Journal of Cardiovascular Disease Research

Journal of Cardiovascular Disease Research, 12 (1)
ISSN: 0975-3583, 0976-2833
DOI: 10.31838/jcdr.2021.12.01.22

ORIGINAL ARTICLE

Hematological Indices and Clinical Factors Predicting the Coronary Slow Flow Phenomenon in Coronary Angiography

Bhupinder Singh[1]*, Ankita Soni[2], Abhishek Goyal[1], Gurbhej Singh[1], Shibba Takkar Chhabra[1], Rohit Tandon[1], Naved Aslam[1], Bishav Mohan[1], Gurpreet Singh Wander[1]

[1]Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana, Punjab, India
[2]Department of Pathology, Dayanand Medical College and Hospital, Ludhiana, Punjab, India.

***Corresponding author:** Dr. Bhupinder Singh,Dayanand Medical College and Hospital, Udham Singh Nagar, Ludhiana, 141001, India. Email: dr_bhupinders@yahoo.in

Received: 30 January 2021; Accepted: 23 March 2021; Published: 28 April 2021

Abstract

Background: Coronary slowflow phenomenon (CSFP) is an enigmatic entity. Its multifactorial pathophysiology is less well understood.

Objective: To evaluate clinical and hematological parameters predicting the CSFP.

Methods: We accessed the hospital records of the patients undergoing coronary angiography from May 2019–December 2019. The patients with CSFP were compared with the patients having normal epicardial coronary arteries (NECA).

Results: The prevalence of CSFP was 2.9% in this study. CSFP patients had male dominance (72.3%). Body mass index (BMI), and hematological parameters such as hemoglobin, neutrophil–lymphocyte ratio, hematocrit, platelet count, mean platelet volume, and plateletcrit (PCT) were significantly higher in CSFP group compared with that of NECA group. On multivariate logistic regression analysis, high PCT [odds ratio:15.8; 95% CI(3.5–70.1), $p < 0.001$], high BMI [odds ratio:1.6; 95% CI(1.2–2.1), p=0.001], and male gender [odds ratio:5.9; 95% CI(1.3–26.8), $p < 0.023$] were found to be the independent predictors of CSFP. PCT showed strong positive correlation ($r = 0.8$, $p < 0.001$) with the mean thrombolysis in myocardial infarction (TIMI) frame count. Receiver operating curve analysis revealed a cut-off point of 0.24 for PCT with a sensitivity of 94.0% and a specificity of 91.0% ($p < 0.001$, AUC = 0.959) and a cut-off value of 28.9 Kg/m^2 for BMI had a 73% sensitivity and 78% specificity for predicting the CSFP ($p < 0.001$, AUC = 0.816).

Conclusion: Of all hematological indices, only PCT was strongly correlating and it was found to be the robust predictor of CSFP. Future studies evaluating its role in CSF pathophysiology are warranted.

Keywords: coronary angiography; hematology; coronary slow flow; predictors; plateletcrit

Introduction

The coronary slowflow phenomenon (CSFP) is described as the angiographic delay in the opacification of the pre-defined distal endpoints in the studied coronary artery without any coronary abnormalities or structural heart diseases. This delayed opacification is quantified as Thrombolysis in myocardial infarction frame counts (TFC) or corrected TFC (cTFC). The proposed mechanisms for CSFP are multifactorial such that it includes coronary microvascular disease, hemorheological abnormalities,and more recently the biochemical derangements.[1–5] Various hemorheological abnormalities mentioned in the literature include high mean platelet volume, increased viscosity of blood

or increased aggregability of erythrocytes, increased leukocyte count, and high plateletcrit (PCT).[3,4,6] The results of various trials are not consistent.

Our study aimed to investigate the clinico-demographic profile and predictors of CSFP among patients undergoing coronary angiographic in a tertiary care center.

Materials and Methods

We conducted a retrospective study in a high volume tertiary care center. The study was approved by the hospital ethics committee. Between May 2019 and December 2019, a total of 2853 patients had undergone coronary angiography for various indications. The patients' data were gathered in two stages. During Stage 1, records of 2853 patients were screened from the hospital database. The clinical, demographic, hematological, biochemistry, and other laboratory parameters of all patients were collected. Other investigations like electrocardiogram, echocardiogram, treadmill test, stress echocardiogram, and coronary angiography (non-digital) were also obtained from the records. The patients meeting any of the following criteria were excluded from the study group; that included (i) age <18 years, (ii) coronary obstruction of ≥40% in any of the epicardial vessel, (iii) hematological or oncological disorders, (iv) left ventricular ejection fraction (LVEF) ≤ 50%, (v) left ventricular hypertrophy (LVH), (vi) significant valvular heart disease or post-cardiac valve surgery, and (vii) insufficient data. Based on the criteria mentioned above, a total of 182 patients were identified. During Stage 2, the coronary angiography of all these patients was assessed digitally (on computer) by two independent cardiologists. Further, 31 patients having coronary aneurysm or ectasia on angiography were excluded from the study group. Based on the criteria laid by Gibson et al.,[7] 83 patients had CSFP (CSFP group), and 68 patients had normal epicardial coronary arteries (NECA group). The flow chart of patient enrolmentis shown in Figure 1.

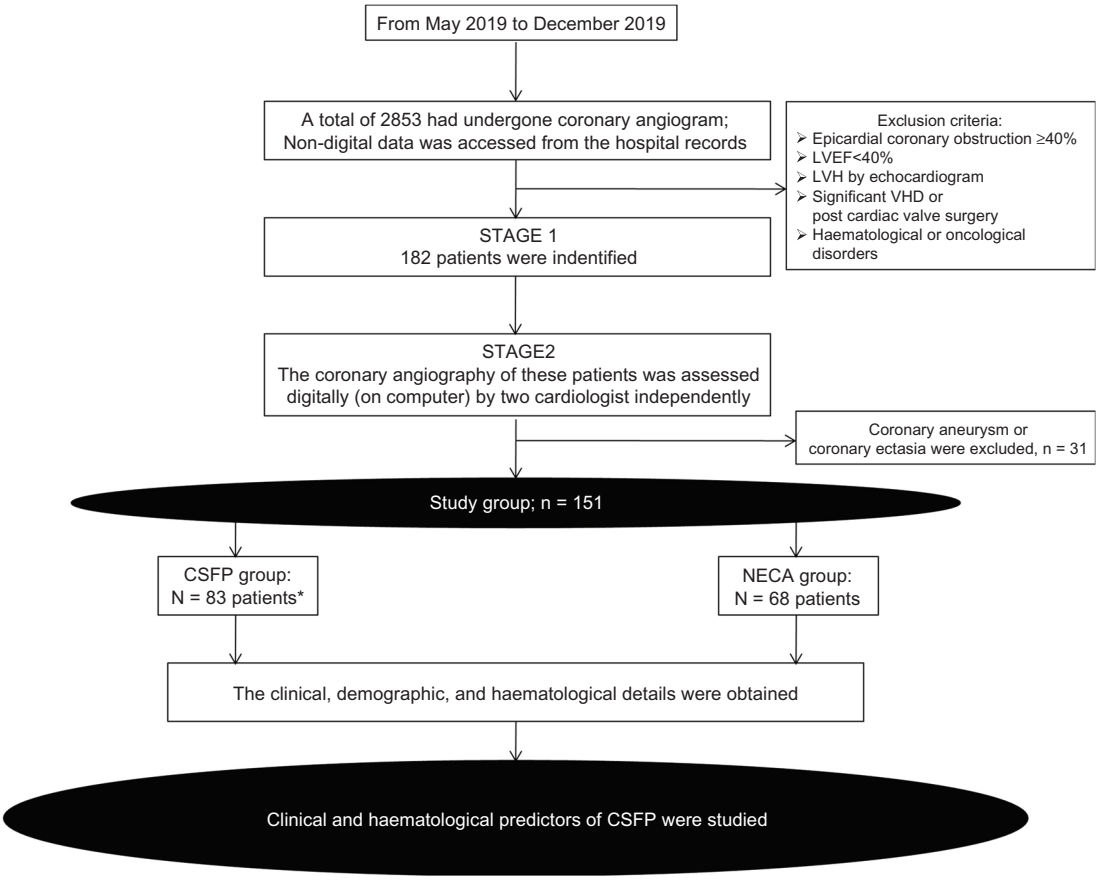

Figure 1 Algorithm ofthe study design. VHD: valvular heart disease, LVEF: left ventricular ejection fraction, LVH: left ventricular hypertrophy, CSFP: coronary slow flow phenomenon, NECA: normal epicardial coronary artery

Definitions

Diabetes mellitus was diagnosed if the patients were either taking oral hypoglycemic agents/insulin or having fasting glucose levels ≥126 mg/dl or post-prandial glucose levels ≥200 mg/dl.[8] Hypertension was defined if the patient was either taking antihypertensive therapy or having sustained diastolic blood pressure (BP) ≥90 mm of Hg or systolic BP ≥140 mm of Hg.[9] Current smoking was defined if the patient had smoked in the last 6 months. The height (in meters) and body weight (in kilograms) of each patient was obtained for calculating the body mass index (BMI) in Kg/m^2. Cockcroft–Gault equation was used to calculate creatinine clearance. Acute coronary syndromes and chronic stable angina were defined as per the guidelines.[10,11] LVH was defined as per the echocardiography criterion.[12] The coronary ectasia or aneurysm was defined as the dilatation of a coronary segment to a diameter of ≥1.5 times that of the adjacent normal coronary segment.[13]

Coronary angiogram

Coronary angiography was done using the Phillips machine (Azurion 7 C20, Philips, Netherland). It was done through a radial or femoral artery route using the Tiger or Judkin's catheter, respectively. The angiographic acquisitions were done at 15 frames per sec (fps). During the second stage, all the angiograms (digitally) were interpreted by a team of two experienced cardiologists as described above. Thrombolysis in myocardial infarction (TIMI) frame counts (TFC) was calculated as per the criteria suggested by Gibson et al.[7] As the acquired frame rate was 15 fps, thereby calculated TFC was multiplied by two to get values at 30 fps. For the left anterior descending (LAD) artery, the cTFC was calculated by dividing the derived TFC with 1.7. A cTFC of >27 (when calculated at a frame rate of 30fps) was taken as the cut off to define the coronary slow flow phenomenon.

Transthoracic echocardiogram

Transthoracic echocardiogram (Affinity 70, Philips, Netherland) was done using a phased arrow transducer of 2.8 MHz frequency. Modified Simpson's method was utilized to compute LVEF. LVH was defined if the LV mass index was ≥125 g/m^2 for males, and ≥110 g/m^2 for females.

Laboratory parameters

Complete hemogram was done using Beckman's coulter DxH 900 analyzer (Miami, FL, USA). Other parameters like fasting plasma glucose (in mg/dl), serum creatinine (in mg/dl), aspartate transaminases (in IU/L), alanine transaminases (in IU/L), serum sodium (in mEq/L), and serum potassium (in mEq/L) were calculated.

Statistical analysis

SPSS statistics 16.0 for windows (Chicago, USA) was used for statistical analysis of data. The normality of the given data was checked with the Kolmogorov–Smirnov test. Continuous data were represented as mean ± standard deviation (SD) or median with an interquartile range if it was distributed normally or skewed respectively. The categorical data were represented as percentages. On univariate analysis, continuous data were compared with the help of either Student's t-test (for normally distribution) or Mann–Whitney U test (for skewed distribution). Categorical data were compared using either the chi-square test or Fisher's exact test (if the cell size is less than five). The two-sided values were taken as the probability values. The p-value of <0.05 was considered statistically significant for the difference between comparison variables. Multicollinearity in the regression model was identified by using the variance inflation factor. The variables found significant on the univariate analysis were further analyzed by multivariate logistic regression analysis (enter method) to determine the independent predictors of CSFP. Receiver operator curve (ROC) analysis was used to derive the cut-off points for the variables found to be significant on multivariate logistic regression analysis. The correlation between two continuous parameters was calculated by the Spearman correlation coefficient (r-value). The strength of correlation was assessed as strong, modest, and weak for 'r' values of >0.7, 0.3–0.7, and <0.3 respectively.

Results

Of all the patients undergoing coronary angiography from January 2019to August 2019, 2.9% (n = 83) of the patients had CSFP.

Clinical parameters

The mean (SD) age of the CSFP group was 53.5 years (10.6) and was comparable to the NECA group. Compared with the NECA group, CSFP group was dominated by male gender (72.3% vs 26.5%; p = <0.0001). The patients in the CSFP group were more obese compared withthose in the NECA group. Other clinical parameters like diabetes mellitus and hypertension were comparable. The clinical and demographic profile of both groups is described in Table 1.

The clinical indication for undergoing coronary angiogram was chronic stable angina in two-third (67.5%) of the patientsand ACS in the rest of the patients in the CSFP group, and these were statistically not different from that of the NECA group. Inthe CSFP group, all epicardial vessels had an equal frequency of involvement with no preponderance of one over the other, and 69.9% (n=58) of the patients had slow flow in >1 epicardial vessel. The frequency of coronary involvement in CSFP is shown in Figure 2. Median TFC was 33 (IQR of 28 to 37) in the CSFP group. The coronary angiographic profile of both groups is described in Table 2.

Hematological indices

The hematological parameters such as the hemoglobin level (median 14.1 mg/dL; IQR 12.7–14.9 vs median 13 mg/dL; IQR 11.9–14.1, p = 0.001), hematocrit level (median 42.9%; IQR 38.9–45.2 vs median 39.1%; IQR 36.9–41.7, p = 0.042) and neutrophil counts (median 60; IQR 55.4–66.9 vs median 58.5; IQR 50.2–67.9, p = 0.042) was significantly higher in CSFP group compared withthat of the NECA group. The platelet count (median $287x10^3$ cells/μL; IQR 255–310 vs median $209x10^3$cells/ μL; IQR 191.5–239.3, p > 0.001) and PCT (median 0.29%; IQR 0.27–0.32 vs median 0.21%; IQR 0.18–0.23, p = 0.001) both were also significantly higher in CSFP group compared with that of the NECA group. Other hematological parameters like lymphocyte and monocyte counts were significantly lower in CSFP group compared with that of the NECA group while eosinophil counts were significantly higher in CSFP group. All hematological parameters in both groups have been described in Table 3. Both PCT (r = 0.8, p < 0.001) and BMI (r = 0.5, p < 0.001) was positively correlating with mean mTFC (Figure 3). ROC analysis (Figure 4) revealed a cut-off point of 0.24 for PCT with a 94.0% sensitivity and a 91.0% specificity (confidence interval: 0.92–0.99, p < 0.001, area under curve = 0.959) and a cut-off value of 28.9 Kg/m^2 for BMI had a 73.0% sensitivity and 78.0% specificity for predicting the CSFP (confidence interval: 0.75–0.88, p <0.001, area under curve= 0.816).

On multivariate logistic regression analysis the male gender, higher BMI, and high PCT were found to be the independent predictors of CSFP (Table 4).

Discussion

CSFP is an entity observed on coronary angiography with the varying incidence of 2–7%.[1,14] In our study, the CSFP was observed with a frequency

Table 1 Clinical and demographic parameters of both the study groups.

Clinical parameters		CSFP group N = 83	NECA group N = 68	p value
Age, mean (SD)		53.5 (10.6)	54.0 (11.1)	0.684
Male gender n (%)		60 (72.3)	18 (26.5)	<0.0001*
Diabetes mellitus n (%)		24 (28.9)	17 (25)	0.590
Hypertension n (%)		49 (59.0)	44 (64.7)	0.476
Smoking n (%)		2 (2.4)	0	—
BMI (in Kg/m^2)		32 (28.8–35.1)	27.9 (25.9–28.9)	<0.0001*
Creatinine clearance eGFR < 60 mL/min/1.73 m^2 n (%)		3 (3.6%)	0	—
Indication of coronary angiography	Chronic stable angina	56 (67.5%)	54 (79.4%)	0.1
	Acute coronary syndrome	27 (32.5%)	14 (20.6%)	

CSFP: coronary slow flow phenomenon, NECA: normal epicardial coronary artery, BMI: body mass index, GFR: glomerular filtration rate. Significant p-values are designated with asterisk (*).

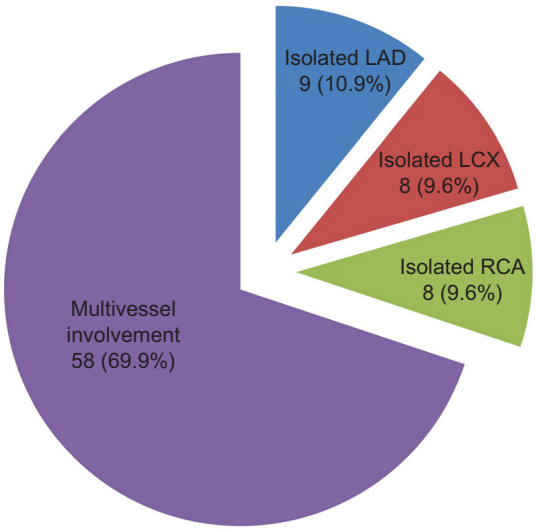

Figure 2 Diagram showing the pattern of coronary artery involvement for the coronary slow flow. LAD: Left anterior descending, LCX: left circumflex, RCA: right coronary artery.

of 2.9%. CSFP is not a benign entity as previously thought to be. CSFP carries a significant disease burden in the form of poor control of symptoms, the need for repeating coronary procedures, and even arrhythmic events.[15,17]

Several hypotheses had been proposed to understand the pathophysiology of CSFP (mentioned above), but it continued to be an enigmatic phenomenon. Various studies had found the correlation of CSFP with smoking, male gender, and metabolic syndrome.[18,19] In our study, the male gender, and high BMI were found to be independent predictors of CSFP.

Even though the CSFP had been connected with hemorheological abnormalities, but still the results of prior studies were variable. Akpinar et al. had proposed CSFP as a state of inflammation by demonstrating its relation with an increased number of neutrophils and total leukocyte count.[6] Our

Table 2 Angiographic profile of the study population.

Coronary indices		CSFP group n = 83	NECA group n = 68	p
Right dominance		66 (79.5%)	40 (58.8%)	0.006*
Corrected TIMI frame count	LAD	29.4 (24.1–41.2)	14.1 (12.9–15.3)	<0.0001*
	LCX	30 (26–40)	20 (19–22)	<0.0001*
	RCA	32 (24–44)	18 (16–20)	<0.0001*
TIMI frame count		33 (28.0–37.0)	17.5 (17–18.1)	<0.0001*
Mean heart rate		68 (60–72)	72 (66–81.5)	<0.0001*

CSFP: coronary slow flow phenomenon, NECA: normal epicardial coronary artery, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction. Significant p-values are designated with asterisk (*).

Table 3 Comparison of the hematological indices of both groups.

Hematological and biochemical parameters	CSFP group N = 83	NECA group N = 68	p
Hemoglobin (mg/dl)	14.0 (12.7–14.9)	13 (11.9–14.1)	0.001*
TLC ($\times 10^3$ cells/ µL)	8.4 (7.5–9.8)	8.8 (7.4–11)	0.223
Neutrophil count (%)	60 (55.4–66.9)	58.5 (50.2–67.9)	0.042*
Lymphocyte count (%)	27.7 (21.4–33)	30.4 (22.725–36.4)	0.010*
Neutrophil lymphocyte ratio	2.1 (1.7–3.1)	1.9 (1.5–2.8)	0.2*
Haematocrit (%)	42.9 (38.9–45.2)	39.1 (36.9–41.7)	<0.001*
RDW (%)	14.2 (13.8–15.1)	14.6 (13.6–15)	0.888
Platelet count ($\times 10^3$ cells/ µL)	287 (255–310)	209 (191.5–239.3)	<0.001*
MPV (fL)	10.7 (9.7–11.8)	9.8 (8.8–10.6)	<0.001*
Plateletcrit (%)	0.29 (0.27–0.32)	0.21 (0.18–0.23)	<0.001*
Sodium (milliEq/L)	138 (137–140)	139 (136.3–140.8)	0.516
Potassium (milliEq/L)	4.2 (4–4.53)	4.31 (4.18–4.40)	0.403

CSFP: coronary slow flow phenomenon, NECA: normal epicardial coronary artery, TLC: total leukocyte count, RDW: red cell distribution width, MPV: mean platelet volume. Significant p-values are designated with asterisk (*).

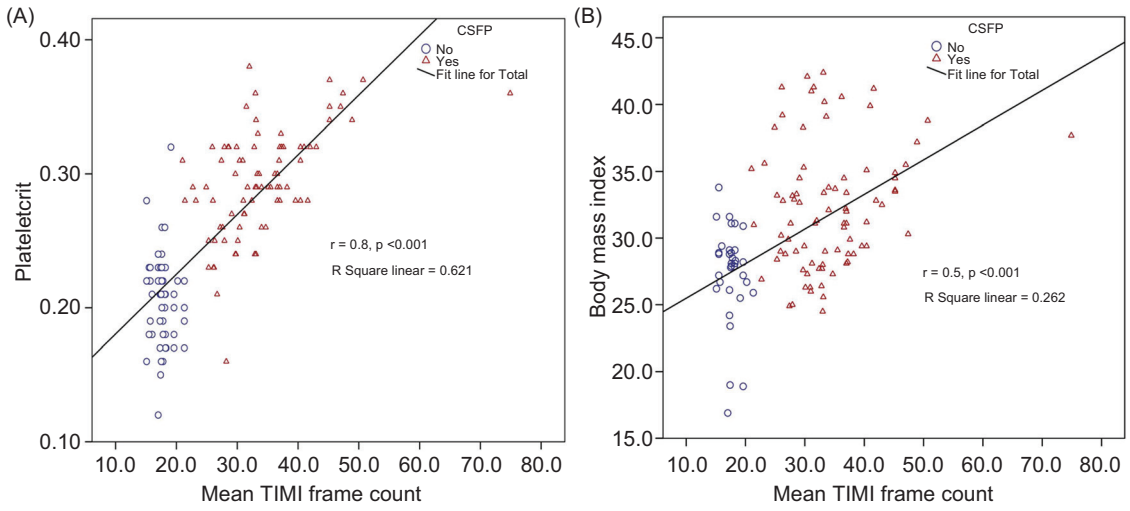

Figure 3 Scatter diagram showing correlation of CSFP with BMI (Panel A) and plateletcrit (Panel B). CSFP: coronary slow flow phenomenon, BMI: body mass index, TFC: Thrombolysis in myocardial infarction frame count.

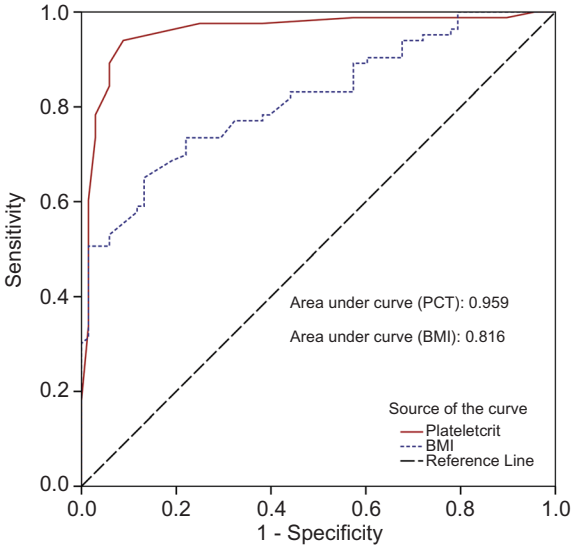

Figure 4 Receiver operator curve analysis for predicting the CSFP showing the cut-off value of 0.24 for PCT (94.0% sensitivity and 91.0% specificity), and 28.9 Kg/m^2 for BMI (73.0% sensitivity and 78.0% specificity). CSFP: coronary slow flow phenomenon, PCT: plateletcrit, BMI: body mass index

Table 4 Independent predictors of coronary slow flow phenomenon on logistic regression analysis.

Predictors	Odds ratio (95% Confidence Interval)	P
Plateletcrit	14.3 (3.1 to 62.3)	0.001*
Male gender	6.1(1.3 to 29.1)	0.022*
Body mass index	1.6 (1.2 to 2.1)	0.001*
Hemoglobin	0.8 (0.3 to 2.6)	0.736
Mean platelet volume	1.3 (0.8 to 2.2)	0.336
Hematocrit	0.9 (0.7 to 1.4)	0.978
Neutrophil lymphocyte ratio	1.4 (0.8 to 2.4)	0.221

Significant p-values are designated with an asterisk (*).

study too demonstrated high neutrophil counts among CSFP group on univariate analysis though it failed to show significance on multivariate analysis. A study by Ghaffari et al. had found higher hematocrit and red cell distribution width in patients with CSFP. Similarly, otherstudies had found a positive correlation between hematocrit and CSFP.[20–22] In a study by Bigli et al, it was found that despite high hematocrit the viscosity of plasma or blood was not high among CSFP patients.[22] The basic mechanism by which these hemorheological abnormalities had been thought to be contributing to the CSFP was by increasing the blood viscosity and increased erythrocyte aggregation. Our study did not demonstrate high hematocrit in patients with CSFP. The correlation of hemoglobin levels or hematocrit with CSFP is not consistent in the literature. Similar to our study, some studies did not demonstrate a significant correlation in this regard.[23,24]

Platelets are believed to play a key role in the inflammation, thrombosis initiation and its perpetuation, destabilization of atherosclerotic plaques in the coronaries, and so on. In our study, we found a strong positive correlation of PCT with the mTFC, and it was found to be the independent predictor of CSFP on multivariate analysis. Our findings were somewhat consistent with the previous studies where they had shown a positive correlation

between hematological parameters such as PCT, MPV, and platelet counts with CSFP.[7] Our study results further strengthen the role of hematological abnormalities especially PCT in CSFP.

Study Limitations

There are a few limitations to our study. First, the design of our study is cross-sectional and retrospective. Thereby it may not be truly representing the causal relationships. Secondly, a relatively small cohort of patients are studied in this study.

Conclusion

In conclusion, PCTis observed to be a strong and independent predictor of CSFP. This suggests that hemorheological factors play an important role in the multifactorial pathogenesis of CSFP. Other clinico-demographic parameters predicting CSFP were male gender and high BMI. A prospective, randomized study is warranted to further strengthen the data.

Conflict of interest

The authors declare no conflicts of interest.

Funding source

The authors received no specific funding for this work.

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