Cardiovascular disease risk prediction in scleroderma

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SUMMARY

OBJECTIVE: Cardiovascular disease risk prediction in scleroderma is important. In this study of scleroderma patients, the aim was to investigate the relationship between cardiac myosin-binding protein-C, sensitive troponin T, and trimethylamine N-oxide and cardiovascular disease risk with the Systematic COronary Risk Evaluation 2 model of the European Society of Cardiology.

METHODS: Systematic COronary Risk Evaluation 2 risk groups of 38 healthy controls and 52 women with scleroderma were evaluated. Cardiac myosin-binding protein-C, sensitive troponin T, and trimethylamine N-oxide levels were analyzed with commercial ELISA kits.

RESULTS: In scleroderma patients, cardiac myosin-binding protein-C and trimethylamine N-oxide levels were higher than healthy controls but sensitive troponin T was not ($p<0.001$, $p<0.001$, and $p=0.274$, respectively). Out of 52 patients, 36 (69.2%) were at low risk, and the other 16 (30.8%) patients were at high-moderate risk with the Systematic COronary Risk Evaluation 2 model. At the optimal cutoff values, trimethylamine N-oxide could discriminate high-moderate risk with sensitivity 76%, specificity 86% and cardiac myosin-binding protein-C with sensitivity 75%, specificity 83%. Patients with high trimethylamine N-oxide levels (≥10.28 ng/mL) could predict high-moderate- Systematic COronary Risk Evaluation 2 risk 15 times higher than those with low trimethylamine N-oxide (<10.28 ng/mL) levels (odds ratio [OR]: 15.00, 95%CI 3.585–62.765, $p<0.001$). Similarly, high cardiac myosin-binding protein-C (≥8.29 ng/mL) levels could predict significantly higher Systematic COronary Risk Evaluation 2 risk than low cardiac myosin-binding protein-C (<8.29 ng/mL) levels (OR: 11.00, 95%CI 2.786–43.430).

CONCLUSION: Noninvasive cardiovascular disease risk prediction indicators in scleroderma, cardiac myosin-binding protein-C, and trimethylamine N-oxide could be recommended to distinguish between high-moderate risk and low risk with the Systematic COronary Risk Evaluation 2 model.

KEYWORDS: Heart disease risk factors. Myosin-binding protein C. Troponin T. Trimethyloxamine. Scleroderma, systemic.

INTRODUCTION

Scleroderma (SSc) is a rare connective tissue disease characterized by endothelial dysfunction, dysregulation of innate and adaptive immunity, and diffuse fibrosis[1]. Cardiopulmonary complications such as heart failure, pulmonary fibrosis, and hypertension are the leading causes of death in SSc[2].

Troponins as cardiac biomarkers emerged as an indicator of myocyte necrosis and damage[3]. Except for cardiac ischemia, cardiac troponin-T (cTrT) levels are known to be an important marker for mortality in other heart diseases[4]. Cardiac myosin-binding protein-C (cMBPC) is a sarcomeric thick filament protein which is crucial in regulating sarcomere structure and function in the heart[5]. The increases and decreases in serum levels of cMBPC following defined myocardial injury are faster than those of sensitive troponin T (sTrT)[6]. cMBPC is degraded after myocardial infarcts, and its fragments cause disturbances in calcium transitions and heart failure in cardiomyocyte cultures[7].

The gut microbiota metabolizes dietary choline, phosphatidylcholine, L-carnitine, and betaine to produce trimethylamine N-oxide (TMAO). High levels of TMAO increase the risk of kidney failure, diabetes mellitus, heart failure, atherosclerosis, hypertension, and cancer and can lead to serious cardiovascular events including death[8,9].

This study investigated the differences in sTrT, cMBPC, and TMAO levels between the low-risk group and the high-moderate-risk group of CVDs with the Systematic COronary Risk Evaluation 2 (SCORE2) risk model in SSc.

METHODS

The study protocol was endorsed by the relevant ethics committee with protocol number 2021.232.09.18. All study participants

gave written informed consent before sample collection or the questionnaire interview.

Participants

This study included 52 female patients with SSc and 38 healthy women aged 18–65 years who applied to the rheumatology outpatient clinic of the research hospital. All the patients fulfilled the new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 classification criteria for SSc[10] and were classified in a limited or diffuse subset according to LeRoy classification[11]. The extension of cutaneous involvement was evaluated with a modified Rodnan skin score[12]. Hypertension was defined by antihypertensive medication or systolic blood pressure (BP) of 140 mm Hg or diastolic BP of 90 mm Hg on at least two occasions. Ejection fraction and pulmonary arterial pressure were evaluated using echocardiography. Patients were evaluated using the Medsger SSc Severity Scale[13] and the SCORE2 model.

Exclusion criteria were pregnancy, symptoms of heart failure, including dyspnea; venous swelling and recent major lower extremity edema; kidney involvement; or serious disease complications, such as cancer or gangrene.

Systematic coronary risk evaluation 2 risk prediction of cardiovascular disease

According to the most recent reports of the World Health Organization, European countries were grouped into four risk regions per 100,000 population, age, and sex standardized overall CVD mortality rates (ICD sections 9, I00-I99). SCORE2 risk models are designed for use in people aged 40–69 years. Since our country was in the high-risk group, it was evaluated using the table used for high-risk countries (C). SCORE2 risk was evaluated according to age, gender, systolic BP, and non-HDL-C, and a value of <10 was defined as low risk, between ≥10 and 20 as moderate risk, ≥20–30 as high risk, and ≥30 as very high risk of CVD[14].

Laboratory assessments

The serum routine biochemical tests were analyzed using Cobas c8000 (Roche Diagnostics; Geneva, Switzerland). Investigated tests were studied with commercial ELISA kits (cMBP-C, catalog no: E3757Hu; sTrT, catalog no: E4862Hu; TMAO, catalog no: E4733Hu).

Statistical analysis

Mean and standard deviation values were given for normal distribution, and the Student's t-test and one-way analysis of variance test were applied. The Mann-Whitney U test was used for the variables that did not have normal distribution. The best cutoff points were calculated using the receiver operating characteristic (ROC) curve for the prediction of CVD risk with the SCORE2 risk model. Univariate and multivariate analyses were performed using a logistic regression model. The odds ratio (OR) was reported with the corresponding 95%CI, and a p<0.05 was considered statistically significant. Statistical analyses were performed using the SPSS Statistic version 22.0 (SPSS Inc., Chicago, IL) software.

RESULTS

The study cohort consisted of 52 SSc patients (11 diffuse and 29 limited), Anti-SCL-70 antibody was positive in 14 (26.92%), and the anti-centromere antibody was positive in 16 (30.77%) patients. There were 28 (54%) patients with a disease duration of 6–10 years. There was no significant difference between the SSc patients and healthy groups in age distribution, and body mass index (BMI) (p=0.096 and p=0.074, respectively). Routine parameters of CRP, TChol, TG, HDL-C, and LDL-C levels were significantly higher in SSc patients compared to those in healthy subjects (p=0.003, p<0.001, p<0.001, p<0.001, and p=0.007, respectively).

Healthy subjects had low risk with the SCORE2 model (3.58 (1.0–10.0)) but SSc patients were in low-, moderate-, and high-risk groups (9.5 (1.0–29.0)). There was a significant difference between healthy subjects and SSc patients (p<0.001) (Table 1). While there was no significant difference in the sTrT levels between the SSc patient and control groups, cMBPC and TMAO were significantly higher in SSc patients (p=0.274, p<0.001, and p<0.001, respectively).

In the CVD risk prediction of SSc patients with the SCORE2 model, 36 (69.2%) of 52 patients were at low risk, and the other 16 (30.8%) patients were at high-moderate risk (Table 1). In this study, cMBPC and TMAO levels in the low-risk group were lower than those in the high-moderate-risk group (both p<0.001) (Figure 1), but there was no significant change in sTrT levels (p=0.297).

The ideal cutoff value for predicting SCORE2 high-moderate risk for TMAO, cMBPC, and sTrT in SSc patients was calculated separately by ROC analysis (Figure 1). The optimal cutoff value for TMAO was 10.28 ng/mL (AUC: 0.873, 95%CI 0.773–973, p<0.001), and the ideal cutoff value for cMBPC was 8.29 ng/mL (AUC: 0.816, 95%CI 0.684–0.948, p<0.001). For sTrT (AUC: 0.595, 95%CI 0.422–0.769, p=0.276), the median value was determined as the cutoff value. In terms of diagnostic value, sensitivity was 75% and specificity was 83% for cMBPC, and sensitivity was 76% and specificity was 86% for TMAO.

Table 1. Demographic and laboratory characteristics of participants.

	Healthy group (n=38)	SSc patients (n=52)
	Mean±SD/ (min-max)	Mean±SD/ (min-max)/n (%)
Demographic characteristics		
Age (year)	51.263±8.83	54.35±8.28
BMI (kg/m²)	28.78±2.21	29.19±3.45
Laboratory characteristics		
Glucose (mg/dl)	93.21±6.52	103.87±17.08***
Creatinine (mg/dl)	0.65±0.09	0.67±0.18
CRP (mg/l)	1.72 (0.2–5.0)	2.24 (0.15–5.93)
TChol (mg/dl)	156.02±15.22	236.23±47.03***
TG (mg/dl)	101.74±29.07	186.86±58.94***
HDL-C (mg/dl)	53.39±11.04	46.83±11.39**
LDL-C (mg/dl)	80.70±13.40	148.57±43.17***
Non-HDL-C (mmol/l)	3.35±0.73	4.96±1.12***
SCORE2	3.58 (1.0–10.0)	9.5 (1.0–29.0)***
cMBPC (ng/mL)	4.92±1.18	8.03±3.29***
sTrT (ng/L)	55.94±20.41	60.13±15.66
TMAO (ng/mL)	6.90±1.23	10.45±3.01***
Clinical characteristics		
Current smoking		22 (42.30)
Disease duration		
1–5 years		14 (27)
6–10 years		28 (54)
>10 years		10 (19)
Diffuse SSc (positive)		11 (21.15)
Localized SSc (positive)		29 (55.77)
Digital ulcer (positive)		11 (21.15)
Digital gangrene (positive)		2 (3.85)
Telangiectasia (positive)		12 (23.08)
Proximal muscle weakness (positive)		14 (26.92)
Gastrointestinal symptoms (positive)		22 (42.31)
Pulmonary symptoms (positive)		4 (7.69)
Cardiovascular symptoms (hypertension)		23 (44.23)
Antibody characteristics		
Anti-cyclic citrullinated peptide (positive)		4 (7.69)
Rheumatoid factor (positive)		8 (15.38)
ANA cytoplasmic speckled (positive)		10 (19.23)
ANA anti-centromere (positive)		16 (30.77)
ANA SCL-70 (positive)		14 (26.92)
ENA anti-Ro (SSA) (positive)		10 (19.23)
ENA anti-centromere B (positive)		16 (30.77)
ENA anti-SCL-70 (positive)		17 (32.69)
ENA Ro-52 recombinant (positive)		11 (21.15)

p<0.05*, p<0.01**, p<0.001***. SSc: scleroderma; SD: standard deviation; min: minimum; max: maximum; BMI: body mass index; cMBPC: cardiac myosin-binding protein-C; sTrT: sensitive troponin T; TMAO: trimethylamine N-oxide; CRP: c-reactive protein; TChol: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SCORE2: the Systematic COronary Risk Evaluation 2 model; ANA: antinuclear antibody; ENA: extractable nuclear antigens; ANA SCL-70: anti-topoisomerase I antibodies (Anti-Scleroderma); ENA anti-SCL 70: extractable nuclear antigens anti-scleroderma antibodies; Ro-52: tripartite motif-containing protein 21.

In SSc patients, SCORE2 model levels were correlated with age (r=638, p<0.001, disease duration (r=-0.406, p=0.032), cMBPC (r=0.319, p=0.021), sTrT (r=0.346, p=0.012), and TMAO (r=0.383, p=0.005) but not correlated with none-HDL-C and BMI.

While cMBPC and sTrT were not correlated in SSc patients, TMAO was correlated with both cMBPC and sTrT (with cMBPC r=0.689, p<0.001; with sTrT r=0.355, p=0.010).

The univariate analysis was established to predict high-moderate SCORE2 risk. Those with high TMAO levels (≥10.28 ng/mL) predicted high-moderate risk 15 times higher than those with low (<10.28 ng/mL) levels (OR: 15.00, 95%CI 3.585–62.765, p<0.001). Similarly, high cMBPC (≥8.29 ng/mL) levels predicted significantly higher SCORE2 risk than low cMBPC (<8.29 ng/mL) levels (OR: 11.00, 95%CI 2.786–43.430, p=0.001) (Table 2).

When high TMAO (OR 9.405, 95%CI 2.020–43.791, p=0.003) and high cMBPC (OR 6.236, 95%CI 1.329–29.256, p=0.020) were evaluated together in the multivariate analysis, SCORE2 showed the predictive model feature in estimating high risk (Table 2).

DISCUSSION

Since the risk of CVD is high in SSc, it is necessary to focus on early risk prediction and to identify risk factors[5]. This study presented two main findings: (1) SSc patients could be distinguished for CVD risk prediction with the SCORE2 model and (2) TMAO and cMBPC were associated with SCORE2 risk. Recent studies have reported the evaluation of sTrT levels as the best indicator and risk marker of CVD in SSc. Avouac et al. and Bosello et al. reported higher sTrT level in patients with SSc than in the control group[3,4]. Both studies investigated sTrT levels in patients with SSc who had CVD complications. Contrary to these findings, in our study, sTrT levels were similar in SSc patients compared to those in healthy controls (p=0.274) (Table 1). However, in terms of the role of cardiac biomarkers in detecting early cardiac disease, there was no significant relationship in studies with cardiac-MRI[15]. Although studies reported hs-cTnT association with both systolic and diastolic function abnormalities, Ross et al. reported that there was a lack of definitive data to support their use[16]. The reason why our and similar studies did not find a significant difference regarding sTrT is that it would not be valuable in CVD risk prediction because of the increase in acute myocardial injury.

Due to these disadvantages in sTrT, the research for alternative CVD risk markers continues in SSc. One of these markers was cMBPC, which was reported in cardiac myocytes in greater

Table 2. Univariate and multivariate analysis of parameters for systematic coronary risk evaluation 2 high-risk prediction.

Variable	Category	Univariate analysis		Multivariate analysis	
		OR (95%CI)	p-value	OR (95%CI)	p-value
TMAO	<10.28/≥10.28	15.000 (3.585–62.765)	**<0.001**	9.405 (2.020–43.791)	**0.004**
cMBPC	8.29/≥8.29	11.000 (2.786–43.430)	**0.001**	6.236 (1.329–29.256)	**0.020**
sTrT	52.24/≥52.24	1.437 (0.439–4.699)	0.549		
CRP	Continuous	0.989 (0.849–1.152)	0.883		
LDL-C	Continuous	1.003 (0.989–1.017)	0.656		
ALB	Continuous	1.965 (0.423–9.140)	0.389		
BMI	Continuous	1.301 (1.033–1.640)	**0.025**		
C3	Continuous	0.695 (0.068–7.098)	0.759		
C4	Continuous	0.004 (<0.001–6.824)	0.147		
IgM	Continuous	0.754 (0.384–1.484)	0.414		
IgG	Continuous	0.938 (0.779–1.131)	0.505		
IgA	Continuous	0.782 (0.433–1.412)	0.414		

Statistically significant p-values are marked in bold. Multivariate analysis was created using the Forward-LR model. TMAO: trimethylamine N-oxide; cMBPC: cardiac myosin-binding protein-C; sTrT: sensitive troponin T; CRP: C-reactive protein; LDL-C: low-density lipoprotein; ALB: albumin; BMI: body mass index; C3: complement 3; C4: complement 4; IgM: immunoglobulin M; IgG: immunoglobulin G; IgA: immunoglobulin A.
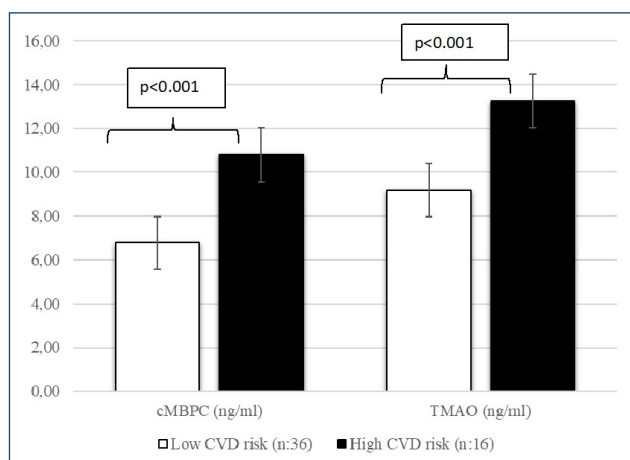
Figure 1. Changes of parameters with low-risk and high-moderate risk in systematic coronary risk evaluation 2 model.

amounts than sTrT. cMBPC was released more rapidly after acute myocardial infarction (AMI) and has been studied as a new cardiac protein of CVD indicator. In literature, cMBPC concentrations in AMI were significantly higher than those without AMI[17]. After a myocardial injury, cMBPC could be detected earlier in the blood, and its concentration has been reported to rise faster and more sensitively than cTnT/I or the new RNA biomarkers[17,18]. To the best of our knowledge, this study was the first to investigate cMBPC levels in SSc. Significantly higher cMBPC levels were found in the SSs patients than in healthy controls (p<0.001) (Table 1).

Trimethylamine N-oxide, an indicator for CVD risk in recent years, is a molecule produced by intestinal bacteria, which is thought to have a powerful effect on human life[14]. TMAO was strongly associated with atherosclerosis[19,20]. However, no study was found in the literature related to TMAO levels in SSc patients. In this study, TMAO levels in SSc patients were significantly higher than those in healthy subjects (p<0.001) (Table 1). It would be better to evaluate TMAO and cMBPC levels in determining cardiac risk in SSc. At the same time, the presence of a positive correlation between sTrT and TMAO levels in our study supports the notion that TMAO is associated with CVD risk.

In this study, we evaluated SSc patients according to the new SCORE2 risk estimation algorithm. Only limited studies are available on this subject. Ozen et al. underestimated the risk of subclinical atherosclerosis in SSc patients using the previous SCORE risk estimation model[21]. Along with the SCORE, the 2013 American College of Cardiology and American Heart Association (ACC/AHA) risk indexes were also reported as insufficient[22]. Similarly, Kurman et al. revealed the inadequacy of the Framingham risk score and ACC/AHA risk indexes in estimating CVD risk[23]. In this study, although there was an increase in serum sTrT levels in the group with high CVD risk in SSc patients separated according to SCORE2, no significant difference was found (p=0.297). Contrary to our findings, Barsotti et al. reported higher sTrT levels in high-risk SSc patients according to the heart involvement index, with the presence of conditions such as unexplained hypertension,

ischemic heart disease, smoking, congenital heart disease, and diastolic dysfunction[24]. Similarly, De Luca et al. reported high sTrT values in 58.1% of SSc patients with arrhythmia and ventricular ectopic beats[25]. However, the performance of sTrT levels was not sufficient in both studies.

In this study, cMBPC and TMAO levels were significantly higher in the high-moderate-risk group than in the low-risk group (both p<0.001) (Figure 1). For SCORE2, high-moderate-risk prediction with optimal cutoff values determined in the ROC curves of TMAO and cMBPC could discriminate cMBPC with 75% sensitivity and 83% specificity and TMAO with 76% sensitivity and 86% specificity. Both parameters gave better results than values for cTrT in a study by Barsotti et al.[24]. cMBPC and TMAO could be used as risk indicators and are compatible with SCORE2 in the evaluation of CVD risk.

In the univariate regression analysis, those with a high TMAO had a 15 times higher efficiency in predicting patients with a high SCORE2 value compared to those with a low value and, similarly, with high cMBPC levels compared to low levels. In the multivariate analysis, high TMAO and high cMBPC were determined as a predictive model feature for estimating high SCORE2 risk. Our findings are a unique and important addition to the literature, and to the best of our knowledge, this is the first study in this evolving field.

Our study should be interpreted with its limitations. The main limitation is the small sample size. Although TMAO levels could be affected by diet, geographical region characteristics and dietary habits were not detailed. Interferences with the tests were ignored.

CONCLUSION

While sTrT did not increase significantly in SSc patients, cMBPC and TMAO levels were higher than those in healthy controls. In addition, cMBPC and TMAO distinguished between high-moderate-risk and low-risk SCORE2 groups as noninvasive CVD risk estimation indicators. Further research is warranted to develop better CVD risk prediction tools in SSc. It is recommended that TMAO and cMBPC levels could be evaluated in order to estimate the 10-year risk of CVD death with SCORE2 in SSc patients.

AUTHORS' CONTRIBUTIONS

AÇ: Conceptualization, Data curation, Formal Analysis, İnvestigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **RM:** Conceptualization, Data curation, Formal Analysis, İnvestigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **SG:** Conceptualization, Data curation, Formal Analysis, İnvestigation, Resources, Supervision, Writing – review & editing. **AY:** Conceptualization, Data curation, Formal Analysis, İnvestigation, Methodology, Project administration, Writing – original draft.

REFERENCES

1. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol. 2012;24(2):165-70. https://doi.org/10.1097/BOR.0b013e32834ff2e8

2. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Campillo-Grau M, Ramos-Casals M, et al. Registry of the Spanish network for systemic sclerosis: survival, prognostic factors, and causes of death. Medicine (Baltimore). 2015;94(43):e1728. https://doi.org/10.1097/MD.0000000000001728

3. Avouac J, Meune C, Chenevier-Gobeaux C, Borderie D, Lefevre G, Kahan A, et al. Cardiac biomarkers in systemic sclerosis: contribution of high-sensitivity cardiac troponin in addition to N-terminal pro-brain natriuretic peptide. Arthritis Care Res. 2015;67(7):1022-30. https://doi.org/10.1002/acr.22547

4. Bosello S, De Luca G, Berardi G, Canestrari G, de Waure C, Gabrielli FA, et al. Cardiac troponin T and NT-proBNP as diagnostic and prognostic biomarkers of primary cardiac involvement and disease severity in systemic sclerosis: a prospective study. Eur J Intern Med. 2019;60:46-53. https://doi.org/10.1016/j.ejim.2018.10.013

5. Offer G, Moos C, Starr R. A new protein of the thick filaments of vertebrate skeletal myofibrils. Extractions, purification and characterization. J Mol Biol. 1973;74(4):653-76. https://doi.org/10.1016/0022-2836(73)90055-7

6. Tong CW, Nair NA, Doersch KM, Liu Y, Rosas PC. Cardiac myosin-binding protein-C is a critical mediator of diastolic function. Pflugers Arch Eur J Physiol. 2014;466(3):451-7. https://doi.org/10.1007/s00424-014-1442-1

7. Witayavanitkul N, Mou YA, Kuster DWD, Khairallah RJ, Sarkey J, Govindan S, et al. Myocardial infarction-induced N-terminal fragment of cardiac myosin-binding protein C (cMyBP-C) impairs myofilament function in human myocardium. J Biol Chem. 2014;289(13):8818-27. https://doi.org/10.1074/jbc.M113.541128

8. Gątarek P, Kałużna-Czaplińska J. Trimethylamine n-oxide (TMAO) in human health. EXCLI J. 2021;20:301-19. https://doi.org/10.17179/excli2020-3239

9. Lippi G, Danese E, Mattiuzzi C, Favaloro EJ. The intriguing link between the intestinal microbiota and cardiovascular disease. Semin Thromb Hemost. 2017;43(6):609-13. https://doi.org/10.1055/s-0036-1597903

10. Van Den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747-55. https://doi.org/10.1136/annrheumdis-2013-204424

11. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202-5. PMID: 3361530

12. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017;2(1):11-8. https://doi.org/10.5301/jsrd.5000231

13. Medsger TA, Bombardieri S, Czirjak L, Scorza R, Della Rossa A, Bencivelli W, et al. Assessment of disease severity and prognosis. Clin Exp Rheumatol. 2003;21(Suppl. 29):S42-6. PMID: 12889222

14. SCORE2 Working Group and ESC Cardiovascular Risk Collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-54. https://doi.org/10.1093/eurheartj/ehab309

15. Sugiyama K, Kobayashi H, Kobayashi Y, Yokoe I, Takei M, Kitamura N, et al. Association of cardiac magnetic resonance-detected myocardial abnormalities with disease characteristics and brain natriuretic peptide levels in systemic sclerosis without cardiac symptoms. Int J Rheum Dis. 2019;22(6):1016-22. https://doi.org/10.1111/1756-185X.13540

16. Ross L, Moxey J, Nikpour M. Are troponin and B-type natriuretic peptides useful biomarkers for the diagnosis of systemic sclerosis heart involvement? A systematic literature review. Semin Arthritis Rheum. 2021;51(1):299-309. https://doi.org/10.1016/j.semarthrit.2020.10.016

17. Kaier TE, Alaour B, Marber M. Cardiac myosin-binding protein C—from bench to improved diagnosis of acute myocardial infarction. Cardiovasc Drugs Ther. 2019;33(2):221-30. https://doi.org/10.1007/s10557-018-6845-3

18. Barefield D, Sadayappan S. Phosphorylation and function of cardiac myosin binding protein-C in health and disease. J Mol Cell Cardiol. 2010;48(5):866-75. https://doi.org/10.1016/j.yjmcc.2009.11.014

19. Yang W, Zhang S, Zhu J, Jiang H, Jia D, Ou T, et al. Gut microbe-derived metabolite trimethylamine N-oxide accelerates fibroblast-myofibroblast differentiation and induces cardiac fibrosis. J Mol Cell Cardiol. 2019;134:119-30. https://doi.org/10.1016/j.yjmcc.2019.07.004

20. Dalla Via A, Gargari G, Taverniti V, Rondini G, Velardi I, Gambaro V, et al. Urinary TMAO levels are associated with the taxonomic composition of the gut microbiota and with the choline TMA-lyase gene (cutC) harbored by enterobacteriaceae. Nutrients. 2020;12(1):62. https://doi.org/10.3390/nu12010062

21. Ozen G, Inanc N, Unal AU, Korkmaz F, Sunbul M, Ozmen M, et al. Subclinical atherosclerosis in systemic sclerosis: not less frequent than rheumatoid arthritis and not detected with cardiovascular risk indices. Arthritis Care Res. 2016;68(1):1538-46. https://doi.org/10.1002/acr.22852

22. Sanz Pérez I, Martínez Valle F, Guillén-del-Castillo A, Roque Pérez A, Cuéllar Calàbria H, Pizzi MN, et al. Subclinical cardiovascular disease and systemic sclerosis: a comparison between risk charts, quantification of coronary calcium and carotid ultrasonography. Autoimmun Rev. 2018;17(9):900-5. https://doi.org/10.1016/j.autrev.2018.03.015

23. Kurmann RD, Sandhu AS, Crowson CS, Matteson EL, Osborn TG, Warrington KJ, et al. Cardiovascular risk factors and atherosclerotic cardiovascular events among incident cases of systemic sclerosis: results from a population-based cohort (1980-2016). Mayo Clin Proc. 2020;95(7):1369-78. https://doi.org/10.1016/j.mayocp.2019.12.015

24. Barsotti S, Bruni C, Orlandi M, Della Rossa A, Marasco E, Codullo V, Guiducci S. One year in review 2017: systemic sclerosis. Clin Exp Rheumatol. 2017;35(Suppl. 106)(4):3-20. PMID: 29035173

25. De Luca G, Bosello SL, Gabrielli FA, Berardi G, Parisi F, Rucco M, et al. Prognostic role of ventricular ectopic beats in systemic sclerosis: a prospective cohort study shows ECG indexes predicting the worse outcome. PLoS One. 2016;11(4):e0153012. https://doi.org/10.1371/journal.pone.0153012