Evaluation of Serum Scube-1 Levels and Affecting Factors in Smokers

Sigara İçenlerde Serum Scube-1 Düzeyleri ve Etkileyen Faktörlerin Değerlendirilmesi

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ÖZ

Amaç: Trombosit aktivasyonunun bir göstergesi olan Serum signal peptide-CUB-EGF domain-containing protein-1 (SCUBE-1), kardiyovasküler hastalık riskini değerlendirmek için kullanılan bir biyokimyasal belirteçtir. Bu çalışma; sigara içenlerde SCUBE-1' in plazma düzeylerinin sağlıklı kontrollere göre değişimini değerlendirmeyi ve etkileyen faktörleri belirlemeyi amaçlamıştır.

Araçlar ve Yöntem: Bu çalışma; kontrol gruplu, deneysel ve tek merkezli bir çalışma olarak tasarlandı. Çalışmaya üçüncü basamak bir hastanenin Sigara Bırakma Kliniği'ne başvuran 18-65 yaş arası sigara içenler ile Aile Hekimliği Polikliniği'ne başvuran ve hiç sigara içmemiş sağlıklı gönüllülerden oluşan kontrol grubu dahil edildi. Tüm katılımcıların sosyodemografik verileri ve sigara içenlerin sigara içme öyküleri ile bağımlılık düzeyleri sorgulandı. Ekshale edilen karbon monoksit (CO) seviyeleri ölçüldü. Plazma SCUBE-1 seviyeleri venöz kandan alınan numunelerden çalışıldı ve karşılaştırıldı.

Bulgular: "Sigara içen" hasta grubu (n=44) ve "sigara içmeyen" kontrol grubu (n=38) olmak üzere toplam 82 kişi çalışmaya dahil edildi. Ortalama SCUBE-1 değeri sigara içenlerde 1.28±0.70 ng/ml, içmeyenlerde 1.54±1.09 ng/ml idi. SCUBE-1 açısından sigara içenler ve içmeyenler arasında istatistiksel olarak fark yoktu (p=0.500). SCUBE-1 düzeyleri ile ekshale CO düzeyi, sigara içme özellikleri ve bağımlılık düzeyleri arasında istatistiksel olarak anlamlı bir ilişki bulunmadı.

Sonuç: Plazma SCUBE-1 değeri sigara içenlerde anlamlı düzeylerde yüksek bulunmamakla birlikte kardiyovasküler hastalık riskinin ve tromboza yatkınlığın değerlendirilmesinde yararlı olup olmayacağı hususunun bu kişilerde hastalık gelişim sürecinin de inceleneceği daha ileri araştırmalar ile açıklığa kavuşturulabileceği düşünülmektedir.

Anahtar Kelimeler: fagerström; karbon monoksit; kardiyovasküler risk; scube-1; sigara içimi

ABSTRACT

Purpose: Serum signal peptide-CUB-EGF domain-containing protein-1 (SCUBE-1), an indicator of platelet activation, is a biochemical marker used to evaluate the risk for cardiovascular diseases. This study aimed to evaluate the alteration of plasma levels of SCUBE-1 in smokers compared to healthy controls and determine the affecting factors.

Materials and Methods: This study was designed as an experimental, single-centered study with a control group. The study included smokers aged 18-65 years who were admitted to the Smoking Cessation Clinic of a tertiary hospital and a control group consisting of healthy volunteers admitted to the Family Medicine Outpatient Clinic and had never smoked. Sociodemographic data of all participants and smoking histories and addiction levels of smokers were questioned. Exhaled carbon monoxide (CO) levels were measured. Plasma SCUBE-1 levels were studied and compared from samples obtained from venous blood.

Results: A total of 82 individuals, consisting of the "smoker" patient group (n=44) and the "non-smoker" control group (n=38), were included in the study. The mean SCUBE-1 value was 1.28±0.70 ng/ml in smokers, 1.54±1.09 ng/ml in non-smokers. There was no statistical difference between groups in terms of SCUBE-1 (p=0.500). There was no statistically significant correlation between SCUBE-1 levels and exhaled CO level, smoking characteristics and addiction levels.

Conclusion: Although the plasma SCUBE-1 value was not found to be significantly higher in smokers, it is thought that whether it will be useful in the evaluation of cardiovascular disease risk and thrombosis susceptibility can be clarified with further studies that will also examine the disease development process in these people.

Keywords: carbon monoxide; cardiovascular risk; fagerström; scube-1; smoking

INTRODUCTION

Smoking causes many severe diseases and deaths and is defined as the most critical public health problem by the World Health Organization.[1] It is one of the most important preventable risk factors for the development of atherosclerosis. The increase in coagulation tendency it causes paves the way for the occurrence of vascular pathologies.[2] Therefore, especially cardiovascular diseases (such as coronary artery disease, cerebrovascular disease, peripheral artery disease, deep vein thrombosis, and pulmonary embolism) have a high prevalence in smokers. Smoking is responsible for approximately 21% of deaths due to cardiovascular diseases, and it is known that the risk of mortality and morbidity increases in those with passive exposure to cigarette smoke.[3] Moreover, the increased risk of developing thrombosis and activation of the coagulation system with smoking accelerates cancer progression in smokers. Smoking is the most important cause of cancer in many organs.[4]

Vascular dysfunction induced by smoking is initiated by increased expression of adhesion molecules and endothelial dysfunction. Thus, measuring the levels of adhesion molecules in the plasma provides information about atherogenesis.[2] Signal Peptide-Cub-Epidermal growth factor domain-containing protein-1 (SCUBE-1) is a cell surface protein belonging to the SCUBE gene family, which consists of three members (SCUBE 1-3).[5,6] The SCUBE gene family is secreted from the gonads and central nervous system during embryogenesis.[7] SCUBE-1 is stored in alpha granules in inactive platelets. Under hypoxia and inflammatory conditions, it is released from vascular endothelial cells and platelets, following platelet activation by thrombin. It dissolves into small soluble fragments and joins the thrombus structure.[6,8,9]

Previous studies have revealed that SCUBE-1, a potential marker indicating platelet activation, is increased in acute ischemic events such as acute coronary syndrome, ischemic stroke, acute mesenteric ischemia, and pulmonary embolism (PE).[9-12] In addition, some studies indicated that it increases in some cancers (e.g., gastric, lung, breast, renal cell cancer).[13-16] It has also been found to be increased in some non-cancer diseases (e.g., gestational diabetes mellitus, diabetic retinopathy, thyroid diseases, hypertension, ovarian and testicular torsion).[17-23] To our knowledge, there is not yet a study in the literature evaluating SCUBE-1 levels in terms of smoking, which is one of the most critical risk factors for ischemic events, cancer, and many non-cancer diseases.

This study aimed to examine and compare SCUBE-1 levels in smokers and non-smokers and investigate the benefit of SCUBE-1 in evaluating the risk of cardiovascular diseases and thrombosis predisposition in smokers.

MATERIALS and METHODS

The study was designed as a prospective, experimental, with the control group, single-centered study. In order to carry out this study, permission was obtained from the Taksim Training and Research Hospital Clinical Research Ethics Committee. (Approval No:18; 22/01/2020). The study was conducted under the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Population

Participants were selected from current chronic smokers who were referred for the first time to the Smoking Cessation Clinic and healthy non-smokers referred to the Family Medicine Outpatient Clinic of a tertiary hospital for any reason from February to March 2020. Forty-four smokers and 38 non-smoker healthy volunteers, those who met the inclusion criteria, aged between 18-65 and agreed to participate, were included in the study.

According to the results of the G-power analysis made in line with the reference studies, when type 1 error is 5% (bidirectional), type 2 error is 5% (power 95%), the approximate effect size for SCUBE-1 among patients/controls is taken as 87%, the minimum required number of cases was found to be 74 in total, with at least 37 in each group.

Exclusion Criteria

Those aged <18 years and those >65 years, those with known cardiovascular and/or cerebrovascular disease, acute/chronic kidney failure, liver failure, peripheral artery

disease, malignancy, collagen tissue diseases, advanced stage chronic obstructive pulmonary disease, rheumatological disease, previous history of PE and/or venous thromboembolism, those who are pregnant and lactating, and those who use acetylsalicylic acid and oral anticoagulants were excluded.

Data Collection Tools

Patient Information Form

A patient information form was formulated, including the participants' sociodemographic characteristics (age, gender, marital status, educational level, working status), medical history, and anthropometric measurements like weight, height, and Body Mass Index (BMI, kg/m^2). The form also includes questions about smoking characteristics (amount of smoking in pieces/day and packs/year, total years of smoking, age when began smoking) and exhaled CO measurements for those who smoke.

Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND), developed by Karl Fagerström and the Turkish validity and reliability study conducted by Uysal et al. in 2004, was used to determine the degree of smokers' nicotine dependence. The scale consists of 6 questions. The dependence level was categorized according to the following FTND scores: 0–3 low; 4-6 moderate; 7-10 high.[24,25]

Exhaled CO Measurement

Exhaled carbon monoxide (CO) increases in smokers and is a biomarker that is frequently used in the diagnosis, treatment, and follow-up stages of nicotine dependence.[26] Exhaled CO measurements (in parts per million, ppm) were performed by authorized healthcare staff using piCO+Smokerlyzer (Bedford Scientific, Maidsytone, UK,2016) devices.

Measurement of SCUBE-1

To determine the SCUBE-1 level, the venous blood sample taken from the patient and control groups was placed in an anticoagulant tube and kept at room temperature for 2 hours, then centrifuged at 3000 rpm for 10 minutes at

+4C for separation of serum and plasma. The samples were placed in Eppendorf tubes and stored at -20 degrees until the measurement time. It was taken to +4ºC 24 hours before the measurement. SCUBE-1 levels were measured in ng/ml with the "enzyme-linked immunoabsorbent assay (ELISA)" method and with an ELISA reader (Organon Teknika Reader 230S), in which 450 nm absorbance values were measured with ELISA kits (Elabscience Biotechnology Co., Cat No: E-EL-H5405) per the manufacturer's measurement instructions. The minimum SCUBE 1 level was 0.38 ng/mL measurable, while the detection range was 0.63-40 ng/mL.

Statistical Analysis of Data

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. The conformity of the parameters to the normal distribution was evaluated with the Shapiro Wilks test. In addition to descriptive statistical methods (mean, standard deviation, frequency), the Oneway Anova test was used to compare the parameters with normal distribution between groups to compare quantitative data, and the Tukey HDS test determined the group that caused the difference. The Kruskal Wallis test compared the parameters that did not show normal distribution, and the Dunn's test was used to determine the group that caused the difference. The student's t-test was used for the comparison of normally distributed parameters between two groups, and the Mann Whitney U test compared two groups of parameters that did not show normal distribution. Chi-square test, Fisher Freeman Halton test, and Continuity (Yates) Correction were used to compare qualitative data. Pearson correlation analysis analyzed the relationships between parameters conforming to the normal distribution, and Spearman's rho correlation analysis was used to analyze the relationships between the parameters not conforming to the normal distribution. The statistical significance was evaluated at the $p < 0.05$ level.

RESULTS

The study was performed with a total of 82 cases (mean 38.78±10.24 years), 45(54.9%) females, and 37(45.1%) males, ranging in age from 19 to 62. The participants were evaluated under two groups as the "smoker" (n=44) patient

group and the "non-smoker" (n=38) control group. Twenty-two (50%) of the smokers were male and 22(50%) female compared to 15(39.5%) males and 23(60.5%) females in the control group. There was no statistically significant difference between the groups regarding age, gender, educational status, and marital status distribution (p=0.553; p=0.339; p=0.104; p=0.905, respectively). Sociodemographic characteristics and anthropometric measurements of both groups are summarized in Table 1.

Table 1. Sociodemographic characteristics and anthropometric measurements of the participants.

Variables		Smokers Mean±SD	Range	Non-smokers Mean±SD	Range	Total Mean±SD	Range	p
Age (years)		39.41±10.66	19-62	38.05±9.82	21-59	38.78±10.24	19-62	[1]0.553
Height (m)		1.68±0.08	1.5-1.9	1.68±0.1	1.6-1.9	1.68±0.09	1.5-1.9	[1]0.769
Weight (kg)		73±12.01	48-96	74.76±15.46	51-109	73.82±13.66	48-109	[1]0.563
BMI (kg/m^2)		25.73±4.04	18.3-35.2	26.31±3.72	20.2-36.7	26±3.88	18.3-36.7	[1]0.507
		Smokers n (%)		Non-smokers n (%)		Total n (%)		p
Gender	Female	22 (50%)		23 (60.5%)		45 (54.9%)		[2]0.339
	Male	22 (50%)		15 (39.5%)		37 (45.1%)		
Working Status	Yes	23 (52.3%)		28 (73.7%)		51 (62.2%)		[3]0.077
	No	21 (47.7%)		10 (26.3%)		31 (37.8%)		
Educational status	Primary school	17 (38.6%)		10 (26.3%)		27 (32.9%)		[2]0.104
	Middle school	7 (15.9%)		6 (15.8%)		13 (15.9%)		
	High school	12 (27.3%)		6 (15.8%)		18 (22%)		
	University	8 (18.2%)		16 (42.1%)		24 (29.3%)		
Marrital status	Married	34 (77.3%)		28 (73.7%)		62 (75.6%)		[2]0.905
	Single	10 (22.7%)		10 (26.3%)		20 (24.4%)		
Passive smoking	No	16 (36.4%)		26 (%68.4)		42 (%51.2)		[2]0.007*
	Yes	28 (63.6%)		12 (%31.6)		40 (%48.8)		
Classification according to BMI	Weak	1 (2.3%)		0 (0%)		1 (1.2%)		[4]0.345
	Normal	23 (52.3%)		14 (36. 8%)		37 (45.1%)		
	Overweight	15 (34.1%)		18 (47.4%)		33 (40.3%)		
	Obesity	5 (11.4%)		6 (15.8%)		11 (13.4%)		

Data are presented as number (%) of participants, mean±standard deviation, median (min:max)
1Student t test   2 Chi-square test   3Continuity (yates) correction   4Fisher Freeman Halton Test   *p<0.05   BMI: Body Mass Index

The mean amount of cigarette consumption of smokers was 27.25±12.39 pieces/day (min:5-max:60), 24.82±13.78 pack-years (min:5-max:55). The total duration of smoking ranged from 5 to 42 years, with a mean of 21.36±10.36 years, and it was observed that 29.5% of them smoked 31 or more cigarettes per day. The mean age of starting smoking was 17.98±7.5 (min:10-max:56). The mean CO value measured in the expiration was 14.52±5.94 ppm (min:4-max:32). The mean score obtained from the FTND applied to measure the degree of addiction to smokers was 6.95±2.31 (min:1-max:10). According to FTND, the level of addiction was mild in 6.8% of smokers, moderate in 43.2%, and high in 50%. Smoking characteristics of smokers are shown in Table 2 (Table 2).

While the SCUBE-1 values of both groups are presented in Table-3, the distribution of SCUBE-1 values according to the characteristics of the participants is also evaluated (Table-3). While the mean SCUBE-1 value was 1.28±0.70 ng/ml in smokers, it was 1.54±1.09 ng/ml in non-smokers. There was no statistically significant difference in terms of SCUBE-1 scores between the smoking and non-smoking groups (p=0.500). SCUBE-1 values of smokers who had additional passive exposure were higher than those who were not passive smokers (p=0.037) (Table 3).

As shown in Table 4, there was no statistically significant correlation between SCUBE-1 levels and exhaled CO level, cigarette consumption amounts (in pcs/day and pack/year), total smoking time, age at onset of smoking, and Fagerström scores in smokers (p=0.910; p=0.744; p=0.802; p=0.948; p=0.560; p=0.769, respectively) (Table 4).

Table 2. Data on smoking characteristics of smokers. (n=44)

Variables			Min-Max	Mean±SD	Median
Amount of smoking					
	Pieces/day		5-60	27.25±12.39	27.5
	Packs/year		5-55	24.82±13.78	23
Total years of smoking			5-42	21.36±10.36	20
Age when began smoking			10-56	17.98±7.5	17
Exhaled CO level (ppm)			4-32	14.52±5.94	13.5
FTND score			1-10	6.95±2.31	7.5
				n	%
Amount of smoking					
	Pieces/day	≤ 10		5	11.4
		11-20		16	36.4
		21-30		10	22.7
		≥ 31		13	29.5
	Packs/year	<20		21	47.7
		>21		23	52.3
Level of dependence according to FTND	Low			3	6.8
	Moderate			19	43.2
	High			22	50.0
Alcohol use	Yes			11	25.0
	No			33	75.0

Data are presented as number (%) of participants, mean±standard deviation, median (min:max)
CO: Carbonmonoxide. FTND: Fagerström Test for Nicotine Dependence.
Ppm: parts per million. SD: standard deviation.

Table 3. Distribution of SCUBE-1 values according to the characteristics of the participants

Variables		SCUBE-1 levels	
		Smokers	**Non smokers**
	Min-max	0.37-3.49	0.09-5.06
	Mean±SD	1.28±0.70 (1.11)	1.54±1.09 (1.26)
	p^1	0.500	
		Mean±SD (median)	
Gender	Female	1.29±0.86 (1)	1.66±1.15 (1.4)
	Male	1.27±0.52 (1.3)	1.36±1 (1)
	p^1	0.496	0.437
Working status	Yes	1.36±0.53 (1.4)	1.67±1.14 (1.3)
	No	1.2±0.86 (1)	1.2±0.91 (0.7)
	p^1	0.086	0.097
Educational status	Primary school	1.19±0.44 (1.2)	1.38±0.96 (1.3)
	Middle school	1.88±1.11 (1.4)	0.79±0.35 (0.7)
	High school	0.98±0.39 (1.1)	2.3±1.61 (1.9)
	University	1.41±0.86 (1)	1.64±1 (1.4)
	p^2	0.271	0.084
Marrital status	Married	13±0.61 (1.3)	1.59±1.12 (1.3)
	Single	1.21±0.99 (0.9)	1.4±1.04 (1)
	p^1	0.213	0.466
Passive smoking	No	1.01±0.5 (1)	1.59±1.05 (1.3)
	Yes	1.44±0.76 (1.3)	1.44±1.22 (1.2)
	p^1	0.037*	0.490
Classification according to BMI	Normal weight	1.34±0.83 (1.2)	1.43±0.91 (1.2)
	Overweight	1.15±0.43 (1.3)	1.82±1.25 (1.3)
	Obesity	1.19±0.72 (1.1)	0.98±0.8 (0.7)
	p^2	0.949	0.238

Data are presented as number (%) of participants, mean±standard deviation and median (min:max).
[1]Mann Whitney U Test   [2]Kruskal Wallis Test   *p<0.05
Note: Those who are underweight according to BMI were excluded from the analysis because n=1.
BMI: Body Mass Index. SD: standard deviation.

Table 4. Evaluation of the relationship between smoking characteristics and SCUBE-1 values in smokers

Variables			SCUBE-1
Exhaled CO[+]		r	-0.018
		p	0.910
Pieces/day [+]		r	0.051
		p	0.744
Total years of smoking[+]		r	-0.010
		p	0.948
Packs/year [+]		r	-0.039
		p	0.802
Age when began smoking [+]		r	-0.090
		p	0.560
FTND score[+]		r	0.046
		p	0.769
			SCUBE-1 levels
			Mean±SD (median)
Alcohol use	Yes		1.22±0.58 (1.2)
	No		13±0.74 (1.1)
		p[1]	0.968
Amount of smoking	≤ 10		1.62±0.6 (1.7)
Pieces/day	11-20		1.23±0.78 (1)
	21-30		0.93±0.34 (0.9)
	≥ 31		1.48±0.78 (1.4)
		p[2]	0.076
Amount of smoking	<20		1.34±0.87 (1.1)
Packs/year	>21		1.23±0.52 (1.2)
		p[1]	0.879
Level of dependence according to	Low		1.43±0.97 (1.4)
FTND	Moderate		1.27±0.73 (1.1)
	High		1.27±0.68 (1.1)
		p[2]	0.892

Data are presented as mean±standard deviation. [1]Mann Whitney U Test   [2]Kruskal Wallis Test. *$p<0.05$.

Pearson Correlation Analysis   [+]Spearman Rho Correlation Analysis

CO: Carbon monoxide. FTND: Fagerström Test for Nicotine Dependence. SD: standard deviation.

DISCUSSION

SCUBE-1 is defined as a potential biomarker in pathologies associated with inflammation, atherosclerosis, and ischemia. In this study, in which the plasma SCUBE-1 level was compared in smokers and non-smokers, it was predicted that the level of SCUBE-1 would be increased in smokers compared to non-smokers, and this would be an indicator of increased risk of cardiovascular diseases and thrombosis in smokers. However, there was no statistically significant difference between these two groups regarding SCUBE-1 values.

SCUBE-1 levels have been shown to increase in acute ischemic events.[6,9-12,27] In the study performed with patients with acute coronary syndrome and acute ischemic stroke by Dai et al., it was found that SCUBE-1 can be detected within 6 hours after the onset of ischemic symptoms.[9] Also, Turkmen et al. found that serum SCUBE-1 levels were higher in the patients with PE than in the control group.[11] As a contribution to this study, Özyurt et al. also found that serum SCUBE-1 levels were higher in high-risk patients and patients with poor prognoses.[27]

In contrast to the data in the study of Dai et al., Günaydın et al. also investigated the benefit of SCUBE-1 levels in diagnosing acute ischemic stroke in their study, and they did not find a significant increase in the patient group.[28] Also, in the studies by Şahin et al. and Özkan et al., no diagnostic value of SCUBE-1 was found in determining the etiology in patients with chest pain and coronary syndrome.[29,30]

Smokers have a severe risk of ischemic events. Early recognition of the risks of smokers in terms of future cardiovascular events is vital for prognosis. However, in our study in which we investigated the relationship between

the SCUBE-1 values and smoking status, smoking characteristics, and exhaled CO levels, no negative or positive relationship was found between them. It was concluded that the reason why SCUBE-1 levels, which are elevated in acute vascular ischemic pathologies, did not increase significantly in smokers might be the development of smoking-related vascular pathologies in a chronic process. In future studies, in which smokers will be followed up for disease development, it is possible that SCUBE-1 will be high in smokers who develop the disease.

It was also reported significantly higher SCUBE-1 levels in patients with non-small cell lung cancer, gastric cancer, breast cancer, renal cell cancer than in healthy controls. In addition, it was concluded that SCUBE-1 could be used to identify those at high risk of thrombosis in patients with cancer.[13-16] In our study, we did not include those with a known cancer diagnosis or previous cancer history. However, no significant relationship was found between smoking, which is also known as the most crucial risk factor for cancer in many organs, and SCUBE-1 values. Also, any tumor markers and/or inflammation marker has not been investigated. In addition to monitoring the development of diseases, a contribution to the literature can be made by examining the correlation of SCUBE-1 with these markers.

SCUBE-1 has also been investigated as a marker and cardiovascular risk indicator in some non-cancer diseases (e.g., thyroid diseases, diabetic retinopathy, gestational diabetes mellitus, ovarian and testicular torsion).[14,17,18,21-23,30] It is a known fact that smoking is a risk factor for all these diseases. In all these studies mentioned, it is seen that smokers were excluded from the study for this reason. Therefore, detailed information about the relationship between SCUBE-1 and smoking could not be obtained in the investigated cases. However, the fact that SCUBE-1 was not found to be higher in smokers suggests that smoking alone may not be sufficient to develop the disease or increase the risk.

As far as we know, there is no study in the literature examining the relationship between SCUBE-1 and smoking in more detail. This point constitutes the strength of our study. However, our study has some limitations. The major limitations of our study are that only one measurement was made from the individuals and the development of the diseases that were thought to increase the risk was not followed. Moreover; the fact that the correlation of SCUBE-1 with any tumor and/or inflammation marker has not been investigated can be counted among the limitations. Finally, it was a single-center study with a small sample size.

In conclusion, in this study examining the plasma SCUBE-1 value in smokers, it was observed that SCUBE-1 did not increase at statistically significant levels in smokers compared to non-smokers. There were no negative or positive correlations between the values of SCUBE-1 and smoking status and smoking characteristics. Although the plasma SCUBE-1 value was not found to be significantly higher in smokers, it is thought that whether it will be useful in the evaluation of cardiovascular disease risk and thrombosis susceptibility in smokers can be clarified with further studies that will also examine the disease development process in these people.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

In order to carry out this study, permission was obtained from the Taksim Training and Research Hospital Clinical Research Ethics Committee. (Approval No:18; 22/01/2020).

Authors' Contributions

Concept/Design: STK, OB. Data Collection and/or Processing: STK, OB. Data analysis and interpretation: STK, OB. Literature Search: STK, OB. Drafting manuscript: STK, OB. Critical revision of manuscript: STK, OB.

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