4%)	3 (17.6%)	12 (35.3%)	
Killip Classification				0.187
- I	36 (70.6%)	10 (58.8%)	26 (76.5%)	
- II	11 (21.6%)	4 (23.5%)	7 (20.6%)	
- III	2 (3.9%)	2 (11.8%)	0 (0%)	
- IV	2 (3.9%)	1 (5.9%)	1 (2.9%)	
Functional Class at admission				0.268
- I	33 (64.7%)	8 (47.1%)	25 (73.5%)	
- II	13 (25.5%)	6 (35.3%)	7 (20.6%)	
- III	3 (5.9%)	2 (11.8%)	1 (2.9%)	
- IV	2 (3.9%)	1 (5.9%)	1 (2.9%)	
Functional Class at 30 days				0.854
- I	47 (92.2%)	15 (88.2%)	32 (94.1%)	
- II	4 (7.8%)	2 (11.8%)	2 (5.9%)	
Functional Class at six months				0.892
- I	43 (84.3%)	15 (88.2%)	28 (82.4%)	
- II	8 (15.7%)	2 (11.8%)	6 (17.6%)	
Length of hospital stay (days)	5.96 (±1.73)	6.47 (±2.12)	5.71 (±1.47)	0.195
Re-intervention	2 (3.9%)	0 (0%)	2 (5.9%)	0.799
Acute Myocardial Infarction	3 (5.9%)	1 (5.9%)	2 (5.9%)	1
Death	6 (11.8%)	4 (23.5%)	2 (5.9%)	0.167
All Events Combined	7 (13.7%)	4 (23.5%)	3 (8.8%)	0.314
Time to Event (days)	1.88 (±5.76)	4.24 (±9.11)	0.71 (±2.39)	0.135
CK-MB level on admission (IU/L)	119.24 (±101.73)	159.94 (±150.62)	98.88 (±58.31)	0.124
CK level on admission (IU/L)	1341.69 (±614.62)	1358.65 (±755.72)	1333.21 (±543.35)	0.903

Table 1: Participants characteristics stratified by gender.

Serial CK-MB values (mg/dl) peaked at six hours after admission and gradually declined until the 96th hour (Figure 1). When evaluating the association between serial CK-MB measurements and various outcomes of interest, there was usually no significant association with re-infarction, death or functional class at the 30-day and six-month follow-up. However, all elevated CK-MB measurements at admission, 18 and 72 hours after admission were significantly associated with increased length of hospital stay after adjusting for age and gender (Table 2). A tree regression model demonstrated that CK-MB values (mg/dl) at 18 hours after admission were the most important predictor of combined outcomes including death, re-infarction or re-intervention, with levels above the 124 mg/dl cut-off CK-MB level being associated with worse outcomes (Figure 2).

Discussion

To our knowledge the role of CK-MB in determining patients' prognoses after acute myocardial infarction in developing countries has not been extensively evaluated.

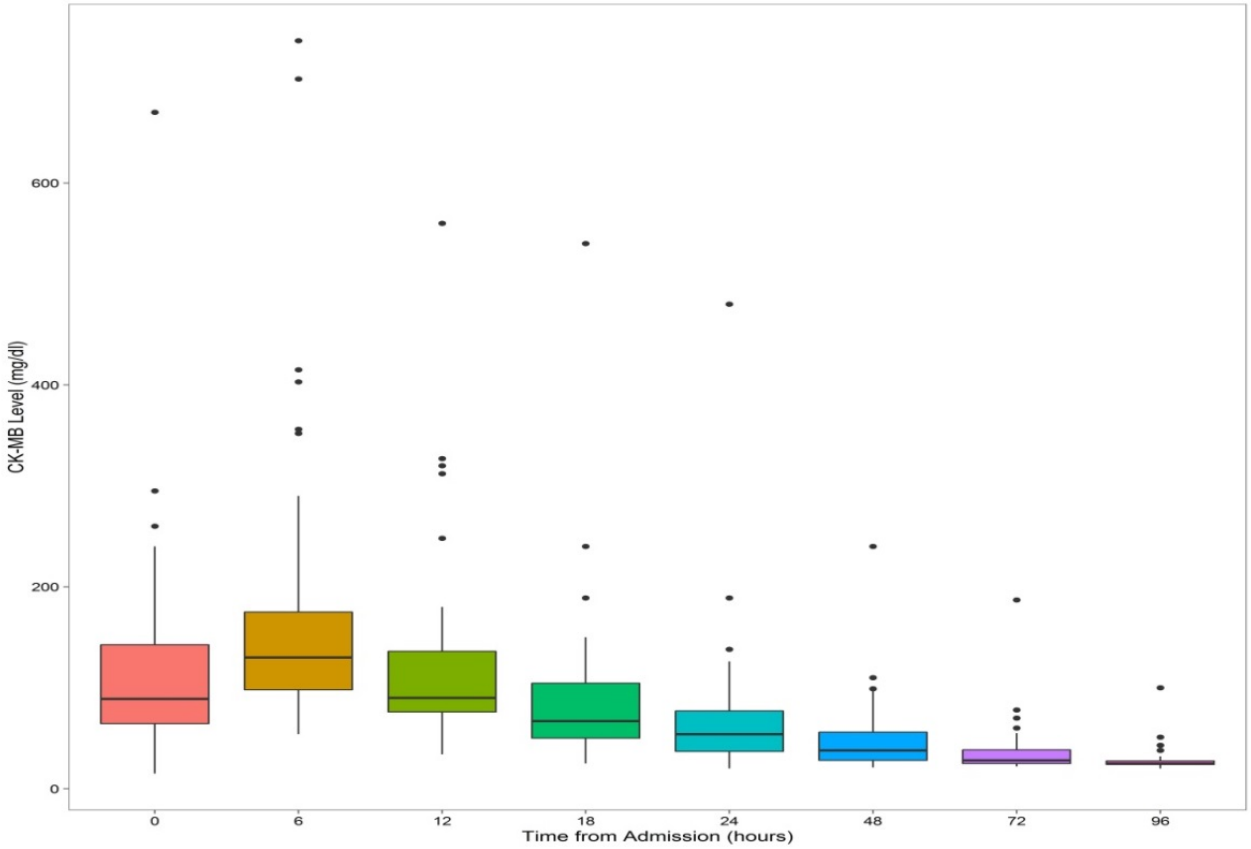

Figure 1: CK-MB measurements (mg/dl) at various times after admission.

Length of stay in days	Admission CK-MB lower	Admission CK-MB upper	six hours CK-MB lower	six hours CK-MB upper	18 hours CK-MB lower	18 hours CK-MB upper	72 hours CK-MB lower	72 hours CK-MB upper
Length of hospital stay (unadjusted)	5.08 (4.47, 5.7)	6.74 (6.16, 7.32)	5.28 (4.65, 5.91)	6.62 (6, 7.23)	5.24 (4.62, 5.86)	6.65 (6.04, 7.27)	5.14 (4.46, 5.83)	6.53 (5.96, 7.11)
Length of hospital stay (adjusted)	5.21 (4.57, 5.85)	6.63 (6.06, 7.19)	5.51 (4.86, 6.15)	6.49 (5.86, 7.12)	5.4 (4.79, 6.01)	6.61 (6.01, 7.22)	5.26 (4.6, 5.93)	6.51 (5.96, 7.06)

Table 2: Associations between CK-MB at 50th percentile and Length of hospital stay.

We found that elevated CK-MB levels measured after admission were significantly associated with increased length of hospital stay, but not with other individual outcomes including re-infarction, death and functional class at the 30-day and six-month follow-up. CK-MB level at 18 hours after admission was the most important predictor of combined outcomes (myocardial re-infarction, re-intervention or death).

Several methods have been proposed to evaluate the prognosis of acute myocardial infarction and other coronary syndromes. For example, the GRACE score can predict cumulative six-month risk of death or myocardial infarction based on clinical parameters including age, heart rate, systolic blood pressure, congestive heart failure, electrocardiogram findings on admission, and cardiac enzyme levels [26]. Cardiac enzymes commonly incorporated into such scores include Troponin T, Troponin I [27,28] and creatine kinase myocardial band [29]. Other predictors of outcome following acute myocardial infarction include the estimation of the mean left ventricular diastolic pressure measured through echocardiography [30]. In such cases, mean ventricular diastolic pressure greater than 15 has been associated with higher mortality after myocardial infarction [30]. Most of these methods are, however, not economically feasible in developing countries. CK-MB is a vital component in assessing re-infarction or infarct extension in patients with acute myocardial infarction [31]. For instance, in patients undergoing percutaneous coronary interventions, those with values greater than five times the normal have been shown to have higher rates of subsequent cardiac death up to four months after the initial procedure [32,33].

Figure 2: Tree regression model with predictor of combined outcome.

In our study, although CK-MB levels at 18 hours after admission were predictive of combined outcomes (myocardial re-infarction, re-intervention or death), there was no significant association between CK-MB and individual outcomes including death, myocardial re-infarction, and functional class. This could be explained since our study did not have a high enough number of events to detect such an association. In addition, since we performed interventions on patients with up to 12 hours after acute myocardial infarction in combination with manual aspiration thrombolysis, our case mix could also be different from those in other studies. Notwithstanding, it has been reported that CK-MB levels might not be associated with outcomes of acute myocardial infarction [34]. Finally, our finding of an association between increased CK-MB levels and increased length of hospital stay opens yet another possibility in relation to the prognostic value of CK-MB.

Resource scarcity ultimately emphasizes the use of CK-MB as a low-cost prognostic marker which could be applied in a number of countries with contexts similar to ours. While one could argue that CK-MB might not be the ideal mechanism to evaluate prognosis, it is important to consider that the cost-effectiveness of different prognostic markers will vary across different contexts. Although, to our knowledge, no previous studies have been conducted on the cost-effectiveness of prognostic markers after acute myocardial infarction, the cost-effectiveness of different therapeutic measures has been shown to vary across therapies and countries [35]. For example, the incremental cost-effectiveness ratio of Lisinopril ($US 2,080 per life-year saved) is lower than the one for rt-PA ($US 32,687 per life-year saved), although this difference varied when considering different health care systems, drug prices, cultures, among other factors [36]. This wide variation is not restricted to comparisons between developing and developed countries, but can also happen within developed countries. For example, although tPA is considered to be more cost-effective than streptokinase, substituting streptokinase by recombinant tissue plasminogen results in incremental costs for each life saved of 30%, 45%, and nearly 100% in Germany, Italy and the United States when compared to the United Kingdom. In summary, clinical practice guidelines devised for developed countries might not necessarily apply to developing countries with scarce resources, potentially making CK-MB an attractive alternative from a health economic perspective.

Although a sample of 51 patients might seem small for a study evaluating the prognosis of Acute Myocardial Infarction, it is important to emphasize that this sample originated from an overall population of 835 patients. This drop of nearly 94% in relation to the original population emphasizes the severe access-to-care issues within the Brazilian context. Not only do these access issues result from the overall low socio-economic status of our patients, but they are also related to the far-from-ideal geographical distribution of tertiary care centers in developing countries [37]. Access-to-care issues have contributed to ischemic heart conditions being the current leading cause of death among developing countries [38]. Factors associated with precarious access to care are primarily related to educational factors where patients are unable to detect early symptoms, access to basic healthcare that would increase their chances of complying with common preventive measures, as well as issues with emergency medical care. Emergency care becomes fundamental when the actual myocardial infarction occurs, with access-to-care issues ranging from the scarcity of transportation to inadequate staff training in recognizing signs of ischemia [38]. Of special interest is the possibility of improving the quality of pre-hospital services to include electrocardiogram and thrombolysis inside ambulances, ultimately reducing door-to-cath time on hospital arrival [39]. Interestingly, access-to-care issues are not restricted to underdeveloped countries, but are often encountered in underserved areas within developed countries. For example, a recent survey focusing on the penetration of primary angioplasty in Europe found that patients' access to reperfusion and other therapies related to acute myocardial infarction varied across different countries. Specifically, countries in the North, West and Central areas of Europe had well-developed care services, offering appropriate care anywhere between 60 and 90% of all patients. In contrast, Southern Europe and the Balkans made use of treatments that were not aligned with clinical practice guidelines, ultimately leading toward higher proportions of patients without reperfusion treatment [40]. This context of severely restricted resources is therefore not inherent to Brazil, but widespread across multiple regions around the world.

Despite filling an important gap in the literature, our study does have a number of limitations. First, our sample size was small when compared to other series. This limitation is explained by the challenges involved in following-up patients in areas with restricted access to care. Second, we made use of a protocol which involves patients undergoing a catheterization, as well as making use of aspiration thrombolysis up to 12 hours after the acute myocardial infarction. Although these procedures were recommended by clinical practice guidelines at the time of the study [15], they are no longer in current guidelines.

Conclusion

Our study demonstrates that increased CK-MB levels are significantly associated with prolonged length of hospital stay as well as with worse combined outcomes of myocardial re-infarction, re-intervention or death. Further exploration of CK-MB in relation to patients' prognoses might add value to the use of this prognostic biomarker in developing countries.

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