Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1491752

J Med Palliat Care. 2024;5(3):182-187

The role of cardiothoracic ratio in predicting coronary artery atherosclerosis in young adult patients

Semih Sağlık

Department of Radiology, Faculty of Medicine, Siirt University, Siirt, Turkiye

Cite this article as: Sağlık S. The role of cardiothoracic ratio in predicting coronary artery atherosclerosis in young adult patients. *J Med Palliat Care*. 2024;5(3):182-187.

Received: 29.05.2024 ◆ **Accepted**: 25.06.2024 ◆ **Published**: 28.06.2024

ABSTRACT

Aims: This study aimed to determine the role of cardiothoracic ratio in predicting coronary atherosclerosis in young adult patients.

Methods: In this single-center retrospective study, young adult patients who underwent coronary computed tomography angiography (CTA) with suspicion of coronary artery disease between October 2022 and May 2024 were included. Demographic and clinical histories of all patients were determined from the medical record system. Coronary artery calcium scores (CACSc) and cardiothoracic ratios (CTR) of the patients in question were calculated and recorded from the coronary CTA images.

Result: A total of 264 young adult patients under the age of 45, with an average age of 42.2±3.1 years, were included in this study. The patients included in the study were divided into two groups according to the presence of atherosclerotic calcific plaque in coronary CTA. Smoking history, hyperlipidemia, hypertension and diabetes mellitus history were significantly different in the two patient groups (for all, $p<0.05$). In univariate regression analysis, hyperlipidemia, diabetes mellitus, hypertension, smoking history and high CTR values were determined as risk factors for coronary atherosclerotic calcific plaque.

Conclusion: Our findings show that the risk of coronary atherosclerosis is high in young adult patients with CTR values above 0.5150.

Keywords: Cardiothoracic ratio, coronary artery calcium score, atherosclerotic plaque, coronary computed tomography angiography

INTRODUCTION

Coronary artery disease (CAD) is among the leading causes of mortality and morbidity worldwide.[1] Atherosclerosis is the most important cause of the disease in its pathophysiological process, and coronary artery calcification is a risk marker for subclinical atherosclerosis.[2,3] Acute coronary events may be the first sign of coronary artery disease in asymptomatic individuals.[4] Therefore, identifying patients at risk before these events occur will significantly reduce cardiovascular mortality rates. Coronary computed tomography angiography (CTA) or coronary angiography, which has a high diagnostic rate, can be used to detect these patients. However, the use of these examinations as a screening method is limited due to reasons such as cost, radiation and potential kidney damage.[5] This has increased the interest in non-invasive screening methods for the detection of potential CAD patients.

Cardiothoracic ratio (CTR) is a radiographic parameter that evaluates heart size and functions, which was first described in 1919.[6] Normal values are between 0.42 and 0.50, and a value above 0.50 is considered cardiomegaly.[7] Studies conducted with the widespread use of computed tomography (CT) have found high correlations and minimal differences between CTR measured by CT and CTR measured by radiographs.[8] CTR has been used in the diagnosis and follow-up of many respiratory and cardiovascular diseases and has even been found to be one of the prognostic factors in terms of cardiovascular mortality.[9]

This study aimed to determine the role of cardiothoracic ratio in predicting coronary atherosclerosis in young adult patients.

METHODS

The study was carried out with the permission of the Siirt University Faculty of Medicine Non-invasive Ethics Committe(Date:04.04.2024, Decision No: 105146).

This single-center retrospective study included young adult patients under 45 years of age who underwent coronary CTA with suspected coronary artery disease between October 2022 and May 2024. The demographic characteristics (age and gender), body-mass index (BMI), diabetes mellitus, hypertension, hyperlipidemia and smoking history of the patients in question before coronary CTA were scanned in the medical record system and recorded. The inclusion criteria

Corresponding Author: Semih Sağlık, drsmhsglk@gmail.com

for diabetes mellitus, hypertension and hyperlipidemia were defined as being diagnosed and/or receiving medication for these diseases. For smoking, the criterion was determined as smoking at least 10 cigarettes per day for at least 1 year. BMI (kg/m^2) was calculated as weight (kg) divided by the square of height (m). Individuals with known or detected respiratory disease and any cardiac disease other than CAD were excluded.

To calculate the calcium load in all patients, the thorax area from the bottom of the tracheal carina to the heart base was imaged without intravenous contrast administration. Imaging was performed with a 128-slice CT device (General Electric Revolution EVO, GE Medical Systems, Milwaukee, WI, USA). The imaging protocol for coronary calcium scoring was as follows: gantry rotation time 0.35 seconds, tube voltage 120 kv, 100 mAs, and slice thickness 2.5 mm. The total coronary artery calcium score (CACSc) of all patients was obtained by summing the calcium values obtained from all coronary artery tracings and Agatston scoring was used.[10]

Coronary CTA images were reconstructed to create a maximum scanning field of view (SFOV). CTR was obtained by dividing the longest transverse heart diameter measured from the outer myocardium to the outer myocardium at the level of the diaphragmatic dome in SFOV axial sections by the longest transverse thoracic diameter measured from the inner thoracic wall to the inner thoracic wall (Figure 1).[8,11]

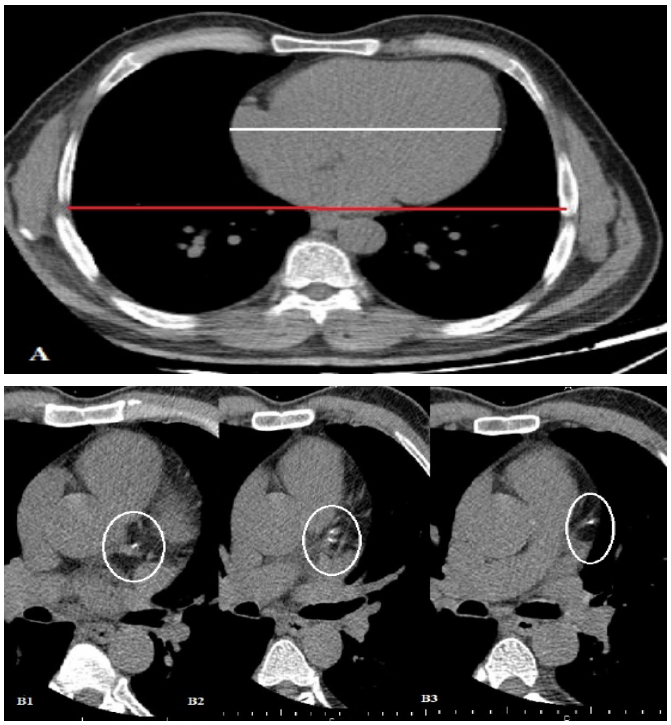

Figure 1 (A-B): Case example of a 44-year-old male patient with a history of smoking and hyperlipidemia, cardiotoxic index of 0.57 and coronary artery calcium score of 61. (A) Axial images of coronary CTA maximum scanning field of view (SFOV) showing measurement of cardiac indices. CT-derived cardiothoracic ratio: The white arrow depicts the greatest transverse cardiac diameter and the red arrow indicates the greatest transverse thoracic diameter (It has been included at this level only to simulate the measurement and to complete the figure). Calcific plaques are observed in the proximal (B1), middle (B2) and distal (B3) segments of the left descending coronary artery on non-contrast CT images.

Statistical Analysis

Data analyzes of our study were determined using SPSS 20.0 software (Statistical Package for the Social Sciences, Chicago, IL). Variables related to qualitative data are expressed as number (n) and percentage (%), and variables related to quantitative data are expressed as mean ± standard deviation (SD).In the evaluation of the study data, Student's t test was used for intergroup comparisons of normally distributed variables and mann-whitney U test was used for intergroup comparisons of non-normally distributed parameters. Chi-square test or Fisher's exact test was applied for the comparison of categorical variables depending on the sample size. univariate and multivariate binary logistic regression analyzes were used to determine the risk factors affecting coronary atherosclerosis. ROC (Receiver Operating Characteristic) curve analysis was used to determine whether CTR was a prognostic indicator in predicting coronary atherosclerosis and to determine optimal cut-off values. The significance level for statistical results was accepted as $p<0.05$.

RESULTS

A total of 264 young adult patients with an average age of 42.2±3.1 years were included in this study. Of all patients, 14.8% had hypertension, 15.9% had hyperlipidemia, 12.5% had diabetes mellitus and 36.8% had a history of smoking. CACSc values of patients with a history of hyperlipidemia, diabetes mellitus, hypertension and smoking were significantly higher than those without ($p<0.05$) (Table 1). A significant strong positive correlation was found between CTR and CACSc values ($r=0.757$, $p<0.001$) (Figure 2).

Table 1. Comparison of clinical variables and coronary artery calcium score values.

Parameters	CACSc	p values
Smoking		
No	4.4±9.6	0.001a
Yes	20.6±32.9	
Hypertension		
No	9.2±19.9	0.009a
Yes	19.6±35.6	
Hyperlipidemia		
No	8.9±22.1	0.005a
Yes	19.8±26.1	
Diabetes mellitus		
No	8.1±17.7	0.001a
Yes	28.3±42.1	

Notes: aMann Whitney U-test with median ± interquartile range (IQR). Statistically significant results ($p < 0.05$).
Abbreviations: CACSc, Coronary artery calcium scoring

The patients included in the study were divided into two groups according to the presence of atherosclerotic calcific plaque in coronary CTA. Group 1 included patients without coronary atherosclerotic calcific plaque and group 2 included patients with coronary atherosclerotic calcific plaque.

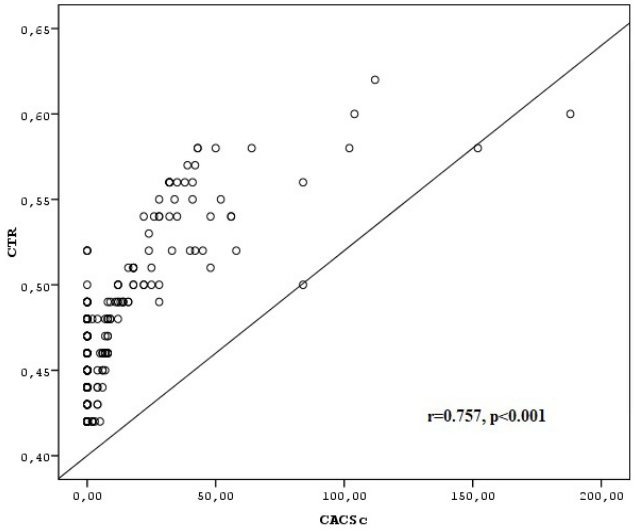

Figure 2. Correlation between coronary artery calcium score and cardiothoracic ratio in patients. Circles are data points, and diagonal lines are means.

No statistically significant difference was found between the two groups in terms of age and BMI (for all, p>0.05). However, smoking, hyperlipidemia, hypertension and diabetes mellitus history were significantly different in the two patient groups (for all, p<0.05). CTR values were statistically higher in group 2 patients (p<0.001, Figure 3). Demographic and clinical characteristics and CTR values between both groups are compared in Table 2.

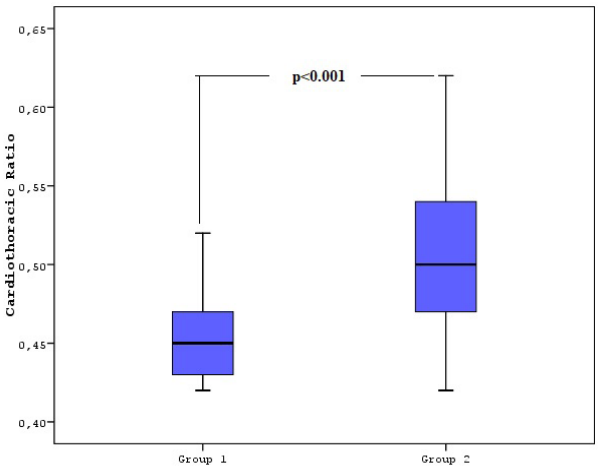

Figure 3. Boxplot of the distribution of cardiothoracic ratio among groups. The horizontal lines inside each box represent the mean values and the lower and upper rows of each box represent the minimum and maximum values, respectively.

In the receiver operating characteristics (ROC) curve analysis test of CTR values, the AUC values were determined as 0.836 (0.783-0.889) with a 95% confidence interval and therefore were considered statistically significant (p <0.001, Figure 4). Accordingly, when the cut-off value of CTR was taken as ≥ 0.5150 in predicting the presence of coronary atherosclerotic calcific plaque, its sensitivity was determined as 80.4% and its specificity was determined as 68.8%.

Regression analysis was used to determine effective parameters in predicting the presence of coronary atherosclerotic calcific plaque. In univariate regression analysis, hyperlipidemia (yes or no), diabetes mellitus (yes or no), hypertension (yes or no), smoking history (yes or no) and high CTR values (≥ 0.5150) were identified as risk factors for coronary atherosclerotic calcific plaque. In multivariate regression analysis, smoking history (p=0.001, OR: 1.55; 95% confidence interval (CI), 0.819-2.93) and CTR values above 0.5150 (p<0.001, OR: 45.8; 95% confidence interval (CI), 14.5-144.4) were independently associated with coronary atherosclerotic calcific plaque (Table 3).

Table 2: Baseline characteristics and comparison of variables among groups

Parameters	Group 1 (n=158)	Group 2 (n=106)	Total (n=264)	p values
Age (years)	42.3±2.8	42.1±3.5	42,2±3,1	0.739a
BMI (kg/m²)	25.3±4.1	25.4±4	25.4±4.1	0.797a
CACSc	0	26.7±30.2	10.7±23.1	<0.001a
Smoking, n (%)				
No	112 (70.9%)	50 (49.1%)	162 (63.2%)	0.001b
Yes	46 (29.1%)	56 (50.9%)	102 (36.8%)	
Hypertension, n (%)				
No	140 (88.6%)	85 (80.2%)	225(85.2%)	0.044b
Yes	18 (11.4%)	21 (19.8%)	39 (14.8%)	
Hyperlipidemia, n (%)				
No	139 (87.9%)	83 (78.3%)	222 (84.1%)	0.04b
Yes	19 (12.1%)	23 (21.7%)	42 (15.9%)	
Diabetes mellitus, n (%)				
No	144 (91.1%)	87 (82.1%)	231 (87.5%)	0.037c
Yes	14 (8.9%)	19 (17.9%)	33 (12.5%)	
CTR	0.4518±0.023	0.5039±0.046	0.4727±0.043	<0.001d

Notes: aStudent's t-test with mean ± standard deviation (SD). bFisher's Exact test with n (%). cChi-Square with n (%).dMann Whitney U-test with median ± interquartile range (IQR). Statistically significant results (p < 0.05).
Abbreviations: CACSc, Coronary artery calcium scoring; BMI, Body Mass Index; CTR, Cardiothoracic ratio

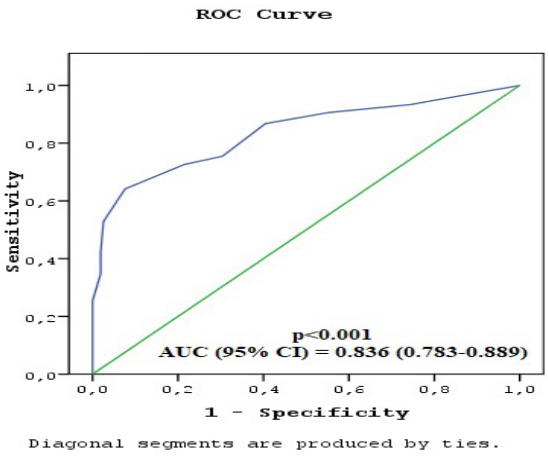

Figure 4. The receiver operating characteristic (ROC) curve and the area under the ROC (AUC) of cardiothoracic ratio in predicting the presence of coronary atherosclerotic calcific plaque

Table 3. Univariate and multivariate binary logistic regression analysis results for determining risk factors for coronary atherosclerotic calcific plaque

	Univariate		Multivariate	
	p values	OR (CI 95%)	p values	OR (CI 95%)
Smoking Yes, against no	<0.001	2.72 (1.63-4.55)	0.001	1.55 (0.819-2.93)
Hyperlipidemia Yes, against no	0.037	2.02 (1.04-3.94)	ns	
Diabetes mellitus Yes, against no	0.032	2.24 (1.07-4.70)	ns	
Hypertension Yes, against no	0.013	1.01 (1.003-1.027)	ns	
CTR ≥0.5150 against <0.5150	<0.001	43.12 (14.88-124.87)	<0.001	45.86 (14.56144.42)

Note: Statistically significant results (p < 0.05).
Abbreviations: ns, not significant; OR, Odds ratio; CI, Confidence interval; CTR, Cardiothoracic ratio

DISCUSSION

CAD is one of the most common causes of death, usually occurring due to atherosclerosis in the coronary arteries. Coronary artery calcification detected by coronary CTA is a highly specific indicator of atherosclerosis.[12] Coronary CTA has become a standard imaging modality for the diagnosis of CAD in symptomatic patients with recent technological advances. However, reasons such as radiation, cost and contrast material requirement prevent this method from being a screening method in asymptomatic individuals.[13] For this reason, many tests such as high-sensitivity C-reactive protein (hs-CRP), carotid intima-media thickness, aortic pulse wave velocity, and ankle-brachial index have been recommended and used to determine subclinical atherosclerosis.[14-20] However, we have not found a comprehensive study in the literature examining the relationship between CTR and coronary artery calcification in young patients. The most important finding of this study was that increased CTR values were independently associated with coronary artery calcification.

Many heart diseases such as cardiomyopathy, pericardiac effusion, heart failure, heart valve diseases, cardiomegaly and congenital heart anomalies can cause an increase in heart size.[21] Ischemic cardiomyopathy is one of the most important causes of heart failure worldwide, resulting from obstructive coronary artery disease.[22] As a result of myocardial damage caused by ischemia, ventricular dysfunction, adverse cardiac remodeling and heart failure may develop.[23] Changes in heart size play an important role in early detection and determining the severity of these diseases.

CTR is a simple and rapid method that reflects functional and morphological changes in the heart.[24] This method has been used as a prognostic factor in many disease groups. During a 4-year follow-up period in hemodialysis patients, high CRT values have been shown to be associated with an increased risk of cardiovascular disease independent of other risk factors.[9] It has also been determined that CTR values above 0.55 are one of the most important independent risk factors affecting mortality rates in hemodialysis patients.[25] In the 4-year follow-up of patients who underwent rheumatic heart valve surgery, it was shown that patients with high CTR values were associated with poor prognosis.[26] Eslami et al.[27] reported that increased CTR values are a strong indicator of mortality in hospitalized patients due to COVID-19 infection. Wilhelmsen et al.[28] argued that increased CRT values could predict CAD mortality independently of other traditional risk factors in a study conducted in middle-aged men. Treasure et al.[29] reported that endothelial dysfunction, which is an early indicator of atherosclerotic coronary artery disease, is associated with increased left ventricular volume. To our knowledge, this is the first study to examine the role of CRT in predicting the presence of coronary artery calcification in young patients. In our study, CRT was significantly higher in the group with coronary artery calcification, and the cut-off value in the ROC analysis was 0.5150. CRT above this value emerged as an independent risk factor for coronary artery calcification in multivariable logistic regression analysis. Therefore, our findings show that CRT levels may be an effective and reliable parameter that can be used to predict coronary artery calcification.

Hypertension, hyperglycemia, dyslipidemia and smoking are the most important known risk factors for CAD.[30] Smoking increases the risk of complications of both the primary pathogenesis of cardiovascular diseases and other etiological causes.[31] The most common risk factor found in young patients with coronary artery disease is smoking with a rate of up to 60%.[32] In this study, consistent with the literature, the most common risk factor detected in young patients with coronary atherosclerosis was smoking, with a rate of 50.9%. Numerous studies show that smoking is independently associated with coronary atherosclerosis.[33-35] In our study, smoking was significantly higher in the group with coronary atherosclerosis and emerged as an independent risk factor in multivariate logistic regression analysis.

Hyperglycemia is a strong risk factor that causes atherosclerosis both directly and indirectly.[36,37] Many studies have found that the risk of coronary atherosclerosis is increased in young patients with diabetes.[36-38] One of the most important risk factors leading to the emergence, progression and complication of atherosclerosis is dyslipidemia.[39-41] Stone et al.[42] found that the risk of atherosclerosis increased with increasing exposure time in young adults with dyslipidemia. Many studies have shown that dyslipidemic status is an independent risk factor for coronary atherosclerosis in all age groups.[43,44] Hypertension is an important risk factor for CAD independent of other risk factors.[33,45] It has been determined that the risk of CAD in hypertensive individuals increases 2-3 times compared to normotensive individuals.[46] Kang et al.[47] reported a gradual increase in the risk of coronary atherosclerosis with increases in systolic blood pressure in young patients in a large-scale study. In our study, consistent with the literature, CACSc values were significantly higher in patients with a history of diabetes, dyslipidemia and hypertension, and they emerged as risk factors in univariate logistic regression analysis.

Limitations

The primary limitation of our study is that it is single-center and retrospectively designed. Second, the patients included in the study were selected patients with clinically suspected coronary artery disease, which reduces the generalizability of the study findings. Third, information about familial CAD history, which is an important risk factor for atherosclerosis, could not be included in the statistical analysis because it was not sufficient in the registry system.

CONCLUSION

In conclusion, our findings show that the risk of coronary atherosclerosis is high in young adult patients with CTR values above 0.5150. Therefore, determining CRT levels at admission may help identify patients at high risk for coronary atherosclerosis. In fact, CTR, which is a simple, non-invasive and rapid method, may be a candidate parameter to be a screening method for the detection of coronary atherosclerosis in the young population.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Siirt University Faculty of Medicine Non-invasive Ethics Committe(Date:04.04.2024, Decision No: 105146).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Lippi G, Favaloro E, Sanchis-Gomar F. Sudden cardiac andnoncardiac death in sports: epidemiology, causes, pathogenesis,and prevention. *Semin Thromb Hemost*. 2018:44:780-786.
2. Wong ND, Hsu JC, Detrano RC, Diamond G, EisenbergH, Gardin JM. Coronary artery calcium evaluation byelectron beam computed tomography and its relation to newcardiovascular events. *Am J Cardiol*. 2000:86:495-8.
3. Budoff, Matthew J., et al. "Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA)." *European heart journa*l. (2018):2401-2408.
4. Garcia-Garcia, Hector M., et al. "Imaging plaques to predict and better manage patients with acute coronary events." Circulation research 114.12(2014):1904-1917.
5. Tang W, Shen X, Li H, et al. The independent and incremental value of ultrasound carotid plaque length to predict the presence and severity of coronary artery disease: analysis from the carotid plaque length prospective registry. *Eur Heart J Cardiovasc Imaging*. 2020:21(4),389-396.
6. Danzer CS. The cardiothoracic ratio. *Am J Med* Sci. 1919;157, 513–554.
7. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol*. 2002:40,1801-1808
8. Gollub MJ, Panu N, Delaney H, et al. Shall we report cardiomegaly at routine computed tomography of the chest? *J Comput Assist Tomogr*. 2012:36(1):67-71.
9. Yotsueda R, Taniguchi M, Tanaka S, et al. Cardiothoracic ratio and all-cause mortality and cardiovascular disease events in hemodialysis patients: T*he Q-Cohort Stu*dy. *AJKD*. 2017:70,84-92.
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte Jr M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *JACC*. 1990:15(4),827-832.
11. Miller JA. Cardiac dimensions derived fromm helical CT: correlation with plain film radiography. *Internet J Radiol*. 2000; 2020;1(1).
12. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *JACC*. 2018; 72(4)434-447.
13. Mortensen MB, Blaha MJ. Is there a role of coronary CTA in primary prevention? Current state and future directions. *Curr Atheroscler Rep*. 2021;23(8),44.
14. Patil VC, Avhad AB, Kulkarni AR, Pandere KA. High-sensitive C-reactive protein in patients with coronary artery disease. *J Nat Sci Biol Med*. 2020;11(1)39.
15. Luo H, Kou T, Yin L. High-Sensitivity C-Reactive Protein to HDL-C Ratio a predictor of coronary artery disease. *Int Heart J*. 2021; 62(6),1221-1229.
16. Liu D, Du C, Shao W, Ma G. Diagnostic role of carotid intima-media thickness for coronary artery disease: a meta-analysis. *Biomed Res Int*. 2020:9879463. doi: 10. 1155 / 2020/ 9879463
17. Bytyçi I, Shenouda R, Wester P, Henein MY. Carotid atherosclerosis in predicting coronary artery disease: a systematic review and meta-analysis. *ATVB*. 2021;41(4), e224- e237.
18. Sang T, Lv N, Dang A, Cheng N, Zhang W. Brachial-ankle pulse wave velocity and prognosis in patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *J Hypertens*. 2021;44(9),1175-1185.
19. van Hout MJ, Dekkers IA, Westenberg JJ, et al. Normal and reference values for cardiovascular magnetic resonance-based pulse wave velocity in the middle-aged general population. *JCMR*. 2021;23(1),46.
20. Xu C, Tian Q, Yu H, Ge W, Zheng H, Huang D. Predictive value of the ankle-brachial index for all-cause and cardio-cerebrovascular mortality. *Angiology*. 2023;74(7),649-656.
21. Elasan S, Yilmaz O. Cardiothoracic ratio and left ventricular ejection fraction relationship: A meta-analysis study. *Saudi Med J.* 2023;44(6),529.
22. Felker GM, Shaw LK, O'Connor CM. a standardized definition of ischemic cardiomyopathy for use in clinical research. *J Am Coll Cardiol*. 2002;39:210–218.
23. Chareonthaitawee P, Christian TF, Hirose K, Gibbons RJ, Rumberger JA. Relation of initial infarct size to extent of left ventricular remodeling in the year after acute myocardial infarction. *J Am Coll Cardiol.* 1995;25:567-573.

24. Truszkiewicz K, Poręba R, Gać P. Radiological cardiothoracic ratio in evidence-based medicine. *J Clin Med*. 2021;10(9),2016.
25. Hsu HJ, Wu IW, Hsu KH, Sun CY, Chen CY, Lee CC. Vitamin D deficiency, cardiothoracic ratio, and long-term mortality in hemodialysis patients. *Sci Rep*. 2020;10(1)7533.
26. Ito K, Ookawara S, Ueda Y, et al. A higher cardiothoracic ratio is associated with 2-year mortality after hemodialysis initiation. *Nephron Extra*. 2015;5(3),100-110.
27. Eslami V, Abrishami A, Zarei E, Khalili N, Baharvand Z, Sanei-Taheri M. The association of CT-measured cardiac indices with lung involvement and clinical outcome in patients with COVID-19. *Acad Radiol*. 2021;28(1),8-17.
28. Wilhelmsen L. Cardiothoracic ratio and relative heart volume as predictors of coronary heart disease mortality. *Eur Heart J*. 1998;19(6),826-827.
29. Treasure CB, Klein JL, Vita JA, et al. Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. *Circulation*. 1993;87(1),86-93.
30. Gao P, Wen X, Ou Q, Zhang J. Which one of LDL-C/HDL-C ratio and non-HDL-C can better predict the severity of coronary artery disease in STEMI patients. *BMC Cardiovasc Disord*.2022;22(1),318.
31. Rodgers JL, Jones J, Bolleddu SI, et al. Cardiovascular Risks Associated with Genderand Aging. *J Cardiovasc Dev Dis*.2019; 1;6(2).
32. Zeitouni M, Clare RM, Chiswell K, et al. Risk factor burden and long-term prognosis of patients with premature coronary artery disease. *J Am Heart Assoc*. 2020;9(24), e017712.
33. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *NEJM*. 1997;336(18),1276-1282.
34. Javaid A, Mitchell JD, Villines TC. Predictors of coronary artery calcium and long-term risks of death, myocardial infarction, and stroke in young adults. *J Am Heart Assoc*. 2021;10(22), e022513.
35. Loria CM, Liu K, Lewis CE, et al. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA study. *J Am Coll Cardiol*. 2007;49:2013-2020.
36. Budoff M, Backlund JYC, et al. The association of coronary artery calcification with subsequent incidence of cardiovascular disease in type 1 diabetes: the DCCT/EDIC trials. *J Am Coll Cardiol Img*. 2019;12(7 Part 2)1341-1349.
37. Goldberg RB, Stone NJ, Grundy SM. The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines on the Management of Blood Cholesterol in Diabetes. *Diabetes care*.2020;43(8),1673-1678.
38. Nezarat N, Budoff MJ, Luo Y, et al. Presence, characteristics, and volumes of coronary plaque determined by computed tomography angiography in young type 2 diabetes mellitus. *Am J Cardiol*. 2017;119(10),1566-1571.
39. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25),e1082-e1143.
40. De Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation*. 2019;139(13),e603-e634.
41. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11),e596-e646.
42. Stone NJ, Smith Jr SC, Orringer CE, et al. Managing atherosclerotic cardiovascular risk in young adults: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79(8),819-836.
43. Gaeta G, Cuomo S, Capozzi G,et al. Lipoprotein(a) levels are increased in healthy young subjects with parental history of premature myocardial infarction. *Nutr Metab Cardiovasc Dis*. 2008;18:492–496.
44. Boren J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2020;41(24),2313-2330.
45. Chen L, Chester M, Kaski JC. Clinical factors and angiographic features associated with premature coronary artery disease. *Chest*. 1995;108:364-369
46. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*. 2000;342(7),454-460.
47. Kang J, Chang Y, Kim S, Sung KC, Shin H, Ryu S. Increased burden of coronary artery calcium from elevated blood pressure in low-risk young adults. *Atheroscler*. 2019;282,188-195.