U.PORTO

MESTRADO EM EVIDÊNCIA E DECISÃO EM SAÚDE

Predictive Value of Abdominal Fat Distribution in Coronary Artery Disease Stratification Using Machine Learning in Patients Undergoing Coronary CT Angiography

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PREÂMBULO

Nos últimos dois anos frequentei o Mestrado em Evidência e Decisão em Saúde (MEDS), conciliando este percurso académico com a minha atividade profissional como Study Coordinator em Investigação Cardiovascular na Unidade Local de Saúde de Gaia e Espinho e com a docência de aulas prático-laboratoriais de fisiologia na Escola Superior de Saúde do Instituto Politécnico do Porto. Esta experiência representou uma etapa fundamental no meu desenvolvimento académico e profissional, permitindo-me consolidar competências em investigação clínica e em metodologias de análise de evidência, que constituem a base do trabalho que agora apresento.

Durante o primeiro ano do mestrado, concluí com sucesso as unidades curriculares propostas, adquirindo os fundamentos conceptuais e metodológicos necessários para o trabalho de investigação desenvolvido. No segundo ano, dediquei-me à elaboração da minha dissertação centrada na análise da distribuição de gordura abdominal por tomografia computorizada e na sua associação com a gravidade da doença arterial coronária, avaliada através do sistema de classificação CAD-RADS.

Paralelamente, ao longo deste percurso tive a oportunidade de divulgar os resultados do trabalho desenvolvido em diferentes congressos científicos nacionais e internacionais:

i. **30.º Congresso Português de Cardiopneumologia (março, 2025)** Apresentei a comunicação oral "Predictive Value of Coronary Artery Disease Assessment Using a Machine Learning Model", distinguida com o Prémio de Melhor Comunicação Oral – Trabalho Original. Este estudo, que constitui a

base da presente dissertação, demonstrou que a idade, a área da cavidade ventral e o rácio SAT/TAbd se destacaram como os principais preditores da ausência de doença coronária, contrastando com o menor contributo dos fatores de risco cardiovasculares tradicionais. A presente dissertação foi concebida e redigida em formato de artigo científico, com o intuito de ser submetida a uma revista internacional, representando um passo decisivo no percurso de valorização e disseminação do trabalho desenvolvido.

ii. **Congresso Português de Cardiologia (abril, 2025)**
Apresentei a comunicação oral "Association between Abdominal Fat Distribution and Severity of Coronary Artery Disease: data from a large cohort of patients submitted to cardiac CT scan". Este trabalho evidenciou que rácios baseados em gordura visceral, como VAT/BMI e VAT/AbdVol, se encontravam fortemente associados à gravidade da doença coronária, enquanto rácios envolvendo gordura subcutânea, como SAT/AbdVol, mostraram associação inversa, sugerindo um potencial efeito protetor do tecido adiposo subcutâneo.

iii. **European Society of Cardiology Congress (agosto, 2025)**
Apresentei um póster moderado intitulado "Association between Abdominal Fat Distribution, Coronary Artery Calcium Score, and All-Cause Mortality: data from a large cohort of patients submitted to cardiac CT scan". Este estudo demonstrou que o rácio VAT/SAT foi o preditor mais forte de um score de cálcio coronário positivo, enquanto um rácio SAT/TAbd mais elevado se associou a menor risco de mortalidade por todas as causas, reforçando a hipótese de um papel protetor da gordura subcutânea a longo prazo.

Estes momentos de comunicação científica foram determinantes não apenas para a divulgação do trabalho desenvolvido, mas também para o enriquecimento da investigação através do diálogo com a comunidade académica e clínica. Representaram ainda uma oportunidade para consolidar competências de comunicação em contextos exigentes e competitivos, reforçando o meu compromisso com a qualidade científica e com a relevância clínica da investigação realizada.

Resumo do Estudo

A doença arterial coronária permanece uma das principais causas de morbilidade e mortalidade a nível mundial, constituindo um desafio clínico e científico de enorme relevância. Embora os fatores de risco cardiovasculares tradicionais desempenhem um papel reconhecido na sua estratificação, estes não explicam plenamente a heterogeneidade individual na apresentação e evolução da doença. Entre os determinantes emergentes, a obesidade destaca-se pela sua importância crescente, sendo hoje amplamente aceite que a distribuição da gordura abdominal exerce maior impacto prognóstico do que a quantidade global de adiposidade. Apesar desta evidência, o contributo específico de métricas imagiológicas detalhadas da distribuição de gordura abdominal para a previsão da severidade da doença coronária, avaliada através do sistema CAD-RADS, permanece ainda insuficientemente explorado.

Com este enquadramento, o presente trabalho teve como objetivo avaliar se as métricas de distribuição de gordura abdominal, quando integradas com características demográficas e fatores de risco cardiovasculares clássicos, poderiam prever de forma eficaz a presença e a severidade da doença coronária. Para tal, foi desenvolvido um modelo de machine learning do tipo random forest, treinado a partir de dados de

angiografia coronária por tomografia computorizada e de uma aquisição abdominal única obtida ao nível L4/L5–S1 em 1654 doentes.

Os resultados revelaram uma hierarquia estruturada de preditores. A idade destacou-se como variável dominante, seguida da área da cavidade ventral e do rácio entre gordura subcutânea e área abdominal total, ambos claramente superiores em valor preditivo face aos fatores de risco cardiovasculares tradicionais. Estes biomarcadores imagiológicos mostraram-se mais informativos do que medidas antropométricas globais, como o índice de massa corporal, reforçando a importância da avaliação da distribuição da gordura em detrimento da sua quantificação absoluta. Importa salientar que o modelo apresentou desempenho limitado na diferenciação entre formas obstrutivas e não obstrutivas da doença, mas mostrou-se consistente na identificação de doentes sem doença, reforçando a sua utilidade como ferramenta de exclusão.

Em síntese, este estudo evidencia que a análise detalhada da gordura abdominal por tomografia computorizada acrescenta valor preditivo à estratificação do risco cardiovascular. Embora careça ainda de validação externa, esta abordagem abre caminho para uma avaliação mais personalizada e não invasiva, representando um contributo promissor para a evolução das estratégias diagnósticas e para a otimização da tomada de decisão clínica em doentes com suspeita de doença coronária.

Direções Futuras

No presente ano letivo de 2025/2026 dou início ao Programa Doutoral em Investigação Clínica e em Serviços de Saúde da Faculdade de Medicina da Universidade do Porto. Este passo constitui a continuação natural do percurso iniciado no MEDS e enquadra-se plenamente nos meus objetivos profissionais orientados para a

investigação clínica na área cardiovascular. Ambiciono dar continuidade ao trabalho desenvolvido ao longo do mestrado, aprofundando a análise de biomarcadores imagiológicos de distribuição de gordura abdominal e a sua integração em modelos preditivos mais robustos, capazes de gerar conhecimento clinicamente aplicável.

Assim, esta dissertação não deve ser vista como um ponto de chegada, mas como o alicerce de uma linha de investigação que pretendo expandir no contexto do doutoramento. O objetivo último é contribuir de forma significativa para a melhoria da estratificação de risco e para o desenvolvimento de abordagens mais personalizadas, rigorosas e seguras na avaliação e acompanhamento de doentes com suspeita de doença coronária.

AGRADECIMENTOS

Aos meus pais, pilares da minha vida e da minha educação, a quem devo tudo o que sou. Às minhas irmãs, cúmplices de todas as horas, agradeço o apoio constante nos momentos mais desafiantes.

Aos meus amigos, pela amizade, pelos risos partilhados e por tornarem esta caminhada mais leve.

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Ao meu orientador, Professor Doutor Ricardo Fontes Carvalho, o meu profundo reconhecimento. Mais do que orientador, um verdadeiro líder, cuja visão foi determinante nos momentos decisivos. Foi pela sua confiança e incentivo que dei os primeiros passos no caminho da investigação clínica, área a que hoje me dedico.

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A todos, o meu mais sincero obrigada.

"Sozinhos vamos mais rápido. Juntos vamos mais longe."

Title:

Predictive Value of Abdominal Fat Distribution in Coronary Artery Disease Stratification Using Machine Learning in Patients Undergoing Coronary CT Angiography

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Conflicts of Interest:

The authors declare no conflicts of interest.

Keywords (3-6):

Coronary artery disease, abdominal fat distribution, machine learning, coronary computed tomography angiography

ABSTRACT (250 words limit)

Background:

Obesity is a key risk factor for coronary artery disease (CAD). However, evidence suggests that abdominal fat distribution (AFD), such as the ratio between visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), may better predict CAD presence and severity.

Methods:

This retrospective study included 1654 patients (mean age 57±10 years; 57% male) who underwent coronary computed tomography angiography (CCTA) between 2006 and 2023. Each patient also had a single-slice abdominal CT at the L4/L5–S1 level. Hysteresis thresholding was applied: pixels with attenuation values below –50 Hounsfield Units (HU) were selected, along with connected pixels between –50 and 0 HU, enabling quantification of abdominal fat compartments. CAD-RADS scores were grouped as 0 (no CAD), 1 (minimal or mild nonobstructive), and 2 (moderate or greater stenosis). A random forest model was trained on 75% of the dataset and tested on 25% with stratified sampling.

Results:

Among 1654 patients, 62% were in group 0, 18% in group 1, and 20% in group 2. The model achieved 61.2% accuracy (95% CI: 56.3%–65.9%). The strongest predictors were age, ventral cavity area, and SAT/TAbd ratio, while traditional CVRFs and sex had lesser impact. The model identified patients without CAD with 86.4% accuracy, but performance was lower for groups 1 (22.4%) and 2 (18.3%).

Conclusion:

This model identified key variables for predicting CAD absence, underscoring the value of structured hierarchies of predictors rather than isolated measures. With further validation, imaging-based models could support personalised cardiovascular screening and help reduce unnecessary contrast-enhanced imaging.

ABSTRACT WORD COUNT: 245

Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide, representing a major health and economic challenge despite significant progress in prevention and treatment strategies [1]. Traditional cardiovascular risk factors (CVRFs), such as hypertension, diabetes, dyslipidemia, and smoking, are well established in clinical risk models. However, they do not fully explain the individual variability in CAD development and severity [2,3].

Obesity is a key modifiable risk factor for CAD, and recent evidence has highlighted the importance of fat distribution rather than overall adiposity alone [4]. Among different fat compartments, visceral adipose tissue (VAT) plays a particularly harmful role due to its strong association with systemic inflammation, insulin resistance, and atherosclerotic processes. In contrast, subcutaneous adipose tissue (SAT) appears to have a more neutral or even protective metabolic profile [5–7].

With advances in computed tomography (CT) imaging, it is now possible to quantify VAT and SAT accurately and reproducibly, providing a more precise assessment of abdominal fat distribution (AFD) compared to traditional anthropometric measures such as body mass index (BMI) or waist circumference (WC) [8]. In parallel, the Coronary Artery Disease–Reporting and Data System (CAD-RADS™) has emerged as a standardized framework to classify CAD severity on coronary CT angiography (CCTA), improving consistency in reporting and supporting clinical decision-making [9].

Machine learning (ML) approaches, including random forest models, have shown promise in integrating complex data from imaging and clinical variables to refine CAD

risk stratification and improve prediction accuracy [10,11]. Nonetheless, the potential contribution of detailed AFD metrics to predicting CAD severity classified by CAD-RADS has not yet been fully explored.

This study aimed to evaluate whether AFD metrics, together with demographic characteristics and traditional CVRFs, can effectively predict the presence and severity of CAD classified by CAD-RADS, using a random forest machine learning model trained on CCTA and abdominal CT data.

Methods

Study Population:

This retrospective cohort design study was based on registry data from the Cardiology Department of the Local Health Unit of Gaia and Espinho (ULSGE). The study included all patients who underwent CCTA for CAD assessment between January 2006 and December 2023. In addition to CCTA, a single-slice abdominal CT scan at the L4/L5–S1 level was performed in all patients for abdominal adipose tissue quantification. A total of 1722 patients were initially considered. Patients were excluded if they had a CAD-RADS score of "N" (non-diagnostic study), which refers to cases where obstructive CAD could not be excluded due to severe coronary artery calcification that precluded accurate stenosis assessment. The final study cohort comprised 1654 patients with an available CAD-RADS score. Given the retrospective design and use of a convenience sample, an a priori power calculation was not performed.

This study was conducted in accordance with the ethical principles of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee (reference 67/2022). All patients provided written informed consent prior to undergoing CCTA, as required for the administration of iodinated contrast and exposure to ionizing radiation inherent to the procedure. Collected data were stored in a secure, password protected database specifically developed for this study, containing only pseudonymized patient information.

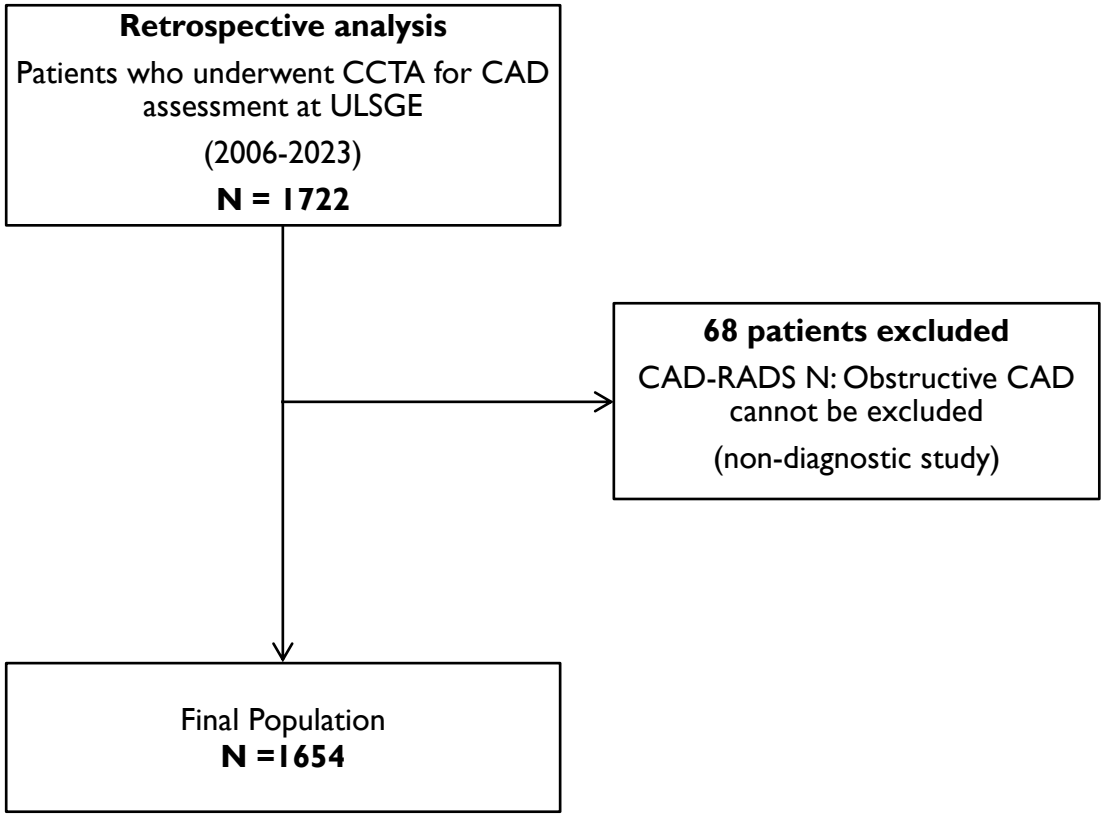


Figure 1. Patient selection flowchart. From the initial 1722 patients referred to CCTA to assess CAD, the final study population comprised 1654 patients with complete abdominal adipose tissue measurements and available CAD-RADS score. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CAD-

RADS, Coronary Artery Disease–Reporting and Data System; ULSGE, Local Health Unit of Gaia and Espinho.

Risk Factor Assessment

Arterial hypertension was defined as a history of hypertension according to the European Society of Cardiology Guidelines [12] or treatment with antihypertensive medication. Smoking history was classified as never, former (participants who smoked for at least 6 months during their lifetime but were not smoking at study entry), or current smoker. Type 2 diabetes mellitus was defined as a history of diabetes according to American Diabetes Association criteria [13] or ongoing medical treatment for diabetes. Family history of premature coronary heart disease was defined as having a first-degree relative with fatal or nonfatal myocardial infarction and/or coronary revascularization before age 55 years in men and 60 years in women. Dyslipidemia was considered present if the patient had a documented history of dyslipidemia or was on lipid-lowering therapy (statins, ezetimibe, or fibrates).

Cardiac Computed Tomography Scan Protocol

All patients underwent cardiac CT imaging using multidetector CT scanners, according to the institutional protocols in place during the respective study periods. The imaging workflow comprised three sequential acquisitions: one for abdominal fat quantification, one for coronary artery calcium (CAC) scoring, and one CCTA. Abdominal fat was assessed using a single axial CT slice obtained between the L4, L5, and S1 vertebral levels, following the method described by Borkan et al. [14]. The scan parameters included a tube voltage of 120 kV, a tube current of 216 mA, and a slice thickness of 5 mm, resulting in an estimated radiation dose of approximately 0.06 mSv.

i) SOMATOM Sensation 64

Between 2006 and 2017, scans were acquired using a 64-slice CT scanner (SOMATOM Sensation 64, Siemens Medical Solutions, Forchheim, Germany).

CAC scoring was performed with a collimation of 24 × 1.2 mm, gantry rotation time of 330 ms, and pitch of 0.2. Tube voltage and current were set at 120 kV and 190 mAs, respectively. CCTA acquisition was conducted using collimation of 64 × 0.6 mm and a tube current of 850 mAs, while all other scan parameters mirrored those used in the CAC acquisition. Tube current modulation with electrocardiographic pulsing was applied to reduce radiation exposure, with full tube current delivered between 60% and 65% of the R–R interval. For patients weighing less than 70 kg, tube voltage was reduced to 100 kV. Contrast enhancement was achieved through the injection of 80 to 100 mL of iopromide (Ultravist 370 mg/mL, Bayer Schering Pharma AG) at 5 mL/s, followed by a 40 mL saline flush, administered via an 18-gauge antecubital catheter. Bolus tracking was triggered when the ascending aorta reached a threshold of 150 Hounsfield units.z

ii) SOMATOM Force

From 2017 to 2023, cardiac CT scans were performed using a third-generation dual-source scanner (SOMATOM Definition Flash FORCE, Siemens Healthineers, Forchheim, Germany).

CAC acquisition used a fixed tube voltage of 120 kV and collimation of 192 × 0.6 mm. Tube current was adjusted according to heart rate: 80 mAs per rotation for heart rates ≤60 bpm, 100 mAs for 60–65 bpm (centered at 70%

of the R–R interval), and 80 mAs for >65 bpm (centered at 35%). Gantry rotation time was 250 ms and automatic exposure control (CAREDose 4D) was enabled. Images were reconstructed with 3 mm slice thickness using a medium-smooth kernel (B35).

CCTA was acquired using the same collimation and rotation parameters. Prospective ECG-triggered sequential scanning was used for heart rates ≤60 bpm, while retrospective ECG-gated helical scanning was applied in patients with higher heart rates. Tube voltage was typically set at 90 kV with CAREkV modulation and increased to 100 kV in patients with a body mass index >25 kg/m². Reference tube current was 366 mAs per rotation, with CAREDose 4D active. Bolus tracking was triggered in the descending aorta once a threshold of 180 HU was reached, preceded by a test bolus of 10 mL contrast followed by 30 mL of saline.

CAD-RADS Score

The severity of CAD was classified using the CAD-RADS™ framework, as described by Cury et al. [9]. CCTA interpretation was performed by the reporting cardiologist using either Syngo.via Frontier – Cardiac Risk Assessment software (Siemens Medical Solutions) or Aquarius Intuition Edition software (version 4.4.11, TeraRecon Inc., Durham, NC, USA). CAD-RADS scores were retrospectively collected from structured clinical reports generated as part of routine diagnostic workflow.

Abdominal Fat Distribution

Adipose tissue segmentation was performed using a U-Net-based deep learning model [15], which enabled accurate delineation of the ventral cavity. Hysteresis thresholding

was then applied to the processed abdominal CT scans: pixels with attenuation values below minus 50 Hounsfield Units (HU) were selected, along with connected pixels between minus 50 and 0 HU, allowing quantification of abdominal fat compartments. The total abdominal area (TAbd) was automatically obtained and represents the entire cross-sectional area of the abdomen. The ventral cavity area (Ventral) was manually segmented by three independent readers, defining the visceral compartment and allowing for separation between VAT and SAT. VAT was defined as the fat within the ventral cavity, while SAT corresponded to the fat between the abdominal wall and the outer boundary of the ventral cavity. Total abdominal fat (TAF) was calculated as the sum of VAT and SAT, reflecting overall abdominal adiposity. For the ventral cavity, the mean of the three manual segmentations was used to ensure consistency.

To further characterize abdominal fat distribution, five ratios were incorporated: VAT/SAT, VAT/BMI, SAT/BMI, VAT/TAbd, and SAT/TAbd. The rationale for using these ratios, rather than relying solely on absolute fat areas, lies in their ability to better reflect the relative distribution and physiological balance between metabolically active fat depots. Several studies have shown that VAT/SAT and other distribution-based indices outperform absolute VAT or SAT areas in predicting atherosclerosis, CAD, and adverse cardiometabolic outcomes [16, 17, 18]. These ratios also account for interindividual variation in body composition, especially when adjusted for body size (e.g., VAT/BMI), allowing for more standardized comparisons across populations. Therefore, the use of these ratios aims to capture not only the burden of abdominal fat, but also its distributional pattern, which may play a more decisive role in cardiovascular disease risk stratification than quantity alone.

Machine Learning Analysis

A random forest model was developed to predict CAD severity using a combination of demographic and clinical data, along with AFD variables (imaging biomarkers). The input features included age, sex, current smoking status, hypertension, diabetes mellitus, dyslipidemia, BMI and WC. Abdominal fat distribution was assessed through CT-based area measurements, as detailed above. During model refinement, the variables referring to family history of premature CAD and former smoking status were excluded due to low predictive contribution.

To enhance model robustness and minimize class imbalance, CAD-RADS scores were grouped into three categories: Group 0 (no CAD), Group 1 (minimal to mild nonobstructive CAD), and Group 2 (moderate to severe stenosis). The dataset was randomly divided into training (75%) and test (25%) subsets using stratified sampling to preserve the proportional distribution of CAD-RADS scores.

Model training and internal validation were performed using stratified 5-fold cross-validation. Predictive performance was evaluated based on overall accuracy, confusion matrices, and 95% confidence intervals. Variable importance was assessed to determine the strongest predictors contributing to model performance. All analyses and visualizations were performed using R software (version 4.1.5). The predictive model development followed the TRIPOD statement (*c.f.* Appendix I).

Results

A total of 1654 patients were included in the analysis (mean age 57 ± 10 years; 57% male), with 62% classified as group 0 (no CAD), 18% as group 1 (minimal to mild nonobstructive CAD), and 20% as group 2 (moderate to severe stenosis).

The random forest model achieved an overall accuracy of 61.2% (95% CI: 56.3%–65.9%) in predicting CAD-RADS scores. Performance was highest for detecting patients without CAD (group 0), with a correct classification rate of 86.4%. By contrast, accuracy was lower for groups 1 and 2, with correct classification rates of 22.4% and 18.3%, respectively (Figure 2). The confusion matrix revealed a pattern of misclassification concentrated between adjacent categories, particularly a tendency to underestimate CAD severity by classifying patients in groups 1 or 2 as group 0. This suggests that the model was more reliable in distinguishing the absence versus presence of CAD than in differentiating levels of disease severity.

Feature importance analysis (Figure 3) identified age as the most influential predictor. The manually segmented ventral cavity area, a surrogate of visceral adiposity, ranked second, reinforcing the role of AFD in CAD risk profiling. The SAT/Abd ratio followed closely, indicating that the relative contribution of subcutaneous fat may also carry independent predictive value. Additional AFD metrics, including VAT/SAT and VAT/BMI, further contributed to model performance. In contrast, traditional anthropometric indices such as BMI and WC showed moderate influence, while conventional CVRF, including smoking, hypertension, diabetes mellitus, and dyslipidemia, were among the least informative variables. Sex also demonstrated limited predictive value. These findings underscore that CT–based measurements of AFD provide clinically relevant risk information beyond what is captured by anthropometric measures and traditional cardiovascular risk factors.

	Group 0 N = 1,025[1]	**Group 1** N = 301[1]	**Group 2** N = 328[1]	**p-value**[2]
Demographics				
Sex	435 (43%)	256 (86%)	240 (74%)	<0.001
Age	56 (48, 63)	59 (53, 65)	60 (54, 66)	<0.001
Anthropometric				
BMI (kg/m^2)	28.0 (25.3, 30.8)	28.4 (26.0, 31.5)	28.2 (26.0, 30.8)	0.044
WC (cm)	95 (88, 102)	99 (95, 107)	99 (93, 105)	<0.001
CVRF				
Dyslipidemia	507 (50%)	190 (64%)	203 (62%)	<0.001
Hypertension	551 (54%)	177 (60%)	226 (70%)	<0.001
Type 2 DM	105 (10%)	57 (19%)	75 (23%)	<0.001
Fam. Hist. of CAD	150 (15%)	40 (14%)	57 (18%)	0.3
Former Smoker	90 (8.8%)	52 (18%)	45 (14%)	<0.001
Current Smoker	134 (13%)	56 (19%)	80 (25%)	<0.001
AFD				
VAT	11,683 (7,778, 16,185)	15,556 (11,513, 19,348)	15,611 (10,821, 19,837)	<0.001
SAT	21,098 (15,141, 28,158)	19,808 (14,717, 24,488)	19,268 (14,497, 24,827)	0.001
TAF	33,968 (25,627, 43,661)	35,670 (29,395, 43,570)	35,327 (28,477, 42,137)	0.029
Ventral	23,198 (18,703, 29,124)	28,437 (23,831, 34,663)	28,058 (22,940, 33,762)	<0.001
TAbd	62,228 (53,125, 72,904)	68,115 (60,394, 78,554)	66,733 (58,499, 74,961)	<0.001
VAT/SAT	0.53 (0.37, 0.79)	0.79 (0.57, 1.08)	0.77 (0.53, 1.10)	<0.001
VAT/TAbd	0.18 (0.14, 0.24)	0.22 (0.18, 0.27)	0.23 (0.17, 0.27)	<0.001

	Group 0 N = 1,025[1]	Group 1 N = 301[1]	Group 2 N = 328[1]	p-value[2]
SAT/TAbd	0.34 (0.27, 0.41)	0.28 (0.24, 0.34)	0.29 (0.23, 0.35)	<0.001
VAT/BMI	398 (293, 553)	540 (416, 667)	547 (396, 672)	<0.001
SAT/BMI	745 (578, 949)	677 (561, 821)	685 (543, 825)	<0.001

Table 1. Comparison of demographic, clinical, and AFD characteristics according to CAD severity. Data are presented as median (IQR) or count (%). CVRF, cardiovascular risk factors; DM, diabetes mellitus; CAD, coronary artery disease; AFD, abdominal fat distribution; BMI, body mass index; WC, waist circumference; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAF, total abdominal fat; TAbd, total abdominal area.

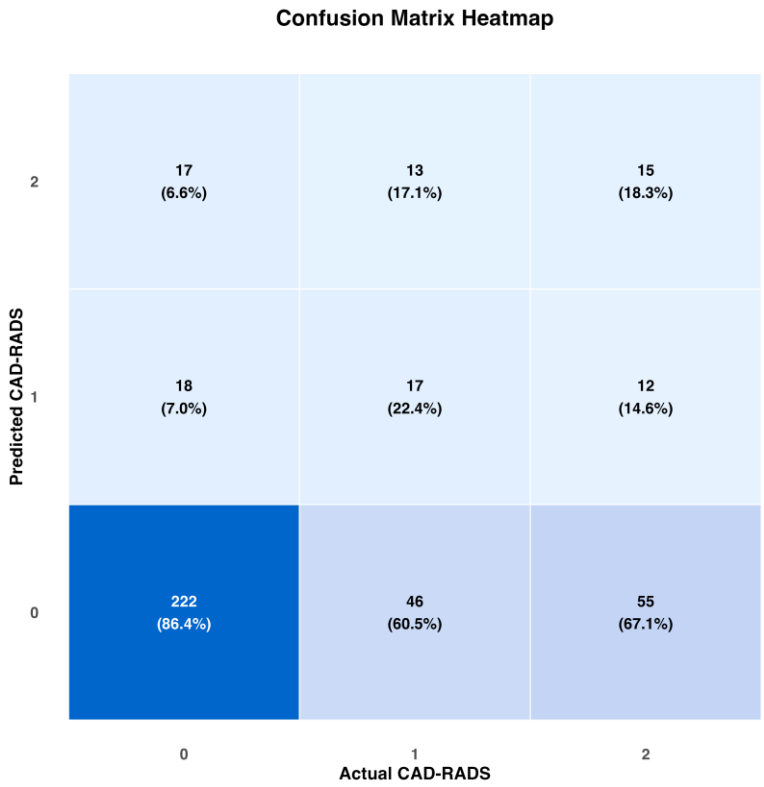


Figure 2. Confusion matrix showing the performance of the random forest model on the test set for CAD-RADS group classification. The model achieved high accuracy in identifying patients without CAD (group 0, 86.4% correct classification), while the classification performance was lower for patients in group 1 (22.4%) and group 2 (18.3%). CAD-RADS, Coronary Artery Disease–Reporting and Data System; CAD, coronary artery disease.

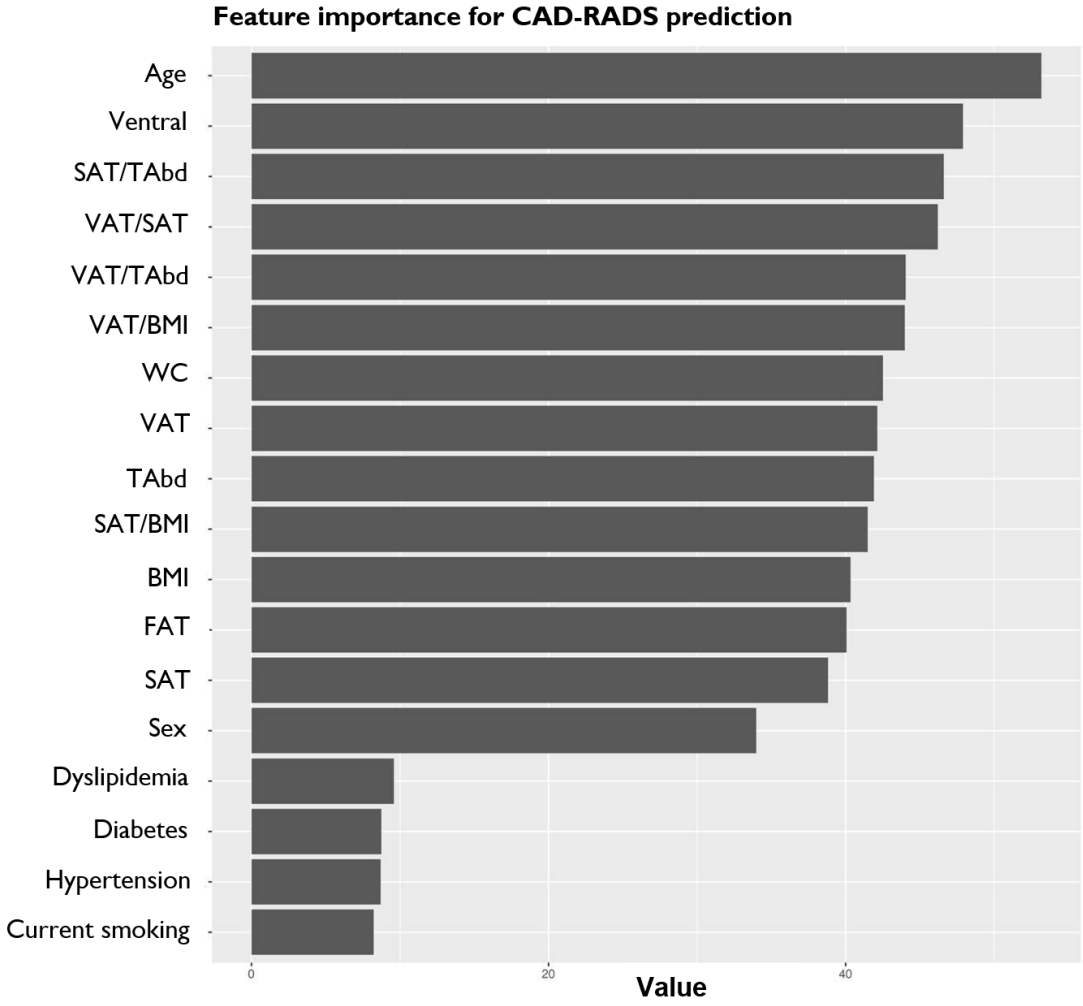


Figure 3. Feature importance plot of the random forest model for CAD-RADS prediction. Age was the most influential predictor, followed by ventral abdominal fat area and the SAT/Abd ratio. Traditional cardiovascular risk factors, including smoking status, hypertension, diabetes, and dyslipidemia, showed comparatively lower

predictive contribution. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; BMI, body mass index; WC, waist circumference; CAD-RADS, Coronary Artery Disease–Reporting and Data System.

Discussion

This study presents a structured hierarchy of predictors of CAD severity using the CAD-RADS classification system. Age was the highest-ranking predictor in the model. This finding aligns with its cumulative influence on vascular ageing and atherosclerotic progression, and it is consistent with previous studies identifying age as the strongest independent contributor in cardiovascular risk prediction models [19, 20].

Among imaging-derived features, the ventral cavity area stands out as highly relevant, ranking just after age and surpassing traditional adiposity metrics such as VAT, SAT, TAF, and TAbd. The ventral cavity represents the anatomical space where intra-abdominal fat accumulates, serving as a structural biomarker rather than a direct fat measurement. Automated segmentation methods, such as those using U-Net architectures, have demonstrated high accuracy and robustness in delineating the ventral cavity, with Dice Score Coefficients comparable to interobserver variability, supporting its measurement consistency and reliability [15]. This consistency is largely due to segmentation based on fixed anatomical landmarks, which reduces variability associated with slice positioning [15].

Additionally, the ventral cavity area reflects a physiological constraint on abdominal fat distribution that is not fully captured by individual fat compartment areas. This structural perspective provides complementary information to relative indices like the SAT/TAbd ratio, which expresses the proportion of the abdominal cross-section

occupied by SAT. Together, these features offer physiologically meaningful insights into fat distribution patterns. Since TAbd approximates the sum of SAT and the ventral cavity, a larger ventral area generally coincides with a smaller SAT/TAbd ratio, and vice versa, highlighting the importance of distribution patterns over total area alone in predicting CAD risk.

Other ratios such as VAT/SAT, VAT/TAbd, and VAT/BMI also contributed meaningfully, reinforcing the added value of CT-derived imaging biomarkers that quantify relative fat distribution, rather than relying on anthropometric proxies or absolute fat areas [5–7, 16–18].

Only after these imaging metrics does BMI appear in the hierarchy. Our findings are in agreement with previous evidence highlighting the importance of AFD over BMI and WC in assessing CAD risk. This is because visceral fat is metabolically active and closely associated with systemic inflammation, insulin resistance, and endothelial dysfunction, key mechanisms driving atherosclerosis and CAD progression [21,22]. In contrast, BMI does not differentiate between fat and lean mass or account for fat distribution, while WC, though a better proxy for central adiposity, still cannot distinguish between subcutaneous and visceral fat compartments [21,22]. Recent imaging and AI-based studies further demonstrate that precise quantification of visceral fat provides stronger associations with cardiometabolic risk and mortality than BMI or WC alone, underscoring the clinical value of AFD metrics in CAD risk stratification [22,23]. Thus, the lower predictive value of BMI likely reflects their inability to capture the pathogenic role of visceral adiposity in cardiovascular disease.

Of particular note, sex and traditional cardiovascular risk factors, including dyslipidemia, hypertension, diabetes mellitus, and current smoking, were among the

lowest-ranking variables in the model. Although these factors are widely used in clinical risk stratification, several reasons may account for their limited predictive contribution in this setting. First, CT-derived biomarkers provide continuous, quantitative measures of body composition that may better capture subtle variations in disease risk than binary clinical variables. Second, the high prevalence and co-occurrence of traditional risk factors in a cohort referred for coronary imaging can reduce their ability to discriminate risk across individuals. Third, the effect of sex on CAD is biologically complex and may be mediated by differences in fat distribution and hormonal status across the lifespan, particularly in women after menopause. Previous studies have shown that visceral fat accumulation tends to increase in women after the loss of estrogenic protection, thereby altering the relationship between sex and cardiovascular risk . Finally, growing evidence supports the superiority of models that incorporate imaging data for refined phenotyping over those based solely on conventional clinical variables [24-26].

The overall accuracy of the model was approximately 61.2%, with a notably high performance in identifying patients without CAD (correct classification in over 86.4% of individuals in group 0). However, classification performance was limited between groups 1 and 2, which likely reflects the biological overlap between non-obstructive and obstructive CAD, as well as class imbalance and potential variability in clinical reporting. Future modelling efforts may benefit from the use of ordinal classification techniques, improved probability calibration, and multicentre training to enhance model generalisability.

From a clinical perspective, the present findings suggest that CT-derived measures of AFD, such as the ventral area and SAT/TAbd ratio, may provide complementary

information to traditional cardiovascular risk factors. These imaging biomarkers capture meaningful anatomical and metabolic characteristics that are not reflected in anthropometric indices like BMI and WC [21-23]. While the model showed limited performance in classifying CAD severity, its ability to reliably identify patients without disease could be clinically useful for exclusion strategies. With further optimisation and external validation, imaging-based models may support more personalised and efficient cardiovascular screening. In selected patients, these models may also reduce the need for contrast-enhanced imaging, thereby lowering exposure to iodinated contrast and radiation. Ongoing research should assess their integration into routine clinical workflows, including evaluation of cost-effectiveness, applicability in diverse populations, and performance within decision-support systems.

Limitations

This study has certain limitations that should be acknowledged when interpreting its findings. First, it was based on a retrospective observational design, which limits the ability to establish causal relationships between AFD and CAD severity. Although the use of real-world clinical data enhances external validity, it also introduces potential confounding and selection bias inherent to non-randomised studies.

Second, the majority of patients included did not present with CAD, corresponding to group 0 in the CAD-RADS classification. This is likely related to the typical clinical indication for CCTA, which is often used to rule out CAD in low-to intermediate-risk individuals. As a result, the cohort underrepresents individuals with more advanced stages of the disease.

Finally, the study was conducted in a single Portuguese centre, which may limit the applicability of the findings to other populations or healthcare settings. These findings would benefit from external validation in independent multicentre cohorts that include broader demographic and clinical diversity, in order to strengthen their generalisability.

Nevertheless, an important strength of this work is the size and detail of the dataset analysed, which includes more than 1600 patients with paired abdominal fat and CCTA data. To the best of our knowledge, this constitutes one of the largest national and international databases of its kind, providing a strong foundation for the investigation of imaging-derived biomarkers in CAD risk stratification. Additionally, the use of CT-based body composition assessment enabled the evaluation of multiple abdominal fat ratios, offering a more refined characterisation of adiposity beyond conventional measures.

Conclusions

This study demonstrated that AFD metrics derived from computed tomography, particularly the ventral cavity area and the SAT/TAbd ratio, were among the most important predictors in a machine learning model trained to classify CAD-RADS scores. These imaging biomarkers outperformed conventional anthropometric and clinical risk factors, highlighting the relevance of fat distribution over general adiposity. Although the model had lower performance in differentiating non-obstructive from obstructive forms of CAD, it consistently identified patients without disease with high classification accuracy, supporting its potential utility in clinical exclusion pathways. Imaging-based body composition analysis may therefore contribute to more

personalised risk stratification and represents a promising, non-invasive complement to traditional approaches in the evaluation of coronary artery disease.

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APPENDIX I

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	8
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	10,11
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	12
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	13
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	13,14
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	13
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	13
	5b	D;V	Describe eligibility criteria for participants.	13,14
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	19
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	19
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	13
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	NA
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	19
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	19
	10c	V	For validation, describe how the predictions were calculated.	19
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	19
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	19
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	14
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	19-22
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	21-23
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	19,20
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	22,23
	15b	D	Explain how to the use the prediction model.	NA
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	19,20
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	27,28
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	24-27
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	24-28
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	26,27
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	9

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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