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Original Article

The Degree of Hair Graying as an Independent Risk Marker for Coronary Artery Disease: A Coronary Angiographic Study

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ABSTRACT

Background and Aim: Cardiovascular disease is one of the leading causes of death worldwide. Graying hair, a visible indicator of aging, is associated with an increased risk of coronary artery disease (CAD). Dermatological signs, such as hair graying, may reflect an elevated coronary risk, as age is an unavoidable risk factor for CAD. This study aimed to evaluate the extent of hair graying as an independent risk marker for CAD.

Methods: In an observational cross-sectional study, 100 patients with suspected CAD (presenting with chest discomfort) underwent coronary angiography at the Cardiovascular Departments of Mansoura University Hospitals and Mansour Specialized Medical Hospital between August 2020 and August 2021.

Results: A statistically significant positive association was observed between the presence of xanthelasma and the risk factors of smoking (72.2%), diabetes (58.3%), dyslipidemia (100%), and family history of CAD (50%). Additionally, a statistically significant positive association was found between the presence of xanthelasma and the Gensini score, with 80.6% of individuals with xanthelasma exhibiting atherosclerotic CAD and a Gensini score < 20. However, the relationship between the presence of xanthelasma and the hair whitening score was nonsignificant ($P = 0.703$).

Conclusions: In our cohort, an elevated hair whitening score was associated with a higher likelihood of developing CAD, independent of chronological age and other conventionally recognized cardiovascular risk factors. This preliminary study suggests a relationship between CAD and hair graying. It is plausible that hair graying should be considered a coronary risk factor and utilized for identifying individuals at higher risk.
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KEYWORDS: Cardiovascular, Coronary angiography, Coronary artery disease, Hair graying

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Coronary artery disease (CAD) occurs when the myocardium is exposed to inadequate oxygen and blood supply due to the obstruction of the coronary arteries. This condition leads to an imbalance between oxygen demand and supply. CAD often involves the formation of plaques that obstruct blood flow within the lumen of the coronary arteries. [1]

Globally, CAD is one of the leading causes of morbidity and mortality. Traditional cardiovascular risk factors (CVRFs) are closely associated with CAD. [2, 3] Recently, numerous studies have suggested a potential link between various cutaneous markers and CAD, which may allow for the early identification of at-risk populations. [4, 5]

Graying hair is a physiological process that occurs in both men and women as they age. [6] Currently, age is the most significant and irreversible risk factor for CAD. [7] In clinical practice, it may be beneficial to assess biological aging rather than relying solely on chronological age. Graying hair is the most visible sign of biological aging in humans, yet the underlying mechanisms of this process remain poorly understood. [8] The possibility that oxidative stress contributes to hair graying [9] has prompted researchers to investigate premature graying as a risk factor for age-related diseases such as osteoporosis and CAD. Oxidative stress causes erratic differentiation of melanocytic stem cells, reducing the pool of stem cells available to replace dying melanogenic melanocytes. [10] The etiopathogenesis of CAD in young individuals is predominantly influenced by smoking. [11] Premature graying of hair is one of the earliest clinical indicators that could potentially aid in the early detection of CAD in young smokers. [10]

The mammalian hair follicle is a unique, highly regenerative system containing a large population of stem cells. These stem cells, located at the base of hair follicles, generate melanocytes, which are responsible for producing and storing hair pigment. Graying begins with the death or dysfunction of melanocyte stem cells. [12] These stem cells express CD34, similar to the vascular system, and may play a role in the functional maintenance of human hair follicles. [13] Premature graying has been associated with CAD in previous studies with varying sample sizes and patient populations, including those with myocardial infarction [14-16] and CAD. [17] Although some of these studies are dated and have significant methodological limitations, particularly in assessing the severity of CAD and premature hair whitening, several have demonstrated a correlation between myocardial infarction and premature hair whitening. [8]

Therefore, this study aimed to evaluate the extent of hair graying as an independent risk factor for CAD.

METHODS

Study Design

A total of 100 patients with suspected CAD, specifically those experiencing chest discomfort, underwent coronary angiography at the Cardiovascular Department of Mansoura University Hospitals and Mansour Specialized Medical Hospital between August 2020 and August 2021 as part of an observational cross-sectional study.

Ethical Considerations

The Mansoura Medical Research Ethics Committee approved the study protocol (IRB approval number: MS.20.10.2). Each participant provided informed oral consent to take part in the research. Confidentiality and personal privacy were maintained at all stages of the investigation, and the collected data will not be used for any other purposes. All participants who agreed to take part provided signed informed consent after being informed of the trial's benefits and

risks, and following approval from the local ethics committee. All procedures were conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments, as well as comparable ethical standards, in addition to the ethical requirements of the institutional and/or national research committee. The investigation received approval from the local ethics committee of the Mansoura University Faculty of Medicine, and the study's reporting complies with CONSORT guidelines.

Inclusion Criteria

Any male patient with suspected CAD (cases included angina-like symptoms or chest pain accompanied by either ECG ischemic changes such as ST-segment depression, T-wave inversion, poor R-wave progression, or the presence of pathological Q-waves; echocardiographic findings such as segmental wall motion abnormalities and reduced ejection fraction; or positive stress test results from stress ECG or dobutamine stress echocardiography) who underwent coronary angiography was included in the study.

The study population was divided into subgroups based on the presence or absence of CAD, as determined by coronary angiography, into normal coronaries or atherosclerotic CAD. The hair whitening score (HWS) was defined as follows: HWS 1 (trace): ≤ 25%, HWS 2 (mild): 25%–50%, HWS 3 (moderate): 50%–75%, HWS 4 (manifest): 75%–100%, and HWS 5 (complete): 100%. [16]

Based on the Gensini score, atherosclerotic CAD was classified as either low (score < 20) or high (score ≥ 20). [18]

Exclusion Criteria

Patients with recent unstable angina, ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction (NSTEMI) were excluded from the study. Additional exclusion criteria included patients with ongoing infection or inflammation, hepatic disease, renal impairment (serum creatinine > 1.4 mg/dL), hematological disorders, or known malignancy. Women were excluded due to the inability to accurately determine the HWS in cases where hair coloring was used.

Each patient included in the study underwent a comprehensive evaluation, which included full history taking to document current histories of smoking, hypertension, diabetes, and dyslipidemia, as well as personal information such as name, age, and sex. Additionally, early hair graying and a family history of vascular ischemic events (eg, CAD and cerebrovascular disorders) were recorded, along with any history of previous drug use or ischemic heart disease. A thorough general and local cardiac examination was also conducted. Hair graying was assessed using the HWS, determined by the percentage of gray/white hair as follows:

Pure black (trace ≤ 25%), Black > white (mild 25%–50%), Black = white (moderate 50%–75%), White > black (manifest 75%–100%), and Pure white (complete 100%). [8]

The presence of xanthelasma, characterized by plaque-like yellow lesions near the inner canthus of the eyelids, was noted. [19] Frank's sign, defined as a diagonal ear lobe crease running from the lower tip of the ear to the bottom of the ear hole, was also evaluated. [20] Furthermore, arcus senilis, a yellowish-white ring around the cornea, was documented.

Each patient underwent several laboratory tests upon admission, including a complete blood count, renal function tests (urea and serum creatinine), and a lipid profile. The lipid profile measurements included low-density lipoprotein cholesterol (LDL-C),

total cholesterol, triglycerides (TGs), and high-density lipoprotein cholesterol (HDL) for each patient.

Elective coronary angiography was performed using the Judkins procedure, which included 2 views of the right coronary system and 4 views of the left coronary system via the femoral artery. The coronary angiograms were stored in DICOM format on compact discs.

All patients also had a resting normal 12-lead surface ECG. All ECGs were calibrated using a standard of 25 mm/s and 10 mm/mV.

Transthoracic echocardiography was performed on each patient to evaluate the left ventricular ejection fraction and determine whether there were any segmental wall motion abnormalities.

Statistical Analysis

The data were entered into a computer and analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, released in 2013, Armonk, New York). Qualitative data were expressed as numerical values and percentages, while quantitative data were described using the mean and median (along with minimum and maximum values) for appropriately distributed data. The Monte Carlo test was used to compare 2 or more groups with qualitative data. For comparisons involving more than 2 independent groups, a one-way ANOVA test was employed, supplemented by a post hoc Tukey test for pairwise comparisons. The Spearman rank-order correlation was used to assess the magnitude and direction of a linear relationship between 2 ordinal or continuous variables with non-normal distributions. Receiver operating characteristic (ROC) curve analysis was performed to determine specificity and sensitivity, and cross-tabulation calculations were used to derive accuracy, positive predictive values, and negative predictive values. Linear regression analysis was conducted to predict independent variables for a continuous parametric outcome.

A *P*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Figure 1 illustrates a flowchart of the study population. Out of 120 cases with CAD identified in the Cardiology Department at Mansoura University Hospitals, 20 cases were excluded. (12 declined to participate, and 8 did not meet the inclusion criteria.) Written informed consent was obtained from the parents and caregivers of the remaining 100 patients after explaining the study's purpose. These cases were categorized into 5 groups based on the HWS: Group I (n = 5) consisted of cases with pure black hair; Group II (n = 19); Group III (n = 32); Group IV (n = 31); and Group V (n = 13) comprised cases with white > black hair.

The current study found that the ages of the analyzed patients ranged from 39 to 76 years, with a mean age of 54.93 years. Among the participants, 61% were smokers, 61% had hypertension, 39% were diabetic, 65% had dyslipidemia, 36% had a family history of CAD, 36% had xanthelasma, 8% had arcus senilis, and 30% had Frank's sign. Regarding CAD distribution, the median Gensini score was 19.75 (range: 0–166), with 16% having normal coronary arteries, 34% having atherosclerotic CAD with a score < 20, and 50% having atherosclerotic CAD with a score ≥ 20. Additionally, 73% showed ischemia on ECG, 54% exhibited segmental wall motion abnormalities on echocardiography, and the mean left ventricular ejection fraction was 57.1 (standard deviation: 8.75; range: 33–75) (Table 1).

Table 1. Cardiovascular risk factors and disease distribution among the studied cases

	N=100	%
Age, y Mean ± SD. (Min-Max)	54.93±7.97 (39-76)	
Smoking Nonsmoker smoker	 41 59	 41.0 59.0
Hypertensive -ve +ve	 39 61	 39.0 61.0
DM -ve +ve	 61 39	 61.0 39.0
Hyperlipidemia -ve +ve	 35 65	 35.0 65.0
Family history of CAD -ve +ve	 64 36	 64.0 36.0
Xanthelasma -ve +ve	 64 36	 64.0 36.0
Arcus senilis -ve +ve	 92 8	 92.0 8.0
Frank's sign -ve +ve	 70 30	 70.0 30.0
Gensini score Median (Min-Max)	19.75 (0.0-166)	
Normal coronary angiography	16	16.0
Atherosclerotic CAD Gensini score < 20	34	34.0
Atherosclerotic CAD Gensini score ≥20	50	50.0
ECG ischemia	73	73.0
Echocardiography SWMA	54	54.0
Echocardiography LVEF % Mean ± SD (Min-Max)	57.10±8.75 (33.0-75.0)	

DM: diabetes mellitus, CAD: coronary artery disease, SWMA: segmental wall motion abnormalities, LVEF: left ventricular ejection fraction

Additionally, the HWS categorized the analyzed cases into 4 groups: 5% pure black, 32% black equal to white hair, 31% white more than black hair, and 13% pure white (Fig. 2). Moreover, a statistically significant positive association was found between the age of the examined cases and the degree of hair whitening, with cases exhibiting pure white hair having a mean age of 64.92 years compared with 41 years for those with pure black hair. The study also revealed a statistically significant difference in the prevalence of hypertension between individuals with pure white hair (84.6%) and those with black and white hair (31.6%). Furthermore, a statistically significant positive association was observed between the HWS and arcus senilis, with 38.5% of cases with pure white hair and 9.7% of cases with white > black hair showing arcus senilis.

A statistically significant positive association was observed between the HWS and the Gensini score among the studied cases, with higher Gensini scores corresponding to higher grades of the HWS. Specifically, 84.6% of cases with pure white HWS had atherosclerotic CAD with a Gensini score ≥ 20, compared with 58.1% of cases with white > black HWS, 46.9% with black = white HWS, 26.3% with black > white HWS, and 20% with pure black HWS. A statistically significant correlation was found between the HWS and abnormal echocardiographic findings. Segmental wall motion abnormalities were observed in 69.2% of cases with pure white HWS, 64.5% with white > black HWS, 43.8% with black = white HWS, and 57.9% with pure white HWS (Table 2).

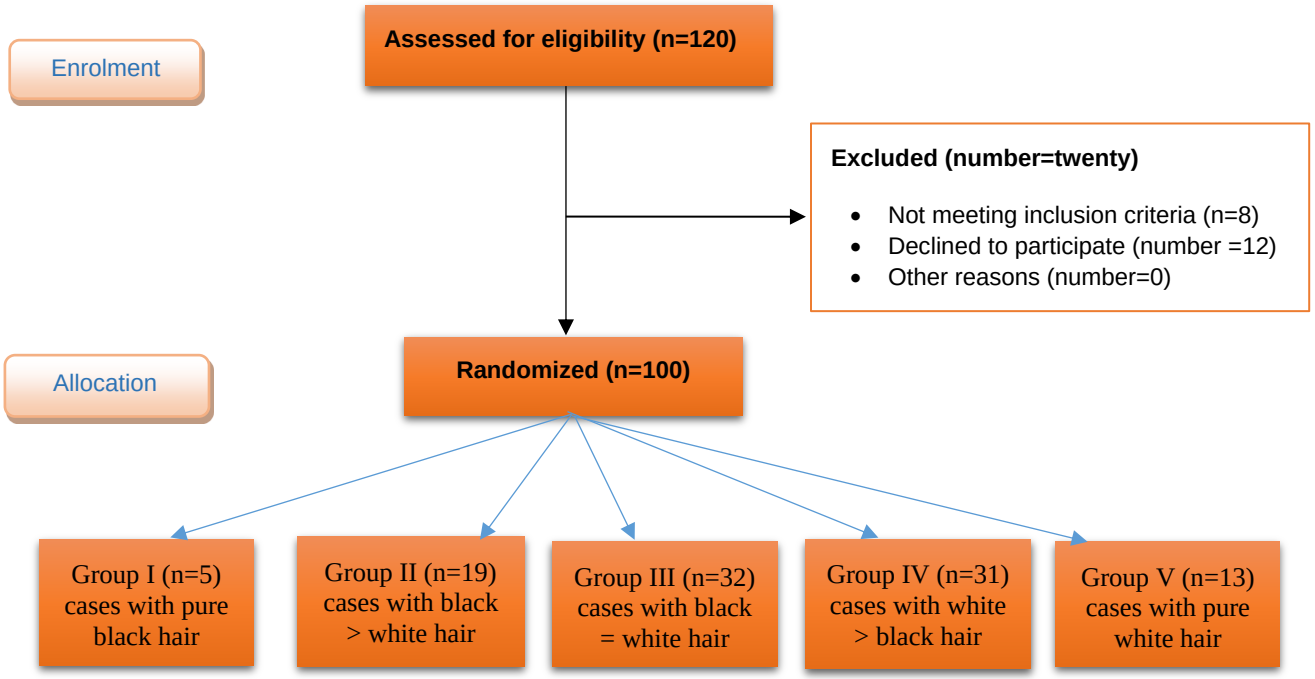

Figure 1. The image depicts the flowchart of the studied groups.

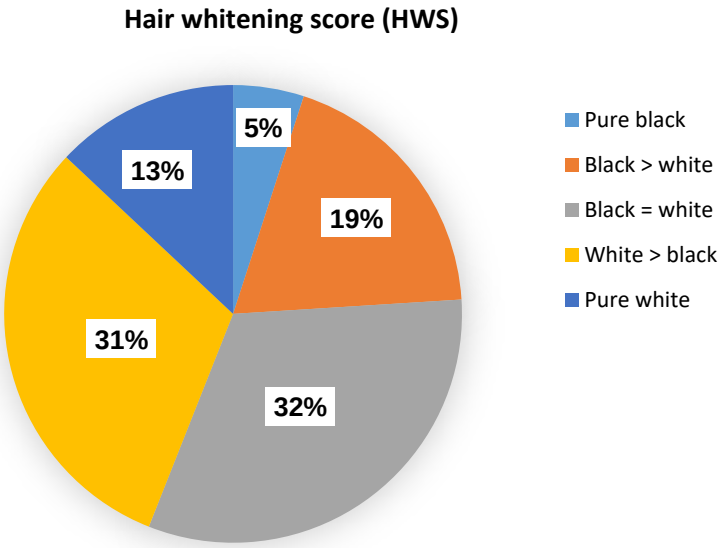

Figure 2. The image showcases this study's hair graying assessment using the hair whitening score (HWS).

Table 2. The relationship between cardiovascular risk factors and diagnosis and the hair whitening scale among the studied cases

	Pure Black N=5(%)	Black > White N=19(%)	Black = White N=32(%)	White > Black N=31(%)	Pure White N=13(%)	Test of Significance
Cardiovascular Risk Factors						
Age, y Mean ±SD	41.0±1.87	46.53±2.56	52.88±4.18	60.26±4.19	64.92±6.21	*F=65.97* *P<0.001**
Smoking Nonsmoker Smoker	4(80.0) 1(20.0)	11(57.9) 8(42.1)	12(37.5) 20(62.5)	11(35.5) 20(62.5)	3(23.1) 10(76.9)	χ^{2MC}=7.66 *P=0.105*
Hypertensive -ve +ve	5(100) 0	13(68.4) 6(31.6)	13(40.6) 19(59.4)	6(19.4) 25(80.6)	2(15.4) 11(84.6)	χ^{2MC}=22.85 *P<0.001**
DM -ve +ve	3(60.0) 2(40.0)	13(68.4) 6(31.6)	23(71.9) 9(28.1)	15(48.4) 16(51.6)	7(53.8) 6(46.2)	χ^{2MC}=4.38 *P=0.356*
Dyslipidemia -ve +ve	2(40) 3(60)	8(42.1) 11(57.9)	14(43.8) 18(56.2)	8(25.8) 23(74.2)	3(23.1) 10(76.9)	χ^{2MC}=3.52 *P=0.475*
Family history of CAD -ve +ve	2(40) 3(60)	15(78.9) 4(21.1)	18(56.2) 14(43.8)	23(74.2) 8(25.8)	6(46.2) 7(53.8)	χ^{2MC}=7.12 *P=0.130*
Xanthelasma -ve +ve	3(60.0) 2(40.0)	14(73.7) 5(26.3)	22(68.8) 10(31.2)	18(58.1) 13(41.9)	7(53.8) 6(46.2)	χ^{2MC}=2.18 *P=0.703*
Arcus senilis -ve +ve	5(100) 0	19(100) 0	32(100) 0	28(90.3) 3(9.7)	8(61.5) 5(38.5)	χ^{2MC}=21.38 *P<0.001**
Frank's sign -ve +ve	5(100) 0	19(100) 0	28(87.5) 4(12.5)	16(51.6) 15(48.4)	2(15.4) 11(84.6)	χ^{2MC}=38.41 *P=0.356*
Cardiovascular Diagnosis						
Gensini score Normal CA Gensini score < 20 Gensini score ≥20	4(80) 0 1(20)	3(15.8) 11(57.9) 5(26.3)	6(18.8) 11(34.4) 15(46.9)	3(9.7) 10(32.3) 18(58.1)	0 2(15.4) 11(84.6)	χ^{2MC}=28.66 *P<0.001**
ECG ischemia -VE +VE	4(80) 1(20)	10(52.6) 9(47.4)	6(18.8) 26(81.2)	7(22.6) 24(77.4)	0 13(100)	χ^{2MC}=19.68 *P=0.001**
Echocardiography LVEF %	64.80±6.64^{AB}	57.11±7.06	58.97±8.21	55.26±9.35^{A}	53.92±9.56^{B}	*F=2.22* *P=0.072*
Echocardiography Normal SWMA	5(100) 0	8(42.1) 11(57.9)	18(56.2) 14(43.8)	11(35.5) 20(64.5)	4(30.8) 9(69.2)	χ^{2MC}=9.93 *P=0.042**

Similar superscript letters denote nonsignificant differences between the groups within the same row according to the post hoc Tukey test.

* statistically significant

F: one-way ANOVA test, MC: Monte Carlo test, DM: diabetes mellitus, CAD: coronary artery disease, CA: coronary angiography, LVEF: left ventricular ejection fraction, SWMA: segmental wall motion abnormalities

Furthermore, a statistically significant positive association was observed between the presence of xanthelasma and the risk factors of smoking (72.2%), diabetes (58.3%), dyslipidemia (100%), and family history of CAD (50%). Additionally, a

statistically significant positive association was found between xanthelasma and the Gensini score, with 80.6% of individuals with xanthelasma having atherosclerotic CAD and a Gensini score < 20. Nonetheless, the relationship between xanthelasma and the HWS was nonsignificant (P = 0.703) (Table 3). Further, a statistically significant association (P = 0.001) was found between the risk factors of older age, smoking, hypertension, and arcus senilis with the presence of Frank's sign. A statistically significant correlation was also observed between the Gensini score and the presence of Frank's sign, with 73.3% of cases exhibiting Frank's sign having atherosclerotic CAD and a Gensini score ≥ 20, 13.3% having atherosclerotic CAD with a Gensini score < 20, and 13.3% having normal coronary arteries. A statistically significant relationship was also identified between the presence of Frank's sign and the HWS, with HWS 4 (manifest) present in 50% of cases with positive Frank's sign, HWS 5 (complete) in 36.7% of cases, and HWS 3 (moderate) in 13.3% of cases (Table 4).

Regarding the Gensini score, the area under the ROC curve effectively distinguished cases with atherosclerotic CAD (Gensini score ≥ 20) from other cases. The optimal cutoff point was identified as 21.75, providing a 75% specificity and a 65.9% sensitivity (Table 5 & Fig. 3). Hypertension (adjusted odds ratio [AOR] = 68.99), diabetes (AOR = 32.78), dyslipidemia (AOR = 28.99), family history of CAD (AOR = 25.22), smoking (AOR = 8.22), and Hair Whitening Scale 5 (AOR = 21) were identified as statistically significant predictors of CAD with a Gensini score ≥ 20. Collectively, these predictors accurately identified 95.6% of cases with atherosclerotic CAD and a Gensini score ≥ 20 (Table 6). In addition, the HWS was found to be a statistically significant predictor of the Gensini score, with the HWS able to predict the Gensini score with an accuracy of 41.8% using the following prediction equation: Gensini score = −16.96 + 0.462 × HWS (Table 7).

Table 3. The relationship between cardiovascular risk factors, disease classification, and the HWS and xanthelasma among the studied cases

	Xanthelasma		Test of Significance
	-ve n=64(%)	+ve n=36(%)	
Age, y Mean ±SD	55.08±7.94	54.67±8.13	t=0.247 P=0.806
Smoking Nonsmoker Smoker	 31(48.4) 33(51.6)	 10(27.8) 26(72.2)	χ^2=4.07 P=0.04*
Hypertensive -ve +ve	 29(45.3) 35(54.7)	 10(27.8) 26(72.2)	χ^2=2.98 P=0.084
DM -ve +ve	 46(71.9) 18(28.1)	 15(41.7) 21(58.3)	χ^2=8.84 P=0.003*
Dyslipidemia -ve +ve	 35(54.7) 29(45.3)	 0 36(100)	χ^2=30.29 P<0.001*
Family history of CAD -ve +ve	 46(71.9) 18(28.1)	 18(50.0) 18(50.0)	χ^2=4.79 P=0.029*
Arcus senilis -ve +ve	 59(92.2) 5(7.8)	 33(91.7) 3(8.3)	χ^2=0.008 P=0.927

Frank's sign -ve +ve	 47(73.4) 17(26.6)	 23(63.9) 13(36.1)	 χ^2=1.0 P=0.317
Gensini Score Normal CA Gensini score < 20 Gensini score ≥ 20	 13(20.3) 30(46.9) 21(32.8)	 3(8.3) 4(11.1) 29(80.6)	 χ^{2MC}=21.24 P<0.001*
ECG ischemia -VE +VE	 19(29.7) 45(70.3)	 8(22.2) 28(77.8)	 χ^2=0.651 P=0.420
Echocardiography LVEF %	57.94±7.76	55.61±10.16	t=1.29 P=0.202
Echocardiography Normal SWMA	 31(48.4) 33(51.6)	 15(41.7) 21(58.3)	 χ^2=0.425 P=0.514
HWS			
1	3 (4.7)	2 (5.6)	MC=2.18 p=0.703
2	14 (21.9)	5 (13.9)	
3	22 (34.4)	10 (27.8)	
4	18 (28.1)	13 (36.1)	
5	7 (10.9)	6 (16.7)	

χ^2: chi-square test, t: Student's *t*-test, MC: Monte Carlo test, DM: diabetes mellitus, CAD: coronary artery disease, CA: coronary angiography, LVEF: left ventricular ejection fraction, SWMA: segmental wall motion abnormalities, HWS: hair whitening score

*statistically significant

Table 4. The relationship between cardiovascular risk factors, disease classification, and the HWS and Frank's sign among the studied cases

	Frank's Sign		
	-ve n=70	+ve n=30	Test of Significance
Age, Mean ±SD	51.53±6.56	62.87±4.64	t=8.58 P<0.001*
Smoking Nonsmoker Smoker	 34 (48.6) 36 (51.4)	 7 (23.3) 23 (76.7)	 χ^2=5.53 P=0.019*
Hypertensive -ve +ve	 36 (51.4) 34 (48.6)	 3 (10.0) 27 (90.0)	 χ^2=15.15 P<0.001*
DM -ve +ve	 43 (61.4) 27 (38.6)	 18 (60.0) 12 (40.0)	 χ^2=0.018 P=0.893
Dyslipidemia -ve +ve	 27 (38.6) 43 (61.4)	 8 (26.7) 22 (73.3)	 χ^2=1.31 P=0.253
Family history of CAD -ve +ve	 44 (62.9) 26 (37.1)	 20 (66.7) 10 (33.3)	 χ^2=0.132 P=0.716
Arcus senilis -ve +ve	 69 (98.6) 1 (1.4)	 23(76.7) 7 (23.3)	 χ^2=13.69 P<0.001*
Gensini Score Normal CA Gensini score < 20 Gensini score ≥ 20	 12 (17.1) 30 (42.9) 28 (40)	 4 (13.3) 4 (13.3) 22(73.3)	 χ^{2MC}=10.24 P=0.006*
ECG ischemia -VE	 21 (30)	 6 (20)	 χ^2=1.07

+VE	49 (70)	24(80)	P=0.302
Echocardiography LVEF %	57.94±7.76	55.61±10.16	t=1.28 P=0.203
Echocardiography Normal SWMA	34 (48.6) 36 (51.4)	12(40) 18(60)	χ^2=0.621 P=0.431
HWS			
1	5 (7.1)	0	MC=38.41 p<0.001*
2	19 (27.1)	0	
3	28 (40.0)	4 (13.3)	
4	16 (22.9)	15 (50.0)	
5	2 (2.9)	11 (36.7)	

χ^2: chi-square test, MC: Monte Carlo test, t: Student's *t*-test, DM: diabetes mellitus, CAD: coronary artery disease, CA: coronary angiography, LVEF: left ventricular ejection fraction, SWMA: segmental wall motion abnormalities, HWS: hair whitening score

*statistically significant

Table 5. The validity of the Gensini score in differentiating cases with atherosclerosis

	AUC (95% CI)	*P*	Cutoff Point	Sensitivity%	Specificity%
Gensini Score	0.719 (0.616-0.822)	0.05	21.75	65.9	75.0

AUC: area under the curve

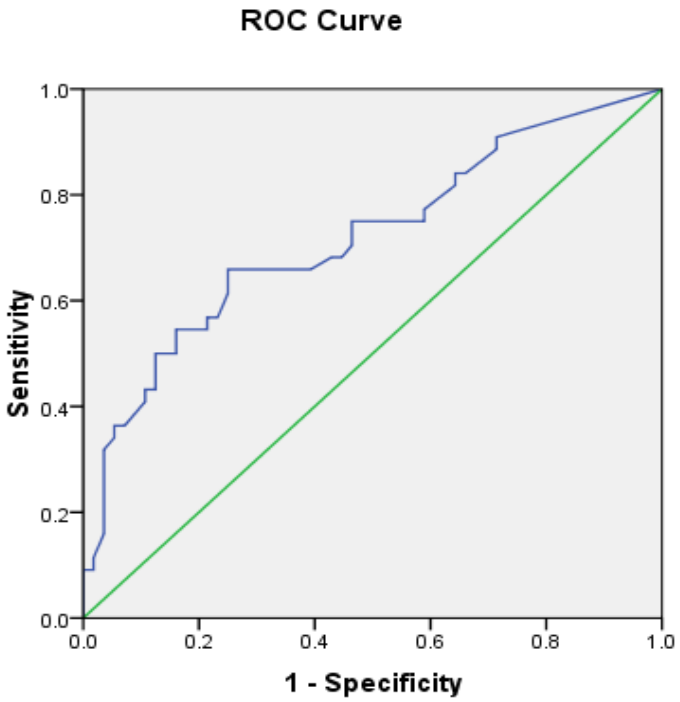

Figure 3. The image depicts the sensitivity and specificity of the receiver operating characteristic (ROC) curve of the Gensini Score in differentiating cases with atherosclerosis.

Table 6. Univariate and multivariate analyses for predictors of atherosclerosis among the studied cases

	Univariate Analysis				Multivariate Analysis		
	Normal/CAD Gensini Score <20	CAD with Gensini Score ≥20	*P*	COR (95% CI)	β	*P*	AOR (95% CI)
Age, y	53.90±8.03	55.96±7.86	t=1.29 p=0.198	1.03(0.983-1.09)			
Smoking Nonsmoker Smoker	31(62.0) 19(38.0)	10(20.0) 40(80.0)	χ^2=18.23 P<0.001*	1 6.26(2.65-16.02)	2.11	0.028*	8.22 (1.26-53.76)
Hypertensive -ve +ve	33(66.0) 17(34.0)	6(12.0) 44(88.0)	χ^2=30.63 P<0.001*	1 14.24(5.06-40.05)	4.23	0.001*	68.99(5.41-87.25)
DM -ve +ve	36(72.0) 14(28.0)	25(50.0) 25(50.0)	χ^2=5.09 P=0.024*	1 2.57(1.12-5.89)	3.49	0.003*	32.78(3.25-37.69)
Dyslipidemia -ve +ve	25(50.0) 25(50.0)	10(20.0) 40(80.0)	χ^2=9.89 P=0.002*	1 4.0(1.65-9.72)	3.37	0.005*	28.99(2.69-30.79)
Family history of CAD -ve +ve	39(78.0) 11(22.0)	25(50) 25(50)	χ^2=8.51 P=0.004*	1 3.55(1.49-8.45)	3.23	0.006*	25.22(2.55-35.87)
Xanthelasma -ve +ve	43(86.0) 7(14.0)	21(42.0) 29(58.0)	χ^2=21.01 P<0.001*	1 8.48(3.19-22.52)	0.87 0	0.413	2.38(0.298-19.16)
Arcus senilis -ve +ve	47(94.0) 3(6.0)	45(90.0) 5(10.0)	χ^2=0.543 P=0.461	1 1.74(0.393-7.71)			
Frank's sign -ve +ve	42(84.0) 8(16.0)	28(56.0) 22(44.0)	χ^2=9.33 P=0.002*	1 4.13(1.61-10.56)	1.48	0.184	4.41(0.493-39.43)
ECG ischemia -VE +VE	21(42.0) 29(58.0)	6(12.0) 44(88.0)	χ^2=11.42 P=0.001*	1 5.31(1.91-14.75)	1.69	0.078	5.46(0.828-35.99)
Echocardiography Normal SWMA	27(54.0) 23(46.0)	19(38.0) 31(62.0)	χ^2=2.58 P=0.108	1 1.92(0.863-4.25)			
HWS 1 2 3 4 5	4(8.0) 14(28.0) 17(34.0) 13(26.0) 2(4.0)	1(2.0) 5(10.0) 15(30.0) 18(36.0) 11(22.0)	χ^{2MC}=13.23 P=0.01*	1 1.43(0.127-16.03) 3.53(0.354-35.16) 5.54(0.553-55.49) 22.0(1.54-30.29)	0.357 1.261 1.713 3.09	0.772 0.282 0.145 0.023*	1.6(0.14-17.54) 4.1(0.458-36.2) 6.20(0.614-50.69) 21(2.58-31.14)
Overall % predicted =95.6%							

r: reference groups, AOR: adjusted odds ratio, COR: crude odds ratio χ^2: chi-square test, MC: Monte Carlo test, DM: diabetes mellitus, CAD: coronary artery disease, CA: coronary angiography, LVEF: left ventricular ejection fraction, SWMA: segmental wall motion abnormalities, HWS: hair whitening score

Table 7. The multiple linear regression for predicting the Gensini score according to the HWS

	B	t	*P*	F=26.643 *P*<0.001*	R^2=0.418
(Constant)	-16.961	-1.768	0.080		
HWS	0.462	5.162	0.001*		
Prediction equation Gensini score = −16.96 + 0.462 × HWS					

HWS: hair whitening score

DISCUSSION

As individuals age, they are more likely to experience hair graying and atherosclerotic vascular changes. Currently, age is the most significant and irreversible risk factor for CAD. In clinical practice, assessing biological aging, rather than relying solely on chronological age, may be more useful. Graying hair is the most visible indicator of biological aging in humans, yet the underlying mechanisms remain poorly understood. [20] The hypothesis that CAD and premature hair graying are related prompted this study. We aimed to determine whether hair graying among Egyptian patients serves as a marker for CAD by examining its correlation with coronary atherosclerotic burden and CVRFs. Analysis of our data revealed that the mean age of the studied patients ranged from 39 to 76 years. Among them, 59% were smokers, 61% had hypertension, 39% were diabetic, 65% had dyslipidemia, 36% had a family history of CAD, 36% had xanthelasma, 8% had arcus senilis, and 30% had a positive Frank's sign. Consistent with our findings, the cross-sectional study by El-Faramawy et al [15] aimed to determine the prevalence and degree of hair graying in a cohort of men with suspected CAD who underwent computed tomography coronary angiography, as well as to assess whether hair graying served as an independent marker for CAD. Their study involved 545 male cases with a mean age of 53.2 ± 10.7 years, and dyslipidemia and hypertension were the most common traditional CVRFs. [21–23] In the current study, the median Gensini score was 19.75 (range: 0–166), with 16% of cases having normal coronary arteries, 34% having atherosclerotic CAD with a low Gensini score (< 20), and 50% having atherosclerotic CAD with a high Gensini score (≥ 20). Additionally, 73% of cases showed ischemia on ECG, 54% exhibited segmental wall motion abnormalities on echocardiography, and the mean left ventricular ejection fraction was 57.1 (standard deviation: 8.75; range: 33–75). In comparison, a study by Yokokawa et al [24] reported an average subject age of 70.1 years, with 72.9% of participants being male. The median Gensini score at initial coronary angiography was 36 (IQR: 18–56), and 65 individuals (32.7%) had a history of percutaneous coronary intervention. During the study period, the interventional procedure was performed on 166 patients (83.4%).

Based on the hair graying assessment using the HWS, the examined cases were divided into 4 groups: 5% pure black, 32% black = white hair, 31% white > black hair, and 13% pure white. In comparison, the study by El-Faramawy et al [18] reported that 298 (54.7%) patients had predominantly white hair (HWS 3). The cases were categorized into subgroups based on the percentage of white or gray hair and the presence or absence of CAD. Cases with predominantly white hair (higher HWS) exhibited significantly higher levels of age, diabetes, and hypertension among traditional CVRFs, while cases with lower HWS showed significantly higher levels of smoking. Further, cases with an HWS ≥ 3 were statistically significantly more likely to have coronary calcification and CAD (73.5% vs 45.7%).

In the current study, the age of the examined cases showed a strong positive correlation with the HWS, with older age being associated with higher grades of the HWS. Specifically, 84.6% of individuals with pure white hair and 31.6% of cases with black hair mixed with white hair had hypertension. Additionally, arcus senilis was present in 38.5% of cases with pure white hair and 9.7% of cases with white > black hair. Consistent with our findings, the study by Avila et al [25] collected data on CVRFs and aging indicators, such as the degree of gray hair, baldness, arcus senilis, and facial wrinkles, from a random sample of 20,000 men and women. The association between all-cause mortality and these aging indicators was analyzed using a descriptive approach, with age included as an explanatory variable in the Cox regression model for proportional hazards. The study found no association between mortality and the degree of baldness, facial wrinkles, or hair graying in either sex, regardless of age. Nevertheless, the report by Cetin et al [26] noted that patients with the highest HWS were older, had a higher prevalence of hypertension, and had a family history of hair whitening. Moreover, this subgroup exhibited larger ascending aortas, higher serum uric acid levels, and lower total bilirubin levels.

In the present study, 84.6% of cases with pure white HWS had a Gensini score ≥ 20, compared with 20% of cases with pure black HWS. Furthermore, 58.1% of cases with white > black HWS, 46.9% with black = white HWS, and 26.3% with black > white HWS had a Gensini score ≥ 20. Segmental wall motion abnormalities were detected by echocardiography in 69.2% of cases with pure white HWS, 64.5% with white > black HWS, 43.8% with black = white HWS, and 57.9% with pure white HWS. Subsequently, further studies were conducted in diverse populations, including cases of myocardial infarction and CAD in both white and black males and females. [27] Some of these studies also associated premature hair whitening with myocardial infarction, although many are somewhat outdated and have methodological limitations, particularly in assessing the severity of CAD and the degree of hair whitening. Consequently, the literature has yielded inconsistent findings.

In our study, we further tested this earlier hypothesis and obtained promising results. An elevated HWS may serve as a risk indicator for atherosclerotic vascular involvement. Although gray hair is not a prerequisite for the development of CAD, it can manifest at any age. Conversely, the presence of biological aging markers, such as hair graying, may aid in identifying individuals at higher risk of cardiovascular disease when combined with cumulative assessments of CVRFs. Since premature hair graying was identified as an independent CVRF unrelated to chronological age, it could serve as a marker for atherosclerosis that is not predicted by conventional risk scores or explained by traditional CVRFs.

Premature hair graying has not previously been recognized as a risk factor for atherosclerosis severity, as no studies have investigated the relationship between coronary atherosclerotic burden and premature hair graying. Still, prior studies by Agarwal et al [28] and Acer et al [29] have demonstrated an association between hair whitening and the frequency of myocardial infarction or the presence of CAD. In the current study, the presence of xanthelasma showed a significant correlation with smoking (72.2%), diabetes (58.3%), dyslipidemia (100%), and a family history of CAD (50%). Additionally, a strong association was observed between xanthelasma and the Gensini score, with 80.6% of cases with xanthelasma having atherosclerotic CAD and a Gensini score ≥ 20. Consistent with our findings, Hassanin et

al [30] reported that cases with xanthelasma had significantly more severe CAD than those without it (single-vessel disease: 9 [20.9%] vs 1 [2.3%]; *P* = 0.001; two-vessel disease: 7 [16.3%] vs 0; three-vessel disease: 13 [30.2%] vs 0; and the left main artery disease: 4 [9.3%] vs 0; *P* = 0.001). On the other hand, we found no association between the degree of hair whitening and the presence of xanthelasma. Nonetheless, our study demonstrated a strong correlation between the presence of Frank's sign and aging, smoking, hypertension, and the presence of arcus senilis. Further, we observed that 73.3% of cases with Frank's sign had atherosclerotic CAD with a Gensini score ≥ 20, 13.3% had atherosclerotic CAD with a Gensini score < 20, and 13.3% had normal coronary arteries. Among cases with a positive Frank's sign, 50% had HWS 4, 36.7% had HWS 5, and 13.3% had HWS 3. El-Faramawy et al [18] found that cases with atherosclerotic CAD were older, and hypertension, diabetes, and dyslipidemia were more prevalent among all CVRFs. Furthermore, a higher HWS was associated with an increased risk of CAD, independent of chronological age and other established CVRFs, thereby supporting our findings. Premature hair graying may be linked to CAD or myocardial infarction in both sexes according to evidence from numerous studies with varying patient groups and sample sizes. In addition to the aforementioned findings, we observed that the area under the ROC curve for the Gensini score effectively distinguished cases with atherosclerotic CAD (Gensini score ≥ 20) from other cases. The optimal cutoff point was identified as 21.75, yielding a sensitivity of 65.9% and a specificity of 75%. A study by Avci et al, [31] which reported a Gensini score cutoff value of 50.5 for predicting severe carotid stenosis with 63% specificity and 77% sensitivity (AUC 0.778, 95% CI 0.712 to 0.843), aligns with our findings. In the present study, hypertension (AOR = 68.99), diabetes (AOR = 32.78), dyslipidemia (AOR = 28.99), family history of CAD (AOR = 25.22), smoking (AOR = 8.22), and HWS 5 (AOR = 21) were identified as statistically significant predictors of CAD with a Gensini score ≥ 20. Collectively, these factors predicted 95.6% of cases with atherosclerotic CAD and a Gensini score ≥ 20. Notably, we found a strong positive association between the Gensini score and the HWS. Furthermore, the HWS was able to predict 41.8% of the Gensini score, consistent with the results of Kocaman et al, [8] who reported that age, family history of CAD, hyperlipidemia, and creatinine levels were independent variables associated with the HWS.

In contrast to Zayed et al, [32] who found no significant association between elevated fasting blood sugar or hypertension and hair graying, our study revealed that age was the only factor significantly associated with an increased HWS when examining the impact of CVRFs on hair graying through linear regression analysis.

CONCLUSIONS

In our cohort, an elevated HWS was associated with a higher risk of developing CAD, independent of chronological age and other conventionally recognized CVRFs. This preliminary study suggests a relationship between CAD and hair graying. It is plausible that hair graying should be considered a coronary risk factor and utilized for identifying individuals at higher risk.

Data Sharing Statement: All data and materials used in this study are available upon request.

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REFERENCES

1. Dalen JE, Alpert JS, Goldberg RJ, Weinstein RS. The epidemic of the 20th century: coronary heart disease. The American journal of medicine. 2014 Sep 1; 127(9):807-12. https://doi.org/10.1016/j.amjmed.2014.04.015

2. Panwar RB, Gupta R, Gupta BK, Raja S, Vaishnav J, Khatri M, Agrawal A. Atherothrombotic risk factors & premature coronary heart disease in India: a case-control study. The Indian journal of medical research. 2011 Jul; 134(1):26. https://pubmed.ncbi.nlm.nih.gov/21808131/

3. ElFaramawy AA, Hanna IS, Darweesh RM, Ismail AS, Kandil HI. The degree of hair graying as an independent risk marker for coronary artery disease, a CT coronary angiography study. The Egyptian Heart Journal. 2018 Mar 1; 70(1):15-9. https://doi.org/10.1016/j.ehj.2017.07.001

4. Dwivedi S, Jhamb R. Cutaneous markers of coronary artery disease. World journal of cardiology. 2010 Sep 9; 2(9):262. https://doi.org/10.4330/wjc.v2.i9.262

5. Hu Y, Qiu S, Cheng L. Integration of multiple-omics data to analyze the population-specific differences for coronary artery disease. Computational and Mathematical Methods in Medicine. 2021 Aug 17; 2021. https://doi.org/10.1155/2021/7036592

6. Anastassakis K, Anastassakis K. The Effects of Aging on the Hair Follicle. Androgenetic Alopecia From A to Z: Vol. 1 Basic Science, Diagnosis, Etiology, and Related Disorders. 2022:83-94. https://link.springer.com/chapter/10.1007/978-3-030-76111-0_8

7. Harrington CR, Levy P, Cabrera E, Gao J, Gregory DL, Padilla C, Crespo G, VanWagner LB. Evolution of pretransplant cardiac risk factor burden and major adverse cardiovascular events in liver transplant recipients over time. Liver Transplantation. 2023 Jun:10-97. https://doi.org/10.1097/lvt.0000000000000013

8. Kocaman SA, Çetin M, Durakoglugil ME, Erdogan T, Çanga A, Çiçek Y, Dogan S, Sahin I, Satiroglu Ö, Bostan M. The degree of premature hair graying as an independent risk marker for coronary artery disease: a predictor of biological age rather than chronological age/Koroner arter hastaligi için bagimsiz bir risk öngörücüsü olarak saçin erken beyazlama düzeyi: Zamansal yastan çok biyolojik yasin öngörücüsü. The Anatolian Journal of Cardiology. 2012 Sep 1;12(6):457. https://doi.org/10.5152/akd.2012.150

9. O'Sullivan JD, Nicu C, Picard M, Chéret J, Bedogni B, Tobin DJ, Paus R. The biology of human hair greying. Biological Reviews. 2021 Feb; 96(1):107-28. https://doi.org/10.1111/brv.12648

10. Aggarwal A, Srivastava S, Agarwal MP, Dwivedi S. Premature graying of hair: An independent risk marker for coronary artery disease in smokers-A retrospective case control study. Ethiopian journal of health sciences. 2015; 25(2):123-8. https://doi.org/10.4314%2Fejhs.v25i2.4

11. Hahad O, Arnold N, Prochaska JH, Panova-Noeva M, Schulz A, Lackner KJ, Pfeiffer N, Schmidtmann I, Michal M, Beutel M, Wild PS. Cigarette smoking is related to endothelial dysfunction of resistance, but not conduit arteries in the general population—results from the gutenberg health study. Frontiers in Cardiovascular Medicine. 2021 May 19; 8:674622. https://doi.org/10.3389/fcvm.2021.674622

12. Nishimura EK, Granter SR, Fisher DE. Mechanisms of hair graying: incomplete melanocyte stem cell maintenance in the niche. Science. 2005 Feb 4; 307(5710):720-4. https://doi.org/10.1126/science.1099593

13. Wang B, Liu XM, Liu ZN, Wang Y, Han X, Lian AB, Mu Y, Jin MH, Liu JY. Human hair follicle-derived mesenchymal stem cells: Isolation, expansion, and differentiation. World journal of stem cells. 2020 Jun 6; 12(6):462. https://doi.org/10.4252%2Fwjsc.v12.i6.462

14. Mansouri P, Mortazavi M, Eslami M, Mazinani M. Androgenetic alopecia and coronary artery disease in women. Dermatology online journal. 2005; 11(3). https://pubmed.ncbi.nlm.nih.gov/16409898/

15. Mirić D, Fabijanić D, Giunio L, Eterović D, Čulić V, Božić I, Hozo I. Dermatological indicators of coronary risk: a case-control study. International journal of cardiology. 1998 Dec 31; 67(3):251-5. https://doi.org/10.1016/S0167-5273(98)00313-1

16. Schnohr P, Nyboe J, Lange P, Jensen G. Longevity and gray hair, baldness, facial wrinkles, and arcus senilis in 13,000 men and women: the Copenhagen City Heart Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 1998 Sep 1; 53(5):M347-50. https://doi.org/10.1093/gerona/53A.5.M347

17. Mahendiratta S, Sarma P, Kaur H, Kaur S, Kaur H, Bansal S, Prasad D, Prajapat M, Upadhay S, Kumar S, Kumar H. Premature graying of hair: Risk factors, co-morbid conditions, pharmacotherapy and reversal—A systematic review and meta-analysis. Dermatologic Therapy. 2020 Nov; 33(6):e13990. https://doi.org/10.1111/dth.13990

18. El-Faramawy AA, Hanna IS, Darweesh RM, Ismail AS, Kandil HI. The degree of hair graying as an independent risk marker for coronary artery disease, a CT coronary angiography study. The Egyptian Heart Journal. 2018 Mar 1; 70(1):15-9. https://doi.org/10.1016/j.ehj.2017.07.001.

19. Aggarwal A, Srivastava S, Agarwal MP, Dwivedi S. Premature graying of hair: An independent risk marker for coronary artery disease in smokers-A retrospective case control study. Ethiopian journal of health sciences. 2015; 25(2):123-8. DOI: 10.4314/ejhs. v25i2.4.

20. Chen J, Chen MH, Li S, Guo YL, Zhu CG, Xu RX, Zhang Y, Sun J, Qing P, Liu G, Li JJ. Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of coronary artery disease: a Gensini score assessment. Journal of atherosclerosis and thrombosis. 2014 Dec 17; 21(12):1271-82. https://doi.org/10.5551/jat.25940.

21. Kim YG, Oh JW, Lee KC, Yoon SH. Clinical association between serum cholesterol level and the size of xanthelasma palpebrarum. Archives of Craniofacial Surgery. 2022 Apr; 23(2):71. doi: 10.7181/acfs.2022.00185.

22. Stoyanov GS, Dzhenkov D, Petkova L, Sapundzhiev N, Georgiev S. The histological basis of Frank's Sign. Head and neck pathology. 2021 Jun; 15:402-7. https://doi.org/10.1007/s12105-020-01205-4.

23. Basiak M, Kosowski M, Hachula M, Okopien B. Plasma concentrations of cytokines in patients with combined hyperlipidemia and atherosclerotic plaque before treatment initiation—a pilot study. Medicina. 2022 Apr 29; 58(5):624. https://doi.org/10.3390/medicina58050624.

24. Yokokawa T, Yoshihisa A, Kiko T, Shimizu T, Misaka T, Yamaki T, Kunii H, Nakazato K, Ishida T, Takeishi Y. Residual Gensini score is associated with long-term cardiac mortality in patients with heart failure after percutaneous coronary intervention. Circulation reports. 2020 Feb 10; 2(2):89-94. https://doi.org/10.1253/circrep.CR-19-0121.

25. Avila FR, Torres-Guzman RA, Maita KC, Garcia JP, Haider CR, Ho OA, Carter RE, McLeod CJ, Bruce CJ, Forte AJ. Perceived age as a mortality and comorbidity predictor: a systematic review. Aesthetic Plastic Surgery. 2023 Feb; 47(1):442-54. https://doi.org/10.1007/s00266-022-02932-5.

26. Cetin M, Bozbeyoglu E, Erdogan T, Kocaman SA, Satiroglu O, Durakoglugil ME. Hair whitening and obesity are independently related to ascending aorta

dilatation in young-middle aged men. Northern Clinics of İstanbul. 2019; 6(1):33-9. doi: 10.14744/nci.2017.43433.

27. Mansouri P, Mortazavi M, Eslami M, Mazinani M. Androgenetic alopecia, and coronary artery disease in women. Dermatology online journal. 2005; 11(3). https://doi.org/10.5070/D38525g87b.

28. Agarwal S, Choudhary A, Kumar A, Zaidi A, Mohanty S, Yadav S. A study of association of premature graying of hair and osteopenia in North Indian population. International journal of trichology. 2020 Mar; 12(2):75. Doi: 10.4103/ijt.ijt_123_19.

29. Acer E, Arslantaş D, Emiral GÖ, Ünsal A, Atalay BI, Göktaş S. Clinical, and epidemiological characteristics and associated factors of hair graying: a population-based, cross-sectional study in Turkey. Anais brasileiros de dermatologia. 2020 Aug 7; 95:439-46. https://doi.org/10.1016/j.abd.2020.03.002.

30. Hassanin N, Bakhoum SW, Saraya ME. Coronary angiographic profile in Egyptian patients with xanthelasma palpebrarum. Kasr Al Ainy Medical Journal. 2020 May 1; 26(2):83. DOI: 10.4103/kamj.kamj_30_20.

31. Avci A, Fidan S, Tabakçı MM, Toprak C, Alizade E, Acar E, Bayam E, Tellice M, Naser A, Kargın R. Association between the Gensini score and carotid artery stenosis. Korean circulation journal. 2016 Sep 1; 46(5):639-45. https://doi.org/10.4070/kcj.2016.46.5.639.

32. Zayed AA, Shahait AD, Ayoub MN, Yousef AM. Smokers' hair: Does smoking cause premature hair graying. Indian dermatology online journal. 2013 Apr; 4(2):90. doi:10.4103/2229-5178.110586.