

PTEN gene & TNF-alpha in acute myocardial infarction

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ABSTRACT

Background: PTEN gene triggers cells to undergo apoptosis and promotes myocardial dysfunction. Several TNF family cytokines are elevated during acute myocardial infarction (AMI). Their role in predicting subsequent prognosis in these setting remains poorly understood. We assessed serum levels of PTEN gene activity & TNF- α in acute ST elevation myocardial infarction and determined the impact of their levels on both left ventricular function and the clinical outcome in these patients.

Methods and results: Seventy patients with AMI and seventy persons as control group were subjected to: ECG, echocardiography, serum TNF- α and PTEN gene assessment. Patients were classified into: Group I (n = 32): All had left ventricular systolic failure. Group II (n = 38): without left ventricular systolic failure. Group I had a statistically significant higher serum levels of both TNF- α & PTEN gene activity as compared to group II. EF% at presentation was weakly correlated with serum levels of both markers in both groups. However at follow up, EF% in group I showed a significant negative correlations with both serum levels of TNF- α and PTEN gene activity (r = 0.77 & r = 0.67, respectively). During one year follow, 5 patients died of cardiovascular causes and 6 patients had recurrent hospitalization with heart failure. These patients had statistically significant increased serum levels of TNF- α & PTEN gene activity levels as compared by other patients.

Conclusions: Patients with acute myocardial infarction had statistically significant increased serum levels of PTEN & TNF- α gene activity. Both markers predict worsening of left ventricular systolic functions, development of heart failure and death.

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1. Introduction

Phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene acts as a tumor suppressor gene. It regulates the cycle of cell division and modifies proteins and fats by removing phosphate groups. It acts as part of a chemical pathway that signals cells to stop dividing, triggers cells to self-destruct (undergo apoptosis) [1] and promotes myocardial dysfunction. Moreover, cardiac-specific PTEN inactivation protects the heart from functional failure and fibrosis in a mouse model [2].

Tumor necrosis factor-alpha (TNF- α) is a master cytokine that is produced in significant quantities within the infarcted myocardium very soon after myocardial infarction (MI). It activates other cytokines such as interleukin-1 (IL-1) and IL-6 and orchestrates the host tissue response to acute injury [3]. Despite several TNF family cytokines are elevated during acute MI, their role in predicting subsequent prognosis in these setting remains poorly understood [4].

We assessed serum levels of TNF- α & PTEN gene activity in acute ST elevation myocardial infarction and determined the impact of their

levels on both left ventricular function and the clinical outcome in these patients.

2. Methods

2.1. Study population

This is an observational comparative study that included seventy patients with acute ST elevation myocardial infarction as defined in the 3rd universal definition of myocardial infarction [5] and seventy persons (age & sex matched) as a control group.

Patients with any of the following criteria had been excluded from the study: old myocardial infarction, atrial flutter, atrial fibrillation, valve prosthetic, any systemic disease can elevate TNF- α , rheumatic valvular affection, left ventricular aneurysm, previous history of heart failure, poor echocardiographic view. Informed consent was obtained from each patient. All included patients were medically managed at time of this study including thrombolytic therapy, aspirin, clopidogrel, enoxaparin, nitroglycerine, ACE-I, B-blockers and statins.

After obtaining Minia University review board approval, all patients and controls were subjected to: (A) Assessment of typical chest pain. (B) Assessment of Killip class [6], Class I: No evidence of congestive

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heart failure. Class II: Rales, increased jugular venous pressure or S3 gallop. Class III: acute pulmonary edema. Class IV: cardiogenic shock. (C) Assessment of coronary risk factor.

2.2. Twelve leads ECG

To confirm the diagnosis of AMI, to determine the extent of AMI according to Aldrich score [7] by quantitating initial ST-segment changes on the presenting ECG.

2.3. Laboratory investigation

Venous blood samples were obtained from all controls and included patients, 24 hour post admission. Serum TNF- α samples were frozen for use within 6 month at -80°C [8], were not run in duplicate and had been determined at one session by human TNF-alpha kit supplied by Koma Biotech Incorporation using sandwich ELISA protocol. PTEN gene activity was determined by its phosphatase activity using P-Nitrophenyl phosphate as a colorimetric substrate exactly as described [9].

2.4. Echocardiography

All patients underwent echocardiographic examination within 2 days of admission. The measurements represent a mean of at least three consecutive cardiac cycles. Diastolic parameters as trans-mitral early and late diastolic velocities and E/A ratio were assessed. Left Ventricular ejection fraction % was calculated from apical 4-chamber view with modified Simpson's method [10]. Left ventricular systolic dysfunction was defined as a decreased LV (<50%) effective ejection fraction [11–14]. Left ventricular diastolic dysfunction was defined as impaired left ventricular filling or impaired left ventricular distensibility [11–14]. Wall motion score index (WMSI) was assessed according to the standard 16 segment model of the American society of echocardiography [15]. Wall motion score index equals the sum of these scores divided by number of scored segments.

2.5. Follow up

All the patients were discharged after optimizing their medical treatment. Follow up visit was performed after one month and included assessment of recurrent anginal pain, heart failure (either new onset or deterioration of the functional class), ECG, physical examination and echocardiography. Then, one year clinical follow up for any cardiovascular events (Death was considered as cardiac related unless proved otherwise, recurrent hospitalization with heart failure).

2.6. Statistical analysis

Discrete values were presented as counts and percentages and compared using chi square test. Continuous values were expressed as mean \pm SD. Significance was determined using *t*-test. A probability level of $P < 0.05$ was considered significant. Changes of parameters between baseline and subsequent measurements were evaluated by a paired *t*-test. A student unpaired *t*-test was used to analyze differences between patients groups and subgroups. Data were analyzed by SPSS version 16 software for windows (SPSS Inc.; Chicago; Illinois; USA).

3. Results

Out of 70 patients, 43 (61.4%) were males. Their mean age was (55 ± 10) years ranged from 35 to 75 years. Patients were classified into two groups: Group I ($n = 32$): All had acute STEMI with left ventricular systolic failure. They had been sub-classified into sub-group IA ($n = 20$): in whom EF% had been deteriorated at follow up and sub-group IB ($n = 12$): in whom EF% had stable at follow up. Group II ($n = 38$):

Table 1

Comparison between Group I & Group II regarding their age, sex, major risk factors for CAD.

	Group I (n = 32)	Group II (n = 38)	P value
Age (mean \pm SD), y	59 \pm 8	54 \pm 9	0.02
Men, n (%)	20 (62.5%)	23 (60.5%)	0.94
Diabetes mellitus, n (%)	14 (43%)	10 (26%)	0.21
Hypertension, n (%)	11 (34%)	6 (15%)	0.11
Smoker, n (%)	24 (75%)	27 (71%)	0.91
Dyslipidemia, n (%)	14 (44%)	20 (52%)	0.72
Hyperuricemia, n (%)	4 (13%)	6 (16%)	0.83
+ ve family history for premature CAD, n (%)	1 (1.25%)	1 (1.25%)	0.28

All had acute STEMI without left ventricular systolic failure. Group III ($n = 70$): Age and sex matched normal persons as a control group.

There was statistically nonsignificant difference between groups or subgroups regarding the major risk factors for CAD as diabetes mellitus, hypertension, smoking, dyslipidemia or positive family history for premature CAD (Table 1). Out of 32 patients in group I, 22 (27%) were in Killip class II, 8 (10%) were in Killip class III and 2 (2%) were in Killip class IV. All patients in group II had Killip class I.

3.1. ECG data

Group I had statistically significant increased percentage of myocardium at risk as compared to group II (22.8 ± 4.8 vs 13.9 ± 3.6 , $P = 0.001$). However, there was no significant correlation between the extent of myocardium at risk on ECG and TNF- α or PTEN serum levels in either group I ($r = 0.29$ & $r = 0.19$ respectively) or group II ($r = 0.23$ & $r = 0.13$, respectively).

3.2. Echocardiographic data

Proper endocardial definition was feasible in all patients. Group I had a statistically significant lower EF% as compared to both group II ($42 \pm 7\%$ vs $53 \pm 3\%$, $P = 0.001$) and group III ($42 \pm 7\%$ vs $63 \pm 4\%$, $P = 0.001$). Group II had a statistically significant lower EF% as compared to group III ($53 \pm 3\%$ vs $63 \pm 4\%$, $P = 0.001$). During follow up period EF% was significantly deteriorated from 42 ± 7 to $39 \pm 13\%$, $P = 0.03$ in group I. However, it was significantly improved from $53 \pm 3\%$ to $58 \pm 4\%$, $P = 0.001$ in group II.

Table 2

Comparison between groups regarding their EF%, WMSI and diastolic dysfunction both at presentation and follow up.

	Group I n = 32	Group II n = 38	Group III n = 10	P value
• Ejection fraction %				0.001*
At presentation	42 \pm 7%	53 \pm 3%	63 \pm 4%	0.001** 0.001***
At follow up	39 \pm 13%	58 \pm 4%	62 \pm 4%	0.001* 0.004** 0.001***
• WMSI				0.001*
At presentation	1.5 \pm 0.2	1.3 \pm 0.1	1.0 \pm 0.0	0.001** 0.001***
At follow up	1.6 \pm 0.5	1.1 \pm 0.1	1.0 \pm 0.0	0.001* 0.001** 0.003***
• Diastolic dysfunction				0.01*
At presentation, n (%)	27 (84%)	21 (55%)	0 (0%)	0.003*
At follow up, n (%)	27 (84%)	19 (50%)	0 (0%)	

* P (group I versus II).

** P (group II versus III).

*** P (group I versus III).

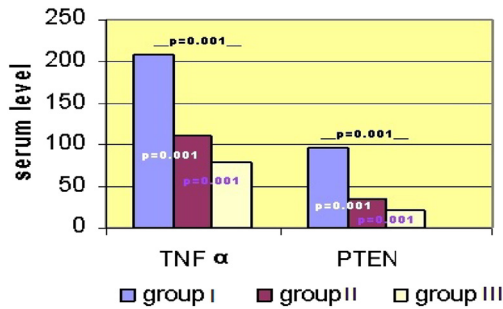


Fig. 1. Comparison between groups regarding their mean serum TNF-α and PTEN gene activity levels.

Out of 32 patients in group I, 27 (84%) had diastolic dysfunction and persists during follow up period. Out of 38 patients in group II, 21 (55%) had diastolic dysfunction, 2 patients had normalized diastolic function during follow up. Group I had a statistically significant increase number & percentage of patients with diastolic dysfunction as compared to group II [27(84%) vs 21(55%), $P = 0.01$] at presentation and [27 (84%) vs 19 (50%), $P = 0.003$] at follow up (Table 2).

3.3. Laboratory data

Group I had a statistically significant higher serum levels of both TNF-α & PTEN gene activity as compared to group II (207 ± 80 vs 111 ± 16 , $P = 0.001$) & (96 ± 41 vs 35 ± 13 , $P = 0.001$) respectively.

Group I had a statistically significant higher serum levels of both TNF-α & PTEN gene activity as compared to group III (207 ± 80 vs 79 ± 16 , $P = 0.001$) & (96 ± 41 vs 20 ± 5 , $P = 0.001$) respectively. Group II had a statistically significant higher serum levels of both TNF-α & PTEN gene activity as compared to group III (111 ± 16 vs 79 ± 16 , $P = 0.001$) & (35 ± 13 vs 20 ± 5 , $P = 0.001$) respectively (Fig. 1).

EF% at presentation was weakly correlated with serum levels of TNF-α, and PTEN gene activity in both group I ($r = 0.46$ & $r = 0.38$, respectively) and in group II ($r = 0.32$ & $r = 0.10$, respectively) (Fig. 2). However, at follow up EF% in group I showed a significant negative correlations with both serum levels of TNF-α and PTEN gene activity ($r = 0.77$ & $r = 0.67$, respectively). But it showed a weak correlations in group II ($r = 0.22$ & $r = 0.27$, respectively) (Fig. 3).

Sub-group IA had statistically significant higher serum levels of TNF-α & PTEN gene activity [240 ± 82 and 115 ± 38 versus 151 ± 34 and 64 ± 22 , $P = 0.001$ and $P = 0.001$, respectively] as compared to those in sub-group IB. There is no statistically significant difference in EF% at presentation between both sub-groups. However, at follow up, sub-group IA had a statistically significant deterioration in EF% from $42 \pm 7\%$ to $32 \pm 6\%$, ($P = 0.001$) and sub-group IB had a statistically significant improvement in EF% from $44 \pm 5\%$ to $50 \pm 2\%$ ($P = 0.001$) (Table 3). 19 out of 20 patients in sub-group IA had serum level of TNF-α ≥ 151 mg/dl & 10 out of 12 patients in sub-group IB had serum level of TNF-α < 151 mg/dl (Table 4). TNF-α ≥ 151 mg/dl had a sensitivity, specificity, positive predictive value and negative predictive value of 90.8%, 90.9%, 83.3% and 90.6% respectively.

15 out of 20 patients in sub-group IA had serum level of PTEN gene activity ≥ 83 pg/dl & 11 out of 12 patients in sub-group IB had serum

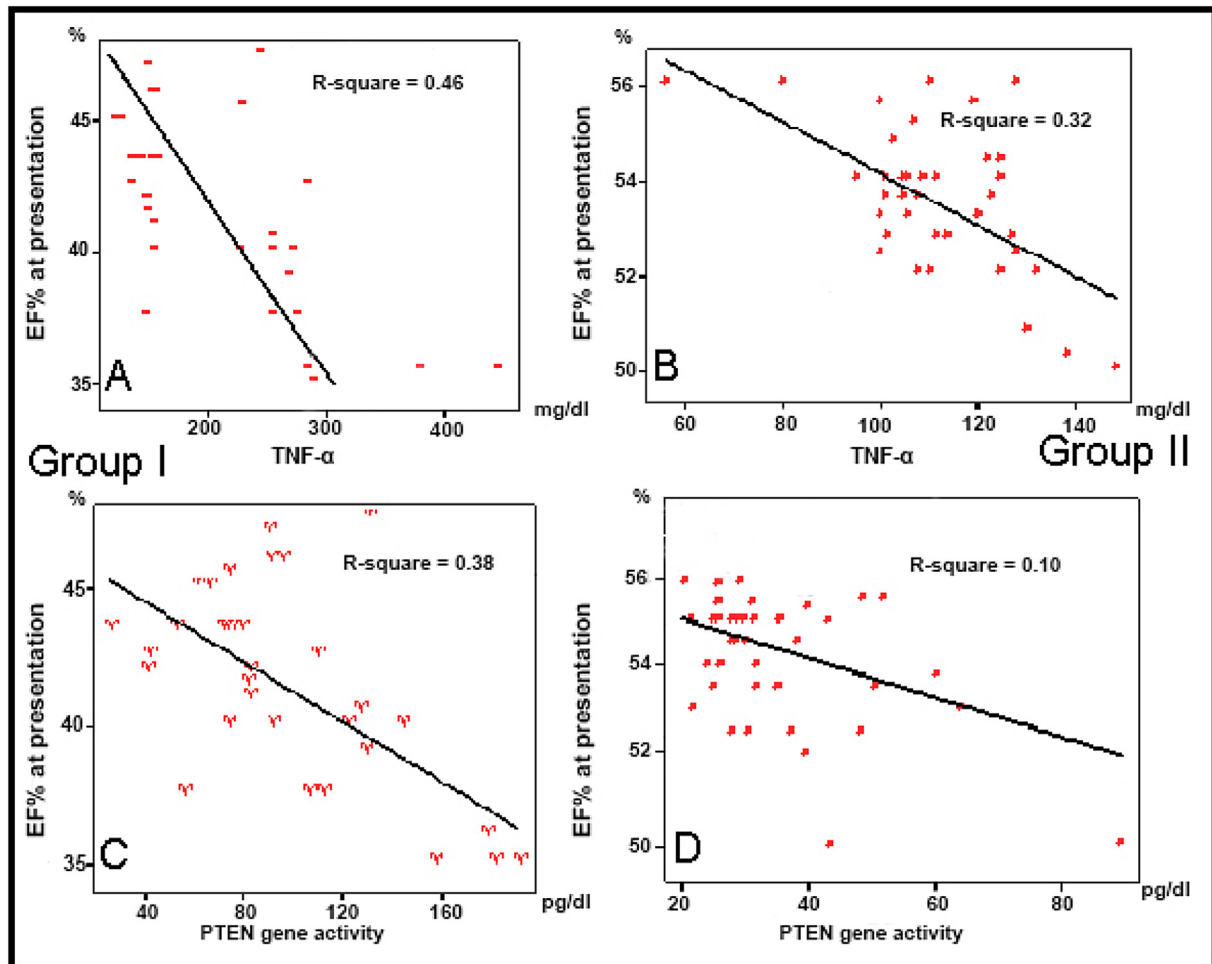


Fig. 2. Correlation between EF% at presentation and serum levels of TNF-α [A & B] and PTEN gene activity [C & D] in Group I & II.

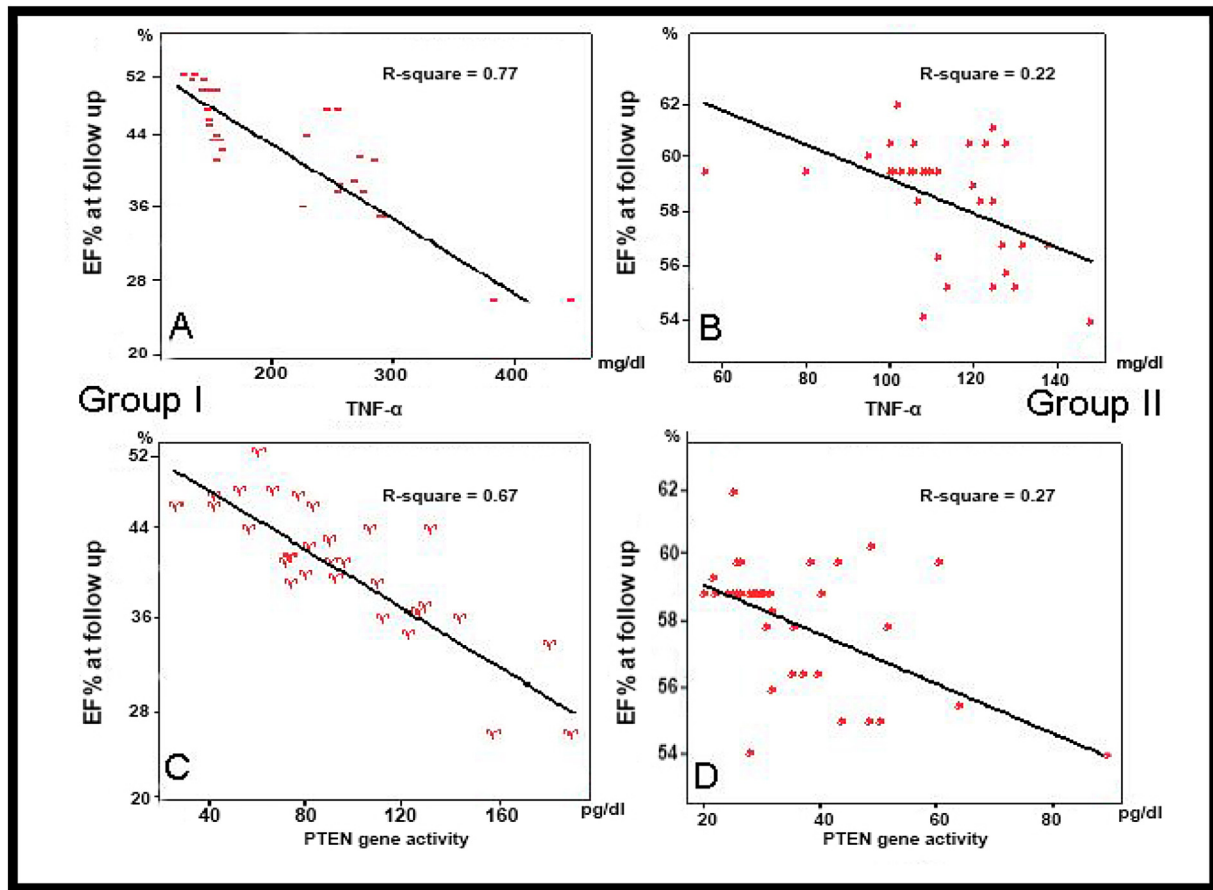


Fig. 3. Correlation between EF% at Follow up and serum levels of TNF-α [A & B] and PTEN gene activity [C & D] in Group I & II.

level of PTEN gene activity <83 pg/dl (Table 5). PTEN gene activity ≥83 pg/dl had a sensitivity, specificity, positive predictive value and negative predictive value of 93.7%, 68.7%, 75% and 91.6% respectively.

During one year follow up (ranged from 331 to 389 days), 5 patients died, all were of cardiovascular causes and 6 patients had recurrent hospitalization with heart failure. These patients had a statistically significant increased serum levels of TNF-α & PTEN gene activity levels as compared by other patients (266 ± 95 vs 134 ± 44, P = 0.001), (123 ± 46 vs 52 ± 30, P = 0.001), respectively. Also, all these patients had serum TNF-α ≥ 151 mg/dl and PTEN gene activity levels ≥83 pg/dl.

4. Discussion

4.1. Principal findings

Our study revealed that patients with acute STEMI had statistically significant increased serum levels of TNF-α & PTEN gene activity as compared to normal controls. Patients with acute STEMI and left ventricular systolic failure in whom EF% deteriorated at follow up had a statistically significant increased serum levels of TNF-α & PTEN gene activity as

Table 3 Comparison between sub-group IA, and sub-group IB regarding their serum TNF-α, PTEN levels and EF%.

	Sub-group 1A n = 20	Sub-group 1B n = 12	P value
TNF-α	240 ± 82	151 ± 34	0.001
PTEN	115 ± 38	64 ± 22	0.001
EF%			
*At presentation	42 ± 7%	44 ± 5%	0.47
*At follow-up	32 ± 6%	50 ± 2%	0.001

compared to those, in whom EF% not deteriorated at follow up, in spite of nonstatistically significant difference between their EF% at time of presentation. Also, patients with worse clinical outcome (death & recurrent hospitalization by heart failure) had significantly increased serum levels of TNF-α & PTEN gene activity as compared to others.

Shimoda et al. [16] assessed tissue ACE and TNF-α levels in acute MI patients. Their levels were higher in acute MI patients than in controls (P = 0.001). In acute MI patients with in-hospital complications spontaneous and stimulated levels of tissue ACE and TNF-alpha were higher than in patients without complications (P = 0.01). Also, Fahim et al. [17] conducted a study on 20 acute MI patients and 10 healthy age and sex matched controls. Sequential estimation of plasma TNF-α level was carried out on admission, at 24 and at 48 h post admission using ELISA. Acute MI patients showed a significant increase of plasma TNF-α level on admission and 24 h post admission but not after 48 h. However, a significant increase was still seen at 48 h post admission in patients with signs of heart failure compared to those without signs of heart failure. They concluded that TNF-α might be an early marker of myocardial damage because of the early increase of its level after ischemic injury and TNF-α level may be an important indicator for the occurrence of heart failure in acute MI.

Table 4 Agreement between TNF-α levels in both subgroups.

	TNF-α ≥151 mg/dl	TNF-α <151 mg/dl
Subgroup IA, n = 20	19	1
Subgroup IB, n = 12	2	10

Table 5

Agreement between PTEN levels in both subgroups.

	PTEN ≥83 pg/dl	PTEN <83 pg/dl
Sub-group IA, n = 20	15	5
Sub-group IB, n = 12	1	11

Debrunner et al. [18] revealed that the inflammation-associated cytokines TNF- α , IL-6 and IL-1Ra were significantly elevated in patients with MI complicated by cardiogenic shock when compared to patients with uncomplicated MI. Also, González et al. [19] found that TNF- α concentrations were greater in patients with ischemic events or heart failure both at admission and at 48 h. Specifically, TNF- α concentrations were analyzed in the group of 9 patients who died. At admission, these values were not significantly greater in this group compared to those in the surviving patients. Nevertheless, at 48 h, TNF- α concentrations were significantly greater in the patients who died than in surviving patients. TNF- α concentrations recorded at 48 h were significantly negatively correlated with LVEF ($r = 0.416$; $P < 0.001$); this correlation was maintained at 6 months among the 65 surviving patients ($r = 0.256$; $P = 0.039$). In addition, there was a positive correlation between TNF- α concentrations and IL-6, sICAM-1, and CRP concentrations at admission ($r = 0.269$, $P = 0.02$; $r = 0.444$, $P < 0.001$; and $r = 0.286$, $P = 0.01$, respectively), and after 48 h ($r = 0.309$, $P = 0.007$; $r = 0.163$, $P = 0.1$; and $r = 0.418$, $P = 0.001$, respectively). It had also been directly associated with myocardial damage after ischemia/reperfusion, oxidative stress in patients with STEMI, myocardial rupture and chronic ventricular dysfunction, apoptosis, and peripheral endothelial dysfunction.

On the other hand, Puhakka et al. [20] studied the interrelationships of IL-6, TNF- α , tissue injury, infarct size, cardiac function, and collagen formation in humans. They revealed that patients with left ventricular dysfunction (EF < 40%) had similar TNF- α levels as those with preserved left ventricular function and concluded that TNF- α measurement is useless in the assessment of infarct size or left ventricular function during the immediate post-infarction period. The regulatory role of PTEN in post-MI remodeling was further supported by Nirmal et al. [21] findings in mice over expressing PTEN, which exhibited increased cardiac dysfunction and mortality. Heart failure and LV rupture might result from massive cell death and degradation of extracellular matrix [22]. Moreover, it has been reported that PI3K/Akt signaling is required for angiogenesis and cardiac repair after MI, and that this signaling pathway was impaired in the infarcted heart [23]. Also, Nirmal et al. [21] demonstrated that PTEN expression is upregulated in WT mice after MI, suggesting that increased PTEN activity may inhibit the activation of the PI3K/Akt signaling pathway in the infarcted heart. Furthermore, PTEN promotes post-MI remodeling by regulating inflammation, cytokine production, and MMP expression. Cardiac-specific PTEN deletion or pharmacological inhibition of PTEN has been shown to inhibit apoptosis and limit infarct size after ischemia-reperfusion. Decreased PTEN activity was associated with subsequent reduced extracellular matrix remodeling and improved LV function [24].

4.2. Limitations of study

PTEN gene is very difficult target in experimental studies and lack of highly specific commercially available activator or inhibitors led to limited available data. Also, small number of patients included in this study is another limitation.

5. Conclusions

Patients with acute STEMI had statistically significant increased serum levels of TNF- α & PTEN gene activity. Both markers reflect the extent of myocardial damage and hence predict worsening of EF%, development of heart failure and death.

5.1. Clinical implication

Serum levels of TNF- α ≥ 151 mg/dl and PTEN gene activity ≥ 83 pg/dl were recommended as markers in acute STEMI for predicting heart failure and death during the next year.

5.2. Further directions

Targeting PTEN gene & TNF- α may be an effective approach to enhance cardiac repair following acute MI.

Conflict of interest

None of the authors has any conflict of interest to report.

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