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Prognostic Value of Adrenomedullin in Patients with Left Ventricular Systolic Dysfunction After an Acute Myocardial Infarction

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ABSTRACT

This study sought to assess the prognostic impact of adrenomedullin ADM after an acute myocardial infarction (AMI). Adrenomedullin (ADM) is elevated in heart failure (HF) and after AMI and compared it with N-terminal pro-B-type natriuretic peptide (NTproBNP), a marker of death and HF. We measured plasma ADM and NTproBNP in 60 consecutive post-ST elevated AMI patients with systolic dysfunction (< EF 50%), (45 men, represents 75% with mean age57.6±8.4 years old), 3 to 5 days after chest pain onset. Mean age of studied patients was 57.6±8.4 years old (Range 35-80). Males constituted 73.3% of our study population (44 males), we found mean NYHA 2.8, mean Killip class of 2.9 and mean TIMI risk score of 8.3. Follow-up was done at 90 days. Forty eight patients survived (80%). Two patients experienced cerebrovascular events (3.3%), two patients experienced re-infarction (3.3%), and seven patients experienced life-threatening arrhythmias (11.7%). ADM had proved to have a significant prognostic value in predicting mortality if compared to Pro-BNP as evidenced by plotting the ROC curve that revealed AUC for ADM to be 0.977 and 0.775 for Pro-BNP. The same significant higher prognostic power for ADM applies for predicting MACE using ROC curve and estimating AUC. Multivariate analysis showed that ADM was the only predictor for MACE. ADM: (OR 1.62, CI 95%: 1.19-2.20, P value .002). The ADM system is activated after AMI. The ADM may represent a clinically useful marker of prognosis in patients with LV dysfunction after an acute AMI.

Keywords: ADM (adrenomedullin), AMI (acute myocardial infarction), AUC (area under the curve, MACE (major adverse cardiovascular events).

INTRODUCTION

One of the most common complication after an acute myocardial infarction is Heart failure, which considered to be a major and growing public health problem, appears to result not only from cardiac overload or injury but also from a complex interplay among genetic, neurohormonal, inflammatory, and biochemical changes acting on cardiac myocytes, the cardiac interstitium, or both.

An increasing number of enzymes, hormones, biologic substances, and other markers of cardiac stress and malfunction, as well as myocyte injury — collectively referred to as biomarkers — appear to have growing clinical importance. Although biomarkers include genetic variants, clinical images, physiological tests, and tissue specimen biopsies, this thesis focuses on biomarkers derived from the blood or urine other than serum levels of hemoglobin, electrolytes, liver enzymes, and creatinine, which are routinely determined as part of clinical care. Morrow and de Lemos1 have set out three criteria a biomarker should fulfill to be useful clinically. First, accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times; second, the biomarker must provide information that is not already available from a careful clinical assessment; and finally, knowing the measured level should aid in medical decision making.

The early 1960s it was reported that patients with heart failure had abnormally elevated levels of plasma norepinephrine at rest and that further elevations occurred during exercise (Chidsey et al 1962).The urinary excretion of norepinephrine was also increased (Chidsey et al 1965). These findings suggested that the

sympathetic nervous system is activated in patients with heart failure and that a neurohormonal disturbance might play a pathogenetic role in heart failure*.* **(**Cohn et al 1984**)** subsequently demonstrated that plasma norepinephrine level was an independent predictor of mortality.

Adrenomedullin is a peptide of 52 amino acidsand a component of a precursor, pre-proadrenomedullin, which is synthesized and present in the heart, adrenal medulla, lungs, and kidneys (Kato ey al 1969). It is a potent vasodilator, with inotropic and natriuretic properties, the production of which has been shown to be stimulated by both cardiac pressure and volume overload (Najaya et al 2000). The level of circulating adrenomedullin is elevated in patients with heart failure and is higher in patients with more severe heart failure *(*Joujasaki et al 1995*).*

This peptide hormone is expressed in normal adrenal medulla, but is widely distributed throughout the body including lungs, kidney tissues, endothelial cells, brain and embryonic skeleton (Ichiki, 1994).

Besides controlling fluid-electrolyte homeostasis, it is a potent vasodilator and can inhibit pituitary ACTH secretion (Kitamura, 1994). It circulates in picomolar concentrations in both rats and humans. Recently a second peptide AM2 has been recognised, exhibiting similar functions (Fujisawa et al., 2004).

Aim of Work:

To assess the cardiovascular prognostic value of adrenomedullin (ADM) and compare this with B-type natriuretic peptide (BNP) in predicting   composite end point(death and MACE) within 90 days from the onset of MI.

METHODS

Patients

The present study is a prospective observational study conducted on 60 patients diagnosed to have acute MI complicated by LV dysfunction & admitted to critical care department of Kasr El-Aini Hospital, Cairo University.

Our patients included :

Cases who diagnosed to have STEMI (46 pts) and underwent primary intervention by PCI, and those received thrombolytic therapy (14 pts).

Inclusion Criteria:

Adult patients Diagnosed to have an acute myocardial infarction (STEMI), only if (at least 2 criteria of the following) were met:
1. Typical retro sternal chest pain (relieved by nitrates).
2. ST segment elevated greater than 0.1mV in limb leads or 0.2mV in precordial leads or new or indeterminate LBBB.
3. Elevated cardiac biomarker suggestive of myocardial injury in early few hours.
Echocardiographic evidence of LV systolic dysfunction (LVEF<50%).

Exclusion Criteria:

1. Renal impairment defined as serum creatinine level more than 1.5mg/dl that causes a non-specific elevation of troponin.
2. Systemic sepsis that also causes a non-specific elevation of troponin.
3. Cardiac arrest before taking samples.
4. Patients with cerebro vascular stroke .
5. Advanced malignancy.

All patients were subjected to the following:
1. Informed consent from the patient or the closest family member.
2. Detailed medical history taken from the patient or a family member .
3. Clinical assessment
4. Surface 12 leads ECG
5. Transthoracic echocardiographic examination:
6. Biochemical measurement
7. Coronary Angiography.

Clinical assessment in the form of:
- Full physical examination .
- Clinical scoring systems: used to evaluate patients with heart failure after an acute MI.

A. **New York Heart Association** functional classification based on severity of symptoms and physical activity (table 1).

Surface 12 leads ECG:
Twelve lead ECG with consistent chest leads positioning performed daily for 5 days.

ECG was considered abnormal if the following was detected:
- ST segment elevation greater than 0.1mV in limb leads or 0.2mV in precordial leads.
- Arrhythmias.

Transthoracic echocardiographic examination:
Each patient was examined in the left lateral position according to the recommendations of the American Society of Echocardiography (ASE). Images obtained from each part of the examination together with standard ECG were stored for subsequent analysis. The study was conducted using an ATL HDI 5000 colored echocardiographic machine, using a 3.5 MHz transducer. 2D and M-mode for assessment of;
- Left Ventricular End diastolic & End systolic dimensions (EDD, ESD),
- Left Ventricular Ejection Fraction (EF) ,
- Regional Wall Motion Abnormalities (RWMAs) ,and
- Valvular affection.

Biochemical measurement:
- Full laboratory investigation.
- Cardiac biomarkers (Cardiac troponin I, CK MB, CPK, were measured on admission).
- Plasma Samples withdrawn from every patient in our study in the first 48 hrs, to assess levels of
  1. Adrenomedullin, and
  2. N terminal Pro BNP.

Coronary Angiography

All patients were informed & had a written consent.

The diagnostic angiograms were obtained using Digital Imaging and Communications in Medicine (DICOM)-compatible digital systems: Siemens AG model No.07555126 & Philips CV20 with imaging speed: 15 frame per second (fps).

Quantitative Coronary Analysis (QCA)

The coronary parameters of major interest are summarized in Table-1.

Table-1. Main parameters obtained with QCA (adapted from Garrone et al., 2009)

Commonly used parameter range meaning	Range
Minimal Luminal Diameter (MLD): The smallest lumen diameter in the segment of interest.	0–6.00 mm
Reference Vessel Diameter (RVD): The averaged diameter of the coronary assumed without atherosclerotic disease	1.5–6.0 mm
Lesion length: Length of the stenosis as measured by 2 points where the coronary margins change direction, creating a shoulder between the angiographically normal subsegment and the diseased subsegment.	0–60.0 mm
Diameter stenosis (DS) : (RVD-MLD)/RVD	0–100%

N.B. *The reference segment was defined as the segment least affected by atherosclerosis within a 10 mm span proximal and distal to the target lesion.*

Percutaneous Coronary Intervention

Percutaneous Coronary Intervention was done using either bare- metal or drug-eluting stents, Pre-dilatation, post-dilatation & direct stenting techniques were used.

RESULTS

M.I. territory

Forty three patients (71.66%), had acute anterior MI, fifteen patients(25%) were diagnosed as having acute inferior MI (25%), and two patients(3.34%) had anterior and inferior MI.

Forty six patients (76.7%) were subjected to primary percutaneous coronary intervention while fourteen pts (23.3%) received medical treatment.

As illustrated in coronary angiography results figure (2), twenty nine patients had single vessel affection, 23 pts had two vessel affection while 5 patients had multi vessel disease.

Clinical Examination

Risk category stratification in our patients, showed mean NYHA 2.8,Killip class of 2.9 and TIMI risk score of 8.3. as shown in table-2.
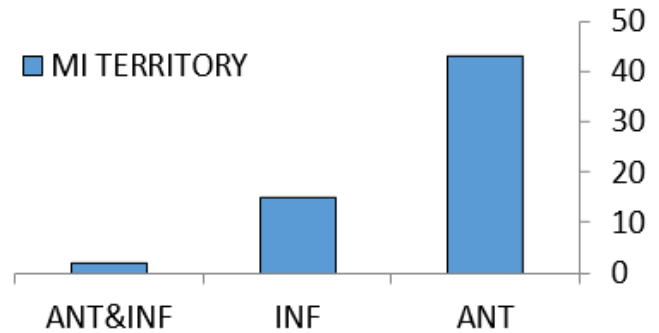
Clinical examination	
NYHA	2.8±0.8
KILLIP class	2.8±0.8
TIMI risk point	7.8±2.4

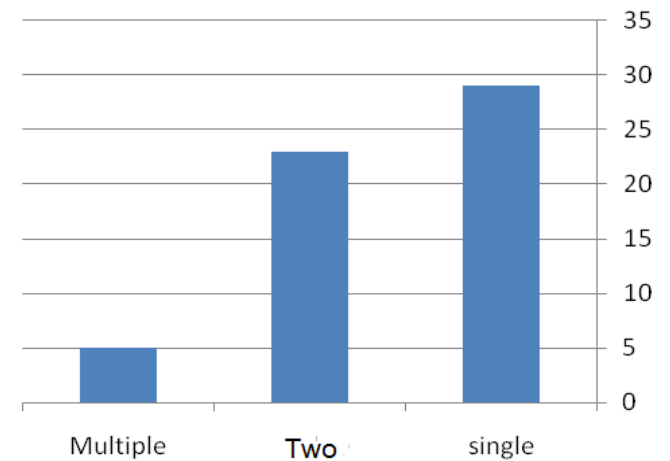| Laboratory Data	
ADM (pg/ml)	4.4±5.9
Pro-BNP (pg/ml)	23400±4.300

Figure-1. MI Territory

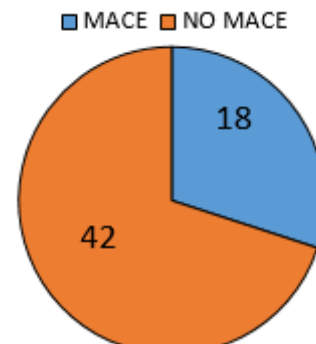**Figure-2. Coronary Angio Results**

Follow-up clinical examination was done for survivors and showed a mean NYHA: 1.9 ± 0.7.

MACE

Follow-up was done at 90 days. Forty eight patients survived (80%). Two patients experienced cerebrovascular events (3.3%), two patients experienced re-infarction (3.3%), and seven patients experienced life-threatening arrhythmias (11.7%).
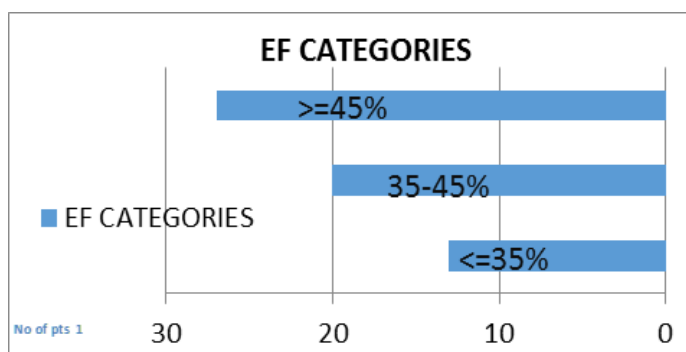
Figure-3. MACE

Follow up clinical examination

Initial Echocardiographic Examination

Echocardiographic examination was done for all patients and showed a mean EF of 41.9±8% with RWMA: 13.3±3.3 as shown in table-3.

Echocardiographic examination	
LVEF	41.9±8%
RWMA	13.3±3.3

Figure-4. EF Categories

Twenty seven patients had initial EF value higher than or equal to 45%, while 20 patients had EF values ranging between 35 and 45% and only 13 patients had values lower than or equal to 35%.

Follow Up Echocardiographic Examination

Follow-up echocardiographic examination was done for survivors and showed a mean EF of 46.7±8.8% with RWMA: 8.7±4.1 as shown in table (4):

ECHO examination	
EF	46.7±8.8%
RWMW	8.7±4.1

Laboratory data:

Also, mean ADM in our studied population averged 4.4 while mean pro-BNP was 3.4.

Exploring the role of ADM (adrenomedullin) & pro-BNP as predictors of MACE and mortality.

ADM and pro-BNP among initial EF categories

Thirteen pts had EF <= 35% , 20 pts had EF 35-45% and 27 pts had EF > =45% .ADM showed significant differences among the three EF groups (p value 0.0001),on the other hand pro-BNP revealed no significant difference among these groups.

Table-5. Correlation between mean levels of ADM &Pro BNP and initial EF in our pts:

EF Group	ADM Level	No of pts	P Value
>=45%	1.46±2.33	27	
35-45%	4.9775±6.07	20	0.0001
<=35%	9.6 ±7.14	13	

EF Group	Pro-BNP level	No of pts	P Value
>=45%	2512.1± 1037.8	27	
35-45%	4389.2 ± 7269.8	20	0.339
<=35%	3494.7 ± 1352.7	13	

The same findings applied upon estimating EF change and categorizing patients into the same three groups, ADM differed significantly among the three groups with p value 0.001 ,yet pro-BNP didn't with a p value: 0.915.

Table-6. Correlation between mean levels of ADM & Pro BNP and follow up EF in our pts:

	ADM Level	No of pts	P Value
>=45%	1.04±1.68	33	
35-45%	4.17±3.7	10	0.001
<=35%	4.74±5.45	5	
F/U EF group	Pro-BNP level	No of pts	P value
>=45%	2891.8±1085.8	33	
35-45%	2768.3 ±1002.95	10	0.915
<=35%	3446.2 ±5748.5	5	

Correlation with RWMA and EF:

Also, ADM levels were correlated significantly to LVEF and RWMA scores whereby increases in ADM were associated with depressed LVEF and increased in RWMA scores , (LVEF: r value -.423, P value .001 and RWMA scores: r value .505, P value <.001). There was no significant correlation between pro-BNP and echocardiographic data.

ADM and proBNP relations to NYHA&KILLIP class

There were significant differences in ADM among different NYHA categories, (P value .002). There were also significant differences in pro-BNP among different NYHA categories upon follow-up, (P value .014).

ADM & pro-BNP in correlation with severity of coronary artery disease :

Only ADM yielded significant statistical difference between single coronary artery disease group versus multivessel disease group with P value <(0.001) as shown in table-7.

Coronary angiography	Average of ADM pg/ml	Average of Pro BNP ng/ml
Single vessel disease	0.44±2.9	3.54±6.12
Two vessel disease	7.2±6.6	2.82±1.05
MVD	9.8±5.0	4.5±1.3
P value	<0.001	0.7

Figure-5. Correlation with RWMA and EF

Figure-6. ADM and proBNP relations to NYHA

P Value (ADM) 0.002; P value (pro-BNP) 0.014
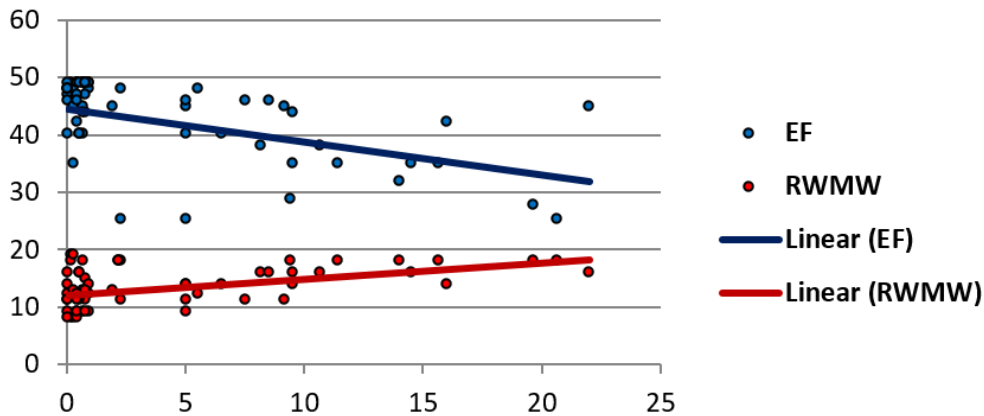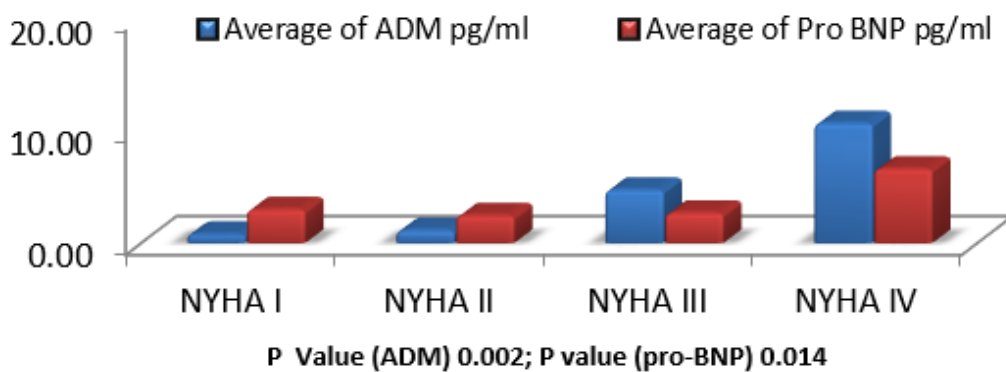
Plotting ROC curve to estimate the best predictive cutoff points as predictors of MACE and mortality for ADM and pro-BNP revealed the following:

Table-8. Cut off points of Pro BNP & ADM for mortality.

Mortality	AUC	P	Cut-off	Sensitivity	specificity
Pro BNP (ng/ml)	77.5%	<.001	3.2	70%	67.5%
ADM (pg/ml)	97.7%	.003	9.3	91.7%	97.9%

Table-9. Cut off points of Pro BNP& ADM for MACE:

MACE	AUC	P	Cut-off	Sensitivity	specificity
Pro BNP (ng/ml)	69.6%	.017	3.13	72.2%	61.9%
ADM (pg/ml)	94.8%	<.001	5.3	83.3%	92.9%

Subgroup comparative analysis (anterior Vs inferior MI, survivors Vs non-survivors and MACE Vs non-MACE) groups

Table-10. MI location (Anterior Vs inferior MI)

MI location	Anterior AMI	Inferior AMI	P value
Age	57.5±9.1	57.8±5.8	0.887
Gender (Male)	35 (77.8%)	9 (60.0%)	0.195
Primary PCI	35 (77.8%)	11 (73.3%)	0.734
EF	42.0±6.8	41.8±11.1	0.954
RWMW	13.3±3.3	13.4±3.4	0.892
NYHA	2.9±0.8	2.4±0.5	0.031
KILLIP class	3.0±0.8	2.4±0.5	0.014
TIMI risk point	8.2±2.4	6.6±2.2	0.022
ADM pg/ml	4.8±5.9	3.1±5.7	0.319
Pro BNP ng/ml	3.8±4.9	2.1±0.8	0.200
Mortality	11 (24.4%)	1 (6.7%)	0.262
MACE	16 (35.6%)	2 (13.3%)	0.192

Survivors Vs non-Survivors

Compared to survivors, non-survivors have shown significantly lower EF, higher RWMA, NYHA, KILLIP and TIMI risk scale and ADM levels, on the other hand, pro-BNP levels showed no significant difference.

DISCUSSION

Morrow and de Lemos have set out three criteria a biomarker should fulfill to be useful clinically.*(Morrow et al 2007).*

First, accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times; second, the biomarker must provide information that is not already available from a careful clinical assessment; and finally, knowing the measured level should aid in medical decision making.

In the early 1960s it was reported that patients with heart failure had abnormally elevated levels of plasma nor epinephrine at rest and that further elevations occurred during exercise *(Chidsey et al 1962)* . Theurinary excretion of norepinephrine was also increased.*(Chidsey et al 1965)* These findings suggested that the sympathetic nervous system is activated in patient with heart failure and that neurohormonal disturbance might play a pathogenetic role in heart failure.

BNP causes arterial vasodilation, diuresis, and natriuresis, and reduces the activities of the renin–angiotensin–aldosterone system and the sympathetic nervous system. Thus, when considered together, the actions of BNP oppose the physiological abnormalities in heart failure. The natriuretic peptides are cleared by the kidneys, and the hypervolemia and hypertension characteristic of renal failure enhance the secretion and elevate the levels of BNP, especially the NT-pro-BNP.*(Vickery et al 2005).*

Adrenomedullin is a peptide of 52 amino acids and a component of a precursor, pre-proadrenomedullin, which is synthesized and present in the heart, adrenal medulla, lungs, and kidneys *(Kato et al 1996)*. It is a potent vasodilator, with inotropic and natriuretic properties, the production of which has been shown to be stimulated by both cardiac pressure and volume overload. The level of circulating adrenomedullin is elevated in patients with heart failure and is higher in patients with more severe heart failure *(Nagaya et al 2000)*. The midregional fragment of the proadrenomedullin molecule, consisting of amino acids 45 to 92, is more stable than adrenomedullin itself and easier to measure *(Jougasaki et al 1995).*

Adrenomedullin may have a number of advantageous effects in the post-AMI period, causing vasodilation (with reduction of arterial and cardiac filling pressures) at a time when the myocardium has been compromised .Beside it may cause increased myocardial contractility via its downstream actions on cAMP*(Takahashi et al 1997).*

Our study is one of the early reports in Egypt investigating the prognostic potential of Adrenomedullin after acute MI in a cohort of patients from a single center. Moreover, we compared this with NT-proBNP, a well-established prognostic marker of death and heart failure after AMI. Survival analysis of our data using both Kaplan-Meier and Cox proportional hazard models shows that ADM is a powerful independent predictor of death and heart failure, with combined levels of ADM and NT-proBNP giving additive prognostic information Reperfusion therapy and the application of secondary prevention therapies have improved survival after AMI. Despite this, outcome remains poor for some patients A multi marker strategy for outcome after AMI using independent biomarkers may provide complementary information through integrating the different mechanistic pathways involved.

In this study "called LIPID study" pts were randomised over 3–36 months after an acute coronary syndrome , to placebo or statin(pravastatin 40 mg). MR-proADM plasma concentrations at baseline and one year later were determined in 7863 and 6658 patients, respectively. These were categorised into quartiles to perform Cox regression analysis, adjusting for baseline parameters.

The results of the LIPID study revealed that baseline MR-proADM concentrations predicted major CHD events (non-fatal MI or CHD death; hazard ratio (HR) 1.52, 1.26–1.84 for Q4–Q1), CHD death (HR 2.21, 1.67–2.92). Heart failure (HR 2.30, 1.78–2.97) and all-cause mortality (HR 1.82, 1.49–2.23).

Our data were in accordance with the previous study whereby we found that ADM plasma concentration in early phase after an acute MI in patients with LV dysfunction (EF <50 %) could predict mortality ,adverse cardiac events and worsening of heart failure as sensitive prognostic marker and even more accurate than Pro BNP, in prediction systolic dysfunction 90 days after an acute MI .

Using Kaplan Meier analysis to calculate cut off point above which ADM could predict mortality,our data showed that rise of ADM above 9.3 pg/ml had a significant impact upon survival, (OR 0.09 [CI 95%: 0.0923-0.0999], P value <.001).

Similar findings were reported by Matthew and colleagues in a systematic review in 2015. They showed that adrenomedullin is an independent predictor of death in pts with heart failure, as well as MACE and death in patients who had suffered an acute MI . More ever they showed that quantification of this peptide might contribute to improved risk stratification in settings of heart failure and MI . Similar to this retrospective study ,"our prospective data showed that quantitative analysis of ADM could improve prediction mortality and MACE , by calculation of AUC (area under the curve) with high sensitivity 91.7 % for mortality and 83.3% for MACE ,and a high specify of 97,5% for mortality and 92.9% for MACE at a cutt off point at 5.3 pg /ml , p value <001.

In accordance with our findings , *Zhengbing et al, in 2013,*concluded that "ADM could be used as a marker to reflect the severity of the coronary stenosis. Comparing 20 pts with acute STEMI to pts with stable CAD and a control group, he found a statistically significant correlation between levels of ADM and severity of stenosis.

Similarly in our study, plasma levels of Adrenomedullin had significant correlation with

quantitave assay of the extent of CAD (number of coronary arteries showed significant leaions> 70%) .

In contrast to qualitiave comparison done by Zhengbing, we did quantitative assay of coronary stenosis in correlation with plasma level of adrenomedullin in 1st 48 hrs,as we did not study patients with stable coronary disease ,and all our population experienced STEMI and all of them had significant lesions (> 70%) .

In contrast to our data , Philip and colleagues in a study published in 2013 , on 1179 pts with acute chest pain , found that MR-proADM did not have clinical utility in the early diagnosis of AMI nor predicting cardiovascular events in patients with acute chest pain, in contrast to our findings and to the majority of investigators finding over more than the last decade .

According to the latter study"MR –pro adrenomedullin , might provide prognostic value for all-cause mortality, with cut off value of plasma of MR – proADM (by calculation area under the curve) (0.90nmol/l) and for prediction adverse cardiac events the cut off value (0.63nmol/l).

Our data showed that ADM hormone is valuable in predicting mortality(within 90 days),in patients with STEMI .
The same finding was confirmed by a study published in 2012 by Silvain and his collegues,done on 283 patients with acute STEMI .

They found that early measurement of MR-proADM during the acute phase of AMI is a powerful predictor of short and long term mortality in STEMI patients.

Klip and colleague in an abstract of presented in 2011 on 214 patients from the OPTIMAAL study, analyzed blood samples obtained at a median of 3 days after AMI in patients who had developed signs and/or symptoms of heart failure or EF <0.35%. End points were all-cause mortality and a composite end point, including death, myocardial reinfarction, stroke and/or resuscitated cardiac arrest. Almost the same as we did in our research as regarding comparison between N-terminal pro BNB and adrenomedullin .

Table-11. Sensitivity and specifity of ADM & ProBNP in predicting mortality and MACE in our pts.

Mortality	AUC	P value	Cut-off	Sensitivity
Pro BNP (ng/ml)	77.5%	<.001	3.2	70%
ADM (pg/ml)	97.7%	.003	9.3	91.7%

MACE	AUC	P value	Cut-off
Pro BNP (ng/ml)	69.6%	.017	3.13
ADM (pg/ml)	94.8%	<.001	5.3

Concluding Discussion

ADM is useful and promising new biomarker in predicting death and MACE in pts developed LV systolic dysfunction(EF<50) after an AMI also proved to be more sensitive biomarker than Pro –BNP in predicting outcome in these pts, when added to TIMI and KILLIP risk scoring systems it could improve risk stratification in pts with STEMI complicated by LV systolic dysfunction.

Study limitations.
This was a single-center study, and the results need to be replicated in larger multicenter studies.

6. SUMMARY

The main goal was to assess the prognostic impact of adrenomedullin (ADM)following an acute myocardial infarction (AMI) complicated by LV systolic dysfunction.

- Plasma ADM and NTproBNP were measured within 48 hours from onset of MI in60 consecutive post-ST elevated AMI patients with systolic dysfunction (EF< 50%).
- All of our patients were subjected to clinical and echocardiographic evaluation within the first 48 hours of hospital admission and followed 90 days later for those who survived . Clinical outcome of our study population was assessed entailing mortality as a primary endpoint and MACE as secondary endpoints.
- Follow-up was done at 90 days. Forty eight patients survived (80%). Two patients experienced cerebrovascular events (3.3%), two patients experienced re-infarction (3.3%), and seven patients experienced life-threatening arrhythmias (11.7%).
- ADM had proved to have a significant prognostic value in predicting mortality if compared to Pro-BNP as evidenced by plotting the ROC curve that revealed AUC for ADM to be 0.977 and 0.775 for Pro-BNP .

The same significant higher prognostic power for ADM applied for predicting MACE using ROC curve and estimating AUC. Univariate regression analysis for MACE identified LVEF, RMWA score, MVD and ADM as independent variables. Multivariate analysis showed that ADM was the only predictor for MACE. ADM: (OR 1.62, CI 95%: 1.19-2.20, P value .002).

- In conclusion the ADM system is activated after AMI. The ADM may represent a clinically useful marker of prognosis in patients with LV dysfunction after an acute AMI.

Conclusion

ADM is a useful and promising new biomarker in predicting death and MACE in pts who developed LV systolic dysfunction (EF<50) after an AMI . It also proved to be a more sensitive biomarker than Pro –BNP in predicting outcome in these pts . When added to TIMI and KILLIP risk scoring systems it could improve risk stratification in pts with STEMI complicated by LV systolic dysfunction.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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