ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 9, Issue – 3, May – 2024 , Page No. : 67 – 82

Serum YKL - 40 in patients with and without acute coronary syndrome

[1]Rabin Rai, Consultant, Department of Biochemistry, District Hospital Namchi, Sikkim, India
[2]Sangeeta Naorem, Associate Professor, Department of Biochemistry, Regional Institute of Medical College, Imphal,
[3]Niren Singh Koch, Associate Professor, Zoram Medical College, Aizawal, Mizoram
[4]Victoria Kshetrimayum, Assitant Professor, Department of Biochemistry, Regional Institute of Medical College, Imphal,
[5]Sachin Deba, Professor, Department of Cardiology, Regional Institute of Medical College, Imphal,
[6]Tashi Chopel Bhutia, Post Graduate Trainee, Department of Biochemistry, Regional Institute of Medical College, Imphal,
[7]Guiphiuliu Kamei, Post Graduate Trainee, Department of Biochemistry, Regional Institute of Medical College, Imphal,
[8]Bidya Nongmaithem, Post Graduate Trainee, Department of Biochemistry, Regional Institute of Medical College, Imphal,
Corresponding Author: Tashi Chopel Bhutia, Post Graduate Trainee, Department of Biochemistry, Regional Institute of Medical College, Imphal,

Citation this Article: Rabin Rai, Sangeeta Naorem, Niren Singh Koch, Victoria Kshetrimayum, Sachin Deba, Tashi Chopel Bhutia, Guiphiuliu Kamei, Bidya Nongmaithem, "Serum YKL - 40 in patients with and without acute coronary syndrome", IJMSIR - May - 2024, Vol – 9, Issue - 3, P. No. 67 – 82.
Type of Publication: Original Research Article
Conflicts of Interest: Nil

Abstract

Background and aims: Coronary heart disease (CHD) remains the major cause of mortality and morbidity in the entire world population despite therapeutic advances that control many risk factors. YKL-40 is a glycoprotein secreted by various cell-types including human macrophages, synovial cells, chondrocytes, neutrophils, and vascular smooth muscle cells. Several studies have shown up regulation of YKL-40 in acute coronary syndrome (ACS). The study aims to determine and compare serum YKL 40 level in patients with and without ACS andto correlate diagnostic performance of serum YKL 40 with troponin I in patients with ACS.

Materials and Methods: This cross-sectional study was done in the Department of Biochemistry in collaboration with the Department of Cardiology, RIMS, Imphal on diagnosed cases of ACS between January 2021 to October 2022. Estimation of serum YKL-40 and troponin I was done by ELISA method. Data were analysed using descriptive measures, and statistical significances were set at $p< 0.05$.

Conclusion: This study showed that level of serum YKL-40 was much higher in cases of ACS as compared to the healthy controls and also showed a positive significant correlation between serum YKL-40 level and trop I level among the ACS cases which were found to be significant.

Keywords: Acute Coronary Syndrome, YKL 40, Troponin T, Blood Pressure

Introduction

Acute coronary syndrome (ACS) is a syndrome due to decreased blood flow in the coronary arteries such that part of the heart muscle is unable to function properly. ACS is one of the leading causes of increased morbidity

and mortality worldwide. As per WHO 2015 report an estimated 7.4 million people died from coronary artery disease worldwide. Similarly, the incidence in India is estimated about per 1,00,000 population in the year 2016. Although substantial progress has been made in the diagnosis and treatment of acute coronary syndromes, cardiovascular disease remains the leading cause of death worldwide, with nearly half of these deaths due to ischaemic heart disease[1]. YKL-40 is a glycoprotein encoded by the CHI3L1 gene in humans, which is assigned to chromosome 1q31-32, and is approximately 40 k Da in size[2]. The abbreviation YKL-40 is based on the 1-letter code for the first three N-terminal amino acid residues: tyrosine (Y), lysine (K), and leucine (L)[3]. It is a phylogenetically highly conserved chitin-, heparin-, and collagen-binding protein with homologues in vertebrates and invertebrates[4].It has been widely suggested that YKL-40 is a kind of highly conserved protein mainly secreted by various cell-types including human macrophages, synovial cells, chondrocytes, neutrophils, and vascular smooth muscle cells[5]. Atherosclerotic plaque macrophages, particularly those macrophages that have infiltrated deeper into the lesion express YKL-40[6]. Hence, this study was conducted with an aim to evaluate the diagnostic value of the biomarker YKL-40, in patients with acute coronary syndrome beyond other diagnostic tests to reliably detect myocardial ischemia and necrosis and to find its role in providing clinical utility compensatory to that of troponin I, the established biomarker of myocardial necrosis in ACS.

Materials and Methods

Study design: Cross sectional study

Study setting: Department of Biochemistry in collaboration with the Department of Cardiology, RIMS, Imphal, Manipur.

Study Population: Patient attending the RIMS Hospital

Duration: January 2021 to October 2022.

Inclusion criteria: Diagnosed cases of acute coronary syndrome above 18 years of age.

Exclusion criteria: Presence of renal diseases, presence of hepatic diseases, diabetes mellitus, recent infection, COPD, osteoarthritis, malignant diseases and peripheral artery disease.

Sampling: Eligible participants with ACS were recruited consecutively from Casualty, Medicine OPD & Wards and ICCU of RIMS Imphal. When one ACS patient was recruited, one eligible participant without ACS was also recruited conveniently from the patient party or OPD attendees in Medicine or Cardiology Departments. Blood sample was collected after taking informed consent from the participants.

Laboratory tests done

Estimation of serum YKL 40

Method: Serum YKL 40 was estimated by the enzyme-linked immunosorbent assay system method adopted by Porstmann T and Kiessig ST [64].

Principle of the test: The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of YKL 40 [Human Chitinase-3-like Protein 1(CHI3L1)] in samples. The sample is added to wells pre-coated with monoclonal YKL-40 (CHI3L1) antibody. After incubation, added YKL-40 (CHI3L1) secondary antibodies labelled with biotin followed by Streptavidin-HRP to form immune complex. Unbound immune complex is removed by washing step. Then addition of Chromogenic Solution A and B, develops blue colour, and stop solution is added to stop the reaction. The concentration of YKL-40 (CHI3L1) is directly proportional to the colour developed.

Statistical Analysis

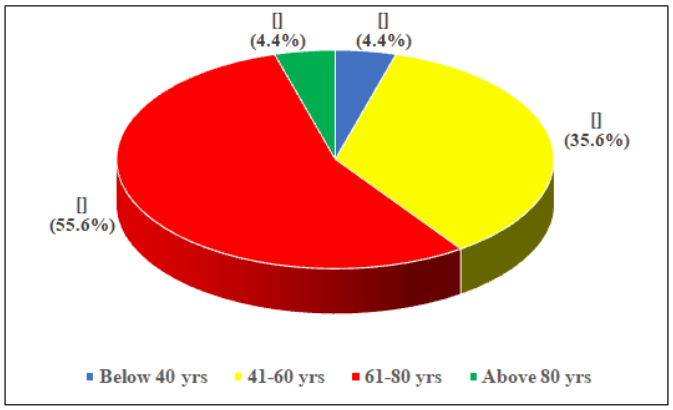
The collected data were analysed using IBM SPSS version 21.0 for windows.Statistics like mean, SD,

frequency and proportion were used to summarise the findings. Continuous data like age of the participants and serum YKL 40 level were expressed in mean and standard deviation and categorical data like gender, hypertension and smoking history were expressed in frequency and proportion. To compare the serum YKL 40 level between patients with acute coronary syndrome and the individuals without ACS, student's t-test was used. Pearson correlation was used to measure the correlation between dependent variables.ROC curve analysis was performed to see the diagnostic power of YKL-40 and trop I. A p value< 0.05 was taken as significant.

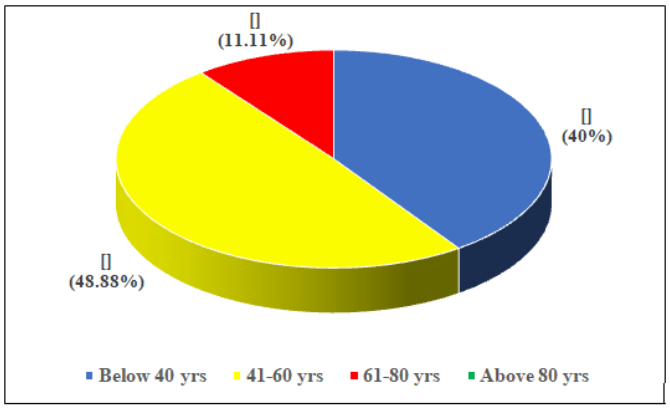
Ethical Issues

Written informed consent was obtained from each patient before recruiting for the study. Confidentiality was strictly maintained. Ethical approval was obtained from the Institutional Ethics Committee, RIMS, Imphal before the start of the study.

Results



(a)



(b)

Figure 1: Pie-chart showing age distribution of the respondents among cases and controls:

Table 1: Distribution of the respondents by age stratified by cases and controls:

Age	Group	Number	Mean ± Sd (Years)	P-Value
	Case	67	63.69±12.11	0.00
	Control	67	45.47±11.75	

*Independent student t-test

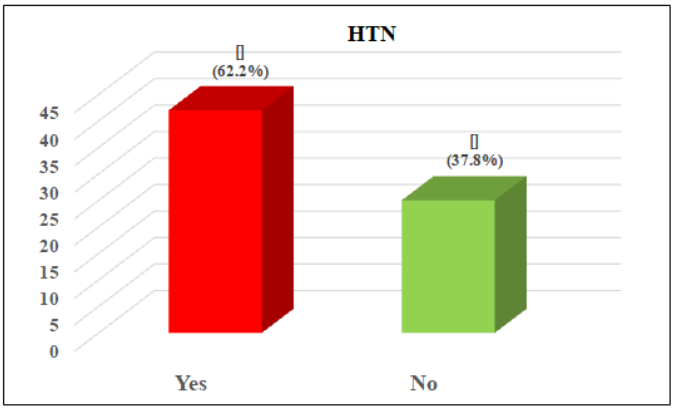


Figure 2: Distribution of the cases according to history of hypertension (HTN)

Table 2: Distribution of the respondents by other variables stratified by cases and controls:

Other Variables	Cases (n=67) Mean ± SD	Controls (n=67) Mean ± SD	P value
SBP (mmHg)	112.67±17.35	125.22±5.89	0.000
DBP (mmHg)	73.38±11.63	84.07±4.77	0.000
RBS (mg/dl)	133.11±64.28	105.26±14.38	0.000

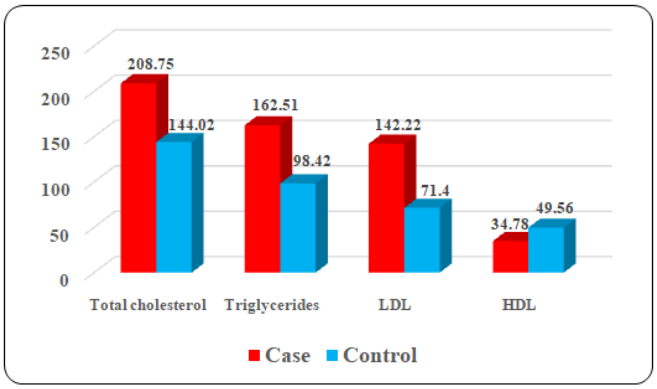


Figure 3: Distribution of the respondents by lipid profile in cases and controls

Table 3: Distribution of the respondents by lipid profile in the cases:

Total	TC>200 mg/dl	TG>150 mg/dl	LDL>100 mg/dl	HDL<40 mg/dl
67	39 (57.77 %)	42 (62.2%)	58 (86.66%)	43 (64.44%)

Figure 4: Distribution of respondents by serum YKL 40 levels in cases and controls

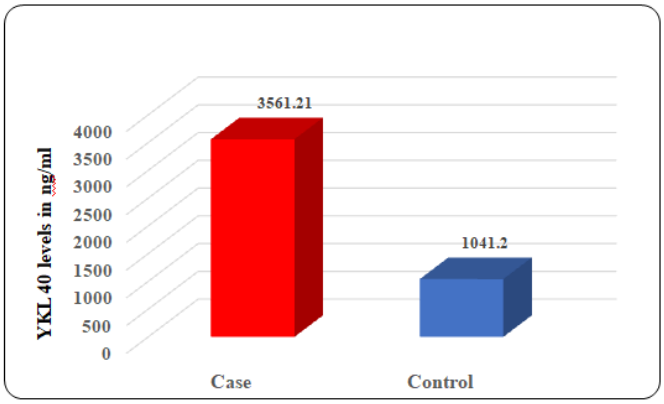


Table 4: Correlation between serum YKL 40 and lipid profile

	Coefficient of correlation (r)	P value
Total Cholesterol (mg/dl)	0.602	0.000
Triglycerides (mg/dl)	0.584	0.000
LDL (mg/dl)	0.658	0.000
HDL (mg/dl)	-0.702	0.000

Figure 5: Levels of YKL 40 in different groups of ACS patients (STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction and UA, unstable angina)

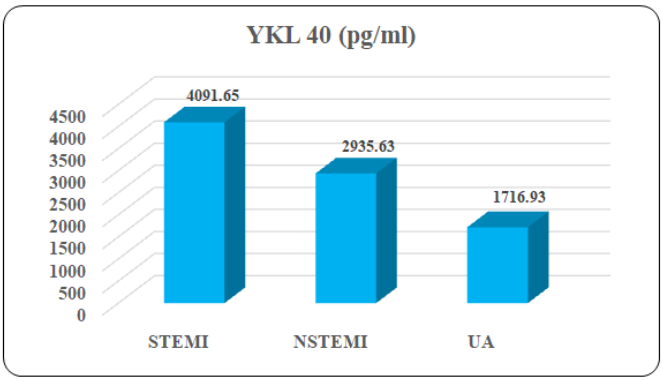


Figure 6: Levels of Trop I in different groups of ACS patients (STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction and UA, unstable angina)

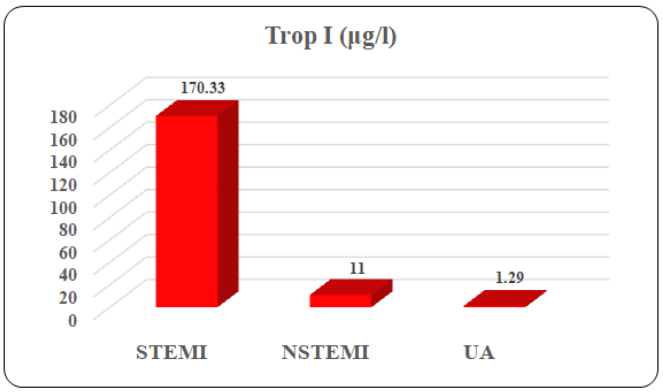


Table 5: Correlation between serum YKL 40 levels and Trop I levels among the cases

	Mean ± SD	Coefficient of correlation (r)	*P* value
YKL 40	2068.29±1624.71	0.819	0.000
Trop I	102.41±163.18		

Figure 7: Scattered diagram showing correlation between serum YKL 40 and Trop I among the cases

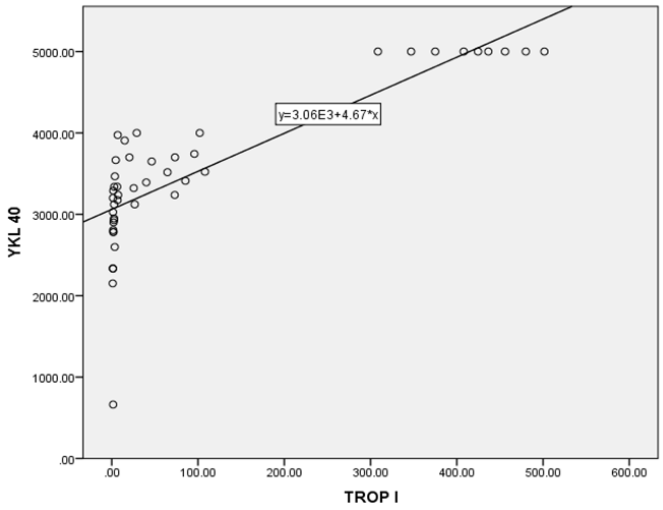


Figure 8: Receiver operating characteristics curve between acute coronary syndrome patients and controls as regards YKL 40 and Trop I

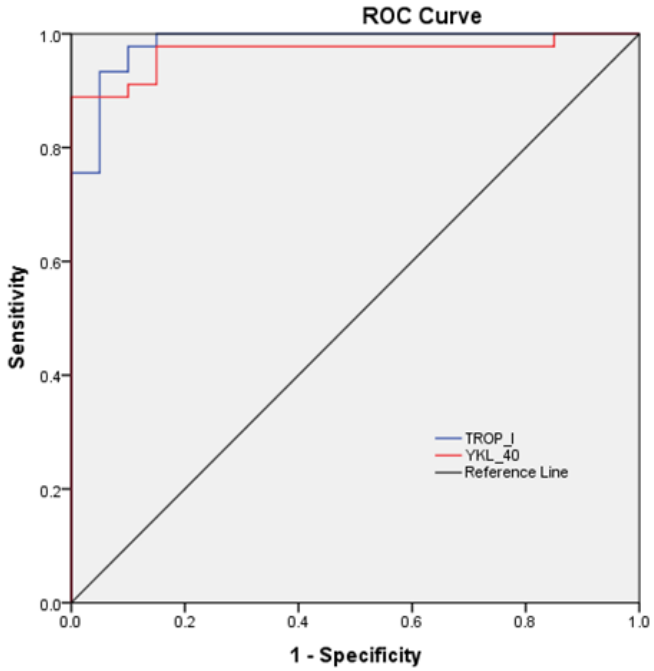


Table 6: The YKL-40 cutoff point, sensitivity, specificity, positive predictive value, negative predictive value, and AUC between acute coronary syndrome patients and controls

Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
YKL 40 (Less than 2734.12)	97.7%	100%	97.8%	100%	0.969
Trop I (Less than 0.7)	100%	80%	91.8%	100%	0.983

PPV, positive predictive value; NPV, negative predictive value

Discussion

This study was conducted to estimate serum YKL 40 in patients with acute coronary syndrome (ACS) and normal individuals and to compare the findings between normal individuals and patients with ACS.

In the present study, 55.6% of the ACS cases were in the age group of 61-80 years, followed by 35.6% in the age group of 41-60 years, and 4.4% each in the age groups of <40 and >80 years. Among the controls, 48.88% are in the age group of 41-60 years, followed by 40% in the age group of <40 years of age, 11.11% in the age group of 61-80 years and none in the age group of >20-30 years. In this study the prevalence of ACS was highest in the group of 61-80 years of age, followed by those age group of 61-80 years and the age groups of <40 years and >80 years. The reason for this could be, in older adults, there appears to be more extensive calcifications of coronary atherosclerosis with more multi-vessel and left main vessel involvement. These adverse changes increase the risk for myocardial injury without new thrombosis. This finding was supported by the study conducted by Ahmed E et al[72] where among 7930 consecutive ACS patients; 2755 (35%) were ≤50 years, 4110 (52%) were in 51–70 years and 1065 (13%) >70 years old. The proportion of women increased with increasing age (13% among patients ≤50 years to 31% among patients > 70 years). The elderly has the highest incidence of cardiovascular disease and frequently present with ACS. Elderly patients (>75 years of age)[73] constitute a large proportion of

those patients presenting with acute coronary syndrome (ACS), and temporal trends in the incidence of myocardial infarction document a shift toward older adults [74].The mean ± SD of age (63.9±12.11 years) was significantly higher in ACS patients compared with the control group (45.47±11.75 years) with $p<0.05$. The finding is supported by the study conducted by Zaky Doaa SE et al[6] where they found the mean ± SD of age for the ACS cases was 56.28±10.66 years and for the controls it was 53.1±11.47 years.

The present study shows that number of males was 49 (73.3%) and of females was 18 (26.7%) in the ACS cases. Among the controls, 31 (46.7%) and 36 (53.3%) were males and females respectively. This is due to the fact that men possess more coronary risk factors like smoking, high cholesterol and high blood pressure and they also occupy more stressful job roles. Moreover, there is higher myocardial blood flow in women compared to men. Various studies have reported more prevalence of ACS in males than in females which are similar to our findings. A study done by Zaky Doaa SE et al[6] also reported a higher prevalence of ACS in males (69.3%) than females (30.7%). Duan JG et al[7] in their study also found that men had a higher incidence of ACS than women (24.1% men & 17.0% women, p<0.001). The women benefit from the protective effects of endogenous estrogens, including estradiol, which may inhibit age-related vascular remodelling [76], such as vascular smooth muscle cell proliferation and endothelial dysfunction.

Coming to the prevalence of ACS among urban and rural population in this study, it was found that the prevalence was higher in urban areas as compared to rural areas (57.78% and 42.22%). This could be due to the fact that dwellers in urban areas may be associated with higher fat intake and with significantly lower physical activity. Moreover, the study was conducted in the urban area. The findings were in accordance with the cross-sectional study conducted by Oommen AM et al [77]. They found the prevalence of CHD was 3.4% (95% CI: 1.6–5.2%) among rural men, 7.4% (95% CI: 4.7–10.1%) among rural women, 7.3% (95% CI: 5.7–8.9%) among urban men, and 13.4% (95% CI: 11.2–15.6%) among urban women in 2010–2012. While the prevalence rates of CHD rates among rural males showed no change in the 20-year period, the rates in urban males rose marginally and the rates in females rose to more than twice the previous rates, with an increase in premature CHD. Rural males have been protected due to their higher activity levels and lower body mass indices. An article by Khanna T et al[78] in their article stated that the prevalence of CAD has increased seven-fold in urban India and fourfold in rural areas between 1970 and 2013. Current prevalence is 14% in the urban and 7% in the rural populations.

It was found that majority of cases, 55 (82.2%) were Hindus followed by Muslim 8 (11.9%) and Christian 4 (5.9%). The majority of the controls were Hindus 46 (68.9%) followed by Christian 12 (17.8%) and Muslim 9 (13.3%). The difference was statistically insignificant with $p>0.05$. This is due to the fact that the study was done in the Hindu dominated area. The study conducted by Gupta R et al[79] that employed a cross-sectional survey design and stratified random sampling technique consisting of 1,415 males and 797 females. Among males there were 1,092 Hindus (77.2%) and 272 Muslims (19.2%) while in females there were 685 Hindus (85.9%) and 91 Muslims (11.4%).

As regards to education, 30 cases (44.4%) had secondary level education, 22 (33.3%) primary and 15 (22.2%) upto graduation whereas 24 controls (35.5%) had upto graduation level education, 22 (33.3%) secondary, 12

(17.7%) primary and 9 (13.3%) above graduation. The difference was statistically insignificant with p>0.05

It was observed that 62.2% (42) of the cases had history of HTN and 37.8% (25) had no history of HTN. 26.6% of the cases were smokers as. The study also showed that 45 (66.7%) cases had comorbidity like hypothyroidism, bronchial asthma and HTN. The findings were similar to the study conducted by Alberty R et al[80] where 83.5% (95% CI, 81.6-85.2%) of the patients with ACS had hypertension, 65.0% (62.5-67.2%) had a hyperlipidemic profile, 32.6% (30.3-34.9%) were diagnosed with diabetes, and 27.6% (25.1-29.8%) were smokers at the time of a heart-related event. Rashid MH et al[8][81] also found that prevalence of risk factors in 160 cases were hypertension (101, 63%), lack of exercise (91, 57%), smoking (70, 44%), diabetes mellitus (61, 38%), dyslipidaemia (50, 31%). And the results were statistically significant ($p < 0.05$). The findings are also supported by the cross-sectional descriptive study conducted by Ralapanawa U et al.[82] They found that approximately 55.8% STEMI patients, 39.8% UA and 35.5% NSTEMI patients were smokers indicating a significant association between smoking and STEMI ($P = 0.017$). Almost 51.8% NSTEMI patients, 47.8% UA patients and 29.9% STEMI patients had hypertension ($P = 0.008$) indicating significant association of HT with UA and NSTEMI.

The random blood glucose of the cases was significantly higher than the controls (133.11±64.28 and 105.26±14.38 mg% respectively). Deedwania P et al [83] in their article stated that higher glucose levels in patients with ACS have also been associated with higher free fatty acid concentrations, insulin resistance, and impaired myocardial glucose utilization, thus increasing the consumption of oxygen and potentially worsening ischemia. Higher free fatty acid concentrations have been linked to increased incidence of malignant ventricular arrhythmias. Finally, hyperglycaemia has been linked to an impaired immune response. Badiger S[84] in his article stated that acute hyperglycaemia is common in patients with ST- elevation myocardial infarction (STEMI) even in the absence of a history of type 2 diabetes mellitus (DM). Hyperglycaemia is encountered in up to 50% of all STEMI patients, whereas previously diagnosed DM is present in only 20% to 25% of STEMI patients. The prevalence of type 2 DM or impaired glucose tolerance may be as high as 65% in myocardial infarction patients without prior DM when oral glucose tolerance testing is performed.

As regards to blood pressure, systolic blood pressure and diastolic blood pressure were significantly lower in cases than the controls (SBP: 112.67±17.35 mmHg and 125.22±5.89 mmHg respectively; DBP: 73.38±11.63 mmHg and 84.07±4.77 mmHg respectively). This is because in most patients with right ventricular MI, the inferior wall of the left ventricle is involved (usually in the form of a STEMI) as a result of occlusion of the right coronary artery proximal to the right ventricular branch. The findings are supported by Owens P et al[85] where they found mean supine resting systolic/diastolic blood pressure was 131(24)/77(11) mmHg in coronary disease patients. Twenty patients exhibited a fall in systolic blood pressure on standing at five minutes (mean 12(14) mmHg, $p < 0.001$), while 13 patients showed a fall in diastolic blood pressure at five minutes' standing (mean 2(9) mmHg, p = NS).

As regards to the lipid profile in the study, it was found that the mean ± SD of total cholesterol was 208.75±31.25 mg/dl in the cases and 144.02±19.57 mg/dl in the controls, triglycerides in cases was 162.51±39.81 mg/dl and 98.42±16.96 mg/dl in controls and LDL was 142.22±31.31 mg/dl in the cases and 71.40±21.24 md/dl

in controls showing that the values were higher in the cases as compared to the control group and the difference were found to be statistically significant with $p<0.05$. However, the mean ± SD of HDL in the cases 34.78±6.44 mg/dl was lower as compared to the controls (49.56±5.72 mg/dl) and the difference was statistically significant with $p<0.05$. In this study, it was observed that there were high TC, TG and LDL and low HDL. The common risk factors for ACS were dyslipidemia, diabetes, and hypertension which are similar to other studies[86,87] which demonstrated a high prevalence of one or more major risk factors for CAD and ACS. Dyslipidemia is an independent major risk factor for CAD. A combination of low HDL-C and high TG referred to as atherogenic dyslipidemia, have been implicated as important predictors of CAD [88][89]. The findings of this study are also supported by the study conducted by Zaky Doaa SE et al [6].In this study, 39 (57.77%) patients were observed to have TC>200mg/dl, 42 (62.2%) had TG>150mg/dl, 58 (86.66%) had LDL>100mg/dl and 43 (64.44%) had HDL<40mg/dl . A study conducted by Penalva RA et al[90] where a total of 107 patients were included, they found 64 (59.8%) patients had TC<200mg/dl, 33(30.8%) had HDL<40 mg/dl, and 38(35.5%) had LDL<100mg/dl. The imbalance between TC and HDL levels plays a more important role in the pathophysiology of atherogenesis. It is important to consider that the atheroprotective function of HDL is not restricted to reverse cholesterol transport, but can also transport antioxidant enzymes, break down oxidized lipid fractions, and neutralize their proinflammatory effects [91]. It is noteworthy that 64.44% of the cases had HDL < 40mg/dl, and only 35.56% had levels considered at hero protective.

In the present study, the mean YKL 40 levels of ACS cases were significantly higher than the controls (3561.21 ng/ml and 1041.2 ng/ml respectively). Similar findings of higher YKL 40 level in IHD cases as compared to controls were observed in the studies done by Zaky Doaa SE et al[6], Nojgaard C et al[6] and Hedegaard A et al [93]. YKL-40, an acute phase glycoprotein [94],is expressed in association with inflammatory process, extracellular matrix degradation, and angiogenesis [95]. It has been well established that inflammation plays an important role in the development and progression of atherosclerosis of the coronary arteries [96]. The participation of YKL-40 in inflammatory states and vascular processes implies that it may play a role in endothelial dysfunction and atherosclerosis [97]. The cellular background of increased serum levels of YKL-40 in ACS is probably from activated inflammatory cells in ischemic areas of the heart and in atherosclerotic plaques, but may have originated from injured and stressed cardiomyocytes. It is well known that human macrophages in atherosclerotic plaques express YKL-40 mRNA, particularly macrophages that infiltrate deeper in the lesion, and the highest YKL-40 expression is found in macrophages in the early atherosclerotic lesion [86]. It has recently been shown that serum YKL-40 is associated with the extent of CAD defined by the number of vessels with stenosis [98].

In this study, serum YKL-40 levels were found to be strongly correlated with lipid profile parameters. It showed strong positive correlation with TC, TG and LDL and showed strong negative correlation with HDL. Dyslipidemia is a primary, widely established as an independent major risk factor for acute coronary syndrome. The findings are supported by the study conducted by Pei Q et al[99] where the levels of YKL-40 and hs-CRP, and the correlation of severity degree were analysed. Before and after treatment levels of triglyceride (TG), total cholesterol (TC), high density lipoprotein

cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) were measured. They found that compared with before treatment, the levels of YKL-40 and hs-CRP significantly decreased in both groups after two weeks of treatment ($P < 0.05$).

The level of YKL-40 is an important regulator of acute and chronic inflammation and tissue remodelling [100]. The participation of YKL-40 in inflammatory states and vascular processes implies that it may play a role in endothelial dysfunction and atherosclerosis [101]. The results revealed significantly increased mean value of YKL-40 in patients with ACS compared with age and sex matched healthy controls, with a cutoff value of 2734.12 pg/ml, at which the sensitivity was 97.7%, the specificity was 100% and AUC was 0.969. These data are in agreement with those of Rathcke CN et al. [102] 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 CL et al [103] 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 be the potential heterogeneity resource of this outcome.

YKL-40 may mirror an inflammatory stimulus, and may also have a direct effect promoting atherosclerotic propagation and destabilizing plaque [104]. This analysis can also be intensified by the study finding as the mean 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 Zaky Doaa SE et al[6] and Nojgaard C et al[92], where 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 A et al [105].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 [106].

YKL-40 in this study was positively correlated to Trop I in patients with ACS . The ROC curve analysis in this study shows that trop I had high AUC value of 0.983 using the study specific cut off value of 0.7 microgram/l (sensitivity 100%, specificity 80%). These results are in agreement with those of Fang C et al [107] who revealed that when combined with the traditional diagnostic model cTnI, YKL 40 had higher diagnostic value, stronger sensitivity, and specificity, and could provide a reliable basis for the diagnosis and treatment of STEMI.

Conclusion

The present study was carried out to evaluate the levels of serum YKL-40 in acute coronary syndrome (ACS) subjects and normal healthy controls without ACS and to find the correlation of serum YKL-40 levels with ACS.

The study shows the level of serum YKL-40 was much higher in cases of ACS as compared to the healthy controls. The ACS cases had higher serum YKL-40 with mean value of 3561.21 ng/ml as compared to the controls with mean value of 1041.20 ng/ml and there was positive correlation between serum YKL-40 levels and ACS

cases. Increased level of random blood sugar was seen in ACS cases. Serum YKL-40 was found to be positively correlated with serum cholesterol, triglycerides and LDL levels and negatively correlated with serum HDL level. The study also shows a positive significant correlation between serum YKL-40 level and trop I level among the ACS cases. The findings were found to be significant.

Many studies show that serum YKL-40 level in ACS was higher as compared to the healthy age matched controls. Thus, it can be concluded that serum YKL-40 might play an important role as a diagnostic and prognostic marker in patients with ACS. However, the study had some limitations that the sample size was relatively small and this was a single centre study done in Imphal. Hence, the results of this research need to be proved through multi-centric surveys with larger sample sizes.

Reference

1. Padilla IM, Martín-Asenjo R, Bueno H. Management of acute coronary syndromes in geriatric patients. Heart, Lung and Circulation. 2017 Feb 1;26(2):107-13.
2. World Health Organisation. Cardiovascular Diseases. 2021 Jun 11. [1 screen]. Available from https://www.who.int/health-topics/cardiovascular-diseases.
3. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: current epidemiology and future directions. Circulation. 2016 Apr 19;133(16):1605-20.
4. Gupta R, Gaur K. Epidemiology of acute coronary syndromes in India. In Acute Coronary Syndromes. CRC Press. 2020 Jul 15:1-11.
5. Becker D, Merkely B. Acute coronary syndrome–2012. Orvosihetilap. 2012 Dec 1;153(51):2009-15
6. Zaky Doaa SE, Mabrouk FM, Zaki ER, Hendy OM. The value of YKL-40 in ischemic heart disease patients. The Egyptian Journal of Internal Medicine. 2016 Jun;28(2):71-7.
7. Azeredo-Da-Silva AL, Perini S, Soares PH, Polaczyk CA. Systematic review of economic evaluations of units dedicated to acute coronary syndromes. Value Health. 2016 Mar 1;19(2):286-95.
8. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2021 Apr 7;42(14):1289-367.
9. Omer MA, Tyler JM, Henry TD, Garberich R, Sharkey SW, Schmidt CW, et al. Clinical characteristics and outcomes of STEMI patients with cardiogenic shock and cardiac arrest. Cardiovascular Interventions. 2020 May 25;13(10):1211-9.
10. Bracey A, Meyers HP. Posterior Myocardial Ischemia. InStatPearls [Internet]. StatPearls Publishing. 2021 Aug 6.
11. Singh A, Museedi AS, Grossman SA. Acute coronary syndrome. StatPearls Publishing, Treasure Island (FL). 2017 Oct 31.
12. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003 Oct 7;108(14):1664-72.
13. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation. 2001 Feb 20;103(7):934-40.

14. Feigin V. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1736-88.
15. Plebani M. Biochemical markers of cardiac damage: from efficiency to effectiveness. Clin Chim Acta. 2001 Sep 15;311(1):3-7.7.
16. Diseases Conditions. Acute Coronary Syndrome. 2020 May. [1 Screen]. Available from:https://www.mayoclinic.org/diseases-conditions/acute-coronary-syndrome/ symptoms-causes/syc-20352136. Accessed Nov 10, 2020.
17. Lopes RD, Lokhnygina Y, Hasselblad V, Newby KL, Yow E, Granger CB, et al. Methods of creatine kinase-MB analysis to predict mortality in patients with myocardial infarction treated with reperfusion therapy. Trials. 2013 Dec 1;14(1):123.
18. Casals G, Filella X, Augé JM, Bedini JL. Impact of ultrasensitive cardiac troponin I dynamic changes in the new universal definition of myocardial infarction. Am J Clin Pathol. 2008 Dec 1;130(6):964-68.
19. Radosavljevic-Radovanovic M, Radovanovic N, Vasiljevic Z, Marinkovic J, Mitrovic P, Mrdovic I, et al. Usefulness of NT-proBNP in the follow-up of patients after myocardial infarction. J Med Biochem. 2016 Apr 1;35(2):158-65.
20. Johansen JS, Olee T, Price PA, Hashimoto S, Ochs RL, Lotz M. Regulation of YKL-40 production by human articular chondrocytes. Arthritis & rheumatism. 2001 Apr;44(4):826-37.
21. Rathcke CN, Vestergaard H. YKL-40-an emerging biomarker in cardiovascular disease and diabetes. Cardiovasc Diabetol. 2009 Dec;8(1):1-7.
22. Chen XL, Li Q, Huang WS, Lin YS, Xue J, Wang B, et al. Serum YKL-40, a prognostic marker in patients with large-artery atherosclerotic stroke. Acta Neurol Scand. 2017 Aug;136(2):97-102.
23. Johansen JS, Jensen BV, Roslind A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients?. Cancer Epidemiol Biomarkers Prev. 2006 Feb 1;15(2):194-202.
24. Bussink AP, Speijer D, Aerts JMFG, Boot RG. Evolution of mammalian chitinase(- like) members of family 18 glycosyl hydrolases. Genetics 2007;177:959 –70.
25. Shao R, Hamel K, Petersen L, Cao QJ, Arenas RB, Bigelow C, et al. YKL-40, a secreted glycoprotein, promotes tumour angiogenesis. Oncogene. 2009 Dec;28(50):4456-68.
26. Boot RG, Van Achterberg TA, Van Aken BE, Renkema GH, Jacobs MJ, Aerts JM, et al. Strong induction of members of the chitinase family of proteins in atherosclerosis: chitotriosidase and human cartilage gp-39 expressed in lesion macrophages. ArteriosclerThrombVasc Biol. 1999 Mar;19(3):687-94.
27. Kronborg G, Ostergaard C, Weis N, Obel N, Johansen JS, Price PA, et al. Serum level of YKL-40 is elevated in patients with Streptococcus pneumoniae bacteremia and is associated with the outcome of the disease. Scand J Infect Dis. 2002 Jan 1;34(5):323-6.
28. Chupp GL, Lee CG, Jarjour N, Shim YM, Holm CT, He S, et al. A chitinase-like protein in the lung and circulation of patients with severe asthma. N Engl J Med. 2007 Nov 15;357(20):2016-27.
29. Johansen JS. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibrosis and cancer. Dan Med Bull 2006;53:172 –209

30. Recklies AD, White C, Ling H. The chitinase 3-like protein human cartilage 39 (HC-gp39) stimulates proliferation of human connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways. Biochem J 2002;365:119-26.
31. Ling H, Recklies AD. The chitinase 3-like protein human cartilage glycoprotein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumour necrosis factor-alpha. Biochem J. 2004 Jun 15;380(3):651-9.
32. Shackelton LM, Mann DM, Millis AJ. Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling. J Biol Chem. 1995 Jun 2;270(22):13076-83.
33. Malinda KM, Ponce L, Kleinman HK, Shackelton LM, Millis AJ. Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells. Exp Cell Res. 1999 Jul 10;250(1):168-73.
34. Saidi A, Javerzat S, Bellahcène A, De Vos J, Bello L, Castronovo V, et al. Experimental anti-angiogenesis causes upregulation of genes associated with poor survival in glioblastoma. Int J Cancer. 2008 May 15;122(10):2187-98.
35. Johansen JS, Schultz NA, Jensen BV. Plasma YKL-40: a potential new cancer biomarker?. Future Oncol. 2009 Sep;5(7):1065-82.
36. Johansen JS, Hvolris J, Hansen M, Backer V, Lorenzen I, Price PA. Serum YKL-40 levels in healthy children and adults. Comparison with serum and synovial fluid levels of YKL-40 in patients with osteoarthritis or trauma of the knee joint. Rheumatology. 1996 Jun 1;35(6):553-9.
37. Kucur M, Isman FK, Karadag B, Vural VA, Tavsanoglu S. Serum YKL-40 levels in patients with coronary artery disease. Coronary artery disease. 2007 Aug 1;18(5):391-6.
38. Duseja R, Feldman JA. Missed acute cardiac ischemia in the ED: limitations of diagnostic testing. Am J Emerg Med. 2004 May 1;22(3):219-25.
39. Makki N, Brennan TM, Girotra S. Acute coronary syndrome. Journal of intensive care medicine. 2015 May;30(4):186-200.
40. Nojgaard C, Host NB, Christensen IJ, Poulsen SH, Egstrup K, Price PA, et al Serum levels of YKL-40 increases in patients with acute myocardial infarction. Coronary Artery Disease. 2008 Jun 1;19(4):257-63.
41. Kastrup J, Johansen JS, Winkel P, Hansen JF, Hildebrandt P, Jensen GB, et al. High serum YKL-40 concentration is associated with cardiovascular and all-cause mortality in patients with stable coronary artery disease. Eur Heart J. 2009 May 1;30(9):1066-72.
42. Hedegaard A, Sejersten Ripa R, Johansen JS, Jorgensen E, Kastrup J. Plasma YKL-40 and recovery of left ventricular function after acute myocardial infarction. Scand J Clin Lab Invest. 2010 Jan 1;70(2):80-6.
43. Zheng JL, Lu L, Hu J, Zhang RY, Zhang Q, Chen QJ, et al. Increased serum YKL-40 and C-reactive protein levels are associated with angiographic lesion progression in patients with coronary artery disease. Atherosclerosis. 2010 Jun 1;210(2):590-5.
44. Kjaergaard AD, Bojesen SE, Johansen JS, Nordestgaard BG. Elevated plasma YKL-40 levels and ischemic stroke in the general population. Ann Neurol. 2010 Nov;68(5):672-80.

45. Zheng JL, Lu L, Hu J, Zhang RY, Zhang Q, Chen QJ, et al. Genetic polymorphisms in chitinase 3-like 1 (CHI3L1) are associated with circulating YKL-40 levels, but not with angiographic coronary artery disease in a Chinese population. Cytokine. 2011 Apr 1;54(1):51-5.
46. Mathiasen AB, Harutyunyan MJ, Jorgensen E, Helqvist S, Ripa R, Gotze JP, et al. Plasma YKL-40 in relation to the degree of coronary artery disease in patients with stable ischemic heart disease. Scand J Clin Lab Invest. 2011 Sep 1;71(5):439-47.
47. Kim HM, Lee BW, Song YM, Kim WJ, Chang HJ, Choi DH, et al. Potential association between coronary artery disease and the inflammatory biomarker YKL-40 in asymptomatic patients with type 2 diabetes mellitus. Cardiovascular diabetology. 2012 Dec;11(1):1-8.
48. Çetin MU, Kocaman SA, Canga A, Kırbaş A, Yılmaz A, Erdoğan TU, et al. Elevated serum YKL-40 level predicts myocardial reperfusion and in-hospital MACE in patients with STEMI. Herz. 2013 Mar;38(2):202-9.
49. Harutyunyan M, Gotze JP, Winkel P, Johansen JS, Hansen JF, Jensen GB, et al Serum YKL-40 predicts long-term mortality in patients with stable coronary disease: a prognostic study within the CLARICOR trial. Immunobiology. 2013 Jul 1;218(7):945-51.
50. Sui X, Gao C. Association of serum YKL-40 levels with the presence and severity of coronary artery disease in patients with obstructive sleep apnea syndrome. Clinical and Investigative Medicine. 2013 Dec 1;E306-11.
51. Harutyunyan M, Johansen JS, Mygind ND, Reuter SB, Kastrup J. Serum YKL-40 for monitoring myocardial ischemia after revascularization in patients with stable coronary artery disease. Biomarkers in medicine. 2014 Aug;8(8):977-88.
52. Kjaergaard AD, Johansen JS, Bojesen SE, Nordestgaard BG. Elevated plasma YKL-40, lipids and lipoproteins, and ischemic vascular disease in the general population. Stroke. 2015 Feb;46(2):329-35.
53. Song CL, Diao HY, Wang JH, Shi YF, Lu Y, Wang G, et al. Diagnostic Value of Serum YKL-40 Level for Coronary Artery Disease: A Meta-Analysis. J Clin Lab Anal. 2016 Jan;30(1):23-31.
54. Jin Y, Cao JN, Wang CX, Feng QT, Ye XH, Xu X, et al. High serum YKL-40 level positively correlates with coronary artery disease. Biomarkers in medicine. 2017 Feb;11(2):133-9.
55. Sciborski K, Kuliczkowski W, Karolko B, Bednarczyk D, Protasiewicz M, Mysiak A, et al. Plasma YKL-40 levels correlate with the severity of coronary atherosclerosis assessed with the SYNTAX score. Polish Arch Intern Med. 2018 Jan 1;128:644-8.
56. Pala S, Sari M, Kahveci G, Alizade E, Arslantas U, Uslu A. Plasma YKL-40 elevation on admission and follow-up is associated with diastolic dysfunction and mortality in patients with acute myocardial infarction. Cardiology research and practice. 2018 Oct.
57. Yang L, Dong H, Lu H, Liao Y, Zhang H, Xu L, et al Serum YKL-40 predicts long-term outcome in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Medicine [Internet]. 2019 Mar[cited 2020 Nov 20];98(12):[about 5p.].
58. Schroder J, Jakobsen JC, Winkel P, Hilden J, Jensen GB, Sajadieh A, et al. Prognosis and reclassification by YKL-40 in stable coronary artery disease. JAm Heart Assoc. 2020 Mar 3;9(5):e014634.

59. Ściborski K, Gierlotka M, Protasiewicz M, Karolko B, Negrusz-Kawecka M, Kuliczkowski W. YKL-40 as a predictor of mortality after acute coronary syndrome. Polish Archives of Internal Medicine. 2020 Apr 6;130(4):343-5.
60. Fang C, Chen Z, Zhang J, Pan J, Jin X, Yang M, et al. The Value of Serum YKL-40 and TNF-α in the Diagnosis of Acute ST-Segment Elevation Myocardial Infarction. Cardiology Research and Practice. 2022 Aug 23.
61. Porstmann T, Kiessig ST. Enzyme immunoassay techniques an overview. J Immunol Methods. 1992 Jun 24;150(1-2):5-21.
62. Takahashi M, Lee L, Shi Q, Gawad Y, Jackowski G. Use of enzyme immunoassay for measurement of skeletal troponin-I utilizing isoform-specific monoclonal antibodies. Clinical biochemistry. 1996 Aug 1;29(4):301-8.
63. Keyser JW, Spillane MT. Estimation of Blood Glucose by Glucose Oxidase Methods: The Effect of Fluoride. Proceedings of the Association of Clinical Biochemists. 1963 Nov;2(8):217-8.
64. Henry RJ. Clinical Chemistry: principles and techniques. 2nd ed. New York: Harper Row publishers.1974.
65. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974 Apr;20(4):470-5.
66. Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 1973 May;19(5):476-82.
67. Steele BW, Koehler DF, Azar MM, Blaszkowski TP, Kuba K, Dempsey ME. Enzymatic determinations of cholesterol in high-density-lipoprotein fractions prepared by a precipitation technique. Clin Chem 1976 Jan;22(1):98-101.
68. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502.
69. Ahmed E, Al Habib KF, El-Menyar A, Asaad N, Sulaiman K, Hersi A, et al. Age and clinical outcomes in patients presenting with acute coronary syndromes. Journal of cardiovascular disease research. 2013 Jun 1;4(2):134-9.
70. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: non–ST-segment–elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007 May 15;115(19):2549-69.
71. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in myocardial infarction incidence and survival. Olmsted County, Minnesota–1979 to 1994. Ann Int Med. 2002;136(5):341-8.
72. Duan JG, Chen XY, Wang L, Lau A, Wong A, Thomas GN, et al. Sex differences in epidemiology and risk factors of acute coronary syndrome in Chinese patients with type 2 diabetes: a long-term prospective cohort study. PLoS One. 2015 Apr 1;10(4):e0122031.
73. Dubey RK, Imthurn B, Barton M, Jackson EK. Vascular consequences of menopause and hormone therapy: importance of timing of treatment and type of estrogen. Cardiovascular research. 2005 May 1;66(2):295-306.
74. Oommen AM, Abraham VJ, George K, Jose VJ. Prevalence of coronary heart disease in rural and

urban Vellore: a repeat cross-sectional survey. Indian Heart J. 2016 Jul 1;68(4):473-9.

75. Khanna T, Rangan VK, Manocaran M. Narayana Hrudayalaya heart hospital: cardiac care for the poor. Harvard Business School Case. 2005 Jun 14;505078.
76. Gupta R, Gupta VP, Prakash H, Sarna M, Sharma AK. Hindu-Muslim differences in the prevalence of coronary heart disease and risk factors. J Indian Medical Assoc. 2002 Apr 1;100(4):227-30.
77. Alberty R, Studenčan M, Kovář F. Prevalence of conventional cardiovascular risk factors in patients with acute coronary syndromes in Slovakia. Cent Eur J Public Health. 2017 Mar 1;25(1):77-84.
78. Rashid MH, Yaseen G, Ghaffar U, Khan AA, Kabir A, Aisha A, et al. Prevalence of Acute Coronary Syndrome and Various Risk Factors in Acute Stroke Patients. Cureus. 2020 Aug 4;12(8).
79. Ralapanawa U, Kumarasiri PV, Jayawickreme KP, Kumarihamy P, Wijeratne Y, Ekanayake M, et al. Epidemiology and risk factors of patients with types of acute coronary syndrome presenting to a tertiary care hospital in Sri Lanka. BMC cardiovascular disorders. 2019 Dec;19(1):1-9.
80. Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, et al. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2008 Mar 25;117(12):1610-9.
81. Badiger S. Hyperglycaemia and Myocardial Infarction.
82. Owens P, O'Brien E. Hypotension in patients with coronary disease: can profound hypotensive events cause myocardial ischaemic events?. Heart. 1999 Oct 1;82(4):477-81.
83. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. Jama. 2003 Aug 20;290(7):891-7.
84. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. Jama. 2003 Aug 20;290(7):898-904.
85. Harchaoui KE, Visser ME, Kastelein JJ, Stroes ES, Dallinga-Thie GM. Triglycerides and cardiovascular risk. Current cardiology reviews. 2009 Aug 1;5(3):216-22.
86. Amarenco P, Labreuche J, Touboul PJ. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. Atherosclerosis. 2008 Feb 1;196(2):489-96.
87. Penalva RA, Huoya MD, Correia LC, Feitosa GS, Ladeia AM. Lipid profile and intensity of atherosclerosis disease in acute coronary syndrome. Arquivosbrasileiros de cardiologia. 2008;90:24-30.
88. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002 Mar 5;105(9):1135-43.
89. Nojgaard C, Host NB, Christensen IJ, Poulsen SH, Egstrup K, Price PA, et al. Serum levels of YKL-40 increases in patients with acute myocardial infarction. Coronary Artery Disease. 2008 Jun 1;19(4):257-63.
90. Hedegaard A, Sejersten Ripa R, Johansen JS, Jørgensen E, Kastrup J. Plasma YKL-40 and recovery of left ventricular function after acute myocardial infarction. Scandinavian journal of clinical and laboratory investigation. 2010 Jan 1;70(2):80-6.
91. Lee CG, Da Silva CA, Dela Cruz CS, Ahangari F, Ma B, Kang MJ, et al. Role of chitin and

chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. Annu Rev Physiol 2011; 73:479–501.

92. Johansen J. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodeling, fibrosis and cancer. Dan Med Bull 2006; 53:172–209.
93. Rathcke C, Vestergaard H. YKL-40-an emerging biomarker in cardiovascular disease and diabetes. Cardiovasc Diabetol 2009; 8:1–7.
94. Boot RG, van Achterberg TA, van Aken BE, Renkema GH, Jacobs MJ, Aerts JM, et al. Strong induction of members of the chitinase family of proteins in atherosclerosis: chitotriosidase and human cartilage gp-39 expressed in lesion macrophages. Arteriosclerosis, thrombosis, and vascular biology. 1999 Mar;19(3):687-94.
95. Fiechter M, Ghadri JR, Jaguszewski M, Siddique A, Vogt S, Haller RB, et al. Impact of inflammation on adverse cardiovascular events in patients with acute coronary syndromes. J Cardiovasc Med (Hagerstown) 2013; 14:807–14.
96. Pei Q, Sang WF, Zhao XD. Effects of Guizhi Fuling Decoction on YKL-40 and hs-CRP of patients with non-ST segment elevation acute coronary syndrome. Zhongguo Zhong xi yijie he za zhiZhongguoZhongxiyiJieheZazhi= Chinese Journal of Integrated Traditional and Western Medicine. 2013 Feb 1;33(2):186-90.
97. Lee CG, Da Silva CA, Dela Cruz CS, Ahangari F, Ma B, Kang MJ, et al. Role ofchitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, andinjury. Annual review of physiology. 2011 Mar 17;73:479-501.
98. Rathcke CN, Vestergaard H. YKL-40-an emerging biomarker in cardiovascular disease and diabetes. Cardiovasc diabetol. 2009 Dec;8(1):1-7.
99. Rathcke CN, Kistorp C, Raymond I, Hildebrandt P, Gustafsson F, Lip GY, et al. Plasma YKL-40 levels are elevated in patients with chronic heart failure. Scandinavian Cardiovasc J. 2010 Jan 1;44(2):92-9.