Application of machine learning to determine top predictors of noncalcified coronary burden in psoriasis: An observational cohort study

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Background: Psoriasis is associated with elevated risk of heart attack and increased accumulation of subclinical noncalcified coronary burden by coronary computed tomography angiography (CCTA). Machine learning algorithms have been shown to effectively analyze well-characterized data sets.

Objective: In this study, we used machine learning algorithms to determine the top predictors of noncalcified coronary burden by CCTA in psoriasis.

Methods: The analysis included 263 consecutive patients with 63 available variables from the Psoriasis Atherosclerosis Cardiometabolic Initiative. The random forest algorithm was used to determine the top predictors of noncalcified coronary burden by CCTA. We evaluated our results using linear regression models.

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Results: Using the random forest algorithm, we found that the top 10 predictors of noncalcified coronary burden were body mass index, visceral adiposity, total adiposity, apolipoprotein A1, high-density lipoprotein, erythrocyte sedimentation rate, subcutaneous adiposity, small low-density lipoprotein particle, cholesterol efflux capacity and the absolute granulocyte count. Linear regression of noncalcified coronary burden yielded results consistent with our machine learning output.

Limitation: We were unable to provide external validation and did not study cardiovascular events.

Conclusion: Machine learning methods identified the top predictors of noncalcified coronary burden in psoriasis. These factors were related to obesity, dyslipidemia, and inflammation, showing that these are important targets when treating comorbidities in psoriasis. (J Am Acad Dermatol 2020;83:1647-53.)

Key words: atherosclerosis; cardiometabolic disease; coronary artery disease; machine learning; psoriasis; random forest algorithm.

CAPSULE SUMMARY

- Inflammation and dyslipidemia are known to play major roles in the development of atherosclerosis.
- Our machine learning methods identified the top predictors of coronary artery burden in patients with psoriasis, which were markers related to obesity, dyslipidemia, and inflammation, showing that these are potentially important comorbidities to treat in psoriasis.

Psoriasis, a chronic inflammatory disease, is associated with elevated rates of acute coronary syndrome, stroke, and cardiovascular mortality.[1,2] Patients with psoriasis develop accelerated atherosclerosis, which leads to an increase in coronary artery disease and its complications, such as incident myocardial infarction.[3,4] For example, patients with psoriasis have greater coronary artery disease burden, which is predominantly noncalcified on coronary computed tomography angiography (CCTA).[3,4] Given the acceleration of myocardial infarction risk, the characterization of noncalcified coronary burden via CCTA may yield valuable information before cardiovascular events.[3,5]

Preventive cardiology hinges on the ability to accurately assess cardiovascular risk and predict prospective major adverse cardiac events. Conclusions derived from large prospective studies show our ability to calculate the long-term likelihood of major adverse cardiovascular events and to elucidate important risk factors of cardiovascular disease. Current statistical models rely on only a few variables to predict complex outcomes. Machine learning algorithms open the opportunity to map multiple complex data variables to clinical outcomes that are crucial for the advancement of our understanding of cardiovascular disease risk factors. Thus, machine learning is potentially well equipped to use multiple variables to predict a complex outcome.

By combining clinical and CCTA data via machine learning, performance from machine learning algorithms has been shown to be a superior predictor of 5-year all-cause mortality than current clinical or CCTA data alone.[6] Another study showed that a risk score developed by using machine learning algorithms had greater prognostic accuracy for cardiovascular disease risk stratification from CCTA readings than the standard CCTA integrated risk scores.[7] Similarly, machine learning algorithms can be applied to better understand the relationship between various clinical variables and noncalcified coronary burden in psoriasis. Thus, we hypothesized that machine learning algorithms would be able to accurately determine the top predictors of noncalcified coronary burden in psoriasis.

METHODS

Patient population

The machine learning algorithm was developed by using 263 consecutive patient records (January 2013 through January 2018) with 93 phenotypic variables measured at baseline from the Psoriasis Atherosclerosis Cardiometabolic Initiative, an ongoing prospective trial to understand the relationship between psoriasis and cardiometabolic diseases (Supplemental Methods; available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6345554/bin/NIHMS1506378-supplement-Supplemental.docx).[8]

Abbreviations used:

CCTA: coronary computed tomography angiography
CRP: C-reactive protein

CCTA acquisition

All participants underwent CCTA, on the same day as blood draw, using the same computed tomography scanner (320-detector row Aquilion ONE ViSION, Toshiba, Japan). Guidelines implemented by the National Institutes of Health (NIH) Radiation Exposure Committee were followed. Scans were performed with prospective electrocardiography gating, 100- or 120-kV tube potential, tube current of 100 to 850 mA adjusted to the patient's body size, and a gantry rotation time of 275 ms. Images were acquired at a slice thickness of 0.5 mm, with a slice increment of 0.25 mm.

CCTA analysis

All scans were read with blinding to patient characteristics, visit date, and treatment. Coronary characteristics were analyzed across each of the main coronary arteries greater than 2 mm by using dedicated software (QAngio CT; Medis, The Netherlands) (Fig 1).[3,9] Automated longitudinal contouring of the inner lumen and outer wall was performed, and results were manually adjusted when clear deviations were present.[10] The results of the automated contouring were also reviewed on transverse reconstructed cross sections of the artery on a section-by-section basis at 0.5-mm increments. Lumen attenuation was adaptively corrected on an individual scan basis by using gradient filters and intensity values within the artery. Intrarater reliability was high, with an intraclass correlation coefficient of 0.900 (95% confidence interval, 0.903-0.919).

To account for variable coronary artery lengths, coronary burden (in cubic millimeters) was divided by the corresponding segment length (in millimeters), yielding a coronary burden index.[9] Total burden was defined as the sum of noncalcified and densely calcified coronary burden. Noncalcified coronary burden was obtained after adaptively correcting for lumen attenuation and depicted based on Hounsfield units derived by the software.

Machine learning algorithm

Removing excessive variables in large data sets improves model accuracy, performance, and interpretability and reduces overfitting.[11] One method of removing excessive variables in a data set is through the use of random forest ensembles. In addition to the algorithm's high predictive performance, random forests are particularly well suited for our data set because of some important characteristics: (1) the construction of decision trees that are unique to every data set, (2) the capacity to handle both categorical and continuous variables, and (3) the ability to process missing values or invalid/erroneous datasets (Supplemental Table I).[12] In this method, we begin by manually removing variables in the data set, and then we grow an ensemble of decision trees to measure variable importance by permutation. The variable importance value that is outputted by the machine learning algorithm indicates the predictive power of that variable in determining noncalcified coronary plaque burden.

Out of the initial 93 variables, excluding noncalcified coronary burden, 29 variables were deemed to be redundant (eg, basophil count vs absolute basophil count) and were thus removed before analysis by the random forest algorithm. The importance of the remaining 63 variables with respect to noncalcified coronary burden was determined by permutation within a random forest algorithm of 200 regression trees. Using the method introduced by Breiman et al,[13] we measured the accuracy of each phenotypic variable for predicting noncalcified coronary burden. After determining the importance values of each predictor variable, a simple unadjusted linear regression was performed between the predictor variable and noncalcified coronary burden. All machine learning algorithms were implemented by using MATLAB, 2018a version, Statistics and Machine Learning toolbox (MathWorks, Natick, MA).

Statistical analyses

Skewness and kurtosis measures were considered to assess normality. Data were reported as mean with standard deviation for parametric variables, median with interquartile range for nonparametric variables, and percentages for categorical variables. We conducted linear and logistic regression between noncalcified coronary burden and the predictor variables. For predictor variables with binary outputs, noncalcified coronary burden was dichotomized by median noncalcified coronary burden value of our cohort to perform logistical regressions if necessary. A P value of less than .05 was considered statistically significant. Statistical analysis was performed using STATA-12 software (StataCorp, College Station, TX).

RESULTS

At baseline, patients with psoriasis were middle aged, predominantly male, had low cardiovascular

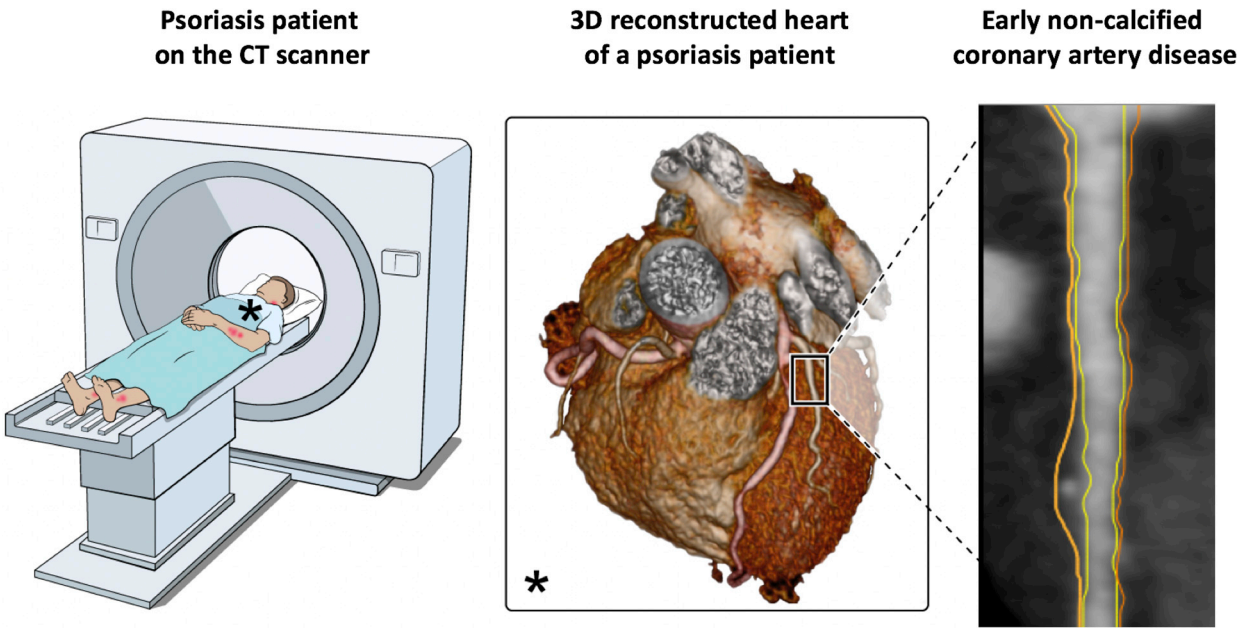

Fig 1. Psoriasis and noncalcified coronary artery disease by coronary computed tomography angiography. **A,** A patient with psoriasis undergoing a CT scan. **B,** A 3D reconstruction of the coronary artery obtained from a coronary computed tomography angiography scan of the patient with psoriasis. **C,** Planar reconstruction of the coronary artery obtained from coronary computed tomography angiography. The orange line represents the outer border (total volume), and the yellow line represents the inner border (lumen volume). *3D,* 3 Dimensional; *CT,* computed tomography.

risk by Framingham risk score, and had mild to moderate skin disease (Table I). Of the initial 93 variables available in the data set, 29 were manually removed from the machine learning algorithm due to redundancy of the variables (eg, neutrophil count vs absolute neutrophil count). The target variable (noncalcified coronary burden) was removed, and the remaining 63 variables were ranked for importance using the random forest algorithm.

The top 20 variables ranked by random forest algorithm are listed in Table I: body mass index, visceral adiposity, total adiposity, apolipoprotein A1, high-density lipoprotein, erythrocyte sedimentation rate, subcutaneous adiposity, small low-density lipoprotein particle, cholesterol efflux capacity, absolute granulocyte count, total cholesterol, waist-to-hip ratio, apolipoprotein B, very-low-density lipoprotein particle, absolute monocyte count, high-sensitivity C-reactive protein (CRP), large very-low-density lipoprotein particle, large medium high-density lipoprotein particle, large medium very-low-density lipoprotein particle, and white blood cells (Table II). The importance values output by the random forest algorithm indicate how important that variable is in predicting noncalcified coronary burden with the highest possible importance value of 1.0. The importance values are absolute values and do not suggest whether the variables have a positive or negative relationship with noncalcified coronary burden. By running an unadjusted linear regression between noncalcified coronary burden and each of these top predictors, these top variables with noncalcified coronary burden yielded similar results consistent with our machine learning outputs (Table III). The standardized correlation coefficient (beta coefficient) for each variable in order of variable importance is shown in Table III, which, in contrast to Table II, shows whether the predictor has a positive or negative association with noncalcified coronary burden. The correlation coefficient of these predictor variables with noncalcified coronary burden, shown in Table III, was obtained from an unadjusted linear regression model. Apolipoprotein A1, high-density lipoprotein, cholesterol efflux capacity, and large medium high-density lipoprotein particle had a statistically significant negative association with noncalcified coronary burden. Erythrocyte sedimentation rate, absolute immature granulocyte count, total cholesterol, apolipoprotein B, very-low-density lipoprotein particle, absolute monocyte count, large very-low-density lipoprotein particle, and large medium very-low-density lipoprotein particle did not have a statistically

Table I. Description of participants with psoriasis at baseline visit (N = 263)

Variable	Total
Demographics and clinical history	(N = 263)
Age, y, mean ± SD	47.6 ± 14.0
Sex, male, n (%)	175 (67)
Hypertension, n (%)	73 (28)
Hyperlipidemia, n (%)	120 (46)
Type 2 diabetes mellitus, n (%)	24 (9)
Body mass index, kg/m^2, mean ± SD	28.8 ± 5.8
Current smoker, n (%)	19 (7)
Statin use, n (%)	77 (29)
Lipid and cell characterization	
Total cholesterol, mg/dL, mean ± SD	172.6 ± 42.1
HDL cholesterol, mg/dL, mean ± SD	56.7 ± 17.7
LDL cholesterol, mg/dL, mean ± SD	104.0 ± 36.2
Triglycerides, mg/dL, mean ± SD	115.6 ± 70.4
Framingham risk score, median (IQR)	2 (1-6)
High sensitivity CRP, mg/L, median (IQR)	1.5 (2.8-4.1)
Cholesterol efflux capacity	0.99 ± 0.18
Psoriasis characterization	
Psoriasis Area Severity Index, median (IQR)	6 (3-10)
Systemic/biologic treatment, n(%)	67 (26)
Coronary characterization, mm^2 (×100), mean ± SD	
Noncalcified coronary burden	1.10 ± 0.41
Adipose characterization, cm^3, mean ± SD	
Visceral adiposity	15 364.8 ± 9128.2
Subcutaneous adiposity	18 808.1 ± 10 484.6

CPR, C-reactive protein; *HDL,* high-density lipoprotein; *IQR,* interquartile range; *LDL,* low-density lipoprotein; *SD,* standard deviation.

Table II. Top 20 predictors of noncalcified coronary burden by using the random forest algorithm in psoriasis (N = 263)

Variable (N = 263)	Importance
Body mass index	0.66
Visceral adiposity	0.64
Total adiposity	0.41
Apolipoprotein A1	0.22
High-density lipoprotein	0.19
Erythrocyte sedimentation rate	0.17
Subcutaneous adiposity	0.15
Small low-density lipoprotein particle	0.13
Cholesterol efflux capacity	0.11
Absolute granulocyte count	0.11
Total cholesterol	0.10
Waist-to-hip ratio	0.09
Apolipoprotein B	0.09
Very-low-density lipoprotein particle	0.06
Absolute monocyte count	0.06
High-sensitivity C-reactive protein	0.06
Large very-low-density lipoprotein particle	0.05
Large medium high-density lipoprotein particle	0.04
Large medium very-low-density lipoprotein particle	0.04
White blood cells	0.04

significant correlation coefficient in the unadjusted regression models. The remainder of the predictor variables had statistically significant positive correlations with noncalcified coronary burden (Table III).

DISCUSSION

In our study, we show that machine learning methods can be leveraged to identify the top predictors of noncalcified coronary burden in patients with psoriasis. These were confirmed by unadjusted linear regression models. Known traditional risk factors for cardiovascular disease provide a risk assessment at the population level but often fall short when precisely assessing an individual's risk.[14,15] For instance, a prior study showed that the Atherosclerotic Cardiovascular Disease Score, which is commonly used in clinical practice to determine whether someone needs to be taking a statin, often overestimates risk in both male and female patients in multiple ethnic groups in the modern US primary prevention cohort.[16] Machine learning is promising in that it can be potentially applied to provide a more personalized risk assessment of a patient's subclinical disease and future cardiovascular event risk, given the patient's clinical characteristics (eg, psoriasis). In fact, machine learning has been applied previously to offer cardiovascular disease risk prediction and evaluation in multiple studies.[17-19] However, to our knowledge, none have applied machine learning to identify top predictors of early rupture—prone plaque as assessed by noncalcified coronary burden.

Patients with chronic systemic inflammatory diseases, such as psoriasis, have accelerated atherosclerosis with increased cardiovascular disease risk and events,[2,20,21] in part due to the impact of chronic inflammation on subclinical cardiovascular disease (elevated noncalcified coronary burden by CCTA).[3] Obesity and metabolic syndrome, which are associated with these inflammatory states, promote a proinflammatory profile with increased inflammatory cytokines such as interferon gamma, interleukin 1β, interleukin 6,

Table III. Unadjusted linear regression of top 20 predictors by using machine learning with noncalcified coronary burden in psoriasis

Variable (N = 263)	β (*P* value)*
Body mass index	**0.64 (<.001)**
Visceral adiposity	**0.58 (<.001)**
Total adiposity	**0.54 (<.001)**
Apolipoprotein A1	**−0.40 (<.001)**
High-density lipoprotein	**−0.42 (<.001)**
Erythrocyte sedimentation rate	−0.05 (.52)
Subcutaneous adiposity	**0.34 (<.001)**
Small low-density lipoprotein particle	**0.27 (<.001)**
Cholesterol efflux capacity	**−0.28 (<.001)**
Absolute granulocyte count	0.03 (.69)
Total cholesterol	−0.15 (.06)
Waist-to-hip ratio	**0.33 (<.001)**
Apolipoprotein B	0.03 (.69)
Very-low-density lipoprotein particle	−0.05 (.50)
Absolute monocyte count	−0.04 (.60)
High-sensitivity C-reactive protein	**0.16 (.02)**
Large very-low-density lipoprotein particle	0.07 (.32)
Large medium high-density lipoprotein particle	**−0.18 (.01)**
Large medium very-low-density lipoprotein particle	0.08 (.28)
White blood cells	**0.15 (.03)**

*Data are represented as standardized beta correlation coefficient (*P* value). Beta correlation cofficients in bold are significant.

tumor necrosis factor α, CRP, and reduced anti-inflammatory mediators such as adiponectin.[22] The interplay between inflammation and metabolic syndrome contributes to the pathogenesis of coronary artery disease. Thus, it is interesting that the top predictors of noncalcified coronary burden by machine learning were related to obesity, dyslipidemia, and inflammation.

CCTA has long been used for the characterization of coronary plaque burden and has been extensively compared with and validated against the criterion standard, intravascular ultrasonography.[23] CCTA provides characterization of not only lumen stenosis and arterial remodeling but also plaque subcomponents, including calcified, noncalcified, and high-risk features.[5] Studies have shown that there is an increase in high-risk noncalcified coronary burden in patients with acute coronary syndrome, who in turn are prone to rupture, which consequently causes future cardiovascular events.[5,24] Our machine learning algorithm showed that the top predictors of noncalcified coronary burden in patients with psoriasis were factors related to markers of obesity (body mass index, adiposity, waist-to-hip ratio), dyslipidemia (apolipoprotein A1, lipoprotein particles, cholesterol efflux capacity, apolipoprotein B), and inflammation (erythrocyte sedimentation rate, high-sensitivity CRP, absolute granulocyte count, absolute monocyte count, white blood cells), which is consistent with our understanding of the pathophysiology of atherosclerosis.[25] Each of these top predictors determined by the machine learning algorithm was evaluated via simple linear regressions. Apolipoprotein A1, high-density lipoprotein, and cholesterol efflux capacity were found to be negatively associated with noncalcified coronary burden, consistent with our understanding of atherogenesis in patients with psoriasis.[10] The importance of the machine learning algorithm is that it takes into consideration multiple variables, which permits ranking of each variable in predicting noncalcified coronary burden, which is not provided by linear regression models.

A major limitation of this study is that the analysis included only baseline values from each patient's first visit. Additional follow-up, along with recorded cardiovascular events in the future, will be required to provide better insight into whether the machine learning algorithm can correctly stratify a patient into the appropriate risk category based on his/her estimated noncalcified coronary burden. Finally, given that machine learning was applied to a specific population, namely, patients in the Psoriasis Atherosclerosis Cardiometabolic Initiative, we were unable to provide any prognostic accuracy and validation on an external cohort with noncalcified coronary burden and these clinical values to further confirm our results.

In conclusion, our findings highlight the importance of features related to obesity, dyslipidemia, and inflammation in predicting noncalcified coronary burden in patients with psoriasis and also show how well-characterized data sets can be leveraged by using machine learning algorithms to facilitate exploring the determinants of noncalcified coronary burden by CCTA. Further investigation into these top predictors of noncalcified coronary burden over time may provide insight into the treatment of inflammation and comorbidities in psoriasis to reduce cardiovascular disease risk.

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REFERENCES

1. Mehta NN, Yu Y, Pinnelas R, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. *Am J Med*. 2011;124(8), 775.e1-6.
2. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol*. 2009; 129(10):2411-2418.

3. Lerman JB, Joshi AA, Chaturvedi A, et al. Coronary plaque characterization in psoriasis reveals high-risk features that improve after treatment in a prospective observational study. *Circulation*. 2017;136(3):263-276.
4. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741.
5. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66(4):337-346.
6. Motwani M, Dey D, Berman DS, et al. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. *Eur Heart J*. 2017;38(7):500-507.
7. Rosendael Av, Maliakal G, Kolli K, et al. Maximization of the usage of coronary CTA derived plaque information using a machine learning based algorithm to improve risk stratification. Insights from the CONFIRM registry. *J Cardiovasc Comput Tomogr*. 2018;12(3):204-209.
8. Harrington CL, Dey AK, Yunus R, Joshi AA, Mehta NN. Psoriasis as a human model of disease to study inflammatory atherogenesis. *Am J Physiol Heart Circ Physiol*. 2017;312(5):H867-H873.
9. Kwan AC, May HT, Cater G, et al. Coronary artery plaque volume and obesity in patients with diabetes: the factor-64 study. *Radiology*. 2014;272(3):690-699.
10. Salahuddin T, Natarajan B, Playford MP, et al. Cholesterol efflux capacity in humans with psoriasis is inversely related to non-calcified burden of coronary atherosclerosis. *Eur Heart J*. 2015;36:2662-2665.
11. Boulesteix AL, Janitza S, Kruppa J, Konig IR. Overview of random forest methodology and practical guidance with emphasis on computational biology and bioinformatics. *Wires Data Min Knowl*. 2012;2(6):493-507.
12. Westreich D, Lessler J, Funk MJ. Propensity score estimation: neural networks, support vector machines, decision trees (CART), and meta-classifiers as alternatives to logistic regression. *J Clin Epidemiol*. 2010;63(8):826-833.
13. Breiman L. Random forests. *Mach Learn*. 2001;45(1):5-32.
14. Franco M, Cooper RS, Bilal U, Fuster V. Challenges and opportunities for cardiovascular disease prevention. *Am J Med*. 2011;124(2):95-102.
15. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290(7):891-897.
16. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. *Eur Heart J*. 2017;38(8):598-608.
17. Kalscheur MM, Kipp RT, Tattersall MC, et al. Machine learning algorithm predicts cardiac resynchronization therapy outcomes: lessons from the COMPANION trial. *Circ Arrhythm Electrophysiol*. 2018;11(1):e005499.
18. Colombet I, Ruelland A, Chatellier G, Gueyffier F, Degoulet P, Jaulent MC. Models to predict cardiovascular risk: comparison of CART, multilayer perceptron and logistic regression. *Proc AMIA Symp*. 2000:156-160.
19. Ambale-Venkatesh B, Yang X, Wu CO, et al. Cardiovascular event prediction by machine learning: the multi-ethnic study of atherosclerosis. *Circ Res*. 2017;121(9):1092-1101.
20. Naik HB, Natarajan B, Stansky E, et al. Severity of psoriasis associates with aortic vascular inflammation detected by FDG PET/CT and neutrophil activation in a prospective observational study. *Arterioscler Thromb Vasc Biol*. 2015;35(12):2667-2676.
21. Mehta NN, Azfar RS, Shin DB, Neimanns AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J*. 2010;31(8):1000-1006.
22. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm*. 2010;2010.
23. Fischer C, Hulten E, Belur P, Smith R, Voros S, Villines TC. Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. *J Cardiovasc Comput Tomogr*. 2013;7(4):256-266.
24. Dey D, Achenbach S, Schuhbaeck A, et al. Comparison of quantitative atherosclerotic plaque burden from coronary CT angiography in patients with first acute coronary syndrome and stable coronary artery disease. *J Cardiovasc Comput Tomogr*. 2014;8(5):368-374.
25. Linton MF, Yancey PG, Davies SS, Jerome WGJ, Linton EF, Vickers KC. The role of lipids and lipoproteins in atherosclerosis. Endotext. Available at: https://www.ncbi.nlm.nih.gov/books/NBK343489/. Accessed November 13, 2019.