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EVALUATION OF THE RELATIONSHIP GENERATED BETWEEN SERUM BIOMARKERS (HS-CRP, PLASMA FIBRINOGEN) WITH SIGNIFICANT CORONARY ARTERY DISEASE AND NUMBER OF CORONARY VESSELS INVOLVMENT

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Abstract:

Background: Inflammation is widely considered to be an important contributing factor of the pathophysiology of coronary heart disease (CHD), and it is particularly important in the atherosclerotic process; recent work has been focused on whether biomarkers of inflammation may help to anticipate coronary artery lesions before the diagnostic coronary angiography done, hs C-reactive protein (hs-CRP) & plasma fibrinogen (PF) level has emerged as one of the most important novel inflammatory markers.

Aim of study:

Determine the relationship between serum biomarkers (hs-CRP, Plasma Fibrinogen) with:

1-Significant coronary artery disease.

2- Number of coronary vessels involvment.

Patients and methods: A case control study was conducted at Iraqi Center for Heart Diseases (ICHD) at Medical city/Baghdad from November 2018 to April 2019.

It includes one hundred patients who were referred to ICHD and has undergone coronary angiography. Serum level of plasma fibrinogen & hs C-reactive protein were measured in these patients before undergone coronary angiography. The cases with normal angiography considered as control group one, and those with significant CAD considered as group two and correlate them with the levels of hs-CRP and Plasma Fibrinogen; the extent of coronary artery disease was determined by angiography according to the number of coronary arteries involved, Serum level of plasma fibrinogen were measured by STAGO method & hs C-reactive protein by NEPHLOMETRY method.

Result: plasma fibrinogen and hs-CRP levels demonstrate a stepwise increase from control group to angiographicaly significant and advanced CAD. Area under the receiver operating characteristic curve of fibrinogen was (0.83) for predicting significant coronary artery diseases. Fibrinogen value higher than (411mg/dl) has a sensitivity of (83%) and specificity (81%) for predicting significant coronary artery diseases. Area under the receiver operating characteristic curve of hs-CRP was (0.87) for predicting significant coronary artery diseases. Hs-crp higher than (11.3mg/dl) has a sensitivity of (83 %) and specificity (86%) for predicting significant coronary artery diseases.

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Conclusion:
Overall, our study found that hs-CRP and Plasma Fibrinogen levels were higher in patients with significant coronary artery disease compared to normal subjects. And higher levels of hs-CRP and Plasma Fibrinogen are associated with advanced coronary artery disease. By this finding, hs-CRP and Plasma Fibrinogen levels could be used as a predictive biomarkers of advanced coronary artery diseases.

Keywords: ICHD, hs-CRP, Plasma

INTRODUCTION

C-reactive protein (CRP) was first discovered in 1930 by William Tillet and Thomas Francis at the Rockefeller Institute for Medical Research in New York. In studying the blood of patients suffering from acute Streptococcus pneumonia infection, it was found that the sera of these patients formed a precipitin with an extract from the streptococcal bacterium. The extract was originally labeled Fraction C and was later confirmed as a polysaccharide. Hence, as a result of its reactivity with the C polysaccharide of the Streptococcus cell wall, the 'substance' in the sera was named CRP [1]. A decade later, Oswald Avery and Maclyn McCarty-the research team who originally described the "transforming principle" and the concept that genes are made of DNA also described CRP as an "acute-phase reactant" that was increased in serum of patients suffering from a spectrum of inflammatory stimuli, including myocarditis and the inflammation associated with rheumatic fever [2,3].

C-reactive protein (CRP), a nonspecific inflammatory marker, a stable pentameric protein, has a half-life of 19 hr, is not subject to diurnal variation, is manufactured throughout the body, especially by immune cells, the liver, and by adipocytes (fat cells). During the early phase of an inflammatory stimulus (such as infection or tissue injury), CRP levels rise dramatically. An elevated C-reactive protein level is identified with blood tests and is considered a non-specific "marker" for disease.

CRP can signal flare-ups of inflammatory diseases such as rheumatoid arthritis, lupus, and vasculitis, a sedentary lifestyle, too much stress, and exposure to environmental toxins such as secondhand tobacco smoke. Diet has a huge impact on its level, particularly one that contains a lot of refined, processed, and manufactured foods. The CRP level may be influenced more by lifestyle than by genetics. Monozygotic twins may not have the same CRP level; within each twin pair, the one with higher adiposity generally has a higher CRP level than the one with low adiposity. Note that CRP levels may also be elevated for those taking birth control pills [4].

Early clues that this inflammatory biomarker might be linked to atherothrombosis are evident in 2 case reports presented by Gunnar Lofstrom from the State Bacteriologic Laboratory in Stockholm in 1943, in which increases in CRP following AMI was described [5]. In the mid-1950s, case series presented by Irving Kroop and others indicated that CRP concentrations consistently increased after coronary ischemia and myocardial necrosis [6]. Despite these early findings, it was not until the 1990s that cardiovascular interest in CRP was revitalized. In the mid-1990s, immunoassays for CRP (hs-CRP), with greater sensitivity than those previously routine uses, revealed that increased CRP values, even within the range previously considered normal, strongly predict future coronary events.

MATERIAL AND METHOD

Patient sample

collected one hundred patients from at Iraqi Center for Heart Diseases
(ICHD) / Medical City / Baghdad who were referred to ICHD and has undergone coronary angiography.

Study design

A convenient sample of one hundred patients who were presented with suspicion of coronary artery disease, Serum level of plasma fibrinogen & hs C-reactive protein were measured in these patients before undergoing Coronary angiography; the studied sample divided into two groups:

1-group one with normal coronary artery and considered as control, it includes thirty-seven patients.
2- group II with significant coronary artery disease, it includes sixty-three patients.
Serum level of plasma fibrinogen were measured by STAGO method & hs C-reactive protein by NEPHLOMETRY method.

Inclusion criteria consisted of adult patients of both sexes with suspicions of ischemic heart disease and are planned for doing coronary angiography.

Exclusion criteria included acute or chronic renal diseases, thyroid disor¬ders, chronic infalmation (SLE, RA, Seronegative arithritis), diabetic ketoacidosis, non-ketotic hyperos¬molar diabetes, tumours and autoimmune diseases, any recent surgery in the last two months, recent trauma, recent infections (e.g., pneumonia …etc.), recent stroke.

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Weight was measured in kilograms and height in centimeters. Body mass index (BMI) was calculated as weight / height.

Study period

A case control study was conducted in cardiac catheterization unit at Iraqi Center for Heart Diseases (ICHD) / Medical City / Baghdad from November 2018 to April 2019.

Aim of research

Determine the relationship between serum biomarkers (hs-CRP, Plasma Fibrinogen) with:
1-Significant coronary artery disease.
2- Number of coronary vessels involvment.

Statistical Analysis

The analysis of data was carried out by using SPSS version 23. Number and percentage were used to express the categorical data, while the mean and standard deviation were used to express the numerical data. Anova, independent student test, Pearson correlation, Chi-square tests (fisher exact test when not applicable) were used to confirm significance, as well as the ROC curve was used to evaluate the usefulness of the test to predict the outcome under study. Statistically significant considered whenever the P-value was less than 0.05.

RESULTS

A total of 100 patients [51 (51%) males,49 (49%) females] were enrolled in current study. The age was range (30 - 80 years old); while the mean of patients age was (55.97 ± 9.69).

The numbers of current smokers were 26 (26%), Ex-smoker 11 (11%), non-smokers 63 (63%). Family history was positive in 10 (10%), family history negative in 90 (90%).

Diabetes mellitus was in 40 (40%), 60 (60%) had no history of Diabetes mellitus. Hypertention was in 57(57%), 43(43%) had no history of hypertention.

Dyslipidemia was in 2 (2%), 98 (98%) had no dyslipidemia.

Normal coronary angiography was in 37 (37%), mean Plasma Fibrinogen was (299.2 ± 77.7), mean hs-CRP was (2.92 ± 2.9). 11 (29.7%) of them were males, 26 (70.3%) of them were females. Abnormal coronary artery angiography was in 63 (63%), 23 (36.50 %) of them were females, 40 (63.5 %) of them were males, Single vessel diseases were in 16 (16%) of them, mean Plasma Fibrinogen was (419.2 ± 73.5), mean hs-CRP was (13.77 ± 3.7). Two vessel diseases were in 22 (22%) of them, mean Plasma Fibrinogen was (438 ± 61.6), mean hs-CRP was (14.19 ± 3.5). Multi-vessel diseases in 25 (25%) of them, mean Plasma Fibrinogen was (376±106), mean hs-CRP was (10.5±7.3). As shown in table 1.

Table 1. Descriptive Characteristics of studied group

P		Mean (SD) or no (%)
age		56.0±9.7
BMI		28.81±4.98
Gender	Male	51(51.0%)
	Female	49(49.0%)
Smoking status	Current smoker	26(26.0%)
	Ex-smoker	11(11.0%)
	Non-smoker	63(63.0%)
Family history	Yes	10(10.0%)
	No	90(90.0%)
DM	Yes	40(40.0%)
	No	60(60.0%)
HT	Yes	57(57.0%)
	No	43(43.0%)

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Dyslipidemia	Yes	2(2.0%)
	No	98(98.0%)
Stenosis	Normal/Nonsignificant	37(37%)
	Single	16(16.0%)
	Two vessels	22(22.0%)
	MVD	25(25.0%)
PF		376±106
CRP		10.5±7.3

In table 2, we observed significantly higher Plasma fibrinogen levels in single-vessel disease than in normal vessel disease (419.7±73.5 Vs. 299.2 ± 77.7; p=0.001); in this study, we observed higher Plasma fibrinogen levels in two vessels diseases than in normal coronary vessel (438 ± 61.6 Vs. 299.2 ± 77.7; P = 0.001), significantly higher Plasma fibrinogen levels are observed in multi vessel disease than in normal coronary vessel (477.5 ± 78.1 Vs. 299.2 ± 77.7; P = 0.001).

In current study, we observed significantly higher Plasma fibrinogen levels in two-vessel disease than in single-vessel disease (438 ± 61.6 Vs. 419.7 ± 73.5; P = 0.04). Also, significantly higher Plasma fibrinogen levels are observed in multi vessel disease than in single coronary vessel (477.5 ± 78.1 Vs. 419.7 ± 73.5; P = 0.02), significantly higher Plasma fibrinogen level in multi vessel diseases than in two vessels disease (477.5 ± 78.1 Vs. 438 ± 61.6; P = 0.02.) as shown in table 2

Table 2. The difference in Plasma Fibrinogen according to coronary angiographic findings.

Mean ± SD	Mean ± SD	P. Value
Normal 299.2 ± 77.7	One vessel 419.7 ± 73.5	0.001
Normal 299.2 ± 77.7	Two vessels 438 ± 61.6	0.001
Normal 299.2 ± 77.7	≥ 3 vessels 477.5 ± 78.1	0.001
One vessel 419.7 ± 73.5	Two vessels 438 ± 61.6	0.04
One vessel 419.7 ± 73.5	≥3 vessels 477.5 ± 78.1	0.02
Two vessels 438 ± 61.6	≥ 3 vessels 477.5 ± 78.1	0.02

In table 3, we observed significantly higher hs-CRP levels in single-vessel disease than in normal vessel disease (13.77 ± 3.7 Vs. 2.92 ± 2.9; P = 0.001), we observed higher hs-CRP levels in two vessels diseases than in normal vessel disease (14.19 ± 3.5 Vs. 2.92±2.9; P = 0.001), we observed significantly higher hs-CRP levels are observed in multi vessel disease than in normal vessel angiography (19.41±1.7Vs2.92 ± 2.9 P = 0.001).

When comparing the values between the two and one vessel diseases current study shows non-significant difference in hs-CRP levels (14.19 ± 3.5 Vs. 13.77 ± 3.7 P=0.6). We observed significantly higher hs-CRP levels are observed in multi vessel disease than in two vessel diseases (19.41 ± 1.7 Vs. 14.19 ± 3. P = 0.001)

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Table 3. The difference in hs C-reactive protein according to coronary angiographic findings

Mean ± SD	Mean ± SD	P. Value
Normal 2.92 ± 2.9	One vessel 13.77 ± 3.7	0.001
Normal 2.92 ± 2.9	Two vessels 14. 19 ± 3.5	0.001
Normal 2.92 ± 2.9	≥ 3 vessels 19.41 ± 1.7	0.001
One vessel 13.77 ± 3.7	Two vessels 14.19 ± 3.5	0.6
One vessel 13.77 ± 3.7	≥ 3 vessels 19.41 ± 1.7	0.001
Two vessels 14.19 ± 3.5	≥ 3 vessels 19.41 ± 1.7	0.001

In table (4), we study whether plasma fibrinogen level is associated with coronary complexity and extent assessed by SYNTAX (Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery) score (SS). We enrolled the patients in current Study who underwent coronary angiography. The patients were classified into three groups by values of SS (SS, control group = 0; intermediate group **≤** 22; and high group ≥ 22). Results: Plasma fibrinogen levels demonstrated a stepwise increase from control group, which were (299.2 mg /l) with SD (75.9) to intermediate group **≤** 22 were Plasma fibrinogen (405.5 mg /l) with SD (70.5) to high group ≥ 22 were plasma fibrinogen (430.3 mg /l) with SD (88.8). There was a strong correlation between plasma fibrinogen and the SS (P = 0.01).

Again, in table (4), we study whether hs-CRP level is associated with coronary complexity and extent assessed by SYNTAX (Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery) score (SS). The patients were classified into three groups by values of SS (SS, control group = 0; intermediate group **≤** 22; and high group ≥ 22). Results: hs-CRP levels demonstrated a stepwise increase from control group which were (2.92 mg /l) with SD (1.5) to intermediate group **≤** 22 were hs-CRP (15.05 mg /l) with SD (4.07) to high group ≥ 22 were hs-CRP (18.0 mg /l) with SD (2.17). There was a strong correlation between hs-CRP and the SS (P = 0.01).

Table 4. Mean value of Plasma Fibrinogen and hs-Creactive protein according to SYNTX Score

p		**Mean**	**SD**	**P. Value all**	**P. Value ≤ 22 vs. ≥22**
PF	Normal	299.2	75.9	0.01	0.04
	≤ 22	405.5	70.5		
	≥22	430.3	88.8		
CRP	Normal	2.92	1.5	0.01	0.01
	≤ 22	15.05	4.07		
	≥ 22	18.0	2.17		

Association Between the Plasma Fibrinogen Levels and C-reactive protein and SS

To explore whether plasma fibrinogen levels were related to the SS and other biomarkers in patients with CAD, we performed a correlation evaluation. Spearman's correlation analysis revealed a significant association between plasma fibrinogen levels and SS (P < 0.001; Figure 4). Similarly, there was a positive correlation between CRP and SS (P = 0.001; Figure 5). In addition, an association between CRP and plasma fibrinogen levels was found (P = 0 .001; Table 5).

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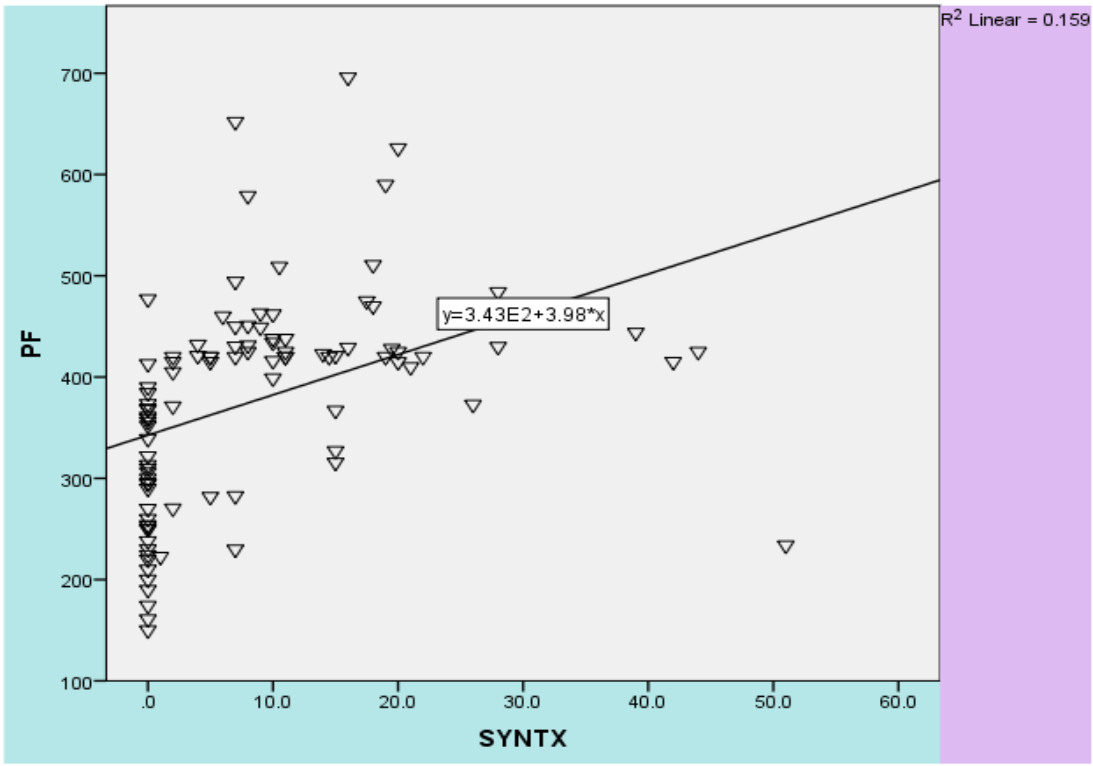

Figure 4. Correlation of Plasma Fibrinogen and SYNTAX level

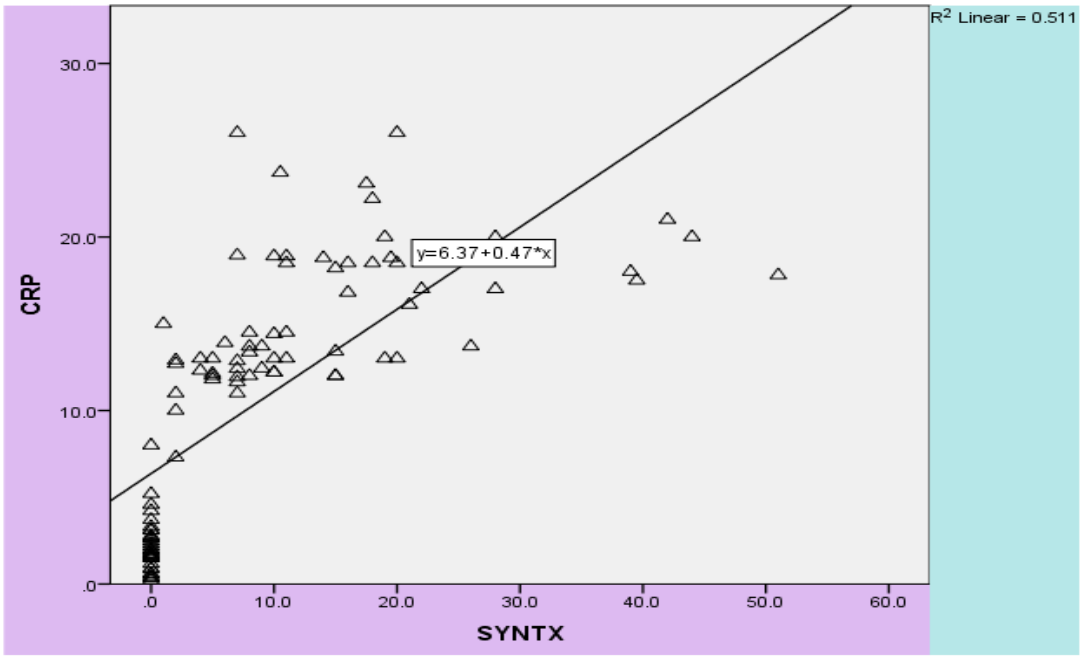

Fig.5. Correlation of hs C-reactive protein and SYNTAX level.

The findings of current study revealed there was significant direct correlation between PF and CRP measurements, which mean when one of these parameters increased, the other parameter will be increased, and when decreased, the other parameter will be also decreased (P = 0.001, r = 0.7) (r-value ranged from zero to one, zero for no correlation and one for strongest correlation). As seen in Table 5

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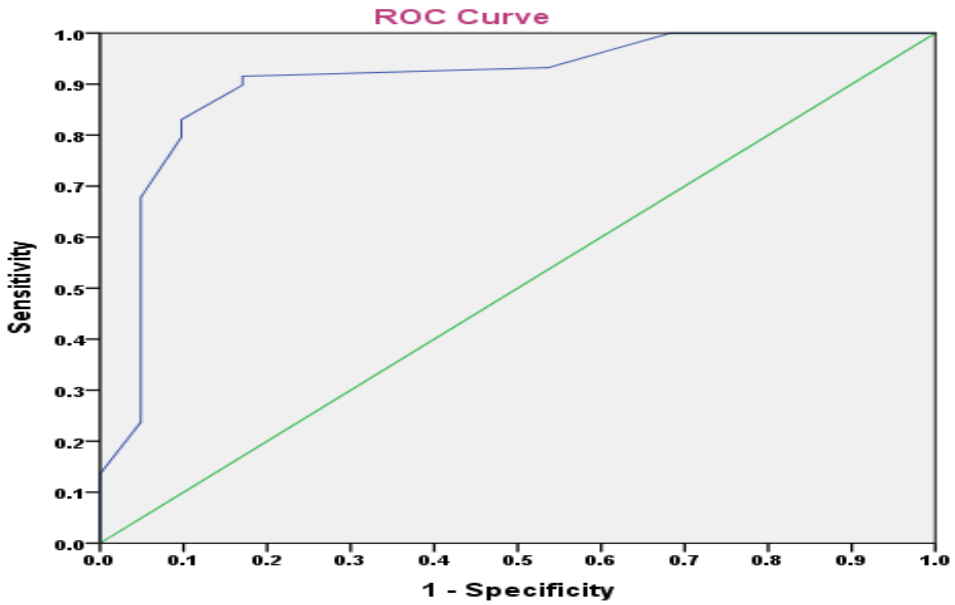
Table 5. Correlation of Plasma Fibrinogen, hs-Creactive protein, and SYNTAX level

Correlations				
		PF	CRP	SYNTX
PF	Pearson Correlation®	1	0.7**	0.39**
	P. Value		0.001	0.001
CRP	Pearson Correlation®	0.7**	1	0.7**
	P. Value	0.001		0.001

The area under the receiving operating characteristic (ROC) curve for serum hs-CRP was 0.87. The optimal values for the cut-off point were a serum hs-CRP of 11.3 mg/l (sensitivity 83%, specificity 86%) to predict severity of CAD. Any hs-CRP value higher than 11.3 mg/dl has a sensitivity of 83% and a specificity of 86%.



Hs-C reactive protein

Fig 6. Sensitivity = 83%, Specificity = 86%, Cutoff =11.3 AUC= 0.87

The area under the receiving operating characteristic (ROC) curve for plasma fibrinogen was 0.83. The optimal values for the cut-off point were a plasma fibrinogen of 411 mg/l (sensitivity 83%, specificity 81%) to predict CAD. Any fibrinogen value higher than 411mg/dl has a sensitivity of 83% and a specificity of 81%.

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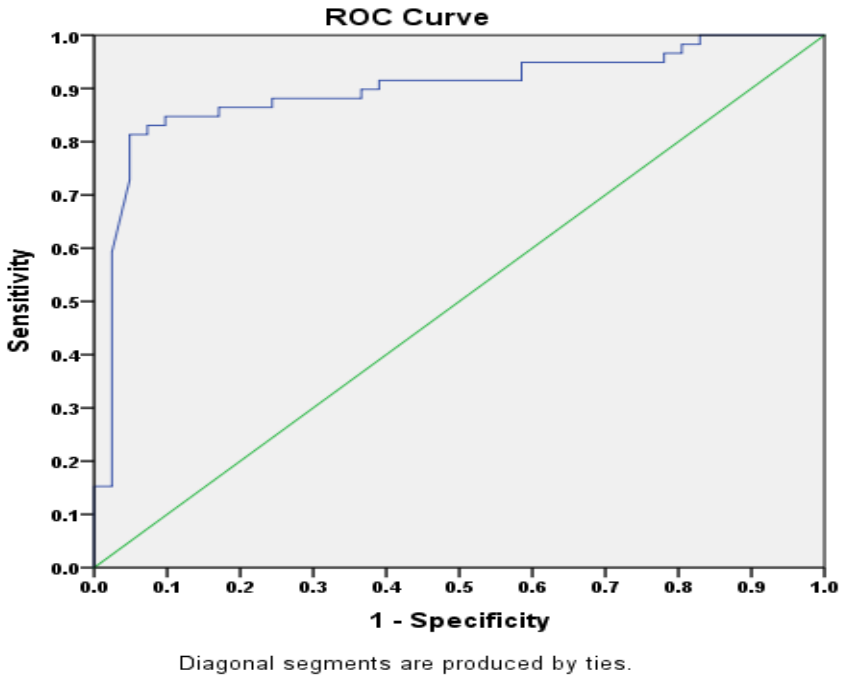

Plasma Fibrinogen
Fig.7. Sensitivity=83, specificity=81, cutoff=411, AUC=0.83

DISCUSSION

Available evidence in the literature shows that higher levels of hs-CRP are observed in CAD patients than normal subjects. In the present study, higher levels of hs-CRP were observed in patients when compared to controls (P < 0.001), and the finding of Gjin Ndrepepa, Siegmund Braun et al. is agree with this finding [7].

When comparing the values in groups of CAD patients, significantly higher levels were observed in patients with Multi vessel disease when compared to normal coronary persons. When comparing the values in four groups of CAD patients, our findings are in agreement with the findings of the Fadhil Jawad et al. study, in which they found that there is a significant strong positive correlation between the extent of CAD and the serum level hs-CRP [8].

In this conducted study, we see a differences in PF values according to angiographic findings, and it show a significant difference between normal and significant coronary vessels, whether single or two or multi vessels (P = 0.001), and significant difference between one and two-vessel (P = 0.04), and significant difference between one and multi vessels (P = 0.02), the difference between two and multi vessel disease is significant too (P = 0.02). This study also is in agreement withthe findings of the Bin Song et al. study; in this study, they found the plasma fibrinogen level was correlated with CHD [9].

In this study, we observed significantly higher plasma fibrinogen levels in diseased coronary artery patients, whether one, two, multi vessel, than in normal coronary artery finding. This study also is in agreement with the findings of Luciana Moreira Lima et al., in which they found that Plasma fibrinogen levels were higher in patients with coronary artery disease compared to angiographically normal subjects [10].

In this study, we observed significantly higher hs-CRP levels in single-vessel disease than in normal vessel disease (13.77±3.7 Vs. 2.92 ± 2.9; p=0.001); also in this study, we observed higher hs-CRP levels in two vessels diseases than in single-vessel disease (14.19 ± 3.5 Vs. 13.77 ± 3.7; P = 0.6). Also, significantly higher hs-CRP levels are observed in Multi vessel than in single-vessel disease (19.41 ± 1.7 Vs. 13.77 ± 3.7, P = 0.001). When comparing the values between the one and two-vessel diseases, our study shows no significance in hs-CRP levels (13.77 ± 3.7 Vs. 14.9 ± 3.5) this study are in agreement with the findings of the Syed Shahid Habib and Abeer A. Al Masri in which they found that triple vessel disease patients had significantly higher hs CRP levels than one vessel and two-vessel disease, while the difference was non-

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significant between one and two-vessel disease groups [11].

Increased serum hs-CRP levels are significantly associated with angiographic severity of CAD, suggesting its value as a
biomarkers for predicting CAD. This is with agreement the finding of S. Guruprasad et al., where their findings suggest that higher levels of hs-CRP are independently associated with an increased risk of CAD [12].

Increased plasma fibrinogen levels are significantly associated with angiographic CAD, suggesting its value as a biomarker for predicting CAD. This is with agreement the finding of Xiong-Yi Gao, Bing-Yang Zhou, Min-Zhou Zhang, et al., and Mehmet Mustafa et al., who found that Fib was an independent indicator for the presence and severity of coronary artery stenosis [13,14].

The findings of current study revealed there was significant direct correlation between PF and CRP measurements, which mean when one of these parameters increased, the other parameter will be increased, and when decreased, the other parameter will be also decreased ($P = 0.001$, $r = 0.7$) (r-value ranged from zero to one, zero for no correlation and one for strongest correlation). as seen in table 5. this is in agreement with Xiong-Yi Gao, Bing-Yang Zhou, Min-Zhou Zhang, et al. study

Risk stratification of individuals at risk for atherosclerotic cardiovascular disease (ASCVD) plays an important role in primary prevention of cardiovascular disease. In addition to risk scores derived from conventional cardiovascular risk factors.

CONCLUSION

CRP can be used to risk-stratify patients with CAD and can be used along with other risk-scoring systems.

Patients with abnormal CRP and complaining from signs and symptoms of CAD should undergos coronary angiography either on-site or transferred to a centre with a catheterisation facility during the index hospital admission. Patients with normal CRP can be managed with optimisation of antianginal therapy, followed by elective coronary angiography at a later date.

RECOMMENDATIONS:

1. Routine measurement of both hs-CRP and PF in patient at intermediate risk of CAD.
2. Long-term follow-up to assess the hs-CRP and PF values and its prognostic significance in CAD patients.

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