Study the Value of Interleukin-6 as Diagnostic Marker and Pridective of Cardiac Events in ST Segment Elevation Myocardial Infarction

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Abstract: Introduction: Interleukin-6 (IL-6) is an inflammatory cytokine produced by endothelial cells, smooth muscle cells, fibroblasts, lymphocytes and macrophages. Atherosclerosis is currently considered a systemic inflammatory disease and elevated levels of IL-6 have been associated with the progression of coronary artery disease (CAD). Patients with ST segment myocardial infarction have increased circulating levels of IL-6 compared with those patients who have stable angina. **Aim of Work:** To assess the diagnostic value of interleukin 6 compared to troponin I in ST segment elevation MI. To assess the predictive value of elevated interleukin 6 in ST segment elevation myocardial infarction. **Methods:** This prospective study was included sixty adult patients of both sex meeting the American Heart Association (AHA) recommendations for diagnosis of ST segment elevation myocardial infarction from those attending the Critical Care Units, Critical Care Medicine Department, Faculty of Medicine, Alexandria University. Patients were classified into the following groups: Patient Group I: ST segment elevation myocardial infarction: Group IA**:** with successful thrombolytic therapy. Group IB**:** with failed thrombolytic therapy. Control group II: The study will also include ten healthy control patients of same age and sex. Then each patient had been subjected to the following: Cardiac enzymes: creatine kinase-myocardial band (CK-MB) (ng/ml) and troponin I (ng/ml) once on admission using dimension RxL Siemens. Enzyme-linked immunosorbent assay (ELISA) for quantitative detection of human IL-6(pg/ml) in the serum once on admission. **Results:** There was significant statistical difference between group I (Patient group) and control group as regard to troponin I level ($p< 0.001$). Interleukin-6 was showed significant increase in group IA and it was ranged from 105 pg/ml to 634 pg/ml with mean 346.9 pg/ml which was higher than group IB, Also Interleukin-6 was showed significant increase in group IB and it was ranged from 134–590 pg/ml with mean 293 pg/ml, While in group II (Control group) it was ranged from 2.30 to 5.90 pg/ml with mean 4.04 pg/ml. So there was significant statistical difference between both group I and control group as regard to interleukin-6 level ($p <0.001$). Also there was significant statistical difference between both group I and control group as regard to CK-MB level ($p <0.001$). **Conclusion:** STEMI patients have increased level of IL-6 compared to those normal persons. IL-6 may be a potentially useful marker for diagnosis of STEMI. IL-6 may be helpful prognostic value for future cardiac mortality in patients with STEMI. The level of IL-6 is not affected by the extent of myocardial damage and necrosis.

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1. Introduction

Owing to major changes in the biomarkers available for diagnosis, criteria for acute myocardial infarction have been revised. The current international consensus definition states that the term acute myocardial infarction (AMI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.[(1)] The present guidelines pertain to patients presenting with ischemic symptoms and persistent ST-segment elevation on the electrocardiogram (ECG). Most of these patients will show a typical rise in biomarkers of myocardial necrosis and progress to Q-wave myocardial infarction. Separate guidelines have recently been developed by another Task Force of the ESC (European Society of Cardiology) for patients presenting with ischemic symptoms but without persistent ST-segment elevation and for patients undergoing myocardial revascularization in general.[(2,3)]

The general definition of acute myocardial infarction is a definition of the underlying pathology and remains unchanged. Acute myocardial infarction is thus defined as myocardial necrosis due to prolonged myocardial ischemia. Ideally, to diagnose the two components of the definition myocardial necrosis and myocardial ischemia, two different biomarkers, indicating each of these components, should be available. Unfortunately, while cardiac troponins are

very specific markers of myocardial cell necrosis, good markers of ischemia are currently lacking. Thus, other criteria have to support the diagnosis of AMI. These basic criteria for the AMI diagnosis were not altered in the new definition, except for a small amendment regarding the identification of an intracoronary thrombus by angiography or autopsy, which was added as a relevant criterion.[4]

The measurement of serum cTnI and cTnT is superior in terms of sensitivity and specificity to cardiac muscle enzyme measurements in the identification of cardiac muscle damage.[5] Raised cardiac troponin concentrations are now accepted as the standard biochemical marker for the diagnosis of myocardial infarction.[6,7]

There is an extensive body of the literature that supports the role of chronic inflammation in the development and progression of atherosclerosis. It has been reported that increased levels of inflammatory agents, including IL-6, are associated with acute ischemic conditions and are predictors of recurrent events in patients with CAD.[8,9,10]The serum level of IL-6, along with other cytokines, is also associated with unfavorable clinical outcomes in patients hospitalized for unstable angina and ST-elevated myocardial infarction (STEMI).[11,12,13] Furthermore, many chronic conditions that are common causes of death in older persons may stimulate and sustain a systemic inflammatory state, which can be measured by increased levels of serum IL-6 or other pro inflammatory cytokines. The secretion of IL-6, which is a major determinant of the production of acute-phase proteins, is increased in clinical situations characterized by tissue injury, including infections, malignant neoplasms, ischemic diseases, and trauma. This pathophysiology may also explain the elevated risk of mortality associated with increased circulating levels of inflammatory markers.[14]

A large number of studies report a positive association between serum IL-6 concentration and the risk of mortality from CAD.[8,11,15,16] However, whether elevated serum IL-6 plays a causal role in CAD mortality remains unclear. A recent report showed that IL-6 may play a causal role in the development of coronary heart disease.[17,18] As interleukin-6 receptor (IL6R) blockade reduced systemic and articular inflammation. Furthermore, this causal association between IL6R-related pathways and coronary heart disease is also strongly supported by a collaborative meta-analysis. These results suggest that targeting IL6R could provide a novel therapeutic approach to the prevention of coronary heart disease.[17-19] This study found that serum IL-6 levels were significantly higher at baseline in patients who died during follow up, in line with previous studies, thus supporting the notion that the chronic inflammatory process may play a causal role in the development and prognosis of atherosclerotic disease. Further research is needed to confirm the causality of association between serum IL-6 levels and mortality in long time period after onset of myocardial infarction.

2. Patients and Methods

This prospective study was included sixty adult patients of both sexes meeting the American Heart Association (AHA) recommendations for diagnosis of ST segment elevation myocardial infarction from those attending the Critical Care Units, Critical Care Medicine Department, Faculty of Medicine, Alexandria University to be included in the current study.

This prospective study with approval of the medical ethics committee of Alexandria faculty of medicine and an informed consent from the patients of kin will be taken before inclusion in the study.

Inclusion criteria:

Patients were fulfilled the criteria of diagnosis ACS and diagnosed as ST segment elevation MI according to American Heart Association (AHA) criteria which included patient ranged between 30 to 70 years and presented with active chest pain, a 12-lead electrocardiogram and showing:

1. ST-segment elevation ≥ 1 mm (0.1 mV) in 2 or more adjacent limb leads (from aVL to III, including -aVR).
2. ST-segment elevation ≥ 1 mm (0.1 mV) in precordial leads V4 through V6.
3. ST-segment elevation ≥ 2 mm (0.2 mV) in precordial leads V1 through V3.
4. New left bundle-branch block.

In addition to positive tests for cardiac enzymes troponin and creatinine kinase isoenzyme MB are helpful, but not essential. Therapy should not be delayed while awaiting results.

Reciprocal depressions (ST depressions in the leads corresponding to the opposite side of the heart) make the diagnosis of STEMI more specific.

Exclusion criteria:

Patients were excluded from this study if they have:

1. Recent MI in the last three months.
2. Recent cardiological intervention in the last three months.
3. Recent ischemic cerebrovascular stroke in the last three months.
4. Non-ST segment elevation myocardial infarction and unstable angina according to Electrocardiographic changes, cardiac markers and clinical condition of the patient.
5. Acute infectious diseases that leads to elevation of troponin I and interleukin 6.
6. Active immunological diseases.
7. Renal impairment.

Patients were classified into the following groups:
Patient Group I: ST segment elevation myocardial infarction:
Group IA: STEMI with successful thrombolytic therapy.
Group IB: STEMI with failed thrombolytic therapy.
Control group II: The study would also included ten healthy control patients of same age and sex.
Then each patient had been subjected to the following:

- Thorough clinical examination including chest and heart examination.
- Serial daily ECG every 12 hours.
- Laboratory tests (on admission) including:
- Cardiac enzymes: creatine kinase-myocardial band (CK-MB) (ng/ml) and troponin I (ng/ml) once on admission using dimension RxL Siemens.
- Enzyme-linked immunosorbent assay (ELISA) for quantitative detection of human IL-6(pg/ml) in the serum once on admission.

Data were fed to the computer and analyzed using IBM SPSS (Statistical Package for Social Science Version) software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum) mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between the two studied groups were done using independent t-test while for abnormally distributed data, comparison were done using Mann Whitney test while Kruskal Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney test. Correlations between two quantitative variables were assessed using spearman coefficients regarding normality of the data. Significance of the obtained results was judged at the 5% level.

Agreement of the different predictive with the outcome was used and was expressed in sensitivity, specificity, positive predictive value, negative predictive value and accuracy. *Receiver operating characteristic curve (ROC)* was plotted to analyze a recommended cutoff, the area under the ROC curve denotes the diagnostic performance of the test.

3. Results

There were significant statistical difference between the studied groups as regard to sex as it was (p1= 0.013) when compared between STEMI with failed thrombolysis and STEMI with successful thrombolysis while there were no significant statistical difference as regards to age of studied groups.

Table (1): Comparison between the two studied groups according to demographic data

	STEMI with successful thrombolysis (n = 24)		STEMI with failed thrombolysis (n = 36)		Test of sig.	p
	No	%	No	%		
Sex						
Male	19	79.2	17	47.2	χ^2= 6.123*	0.013*
Female	5	20.8	19	52.8		
Age						
Min. – Max.	39.0 – 74.0		42.0 – 74.0		t = 1.079	0.285
Mean ± SD.	55.29 ± 10.63		57.94 ± 8.37			
Median	53.50		59.0			

χ^2: Chi square test, t: Student t-test *: Statistically significant at $p \leq 0.05$

In this study there were in group IA 14 smoker patients and they were represented (58.3%) while 10 patients were not smoker and they were represented (41.7%) of total percentage of studied group.

In group IB there were 14 smoker patients and they were represented (38.9 %) while 22 patients not smoker and they were represented (61.1%) of total percentage of studied group.

In group IA there were 15 diabetic patients and they were represented (62.5%) of total group while there were 9 patients not diabetic and they were represented (37.5%) of total number and percentage of that group.

In group IB there were 20 diabetic patient and they were represented (55.6%) of total group while there were 16 patients not diabetic and they were represented (44.4%) of total number and percentage of that group.

In group IA there were 18 hypertensive patients by history and they were represented (75%) of total group while there were six patients not hypertensive by history and they were represented (25%) of total group percentage.

In group IB there were 20 hypertensive patients by history and they were represented (55.6%) while there were 16 patients not hypertensive and they were represented (44%) of total group percentage.

In group IA there were 10 patients with history of ischemic heart disease and they were represented (41.7%) of total group percentage while there were 14 patients not known to have ischemic heart disease by history and they were represented (58.3%) of total group percentage.

In group IB there were 17 patients with history of ischemic heart disease and they were represented (47.2%) of total group percentage while there were 19 patients not known to have ischemic heart disease by history and they were represented (52.2%) of total group percentage.

So according to risk factors (smoking, DM, HTN, and old history of IHD) there is no significant statistical difference between studied groups.

Table (2): Comparison between the two studied groups according to risk factors

	STEMI with successful thrombolysis (n = 24)		STEMI with failed thrombolysis (n = 36)		χ^2	p
	No	%	No	%		
Smoker						
No	10	41.7	22	61.1	2.188	0.139
Yes	14	58.3	14	38.9		
DM						
No	9	37.5	16	44.4	0.286	0.593
Yes	15	62.5	20	55.6		
HTN						
No	6	25.0	16	44.0	2.344	0.126
Yes	18	75.0	20	55.6		
IHD						
No	14	58.3	19	52.8	0.180	0.672
Yes	10	41.7	17	47.2		

Troponin I was showed significant increase in group IA and it ranged from 29.10 ng/ml to 93.40 ng/ml with mean 63.45 ng/ml, which was higher than group IB. Also, troponin I showed significant increase in group IB and ranged from 13 ng/ml to 89.80 ng/ml with mean 39.23 ng/ml. The control group II ranged from 0.01 ng/ml to 0.05 ng/ml with mean 0.02 ng/ml.

Therefore, there was significant statistical difference between between group I and control group as regard to troponin I level ($p< 0.001$).

Table (3): Comparison between the different studied groups according to troponin I

	STEMI with Successful thrombolysis (n = 24)	STEMI with failed thrombolysis (n = 36)	Control group (n = 10)	$KW\chi^2$	p
Troponin I					
Min. – Max.	29.10 – 93.40	13.0 – 89.30	0.01 – 0.05	20.616*	<0.001*
Mean ± SD.	63.45 ± 22.15	39.23 ± 20.04	0.02 ± 0.01		
Median	64.15	32.35	0.03		
Sig. bet. grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$				

Interleukin-6 showed significant increase in group IA and it ranged from 105 pg/ml to 634 pg/ml with mean 346.9 pg/ml, which is higher than group IB. Also interleukin-6 showed significant increase in group IB and ranged from 134 to 590 pg/ml with mean 293 pg/ml. The control group II ranged from 2.30 to 5.90 pg/ml with mean 4.04 pg/ml.

Therefore, there was significant statistical difference between both group I and control group as regard to interleukin-6 level (p <0.001).

Table (4): Comparison between the different studied groups according to interleukin-6

	STEMI with successful thrombolysis (n = 24)	STEMI with failed thrombolysis (n = 36)	Control group (n = 10)	KW	p
Interleukin-6					
Min. – Max.	105.0 – 634.0	134.0 – 590.0	2.30 – 5.90	20.575*	<0.001*
Mean ± SD.	346.96 ± 148.18	293.06 ± 117.28	4.04 ± 1.12		
Median	369.0	265.0	4.0		
Sig. bet. grps	p_1= 0.004*, p_2<0.001*, p_3<0.001*				

CK-MB showed significant increase in group IA and it ranged from 8.40 mg/dl to 36.50 mg/dl with mean 24.72 mg/dl which higher than group IB. Also, CK-MB showed significant increase in group IB and it ranged from 7.20 mg/dl to 33.70 mg/dl with mean 18.31 mg/dl. The control group II ranged from 1 mg/dl to 3.10 mg/dl with mean 1.94 mg/dl.

Therefore, there was significant statistical difference between both group I and control group as regard to CK-MB level (p <0.001).

Table (5): Comparison between the two studied groups according to CK-MB

	STEMI with successful thrombolysis(n = 24)	STEMI with failed thrombolysis(n = 36)	Control group(n = 10)	KW	p
CK-MB					
Min. – Max.	8.40 – 36.50	7.20 – 33.70	1.0 – 3.10	20.575*	<0.001*
Mean ± SD.	24.72 ± 8.60	18.31 ± 7.67	1.94 ± 0.72		
Median	27.05	18.10	1.90		
Sig. bet. grps	p_1= 0.115, p_2<0.001*, p_3<0.001*				

According to statistical data group IA was showed increase in days of staying in hospital which ranged from two to six days with mean 3.67 days, Also in group IB was showed increase in days of staying in hospital which ranged from two to seven days with mean 4.50 days.

So there was significant statistical difference between both groups as regard to duration of stay in ICU (p <0.025).

Table (6): Comparison between the two studied groups according duration of stay in ICU in days

	STEMI with successful thrombolysis (n = 24)	STEMI with failed thrombolysis (n = 36)	Z	p
Duration of stay in ICU per days				
Min. – Max.	2.0 – 6.0	2.0 – 7.0	2.242*	0.025*
Mean ± SD.	3.67 ± 1.24	4.50 ± 1.25		
Median	3.50	4.0		

Z: Z for Mann Whitney test *: Statistically significant at p ≤ 0.05

Table (7): Relation between interleukin-6 with risk factors in STEMI with successful thrombolysis cases

	N	Interleukin - 6			Z	p
		Min. – Max.	Mean ± SD.	Median		
DM						
No	**9**	105.0 - 634.0	374.22 ± 163.65	410.0	0.895	0.371
Yes	**15**	110.0 - 634.0	330.60 ± 141.43	315.0		
HTN						
No	**6**	110.0 - 634.0	330.83 ± 195.40	341.50	0.433	0.665
Yes	**18**	105.0 - 634.0	352.33 ± 135.48	379.0		
IHD						
No	**14**	110.0 - 634.0	353.07 ± 157.87	337.0	0.000	1.000
Yes	**10**	105.0 - 490.0	338.40 ± 141.31	397.50		
Smoker						
No	**10**	132.0 - 468.0	330.30 ± 108.19	363.50	0.586	0.558
Yes	**14**	105.0 - 634.0	358.86 ± 174.29	399.0		

Table (8):Relation between interleukin-6 with risk factors in STEMI with failed thrombolysis cases

	N	Interleukin - 6			Z	p
		Min. – Max.	Mean ± SD.	Median		
DM						
No	**16**	134.0 – 590.0	344.0 ± 142.14	348.50	2.117*	0.034*
Yes	**20**	145.0 - 410.0	252.30 ± 73.83	244.50		
HTN						
No	**16**	160.0 - 577.0	322.81 ± 117.58	282.50	1.385	0.166
Yes	**20**	134.0 - 590.0	269.3± 114.36	245.50		
IHD						
No	**19**	134.0 - 590.0	271.79 ± 103.57	247.0	1.041	0.310
Yes	**17**	145.0 - 577.0	316.8 ± 129.93	295.0		
Smoker						
No	**22**	145.0 - 590.0	301.27 ± 125.70	259.0	0.179	0.858
Yes	**14**	134.0 - 435.0	280.14 ± 105.89	278.50		

Table (9):Relation between interleukin-6 with all types of complication in STEMI with successful thrombolysis

	N	Interleukin - 6			Z	p
		Min. – Max.	Mean ± SD.	Median		
Incidence re infarction						
No	**22**	105.0 - 634.0	354.55 ± 149.85	379.0	1.045	0.296
Yes	**2**	168.0 - 359.0	263.50 ± 135.06	263.50		
Cardiogenic pulmonary edema						
No	**22**	132.0 – 634.0	368.73 ± 134.50	379.0	2.298*	0.022*
Yes	**2**	105.0 – 110.0	107.50 ± 3.54	107.50		
Type of Arrhythmia						
No	**20**	105.0 - 634.0	353.45 ± 157.59	379.0	0.620	0.535
Yes	**4**	190.0 - 410.0	314.50 ± 96.75	329.0		
Congestive heart failure						
No	**21**	105.0 – 634.0	338.90 ± 157.12	359.0	0.742	0.458
Yes	**3**	388.0 – 415.0	403.33 ± 13.87	407.0		
Pericarditis						
No	**23**	105.0 - 634.0	357.26 ± 142.45	370.0	-	-
Yes	**1**	110.0				
Cardiogenic shock						
No	**22**	105.0 – 634.0	343.55 ± 154.40	369.0	0.209	0.834
Yes	**2**	359.0 – 410.0	384.50 ± 36.06	384.50		

Z: Z for Mann Whitney test

Table (10): Relation between interleukin-6 with all types of complication in STEMI with failed thrombolysis

	N	Interleukin - 6			Z	p
		Min. – Max.	Mean ± SD.	Median		
Incidence reinfarction						
No	**32**	134.0 – 590.0	294.84 ± 117.09	265.0	0.277	0.782
Yes	**4**	160.0 – 435.0	278.75 ± 135.92	260.0		
Cardiogenic pulmonary edema						
No	**31**	134.0 – 577.0	279.23 ± 103.09	260.0	1.212	0.225
Yes	**5**	220.0 – 590.0	378.80 ± 173.11	297.0		
Type of Arrhythmia						
No	**30**	134.0 - 590.0	284.93 ± 108.99	254.0	0.743	0.457
Yes	**6**	168.0 - 577.0	333.67 ± 158.12	325.0		
Congestive heart failure						
No	**32**	134.0 – 590.0	293.28 ± 118.90	254.0	0.151	0.880
Yes	**4**	145.0 – 435.0	291.25 ± 119.82	292.50		
Pericarditis						
No	**35**	134.0 - 590.0	295.31 ± 118.19	270.0	-	-
Yes	**1**	214.0				
Cardiogenic shock						
No	**31**	134.0 – 590.0	292.26 ± 122.47	260.0	0.435	0.664
Yes	**5**	170.0 – 380.0	298.0 ± 88.37	347.0		

Z: Z for Mann Whitney test

Table (11): Relation between interleukin-6 with mortality in each group

Interleukin-6	Mortality		Z	p
	Died	Still alive		
STEMI with successful thrombolysis	**(n= 3)**	**(n= 21)**		
Min. – Max	410.0 - 634.0	105.0 – 496.0	2.226*	0.026*
Mean. ± SD	559.33 ± 129.33	316.62 ± 125.88		
Median	634.0	359.0		
STEMI with failed thrombolysis	**(n= 5)**	**(n =31)**		
Min. – Max	217.0 - 590.0	134.0 – 540.0		
Mean. ± SD	431.40 ± 158.65	270.74 ± 94.79	2.082*	0.037*
Median	433.0	248.0		

According to ROC (*Receiver operating characteristic curve)* curve to predict mortality for total cases there was cutoff value more than 407 pg/dl and with sensitivity 75% and specificity 82.69 %.

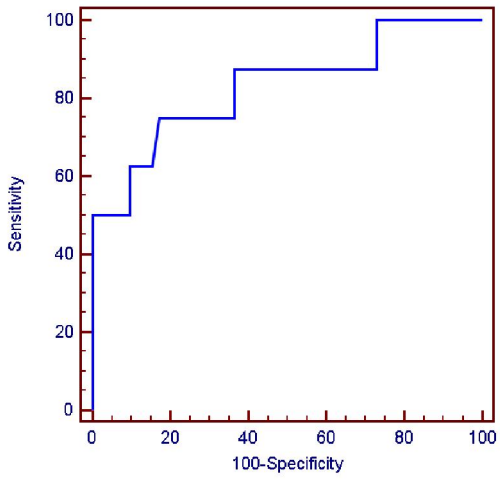

Figure (1): ROC curve (*Receiver operating characteristic curve)* for interleukin-6 to predict mortality for total cases

Table (12):Agreement (sensitivity, specificity and accuracy) for Interleukin-6 to predict mortality for total cases

Overall	AUC	p	Youden index	Cutoff	Sensitivity	Specificity	PPV	NPV
Interleukin-6	0.830*	0.001*	0.576	>407	75.0	82.69	40.0	95.6

Regarding the correlation between IL-6 and troponin I, there was no correlation between IL-6 and troponin I in both groups (IA and IB) as it was in group IA (r = 0.296, p =0.161) and was in group IB (r = 0.135, p = 0.433)

Table (13):Correlation between interleukin-6 and troponin I in both groups

	Interleukin-6	
	r_s	P
Troponin I		
STEMI with successful thrombolysis	0.296	0.161
STEMI with failed thrombolysis	0.135	0.433

r_s: Spearman coefficient

Regarding the correlation between IL-6 and CK-MB enzyme, there was no correlation between IL-6 and CK-MB in both groups (IA and IB) as it was in group IA (r = 0.148, p=0.491) and was in group IB (r = -0.052, p = 0.762).

Table (14): Correlation between interleukin-6 with troponin I and CK MB in each studied group

		Interleukin-6	
		STEMI with successful thrombolysis	STEMI with failed thrombolysis
Troponin I	r_s	0.296	0.135
	P	0.161	0.433
CK MB	r_s	0.148	-0.052
	p	0.491	0.762

r_s: Spearman coefficient

4. Discussion

In this current study, all selected patients were between 39 and 74 years and mean age in all patients was 56.5 years. According to age there was no statistically significant difference between the studied group patients and control group.

According to sex, males were more affected (97.2%) than females (20.8%) in group IA as compared in the same group while females were more affected (52.8%) than males (47.2%) in group IB. This is may be due to high incidence of cigarette smoking in males compared to females and the protective effect of female sex hormone in the prevention of cardiovascular disease. The incidence of CHD is markedly lower among women than men prior to the age of 50 years after which time CHD increases and approaches that seen among men by the eighth decade. Although the Framingham study described risk factors for CHD in women, the study was limited to white Caucasians living in the USA, and was unable to explain the later age of first occurrence of myocardial infarction (MI) among women compared to men. This may be because Framingham only measured a limited number of risk factors.[20,21,22] It is generally believed that the later age of myocardial infarction in women is due to the protective effects of female sex hormones, but differences in diet and smoking may also be important.[23,24]

In this current study, Smoker patients were more in group IA than group IB compared to non smoker patients in both two groups, Cigarette smoking is continues to be the major health hazards and it contributes significantly to cardiovascular morbidity and mortality, Although there was no statistically significant difference in this current study, the data of this study demonstrate the enhancing effect of smoking in the inflammatory process where IL-6 was significantly higher in smoker with significant

reduction of CRP that reflect a modest anti inflammatory activity. This finding agree with the result found by Sunyer et al[25] who found a potential role of the IL-6 gene in the inflammatory response associated with smoking, Cigarette smoking is continues to be the major health hazards and it contributes significantly to cardiovascular morbidity and mortality[26]. Other Studies showing that cigarette smoking affect all phases of atherosclerosis from endothelial dysfunction to acute clinical events that later become large thrombotic, Also some studies showing both active and passive cigarette smoke exposure predispose to cardiovascular events [27,28].

In this current study, There no statistically significant differences between group IA and group IB as regard to diabetes mellitus, But this risk factor were more in group IA and it was represented (62.5%) of total group percentage and in group IB and it was represented (55.6%) of total group percentage, So patients with diabetes mellitus presented with acute coronary syndrome had a higher risk of cardiovascular complications and recurrent ischemic events when compared to non diabetic counterparts. Different mechanisms including endothelial dysfunction, platelet hyperactivity, and abnormalities in coagulation and fibrinolysis have been implicated for this increased atherothrombotic risk in DM patients[29,30]. Patients with DM have increased circulating levels of inflammatory markers including C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). Furthermore increased levels of circulating inflammatory markers predict cardiovascular risk in DM patients[31,32].

In this current study, there no statistically significant difference between studied group as regard presence of hypertension or not, This risk factor in group IA was represented (75%) of total group percentage while not known to have hypertension patients were represented (25%) of total group percentage, In group IB hypertensive patients were represented (55.6%) of total percentage while patients not known to have hypertension were represented (44%) of total percentage of the same group, Several studies reported that a history of hypertension was associated with an increased rate of adverse outcomes after AMI such as heart failure, and cardiovascular death and arrhythmia [33,34] .

In this current study troponin I was measured for all patients in studied group and it was elevated in studied groups in both group I A and group I B and it was significantly elevated.

An elevated troponin I level was helpful in identifying patients at increasing risk for death or the development of acute myocardial infarction.[35,36]

Troponin I was showed significant increase in group IA which ranged from 29.10 ng/ml to 93.40 ng/ml with mean 63.45 ng/ml which higher than group I B, Also tropnine I was showed significant increase in group I B which ranged from 13 ng/ml to 89.80 ng/ml with mean 39.23 ng/ml but lower than group IA, While in group II (control group) is ranged from 0.01 ng/ml to 0.05 ng/ml with mean 0.02 ng/ml.

So there was significant statistical difference between group I and control group as regard to troponin I level ($p< 0.001$).

Other studies revealed that an elevated troponin level at baseline was an independent predictor of mortality even in patients with chest pain and acute MI with ST-segment elevation who were eligible for reperfusion therapy [35-37].

In this current study, CK-MB was showed significant difference between studied groups where it became more elevated in group IA more than group IB while it within normal ranges in control group.

CK-MB was showed significant increase in group IA which ranged from 8.40 mg/dl to 36.50 mg/dl with mean 24.72 mg/dl which is higher than group IB , Also CK-MB show significant increase in group IB which ranged from 7.20 mg/dl to 33.70 mg/dl with mean 18.31 mg/dl, While in group II (control group) was ranged from 1 mg/dl to 3.10 mg/dl with mean 1.94 mg/dl.

So this current study was showed significant statistical difference between both group I and group II (control group) as regard to CK-MB level ($p <0.001$).

CK-MB has high specificity for cardiac tissue and was the preferred marker of cardiac injury for many years, CK-MB typically begins to rise four to six hours after the onset of infarction but is not elevated in all patients until about 12 hours.[38,39]

In this current study, IL-6 was elevated in group I A with mean 634 pg/ml and also it was elevated in group IB with mean 590 pg/ml while it within normal ranges in control group and a mean of 4.04 pg/ml.

In this current study serum IL-6 level were significantly higher in studied group patients group IA and group IB than that in control group ($p=0.001$). Interleukin-6 was showed significant increase in group IA which ranged from 105 pg/ml to 634 pg/ml with mean 346.9 pg/ml which is higher than group I B, Also interleukin-6 was showed significant increase in group I B which range from 134 to 590 pg/ml with mean 293 pg/ml which is lower than group IA, While in group II (control group) ranged from 2.30 to 5.90 pg/ml with mean 4.04 pg/ml, So there was significant statistical difference between both group I (patients groups) and control group (healthy group) as regard to Interleukin-6 level ($p <0.001$).

Few studies reported that IL-6 elevation seen in STEMI might develop due to the myocardial necrosis rather than plaque rupture.[40,41,42]

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that is triggered by vulnerable plaque or necrotic

myocardium and correlates with the severity of coronary artery disease (CAD).[43]

In this study serum IL-6 level was showed statistically significant in group IA between IL-6 and mortality with p value=0.0026, Also it was showed statistically significant in group IB between IL-6 and mortality with p value=0.0037, Also ROC (*Receiver operating characteristic curve)* curve showed that cutoff value to predict mortality in group IA was more than 407 pg/ml with sensitivity 100% and specificity 71.43 %, Also ROC curve (*Receiver operating characteristic curve*) showed that cutoff value to predict mortality in group IB was more than 321 pg/ml with sensitivity 80% and specificity 74.19%.

In the FRISC (Fragmin and/or early Revascularization during in stability in Coronary artery disease) study, increased serum IL-6 level (>5pg/ml) was associated with mortality after 6 and 12 months. The elevated serum IL-6 level was also identified in patient subgroup who obtained the highest benefit mortality reduction in early invasive strategy. This was showed that elevated serum IL-6 level could identify patients with more severe event index who received the benefit with more aggressive treatment.[44]

The relation between IL-6 myocardial necrosis and infarct size is well known. Other studies was showed an association between IL-6 with high levels of peak Troponin I are thus in accordance confirming the connection between inflammation and infarct size.[35,37,45]

Control group had no inflammation so inflammatory and anti-inflammatory cytokines and their level were normal, The result of this current study are in keeping with recent in vitro and in vivo studies in animals which have suggested a protective role of IL-6 in both atherosclerotic lesion formation and stability[46,47].

This current study was showed that IL-6 serum level did not correlate with cardiac troponin levels in all patients group. Also it did not correlate with any of risk factors as history of IHD, medical history of HTN and also with smoking. Also this study revealed that IL-6 showed no statistically significant correlation between increased of it and incidence of complication except for pulmonary oedema this confirm that Interleukin-6 (IL-6) is a pro-inflammatory cytokine.

IL-6 is a cytokine associated with inflammation. Others studies have reported its value in predicting prognosis in patients during a 3 year follow up of patients with acute STEMI. The IL-6 concentrations and 2 promoter polymorphisms of the *IL-6* gene in STEMI patients treated with thrombolysis have also helped to identify higher-risk patients. Lindmark et al[42] have shown a relationship between IL-6 levels and mortality in patients with unstable coronary artery disease. Biasucci et al [40] have shown that IL-6 levels are elevated in patients with ST segment elevation myocardial infarction. In the Prospective Epidemiological Study of Myocardial Infarction study, Empana et al[48] showed that C-reactive protein, IL-6, and fibrinogen levels are related to the risk of sudden death in European middle aged men. Ridker et al[49] have shown that IL-6 levels predict the risk of future myocardial infarctions in apparently healthy men. So IL-6 serum levels were well established as a prognostic marker for patients with ST segment elevation myocardial infarction.

Conclusion

From this current study, we were revealed that:

- STEMI patients have increased level of IL-6 compared to those normal persons.
- IL-6 may be a potentially useful marker for diagnosis of STEMI.
- IL-6 can may be helpful prognostic value for future cardiac mortality in patients with STEMI.
- The level of IL-6 is not affected by the extent of myocardial damage and necrosis.

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