The value of YKL-40 in ischemic heart disease patients

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Introduction
Atherosclerotic coronary artery disease is considered to be the most common cause of myocardial ischemia. YKL-40, a chitin-binding acute phase glycoprotein, has been found to be expressed by macrophages in atherosclerotic plaques. The YKL-40 could potentially be a new useful biomarker to monitor severity and predict early diagnosis of acute coronary syndrome (ACS) in ischemic heart disease (IHD) patients.

Aim
The aim of this study was to measure the level of serum YKL-40 in IHD patients and to clarify its role as a potentially beneficial diagnostic marker in those patients.

Patients and methods
Serum YKL-40 was measured in 60 IHD patients and 30 healthy controls. According to chest pain analysis, ECG changes, and cardiac enzymes, the IHD patients were categorized into patients with stable angina and patients with ACS.

Results
The median level of YKL-40 (pg/ml) was significantly elevated in patients with IHD compared with the control group (2080 (575.5–5974.6) vs 522.6 (133.2–769.5), respectively; $P<0.001$). The median level of YKL-40 was also significantly higher in patients with ACS compared with patients with stable angina (2436 (576–5975) vs 1015 (675–1822), respectively; $P<0.001$). There was a positive correlation between YKL-40 levels and high-sensitivity C-reactive protein (mg/dl) in all studied groups of IHD patients. However, no significant correlation was detected between YKL-40 and age, systolic or diastolic blood pressure, and lipid profile in patients with IHD.

Conclusion
YKL-40 might play an important role as a diagnostic and prognostic marker in patients with IHD and in patients with ACS.

Keywords:
Acute coronary syndrome, ischemic heart disease, YKL-40 level

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Introduction

Ischemic heart disease (IHD) was the main cause of death globally during the last 15 years and continues to grow at exponential rates [1]. It contributes to more than 15% of all deaths in Egypt [2]. Atherosclerotic coronary artery disease (CAD) is considered to be the most common cause of IHD [3]. It has been well established that inflammation plays an important role in the development and progression of atherosclerosis of the coronary arteries [4]. Acute coronary syndrome (ACS) describes the continuum of myocardial ischemia, which includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [5]. YKL-40 is a chitin-binding acute phase glycoprotein [6] that is expressed in association with inflammatory process, extracellular matrix degradation, and angiogenesis [7]. It was identified in 1989 to be secreted by the human osteosarcoma cell line [8]. The human gene encoding YKL-40 was assigned to chromosome 1q31-q32 [9]. YKL-40 is produced by a variety of cells, including embryonic stem cells [10], macrophages [11], neutrophil granulocytes, chondrocytes, synoviocytes, and vascular smooth muscle cells [12]. YKL-40 promotes vascular smooth muscle cell attachment, spreading, and migration, suggesting that YKL-40 has a role in the process of atherosclerotic plaque formation wherein smooth muscle cells are induced to migrate through the intima in response to exogenous signals [13]. Atherosclerotic plaque macrophages also were found to express YKL-40 [14]. Therefore, YKL-40 could potentially be a new useful biomarker to monitor disease severity and predict prognosis and survival in patients with IHD [15].

Aim

This study was aimed to measure the level of serum YKL-40 protein in ACS patients, including its three

entities, and to clarify its role as a potentially beneficial diagnostic and prognostic tool in IHD patients.

Patients and methods

Study population

This study was conducted on 60 patients with IHD and age and sex matched 30 healthy volunteers who served as a control group. The IHD patients were admitted in the Internal Medicine and Cardiology Departments at Al-Zahra Hospital of Al-Azhar University. All participants provided written consent to participate in the study. The study was approved by the Ethical Committee of Faculty of Medicine for Girls, Al-Azhar University. The patients included in the study were older than 18 years and had typical chest pain and/or ECG changes and/or elevated cardiac enzymes. Patients with diabetes mellitus, recent infection, chronic inflammation, chronic obstructive pulmonary disease, renal disease, hepatic disease, malignant disease, peripheral artery disease, chronic heart failure, atrial fibrillation, a history of myocardial infarction or UA within the previous 3 months, or percutaneous transluminal coronary angioplasty or coronary bypass surgery within the previous 6 months were excluded from the study. According to chest pain analysis, ECG changes, and cardiac enzymes, CAD patients were categorized into two groups. Group I included 15 patients with stable angina (SA) and group II included 45 patients with ACS. ACS patients were further divided into three subgroups: group IIa (15 patients with STEMI), group IIb (15 patients with NSTEMI), and group IIc (15 patients with UA). All patients included in the study were subjected to the following: detailed history taking, laboratory investigations, 12-lead surface ECG, and resting conventional transthoracic echo-Doppler.

Detailed history

Detailed history taking, with special emphasis on current smoking as regards number of cigarettes/day, as well as smoking duration, and family history of IHD, and complete physical examination were carried out. The mean of three blood pressure (BP) measurements taken at three different occasions in the sitting position was considered. Hypertension was diagnosed as BP greater than or equal to 140/90 according to the 8th Joint National Committee of hypertension [16].

Laboratory investigations

Blood samples were obtained from all patients after 12–14 h of fasting in a sterile vacutainer tube and divided into two parts. One part was added into an EDTA tube for complete blood count (measured using a 'Coulter counter apparatus; Hitachi 912 apparatus' Hitachi company in Chiyoda, Tokyo, Japan) and the second part was collected into a plain vacutainer tube and left to clot for 30 min at room temperature before centrifugation for 15 min at 1000g. Thereafter, the serum was immediately separated. A part of the serum was stored at less than or equal to −20°C until use for YKL-40 measurement and the other part was used for other investigations measured using a Hitachi 912 apparatus, including cardiac biomarkers (CKT, CKMB, and troponin I), glycated hemoglobin (Hb A1C), kidney function tests, liver function tests, erythrocyte sedimentation rate, high-sensitivity C-reactive protein (HsCRP), and lipid profile [including total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG)]. Serum concentrations of YKL-40 were measured using an enzyme-linked immunosorbent assay technique.

Laboratory investigations

12-Lead surface ECG was performed to categorize the patients and evaluate for the presence of ST-segment deviation, T-wave changes, and arrhythmias.

Resting conventional transthoracic echo-Doppler

Resting conventional transthoracic echo-Doppler examination was performed for all participants using a Vivid-7 using multifrequency (2.5 MHz; 'GE System' from KPI California, US) matrix probe M3S with simultaneous ECG physio signal displayed with all recorded echo images and loops. Patients were examined in both supine and left lateral positions. The studied views from accessible windows (parasternal long axis, parasternal short axis, apical four-chamber, apical two-chamber, and apical five-chamber views) were obtained using different echo modalities (m-mode, 2-D echo, and Doppler flow) to study ventricular dimensions and function and evaluate CAD and its complications, including resting segmental wall motion abnormalities, functional or mechanical complications.

Statistical analysis

Data were analyzed using Microsoft Office 2003 from Microsoft Corporation, Redmond, Washington (excel) and statistical package for social science, version 16 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean±SD for quantitative parametric measures in addition to median percentiles for quantitative nonparametric measures and both number and percentage for categorized data. Paired and unpaired Student's *t*-test was performed to compare the mean±SD of two groups. The mutual

correspondence between two values was measured using the Spearman correlation coefficient. Linear correlation coefficient was used for the detection of correlation between two quantitative variables in one group. A *P* value less than 0.05 was considered statistically significant and a *P* value less than 0.01 was considered highly significant. Receiver operating characteristic curve (ROC) analysis was performed to identify the sensitivity (true-positive rate, expressed as a percentage) and specificity (true-negative rate, expressed as a percentage) of the cutoff value.

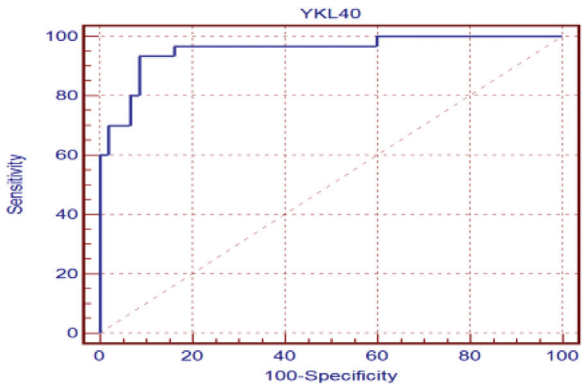
Results

The study was conducted on 90 participants, 60 IHD patients and 30 age and sex matched healthy controls. The clinical and laboratory data of the patients and controls are presented in Table 1. Among IHD patients, 51.7% were smokers and about 83.3% had typical chest pain. The mean±SD of serum cholesterol (mg/dl) (205±34.2), TG (mg/dl) (153±59.7), and LDL (mg/dl) (140.7±33) was significantly higher in IHD patients compared with the control group (103±26.6, 145.1±33.2, and 74.3±35.9, respectively) ($P<0.01$). However, the mean HDL cholesterol level in IHD patients (33.6±6.3) was significantly decreased compared with the control group (50.13±8.32) ($P<0.01$). The median value of YKL-40 (pg/ml) (2080) (575.5–5974.6) was significantly increased in IHD patients compared with the control group (522.6) (133.2–769.5) ($P<0.01$). The median HsCRP (mg/dl) value also significantly increased in patients with IHD (15.2) (3.1–31) compared with the control group (3.8) (1.4–6).

The cutoff point for YKL-40 level was less than 784.52 pg/ml for discriminating between IHD patie nts and the control group, with a sensitivity of 93.3 % and the specificity of 91.4 %, 75.7 % PPV, 98% NPV, and area under ROC of 0.95 (Table 2 and Fig. 1).

According to chest pain analysis, ECG changes, and cardiac enzymes, the IHD patients were subdivided into SA patients (group I) and ACS patients (group 2). Comparison between clinical and laboratory data of the two groups is presented in Table 3. Both groups were age matched, had male predominance, and high smoking percent. The mean level of systolic and diastolic BP was higher in SA patients than in patients with ACS (142.3±16.3 and 90±10.6 vs 132.6±14.4 and 85.5±9.6, respectively). However, no significant difference was found between the two groups. TC and LDL levels were significantly

Figure 1



Receiver operating characteristic curve between ischemic heart disease patients and controls as regards YKL-40.

Table 1 Clinical and laboratory data of ischemic heart disease patients and the control group

Variables	CAD patients (*N*=60)	Control group (*N*=30)	*P* value
Age (years)	56.28±10.66	53.1±11.47	
Male sex (%)	69.3	70	
Smoking (%)	51.7	10	
Triglycerides (mg/dl)	153±59.7	103±26.6	0.001
Total cholesterol (mg/dl)	205±34.2	145.1±33.2	0.001
LDL (mg/dl)	140.7±33	74.3±35.9	0.0001
HDL (mg/dl)	33.6±6.3	50.13±8.32	0.001
HsCRP (mg/dl)	15.2 (3.1–31)	3.8 (1.4–6)	0.0001
YKL-40 (pg/ml)	2080 (575.5–5974.6)	522.6 (133.2–769.5)	0.0001

CAD, coronary artery disease; HDL, high-density lipoprotein; HsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Table 2 The YKL-40 cutoff point, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy between ischemic heart disease patients and controls

	YKL-40				
Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Less than 784.52	93.3	91.4	75.7	98.0	0.95

NPV, negative predictive value; PPV, positive predictive value.

Table 3 Comparison between clinical and laboratory data of stable angina patients (group 1) and acute coronary syndrome patients (group II)

Variables	Group I: SA patients (*N*=15)	Group II: ACS patients (*N*=45)	*P* value
Age (years)	55.3±5.9	56.6±11.8	0.59
Male sex (%)	66.7	69	
Smoking (%)	46.7	53.3	
Systolic BP (mmHg)	142.3±16.3	132.6±14.4	0.054
Diastolic BP (mmHg)	90±10.6	85.5±9.6	0.167
Cholesterol (mg/dl)	189±36.3	210.4±32.2	0.05
LDL (mg/dl)	120.8±32.8	147.3±30.6	0.01
HDL (mg/dl)	39.4±6.7	31.6±4.9	0.001
Triglycerides (mg/dl)	144±41.6	157±64.7	0.3
HsCRP (mg/dl)	7.5 (3.1–24)	17.8 (5.4–31)	0.000
YKL-40 (pg)	1015 (675–1822)	2436 (576–5975)	0.000

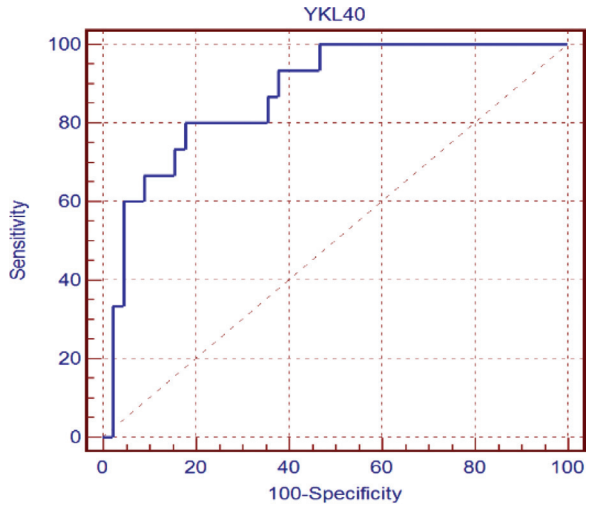
ACS, acute coronary syndrome; BP, blood pressure; HDL, high-density lipoprotein; HsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SA, stable angina.

Table 4 The YKL-40 cutoff point, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy between stable angina patients and acute coronary syndrome patients

Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Less than 1149.28	80.0	82.2	60.0	92.5	0.87

NPV, negative predictive value; PPV, positive predictive value.

Figure 2



Receiver operating characteristic curve between acute coronary syndrome patients and stable angina patients as regards YKL-40.

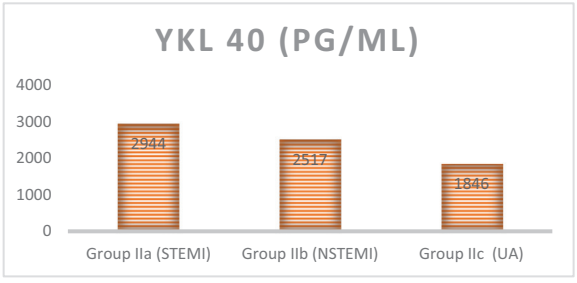
elevated in patients with ACS compared with SA patients (210.4±32.2 and 147.3±30.6 vs 189±36.3 and 120.8±32.8, respectively) ($P<0.05$). HDL was low in all patients with IHD, but it was highly significantly lower in ACS patients than in patients with SA (31.6±4.9 vs 39.4±6.7). The median value of YKL-40 in ACS patients was highly significantly elevated compared with patients with SA [2436 (576–5975) vs 1015 (675–1822)] as well as HsCRP [17.8 (5.4–31) versus 7.5 (3.1–24) (*P*? 0.01)].

The cutoff point for YKL-40 level was less than 1149.28 pg/ml for discriminating between ACS patients and SA patients, at which the sensitivity was 80% and the specificity was 82.2% with 60.0% PPV, 92.5% NPV, and area under ROC of 0.87 (Table 4 and Fig. 2).

ACS patients were further divided into three subgroups: group IIa included patients with STEMI, group IIb included patients with NSTEMI, and group IIc included patients with UA. The median value of YKL-40 was higher in STEMI than in NSTEMI patients and in NSTEMI than in US patients. However, these increased levels did not reach a significant value ($P>0.5$). However, HsCRP was significantly higher in STEMI than in NSTEMI patients and in NSTEMI than in USA patients ($P<0.5$). The data are presented in Table 5 and Figs 3 and 4.

The median level of YKL-40 showed a significant positive correlation with HsCRP in group IIa patients with STEMI ($r=0.7734$; $P<0.01$), group IIb patients

Figure 3



Levels of YKL-40 in all groups of acute coronary syndrome patients. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Table 5 Comparison between YKL-40 in the three groups of acute coronary syndrome patients

Variables	Group IIa (STEMI) (*N*=15)	Group IIb (NSTEMI) (*N*=15)	Group IIc (UA) (*N*=15)	*P* value
YKL-40 (pg/ml)	2944 (576–5975)	2517 (1076–5719)	1846 (988–3930)	0.16
HsCRP (mg/dl)	21.6 (3.1–24)	18.3 (10–25.1)	13.6 (4.5–20)	0.0001

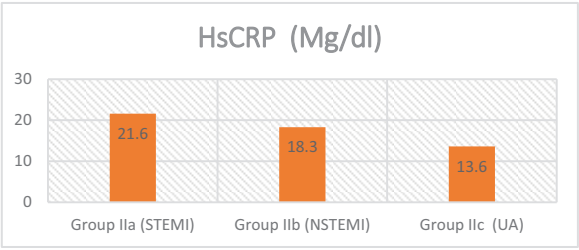
HsCRP, high-sensitivity C-reactive protein; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

with NSTMI (r=0.637; P<0.05), and group IIc patients with UA (r=0.632; P<0.05) (Fig. 4); but no significant correlation was found between YKL-40 and cardiac enzymes (CK and CKMB) or lipid profile (TC, TG, LDL, and HDL) (Table 6 and Fig. 5a–c).

Discussion

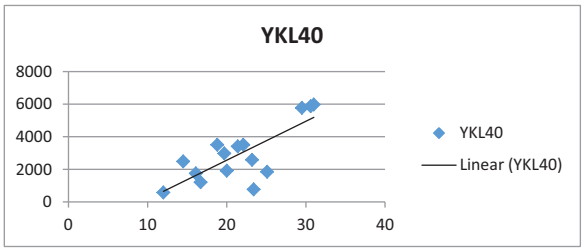
The level of YKL-40 is an important regulator of acute and chronic inflammation and tissue remodeling [6]. The participation of YKL-40 in inflammatory states and vascular processes implies that it may play a role in endothelial dysfunction and atherosclerosis [17]. The present study was designed to clarify the role of YKL-40 in IHD patients. Our results revealed significantly increased median value of YKL-40 in patients with IHD compared with age and sex matched healthy controls, with a cutoff value of 784.52 pg/ml. YKL-40 was also significantly elevated in patients with ACS compared with those with SA, with cutoff point of less than 1149.28, at which the sensitivity was 80% and the specificity was 82.2%. These data are in agreement with those of Rathcke *et al.* [18], who found that the level of YKL-40 was elevated in patients with symptoms of CAD and myocardial perfusion defects. Moreover, they implied that YKL-40 could be used as screening modality before myocardial perfusion image. Another meta-analysis by Song *et al.* [19] showed that serum YKL-40 levels in IHD patients were significantly higher than that in controls among Chinese, Korean, and Danish populations, whereas no such observation was detected among the populations of Turkey. These results suggested that ethnicity may

Figure 4

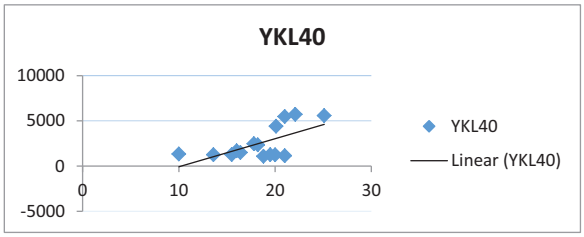


Levels of HsCRP in all groups of ACS patients. ACS, acute coronary syndrome; HsCRP, high-sensitivity C-reactive protein; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

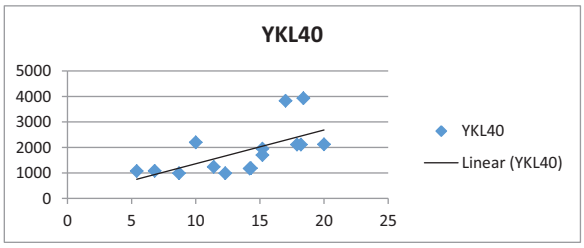
Figure 5



(a)



(b)



(c)

Positive correlation between YKL-40 and HsCRP in subgroups of ACS patients. (a) Positive correlation between YKL-40 and HsCRP in group IIa patients with STEMI. (b) Positive correlation between YKL-40 and HsCRP in group IIb patients with NSTEMI. (c) Positive correlation between YKL-40 and HsCRP in group IIc patients with UA. ACS, acute coronary syndrome; HsCRP, high-sensitivity C-reactive protein; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Table 6 Correlation between YKL-40 and various data in subgroups of acute coronary syndrome patients

	YKL-40								
	Group IIa (STMI)			Group IIb (NSTMI)			Group IIc (UA)		
Variables	*r*	*P*	Significance	*r*	*P*	Significance	*r*	*P*	Significance
CKT (I/U)	0.1	0.4	NS	0.2	0.3	NS	0.3	0.1	NS
CKMB (I/U)	0.02	0.9	NS	0.5	0.02	S	0.1	0.6	NS
Cholesterol (mg/dl)	0.07	0.8	NS	0.1	0.7	NS	0.4	0.05	NS
LDL (mg/dl)	0.06	0.8	NS	0.07	0.7	NS	0.3	0.1	NS
HDL (mg/dl)	0.04	0.8	NS	0.1	0.6	NS	0.04	0.8	NS
Triglyceride(mg/dl)	0.01	0.9	NS	0.02	0.9	NS	0.1	0.4	NS
HsCRP (mg/dl)	0.7734	0.001	HS	0.6	0.01	S	0.6	0.01	S

HDL, high-density lipoprotein; HsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NS, nonsignificant; NSTMI, non-ST-segment elevation myocardial infarction; S, significant; STMI, ST-segment elevation myocardial infarction; UA, unstable angina.

be the potential heterogeneity resource of this outcome. A possible explanation for the differences between countries could be the divergence in environment, genetic backgrounds, and risk factors relating to the lifestyle among various populations. It has been well established that inflammation plays an important role in the development and progression of atherosclerosis in the coronary arteries [4]. YKL-40 may mirror an inflammatory stimulus, and may also have a direct effect promoting atherosclerotic propagation and destabilizing plaque [20]. This analysis can also be intensified by our study finding as the median values of YKL-40 were significantly higher in AMI patients (STEMI and NSTEMI) than in those with UA, despite the nonsignificant difference between STEMI and NSTEMI patients. These results are in agreement with those of Nøjgaard *et al.* [20], as they reported that serum YKL-40 levels in the patients with AMI were higher than those in the patients with SA. No difference in serum YKL-40 between AMI patients with or those without ST-elevations was found. Moreover, Hedegaard *et al.* [21] documented significantly higher levels of plasma YKL-40 in patients with AMI when compared with controls. It is interesting that YKL-40 is increased very early after the acute onset of myocardial infarction symptoms and also in patients with the unstable coronary syndrome non-STEMI, which might indicate that YKL-40 could be potentially used for early detection of an unstable plaque, if the origin of the increased level of YKL-40 is from macrophages in the unstable plaque and not from the myocardium during the early necrosis of infracted myocardium [14]. YKL-40 in this study was positively correlated to HsCRP in patients with ACS as well as SA patients, but not correlated to lipid profile or cardiac enzymes. These results are in agreement with those of Wang *et al.* [22], who revealed that plasma YKL-40 was correlated significantly with serum HsCRP in patients with SA and STEMI patients. Moreover, our results are in accordance with those of Cetin *et al.* [23] and Hedegaard *et al.* [21] as they stated that YKL-40 levels correlated to HsCRP levels in STEMI patients. However, Mathiasen *et al.* [24] obtained contradictory results as they reported no significant correlation between YKL-40 and HsCRP in their SA patients.

Summary

In the present study, YKL-40 level was significantly higher in IHD patients in comparison with age and sex matched controls. YKL-40 was increased in stepwise manner in ACS patients in comparison with SA patients and in AMI patients (STEMI and NSTEMI) in comparison with UA patients. YKL-40 levels were positively correlated to HsCRP in all studied groups.

Conclusion

YKL-40 might play an important role as an early diagnostic and prognostic biomarker in IHD patients as well as in ACS. Larger-scale research studies are needed to make it clinically applicable.

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Conflicts of interest

There are no conflicts of interest.

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