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PROTEIN C AND S DEFICIENCY IN MYOCARDIAL INFARCTION IN THE YOUNG

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ABSTRACT

Background- Thrombophilia refers to a series of acquired and inherited conditions that confer an increased risk for thrombus formation. Protein C and S deficiency are hereditary conditions associated with thrombophilia..(1) MI (Myocardial Infarction) with non-obstructive coronary arteries (MINOCA) is being increasingly recognized with the frequent use of angiography. To diagnose MINOCA, it is very important to identify the underlying different potential mechanisms like thrombophilia that may require different managements, especially in young individuals.(2)

Objectives- 1)To estimate the proportion of young MI patients with low protein S and protein C profile with their first episode of MI

2)To determine the clinical outcome of these patients during the period of hospitalization.

Methodology-After identifying the study population based on the inclusion criteria, study participants were selected. Also,details of echocardiography, angiographic results if any,ECG and clinical history were noted in each case during their presentation. Patients were followed up for 3 weeks until next review in OPD, and blood samples were then obtained in citrated tubes. The platelet poor plasma obtained from these samples were stored at -70 degree Celsius, and later performed coagulation screening tests, Protein C and S assay.

Results- Out of 112 cases studied, 6.2% (7 cases) were detected with protein C deficiency and 4.4 % (5 cases) with protein S deficiency,and 2 cases had a combined protein C and S deficiency.

Conclusion- Protein C/S deficiency were detected in a minor proportion of cases with coronary- arterial thrombosis in the young. Tests for protein C/S could be included in the workup for MINOCA in young individuals.

.**Key words:** Protein C, Protein S, young MI, MINOCA, arterial thrombosis, thrombophilia.

INTRODUCTION- Protein C is a vitamin K-dependent plasma glycoprotein that is synthesized by the liver and in its activated form mediates the inactivation of clotting factors- FVa and FVIIIa.. Protein S is a vitamin K dependent protein that functions as a cofactor for activated protein C mediated inactivation of FVa and FVIIIa. Thus deficiency of Protein S reduces the inactivation of FVa and FVIIIa, resulting in an increased production of thrombin, which generates fibrin. This along with the cyto-protective role of protein C confers an increased risk for thrombosis in case of Protein C deficiency. Protein C values reduced to ~50% of normal predisposes an individual to venous thrombosis.(1) Its role in arterial thrombosis is less studied.

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Cardiovascular disorders remain the leading cause of mortality and morbidity globally, and the incidence continues to increase. Acute Coronary Syndrome(ACS) may result from non- atherosclerotic etiologies, ie . congenital anomalies of coronary artery, spontaneous coronary artery dissection, vasospasm, use of illicit drug, or hypercoagulable states. The absence of coronary disease must divert the differential towards inherited thrombophilia syndromes, especially in young patients who had suffered from acute MI.(3) MI with non-obstructive coronary arteries (MINOCA) is an enigma that is being increasingly identified with the frequent use of angiography following acute MI. (2)That is; a significant proportion of patients presenting with acute myocardial infarction (MI) has no coronary obstruction at coronary angiography and no other obvious non-coronary pathophysiology causing MI. These patients are classified as MI with non-obstructive coronary arteries (MINOCA) and also, data on incidence and predictors of MINOCA are still limited.(4)

In patients who have developed arterial thrombosis at an early stage,(age ≤ 50 [male], ≤ 55 [female]), particularly with no apparent cause of arterial occlusion, evaluation for thrombophilia is important as thrombophilia may play a predisposing role in patients with cerebral, coronary, and peripheral vascular ischemia.(5),(6),(7),(8). The overall incidence of venous thrombotic events in the setting of protein C and/or protein S deficiency is reported to be much higher than that of arterial thrombosis with a ratio of almost 24:1.(9)However very rarely, inherited thrombophilia cause coronary artery thrombosis leading to MI . Arterial thrombotic events have been known to be associated with factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR C677 T) mutations.(10) The likelihood of detecting atleast one thrombophilia marker in young MI patients who have few conventional risk factors is significantly high . In premature and advanced cases of atherosclerosis, both systemic and vascular wall–driven coagulation have increasing role.(11)Patients with severe premature CVD may have both conventional atherosclerosis and concomitant thrombophilia-driven arterial thrombosis,(12),(13),(14),(15),(16),(17) the prevalence of which is less studied.

Tests for thrombophilia is ideally preferred to be done after the acute episode has subsided and during the follow-up period and after making sure that the patient is not on any anticoagulant medications for atleast a period of 10 days.(1) A clot based assay for protein C and protein S is ideal as it is more informative and pertaining to the functional activity of the same that is, can detect both quantitative and qualitative defect.

STUDY POPULATION

People less than 45 years with first episode of myocardial infarction reported in Department of Cardiology, Govt. medical College, Kottayam.

INCLUSION CRITERIA – People <45 years with first episode of MI.

EXCLUSION CRITERIA-

Patients with confirmed diagnosis of malignancy,hyperhomocysteinemia,Antiphospholipid antibody syndromes,fibrinolytic system defects

STUDY PROCEDURE:

After identifying the study population based on the criteria of age and first episode of myocardial infarction and also after routine tests for myocardial infarction, details of echocardiography, angiographic results if any and ECG were noted. The study procedure including the need for blood collection after the required time

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interval was explained and, a written informed consent was obtained. Then detailed history was obtained along with the contact details. Details regarding comorbidities of obesity, hypertension, dyslipidemia, smoking, diabetes mellitus, previous surgery, anticoagulant medication if any, family history were also taken. Patients were followed up till the next review in the OPD(usually after 3 weeks).

Blood collection by direct venipuncture was done after the required time interval of 3 weeks so as to avoid the effects of medications and other factors related to the acute episode. The anticoagulant of choice is 3.2% buffered sodium citrate in a ratio of nine parts of whole blood and one part anticoagulant(9:1). Blood was collected in two citrate tubes (2ml each). Immediately after blood collection, these samples were centrifuged in room temperature at 3500 rpm for 15 minutes, twice . A platelet poor plasma (PPP) was hence obtained, which is the ideal sample for coagulation testing. Using a micropipette, these PPP were separated and stored in cryovials, each of which were labelled with the details of patient ID number and date of collection and kept in a deep freezer at a temperature of -70 degree for testing at a later period. The need for storage in deep freezer arouse due to the fact that the test kit for protein C/S is very expensive and the reagents once reconstituted are stable for only 8 hours at 2-8 degree celsius. So it was only feasible to test the samples together as different batches. Moreover, each sample was obtained during the individual specific time interval and it was impractical to test each samples separately mainly because of the financial constraints and reagent stability issues. Tests such as platelet count, PT, APTT, thrombin time were performed along with the Protein C/S assays on the samples collected and stored. The specific tests for protein C ,protein S deficiency was studied by clot based assays using TriniCLOT PC/S II kit which is intended for the quantitative measurement of the functional C/S level based on the prolongation of the activated partial thromboplastin time and the values were charted and compared with the reference range.

TriniCLOT PC II kit consist of TriniCLOT PC Def Plasma, TriniCLOT PC Activator, each of which are reconstituted with 1 ml of purified water in a vial. These are then allowed to stand at room temperature for 30 minutes. Other materials available in the kit include- buffer solution, calcium chloride, controls and analysers. Once reconstituted, the reagents are stable for 8 hours at 2-8 degree Celsius. Similar kit is available for Protein S. The test as well as the reagent samples were loaded onto an automatic Destiny Plus coagulation analyzer. Reliability of test results were monitored using normal and abnormal control materials within each run (Quality control).

Those samples stored in deep freezer were brought to 37 degree celsius after placing in a water bath and then taken for testing. Data entry, documentation and percentage of Protein C/S deficiency among young MI was then calculated.

DEFINITIONS - 1. Thrombophilia – Any disorder either acquired or inherited associated with an increased risk of thrombosis.(1)

2.Young MI – Persons < 45 years with first episode of MI.(18)

3.Protein C deficiency- <40-60% of normal functional activity(normal value : 3-5 mcg/ml(70-140%)(1)

4.Protein S deficiency – less than normal functional activity reference range(normal value :23 mcg/ml(65-140%)(1)

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RESULTS :

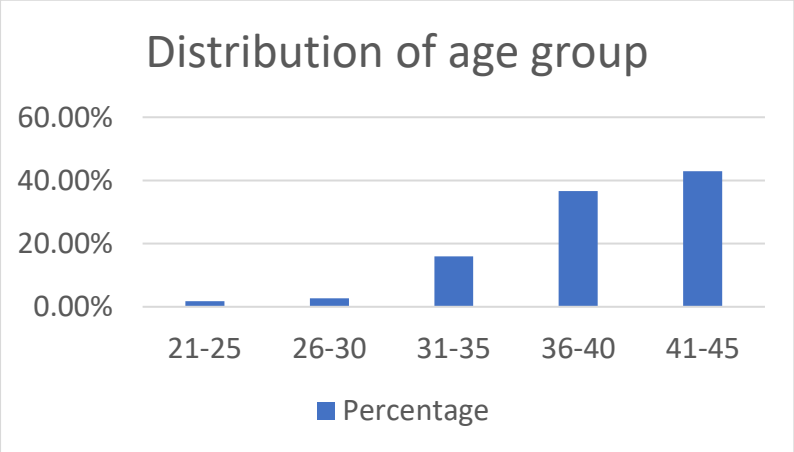
During the study period, 150 young patients were admitted for the management of MI. Two of them were diagnosed with hyperhomocysteinemia, five cases had a recurrent history of MI, two cases expired within 7 days of admission,ie; before the required time interval for sample collection. Hence these were excluded from the study population. 29 participants were lost to follow-up after the required time interval for sample collection (3 weeks) and hence the total sample included in the study was 112.

AGE DISTRIBUTION AMONG STUDY POPULATION (n= 112).

The youngest case in the study was that of a 24 year old male and the oldest was of 44 years of age.

Figure1: Age distribution among study population .(n=112)

Only 2 participants (1.8%) were in the age group of 21-25 years, 3 participants (2.7%) were in the age group of 26-30, 18 participants (16%) were in the age group of 31-35 years, 41 participants (36.6%) were in the age group and majority of 48 participants (42.9%) were in the age group of 41-45 years.



GENDER DISTRIBUTION AMONG STUDY POPULATION.

The study group consisted of 104 males and 8 females with a male: female ratio of 13:1.

Table 1: Gender distribution among study population. (n=112)

GENDER	FREQUENCY	PERCENTAGE
MALES	104	93
FEMALES	8	7
Total	112	100

DISTRIBUTION OF BODY MASS INDEX (BMI) AMONG STUDY POPULATION.

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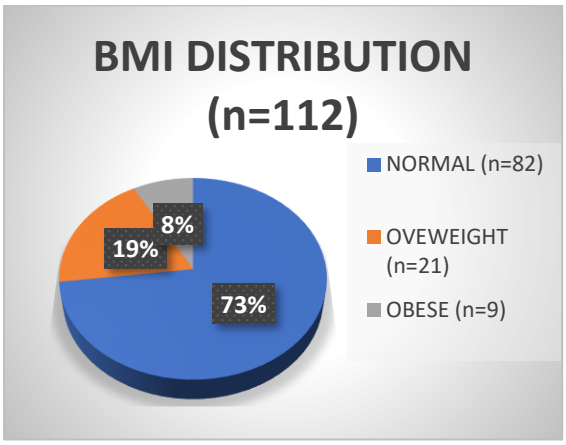
Majority of the study participants (73%) had a normal BMI in the range of 18.5 – 24.9 (82 cases), followed by overweighted individuals (19%) with a BMI in the range of 25 – 29.9 (21 cases). Obesity was found in only 8% cases (9 cases) with the BMI in the range of above 30.

Figure 2: BMI distribution among study population. (n=112)

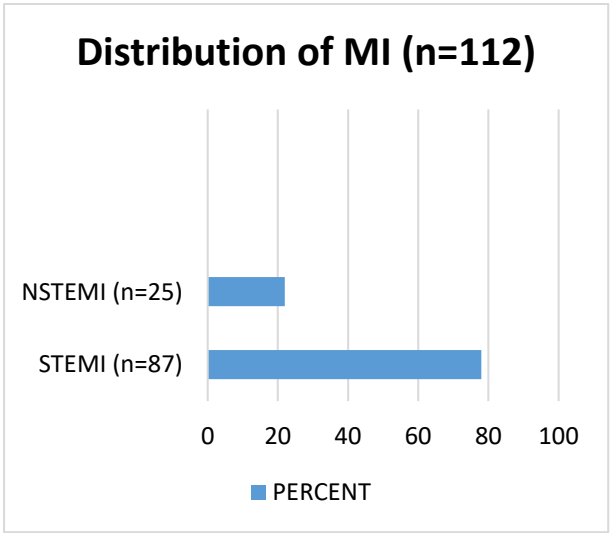


DISTRIBUTION OF TYPE OF MI AMONG STUDY POPULATION.

Majority of the cases(78%) were diagnosed with ST segment elevation myocardial infarction (87 cases) and only 25 cases (22%) with non- ST elevation myocardial infarction.

Figure 3: Distribution of type of MI among study population. (n=112)

Majority of the samples(78%) were diagnosed with ST segment elevation myocardial infarction (87 cases) and only 25 samples (22%) with non- ST elevation myocardial infarction.



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DISTRIBUTION OF RISK FACTORS AMONG STUDY POPULATION

Systemic hypertension was found to be the most common comorbidity among young MI (38%), followed by dyslipidemia (19.6%), diabetes mellitus (17%), smoking (15%).

Eleven cases had a previous history of surgery.

TABLE 2: Distribution of risk factors among study population (n=112)

RISK FACTORS	FREQUENCY	PERCENTAGE (%)
SYSTEMIC HYPERTENSION	42	38
DYSLIPIDEMIA	22	19.6
DIABETES MELLITUS	19	17
SMOKING	17	15
PREVIOUS SURGERY	12	11

DISTRIBUTION OF PROTHROMBIN TIME (PT) AMONG STUDY POPULATION.

Out of the total study participants, 1 had an elevated prothrombin time(0.9%)

Table 3: Distribution of prothrombin time among study population.

(PT) (n=112)

PROTHROMBIN TIME	FREQUENCY	PERCENTAGE(%)
NORMAL	111	99.1
ELEVATED	1	0.9
TOTAL	112	100

DISTRIBUTION OF ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT) AMONG STUDY POPULATION.

Out of the 112 study participants, three had an elevated APTT values.

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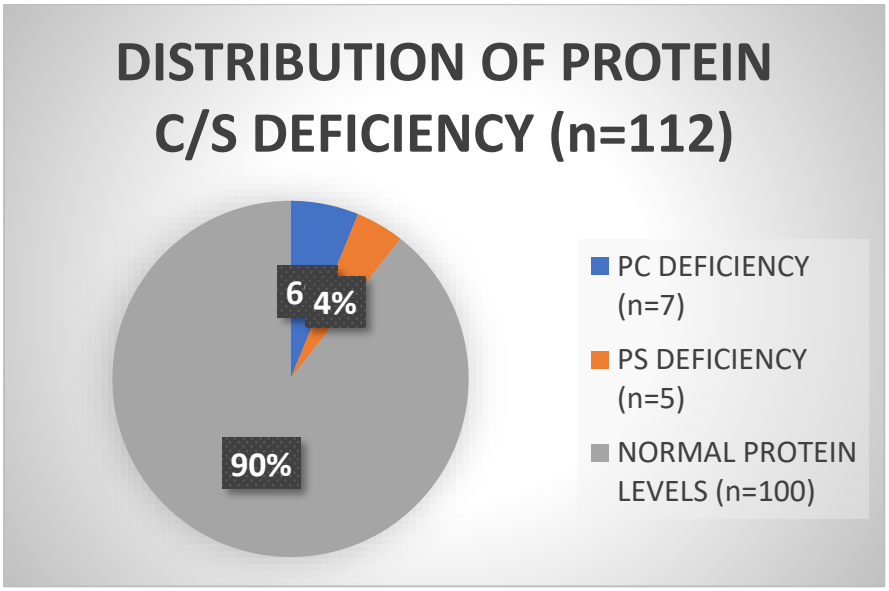
Table 4: Distribution of APTT among study population (n=112)

APTT	FREQUENCY	PERCENTAGE(%)
NORMAL	109	97.3
ELEVATED	3	2.7
TOTAL	112	100

DISTRIBUTION OF PROTEIN C, S DEFICIENCY AMONG STUDY POPULATION.

Deficiency of Protein C was found in 6.2% (7) of the cases and Protein S deficiency was found in only 4.4% of cases (5 cases). Out of these, 2 cases were found to have both Protein C and Protein S combined deficiency.

Figure 4: Distribution of protein C, S deficiency among study population. (n=112)



DISTRIBUTION OF CLINICAL OUTCOME AMONG STUDY POPULATION.

During the time of admission, after the necessary treatment, all cases were relieved off their symptoms before being discharged. Two of them were diagnosed to have complications of severe pump failure ,one with left ventricular wall aneurysm and thirty four cases (30.4%) with LV dysfunction of varying severity detected following Echocardiography. However after necessary management, all of them were asymptomatic at the time of discharge. None of the cases studied developed arrhythmia. Three cases (2.7%) had episodes of recurrent angina. All of them, however became asymptomatic within the discharge period. No mortality was reported among the cases studied. Three weeks follow-up period was uneventful for all the cases.

Figure 5: Distribution of clinical outcome among study population during the period of hospitalization. (n=112)

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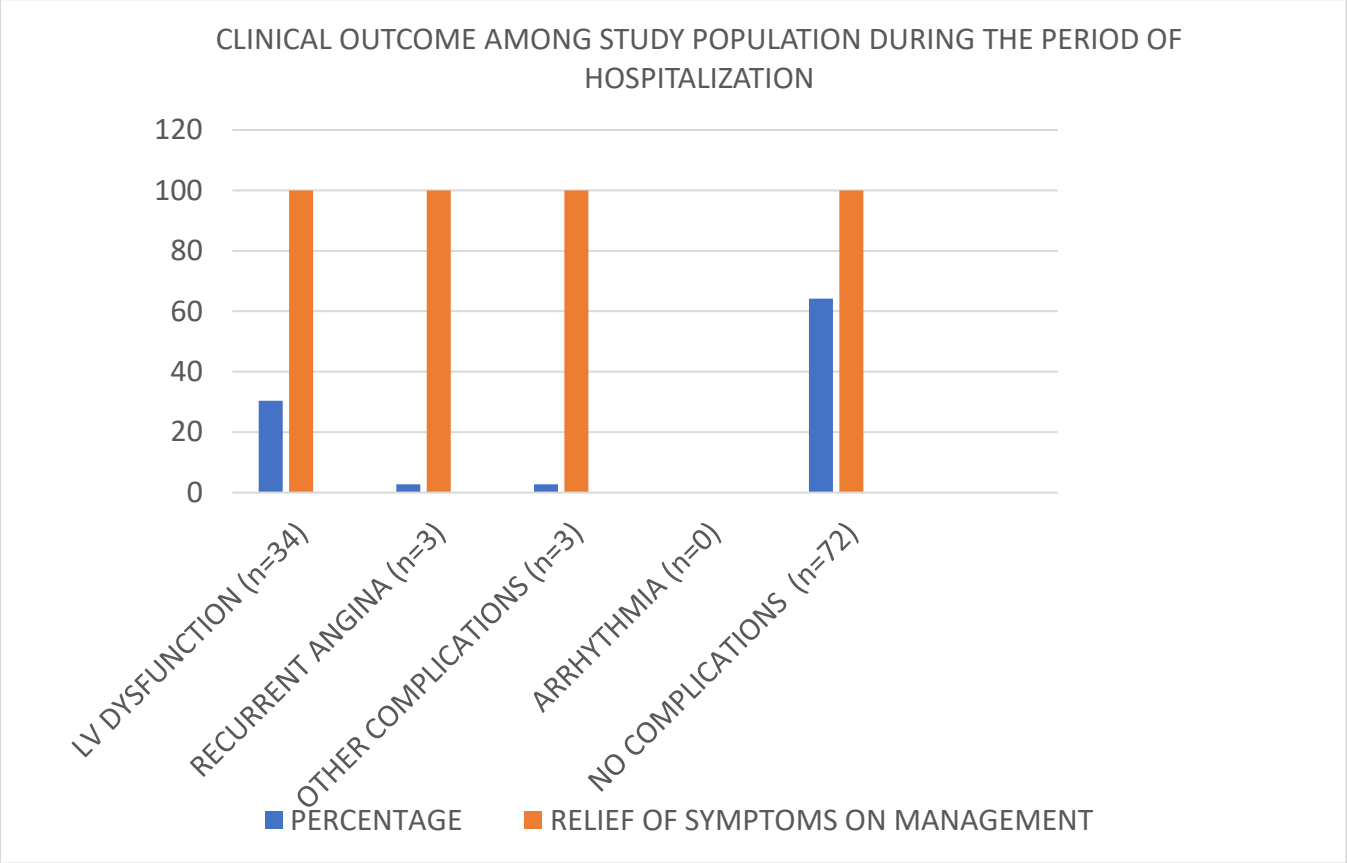

The follow-up period of 3 weeks was uneventful for all.

RISK FACTOR DISTRIBUTION AMONG PROTEIN C/S DEFICIENT POPULATION.

Among the study population detected to have either Protein C/S/ combined deficiency (12 cases), 33.3 % (4 cases) were found to be overweight, 41.6% (5 cases) were found to have hypertension, 58.3% cases with dyslipidemia (7 cases), and 8 % cases (1 case) were found to have diabetes mellitus.41.6% cases (5 cases) had history of smoking and none had a previous history of surgery.

Table 5: Distribution of risk factors among deficient population.(n=12)

RISK FACTORS	FREQUENCY	PERCENTAGE
OVERWEIGHT	4	33.3
HYPERTENSION	5	41.6
DYSLIPIDEMIA	7	58.3
DIABETES MELLITUS	1	8.3
SMOKING	5	41.6

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PREVIOUS SURGERY	0	0

DISTRIBUTION OF CLINICAL OUTCOME AMONG PROTEIN C/S DEFICIENT POPULATION.

All cases who were detected with Protein C/S deficiency were relieved off their symptoms during the admission, none of them developed arrythmia, recurrent angina or mortality. The follow-up period was also uneventful.

Among the 12 deficient cases, 6 cases developed LV dysfunction which was detected following ECHO but were relieved off their symptoms after prompt treatment before being discharged from the hospital.

Among the cases who developed recurrent angina and complications of severe pump failure and LV aneurysm, none had protein C/S deficiency.

Table 6: Distribution of clinical outcome among Protein C/S deficient population.(n=12)

COMPLICATIONS	**FREQUENCY (%)**	**CLINICAL OUTCOME**	**FREQUENCY (%)**
LV DYSFUNCTION	6(50)	RELIEF OF SYMPTOMS	**6(100)**
ARRYTHMIA	0	-	-
RECURRENT ANGINA	0	-	-
MORTALITY	0	-	-
OTHER COMPLICATIONS	0	-	-
NO COMPLICATIONS	6(50)	RELIEF OF SYMPTOMS	**6(100)**
TOTAL	12(100)	RELIEF OF SYMPTOMS	**12(100)**

DISCUSSION- The major objective of our study was to estimate the proportion of young MI patients with low Protein C/S profile. To diagnose conditions such as MI with non- obstructive coronaries(MINOCA), which remains an enigma, it is necessary to understand the underlying different potential mechanisms such as thrombophilic states, as the management of each of these remains different.(2)

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In a retrospective family cohort study by Bakhtawar K. Mahmoodi et al(18) to assess whether hereditary deficiency of Protein C or S confers an increased risk of arterial thromboembolic events at a young age, out of 552 subjects,308 had protein S(35%),protein C (39%), or antithrombin(26%) deficiency. (19)Compared with non deficient family members, subjects with protein S or protein C deficiency but not antithrombin deficiency have a higher risk for arterial thromboembolic events before 55 years of age that is indepenedent of prior venous thromboembolism . Another study by Neila Ben Romdhane et al(20) done to assess the association of the deficiency of protein C/S and antithrombin with the occurrence of MI in young subjects, it was found that protein C and protein S deficits were significantly related to MI (24% and 14% respectively). No antithrombin deficiency was detected in the groups . In a study on common thrombophilia markers and risk factors in young Indian patients with arterial thrombosis by Mahendra Narain Mishra et al(18), 38.8% tested positive for one or more thrombophilia markers. Overall, the risk factor profile was: smoking (33%), positive family history(15.3%), hyperlipidemia(7%),hypertension, diabetes mellitus and obesity(2.3%)each.(18) A study by Amit Segev et al(21) based on prevalence of thrombophilia among young patients with MI and few conventional risk factors, the overall risk factor profile was: smoking in 60%, hyperlipidemia in 42%, positive family history in 29%, hypertension in 18%, diabetes mellitus in 13%, and obesity in 8%. They found that among patients with a few traditional risk factors for atherosclerosis,there is very high likelihood of identifying atleast one thrombophilia marker(50%).(21) Heterozygous protein C deficiency manifests as seven fold increased risk for venous thromboembolism.(22)Rarely, it can also lead to arterial thrombosis in individuals with a positive family history and/or when triggered by smoking, ultimately resulting in premature MI. (3)

The role of Protein C/ S deficiency in causation of arterial thrombosis is less studied. Routinely only aspirin or antiplatelets with statins are given for MI patients for a long term course.The clinical significance of thrombophilia in arterial thrombosis is emphasized by the superiority of oral anticoagulants versus aspirin alone in secondary prevention of the cases of acute arterial ischemia.(23), (24) Since the development of the Xa inhibitors,(25),(26),(27)combined antiplatelet and anticoagulant therapy, particularly for secondary prevention, is now increasingly being used in patients with atherothrombosis and for those with worsening cardiovascular disease (CVD).

The total study participants included in our study were 112 cases of young MI with first episode of MI, who reported to cardiology department of Government medical college, Kottayam . The study period was 18 months from the date of IRB approval .

Among the 112 cases which were studied, deficiency of Protein C was detected in 7 cases (6.2%) and deficiency of Protein S was detected in 5 cases (4.4%). Two cases had combined Protein C and S deficiency. One case had an elevated prothrombin time, which was also found to have deficiency of Protein C. Also, three cases had an elevated APTT values along with deficient Protein S values. Since concomitant testing of PT and APTT along with protein C/S testing can help with the interpretation of results by (1) verifying the integrity of the specimen if the PT and APTT are normal (or appropriate for the patient's known medical condition) and (2) revealing possible alternative explanations for abnormal protein C results, if the PT and/or APTT results are prolonged,(28) hence these four cases were not taken into account in the deficient proportion of cases because it doesnot represent a pure protein C/S deficiency.

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The blood samples must be collected with precaution , since the diagnosis of PC deficiency is complicated for patients who are on oral anticoagulation therapy, and warfarin therapy affects protein C values by reducing the functional and, to a lesser extent, immunologic measurements of PC. In practice, individuals suspected of having PC deficiency should be investigated after discontinuing the oral anti-coagulation for atleast one week.(1)

Table 7: Mean age distribution among study population. Comparison with other studies.

Study	**Mean age. (years)**
Present study	39
M. N Mishra et al(20) (2013)	37.2
Neila Ben Romdhane et al(19) (2012)	43
Bakhtawar K. Mahmoodi et al(18) (2008)	46

The mean age of our study sample was 39 which is comparable with the previous similar study conducted by M. N Mishra et al in the 2013 year where the mean age group was 37.2.(18)

- Gender distribution

Table 8: Gender distribution of among study population. Comparison with other studies.

Study	**Male n(%)**	**Female n(%)**
Present study (n=112)	104 (93)	8 (7)
Bakhtawar K. Mahmoodi et al (2008) n=552	265 (48)	287 (52)
M. N Mishra et al year (2013) n=85	78 (92)	7 (8)
Neila Ben Romdhane et al ((2012) n=50	45(90)	5 (10)

Our ratio was comparable with the observation of M N Mishra et al in the year 2013 where the percentage of males were 92% and females were 8% (n= 18)

- Risk factors .

Table 9: Frequency of risk factors of DM, Dyslipidemia, Hypertension among study population. Comparison with other studies.

Study	**Diabetes mellitus n (%)**	**Dyslipidemia n (%)**	**Hypertension n (%)**
Present study (n=112)	19(17)	22(19.6)	42(38)

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Bakhtawar K. Mahmoodi et al (2008) (n=552)	18(3.3)	55(10)	70(12.7)
M. N Mishra et al (2013) (n=85)	2(2.3)	6(7)	2(2.3)
Neila Ben Romdhane et al (2012) (n=50)	13(26)	17(34)	6(12)

- In our study, hypertension was the predominant risk factor (38%) associated with myocardial infarction in the younger age group, followed by dyslipidemia (19.6%) and diabetes mellitus (17%). Study by Mahmoodi et al (19) in the year 2008, had reported hypertension as the predominant risk factor(12.7%) followed by dyslipidemia(10%).
- Smoking and obesity.

Table 10: Frequency of risk factors of obesity and smoking among study population. Comparison with other study.

Study	**Obesity n(%)**	**Smoking n(%)**
Present Study (n=112)	9(8)	17(15)
M. N Mishra et al (2013) (n= 85)	2(2.3)	28(33)

- In our study, 8% cases were categorized as obese and 15 % cases had a history of chronic smoking. However the study by M.N Mishra had only 2.3% cases with obesity and a higher proportion of cases were chronic smokers (33%).(18)
- Screening tests.

Prothrombin time(PT) and activated partial thromboplastin time(APTT) constitutes the major screening tests. The prolongation of prothrombin time can be brought about by deficiency of factors VII, X, V, II (prothrombin), and fibrinogen or the presence of an inhibitor.(29) Prothrombin time prolongation is also observed with proteins induced by vitamin K absence or antagonists or antagonism. APTT is an important screening test for the laboratory evaluation of patients with inherited or acquired deficiencies of proteins in the intrinsic pathway, Prolongation of APTT can also result from deficiency of FXII, PK, or HK.(1)

Mean values of our PT and APTT was 13.7 and 34.07 respectively which were within the normal reference range of our laboratory values. However, each laboratory has their own reference values for the coagulation screening tests.

Table 11: Mean values of PT and APTT . Comparison with other study.

Study	PT	APTT
Present study (n=112)	13.7	34.07

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M. N Mishra et al. (2013) (n= 85)	12.1	29

Cases with deficient Protein C/S with prolonged PT and APTT values were not taken into account in the final statistics, since they donot represent pure protein deficiency

- Proportion of Protein C and S deficiency.

Out of 112 cases studied, 6.2% (7 cases) were detected to have protein C deficiency and 4.4 % (5 cases) were found to have protein S deficiency, out of which 2 cases had a combined protein C and S deficiency. These values were comparable with the study by M. N Mishra et al(18) where 4.7% cases were detected with protein C deficiency and 9.4% cases with protein S deficiency. Study by M. N Mishra(18) et al and Neila Ben Romdhane(20) et al showed increased proportion of protein S deficiency when compared to protein C deficiency in young MI. However, study by Mahmoodi(19) et al showed increased percentage of protein C deficiency (39%) when compared to protein S deficiency (35%) in young MI.

Table 12: Frequency of Protein C and Protein S deficiency among study population. Comparison with other studies

Study	**Protein C deficiency n(%)**	**Protein S deficiency n(%)**
Present study (n=112)	7(6.2)	5(4.4)
Bakhtawar K. Mahmoodi et al (2008) (n=552)	215(39)	195(35)
M. N Mishra et al (2013) (n=85)	4(4.7)	8(9.4)
Neila Ben Romdhane et al (2012) (n=50)	7(14)	12(24)

- Development of complication.

Among the total 112 samples, 34 cases (30%) were detected to have LV dysfunction on ECHO. Three cases had a history of recurrent angina, two developed severe pump failure and one developed LV aneurysm.Out of the total 12 protein C/S deficient cases, 6 cases (50%) were detected to have LV dysfunction on ECHO.

Limitation

1,Limited sample size.

2.In all cases, details of angiography couldnot be obtained**.**

3.Many confounding factors involved.

4.Study cannot strictly distinguish cases having both inherited and acquired causes of thrombophilia.

Conclusion- The proportion of young MI with deficiency of Protein C and Protein S were found to be 6.2% and 4.4% respectively. These individuals are hence at a risk for recurrent thrombosis, and even at risk for

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arterial thrombosis elsewhere in the body.The risk factors of systemic hypertension, dyslipidemia, smoking, diabetes mellitus were seen only in < 40% cases.

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