CK-MB Activity, Any Additional Benefit to Negative Troponin in Evaluating Patients with Suspected Acute Myocardial Infarction in the Emergency Department

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Background: *Coronary heart disease is now the leading cause of death. Diagnosing myocardial infraction (MI) needs cardiac marker in case of equivocal clinical presentations and EKG interpretations. Troponin yields high sensitivity and specificity and could be used as a single screening assay. However, in actual practice, clinicians send CK-MB activity (CKMBa) as a combined marker with an expectation of providing additional diagnostic value due to large historical data. Discordant results from both markers lead to unclear management. Our study was to determine whether CKMBa has potential benefit for initial screening of MI in addition to cardiac troponin T (cTpT) in the Emergency Department (ED), and can this marker be safely removed from the routine laboratory panel in the emergency setting in Thailand.*

Material and Method: *We conducted a retrospective cohort single-center study to examine the usefulness of CKMBa in the ED from 907 patients who presented with clinically suspected acute MI, and investigated with both biomarkers (CKMBa and cTpT). In these patients, 97 patients were included in the final analysis as they had negative cTpT associated with positive CKMBa or CKMBa turned to be positive within 24 hours after serial biomarkers measurements. The outcome was assessed by the final diagnosis, the cause of death if patients died during admission, and the 180-day mortality from medical chart review. In patients highly suspected for MI, further investigations were done including echocardiogram, exercise stress test, and coronary angiogram by experienced cardiologists.*

Results: *During the study period, cTpT were sent 1,772 times and most (95.2%) of the samples were associated with CKMBa results. The outcome showed that no one with negative cTpT was diagnosed as MI on a discharge diagnosis. Fourteen patients died during admission. The definitive cause was not defined as MI. The 180-day mortality was zero. During the follow-up, there was no MI suspected issues that needed further cardiac evaluations. The positive predictive value of CKMBa with negative cTpT was 0% (95% CI, 0-0.047).*

Conclusion: *CKMBa added no benefit to cTpT in diagnosing acute MI in ED. Removing CKMBa from emergency panel could be considered.*

Keywords: *Troponin, CK-MB activity, Myocardial infarction, Emergency department*

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Coronary heart disease is now the leading cause of death in developed countries and it is expected to become more emerging worldwide in 2020 due to the highest rank of predicted disability-adjusted life years (DALYs). It is now the major global burden of disease[1]. Despite the advanced health care, the incidence of myocardial infarction (MI) is gradually rising. It is crucial to make an early accurate diagnosis, especially in patients came with equivocal both clinical presentations and electrocardiogram (EKG) findings. Cardiac markers are needed to play a key role.

Creatine kinase-MB (CK-MB) is one of three isozymes (CK-MB, CK-MM, and CK-BB) of creatine kinase. It mainly contains in myocardium (40%) and has little amount in skeletal muscle (2-3%). This marker was once considered as a gold standard tool for acute MI diagnosis[2]. However, the measurement technique of CKMBa is considered as non-sensitive, non-specific, and takes long turn-around time[3]. After immunoinhibition with antibodies to CK-M subunit of CK-MB and CK-MM, CK-B activity is then measured

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and multiplied by two to provide estimate level of CKMBa. Unfortunately, B-subunit of CK-BB and atypical CK are not inhibited and quantitated, resulted in false high-value[4]. New assay has been introduced known as CK-MB mass (CKMBm), which measures its protein concentration based on electrochemiluminescence technology instead of biologic activity. Although, CK-MB mass provides higher sensitivity and specificity[5], it also has limitations. First, for screening of MI during massive musculoskeletal injury, the result may be falsely high. Second, for late detection of MI, the result may be falsely low due to its early release pattern[6].

The American College of Cardiology Foundation (ACCF), the European Society of Cardiology (ESC), the World Heart Federation (WHF), and the American Heart Association (AHA) Task Force recommend measuring cardiac troponin as a single assay for screening MI because it yields high sensitivity and specificity; they also recommend not performing the CK-MB measurement as a combine marker[7,8]. Sending both tests may have discordant results in which the optimal management is unclear[8]. Troponin is the preferred marker, but if it is not available, the acceptable alternative is CKMBm. It is recommended that CKMBa is not sent for initial screening of MI anymore(7). Even though, historically, CKMBa was widely used because it detects early infarction, currently, the sensitivity of newer troponins is much improved. Therefore, cardiac troponin becomes the key biomarker for MI diagnosis[9].

While only a few medical laboratories in Thailand have specialized equipment and reagent to measure CKMBm, the vast majority of laboratories, even in community hospitals, are able to investigate CKMBa. However, in actual practice, many centers still use CKMBa combined with cardiac troponin for evaluation of clinically suspected MI patients.

Objective

The primary aim of the present study is to determine whether CKMBa has additional diagnostic value to cardiac troponin in the Emergency Department (ED) for initial screening of MI. The secondary aim is to evaluate if CKMBm could be safely removed from laboratory panel in the ED.

Material and Method

Patients

We conducted a retrospective cohort study in a tertiary referral center, King Chulalongkorn Memorial Hospital. Between February 1 and June 30, 2011, all patients presented with signs and symptoms suspected acute coronary syndrome in the ED that was sent for both markers (troponin T and CKMBa) were selected. The inclusion criteria were patients who had negative cardiac troponin T (cTnT) and positive CKMBa at the first time and remained positive for at least 24 hours after serial measurements, or patients that initially tested negative both cTnT and CKMBa and then serial measurements of CKMBa turning to be positive within 24 hours. The exclusion criteria were patients who had initially negative cTnT and positive CKMBa but CKMBa turned to be negative within 24 hours of serial measurements, or patients who initially tested positive cTpT regardless of CKMBa value. All subjects were categorized into outpatient and inpatient subgroup based on admission status to determine the common final diagnosis of both settings.

Data were collected from medical records, including age, sex, clinical presentation, underlying disease, and discharge diagnosis. Patients were followed-up until 180 days after hospitalization. Primary outcomes were the definitive diagnosis, the cause of death if patients died during admission, and the 180-day mortality. The final diagnosis of MI is based on clinical, EKG, and cardiac biomarkers according to the third universal definition of MI[7]. Further investigations including echocardiogram, exercise stress test, and coronary angiogram were reviewed.

Biomarker analysis

Blood samples for measurement of cTpT and CKMBa were drawn along with blood for routine investigations. The measurement of CKMBa was done by using MULTIGENT CK-MB assay analyzed on ARCHITECT *c* Systems according to IFCC method/ immunoinhibition principle (Abbott Diagnostics, USA). CKMBa was defined as CK-B subunit activity multiplied by two. The measurement of cTpT was used Elecsys Troponin T high sensitive (Roche Diagnostics, Germany). The cTpT was analyzed using Elecsys 2010 system. This assay is based on electrochemiluminescence immunoassay technology (ECLIA) using two mouse monoclonal antibodies in a sandwich format, two-step assay. For CKMBa, the detection limit was 3 U/L with an upper limit of 1,000 U/L; and for cTpT, the detection limit was 0.005 ng/mL with an upper limit of 10 ng/mL. The manufacturer's cutoff limit was 0.1 ng/ml for cTpT that optimizing ROC curve showing 99% sensitivity and 98% specificity and 25 U/L for

CKMBa, which is the 99th percentile above reference limit. The precision of CK-MB assay is less than 7.5% total imprecision (CVs) for concentration >25 U/L. The total imprecision (CVs) at the 99th percentile value of cTpT is less than 10%[10,11].

Statistical analysis

Descriptive statistics were used to present the data. The data were analyzed using the Statistical Package for the Social Sciences (SPSS®) software for mac, version 21.

Results

The cTpT was sent 1,772 times from 935 patients. CKMBa was sent as a combined marker 1,687 times (95.2% from all cTnT measurements) from 907 patients (97% of all patients). The initial cTnT was negative in 720 patients. Of these, the initial CKMBa was positive in 127 patients and still positive after 24 hours from serial measurements in 93 patients (turned to negative in 34 patients). For patients with initial negative for both cTnT and CK-MB, 12 had subsequent positive CKMBa and were included in the present study. The data was unavailable in eight patients because the medical records could not be retrieved or were incomplete. Therefore, 97 patients were analyzed.

From the 97 patients, 44.3% were female. The average age was 64.6±16.85 years and the average age of male and female were 62.48±17.63 years and 67.26±15.60 years, respectively. Most patients had no underlying diseases (21.6%). The most common underlying disease was hypertension (20.6%) and dyslipidemia (14.4%), respectively (Table1). The most common clinical presentation was dyspnea (39.2%), followed by chest pain (29.9%). Other presentations included dizziness (3.1%), leg pain and discoloration (3.1%), fever (1%), jaundice (1%), and headache (1%) (Table 2).

Seventy-two patients were admitted in the hospital and 25 patients were discharged from ED. Among inpatient group, 58 were improved and 14 expired. Of the outpatient group, 24 were improved and one patient was referred to another hospital. Cardiovascular diseases were the most common final diagnoses in which heart failure is the highest predominant in both inpatient and outpatient settings (Table 3). From medical chart review, there were eight patients were finally diagnosed as atypical chest pain. Six of them received further studies, coronary angiography in five cases and cardiac stress test in one case. All results were negative. Two of them were observed and follow-up to 180 days. Other final diagnosis included hyperkalemia, sepsis, electrical injury, acute arterial occlusion, acute kidney injury, intracerebral hemorrhage, rhabdomyolysis, stroke, and hyperglycemia (Table 3).

Fourteen patients expired during admission. None was finally diagnosed as acute coronary injury. One of them passed away by cardiac arrest with unknown cause but this patient was prior admitted to another hospital and underwent coronary angiography three months ago with a negative result for coronary artery disease (Table4).

Eighty-two patients were discharged from the hospital or from ED with approval. Two patients were referred to another hospital for admission. One patient did not have an appointment. The follow-up rates at

Table 1. Underlying disease of clinical suspected MI patients presented to the Emergency Department (ED)

	No. of cases	%
HTN+DM+DLP	5	5.2
HTN+DM+CVD	6	6.2
HTN+DM	5	5.2
HTN+CKD	7	7.2
DLP+CKD	4	4.1
HTN	20	20.6
DM	7	7.2
DLP	14	14.4
CKD	3	3.1
CVD	5	5.2
No underlying disease	21	21.6
Total	97	100.0

CKD = chronic kidney disease; CVD = cerebrovascular disease; DM = diabetes mellitus; DLP = dyslipidemia; HTN = hypertension; MI = myocardial infraction

Table 2. Clinical presentations of patients with clinically suspected MI at the ED (n = 97)

	No. of cases	%
Dyspnea	38	39.2
Chest pain	29	29.9
Alteration of consciousness	5	5.2
Syncope	5	5.2
Abdominal pain	5	5.2
Palpitation	4	4.1
Electric shock	2	2.1
Others	9	9.3

Table 3. The final diagnosis of patients with clinically suspected MI at the ED

	Inpatient (n = 72)		Outpatient (n = 25)	
Cardiovascular system				
CHF/AHF	24	50.0	8	72.7
Tachyarrhythmia	9	18.8	-	0.0
Bradyarrhythmia	2	4.2	-	0.0
Ruptured AAA	1	2.1	-	0.0
Cardiac arrest (unknown cause)	2	4.2	-	0.0
Ischemic cardiomyopathy	2	4.2	2	18.2
Vasovagal syncope	1	2.1	-	0.0
Atypical chest pain	7	14.6	1	9.1
Total	48	100.0	11	100.0
Gastrointestinal system				
Dyspepsia	1	11.1	5	83.3
Acute cholecystitis/cholangitis	3	33.3	-	0.0
Hepatitis	1	11.1	-	0.0
Peptic ulcer perforation	1	11.1	-	0.0
Acute gastroenteritis	-	0.0	1	16.7
Ischemic bowel disease	2	22.2	-	0.0
Cholangiocarcinoma	1	11.1	-	0.0
Total	9	100.0	6	100.0
Respiratory system				
Pneumonia	3	42.9	-	0.0
Acute bronchitis	-	0.0	1	50.0
Pleural effusion	1	14.3	1	50.0
COPD	1	14.3	-	0.0
Lung cancer	2	28.6		0.0
Total	7	100.0	2	100.0
Muscle strain/costochondritis	1	100.0	7	100.0
Others*	18	100.0	1	100.0

AAA = abdominal aortic aneurysm; AHF = acute heart failure; AKI = acute kidney injury; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease

* Inpatient: hypokalemia in 5 patients, sepsis in 4, acute peripheral arterial occlusion in 3, electrical injury in 2, AKI in 1, hyperglycemia in 1, rhabdomyolysis in 1, and intracerebral hemorrhage in 1 patient; Outpatient: adjustment disorder 1 patient

30, 60, 90, and 180 days were 72 (87.8%), 70 (85.4%), 68 (82.9%), and 58 (70.7%) patients, respectively. The follow-up duration was counted from the day that the patients presented at emergency room (ER). During follow-up, the mortality rate was zero and no further cardiac investigation was needed. The positive predictive value and negative predictive value of CKMBa with negative cTpT was 0% (95% CI, 0-4.74) and 100% (95% CI, 99.2-100), respectively.

Discussion

During this 5-month period of study, 935 patients were investigated with cTnT for their clinical suspected acute MI at ED. Additionally, 97% of them were tested with CKMBa as a combined marker. Even though, there is a recommendation by the National Academy of Clinical Biochemistry (NACB) practice guideline for not sending CKMBa if troponin or CKMBm is available, which was published in 2007, clinicians still use this marker combined with cardiac troponin in Thailand[12].

Table 4. Cause of death in patients whom admitted to the hospital due to clinical suspected MI

No.	Clinical presentation	Final diagnosis
1	Dyspnea	Septic shock
2	Dyspnea	Cardiac arrest by secretion obstruction
3	Dyspnea	Sepsis, CHF
4	Dyspnea	Lung cancer with bilateral pleural effusion
5	Dyspnea	AHF
6	Dyspnea	AHF due to pulmonary embolism, septic shock
7	Chest pain	AHF due to portal hypertension
8	Chest pain	Septic shock with cholangitis
9	LOC	Cardiac arrest by unknown cause
10	LOC	Hyperkalemia, aspiration pneumonia
11	AOC	Urinary tract infection with sepsis
12	AOC	Peptic ulcer perforation with septic shock
13	Palpitation	Cellulitis with sepsis
14	Dizziness	Pneumonia with hyperglycemia

AHF = acute heart failure; AOC = alteration of consciousness; CHF = chronic heart failure; LOC = loss of consciousness

The outcomes were measured by the final diagnosis, the 180-day mortality, and the cause of death for the patients who died during admission. No one was finally diagnosed MI by all these three outcomes. This finding is similar to several other studies, which indicated that troponin could be used solely without CKMBa. Furthermore, CKMBa provides no additional benefit for diagnosis MI[9,13-17]. Recent study specifically evaluated chest-pain patient with negative troponin but positive CKMB index in the ED. The result supported our study that the true positive rate of CK-MB index with negative troponin was 0%[13]. Moreover, the present study used CK-MB index, which provides higher specificity than CKMBa[18].

Sending both markers can lead to improper management as demonstrated in our study. Six of 97 patients (6.2%) with atypical chest pain and discordant markers (negative cTpT and positive CKMBa) received

further cardiac evaluations (coronary angiogram or cardiac stress test), which all results came back negative. Avoiding these could lead in decreasing cost of healthcare.

CKMBa can be elevated in several conditions beside MI, giving high false positive rate such as extreme physical activity[19], inflammatory myopathy[20], hypothyroidism[21], chronic hemodialysis[22], pulmonary embolism[23], high dose albuterol use in treatment of asthma[24], ulcerative colitis, bladder cancer, prostate cancer[25], and other solid malignancies[26]. Furthermore, CKMBa may be difficult to standardize because there are many manufacturers and it is difficult to control the quality of CK-MB assays. Additionally, it can be incorrectly used because it must be measured according to gender-specific reference ranges and cutoffs value[27]. Several hospitals including Mayo Clinic, Rochester removed CKMBa from cardiac marker panels[8]. CKMBa is similar to myoglobin, which was once used as a very early cardiac marker; however, lately some studies proved that when they use the 99th cut-off high-sensitive troponin at the point-of-care, myoglobin has no additional diagnostic value[28,29].

In this era, due to higher sensitivity and specificity, troponin is the preferred marker over CK-MB according to Joint the ESC/ACCF/WHF and the AHA Task Force. CKMBm is currently still useful when troponin is unavailable. Moreover, after diagnosis of MI is made, serial measurements of this biomarker are useful when it demonstrates rise and fall pattern that could aid in confirming MI. However, it is the case when providing information of infarct size and surveying ongoing or recurrent MI due to the downside of troponin with its long half-life[12]. Therefore, there is no additional benefit for sending with cardiac troponin during first visit in the ED as was reported in previous study[14].

From the present study, CKMBa seems to be useless. However, NACB guidelines allow using CKMBa as an acceptable alternative in the institutions where troponin and CKMBm is not available. However, currently, even community hospitals have cardiac troponin as a basic laboratory panel. Therefore, there is no need to use CKMBa for evaluating acute MI. Nevertheless, based on current actual practice in Thailand, CKMBa has been extensively used to investigate patients suspected with acute MI. Therefore, the authors recommend sending only cardiac troponin to investigate acute MI suspected patients in the emergency setting. Furthermore, the authors are encouraging removal of CKMBa from laboratory panel in the ED. This decrease the cost of healthcare and prevent improper management.

The limitation of study included there were some missing data. Eight patients were not included because of missing medical record. Additionally, the 180 days follow-up rate was only 70.7% because our hospital being a tertiary-care referral center. Some patients might follow-up with their own primary care hospital; however, the short-term 30-day follow-up rate was high as 87.8% and the mortality rate was zero.

Conclusion

CKMBa has no additional benefit on cTnT in diagnosis of acute MI in ED. We recommend not sending CKMBa in patient presenting with clinical suspected MI.

What is already known on this topic?

CK-MB activity has no additional benefit for diagnosis MI.

What this study adds?

To clarify and encourage physician to safely remove CK-MB activity from laboratory panel in emergency setting that will reduce cost of healthcare and prevent improper management if physicians use this biomarker for initial MI screening in the ED, in combination with cTpT.

Authors' contributions

Jaruvongvanich V and Rattanadech W contributed to the acquisition, analysis, and interpretation of the data, as well as the draft the article. All authors read and approved the final manuscript.

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Potential conflicts of interest

None.

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การส่งตรวจ CK-MB activity ไม่ได้ประโยชน์เพิ่มเติมจาก cardiac troponin ในการวินิจฉัยโรคหัวใจขาดเลือดที่ห้องฉุกเฉิน

วีรวิชญ์ จารุวงศ์วณิชย์, วีรนุช รัตนเดช, วิลาวัณย์ ดำเกิงสุนทร, ศุทธินี จารุวงศ์วณิชย์, ยงเกษม วรเศรษฐการกิจ

ภูมิหลัง: *ปัจจุบันโรคหัวใจขาดเลือดเป็นสาเหตุการเสียชีวิตอันดับต้น ๆ ของประเทศไทย การตรวจวัดค่าหัวใจจากการตรวจเลือดมีบทบาทสำคัญในการช่วยวินิจฉัยในผู้ที่มีอาการและคลื่นไฟฟ้าหัวใจไม่ชัดเจน ค่า cardiac troponin T (cTpT) เป็นค่าที่มีความแม่นยำสูงและถูกอ้างอิงว่าสามารถนำมาใช้เพียงค่าเดียวก็ช่วยในการวินิจฉัยได้ อย่างไรก็ตามในทางเวชปฏิบัติ แพทย์จะส่ง CKMB activity (CKMBa) ร่วมไปกับ cTpT เพื่อหวังว่าจะช่วยเพิ่มความแม่นยำในการวินิจฉัย แต่ถ้า CKMBa และ cTpT ให้ค่าที่ไม่ไปในทิศทางเดียวกันจะทำให้มีปัญหาในการวินิจฉัยและการตัดสินใจในรักษาได้ การศึกษานี้เป็นการศึกษาว่าการส่งตรวจ CKMBa ได้ประโยชน์เพิ่มเติมจาก cTpT ในการช่วยตรวจวินิจฉัยโรคหัวใจขาดเลือดในห้องฉุกเฉินหรือไม่ และสามารถนำ CKMBa ออกจากชุดตรวจที่ห้องฉุกเฉินได้หรือไม่*

วัสดุและวิธีการ: *ทำการศึกษาผู้ป่วย 907 ราย มาด้วยอาการแสดงสงสัยภาวะหัวใจขาดเลือดที่ห้องฉุกเฉิน โรงพยาบาลจุฬาลงกรณ์ และได้รับการส่งตรวจทั้ง CKMBa และ cTpT ในช่วงเดือนกุมภาพันธ์ พ.ศ. 2554 ถึง มิถุนายน พ.ศ. 2554 โดย 97 ราย ได้ถูกนำมาวิเคราะห์สุดท้ายเนื่องจากมีผล cTpT ปกติ และ CKMBa ผิดปกติ หรือ ผู้ป่วยที่ CKMBa ตอนแรกปกติแต่เปลี่ยนเป็นผิดปกติภายใน 24 ชั่วโมง โดยเก็บข้อมูลค่าผลตรวจเลือด ข้อมูลทั่วไปของผู้ป่วย การวินิจฉัยสุดท้ายได้มาจากอาการแสดง ผลตรวจคลื่นไฟฟ้าหัวใจ และผลตรวจตัววัดค่าหัวใจในเลือด โดยวัดผลลัพธ์คือ การวินิจฉัยสุดท้าย การตรวจติดตามในช่วง 180 วัน และสาเหตุการเสียชีวิตในผู้ป่วยที่นอนโรงพยาบาลโดยเก็บข้อมูลจากเวชระเบียนผู้ป่วย ในผู้ป่วยที่ยังไม่สามารถวินิจฉัยได้จะได้รับการตรวจเพิ่มเติมโดยการตรวจหัวใจด้วยคลื่นความถี่สูง การตรวจหลอดเลือดหัวใจโดยการฉีดสี และการเดินสายพานเพื่อตรวจสมรรถภาพหัวใจ โดยแพทย์เฉพาะทางด้านหัวใจ*

ผลการศึกษา: *cTpT ถูกส่งทั้งหมด 1,772 ครั้ง โดย 95.2% ของการส่งทั้งหมดได้ส่ง CKMBa ไปร่วมด้วย จากการศึกษาพบว่าไม่พบว่ามีผู้ป่วยที่ได้รับวินิจฉัยสุดท้ายว่าเป็นกล้ามเนื้อหัวใจขาดเลือด และผู้ป่วย 14 ราย ที่เสียชีวิตในโรงพยาบาลก็ไม่ได้มาจากโรคหัวใจขาดเลือด ส่วนผู้ป่วยที่เหลือที่กลับจากโรงพยาบาล จากการตรวจติดตาม 180 วัน พบว่าไม่มีใครเสียชีวิต และไม่มีใครมีอาการแสดงที่สงสัยภาวะหัวใจขาดเลือดที่ต้องการการตรวจเพิ่มเติมทางหัวใจ*

สรุป: *การตรวจ CKMBa ไม่ได้ช่วยในการวินิจฉัยโรคหัวใจขาดเลือดเพิ่มเติมจาก cTpT ในห้องฉุกเฉิน ผู้นิพนธ์แนะนำว่าไม่ควรส่ง CKMBa ในผู้ป่วยที่มีอาการแสดงสงสัยภาวะโรคหัวใจขาดเลือด ซึ่งจะนำไปสู่การรักษาที่ไม่เหมาะสมและสูญเสียทรัพยากรทางการรักษา*