THE VALUE OF SERUM IL-6 LEVELS IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION AND ITS RELATION TO SEVERITY OF CORONARY ARTERY DISEASE BY CORONARY ANGIOGRAPHY

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ABSTRACT:

Background: *Acute coronary syndrome (ACS) is a syndrome that involves multiple forms of myocardial ischemia, as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), also unstable angina pectoris (UA). SYNTAX score predicts prognosis in stable coronary artery disease (CAD) and ACS cases. Use of Syntax score II (SS II) shows an increase in ACS prognostic accuracy.*

Aim: *We aim to evaluate the correlation between Interleukin 6 (IL-6) values and CAD severity after PCI in ACS patients.*

Methods: *Our study was done in the cardiology department, Mansoura university from January to March 2023. The study was conducted on 120 patients.*

In this study, patients suffering from chest pain that were admitted performing coronary angiography were included.

Patients being classified into an acute coronary syndrome (ACS) group and chronic coronary syndrome (CCS) group (individuals with diseased vessels exhibiting>50% luminal stenosis). In order to find predictive value of intermediate-high SS or highly SS II, multivariate logistic regression was performed. A ROC curve was utilized to predict the levels of IL-6.

Results: *For ACS differentiation from SA, IL-6 cutoff value 1.89 has sensitivity of 98.6% and specificity of 92% (P<0.0001). For SS≤ 22, IL-6 cutoff value 3.24 has sensitivity of 89.7% and specificity of 91.7% (P<0.0001). For SS II≤ 25, IL-6 cutoff value 1.92 has sensitivity of 97.1% and specificity of 88.6% (P=0.23).*

Conclusion: *IL-6 concentrations are in direct correlation with the degree of CAD in ACS patients undergoing PCI. Thus, IL-6 levels might be a practical and non-invasive indicator for ACS patients who are at elevated risk.*

Key words: *ACS, IL-6, SYNTAX score II, SYNTAX score*

INTRODUCTION:

Atherosclerotic plaque accumulates within the coronary arteries in coronary artery disease (CAD), obstructing blood from reaching the heart. Regardless of the effort and money invested in teaching doctors and the public about its risk variables, symptoms, and therapy, one woman or man has a CAD incident approximately every 25 seconds [(1)]**.**

ACS, a disorder marked by symptoms of abrupt myocardial ischemia—a rapid

decrease in blood supply to the heart - can result from CAD. Because it was thought that the name ACS better accurately represented the illness course linked to myocardial ischemia, it was chosen. The ACS covers both myocardial infarction (MI) and unstable angina[(2)]**.**

Up till now understanding ACS pathogenesis are lacking, and reaching the optimal treatment for this condition is considered an important global public health goal[(3)]**.**

Inflammation plays an important role in the pathophysiology of ACS, initiating and promoting the development of athero-sclerosis and promoting the instability and destruction of atheromatous plaques. Numerous studies have consistently shown a link between elevated levels of biomarkers suggestive of inflammation and cardiovascular disease (CVD). In particular, the production of high-sensitivity C-reactive protein (hs-CRP), which also contributes to the development and progression of clinical atherosclerosis, and the production of the pro-inflammatory cytokine interleukin-6 (IL-6), which is primarily made by T cells and macrophages, have been identified as major factors in the destabilisation of plaques and the progression of atherosclerosis [(4)]**.**

It is widely established that there are associations between greater IL-6 levels and an increased risk of cardiovascular events in otherwise healthy people. Additionally, IL-6 has been shown to be a predictor of the severity of coronary artery disease (CAD) and related mortality in ACS patients. Furthermore, it has been observed that IL-6 levels are related to plaque burden as measured by intracoronary imaging [(5)]**.**

Prior research has shown that the SYNTAX score (SS), which is often utilized to quantify the intensity and severity of CAD, may predict predictive results in patients with stable CAD and ACS [(6)]**.** The SS II indicator has been expanded to take individual clinical characteristics into account, achieving higher accuracy rates in the prognostic assessment of ACS patients[(7)]**.**

AIM OF THE WORK:

We aimed to evaluate the relationship between IL-6 levels and the angiographic severity of coronary artery disease following percutaneous coronary intervention in acute coronary syndrome patients.

MATERIAL AND METHODS:

Our study was done in the cardiology department, Mansoura university from January to March 2023. The study was conducted on 120 patients.

In this study, Patients who underwent coronary angiography while experiencing chest pain were included. The standards proposed by the ESC guidelines served as the foundation for the diagnostic standards for ACS (including STEMI, NSTEMI, and UA patients)**[(8)].**

Patients who had previously underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG), or who displayed malignancies, autoimmune illness, hepatic failure, renal failure, infectious or inflammatory diseases, were excluded from the study. Patients being classified into an acute coronary syndrome (ACS) group and chronic coronary syndrome (CCS) group (individuals with diseased vessels exhibiting>50% luminal stenosis).

Patient's characteristics: Fasting blood samples were obtained from the peripheral veins of all patients before PCI to assess hematologic indices, hs-CRP levels, biochemical parameters, and IL-6 concentrations using standard approaches in our hospital's clinical laboratory. IL-6 concentrations were measured using an

enzyme-linked immunosorbent assay. Transthoracic echocardiography was conducted prior to angiography. The Cockcroft-Gault equation was utilized to calculate the estimated glomerular filtration rate (eGFR) for each patient.

Coronary angiographic analysis All patients underwent coronary angiography via the femoral approach. syntax score and syntax score II was calculated using SS calculator[9].

Ethical Approval: Each participant in the research provided written informed permission, which was obtained after the project was given the green light by the university's ethics committee. While conducting this human study, the World Medical Association's Declaration of Helsinki, its code of ethics, was adhered to.

Statistical Analysis: IBM-SPSS version 24 was utilized for data analysis (May 2016). The statistical significance was assessed using the Kristall-Wallis and Wilcoxon tests, Spearman's correlation, and logistic regression analysis. Each parameter was evaluated in accordance with the sort of data it held (parametric or not). If the P-values <0.05 (5%), we regarded the findings as statistically substantial.

Ethical consideration:

The protocol was approved by the Institutional Research Board of Faculty of Medicine, Mansoura University (proposal code number R.22.12.1990). Each subject gave informed consent, and he was granted confidentiality and privacy.

RESULTS:

In our study 120 cases were enrolled acute coronary syndrome (ACS) was found in 70 cases and chronic coronary syndrome (CCS) was found in 50 cases.

Regarding Clinical, biochemical, and demographic differences between the ACS and CCS groups, WBC count, NEUT, NLR, Platelet count, IL-6,hs-CRP, Creatinine and Fibrinogen were all substantially increased in ACS group compared with CCS group. However, Hypertension, HDL-c, apoA1 and LVEF were all substantially increased in CCS group compared with ACS **(Table1).**

In ACS group, IL-6, and hs-CRP were all significantly decreased in cases of SS <22 compared to those with SS>22 **as in (Table 2).**

In ACS group, Age, IL-6, and apoA1, were all significantly decreased in cases of SS II <25 compared to those with SS II >25. However, BMI, LYM, eGFR and Albumin were all significantly increased **as in (Table 3).**

For ACS differentiation from CCS, IL-6 cutoff value 1.89 has sensitivity of 98.6% and specificity of 92% (P<0.0001). For SS≤ 22, IL-6 cutoff value 3.24 has sensitivity of 89.7% and specificity of 91.7% (P<0.0001). For SS II≤ 25, IL-6 cutoff value 1.92 has sensitivity of 97.1% and specificity of 88.6% (P=0.23).

Table (1): Clinical, biochemical, and demographic differences between the ACS and CCS groups

Parameters	ACS (n=70)	CCS (n=50)	P. value
Age, years	64.33 ± 10.6	65 ± 11.45	0.7451
Male gender, n (%)	47(67.14%)	40(80%)	0.1199
Hypertension, n (%)	44(62.86%)	46(92%)	0.0003*
Diabetes, n (%)	17(24.29%)	13(26%)	0.8317
Smoking, n (%)	10(14.29%)	10(20%)	0.4076
WBC, 10^9 /L	6.73 ± 2.04	5.87 ± 1.6	0.01094*
NEUT, 10^9 /L	4.37 ± 1.67	3.53 ± 1.3	0.00246*
BMI, kg/m^2	24.8 ± 3.3	24.7 ± 3.6	0.87687
NLR	2.53 ± 1.21	2.13 ± 0.69	0.02363*
LYM, 10^9 /L	1.7 ± 0.61	1.63 ± 0.53	0.50452
RDW	12.9 ± 0.68	12.97 ± 0.53	0.52787
Platelet, 10^9 /L	178 ± 56.77	156.25 ± 57.25	0.0417*
IL-6, pg/ml	7.73 ± 4.62	3.83 ± 2.21	<0.0001*
hs-CRP, mg/	6.3 ± 7.19	1.5 ± 1.76	<0.0001*
Triglyceride, mmol/L	1.43 ± 0.68	1.33 ± 0.69	0.43261
TC, mmol/L	3.9 ± 1	3.9 ± 0.9	0.98
LDL-c, mmol/L	2.17 ± 0.91	2.1 ± 0.92	0.68052
HDL-c, mmol/L	1.1 ± 0.3	1.3 ± 0.31	0.00059*
apoA1, g/L	1.07 ± 0.23	1.17 ± 0.23	0.02053*
Lp(a), mg/L	266.37 ± 277.72	229.23 ± 225.94	0.42181
apoB, g/L	0.8 ± 0.3	0.77 ± 0.23	0.53666
eGFR, ml/min	88.8 ± 34.06	90.33 ± 35.26	0.81254
Albumin, g/L	38.6 ± 3.2	39.8 ± 3.1	0.04135*
Creatinine, umol/L	70.8 ± 21.19	62.2 ± 17.02	0.01529*
LVEF, %	61.67 ± 4.3	63.33 ± 4.4	0.0419*
Fibrinogen, g/L	3.17 ± 0.98	2.83 ± 0.61	0.02111*

Table (2): Low and intermediate-high SYNTAX score (SS) group clinical, biochemical, and angiographic features

Parameters	**SS ≤ 22 (N = 58)**	**SS > 22 (N = 12)**	**P. value**
Age, years	64.33 ± 10.6	65.33 ± 12.98	0.80288
BMI, kg/m^2	24.9 ± 3.5	24.2 ± 2.7	0.4407
WBC, 10^9 /L	6.63 ± 2.04	7.13 ± 2.44	0.50831
LYM, 10^9 /L	1.7 ± 0.61	1.8 ± 0.69	0.64222
NLR	2.53 ± 1.21	2.73 ± 1.22	0.60567
Platelet, 10^9 /L	175.67 ± 53.74	185 ± 61.06	0.62405
RDW	12.9 ± 0.61	12.9 ± 0.69	0.96
NEUT, 10^9 /L	4.27 ± 1.59	4.67 ± 1.76	0.46793
IL-6, pg/ml	6.67 ± 3.71	16.63 ± 10.46	0.00147*
hs-CRP, mg/l	4.93 ± 5.83	13.5 ± 8.63	0.00133*
TG, mmol/L	1.47 ± 0.76	1.53 ± 0.46	0.71859
TC, mmol/L	3.9 ± 1	4 ± 1	0.75307
LDL-c, mmol/L	2.2 ± 0.8	2.4 ± 0.9	0.47684
HDL-c, mmol/L	1.23 ± 0.23	1.21 ± 0.23	0.78442
apoA1, g/L	1.05 ± 0.2	1.1 ± 0.2	0.4321
apoB, g/L	0.77 ± 0.23	0.87 ± 0.38	0.38124
eGFR, ml/min	88.93 ± 34.59	85.7 ± 28.55	0.73203
Creatinine, umol/L	70.77 ± 20.82	71.1 ± 23.2	0.96369
Fibrinogen, g/L	3.13 ± 0.91	3.4 ± 0.92	0.35575
Albumin, g/L	39.47 ± 3.03	38.37 ± 3.59	0.32376
LVEF, %	61.67 ± 5.3	60 ± 9.16	0.54253
SS	11.6 ± 6.66	26 ± 3.82	<0.0001*

Table (3): Clinical, biochemical, and angiographic features of patients with low and high SYNTAX score II group

parameters	SS ≤ 25 (N = 35)	SS > 25 (N = 35)	P value
Age, years	57.33 ± 11.35	70 ± 7.63	<0.0001*
BMI, kg/m^2	25.7 ± 3.6	22.9 ± 2.9	0.00105*
WBC, 10^9 /L	6.87 ± 2.2	6.6 ± 2.06	0.59956
LYM, 10^9 /L	1.85 ± 0.61	1.52 ± 0.61	0.03013*
NLR	2.43 ± 1.21	2.7 ± 1.14	0.34342
Platelet, 10^9 /L	186 ± 56.01	170.67 ± 53.43	0.24949
RDW	12.87 ± 0.61	13.03 ± 0.69	0.3113
NEUT, 10^9 /L	4.3 ± 1.51	4.4 ± 1.76	0.80017
IL-6, pg/ml	6.23 ± 4.09	9.27 ± 7.02	0.03366*
HG, g/L	135.3 ± 15.4	123.7 ± 15.4	0.00339*
hs-CRP, mg/l	5.67 ± 6.74	7.77 ± 9.39	0.29001
TG, mmol/L	1.5 ± 0.76	1.4 ± 0.69	0.56818
TC, mmol/L	4 ± 1	3.9 ± 1	0.67834
LDL-c, mmol/L	2.2 ± 0.7	2.2 ± 0.8	0.98
HDL-c, mmol/L	1.2 ± 0.3	1.23 ± 0.23	0.64171
apoA1, g/L	1 ± 0.2	1.1 ± 0.2	0.04401*
apoB, g/L	0.8 ± 0.3	0.77 ± 0.23	0.64171
eGFR, ml/min	105.63 ± 30.88	70.87 ± 26.64	0.00002*
Creatinine, umol/L	69.07 ± 15.44	73.37 ± 28.47	0.43762
Fibrinogen, g/L	3.03 ± 0.83	3.5 ± 0.99	0.03856*
Albumin, g/L	40.17 ± 2.88	38.23 ± 3.36	0.01391*
LVEF, %	62.33 ± 4.54	59 ± 11.45	0.11898
SS II	20.5 ± 3.86	33 ± 7.25	<0.0001*

Table (4): ROC curve analysis of IL-6 association with different parameters

Diagnosis	Cutoff	AUC	Std. Error	Sensitivity	Specificity	P. Value
ACS	1.89	0.855	0.0334	98.6%	92%	<0.0001
SS ≤ 22	3.24	0.155	0.077	89.7%	91.7%	<0.0001
SS ≤ 25	1.92	0.342	0.067	97.1%	88.6%	0.023

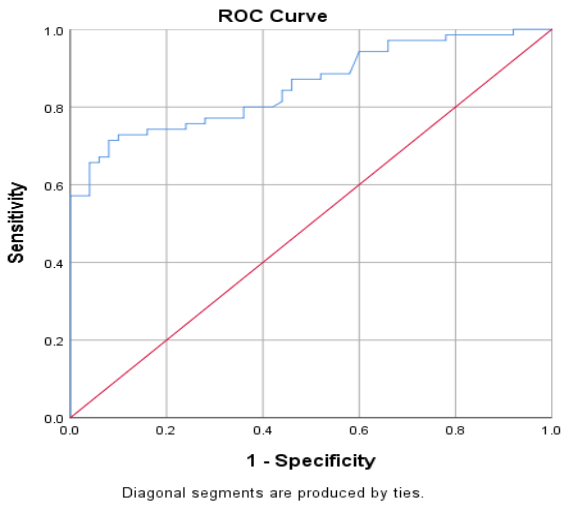

Figure (1): ROC curve analysis of ACS association with IL-6

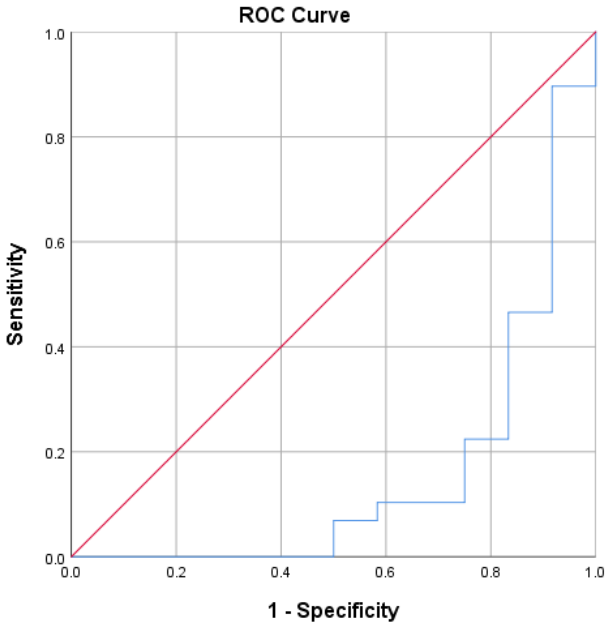

Figure (2): ROC curve analysis of IL-6 association with SS<22.

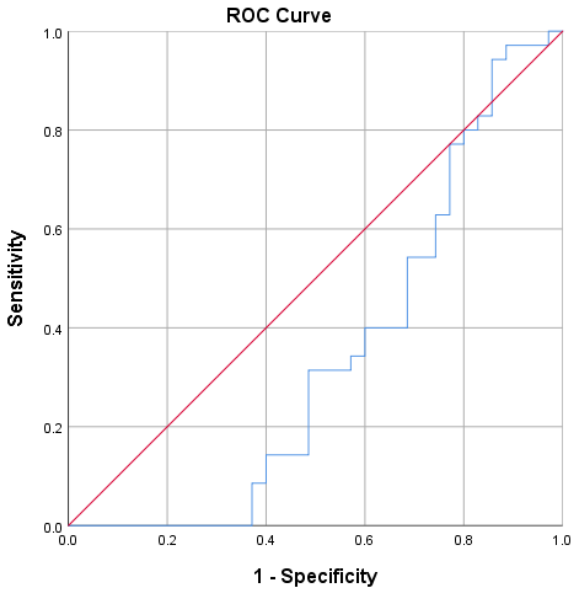

Figure (3): ROC curve analysis of IL-6 association with SS<25

DISCUSSION:

Despite breakthroughs in revascularization procedures and antithrombotic medication, ACS continues to pose the greatest risk to global public health. Therefore, methods for accurately forecasting ACS severity must be developed in order to direct the prevention, diagnosis, and treatment of this crippling illness[10]. Here, we discovered a strong correlation between IL-6 concentrations and the intensity of the ACS as determined by the SS and SS II, with IL-6 concentrations also

serving as a useful independent prediction of intermediate-high SS and highly SS II rates.

A plenty of research indicates that inflammation has a substantial role in the onset, progression, and patient prognosis of ACS. It should be noted that IL-6, which is largely produced by mononuclear cells, can influence the development of CAD through numerous methods [11& 12]**.**

In addition to elevating hepatic CRP synthesis, which in turn raises blood viscosity and platelet counts, IL-6 also has the ability to deposit fibrinogen more quickly **[13].** Further encouraging macrophages to phagocytose lipids, IL-6 may promote the development of foam cells **[14].** Additionally, there are plenty of evidence that IL-6 may speed up insulin resistance by triggering the hypothalamic-pituitary-adrenal axis [4]**.**

In previous investigations, higher IL-6 values in healthy guys were linked to future MI prevalence **[15].** According to a previous study, there were no statistically substantial variations in the concentrations of IL-6 between blood drawn from a peripheral vein and the coronary sinus of ACS patients. This finding supported the idea that systemic instead of local vascular inflammation contributed to the progress of athero-sclerosis**[16].**

The SS is a useful measure that aids in the identification of high-risk ACS cases and is associated with the complexity of atherosclerotic lesions. It can help direct suitable revascularization planning. Additionally, SS levels may accurately indicate the likelihood of developing acute cardiovascular event [4]**.** Furthermore, several investigations have shown a link between IL-6 concentrations, the intensity of coronary stenoses and death. In fact, previous studies have shown a correlation between IL-6 concentrations and the intensity of CAD as determined by the Gensini score. These earlier findings showed a potential correlation between serum IL-6 concentrations and the intensity of ACS as assessed by SS and SS II (**17).** We discovered that IL-6 levels consistently predicted intermediate-to-high SS values and that they were positively linked together. The SS II score was created as a more accurate indicator of CVS incidents among ACS patients via a variety of clinicopathological variables which might affect patient outcome. We found a correlation between IL-6 concentrations and SS II rates that was positive.

Patients with anemia often have impaired LVEF, advanced age, and increased creatinine levels. Therefore, these patients' advanced age, reduced eGFR, and poorer LVEF may be responsible for the correlation between decreasing hemoglobin and a high SS.

Conclusion:

In conclusion, our investigation supported the hypothesis that angiographic complexity in ACS patients is correlated with IL-6 levels. In conclusion, our results imply that IL-6 could be a marker that can be utilized to assess the degree and extent of CAD.

Conflict of interest:

There is no conflict of interest.

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قيمة الانترلوكين 6 فى المرضى الذين يقومون بتركيب دعامات للشرايين التاجية وعلاقته بشدة مرض الشرايين التاجية عن طريق القسطرة

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مقدمه البحث : تتزايد تصلبات الشرايين التاجية في مرض قصور الشريان التاجي وتحد من تدفق الدم إلى القلب. تعاني امرأة أو رجل من مرض الشريان التاجي كل 25 ثانية تقريبًا ، على الرغم من الوقت والموارد التي يتم إنفاقها في تثقيف الأطباء والجمهور حول عوامل الخطر والأعراض والعلاج.

يمكن أن يؤدي مرض الشريان التاجي إلى متلازمة الشريان التاجي الحادة ، والتي تصف أي حالة تتميز بعلامات وأعراض نقص تروية عضلة القلب المفاجئ ، وهو انخفاض مفاجئ في تدفق الدم إلى القلب. تم اعتماد مصطلح متلازمة الشريان التاجى الحادة لأنه كان يعتقد أنه يعكس بشكل أكثر وضوحًا تطور المرض المرتبط بإقفار عضلة القلب. الذبحة الصدرية غير المستقرة واحتشاء عضلة القلب كلاهما يندرج تحت مظلة متلازمة الشريان التاجى الحادة.

تشير مجموعة متزايدة من الأدلة إلى أن النشاط الالتهابي يلعب دورًا أساسيا في سياق الفسيولوجيا المرضية لقصور الشريان التاجى الحاد، مما يؤدي إلى بدء وتطور تصلب الشرايين ، مما يؤدي إلى ذبحة صدرية غير مستقرة. باستمرار ، أفادت العديد من الدراسات بوجود ارتباط بين أمراض القلب والأوعية الدموية وزيادة مستويات المؤشرات الحيوية التي تشير إلى الالتهاب. على وجه الخصوص ، تمت الإشارة إلى السيتوكين الإنترلوكين 6 المؤيد للالتهابات ، والذي يتم إنتاجه بشكل أساسي بواسطة البلاعم والخلايا التائية ، باعتباره المحرك الرئيسي لتطور وتطور تصلب الشرايين السريري.

الهدف من الدراسة: نحن نهدف إلى تقييم العلاقة بين مستويات الانترلوكين 6 فى الدم وشدة تصوير الأوعية الدموية لمرض الشريان التاجي في المرضى الذين يعانون من ألم حاد في الصدر.

تصميم الدراسة: سوف تشمل الدراسه مائة و عشرون مريض يعانون من الم حاد بالصدر وسيخضعون لقسطرة الشرايين التاجية فى مستشفى الباطنه التخصصى فى الفتره من يناير 2023الى الاول من ابريل 2023.

المرضى المستبعدون من الدراسة: - وسوف يستثنى من هذه الدراسه المرضى الذين المرضى الذين خضعوا بالفعل للتدخل التاجي عن طريق الجلد او عملية ترقيع الشرايين التاجية او فشل كبدي متقدم و فشل كلوي متقدم و مرضى المناعة الذاتية و الأمراض المعدية و الأورام النشطة ومرضى الالتهابات النشطه والمرضى الذين يرفضون المشاركة في الدراسة.

سيتم تقسيم المرضى إلى مجموعتين:

مجموعه متلازمة الشريان التاجى الحادة ومجموعه تعانى من ذبحة صدرية مستقرة.

سيخضع جميع المرضى إلى:

- عوامل الخطر القلبية مثل التدخين وارتفاع ضغط الدم والسكري واضطراب شحميات الدم والتاريخ العائلي لمرض الشريان التاجي. وفحص اكلينكى شامل ورسم قلب كهربائى و موجات القلب فوق الصوتيه.

سوف يتم تقييم سيرم الانترلوكين 6 فى الدم فى كل المرضى و ايضا سيتم عمل قسطرة على شرايين القلب التاجية لكافة المرضى . و سيتم حساب شدة قصور الشرايين التاجية عن طريق معدل سينتاكس 1 و 2 و الذين يمكن حسابهم عن طريق ادخال بيانات معينة على تطبيق معين على الموبايل او عن طريق موقع الاكترونى معين.