Correlation of Earlobe Crease and Clinically Identified Forehead Wrinkles with Severity of Coronary Artery Lesions in Patients with Stable Angina Pectoris

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Abstract: Identification of high-risk subjects is crucial in prevention of coronary heart disease. Ear lobe crease and forehead wrinkles are easily identifiable physical signs that could potentially be an indicator of coronary artery lesion severity. This study aimed to determine the relationship between earlobe crease and forehead wrinkles morphology with severity of coronary artery stenosis in patients with stable angina pectoris using modified Gensini score. This was an observational study with a cross-sectional approach. All subjects who met the inclusion criteria were taken photos of their forehead area and both right and left ears. Assessment of scores and correlation analysis of earlobe crease and forehead wrinkles assessment with the severity of coronary artery stenosis using Gensini modification scores were later done. The results showed that from a total of 40 study subjects, 28 patients (70%) were male. Forehead wrinkle scores in patients with stable angina pectoris were mainly classified into score 1 and 2, totalling 32 (80%) patients. Earlobe crease form were dominated by type A (65% vs 35%). Patients with type B morphology on average have a Gensini value of 9 points lower than type A (reference) (p <0.001). As for the Gensini modified score in patients with non-zero forehead wrinkle scores, it was clearly 4−5 units greater than those with a zero score. However, the sample size of patients with zero forehead wrinkle score was indeed too small (n=3) to make the difference meaningful (p=0.507). In conclusion, there is a significant positive relationship between identification of earlobe crease and the severity of coronary artery stenosis but there is no strong relationship between the identification of forehead wrinkles and the severity of coronary artery stenosis in patients with stable angina pectoris, in this case with a modified Gensini score.

Keywords: stable angina; earlobe crease; forehead wrinkles; modified Gensini score

INTRODUCTION

Coronary heart disease (CHD) is a leading cause of disease burden and death globally especially in developing countries.[1,2] According to American Heart Association (AHA) Statistical Update released in March 2019, the total prevalence of CHD was 6.7%. In the United States, the prevalence of CHD of 7.4% for men and 6.2% for women among adults aged >20 years. It is estimated that every 40 seconds an American will experience myocardial infarction.[3] The REGARDS study reported that myocardial infarction sufferers accounted for around 37% of the total number of patients treated, and it was found that patients with lower income and education levels had twice the risk of developing CHD compared to those with higher income and education levels, with a ratio of 10.1 versus 5.2 per 1,000 people a year.[3] In Indonesia, the Basic Health Research (Riskesdas) in 2007 showed that CHD was ranked as 3rd cause of death after stroke and hypertension.[4]

Stable angina pectoris is generally characterized by episodes of mismatched needs and reversible myocardial supply, which are associated with ischemia or

hypoxia. This situation is usually triggered by exercise, emotion or other stresses that occur spontaneously. Episodes of ischemia and hypoxia are usually associated with transient chest pain.[5]

Management of stable angina may include handling risk factors, optimal pharmacological therapy, and revascularization. Indications for revascularization in stable angina patients are if symptoms persist despite receiving therapy according to treatment guidelines to improve prognosis.[6]

Prevention of CHD should be done based on the identification of high-risk patients especially those with stable angina pectoris, so that physical signs can be easily detected including that can be done, namely the examination of earlobe crease (ELC) and forehead wrinkles (FW).[7-9]

METHODS

This is a cross-sectional study involving 40 patients with stable angina treated at the Cardiovascular Clinic and inpatient ward of Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia from May to July in 2019. Inclusion criteria were patients with stable angina pectoris who underwent coronary angiography and were willing to be part of the study. Exclusion criteria were patients who had been pierced or wore earrings in both left and right earlobe areas, had performed botox in the forehead area, had experienced plastic surgery in the forehead and earlobe areas, had suffered injuries or trauma in the forehead and earlobe areas, had acne and other skin diseases, and were not cooperative.

Earlobe creases are categorized based on their length according to Lopez et al[10] (2015) in which it is categorized as complete (type A) when the fold line crosses the entire distance from tragus to the edge of the auricle, and incomplete (type B) when fold line crosses over 1/3 of the earlobe without reaching the border (Figure 1).

Forehead wrinkles are categorized based on the 0-3 score system used in the Visat study by Esquirol et al (2018). Value 0 is given when there are absolutely no wrinkles. Value 1 is given when fine wrinkles appear after moving facial muscle, such as smiling.

Value 2 is given when wrinkles appear at rest. Value 3 is given if wrinkles appear to be deep (Figure 2).[11,12]

Figure 1. Classification of the ELC according to length. (A) Complete and (B) incomplete (Source: Lopez et al, 2015[10]

The severity of coronary lesions was assessed using a modified Gensini score.[13,14]

Statistical analysis was done using R statistical software version 3.5.2. Research data were analyzed at univariate, bivariate, and multivariate levels. Unit analysis was determined by the distribution of variables. In numerical variables, normality of distribution was also needed to be assessed. Histograms, boxplots, and Q-Q plots were used as visual aids to evaluate trends in the distribution of numerical variables, whereas normality was formally tested using the Shapiro-Wilk test. Bar graphs were used to evaluate categorical variables. In descriptive analysis, differences in male and female subjects according to a number of characteristics were further investigated by the use of appropriate statistical methods (U-Mann-Whitney test on numerical variables, $\chi 2$ on categorical variables).

The bivariate relationship between the form of forehead wrinkle, earlobe type, and the severity of coronary artery lesions according to Gensini scores was assessed using the Kruskal-Wallis test and $\chi 2$ test. For the second test, the Gensini score was changed to an ordinal variable based on its mortality risk: 0-6, 7-13, and >13. Quantification of the relationship between these variables with the Gensini score (on a numerical scale) was performed by linear regression analysis.

Score 0   Score 1

Score 2   Score 3

Figure 2. Visual classification of forehead wrinkles using a score system (Visat Study) (Source: Esquirol et al, 2015[11]

Modeling was carried out univariable (without controlling other variables) and multivariable.

RESULTS

This study was conducted from May to July in 2019 on stable angina patients in the outpatient cardiovascular clinic and inpatient ward at Prof. Dr. R. D. Kandou Hospital Manado. There were 40 samples that met the inclusion and exclusion criteria included in this study.

Tabel 1 showed the characteristics of the samples. The form of forehead wrinkles in sufferers of stable angina pectoris in this study were mainly classified into score 1 and 2, in which a total of 32 patients (80%) were included. Meanwhile, earlobe in sufferers of stable angina pectoris was dominated by type A morphology (65% vs 35%). The mean Gensini score in all 40 patients was around 9 (moderate risk) with a deviation of 6 units. If this score was further separated according to risk class, around a quarter (n=10) of study samples were at serious risk with a Gensini value above 13 (Table 1). The difference in the

proportion of study samples according to sexes did not affect other characteristics.

Table 1 indicates that the differences in each characteristic according to sex were not statistically significant. The variations of forehead wrinkles were almost identical on score 1 and 2 between both sexes, while the proportions of score 0 and 3 in both sexes appeared to be contradictory even though p >0.05. The distribution of earlobe shapes according to sex also did not appear to be significant (p= 0.484).

Table 2 compared variations in forehead wrinkle, earlobe, and severity of coronary artery lesions according to Gensini's assessment. Overall, no significant differences were found for each existing bivariate relationship. In the comparison of earlobe types and forehead wrinkle scores, for example, the differences in the proportions of each earlobe type for each class of forehead wrinkle scores were relatively not significantly different (p=0.722). Gensini scores in patients with non-zero forehead wrinkle scores were clearly 4−5 units greater than those with a zero score. However, the sample size of patients with zero forehead wrinkle scores was indeed too small

(n=3) to make the differences meaningful. The classification of Gensini scores according to mortality risk also did not appear to change the relationship between severity of coronary artery lesions with the form of forehead wrinkles.

Table 3 displayed the results of regression modeling of research variables with Gensini scores (on a numerical scale) as outcomes. In the univariable model, the relationship between form of forehead wrinkles and the Gensini value was as expected where patients with score 0 on average had a change in Gensini scores of almost four units smaller

Table 1. Characteristics of stable angina pectoris patients in the study, n (%)

Characteristics	Total (N=40)	Woman (n=12)	Man (n=28)	p^a
Age, μ ±SD	60.7 ± 7.8	63.7 ± 8.5	59.5 ± 7.2	0.119
Hyperuricemia	13 (32)	3 (25)	10 (36)	0.716
Dyslipidemia	11 (28)	3 (25)	8 (29)	>0.999
Type 2 DM	18 (45)	5 (42)	13 (46)	>0.999
Hypertension	19 (48)	6 (50)	13 (46)	>0.999
Number of blood vessels involved				
None/No. Significant	5 (12)	1 (8)	4 (14)	>0.999
1 VD	7 (18)	2 (17)	5 (18)	
2 VD	11 (28)	3 (25)	8 (29)	
3 VD	17 (42)	6 (50)	11 (39)	
Left main	9 (22)	3 (25)	6 (21)	>0.999
Forehead wrinkle				
Skor 0	3 (8)	2 (17)	1 (4)	0.587
Skor 1	17 (42)	5 (42)	12 (43)	
Skor 2	15 (38)	4 (33)	11 (39)	
Skor 3	5 (12)	1 (8)	4 (14)	
Earlobe				
Type A	26 (65)	9 (75)	17 (61)	0.484
Type B	14 (35)	3 (25)	11 (39)	
Gensini, μ ± SD	9,2 ± 5.8	9.4 ± 6.9	9.1 ± 5.4	0.893
0 – 6	15 (38)	5 (42)	10 (36)	>0.999
7 – 13	15 (38)	4 (33)	11 (39)	
>13	10 (25)	3 (25)	7 (25)	

DM, diabetes mellitus; VD, vessel disease. The Mann-Whitney U test on numerical variables, χ2 test on categorical variables

Table 2. Bivariate relationship between classification of forehead wrinkle scores, earlobe types, and Gensini modified scores

Variables	Forehead Wrinkle Scores					
	Total (N = 40)	0 (n = 3)	1 (n = 17)	2 (n = 15)	3 (n = 5)	p^a
Earlobe						
Type A	26 (65)	1 (33)	11 (65)	10 (67)	4 (80)	0.722
Type B	14 (35)	2 (67)	6 (35)	5 (33)	1 (20)	
Gensini, μ ± SD	9.2 ± 5.8	5.3 ± 5.9	8.9 ± 5.2	10.3 ± 6.5	9.2 ± 6.2	
0 – 6	15 (38)	2 (67)	6 (35)	5 (33)	2 (40)	0.940
7 – 13	15 (38)	1 (33)	7 (41)	6 (40)	1 (20)	
>13	10 (25)	0 (0)	4 (24)	4 (27)	2 (40)	

DM, diabetes mellitus; VD, vessel disease. The Kruskal-Wallis test on numerical variables, test χ2 categorical variables.

Table 3. Linear regression model relationship of severity of coronary artery lesions with forehead wrinkle and earlobe classification in stable angina pectoris patients

Variables	Gensini Score Changes			
	Univariable Model		Multivariable Model	
	β (95% CI)	p	β (95% CI)	p
Forehead Wrinkle				
Score 0	-3,61 (-11,05 ; 3,84)	0,332	-0,63 (-5,46 ; 4,19)	0,799
Score 1 (Ref.)	0,00		0,00	
Score 2	1,39 (-2,82 ; 5,61)	0,507	0,48 (-2,19 ; 3,15)	0, 727
Score 3	0,26 (-5,79 ; 6,31)	0,931	-0,56 (-4,60 ; 3,47)	0, 786
Earlobe				
Type A (Ref.)	0,00		0,00	
Type B	-8,70 (-11,40 ; -6,00)	<0,001	-1,10 (-6,99 ; 4,78)	0,716
Confounding variables				
Age	0,01 (-0,24 ; 0,25)	0,960	-0,09 (-0,26 ; 0,07)	0,280
Male vs Female	-0,27 (-4,36 ; 3,82)	0,893	*	
Dyslipidemia	-1,06 (-5,25 ; 3,12)	0,610	*	
Hyperuricemia	1,15 (-2,84 ; 5,13)	0,563	*	
Type II DM	1,81 (-1,91 ; 5,53)	0,330	*	
Hypertension	2,68 (-0,97 ; 6,33)	0,145	*	
Number of coronary arteries involved				
None/not significant (Ref.)				
1 VD	1,23 (-3,11 ; 5,56)	0,569	1,40 (-3,03 ; 5,83)	0,540
2 VD	6,98 (2,99 ; 10,97)	0,001	5,62 (-0,70 ; 11,94)	0,092
3 VD	11,51 (7,74 ; 15,27)	0,000	9,84 (2,72 ; 16,96)	0,011
Left main	6,02 (1,99 ; 10,05)	0,004	2,37 (-0,69 ; 5,43)	0,140

CI, confidence interval; DM, diabetes mellitus; VD, vascular disease. A multivariable model controls the variability of age and the number of blood vessels involved.

than those with a score of one (reference). Meanwhile, patients with score 2 and 3 appeared to have a Gensini value of 0.26 to 1.39 units greater than those with a score of one. Unfortunately, none of these relationships was statistically significant.

Univariable modeling (without controlling for other variables) Gensini score in the form of earlobe as a predictor gave quite an interesting result. More specifically, patients with type B earlobe looked on average had a much smaller Gensini value than type A (reference); their Gensini scores were almost 9 points lower than patients with earlobe A type (p<0.001). Even so, this trend did not continue in models that controlled the variability of other variables.

The results of multivariate modeling did not show any significant results. The direction of the relationship was partly changed but partly remained with a slight change in magnitude (Table 3). For example, patients with type B earlobe only had on average a Gensini score of 1 point lower than those with

type A (p>0.001). In the forehead wrinkle group, the multivariate model did not show any association between the score of this variable and the distribution of Gensini scores.

The final part of Table 3 showed the relationship between the number of blood vessels involved and the Gensini score. This relationship seemed to be of dose-response characteris-tics, where Gensini score tended to be higher the more blood vessels were involved. This were seen in both the univariable and multivariable models. The presence or absence of left main appeared to increase Gensini score (p=0.004), but after the variability of other variables was controlled, the relationship disappeared (p=0.140).

DISCUSSION

This study involved 40 subjects with a male predominant characteristic, in which the percentage of male subjects was 70%. The mean age on the study subjects was almost 61±8 years. Most of the subject population with stable angina pectoris had a history of

hypertension, dyslipidemia, hyperuricemia and type 2 diabetes mellitus.

Based on several studies recorded in a review in the United States in 2017, it was found that stable angina affects more than 8 million people in the United States each year.[15] Patients with stable angina have reduced quality of life and are utilizing greater health resources.[16] Even though the exact number is unknown, nearly 300,000 percutaneous coronary intervention measures have been performed on patients categorized as stable angina pectoris annually in hospitalized patients in the United States. Number of PCI also increased significantly in patients with stable angina pectoris treated as outpatients. Although randomized controlled trials and meta-analyses of these trials indicate that the initial PCI strategy in Stable Angina patients does not improve survival or prevent myocardial infarction beyond what is achieved with optimal medical therapy (OMT), more than half of this procedure has been performed on patients not treated with OMT.[17,18]

The prevalence of angina increases with age in men and women, from 4-7% in men aged 45-64 to 12-14% in men aged 65-84 years, and from 5-7% in women aged 45-64 years to 10-12% in women aged 65-84.48.[19] In Indonesia, based on the 2013 Riskesdas, CHD ranks the second largest cause of death from cardiovascular diseases after stroke.[20]

Lucenteforte et al[21] concluded that ELC was independently associated with an increased risk of coronary artery disease with similar findings for young and old, men and women, and across ethnic groups. This study also showed through coronary angiography examination that some patients experience 3 VD, although the proportion is smaller than patients with 1-2 VD. For the record, there were five patients (12%) without lesions or insignificant vascular involvement. Nine patients (22%) experienced VD accompanied by left main involvement (LM).

The form of forehead wrinkles in sufferers of stable angina pectoris in this study was mainly classified into score 1 and 2, which totaled 32 (80%) patients. Meanwhile, their earlobe forms were dominated by type A (65% vs 35%). The mean Gensini score in all 40 patients was around 9 (moderate risk) with a deviation of 6 units. If these scores were further separated according to risk class, it was shown that around a quarter (n=10) of study populations were at serious risk with a Gensini value above 13.

Table 2 compared variations in forehead wrinkles, earlobe crease, and severity of coronary artery lesions according to Gensini's modified assessment. Overall, no significant differences were found for each existing bivariate relationship. In the comparison of earlobe types and forehead wrinkle scores, for example, the difference in the proportion of each type of earlobe crease for each class of forehead wrinkle scores was relatively not much different (p=0.722). Research that linked the identification of earlobe crease and forehead wrinkles together had never been done before.

In univariable modeling (without controlling other variables), Gensini score with earlobe crease form as a predictor gave quite an interesting result. More specifically, patients with type B earlobe crease morphology on average had a much smaller Gensini value than type A (reference); their Gensini score was almost 9 points lower than patients with type A earlobe crease morphology (p <0.001). Even so, this trend did not continue in models that controlled the variability of other variables. The study of Christoffersen et al. reported that earlobe crease was associated with an increased risk of ischemic heart disease and myocardial infarction that was independent of chronological age and other cardiovascular risk factors.[22]

Multivariate modeling (Table 3) did not show any significant results. The direction of the relationship was partly changed but partly remained with a slight change in magnitude. For example, patients with type B earlobe only had a Gensini score on average about 1 point lower than those with type A (p> 0.001). The Copenhagen City Heart Study had confirmed no association between earlobe crease with blood pressure and diabetes, and also no relationship with lipid levels or other cardiovascular risk factors. There was a relationship with smoking and obesity, as

ELC was independently associated with increased accumulation of smoking exposure (in a year) and body mass index.[23-25]

The Gensini modification score in patients with non-zero forehead wrinkle scores was clearly 4−5 units greater than those with a zero score (Table 2). However, the sample size of patients with zero forehead wrinkle scores was indeed too small (n=3) to make the differences meaningful. The classification of Gensini score according to mortality risk as shown in Table 2 also did not appear to change the relationship between severity of coronary artery lesions and the form of forehead wrinkles.

Table 3 displayed the results of regression modeling of the variables with Gensini scores (on a numerical scale) as outcomes. In the univariable model, the relationship between the form of forehead wrinkles and the Gensini value was seen as expected where patients with zero forehead wrinkle score on average had a Gensini score of almost four units smaller than those with a score of one (reference). Meanwhile, patients with score 2 and 3 appeared to have Gensini values of 0.26 to 1.39 units greater than those with a score of one. Unfortunately, none of these relationships were statistically significant.

In the forehead wrinkle group, the multivariate model did not indicate any association between the score of this variable with the distribution of Gensini scores in patients. The forehead wrinkle score was relatively not much different (p=0.722). This result was indeed different from the first and only study (VISAT study) ever conducted where it was found that the number and depth of forehead wrinkles was related to cardiovascular death regardless of chronological age and classic cardiovascular risk factors.[11]

Limitation of this study is that it is a cross-sectional study with limited length of study duration and number of study samples.

CONCLUSION

There is a strong positive relationship between earlobe crease type and the severity of coronary artery stenosis as assessed by a modified Gensini score, but there is no relationship between the type of forehead wrinkles and the severity of coronary artery stenosis as assessed by modified Gensini score.

Conflict of interest

The authors declare no conflict of interest in this study.

Data Availability Statement

All the data supporting the results were shown in the paper, and can be applicable from the corresponding author.

REFERENCES

1. World Health Organization. World health statistics 2018: monitoring health for the SDGs. 2018. Available from: https://apps.who.int/iris/handle/10665/272596
2. Prabhakaran D, Jeemon P, Sharma M, Roth GA, Johnson C, Harikrishnan S, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the global burden of disease study 1990–2016. Lancet Glob Health. 2018;6(12):1339–51. DOI: 10.1016/S2214-109X(18)30407-8
3. Benjamin EJ, Muntner P, Aonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics - 2019 update: a report from the American Heart Association. Circulation. 2019; 139(10):e56–e528.
4. Badan Penelitian dan Pengembangan Kesehatan Depkes RI. Riset Kesehatan Dasar. 2007. Available from: https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/
5. Juzar DA, Danny SS, Irmalita, Tobing DP, Firdaus I, Rossimarina V, et al. Pedoman Tatalaksana Sindroma Koroner Akut. Jakarta: PP PERKI; 2018.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
7. Oda N, Maruhashi T, Kishimoto S, Kajikawa M, Iwamoto Y, Iwamoto A, et al. Relation of the bilateral earlobe crease to endothelial dysfunction. Am J Cardiol. 2017;119(12):1983-8.
8. Iorgoveanu C, Zaghloul A, Desai A, Krishnan AM, Balakumaran K, et al. Bilateral earlobe crease as a marker of premature coronary artery disease. Cureus. 2018;

10(5):e2616. Doi: 10.7759/cureus.2616

9. Bardawil T, Khalil S, Bergqvist C, Abbas O, Kibbi AG, Bitar F, et al. Genetics of inherited cardiocutaneous syndromes: a review. Open Heart. 2016;3(2):e000442. Doi: 10.1136/openhrt-2016-000442.

10. Lopez CR, Diaz HG, Mariscal RM, Cervilla PJ, Graciani A, Sendon JL, et al. Earlobe creases shapes and cardiovascular events. Am J Cardiol. 2015;116(2):286-93.

11. Esquirol Y, Ferrieres J, Marquie JC, Huo Yung Kai S, Niezborala M, Berard E, et al. Forehead wrinkles and risk of all-cause and cardiovascular mortality over 20-year follow up in working population: VISAT study. Arch Cardiovasc Dis. 2018;10(1):125-6. Doi: 10.1016/j.acvdsp. 2017.11.163.

12. Paul SP. The epistemology of wrinkles: from geology and anatomy to physiology. Int J Biomed. 2016;6(3):237-49.

13. Kashani H, Zeraati H, Mohammad K, Goodarzynejad H, Mahmoudi M, Sadeghian S, et al. Analyzing Gensini score as a semi-continuous outcome. J Tehran Heart Cent. 2016;11(2):55-61.

14. Abaci O, Kocas C, Oktay V, Arslan S, Turkmen Y, Bostan C, et al. Relationship between myocardial performance index and severity of coronary artery disease in patients with non-ST-segment elevation acute coronary syndrome. Cardiovasc J Afr. 2017;28(1):4-7.

15. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics - 2016 update: a report from the American Heart Association. Circulation. 2016;133(4): 38-360.

16. Eisen A, Bhatt DL, Steg PG, Eagle KA, Goto S, Guo J, et al. Angina and future cardiovascular events in stable patients with coronary artery disease: insights from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. J Am Heart Assoc. 2016;5 (10):1-11. Doi: 10.1161/JAHA.116. 004080

17. Mitchell JD, Brown DL. Harmonizing the paradigm with the data in stable coronary artery disease: a review and viewpoint. J Am Heart Assoc. 2017;6(11): 1-12. Doi:10.1161/JAHA.117. 007006.

18. Juzar DA, Firdaus I, Alkatiti AA, Wicaksono SH, Pakpahan H, Dwiputra B. Panduan Evaluasi dan Tatalaksana Angina Pektoris Stabil. Jakarta: PP PERKI; 2019.

19. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.

20. Badan Penelitian dan Pengembangan Kesehatan Depkes RI. Riset Kesehatan Dasar. 2013. Available from://efaidnb mnnnibpcajpcglclefindmkaj/https://pus datin.kemkes.go.id/resources/download

21. Lucenteforte E, Romoli M, Zagli G, Gensini GF, Mugelli A, Vannacci A. Ear lobe crease as a marker of coronary artery disease: a meta-analysis. Int J Cardiol 2014;175(1):171-5.

22. Christoffersen M, Frikke-Schmidt R, Schnohr P, Jensen GB, Nordestgaard BG, Tybjærg-Hansen A. Visible age-related signs and risk of ischemic heart disease in the general population: a prospective cohort study. Circulation 2014;129(9): 990-8.

23. Bawaskar HS, Bawaskar PH, Bawaskar PH. Diagonal ear lobe crease: a premonitory diagnostic sign of impeding ischemic heart disease. J Family Med Prim Care 2018;7(6):1361-7.

24. Koyama T, Watanabe H, Ito H. The association of circulating inflammatory and oxidative stress biomarker levels with diagonal earlobe crease in patients with atherosclerotic diseases. J Cardiol 2016; 67(4):347–351.

25. Kadam YR, Shah YM, Kore P. Diagonal earlobe crease: prevalence and association with medical ailments. J Clin Prev Cardiol. 2018; 7(2):49-53.