METHOD AND SYSTEM FOR DETERMINING VASCULAR REGION PATHOLOGY BASED ON RADIODENSITY AND RADIOMIC FEATURES

FIELD OF THE INVENTION

The present invention relates to methods for characterising the pathology or state of a vascular region of a subject, and to methods for characterising plaque in a blood vessel of a subject, with at least one method step being computer implemented. The methods may be used to monitor the development of plaques, predict the risk of a subject suffering a cardiovascular event, guide pharmacological treatment decisions, and monitor responses to medical treatments.

The invention also provides a computer program product configured to carry out these methods, and to a system comprising one or more processors.

BACKGROUND

Atherosclerosis is a progressive process in which an artery wall thickens as a result of invasion and accumulation of white blood cells. This inflammatory process results in the development of plaques within the vessel wall containing living white blood cells, dead cell debris and fatty deposits including cholesterol and triglycerides.

Stable atherosclerotic plaques, which tend to be asymptomatic, are typically rich in extracellular matrix and smooth muscle cells, while unstable plaques are rich in macrophages and foam cells. The extracellular matrix in unstable plaques separating the lesion from the arterial lumen (also known as the fibrous cap) is usually weak and prone to rupture. Ruptures of the fibrous cap eventually induce clot formation in the lumen, and such clots can block arteries or detach, move into the circulation and eventually block smaller downstream vessels causing thromboembolism. Chronically expanding plaques are frequently asymptomatic until vessel occlusion (stenosis) is severe enough that blood supply to downstream tissue is insufficient.

Atherosclerosis is often asymptomatic for decades because the arteries can enlarge at plaque locations and blood flow is not immediately affected. Indeed, plaque ruptures are also asymptomatic unless they result in sufficient narrowing or closure of an artery that impedes blood flow to different organs so as to induce symptoms. Typically, the disease is only diagnosed when the patient experiences other cardiovascular disorders such as stroke or heart attack.

Atherosclerosis may cause narrowing in the coronary arteries, which are responsible for bringing oxygenated blood to the heart, and this can produce symptoms such as the chest pain of angina, shortness of breath, sweating, nausea, dizziness or light-headedness, breathlessness or palpitations. Cardiac arrhythmias may also result from cardiac ischemia. Atherosclerosis that causes narrowing in the carotid arteries, which supply blood to the brain and neck, can produce symptoms such as a feeling of weakness, not being able to think straight, difficulty speaking, becoming dizzy and difficulty in walking or standing up straight, blurred vision, numbness of the face, arms, and legs, severe headache and losing consciousness. These symptoms may also be present in stroke, which is caused by marked narrowing or closure of arteries going to the brain leading to brain ischemia and death of cells in the brain. Peripheral arteries, which supply blood to the legs, arms, and pelvis may also be affected. Symptoms can include numbness within the affected limbs, as well as pain. Plaque formation may also occur in the renal arteries, which supply blood to the kidneys. Plaque occurrence and accumulation leads to decreased kidney blood flow and chronic kidney disease, which, like all other areas, are typically asymptomatic until late stages.

Vascular inflammation is a key feature in atherogenesis and plays a critical role in atherosclerotic plaque stability by triggering plaque rupture leading to acute coronary syndromes (see Ross R. N Engl J Med 1999;340:115-26, and Major AS *et al* Circulation 2011;124:2809-11). Importantly, more than 50% of acute coronary syndromes are caused by highly inflamed but anatomically non-significant atherosclerotic plaques (Fishbein MC *et al*. Circulation 1996;94:2662-6).

Cardiac computed tomography angiography (CCTA) can quantify the extent, distribution and characteristics of coronary plaques, but this is not sufficient for optimal risk prediction in individuals. It is well known that most acute myocardial infarctions (MIs) occur secondary to occlusion in vessels with minor coronary plaque disease that erodes or ruptures. This relates to the biology of the underlying coronary plaque, particularly inflammation.

In the PROMISE trial, 54% of adverse events occurred in patients without significant stenoses, whereas patients with significant stenoses accounted for only 12% of the population undergoing CCTA. Thus, more than half of the aggregate risk of adverse cardiovascular events is not identified by coronary stenoses in people who undergo CCTA. This limitation is a driver of 'residual risk' that results in adverse cardiovascular outcomes, despite efforts to manage cardiovascular disease (CVD) according to current recommendations.

CCTA can identify patients with plaque characteristics associated with high risk, such as low-attenuation plaque, napkin ring sign, positive remodelling and spotty plaque calcification; however, these provide only modest incremental information in individual patients. The predictive value of high- risk plaque (HRP) features was studied in both the PROMISE and SCOT-HEART trials. In the PROMISE Study, approximately 15% of patients were found to have HRP on their CCTA and HRP was associated with more adverse cardiovascular events, although the major adverse cardiovascular events (MACE) endpoint included revascularisation which may not reflect the additional value of HRP above and beyond stenosis severity.

Nevertheless, most patients with HRP did not have cardiovascular events, whereas many patients without HRP did, indicating the limited predictive value of HRP on CCTA. Indeed, of the 1019 HRPs identified on CCTA, only 24 subsequent non-fatal MIs occurred, demonstrating that the absolute risk of a cardiovascular event in relation to a single plaque, identified at a single time point, is extremely low.

This observation is consistent with other CCTA and intravascular ultrasound (IVUS) studies. In the SCOT-HEART trial, 1376 HRP features on CCTA were

detected in 608 of 1769 participants. The likelihood of an adverse cardiac event during follow-up was increased in the subjects with HRP features, but the absolute increase in risk was very small (4.1% with HRP vs 1.4% without HRP). Importantly, more than one-third of the events occurred in subjects without HRP features. A more detailed analysis identified low-attenuation non-calcified plaque burden as the most specific HRP feature predictive of adverse events. Furthermore, recent discoveries highlight the importance of cellular inflammatory mechanisms in the vascular wall as drivers of disease progression and risk of events.

Coronary artery inflammation is a major factor in CAD progression, and a key determinant of high-risk plaques that drive adverse clinical events, in addition to the contributions of stenosis, flow limitation or high-risk plaque features.

Imaging perivascular adipose tissue (PVAT) around the coronary arteries (pericoronary adipose tissue; PCAT) has emerged as a promising technique to image inflammation in the coronary artery wall. A key recent discovery is that PVAT 'senses' the presence of inflammation in the wall of the coronary artery. These signals transduce changes in PVAT differentiation, leading to smaller, less lipid-rich adipocytes, greater inflammatory cell infiltration and higher tissue water content. These changes modify tissue attenuation values in a 3D distribution around the coronary artery that can be detected using cardiac computed tomography angiography (CCTA). Simple measures of PVAT attenuation require corrections for anatomical, technical factors, and patient and clinical variables. However, the validity of measuring changes in PCAT attenuation has been reproduced in research studies performed using similar techniques in different patient groups.

Goeller et al. (JAMA Cardiol. 2018; 3:858) reported that uncorrected PCAT CT attenuation was increased around culprit lesions compared to nonculprit lesions of patients with ACS and the lesions of matched controls. In a multivariate analysis, low- and intermediate-attenuation non-calcified plaque burden and PCAT CT attenuation were independently associated with the presence of culprit lesions. They concluded that combined quantitative high-risk plaque features and

PCAT CT attenuation may allow for a more reliable identification of vulnerable plaques.

The recent ORFAN (Oxford Risk Factors and Non-invasive imaging) study by the present inventors validated the efficacy of fat attenuation index (FAI) scores, and evaluated its real-world impact on patient management. The study revealed that cardiac death or MACE occurred in 3.4% or 8.7% of patients, respectively, without obstructive CAD. In patients with either obstructive or non-obstructive disease, those with a FAI score in the LAD above the 75th percentile, as compared to the 25th percentile, had 20.2 or 6.7 times higher risk of cardiac death or MACE, respectively. Among those without obstructive CAD, the risk of cardiac death or MACE was still 10.5 or 4.8 times higher, respectively. An artificial intelligence-assisted prognostic model (AI-risk), that included FAI-Score-based inflammatory risk, significantly reclassified the clinical risk of patients compared to a clinical risk factors-based prediction model (QRISK3) in the whole cohort and those without obstructive CAD, resulting in change of treatment for a significant proportion of patients, such as statin initiation, statin-dose intensification and/or additional treatments, such as colchicine. The study concluded that patients with high coronary inflammation, measured by FAI Score, have substantially higher risk for MACE, and the AI-Risk leads to reclassification and change of management in a substantial proportion of patients undergoing routine CCTA. Accordingly, this CCTA risk score can be used as a precision medicine tool.

Although such CCTA approaches have been proven as a promising development in recent years in the monitoring and treatment of coronary disease, there still remains a need to develop more precise and reliable methods for the identification of vulnerable vascular regions and plaques. In particular, there is a need to enable the earlier detection of vascular inflammation and high-risk fatty plaque development, and minimise false negative results obtained through previously known and less-sensitive CCTA functional biomarkers.

SUMMARY OF INVENTION

In a first aspect, the invention provides a method of characterising the pathology or state of a vascular region of a subject, said method comprising:

(a) providing medical imaging data gathered along a length of a blood vessel and:

(i) determining radial segments of the vessel extending from the centreline of the vessel to a distance extending beyond the outer wall of the vessel to the perivascular region;

(ii) determining a value for the radiodensity and/or one or more radiomic features of the radial segment; and

(b) comparing each value determined in (ii) to a pre-determined value or using the absolute value, in order to generate an output value that indicates the pathology or state of the vascular region.

At least one method step is computed-implemented.

According to a second aspect, the invention provides a method of characterising a plaque in a blood vessel of a subject, said method comprising:

(a) providing medical imaging data gathered along a length of the blood vessel and;

(i) identifying voxels corresponding to plaque by their radiodensity;

(ii) determining a radial segment of the vessel comprising voxels corresponding to the plaque, wherein the radial segment extends from the centreline of the vessel to a distance extending beyond the outer wall of the vessel;

(iii) determining a value for the radiodensity and/or one or more radiomic features of the radial segment;

(b) comparing each value determined in (iii) to a pre-determined threshold value, or using the absolute value determined in (iii), in order to generate an output value that indicates inflammation of the plaque.

At least one method step is computer implemented.

The methods according to the first and second aspects can be used to monitor the development of plaques, predict the risk of a subject suffering a cardiovascular event, guide pharmacological treatment decisions, monitor responses to medical treatments by assessing dynamic changes in coronary inflammation, non-invasively monitor aortic aneurisms or carotid plaques, stratify subjects according to their risk of cardiac mortality or risk of suffering a cardiovascular event; quantify vascular inflammation, fibrosis, oedema and vascularity; and compute a local change of inflammatory status.

It is preferable that the output value be corrected for biological and technical factors, to improve accuracy and sensitivity. It is preferred that these corrections be carried out by a processing system i.e. be computer implemented.

In a third aspect, the invention provides a computer program product comprising executable instructions which, when executed by one or more processors, cause the one or more processors to perform the method of the first aspect or the second aspect.

In a fourth aspect, there is provided a system comprising one or more processors configured to perform the method of the first aspect or the second aspect.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1A depicts a blood vessel with a lumen 100, centreline 101, blood vessel wall 102, and a radial segment extending from the centreline 101 to a predetermined distance 104 in the perivascular space 103. Figure 1B illustrates the same blood vessel but with a plaque 105 in the vessel wall. The radial segment in this instance is defined by the physical limits of the plaque.

Figures 2A and 2B similarly illustrate a blood vessel with a lumen 200, centreline 201, blood vessel wall 202, and a radial segment extending from the centreline 201 to a predetermined distance 204 in the perivascular space 203. The thickness of the radial segment in Figure 2A extends along the length of the blood vessel, whereas the thickness of the radial segment in Figure 2B is only a portion of the length of the blood vessel.

Figure 3 illustrates a blood vessel with a lumen 300, centreline 301, blood vessel wall 302, and a perivascular space 303 extending from the vessel wall 302 in a pre-determined distance 304. The vessel is portioned into multiple radial segments separated by dotted lines, in a predefined geometry. A plaque 305 is present in the vessel wall 302, and spans multiple radial segments of the predefined geometry 304.

Figure 4 schematically illustrates an example of a system suitable for implementing embodiments of the method. The system 1100 comprises at least one server 1110 which is in communication with a reference data store 1120. The server may also be in communication with other hardware or system 1130 which may be operated by a healthcare professional, for example over a communications network 1140.

Figure 5 describes an example of a suitable server 1110 which may be used to implement the methods of the invention. In this example, the server includes at least one microprocessor 1200, a memory 1201, an optional input/output device 1202, such as a keyboard and/or display, and an external interface 1203, interconnected via a bus 1204 as shown. In this example the external interface 1203 can be utilised for connecting the server 1110 to peripheral devices, such as the communications networks 1140, reference data store 1120, other storage devices, or the like.

Figure 6 shows digital phantoms of coronary arteries that were constructed in Example 1. Image a) shows a coronary artery without inflammation, b) shows a coronary artery with an added focal inflamed region, c) shows the area which is measured for PVAT attenuation according to the traditional method (i.e. the entire

circumference of the blood vessel is anaylsed and scored), and d) shows the area which was measured for PVAT attenuation within the quarter radial segment of the PVAT region surrounding the coronary artery according to the invention.

Figure 7 shows the increasing inflammation of the measured digital phantoms of coronary arteries according to Example 1, with increasing inflammation intensity from -75 HU to -49 HU.

Figure 8 shows the PVAT attenuation results for 50 simulations of digital phantoms of coronary arteries per inflammation intensity using the full PVAT region (i.e. the entire circumference) versus the quarter PVAT region (i.e. a radial segment according to the invention) of Example 1. The dashed horizonal line on the graph of Figure 8 shows the upper inter quartile range for baseline using the radial segment approach, while the dotted horizontal line shows the equivalent upper interquartile range for the full circumference approach.

Figure 9 shows the PVAT attenuation results for 500 simulations of digital phantoms of coronary arteries per inflammation intensity using the full PVAT region (i.e. the entire circumference) versus the quarter PVAT region (i.e. a radial segment according to the invention) of Example 1.

DETAILED DESCRIPTION

The inventors have developed computer implemented methods which are able to characterise the pathology or state of a vascular region of a subject (for example its phenotype, e.g. composition and/or texture) from medical imaging data, with increased sensitivity and precision. The methods are hence capable of mitigating false negatives frequently obtained from known analytical methods which lack the sensitivity to identify small but highly inflamed vascular regions or plaques.

The characterisation of the vascular region and/or plaque involves the determination of an output value based on the radiodensity and/or one or more radiomic features of a radial segment (e.g. wedge-shaped portion) of the vessel. The radial segment extends from the centreline of the vessel, which may be determined automatically by a processing system (i.e. be computer implemented),

to a pre-determined distance from the outer wall of the vessel. This analysis can enable the identification of inflamed vascular regions around a blood vessel, and characterise plaque connected to inflamed regions based on more limited, local analysis of the vessel of interest. The concentration of the analysis to a specific radial segment enables higher sensitivity analysis, improving the clarity of details within the vascular region, thus aiding in the detection of high-risk features and abnormalities that might be overlooked using current methods which analyse the pathology or state of a vessel by assessing the entirety of the vascular and/or perivascular space.

This targeted approach can lead to more accurate and precise diagnostics, and enable clinicians to make more informed decisions regarding patient care and treatment options. Moreover, the radial segment provides a smaller dataset which can be visualised more effectively, enabling clinicians to navigate through medical imaging data with greater ease and specificity, ultimately aiding in the communication of findings and targeted treatment planning.

The methods of the invention can be used to provide clinically valuable outputs which enable: monitoring the development of plaques, predicting the risk of a subject suffering a cardiovascular event, guiding pharmacological treatment decisions, monitoring responses to medical treatments, non-invasively monitoring aortic aneurisms or carotid plaques, and stratifying subjects according to their risk of cardiac mortality or risk of suffering a cardiovascular event; quantifying one or more of: vascular inflammation, fibrosis, oedema and vascularity; and computing a local change of inflammatory or other pathologic status.

The subject may be an individual who has been diagnosed as suffering from a condition associated with vascular inflammation, or who is suspected of, or at risk of, suffering from a condition associated with vascular inflammation, in particular vascular inflammation affecting the coronary vessels. Alternatively, the patient may be a healthy individual who has not been diagnosed as suffering from a condition associated with vascular inflammation, and/or who is not known to be at risk of suffering from a condition associated with vascular inflammation.

By limiting the analysis of the pathology or state of the vassel to local radial segments, rather than analysing the entirety of the vascular and/or perivascular space, small but aggressive areas of inflammation and/or high-risk plaque can be detected. This is an improvement over known methods which analyse and quantify the vascular and/or perivascular tissue averaged over the entire vascular or perivascular space (including or around the entire circumference of the blood vessel). As such, the present methods can identify inflamed regions with greater sensitivity and improved signal-to-noise ratio than previously known methods, which in turn mitigates false positives and enables earlier detection and intervention.

The vascular region and/or plaque characterisation of the invention can be used as an adjunctive tool in routine clinical CT angiograms to identify patients at high risk of cardiac events and mortality including a sensitive and specific screening tool in people who are apparently healthy and low-risk according to the traditional interpretation of their scans. Thus, the methods as claimed find utility both in primary prevention (healthy population with no diagnosis of heart disease yet) and secondary prevention (patients with a diagnosis of coronary artery disease), to identify an individual's risk status beyond traditional risk factors, to guide pharmacological treatment decisions, and to monitor response to appropriate medical treatments.

Furthermore, the current methods also allow the mapping of high-risk vascular regions and/or high-risk plaques, which facilitates more targeted monitoring of disease progression, improving the efficiency of screening and more targeted care.

In a first aspect, the invention provides a method of characterising the pathology or state of a vascular region of a subject, said method comprising:

(a) providing medical imaging data gathered along a length of a blood vessel and:

(i) determining radial segments of the vessel extending from the centreline of the vessel to a distance extending beyond the outer wall of the vessel to the perivascular region;

(ii) determining a value for the radiodensity and/or one or more radiomic features of the radial segment; and

(b) comparing each value determined in (ii) to a pre-determined value or using the absolute value, in order to generate an output value that indicates the pathology or state of the vascular region;

wherein at least one method step is computer-implemented.

Determining radial segments

The radial segment according to each aspect of the invention is a wedge shape in the plane of the blood vessel circumference which extends from a point in the centre of the vessel to a distance extending beyond the outer wall of the vessel to the perivascular region.

This can be understood with reference to Figure 1A and 1B, which schematically illustrate a radial segment depicted by dashed lines. As can be seen from these drawings, the wedge-shaped radial segment extends radially from the point in the centre of the vessel 101 in the lumen 100 of the vessel, to the perivascular space 103 to a pre-determined distance 104 from the outer wall of the vessel 102. The part of the blood vessel which is not encompassed within the radial segment is not used in the calculation of the value for the radiodensity and/or one or more radiomic features of the vessel.

The radial segment may have a pre-defined geometry. For instance, it may be a fraction of the cross-section of the blood vessel, in a radial direction.

The angle of the radial segment from the point in the centre of the vessel may be from 1 to 359°, preferably from 2 to 270°, more preferably from 10 to 180°C, more preferably from 30 to 150°. This can be visualised with reference to Figure 3, which illustrates a blood vessel with a lumen 300, point in the centre of the vessel

301, blood vessel wall 302, and a perivascular space 303 extending from the vessel wall 302 in a pre-determined distance 304. The vessel is portioned into multiple radial segments separated by dotted lines, in a predefined geometry – in this case each radial segment is 1/8th of the blood vessel, and has an angle of 45 °. A plaque 305 is present in the vessel wall 302, and spans multiple radial segments with the predefined geometry.

The method may involve determining the point in the centre of the vessel 301 of the blood vessel from the medical imaging data, determining radial segments of the blood vessel and analysing each segment in turn to characterise the pathology or state of each vascular region or characterise any plaque 305 which may be present in the vessel wall 302.

The term “point in the centre of the vessel” is a point of the medical imaging data which represents a point in the lumen. This could be the centre point of the vessel, or another point in the lumen. Preferably, the point in the centre of the vessel corresponds to the centreline of the vessel. Methods for determining the centreline are well known to those skilled in the art.

Biological factors may also impact the geometry of the radial segment. For instance, if a potentially high risk or inflamed plaque is identifiable from the medical imaging data, the segment may be adjusted such that it encompasses voxels corresponding to the entirety of, or a portion of the plaque. For example, if a plaque is present on a quarter of the blood vessel, the radial segment may be a quarter of the blood vessel and will encompass the voxels corresponding to plaque. Figure 1B illustrates an embodiment in which the geometry of the radial segment is defined by the physical limits of the plaque 105.

The same applies to vascular regions which do not contain plaque, but that are identifiable from the medical imaging data as highly inflamed, oedemic, fibrosis, vascularity by the radiodensity and/or radiomic measurements of step (ii) of the first aspect or step (iii) of the second aspect of the invention. In those instances, the radial segment may be adjusted such that it contains the voxels corresponding to discrete, inflamed regions.

The thickness of the radial segment may vary. For instance, with reference to Figure 2A, the radial segment may be extended along the length 206 of the blood vessel being analysed. Alternatively, the radial segment may only have a thickness which is a portion of the length 206 of the blood vessel, as is depicted in Figure 2B.

The radial segment has a minimum thickness of one voxel. However, preferably, it has a width of multiple voxels to improve signal to noise ratio. Increasing the number of voxels sampled improves the estimate of the true mean value of the voxels, reducing the “standard error of the mean” in proportion to 1/sqrt(n), where “n” is the number of voxels sampled.

If a plaque is present in the blood vessel, or a discrete, highly inflamed region, the thickness of the radial segment may be adjusted to encompass the voxels corresponding to the plaque or discrete, inflamed region.

For a given medical imaging data set, multiple radial segments may be determined along a length of a blood vessel, which may have varying geometry. They may also have the same geometry e.g. the same wedge angle throughout a given measurement, as shown in Figure 2A.

The distance extending beyond the outer wall of the vessel may depend on the type of vessel being analysed, and its spatial positioning in relation to other bodily tissues, or other surrounding vessels. For instance, if the particular vessel being analysed is positioned close to another type of body tissue, the perivascular space should not include voxels corresponding to the other body tissue.

The distance extending beyond the outer wall of the vessel may also be determined by the radio densities in the image (as for radial extent) or based on patient anatomy. For example, thinner perivascular tissue more distally along the vessel; or to prevent inclusion of other anatomical features e.g. to exclude tissue outside the pericardial sack in the case of the coronary arteries.

Preferably, the distance extending beyond the outer wall of the vessel is determined by the processing system (i.e. this step is computer implemented),

which preferably calculates this distance based on reference data sets. Alternatively, the distance may be manually determined or adjusted by an operator of the processing system.

In one embodiment, the distance extending beyond the outer wall of the vessel may be:

i) a standard distance that is not equal to or related to the diameter or radius of the underlying vessel;

ii) a distance which is a derivative of, a multiple of, or equal to the radius or diameter of the underlying vessel; or

iii) from 0.1mm to 3cm, preferably from 0.2mm to 2.5cm, more preferably from 0.3mm to 2.25cm, more preferably from 0.4mm to 2cm.

The wedge shape of the radial segment has been selected by the inventors over other geometries as it is thought to accurately capture the paracrine effect exerted by mediators released by the vascular wall on neighbouring perivascular tissue, due to the presence of vascular inflammation and oxidative stress (see e.g. Margaritis et al. Circulation 2013; 127(22):2209-21). In addition to the mediators realised from the vessel wall to the perivascular space, is thought that perivascular adipose tissue 'senses' the inflammation in the wall of the adjacent blood vessel, which leads to changes in PVAT differentiation. This communication between cells of the inflamed vessel and the neighbouring perivascular tissue is thought to be exerted radially. Hence, it is envisaged that the radial segment extending beyond the wall of the vessel in this same direction can provide a picture of the impact of biology changes in the perivascular space caused by any vascular inflammation, oedemic, fibrosis or vascularity states in the same radial segment. This specificity would be lost by methods which employ different geometries to analyse when 'zooming in' to medical imaging data.

Another method of defining the quantified segments, beyond the radial lines, would be determine the region of the tissue impacted by paracrine mediators by

simulating the diffusion of these mediators through the perivascular tissue from the plaque/wall interface.

This can be achieved using reaction-diffusion equations. For example, the Diffusion Equation (Fick's 2nd Law) can be used to simulate the diffusion of cytokines or signalling molecules through the perivascular tissue.

$$\frac{\partial c}{\partial t} = D\nabla^2 c = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right)$$

Where:

- c is the concentration of the cytokine or signalling molecule at a given point.
- D is the diffusion coefficient (specific to the cytokine or signalling molecule).
- ∇^2 is the Laplacian operator, with $\nabla^2 c$ representing the concentration gradient.
- x, y and z define the spatial position in 3 dimensions.
- t is time.

A reaction step could be added to the above diffusion equation to, for example, represent metabolism of the cytokine or signalling molecule. In this embodiment, a Reaction-Diffusion equation would be used:

$$\frac{\partial c}{\partial t} = D\nabla^2 c + R(c)$$

Where:

- $R(c)$ is a function accounting for all local reactions involving the cytokine or signalling molecule, for example, the Fisher's equation (Fisher, The Wave of Advantageous Genes, Annals of Eugenics, 1937).

In a medical imaging scan, such as a CCTA of the coronary arteries, the diffusion of cytokines from a plaque/vessel wall interface into the perivascular adipose tissue can be simulated using a continuum approach.

The simulation can be initialised at time t=0 by assigning those voxels corresponding to the plaque and connected vessel wall, a high concentration value (c), and those voxels corresponding to perivascular tissue a concentration (c) of zero.

At each time step in the simulation, the concentration of the cytokine or signalling molecule in each voxel corresponding to perivascular tissue is updated based on both the reactions of molecules within a voxel (if a reaction component is included), and the diffusion between neighbouring voxels based on concentration differences following the above diffusion equation.

This simulation can be performed for a fixed number of iterations, or until the change in concentration in voxels corresponding to perivascular tissue between consecutive time steps falls below a predefined threshold (e.g., a steady state is reached). At this point, a specified concentration threshold can be used to identify which voxels corresponding to perivascular tissue should be included in the region used to quantify radiodensity (i.e., all voxels with a concentration above the threshold).

Vascular Region

The "vascular region" may be a region of a coronary artery, carotid artery, aorta or any other artery in the human body. For example, the vascular region may include the mid right coronary artery.

In a preferred embodiment, vascular region is limited to the perivascular space around the coronary artery, carotid artery, aorta or any other artery in the human body. Alternatively, the vascular region may comprise the entire radial segment, including the lumen of the blood vessel, vessel wall and perivascular space.

The method may further comprise segmenting the vascular region along the length of the blood vessel being analysed, to facilitate the analysis of a smaller portion of the blood vessel in a length-wise direction. For the avoidance of doubt, this length-wise segmentation is distinct from the segmentation of the vascular region radially i.e. it occurs in a distinct plane.

Determining a value for the radiodensity

Radiodensity, which is measured in Hounsfield units (HU), is a measure of the relative inability of X-rays to pass through material. The term "radiodensity" is synonymous with the term "attenuation" and the two terms can be used interchangeably.

Measurement of attenuation values allows tissue types to be distinguished in CT on the basis of their different radio-opacities. Fat is not very radiodense, and it typically provides a much lower radiodensity than muscle, blood and bone. The exact HU ranges which correspond to different tissue types typically vary depending on factors such as CT scan parameters, and the type of software used to analyse the medical imaging data.

For instance, the following software programs designate vascular and perivascular tissue types as follows.

Coronary Plaque Analysis 2.0.3 syngo.via FRONTIER, Siemens

- Calcified plaque: >700HU
- Lumen: 150 – 700 HU
- Non calcified fibrotic plaque: 30 – 150 HU
- Non calcified lipid rich: ≤ 30 HU

QAngioCT version 3.1.3.13 Medis Medical Imaging Systems

- Dense calcium: >351 HU
- Fibrous plaque: 151-350 HU
- Fibrofatty plaque: 31 – 150 HU
- Necrotic core: -30 – 30 HU

SUREPlaque, version 6.3.2; Vital Images

- Calcified plaque: >150 HU
- Fibrous plaque: 50 – 150 HU
- Fatty plaque: -100 – 49 HU

A person skilled in the art of cardiology and medical imaging technology is therefore able to distinguish different tissue types from CT image data depending on the equipment and software used, without the need for an exact definition in HU.

The term “voxel” has its usual meaning in the art and is a contraction of the words “volume” and “element” referring to each of an array of discrete elements of volume that constitute a notional three-dimensional space.

Determining a value for the radiodensity of the radial segment may comprise determining **RSA** – the average radiodensity or attenuation of all voxels within the radial segment. This may be calculated as the cumulative total of all voxels within the radial segment divided by the number of voxels in the radial segment.

In another embodiment, determining a value for the radiodensity of the segment may comprise determining **RSA_{PV}** – the average radiodensity or attenuation of all voxels corresponding to perivascular tissue within the radial segment.

As used therein, the term “perivascular” refers to the space that surrounds a blood vessel. The term “perivascular tissue” or “perivascular space” refers to the tissue that surrounds a blood vessel, and may include perivascular adipose tissue (PVAT).

In one embodiment, a value for the radiodensity may involve determining a radiodensity value of one or more particular types of tissue, for example, one or more of: adipose tissue, fibrous plaque, calcified plaque, or water.

Preferably, the radiodensity value comprises the perivascular tissue in the perivascular space of the radial segment. Preferably, the perivascular tissue comprises perivascular adipose tissue (PVAT) of the radial segment. In some embodiments, voxels corresponding to plaque are not included in the radiodensity value. As calcified plaque is generally considered more stable and is less likely to rupture than fibrous plaque, preferably voxels corresponding to calcified plaque are not included in the radiodensity value.

In the context of the present invention, an “average” value is understood to mean a central or typical value, and it can be calculated from a sample of measured values using formulas that are widely known and appreciated in the art. Preferably, the average is calculated as the arithmetic mean of the sample of attenuation values, but it can also be calculated as the geometric mean, the harmonic mean, the median or the mode of a set of collected attenuation values. The average value may be calculated by reference to data collected from all voxels within a concentric tissue layer or by reference to a selected population of voxels within the concentric tissue layer, for example water- or adipose tissue- or fibrous tissue- containing voxels.

In a preferred embodiment, step (ii) comprises determining the radiodensity of the voxels corresponding to perivascular adipose tissue (PVAT) in the perivascular

region of the radial segment. From this measurement, the metrics Fat Attenuation Index (FAI) and/or perivascular FAI (FAI_{PVAT}) can be determined, which reflects the standardized, weighted average attenuation of a perivascular region around the human coronary arteries. These metrics have been found to be a sensitive and dynamic biomarker of coronary inflammation, and have been identified as a strong and independent predictors of adverse cardiac events.

FAI and FAI_{PVAT} are based on the understanding that in the presence of vascular inflammation, the release of pro-inflammatory molecules from the diseased vascular wall inhibits differentiation and lipid accumulation in pre-adipocytes within the perivascular tissue (PVT), resulting in smaller, less differentiated and lipid-free adipocyte cells. This is associated with a shift in the radiodensity (measured as attenuation values) of PVT in computed tomography (CT) imaging from more negative (closer to -190) to less negative (closer to -30) Hounsfield Unit (HU) values, which may be captured by the FAI and FAI_{PVAT}. Both the biological meaning and clinical value of the FAI have been extensively validated. These biomarkers are described in detail in WO 2016/024128 A1 and WO 2018/078395 A1, the contents of which are herein incorporated by reference.

The limitation of the FAI_{PVAT} and FAI score to radial segments of the blood vessel, rather than being averaged over the entire vascular or perivascular space enable the detection of small but highly inflamed 'hot spots' which could have otherwise gone undetected due to averaging the attenuation over a larger area.

Medical Imaging Data

The medical imaging data may be radiographic data. In a preferred embodiment, the medical imaging data may be computed tomography (CT) data.

The CT scan is preferably taken over the length of a blood vessel, for example, along the length of a right coronary artery, left anterior descending artery, left circumflex artery, aorta, carotid arteries or femoral arteries.

For the avoidance of doubt, the methods of the invention utilise CT scan data that has been obtained *in vivo,* by scanning a living body, but the claimed methods are

not practised on the living human or animal body. Consequently, the method of the invention is non-invasive and is based on the analysis of conventional CT images; it does not require any additional image acquisition.

Vascular Inflammation

The output value determined in step (b) may provide a measure of the inflammation of the vascular region. Vascular inflammation refers to a progressive inflammatory condition characterized by the vascular infiltration by white blood cells, build-up of sclerotic plaques within vascular walls, and in particular, arterial walls.

Vascular inflammation is a key feature in atherogenesis and plays a critical role in atherosclerotic plaque stability by triggering plaque rupture leading to acute coronary syndromes (see Ross R. N Engl J Med 1999;340:115-26, and Major AS *et al* Circulation 2011;124:2809-11). Importantly, more than 50% of acute coronary syndromes are caused by highly inflamed but anatomically non-significant atherosclerotic plaques (Fishbein MC *et al*. Circulation 1996;94:2662-6), which may go undetected with less sensitive methods.

The methods of the invention enable the detection of sub-clinical plaque, a pre-plaque state, and/or early atherosclerotic disease activity, in the blood vessel wall of an inflamed vascular region – owing to the improved sensitivity and more targeted assessment of the pathology or state of the vascular region. Further, the method may identify subclinical extensions to plaque which are already visible on the medical imaging data. Accordingly, the method may identify tissue which is in the process of turning into high-risk fatty plaque tissue beyond current visible clinical margins, enabling earlier risk detection and intervention.

The method according to the first aspect may further comprise the step of identifying inflamed plaque within the vascular region. For instance, if a plaque is present in the radial segment, such as the plaque 305 in Figure 3, the output determined in step (b) can be used to characterise the plaque as inflamed. For

high-risk fatty plaques (which may be non-calcified), the entire plaque can be classed as inflamed by this technique.

Calcified plaques, on the other hand, tend to be more stable and provide a lower risk of rupture which leads to adverse cardiac events. However, they may contain inflamed, non-calcified fatty areas which could be prone to rupture.

Hence, the present method may comprise the step of identifying inflamed portions of plaque within the vascular region. For example, with reference to Figure 3, the plaque 205 in the blood vessel wall 302 spans over four separate radial segments of predefined geometry. If the output value determined in step (b) reveals that a particular segment encompassing the plaque is particularly inflamed, then the portion of the plaque encompassed by that segment may be classified as inflamed. Hence, this method allows the mapping of unstable or inflamed hot-spots on the plaque.

On the other hand, there may be segments encompassing plaque which do not show signs of inflammation, such that the areas of the plaque included in those segments can be classified as low risk. For instance, this would be expected of plaques which are calcified, and which are less likely to lead to adverse cardiac events.

Accordingly, the methods of the invention enable the classification of plaque, or inflamed plaque, as low risk, medium risk, high risk or very high risk.

Plaque Characterisation

According to a second aspect, the invention provides method of characterising a plaque in a blood vessel of a subject, said method comprising:

(a) providing medical imaging data gathered along a length of the blood vessel and;

(i) identifying voxels corresponding to plaque by their radiodensity;

(ii) determining a radial segment of the vessel comprising voxels corresponding to the plaque, wherein the radial segment extends from a point in the centre of the vessel to a distance extending beyond the outer wall of the vessel;

(iii) determining a value for the radiodensity and/or one or more radiomic features of the radial segment;

(b) comparing each value determined in (iii) to a pre-determined threshold value, or using the absolute value determined in (iii), in order to generate an output value that indicates inflammation of the plaque.

At least one method step is computer-implemented.

According to the second aspect of the invention, step (ii) may comprise determining the radiodensity of voxels corresponding to perivascular adipose tissue (PVAT) in the radial segment, the utility of which has been described in detail above.

The radial segment may be:

a) a predefined geometry; or

b) wherein the radii of the radial segment is defined by the physical limits of the voxels corresponding to plaque.

The predefined geometry may be a fraction of the cross-section of the blood vessel, in a radial direction. For instance, the angle of the radial segment from the point in the centre of the vessel may be from 1 to 359°, preferably from 2 to 270°, more preferably from 10 to180°C, more preferably from 30 to 150°.

Alternatively, the radii of the radial segment can be defined by the physical limits of the voxels corresponding to plaque, such that the plaque contained in the vessel wall is entirely encompassed by the radial segment in a given cross-section or along a length of a blood vessel. For example, if a plaque is present on a quarter

of the blood vessel, the radial segment may be a quarter of the blood vessel and will encompass the voxels corresponding to plaque. This is shown in Figure 1B.

The voxels corresponding to plaque may encompass both calcified and non-calcified plaque. Preferably, the plaque is non-calcified, with non-calcified being the higher-risk plaque.

In some embodiments, voxels corresponding to calcified plaque are not included in the analysis in the determination of a value for the radiodensity and/or one or more radiomic features in step (iii), and not used to determine the output value in step (b).

The inflamed plaque may be fibrous plaque or a non-fibrous plaque; and it may further be characterised or classified as one or more of: hot, unstable, high-risk and potential culprit.

When a plaque is characterised as inflamed in step (b), the subject may be administered a therapy in order to treat the plaque or prevent its progression.

The value for the radiodensity and/or one or more radiomic features in step (iii) may be taken from the entirety of the radial segment, including the lumen, vessel wall and perivascular space.

Preferably, the value is taken from the vascular wall and perivascular space. Alternatively, the value for the radiodensity and/or one or more radiomic features is taken from the perivascular space.

The preferences with regards to the radiodensity features are the same as for the first aspect.

Radiomic Features

Step (ii) of the first aspect of the invention and step (iii) of the second aspect of the invention may comprise determining a value for at least two radiomic features from the medical imaging data. The value for each radiomic feature is then

included in step (b) to generate an output value that indicates the pathology or state of the vascular region or the inflammation of the plaque.

In WO 2020/058713 A1, it was identified that the use of radiomic features adds incremental value beyond traditional risk factors and established CCTA risk classification tools in predicting future adverse cardiovascular events and evaluating cardiovascular health and risk, and further aids the detection of vascular inflammation, local plaque inflammation, and the presence of unstable coronary lesions.

Preferably, the radiodensity of the vascular segment is determined in addition to one or more radiomic features, preferably two or more radiomic features. The use of two or more radiomic features provides a 'radiomic signature' and provides a tool for further characterising the vascular segment or plaque within the radial segment.

In a preferred embodiment, the radiomic features are taken from the perivascular space within the radial segment.

It is particularly preferred that a value for the radiodensity of the vascular region (which may be limited to the perivascular space) is determined in addition to the radiomic features.

For embodiments in which one or more radiomic features are determined, the output value determined in step (b) may provide a measure of the texture of the vascular region.

If an indication of texture is to be provided, at least one radiomic feature may provide a measure of the texture. If more than one radiomic feature has been determined, each of the radiomic features may provide a measure of the texture of the radial segment (i.e. each of the at least two radiomic features may be texture statistics). Alternatively, one or more radiomic feature may be required to provide a measure of the texture.

In a preferred embodiment, the methods of the invention comprise determining two or more radiomic features. More preferably, three or more, or four or more radiomic features. The radiomic features may be determined based on the perivascular region of the vascular segment. Alternatively, the radiomic features may be determined based on the entirety of the radial segment (including the blood vessel comprising the lumen and vessel wall).

If two or more radiomic features are determined of the radial segment, a radiomic signature may be calculated for the radial segment. The radiomic signature is described in detail in WO 2020/058713, the entirety of which is herein incorporated by reference.

When deriving a radiomic signature, the method may comprise using a dataset, in particular a radiomic dataset, to construct a radiomic signature or score. This score may then be used to characterise the pathology or state of the vascular region, characterise the inflammation of a plaque, provide a cardiovascular risk score, or guide pharmacological treatment.

The radiomic signature may be calculated on the basis of a (second) plurality of perivascular radiomic features. The dataset may comprise the measured values of a (first) plurality of perivascular radiomic features of a perivascular region obtained from medical imaging data for each of a plurality of individuals. The plurality of individuals may comprise a first group of individuals having reached a clinical endpoint indicative of cardiovascular risk, and/or particular biological state such as inflammation, fibrosis, oedema, vascularity, or combinations thereof; and a second group of individuals having not reached a clinical endpoint indicative of cardiovascular risk and/or the particular biological state(s). The second plurality of radiomic features may be selected from amongst the first plurality of radiomic features, in particular to provide a radiomic signature for predicting cardiovascular risk, as determined from or using the dataset, for example using a machine learning algorithm. The radiomic signature may therefore be calculated on the basis of further radiomic features (for example selected from the (first) plurality of radiomic features) in addition to the at least two radiomic features.

The radiomic features may be selected from the radiomic features of clusters 1 to 9, wherein:

cluster 1 consists of Short Run High Gray Level Emphasis, High Gray Level Emphasis, High Gray Level Run Emphasis, Autocorrelation, Sum Average, Joint Average, and High Gray Level Zone Emphasis;

cluster 2 consists of Skewness, Skewness LLL, Kurtosis, 90th Percentile, 90th Percentile LLL, Median LLL, Kurtosis LLL, and Median;

cluster 3 consists of Run Entropy, Dependence Entropy LLL, Dependence Entropy, Zone Entropy LLL, Run Entropy LLL, and Mean LLL;

cluster 4 consists of Small Area Low Gray Level Emphasis, Low Gray Level Zone Emphasis, Short Run Low Gray Level Emphasis, Low Gray Level Run Emphasis, Low Gray Level Emphasis, Small Dependence Low Gray Level Emphasis, Gray Level Variance LLL (GLSZM), Gray Level Variance (GLDM), Variance, Gray Level Variance (GLDM), Difference Variance LLL, Gray Level Variance LLL (GLRLM), Variance LLL, Gray Level Variance LLL (GLDM), Sum of Squares, Contrast LLL, Mean Absolute Deviation, Interquartile Range, Robust Mean Absolute Deviation, Long Run Low Gray Level Emphasis, Difference Variance, Gray Level Variance (GLSZM), Inverse Difference Moment Normalized, Mean Absolute Deviation LLL, Sum of Squares LLL, and Contrast;

cluster 5 consists of Zone Entropy, Gray Level Non Uniformity Normalized (GLRLM), Gray Level Non Uniformity Normalized LLL (GLRLM), Sum Entropy, Joint Energy, Entropy, Gray Level Non Uniformity Normalized (GLDM), Joint Energy, Gray Level Non Uniformity Normalized LLL (GLDM), Uniformity LLL, Sum Entropy LLL, and Uniformity;

cluster 6 consists of Zone Entropy HHH, Size Zone Non Uniformity Normalized HHH, and Small Area Emphasis HHH;

cluster 7 consists of Strength, Coarseness HLL, Coarseness, Coarseness LHL, Coarseness LLL, Coarseness LLH, Coarseness HHH, Coarseness HLH, Coarseness HHL, and Coarseness LHH;

cluster 8 consists of Cluster Tendency LLL, Cluster Tendency, Sum of Squares LLL, Mean Absolute Deviation LLL, Gray Level Variance LLL (GLDM), Variance LLL, Gray Level Variance LLL (GLRLM), Gray Level Variance (GLRLM), Robust Mean Absolute Deviation LLL, Gray Level Variance (GLDM), Variance, Mean Absolute Deviation, Cluster Prominence, Sum Entropy LLL, Interquartile Range LLL, Gray Level Variance LLL (GLSZM), Sum of Squares, Robust Mean Absolute Deviation, Sum Entropy, Interquartile Range, Cluster Prominence LLL, Entropy LLL, 10th Percentile LLL, 10th Percentile; and

cluster 9 consists of Size Zone Non Uniformity LLL, Dependence Non Uniformity HLL, Gray Level Non Uniformity HLL (GLSZM), Gray Level Non Uniformity (GLSZM), Run Length Non Uniformity HHL, Run Length Non Uniformity LHL, Dependence Non Uniformity LHL, Dependence Non Uniformity, Run Length Non Uniformity HLH, Busyness, Run Length Non Uniformity LLH, Dependence Non Uniformity LLH, Dependence Non Uniformity LLL, Size Zone Non Uniformity, Energy HLL, Run Length Non Uniformity LHH, Size Zone Non Uniformity HLL, Gray Level Non Uniformity LLH (GLSZM), Gray Level Non Uniformity LHL (GLSZM), Gray Level Non Uniformity LLL (GLSZM), Run Length Non Uniformity HLL, Gray Level Non Uniformity HLH (GLSZM), Gray Level Non Uniformity HHL (GLSZM), Run Length Non Uniformity, and Run Length Non Uniformity HHH.

Preferably at least two radiomic features are selected; preferably wherein the at least two radiomic features are each selected from different clusters.

The definitions of the radiomic features referred to herein are generally well understood within the field of radiomics by reference to their name only. However, for ease or reference definitions of the features used herein are provided in Tables R1 to R7 below. The radiomic features in Tables R1 to R7 are defined in accordance with the radiomic features used by the Pyradiomics package (http://pyradiomics.readthedocs.io/en/latest/features.html, see van Griethuysen, J. J. M., Fedorov, A., Parmar, C., Hosny, A., Aucoin, N., Narayan, V., Beets-Tan, R. G. H., Fillon-Robin, J. C., Pieper, S., Aerts, H. J. W. L. (2017). Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Research,

77(21), e104–e107. https://doi.org/10.1158/0008-5472.CAN-17-0339). Most features defined in Tables R1 to R7 are in compliance with feature definitions as described by the Imaging Biomarker Standardization Initiative (IBSI), which are available in Zwanenburg et al. (2016) (Zwanenburg, A., Leger, S., Vallières, M., and Löck, S. (2016). Image biomarker standardisation initiative - feature definitions. In eprint arXiv:1612.07003 [cs.CV]). Where a definition provided below does not comply exactly from the IBSI definition, it should be understood that either definition could be used in accordance with the invention. Ultimately, the precise mathematical definition of the radiomic features is not crucial because slight modifications do not affect the general properties of the image that are measured by each of the features. Thus, slight modifications to the features (for example, the addition or subtraction of constants or scaling) and alternative definitions of the features are intended to be encompassed by the present invention.

a. First Order Statistics

These statistics describe the central tendency, variability, uniformity, asymmetry, skewness and magnitude of the attenuation values in a given region of interest (ROI), disregarding the spatial relationship of the individual voxels. As such, they describe quantitative and qualitative features of the whole ROI (PVR). A total of 19 features were calculated for each one of the eight wavelet transformations and the original CT image, as follows:

Let:

- $\boldsymbol{X}$ be the attenuation or radiodensity values (e.g. in HU) of a set of $\boldsymbol{N_p}$ voxels included in the region of interest (ROI)
- $\boldsymbol{P(i)}$ be the first order histogram with $\boldsymbol{N_g}$ discrete intensity levels, where $\boldsymbol{N_g}$ is the number of non-zero bins, equally spaced from 0 with a width.
- $\boldsymbol{p(i)}$ be the normalized first order histogram and equal to $\frac{\mathbf{P}(i)}{N_p}$

- **c** is a value that shifts the intensities to prevent negative values in X. This ensures that voxels with the lowest gray values contribute the least to Energy, instead of voxels with gray level intensity closest to 0. Since the HU range of adipose tissue (AT) within the PVR (-190 to -30 HU) does not include zero, c may be set at c=0. Therefore, higher energy corresponds to less radiodense AT, and therefore a higher lipophilic content.
- **ϵ** is an arbitrarily small positive number (e.g. $\approx 2.2\times10^{-16}$)

Table R1: First-order radiomic features for PVR characterization

Radiomic feature	**Interpretation**
$\text{Energy} = \sum_{i=1}^{N_p}(\text{X}(i)+c)^2$	**Energy** is a measure of the magnitude of voxel values in an image. A larger value implies a greater sum of the squares of these values.
$\text{Total Energy} = V_{voxel}\sum_{i=1}^{N_p}(\text{X}(i)+c)^2$	**Total Energy** is the value of Energy feature scaled by the volume of the voxel in cubic mm.
$\text{Entropy} = -\sum_{i=1}^{N_g} p(i)\log_2(p(i)+\epsilon)$	**Entropy** specifies the uncertainty/randomness in the image values. It measures the average amount of information required to encode the image values
$\text{Minimum} = min(\text{X})$	The **minimum** gray level intensity within the ROI.
The **10th percentile** of X	The **10th percentile** of X
The **90th percentile** of X	The **90th percentile** of X
$\text{Maximum} = max(\text{X})$	The **maximum** gray level intensity within the ROI.
$\text{Mean} = \frac{1}{N_p}\sum_{i=1}^{N_p}\text{X}(i)$	The average (**mean**) gray level intensity within the ROI.
Median	The **median** gray level intensity within the ROI.
$\text{Interquartile range} = \text{P}_{75} - \text{P}_{25}$	Here P_{25} and P_{75} are the 25th and 75th percentile of the image array, respectively.

$\text{Range} = max(\text{X}) - min(\text{X})$	The range of gray values in the ROI.
$\text{MAD} = \frac{1}{N_p}\sum_{i=1}^{N_p} \lvert \text{X}(i) - \overline{X} \rvert$	**Mean Absolute Deviation (MAD)** is the mean distance of all intensity values from the Mean Value of the image array.
$\text{rMAD} = \frac{1}{N_{10-90}}\sum_{i=1}^{N_{10-90}} \lvert \text{X}_{10-90}(i) - \overline{X}_{10-90} \rvert$	**Robust Mean Absolute Deviation (rMAD)** is the mean distance of all intensity values from the Mean Value calculated on the subset of image array with gray levels in between, or equal to the 10th and 90th percentile.
$\text{RMS} = \sqrt{\frac{1}{N_p}\sum_{i=1}^{N_p}(\text{X}(i) + c)^2}$	**Root Mean Squared (RMS)** is the square-root of the mean of all the squared intensity values. It is another measure of the magnitude of the image values. This feature is volume-confounded, a larger value of c increases the effect of volume-confounding.
$\text{Skewness} = \frac{\mu_3}{\sigma^3} = \frac{\frac{1}{N_p}\sum_{i=1}^{N_p}(\text{X}(i) - \overline{X})^3}{(\sqrt{\frac{1}{N_p}\sum_{i=1}^{N_p}(\text{X}(i) - \overline{X})^2})^3}$	**Skewness** measures the *asymmetry* of the distribution of values about the Mean value. Depending on where the tail is elongated and the mass of the distribution is concentrated, this value can be positive or negative. (Where μ_3 is the 3rd central moment).
$\text{Kurtosis} = \frac{\mu_4}{\sigma^4} = \frac{\frac{1}{N_p}\sum_{i=1}^{N_p}(\text{X}(i) - \overline{X})^4}{(\frac{1}{N_p}\sum_{i=1}^{N_p}(\text{X}(i) - \overline{X})^2)^2}$	**Kurtosis** is a measure of the '*peakedness*' of the distribution of values in the image ROI. A higher kurtosis implies that the mass of the distribution is concentrated towards the tail(s) rather than towards the mean. A lower kurtosis implies the reverse: that the mass of the distribution is concentrated towards a spike near the Mean value. (Where μ_4 is the 4th central moment).
$\text{Variance} = \frac{1}{N_p}\sum_{i=1}^{N_p}(\text{X}(i) - \overline{X})^2$	**Variance** is the mean of the squared distances of each intensity value from the Mean value. This is a measure of the spread of the distribution about the mean.
$\text{Uniformity} = \sum_{i=1}^{N_g} p(i)^2$	**Uniformity** is a measure of the sum of the squares of each intensity value. This is a measure of the heterogeneity of the image array, where a greater uniformity implies a greater heterogeneity or a greater range of discrete intensity values.

b. Shape-related Statistics

Shape-related statistics describe the size and shape of a given ROI, without taking into account the attenuation values of its voxels. Since they are independent of the gray level intensities, shape-related statistics were consistent across all wavelet transformation and the original CT image, and therefore were only calculated once. These were defined as follows:

Let:

V be the volume of the ROI in mm^3

A be the surface area of the ROI in mm^2

Table R2: Shape-related radiomic features for PVR characterization	
Radiomic feature	**Interpretation**
$\mathbf{Volume} = \sum_{i=1}^{N} V_i$	The **volume** of the ROI V is approximated by multiplying the number of voxels in the ROI by the volume of a single voxel $\mathbf{V_i}$.
$\mathbf{Surface\ Area} = \sum_{i=1}^{N} \frac{1}{2} \lvert a_i b_i \times a_i c_i \rvert$	**Surface Area** is an approximation of the surface of the ROI in mm^2, calculated using a marching cubes algorithm, where ***N*** is the number of triangles forming the surface mesh of the volume (ROI), $\boldsymbol{a_i b_i}$ and $\boldsymbol{a_i c_i}$ are the edges of the $\boldsymbol{i^{th}}$ triangle formed by points $\boldsymbol{a_i}$, $\boldsymbol{b_i}$ and $\boldsymbol{c_i}$.
$\mathbf{Surface\ to\ volume\ ratio} = \frac{A}{V}$	Here, a lower value indicates a more compact (sphere-like) shape. This feature is not dimensionless, and is therefore (partly) dependent on the volume of the ROI.
$\mathbf{Sphericity} = \frac{\sqrt[3]{36\pi V^2}}{A}$	**Sphericity** is a measure of the roundness of the shape of the tumor region relative to a sphere. It is a dimensionless measure, independent of scale and orientation. The value range is 0<sphericity≤1, where a value of 1 indicates a perfect sphere (a sphere has the

	smallest possible surface area for a given volume, compared to other solids).
Volume Number	Total number of discrete volumes in the ROI.
Voxel Number	Total number of discrete voxels in the ROI.
Maximum 3D diameter	Maximum 3D diameter is defined as the largest pairwise Euclidean distance between surface voxels in the ROI (Feret Diameter).
Maximum 2D diameter (Slice)	Maximum 2D diameter (Slice) is defined as the largest pairwise Euclidean distance between ROI surface voxels in the row-column (generally the axial) plane.
Maximum 2D diameter (Column)	Maximum 2D diameter (Column) is defined as the largest pairwise Euclidean distance between ROI surface voxels in the row-slice (usually the coronal) plane.
Maximum 2D diameter (Row)	Maximum 2D diameter (Row) is defined as the largest pairwise Euclidean distance between tumor surface voxels in the column-slice (usually the sagittal) plane.
$\text{Major axis} = 4\sqrt{\lambda_{\text{major}}}$	λ_{major} is the length of the largest principal component axis
$\text{Minor axis} = 4\sqrt{\lambda_{\text{minor}}}$	λ_{minor} is the length of the second largest principal component axis
$\text{Least axis} = 4\sqrt{\lambda_{\text{least}}}$	λ_{least} is the length of the smallest principal component axis
$\text{Elongation} = \sqrt{\frac{\lambda_{\text{minor}}}{\lambda_{\text{major}}}}$	Here, $\boldsymbol{\lambda_{\text{major}}}$ and $\boldsymbol{\lambda_{\text{minor}}}$ are the lengths of the largest and second largest principal component axes. The values range between 1 (circle-like (non-elongated)) and 0 (single point or 1 dimensional line).
$\text{Flatness} = \sqrt{\frac{\lambda_{\text{least}}}{\lambda_{\text{major}}}}$	Here, $\boldsymbol{\lambda_{\text{major}}}$ and $\boldsymbol{\lambda_{\text{minor}}}$ are the lengths of the largest and smallest principal component axes. The values range between 1 (non-flat, sphere-like) and 0 (a flat object).

c. Gray Level Co-occurrence Matrix (GLCM)

In simple words, a GLCM describes the number of times a voxel of a given attenuation value i is located next to a voxel of j. A GLCM of size $N_g \times N_g$ describes the second-order joint probability function of an image region constrained by the mask and is defined as $P(i,j|\delta,\theta)$. The $(i,j)^{th}$ element of this matrix represents the number of times the combination of levels i and j occur in two pixels in the image, that are separated by a distance of δ pixels along angle θ. The distance δ from the center voxel is defined as the distance according to the infinity norm. For $\delta=1$, this results in 2 neighbors for each of 13 angles in 3D (26-connectivity) and for $\delta=2$ a 98-connectivity (49 unique angles). In order to get rotationally invariant results, statistics are calculated in all directions and then averaged, to ensure a symmetrical GLCM.

Let:

ϵ be an arbitrarily small positive number **(e.g. $\approx 2.2\times10^{-16}$)**

$P(i,j)$ be the co-occurence matrix for an arbitrary δ and θ

$p(i,j)$ be the normalized co-occurence matrix and equal to $\frac{P(i,j)}{\sum P(i,j)}$

Ng be the number of discrete intensity levels in the image

$p_x(i) = \sum_{j=1}^{N_g} P(i,j)$ be the marginal row probabilities

$p_y(j) = \sum_{i=1}^{N_g} P(i,j)$ be the marginal column probabilities

μ_x be the mean gray level intensity of p_x and defined as $\mu_x = \sum_{i=1}^{N_g} p_x(i)i$

μ_y be the mean gray level intensity of p_y and defined as $\mu_y = \sum_{j=1}^{N_g} p_y(j)j$

σ_x be the standard deviation of p_x

$\boldsymbol{\sigma_y}$ be the standard deviation of $\boldsymbol{p_y}$

$$p_{x+y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j) \text{, where } i+j=k \text{, and } k = 2,3,\ldots,2N_g$$

$$p_{x-y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j) \text{, where } |i-j| = k \text{, and } k = 0,1,\ldots,N_g - 1$$

$HX = -\sum_{i=1}^{N_g} p_x(i)\log_2\left(p_x(i)+\epsilon\right)$ be the entropy of $\boldsymbol{p_x}$

$HY = -\sum_{j=1}^{N_g} p_y(j)\log_2\left(p_y(j)+\epsilon\right)$ be the entropy of $\boldsymbol{p_y}$

$$HXY1 = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j)\log_2\left(p_x(i)p_y(j)+\epsilon\right)$$

$$HXY2 = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p_x(i)p_y(j)\log_2\left(p_x(i)p_y(j)+\epsilon\right)$$

For distance weighting, GLCM matrices are weighted by weighting factor W and then summed and normalised. Weighting factor W is calculated for the distance between neighbouring voxels by $\boldsymbol{W = e^{-\|d\|^2}}$, where d is the distance for the associated angle.

Table R3: Gray Level Co-occurrence Matrix (GLCM) statistics for PVR characterization	
Radiomic feature	**Interpretation**

$$\text{Autocorrelation} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j)ij$$	**Autocorrelation** is a measure of the magnitude of the fineness and coarseness of texture.
$$\text{Joint average} = \mu_x = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j)i$$	Returns the mean gray level intensity of the i distribution.
$$\text{Cluster prominence} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i+j-\mu_x-\mu_y)^4 p(i,j)$$	**Cluster Prominence** is a measure of the skewness and asymmetry of the GLCM. A higher value implies more asymmetry around the mean while a lower value indicates a peak near the mean value and less variation around the mean.
$$\text{Cluster tendency} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i+j-\mu_x-\mu_y)^2 p(i,j)$$	**Cluster Tendency** is a measure of groupings of voxels with similar gray-level values.
$$\text{Cluster shade} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i+j-\mu_x-\mu_y)^3 p(i,j)$$	**Cluster Shade** is a measure of the skewness and uniformity of the GLCM. A higher cluster shade implies greater asymmetry about the mean.
$$\text{Contrast} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i-j)^2 p(i,j)$$	**Contrast** is a measure of the local intensity variation, favoring values away from the diagonal (i=j). A larger value correlates with a greater disparity in intensity values among neighboring voxels.

$\text{Correlation} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j)ij - \mu_x\mu_y}{\sigma_x(i)\sigma_y(j)}$	**Correlation** is a value between 0 (uncorrelated) and 1 (perfectly correlated) showing the linear dependency of gray level values to their respective voxels in the GLCM.
$\text{Difference average} = \sum_{k=0}^{N_g-1} kp_{x-y}(k)$	**Difference Average** measures the relationship between occurrences of pairs with similar intensity values and occurrences of pairs with differing intensity values.
$\text{Difference entropy} = \sum_{k=0}^{N_g-1} p_{x-y}(k)\log_2\left(p_{x-y}(k)+\epsilon\right)$	**Difference Entropy** is a measure of the randomness/variability in neighborhood intensity value differences.
$\text{Difference variance} = \sum_{k=0}^{N_g-1} (k-DA)^2 p_{x-y}(k)$	**Difference Variance** is a measure of heterogeneity that places higher weights on differing intensity level pairs that deviate more from the mean.
$\text{Joint energy} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (p(i,j))^2$	**Joint energy** is a measure of homogeneous patterns in the image. A greater **joint energy** implies that there are more instances of intensity value pairs in the image that neighbor each other at higher frequencies. (also known as Angular Second Moment).
$\text{Joint entropy} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j)\log_2\left(p(i,j)+\epsilon\right)$	**Joint entropy** is a measure of the randomness/variability in neighborhood intensity values.

$\text{IMC 1} = \frac{HXY - HXY1}{max\{HX, HY\}}$	**Informational measure of correlation 1**
$\text{IMC 2} = \sqrt{1 - e^{-2(HXY2 - HXY)}}$	**Informational measure of correlation 2**
$\text{IDM} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{p(i,j)}{1 + \lvert i - j \rvert^2}$	IDM (**inverse difference moment** a.k.a Homogeneity 2) is a measure of the local homogeneity of an image. IDM weights are the inverse of the Contrast weights (decreasing exponentially from the diagonal i=j in the GLCM).
$\text{IDMN} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{p(i,j)}{1 + (\frac{\lvert i - j \rvert^2}{N_g^2})}$	IDMN (**inverse difference moment normalized**) is a measure of the local homogeneity of an image. IDMN weights are the inverse of the Contrast weights (decreasing exponentially from the diagonal i=j in the GLCM). Unlike Homogeneity 2, IDMN normalizes the square of the difference between neighboring intensity values by dividing over the square of the total number of discrete intensity values.
$\text{ID} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{p(i,j)}{1 + \lvert i - j \rvert}$	ID (**inverse difference** a.k.a. Homogeneity 1) is another measure of the local homogeneity of an image. With more uniform gray levels, the denominator will remain low, resulting in a higher overall value.

$\text{IDN} = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{p(i,j)}{1+(\frac{\lvert i-j\rvert}{N_g})}$	IDN (**inverse difference normalized**) is another measure of the local homogeneity of an image. Unlike Homogeneity 1, IDN normalizes the difference between the neighboring intensity values by dividing over the total number of discrete intensity values.
$\text{Inverse variance} = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{p(i,j)}{\lvert i-j\rvert^2}, i \neq j$	
$\text{Maximum probability} = max(p(i,j))$	**Maximum Probability** is occurrences of the most predominant pair of neighboring intensity values (also known as Joint maximum).
$\text{Sum average} = \sum_{k=2}^{2N_g} p_{x+y}(k)k$	**Sum Average** measures the relationship between occurrences of pairs with lower intensity values and occurrences of pairs with higher intensity values.
$\text{Sum entropy} = \sum_{k=2}^{2N_g} p_{x+y}(k)\log_2\left(p_{x+y}(k)+\epsilon\right)$	**Sum Entropy** is a sum of neighborhood intensity value differences.
$\text{Sum squares} = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}(i-\mu_x)^2 p(i,j)$	**Sum of Squares** or Variance is a measure in the distribution of neighboring intensity level pairs about the mean intensity level in the GLCM. (Defined by IBSI as Joint Variance).

d. Gray Level Size Zone Matrix (GLSZM)

A Gray Level Size Zone (GLSZM) describes gray level zones in a ROI, which are defined as the number of connected voxels that share the same gray level intensity. A voxel is considered connected if the distance is 1 according to the infinity norm (26-connected region in a 3D, 8-connected region in 2D). In a gray level size zone matrix ***P(i,j)*** the **(i,j)th** element equals the number of zones with gray level ***i*** and size ***j*** appear in image. Contrary to GLCM and GLRLM, the GLSZM is rotation independent, with only one matrix calculated for all directions in the ROI.

Let:

$\mathbf{N_g}$ be the number of discreet intensity values in the image

$\mathbf{N_s}$ be the number of discreet zone sizes in the image

$\mathbf{N_p}$ be the number of voxels in the image

$\mathbf{N_z}$ be the number of zones in the ROI, which is equal to $\sum_{i=1}^{N_g} \quad \sum_{j=1}^{N_s} \mathrm{P}(i,j)$ and

$\boldsymbol{1 \leq N_z \leq N_p}$

P(i,j) be the size zone matrix

p(i,j) be the normalized size zone matrix, defined as $p(i,j) = \frac{\mathrm{P}(i,j)}{N_z}$

$\boldsymbol{\epsilon}$ is an arbitrarily small positive number (e.g. ≈2.2×10^{-16}).

Table R4: Gray Level Size Zone Matrix (GLSZM) statistics for PVR characterization	
Radiomic feature	**Interpretation**
$\mathrm{SAE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \frac{\mathrm{P}(i,j)}{j^2}}{N_z}$	**SAE (small area emphasis)** is a measure of the distribution of small size zones, with a greater value indicative of smaller size zones and more fine textures.

$\mathrm{LAE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \mathrm{P}(i,j) j^2}{N_z}$	**LAE (large area emphasis)** is a measure of the distribution of large area size zones, with a greater value indicative of larger size zones and more coarse textures.
$\mathrm{GLN} = \frac{\sum_{i=1}^{N_g} (\sum_{j=1}^{N_s} \mathrm{P}(i,j))^2}{N_z}$	**GLN (gray level non-uniformity)** measures the variability of gray-level intensity values in the image, with a lower value indicating more homogeneity in intensity values.
$\mathrm{GLNN} = \frac{\sum_{i=1}^{N_g} (\sum_{j=1}^{N_s} \mathrm{P}(i,j))^2}{N_z^2}$	**GLNN (gray level non-uniformity normalized)** measures the variability of gray-level intensity values in the image, with a lower value indicating a greater similarity in intensity values. This is the normalized version of the GLN formula.
$\mathrm{SZN} = \frac{\sum_{j=1}^{N_s} (\sum_{i=1}^{N_g} \mathrm{P}(i,j))^2}{N_z}$	**SZN (size zone non-uniformity)** measures the variability of size zone volumes in the image, with a lower value indicating more homogeneity in size zone volumes.
$\mathrm{SZNN} = \frac{\sum_{j=1}^{N_s} (\sum_{i=1}^{N_g} \mathrm{P}(i,j))^2}{N_z^2}$	**SZNN (size zone non-uniformity normalized)** measures the variability of size zone volumes throughout the image, with a lower value indicating more homogeneity among zone size volumes in the image. This is the normalized version of the SZN formula.
$\mathrm{Zone\ Percentage} = \frac{N_z}{N_p}$	**ZP (Zone Percentage)** measures the coarseness of the texture by taking the ratio of number of zones and number of voxels in the ROI. Values are in range $\frac{1}{N_p} \leq ZP \leq 1$, with higher values indicating a larger portion of the ROI consists of small zones (indicates a more fine texture).
$\mathrm{GLV} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_s} p(i,j)(i-\mu)^2,$ where $\mu = \sum_{i=1}^{N_g} \sum_{j=1}^{N_s} p(i,j) i$	**Gray level variance (GLV)** measures the variance in gray level intensities for the zones.

$\mathrm{ZV} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_s} p(i,j)(j-\mu)^2$, where $\mu = \sum_{i=1}^{N_g} \sum_{j=1}^{N_s} p(i,j)j$	**Zone Variance (ZV)** measures the variance in zone size volumes for the zones.
$\mathrm{ZE} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} p(i,j)\log_2 (p(i,j) + \epsilon)$	**Zone Entropy (ZE)** measures the uncertainty/randomness in the distribution of zone sizes and gray levels. A higher value indicates more heterogeneneity in the texture patterns.
$\mathrm{LGLZE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \frac{\mathrm{P}(i,j)}{i^2}}{N_z}$	**LGLZE (low gray level zone emphasis)** measures the distribution of lower gray-level size zones, with a higher value indicating a greater proportion of lower gray-level values and size zones in the image.
$\mathrm{HGLZE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \mathrm{P}(i,j)i^2}{N_z}$	**HGLZE (high gray level zone emphasis)** measures the distribution of the higher gray-level values, with a higher value indicating a greater proportion of higher gray-level values and size zones in the image.
$\mathrm{SALGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \frac{\mathrm{P}(i,j)}{i^2 j^2}}{N_z}$	**SALGLE (small area low gray level emphasis)** measures the proportion in the image of the joint distribution of smaller size zones with lower gray-level values.
$\mathrm{SAHGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \frac{\mathrm{P}(i,j)i^2}{j^2}}{N_z}$	**SAHGLE (small area high gray level emphasis)** measures the proportion in the image of the joint distribution of smaller size zones with higher gray-level values.
$\mathrm{LALGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \frac{\mathrm{P}(i,j)j^2}{i^2}}{N_z}$	**LALGLE (low area low gray level emphasis)** measures the proportion in the image of the joint distribution of larger size zones with lower gray-level values.
$\mathrm{LAHGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \mathrm{P}(i,j)i^2 j^2}{N_z}$	**LAHGLE (low area high gray level emphasis)** measures the proportion in the image of the joint distribution of

	larger size zones with higher gray-level values.

e. Gray Level Run Length Matrix (GLRLM)

A Gray Level Run Length Matrix (GLRLM) describes gray level runs, which are defined as the length in number of pixels, of consecutive pixels that have the same gray level value. In a gray level run length matrix ***P(i,j|θ)***, the ***(i,j)th*** element describes the number of runs with gray level ***i*** and length ***j*** occur in the image (ROI) along angle ***θ***.

Let:

N_g be the number of discreet intensity values in the image

N_r be the number of discreet run lengths in the image

N_p be the number of voxels in the image

$N_z(\theta)$ be the number of runs in the image along angle θ, which is equal to $\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} P(i,j|\theta)$ and $1 \leq N_z(\theta) \leq N_p$

P(i,j|θ) be the run length matrix for an arbitrary direction θ

p(i,j|θ) be the normalized run length matrix, defined as $p(i,j|\theta) = \frac{P(i,j|\theta)}{N_z(\theta)}$

ϵ is an arbitrarily small positive number (e.g. $\approx 2.2 \times 10^{-16}$).

By default, the value of a feature is calculated on the GLRLM for each angle separately, after which the mean of these values is returned. If distance weighting is enabled, GLRLMs are weighted by the distance between neighbouring voxels and then summed and normalised. Features are then calculated on the resultant matrix. The distance between neighbouring voxels is calculated for each angle using the norm specified in 'weightingNorm'

Table R5: Gray Level Run Length Matrix (GLRLM) statistics for PVR characterization	
Radiomic feature	**Interpretation**
$\mathrm{SRE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{\mathrm{P}(i,j\|\theta)}{j^2}}{N_z(\theta)}$	**SRE (Short Run Emphasis)** is a measure of the distribution of short run lengths, with a greater value indicative of shorter run lengths and more fine textural textures.
$\mathrm{LRE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \mathrm{P}(i,j\|\theta) j^2}{N_z(\theta)}$	**LRE (Long Run Emphasis)** is a measure of the distribution of long run lengths, with a greater value indicative of longer run lengths and more coarse structural textures.
$\mathrm{GLN} = \frac{\sum_{i=1}^{N_g} (\sum_{j=1}^{N_r} \mathrm{P}(i,j\|\theta))^2}{N_z(\theta)}$	**GLN (Gray Level Non-uniformity)** measures the similarity of gray-level intensity values in the image, where a lower GLN value correlates with a greater similarity in intensity values.
$\mathrm{GLNN} = \frac{\sum_{i=1}^{N_g} (\sum_{j=1}^{N_r} \mathrm{P}(i,j\|\theta))^2}{N_z(\theta)^2}$	**GLNN (Gray Level Non-uniformity Normalized)** measures the similarity of gray-level intensity values in the image, where a lower GLNN value correlates with a greater similarity in intensity values. This is the normalized version of the GLN formula.
$\mathrm{RLN} = \frac{\sum_{j=1}^{N_r} (\sum_{i=1}^{N_g} \mathrm{P}(i,j\|\theta))^2}{N_z(\theta)}$	**RLN (Run Length Non-uniformity)** measures the similarity of run lengths throughout the image, with a lower value indicating more homogeneity among run lengths in the image.

$\mathrm{RLNN} = \frac{\sum_{j=1}^{N_r} (\sum_{i=1}^{N_g} \mathrm{P}(i,j\|\theta))^2}{N_z(\theta)^2}$	**RLNN (Run Length Non-uniformity)** measures the similarity of run lengths throughout the image, with a lower value indicating more homogeneity among run lengths in the image. This is the normalized version of the RLN formula.
$\mathrm{RP} = \frac{N_z(\theta)}{N_p}$	**RP (Run Percentage)** measures the coarseness of the texture by taking the ratio of number of runs and number of voxels in the ROI. Values are in range $\frac{1}{N_p} \leq RP \leq 1$, with higher values indicating a larger portion of the ROI consists of short runs (indicates a more fine texture).
$\mathrm{GLV} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j\|\theta)(i-\mu)^2,$ where $\mu = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j\|\theta) i$	**GLV (Gray Level Variance)** measures the variance in gray level intensity for the runs.
$\mathrm{RV} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j\|\theta)(j-\mu)^2,$ where $\mu = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j\|\theta) j$	**RV (Run Variance)** is a measure of the variance in runs for the run lengths.
$\mathrm{RE} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j\|\theta) \log_2 (p(i,j\|\theta) + \epsilon)$	**RE (Run Entropy)** measures the uncertainty/randomness in the distribution of run lengths and gray levels. A higher value indicates more heterogeneity in the texture patterns.
$\mathrm{LGLRE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{\mathrm{P}(i,j\|\theta)}{i^2}}{N_z(\theta)}$	**LGLRE (low gray level run emphasis)** measures the distribution of low gray-level values, with a higher value indicating a greater

	concentration of low gray-level values in the image.
$\mathrm{HGLRE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \mathrm{P}(i,j\|\theta) i^2}{N_z(\theta)}$	**HGLRE (high gray level run emphasis)** measures the distribution of the higher gray-level values, with a higher value indicating a greater concentration of high gray-level values in the image.
$\mathrm{SRLGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{\mathrm{P}(i,j\|\theta)}{i^2 j^2}}{N_z(\theta)}$	**SRLGLE (short run low gray level emphasis)** measures the joint distribution of shorter run lengths with lower gray-level values.
$\mathrm{SRHGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{\mathrm{P}(i,j\|\theta) i^2}{j^2}}{N_z(\theta)}$	**SRHGLE (short run high gray level emphasis)** measures the joint distribution of shorter run lengths with higher gray-level values.
$\mathrm{LRLGLRE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{\mathrm{P}(i,j\|\theta) j^2}{i^2}}{N_z(\theta)}$	**LRLGLRE (long run low gray level emphasis)** measures the joint distribution of long run lengths with lower gray-level values.
$\mathrm{LRHGLRE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \mathrm{P}(i,j\|\theta) i^2 j^2}{N_z(\theta)}$	**LRHGLRE (long run high gray level run emphasis)** measures the joint distribution of long run lengths with higher gray-level values.

f. Neigbouring Gray Tone Difference Matrix (NGTDM) Features

A Neighbouring Gray Tone Difference Matrix quantifies the difference between a gray value and the average gray value of its neighbours within distance ***δ***. The sum of absolute differences for gray level ***i*** is stored in the matrix. Let $\mathbf{X_{gl}}$ be a set of segmented voxels and $x_{gl}(j_x, j_y, j_z) \in \mathrm{X}_{gl}$ be the gray level of a voxel at postion (j_x, j_y, j_z), then the average gray level of the neigbourhood is:

$$\overline{A}_i = \overline{A}(j_x, j_y, j_z)$$
$$= \frac{1}{W} \sum_{k_x=-\delta}^{\delta} \sum_{k_y=-\delta}^{\delta} \sum_{k_z=-\delta}^{\delta} x_{gl}(j_x + k_x, j_y + k_y, j_z + k_z),$$
where $(k_x, k_y, k_z) \neq (0,0,0)$ and $x_{gl}(j_x + k_x, j_y + k_y, j_z + k_z) \in X_{gl}$

Here, ***W*** is the number of voxels in the neighbourhood that are also in X_{gl}.

Let:

n_i be the number of voxels in X_{gl} with gray level ***i***

$N_{v,p}$ be the total number of voxels in X_{gl} and equal to $\sum n_i$ (i.e. the number of voxels with a valid region; at least 1 neighbor). $N_{v,p} \leq N_p$, where N_p is the total number of voxels in the ROI.

p_i be the gray level probability and equal to n_i/N_v

$s_i = \begin{cases} \sum^{n_i} |i - \overline{A}_i| & \text{for } n_i \neq 0 \\ 0 & \text{for } n_i = 0 \end{cases}$ be the sum of absolute differences for gray level i

N_g be the number of discreet gray levels

$N_{g,p}$ be the number of gray levels where $p_i \neq 0$

Table R6: Neigbouring Gray Tone Difference Matrix (NGTDM) for PVR characterization	
Radiomic feature	**Interpretation**
$Coarseness = \frac{1}{\sum_{i=1}^{N_g} p_i s_i}$	**Coarseness** is a measure of average difference between the center voxel and its neighbourhood and is an indication of the spatial

	rate of change. A higher value indicates a lower spatial change rate and a locally more uniform texture.
$$\boldsymbol{Contrast} = \left(\frac{1}{N_{g,p}(N_{g,p}-1)} \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p_i p_j (i-j)^2 \right) \left(\frac{1}{N_{v,p}} \sum_{i=1}^{N_g} s_i \right),$$ where $p_i \neq 0, p_j \neq 0$	**Contrast** is a measure of the spatial intensity change, but is also dependent on the overall gray level dynamic range. Contrast is high when both the dynamic range and the spatial change rate are high, i.e. an image with a large range of gray levels, with large changes between voxels and their neighbourhood.
$$\boldsymbol{Busyness} = \frac{\sum_{i=1}^{N_g} p_i s_i}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \lvert i p_i - j p_j \rvert},$$ where $p_i \neq 0, p_j \neq 0$	A measure of the change from a pixel to its neighbour. A high value for busyness indicates a 'busy' image, with rapid changes of intensity between pixels and its neighbourhood.
$$\boldsymbol{Complexity} = \frac{1}{N_{v,p}} \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \lvert i-j \rvert \frac{p_i s_i + p_j s_j}{p_i + p_j},$$ where $p_i \neq 0, p_j \neq 0$	An image is considered complex when there are many primitive components in the image, i.e. the image is non-uniform and there are many rapid changes in gray level intensity.

$$\boldsymbol{Strength} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (p_i + p_j)(i-j)^2}{\sum_{i=1}^{N_g} s_i},$$ where $p_i \neq 0, p_j \neq 0$	**Strength** is a measure of the primitives in an image. Its value is high when the primitives are easily defined and visible, i.e. an image with slow change in intensity but more large coarse differences in gray level intensities.

g. Gray Level Dependence Matrix (GLDM)

A Gray Level Dependence Matrix (GLDM) quantifies gray level dependencies in an image. A gray level dependency is defined as the number of connected voxels within distance $\boldsymbol{\delta}$ that are dependent on the center voxel. A neighbouring voxel with gray level $\boldsymbol{j}$ is considered dependent on center voxel with gray level $\boldsymbol{i}$ if $\boldsymbol{|i-j| \leq \alpha}$. In a gray level dependence matrix $\boldsymbol{P(i,j)}$ the $\boldsymbol{(i,j)^{th}}$ element describes the number of times a voxel with gray level $\boldsymbol{i}$ with $\boldsymbol{j}$ dependent voxels in its neighbourhood appears in image.

$\boldsymbol{N_g}$ be the number of discreet intensity values in the image

$\boldsymbol{N_d}$ be the number of discreet dependency sizes in the image

$\boldsymbol{N_z}$ be the number of dependency zones in the image, which is equal to $\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \mathrm{P}(i,j)$

$\boldsymbol{P(i,j)}$ be the dependence matrix

$\boldsymbol{p(i,j)}$ be the normalized dependence matrix, defined as $p(i,j) = \frac{\mathrm{P}(i,j)}{N_z}$

Table R7: Gray Level Dependence Matrix (GLDM) statistics for PVR characterization	
Radiomic feature	**Interpretation**
$$SDE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{P(i,j)}{i^2}}{N_z}$$	**SDE (Small Dependence Emphasis)**: A measure of the distribution of small dependencies, with a greater value indicative of smaller dependence and less homogeneous textures.
$$LDE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} P(i,j) j^2}{N_z}$$	**LDE (Large Dependence Emphasis)**: A measure of the distribution of large dependencies, with a greater value indicative of larger dependence and more homogeneous textures.
$$GLN = \frac{\sum_{i=1}^{N_g} (\sum_{j=1}^{N_d} P(i,j))^2}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} P(i,j)}$$	**GLN (Gray Level Non-Uniformity)**: Measures the similarity of gray-level intensity values in the image, where a lower GLN value correlates with a greater similarity in intensity values.
$$DN = \frac{\sum_{j=1}^{N_d} (\sum_{i=1}^{N_g} P(i,j))^2}{N_z}$$	**DN (Dependence Non-Uniformity)**: Measures the similarity of dependence throughout the image, with a lower value indicating more homogeneity among dependencies in the image.
$$DNN = \frac{\sum_{j=1}^{N_d} (\sum_{i=1}^{N_g} P(i,j))^2}{N_z^2}$$	**DNN (Dependence Non-Uniformity Normalized)**: Measures the similarity of dependence throughout the image, with a lower value indicating more homogeneity among dependencies in the image. This is the normalized version of the DLN formula.
$$GLV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j)(i-\mu)^2,$$	**GLV (Gray Level Variance)**: Measures the variance in grey level in the image.

where $\mu = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} ip(i,j)$	
$\boldsymbol{DV} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j)(j-\mu)^2$, where $\mu = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} jp(i,j)$	**DV (Dependence Variance)**: Measures the variance in dependence size in the image.
$\boldsymbol{DE} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j)\log_2 (p(i,j) + \epsilon)$	**DE (Dependence Entropy)**: Measures the entropy in dependence size in the image.
$\boldsymbol{LGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{\mathrm{P}(i,j)}{i^2}}{N_z}$	**LGLE (Low Gray Level Emphasis)**: Measures the distribution of low gray-level values, with a higher value indicating a greater concentration of low gray-level values in the image.
$\boldsymbol{HGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \mathrm{P}(i,j) i^2}{N_z}$	**HGLE (High Gray Level Emphasis)**: Measures the distribution of the higher gray-level values, with a higher value indicating a greater concentration of high gray-level values in the image.
$\boldsymbol{SDLGLE} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{\mathrm{P}(i,j)}{i^2 j^2}}{N_z}$	**SDLGLE (Small Dependence Low Gray Level Emphasis)**: Measures the joint distribution of small dependence with lower gray-level values.

$$SDHGLE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{P(i,j)i^2}{j^2}}{N_z}$$	**SDHGLE (Small Dependence High Gray Level Emphasis)**: Measures the joint distribution of small dependence with higher gray-level values.
$$LDLGLE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{P(i,j)j^2}{i^2}}{N_z}$$	**LDLGLE (Large Dependence Low Gray Level Emphasis)**: Measures the joint distribution of large dependence with lower gray-level values.
$$LDHGLE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_d} P(i,j)i^2j^2}{N_z}$$	**LDHGLE (Large Dependence High Gray Level Emphasis)**: Measures the joint distribution of large dependence with higher gray-level values.

Output Value

To determine the output value which may be used to characterise the pathology or state of a vascular region or characterise the inflammation of a plaque in step (b) of the first and second aspect of the invention, the value for the radiodensity and/or one or more radiomic features of the radial segment is compared to a pre-determined threshold value. Alternatively, the absolute values are used.

The threshold value may be a distribution of values, more preferably the threshold value is vessel specific and/or specific to how proximal or distal along the vessel the value was derived.

It is particularly preferred that the threshold value and/or output value is adjusted for biological factors, which may impact the expected values. Preferably, the output value is adjusted. The biological factors are preferably selected from one or more of the age of the subject, the gender of the subject, the ethnicity of the subject, the background adipocyte size, partial volume effects, and the type of blood vessel.

The partial volume effects could be determined using an Expectation Maximisation approach to iteratively refine the estimated “partial volume corrected” voxel configuration which when convolved with the point spread function of the imaging system most closely matches the observed voxel configuration.

Technical factors may also impact the expected radiodensity and/or radiomic values obtained. Accordingly, the pre-determined threshold value and/or the output value may be adjusted to take account of these technical factors, such as one or more of: the tube voltage of the CT scanner, reconstruction algorithms, iodinated contrast agent, contrast type, injection rate, aortic contrast opacification, left ventricular blood pool opacification, signal-to-noise, contrast-to-noise, milliamps, method of cardiac gating, single and multiple energy image acquisition, CT scanner type, heart rate, heart rhythm, or blood pressure.

The corrections for biological and/or technical factors are preferably carried out by the processing system i.e. they are computer implemented. Such processing systems may recognise the need for, and implement these corrections automatically.

The coefficients for each variable used in step (b) to generate the output value may be derived from Cox hazard of regression models. Alternatively, the cut-off points may be derived from received operating characteristic (ROC) curves. The corrections could also be determined using linear or non-linear calibration factors derived from repeated scans of the same patient (or phantom object) on different scanner set ups. Alternatively, a neural network based approach could be used.

Computer-Implementation

At least one step of the methods according to the first and second aspects of the invention is computer implemented. Therefore, the present invention requires a processing system. It is particularly preferred that at least two steps are computer implemented. Preferably, the entirety of the methods are computer-implemented, and thereby provide a computer implemented method of characterising the pathology or state of a vascular region of a subject, and a computer implemented method of characterising a plaque in a blood vessel in a subject, according to the first and second aspects

Most preferably, every step is carried out by a processing system, such that the methods of the invention proceed automatically without manual intervention when given input medical imaging data. For the interests of quality control, however, it

is envisaged that a trained operator may check and adjust particular parameters (e.g. the point in the centre of the vessel, the centreline of the vessel, or the pre-determined distance from the outer wall of the vessel) to ensure compliance with established clinical practices.

To this end, the methods of the invention may be implemented automatically using dedicated software providing a rapid, non-invasive estimation of an individual's vascular pathology/state and risk status and likelihood of adverse events, and guide clinical decision making.

In a third aspect, the invention provides a computer program product comprising executable instructions which, when executed by one or more processors, cause the one or more processors to perform the method of the first aspect or the second aspect.

In a fourth aspect, there is provided a system comprising one or more processors configured to perform the method of the first aspect or the second aspect.

Further disclosed is a non-transitory computer readable medium comprising executable instructions which, when executed by one or more processors, cause the one or more processors to perform the method according to the first aspect or second aspect.

Figure 4 schematically illustrates an example of a system suitable for implementing embodiments of the method. The system 1130 comprises at least one server 1110 which is in communication with a reference data store 1120. The server may also be in communication with other hardware which may be operated by a healthcare professional, for example over a communications network 1140.

In certain embodiments the server may obtain, for example using from the reference data store, pre-determined threshold values which may be corrected for biological and technical factors. The server may then provide a corrected output value according to the methods described herein that characterises the pathology or state of a vascular segment and/or the inflammation of a plaque to provide a

useful clinical picture of the subject's current vessel health and risk of suffering adverse cardiac events.

An example of a suitable server 1110 is shown in Figure 5. In this example, the server includes at least one microprocessor 1200, a memory 1201, an optional input/output device 1202, such as a keyboard and/or display, and an external interface 1203, interconnected via a bus 1204 as shown. In this example the external interface 1203 can be utilised for connecting the server 1110 to peripheral devices, such as the communications networks 1140, reference data store 1120, other storage devices, or the like.

Although a single external interface 1203 is shown, this is for the purpose of example only, and in practice multiple interfaces using various methods (e.g. Ethernet, serial, USB, wireless or the like) may be provided.

In use, the microprocessor 1200 executes instructions in the form of applications software stored in the memory 1201 to allow the required processes to be performed, including communicating with the reference data store 1120 in order to receive and process input data, and to provide a preferably corrected output score according to the methods described above. The applications software may include one or more software modules, and may be executed in a suitable execution environment, such as an operating system environment, or the like.

Accordingly, it will be appreciated that the server 1200 may be formed from any suitable processing system, such as a suitably programmed client device, PC, web server, network server, or the like. In one particular example, the server 1200 is a standard processing system such as an Intel Architecture based processing system, which executes software applications stored on non- volatile (e.g., hard disk) storage, although this is not essential. However, it will also be understood that the processing system could be any electronic processing device such as a microprocessor, microchip processor, logic gate configuration, firmware optionally associated with implementing logic such as an FPGA (Field Programmable Gate Array), or any other electronic device, system or arrangement. Accordingly, whilst

the term server is used, this is for the purpose of example only and is not intended to be limiting.

Whilst the server 1200 is a shown as a single entity, it will be appreciated that the server 1200 can be distributed over a number of geographically separate locations, for example by using processing systems and/or databases 1201 that are provided as part of a cloud based environment. Thus, the above described arrangement is not essential and other suitable configurations could be used. In a preferred embodiment, the processing systems are cloud based.

Risk Score

It is envisaged that already established biomarkers of vascular inflammation and biological states such as fibrosis, oedema and vascularity; and established risk factors can be combined with the output values of the invention to provide a more complete risk score for a given subject.

In a preferred embodiment, step (b) of the methods of the invention comprises determining one or more of the following vessel features:

(i) calcium index (Calcium-i);
(ii) perivascular water index (PVWi);
(iii) epicardial adipose tissue volume (EpAT-vol);
(iv) fat attenuation index of epicardial adipose tissue (FAI_{EpAT});
(v) fat attenuation index of perivascular adipose tissue (FAI_{PVAT});
(vi) fibrous plaque index (FPi);
(vii) perivascular water index (PVWi);
(viii) volumetric perivascular characterisation index (VPCI);
(ix) the presence, volume or radiomic profile of plaque;
(x) the presence, volume or radiomic profile of high-risk plaque;
(xi) the presence, volume or radiomic profile of low-attenuation plaque;
(xii) the presence, volume or radiomic profile of lipid-rich plaque;
(xiii) the presence, volume or radiomic profile of fibrous plaque;
(xiv) the presence, volume or radiomic profile of non-calcified plaque;

(xv) the presence, volume or radiomic profile of calcified plaque; and

(xvi) Vessel volume, diameter, cross-sectional area, surface area, length, location or remodelling.

The one or more vessel features could be determined for one or more vessels. The computed risk may comprise determining the number of vessels having the one or more vessel features present or above or below a specified threshold.

Step (b) may further comprise determining one or more of the following plaque features:

(xvii) Plaque density;

(xviii) Composition;

(xix) Calcification;

(xx) Radiodensity;

(xxi) Location;

(xxii) Volume;

(xxiii) surface area;

(xxiv) geometry;

(xxv) heterogeneity;

(xxvi) diffusivity; and

(xxvii) ratio between volume and surface area.

Preferably, the above values (i)-(xxvii) are taken from the radial segment and used in step (b) to generate an output value which characterises the pathology or state of the radial segment or characterises the inflammation of any plaque (if present).

Step (b) of the method may also comprise taking into account one ore more of the following risk factors or characteristics of the subject:

(xxviii) age of the subject;

(xxix) sex/gender of the subject;

(xxx) race/ethnicity of the subject;

(xxxi) coronary calcium;

(xxxii) hypertension;

(xxxiii) hyperlipidemia/hypercholesterolemia;
(xxxiv) diabetes mellitus;
(xxxv) presence of coronary artery disease;
(xxxvi) smoking;
(xxxvii) family history of heart disease; and
(xxxviii) genetic status.

These definitions of these biomarkers are known to the skilled person, and are described extensively in WO 2018/078395 A1, the contents of which are herein incorporated by reference.

In accordance with the first aspect of the invention, there are further provided methods for characterising the pathology or state of a vascular region of a subject according to the following aspects 1-1 to 1-18.

Aspect 1-1: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity is determined in step (ii);
(ii) The vascular region comprises the perivascular space;
(iii) The method is computer implemented.

Aspect 1-2: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity and one or more radiomic features is determined in step (ii);
(ii) The vascular region comprises the perivascular space;
(iii) The method is computer implemented.

Aspect 1-3: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity is determined in step (ii);
(ii) The vascular region comprises entire radial segment, including the lumen, vessel wall and perivascular space;

(iii) The method is computer implemented.

Aspect 1-4: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity is determined in step (ii);

(ii) The vascular region comprises the vessel wall and the perivascular space;

(iii) The method is computer implemented.

Aspect 1-5: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity and two or more radiomic features is determined in step (ii);

(ii) The vascular region comprises the vessel wall and the perivascular space;

(iii) The method is computer implemented.

Aspect 1-6: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity is determined in step (ii);

(ii) The vascular region comprises the vessel wall and the perivascular space;

(iii) The method is computer implemented;

(iv) The predetermined distance is determined by the radiodensities in the image or the patient anatomy by a processing system using reference data sets.

Aspect 1-7: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity and two or more radiomic features is determined in step (ii);

(ii) The vascular region comprises the vessel wall and the perivascular space;

(iii) The method is computer implemented;

(iv) The predetermined distance is determined by the radiodensities in the image or the patient anatomy by a processing system using reference data sets;

(v) The angle of the radial segment from the point in the centre of the vessel is from 2 to 270°.

Aspect 1-8: A method of characterising the pathology or state of a vascular region of a subject, wherein:

(i) A value for the radiodensity and two or more radiomic features is determined in step (ii);

(ii) The vascular region comprises the vessel wall and the perivascular space;

(iii) The method is computer implemented;

(iv) The predetermined distance is determined by the radiodensities in the image or the patient anatomy by a processing system using reference data sets;

(v) The angle of the radial segment from the point in the centre of the vessel is from 2 to 270°;

(vi) The value for the radiodensity comprises FAI_{PVAT}.

In accordance with the second aspect of the invention, there are further provided methods of characterising the plaque in a blood vessel of a subject according to the following aspects 2-1 to 2-8.

Aspect 2-1: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity is determined in step (iii);

(ii) The radiodensity value is taken of the entire radial segment;

(iii) The method is computer implemented.

Aspect 2-2: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity and one or more radiomic features is determined in step (iii);

(ii) The value for the radiodensity and one or more radiomics features is taken from the perivascular space of the radial segment;

(iii) The method is computer implemented.

Aspect 2-3: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity is determined in step (iii);

(ii) The value for the radiodensity is taken from the entire radial segment, including the lumen, vessel wall and perivascular space;

(iii) The method is computer implemented.

Aspect 2-4: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity is determined in step (iii);

(ii) The value for the radiodensity is taken from the vessel wall and the perivascular space in the radial segment;

(iii) The method is computer implemented.

Aspect 2-5: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity and two or more radiomic features is determined in step (iii);

(ii) The value for the radiodensity and two or more radiomics features is taken from the vessel wall and the perivascular space of the radial segment;

(iii) The method is computer implemented.

Aspect 2-6: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity is determined in step (iii);

(ii) The value for the radiodensity is determined from voxels corresponding to the vessel wall and the perivascular space;

(iii) The method is computer implemented;

(iv) The predetermined distance is determined by the radiodensities in the image or the patient anatomy by a processing system using reference data sets;

(v) The angle of the radial segment from the point in the centre of the vessel is from 2 to 270°.

Aspect 2-7: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity and two or more radiomic features is determined in step (iii);

(ii) The plaque is non-calcified;

(iii) The method is computer implemented;

(iv) The predetermined distance is determined by the radiodensities in the image or the patient anatomy by a processing system using reference data sets;

(v) The radii of the radial segment is defined by the physical limits of the voxels corresponding to plaque.

Aspect 2-8: A method of characterising the plaque in a blood vessel of a subject, wherein:

(i) A value for the radiodensity and two or more radiomic features is determined in step (iii);

(ii) The plaque is non-calcified;

(iii) The radii of the radial segment is defined by the physical limits of the voxels corresponding to plaque;

(iv) The method is computer implemented;

(v) The predetermined distance is determined by the radiodensities in the image or the patient anatomy by a processing system using reference data sets;

(vi) The angle of the radial segment from the point in the centre of the vessel is from 2 to 270°;

(vii) The value for the radiodensity is FAI_{PVAT}.

EXAMPLES

Example 1

Digital phantoms of a coronary artery were constructed (Figure 6) using the Python software libraries NumPy, SciPy and Matplotlib. A focal "inflamed" region was added to the phantoms (Figure 6b)), and the intensity of the inflamed region compared to the background PVAT intensity was increased in 2HU increments. Random Gaussian noise and image blur was applied to the phantoms to simulate image acquisition.

The following parameters were controlled to construct the digital phantoms.

Image dimensions:

- Image dimensions: 10 x 10 mm (24 x 24 pixels)
- Pixel size = 0.41 x 0.41 mm

Vessel dimensions:

- Lumen radius = 1.5 mm
- Outer wall thickness = 0.5 mm
- PVAT thickness = 2.0 mm

Image intensities:

- Lumen = 190 HU
- Outerwall = -30 HU
- PVAT = -75 HU

Stepwise increments of focal inflammation:

- -75 to -49 HU in 2 HU increments

The attenuation of PVAT was quantified as the mean attenuation of all voxels within the full circumference of the PVAT region surrounding the coronary artery (Figure 6c)) which represents the traditional method, as well as the radial segment

approach in which the attenuation of PVAT was quantified as the mean attenuation of only those voxels within the quarter radial segment of the PVAT region surrounding the coronary artery according to the invention (Figure 6d)). Multiple simulations were performed at each inflammation intensity using different instances of Gaussian noise.

Changes in the measured PVAT attenuation with increasing inflammation from -75 HU to -49 HU, as shown in Figure 7, were compared across two measurement techniques (radial segment vs. full circumference).

The PVAT attenuation results for 50 simulations of digital phantoms per inflammation intensity is shown in Figure 8, and the results for 500 simulations per inflammation intensity are shown in Figure 9. The inter-quartile range for the radial segment approach becomes distinguishable from baseline (i.e. vessels with no inflammation) at a lower inflammation intensity (-69 HU) than for the full circumference approach (black boxes; -63 HU).

The dashed horizonal line on the graph of Figure 8 shows the upper inter quartile range for baseline using the radial segment approach, while the dotted horizontal line shows the equivalent upper interquartile range for the full circumference approach.

As can be seen from the graphs, the **r**adial segment approach according to the invention is able to detect areas of inflammation at lower intensities than the traditional approach. Accordingly, the method of the present invention facilitates earlier detection of PVAT inflammation and enables earlier medical intervention.

CLAIMS

1. A method of characterising the pathology or state of a vascular region of a subject, said method comprising:

   (i) providing medical imaging data gathered along a length of a blood vessel and:

      (i) determining radial segments of the vessel extending from a point in the centre of the vessel to a distance extending beyond the outer wall of the vessel to the perivascular region;

      (ii) determining a value for the radiodensity and/or one or more radiomic features of the radial segment; and

   (ii) comparing each value determined in (ii) to a pre-determined value or using the absolute value, in order to generate an output value that indicates the pathology or state of the vascular region;

   wherein at least one method step is computer-implemented.

2. The method according to claim 1, wherein step (ii) comprises determining the radiodensity of the voxels corresponding to perivascular tissue in the perivascular region of each radial segment; preferably where step (ii) comprises determining the radiodensity of perivascular adipose tissue (PVAT).

3. The method according to any preceding claim, wherein the distance extending beyond the outer wall of the vessel is:

   (i) a standard distance that is not equal to or related to the diameter or radius of the underlying vessel;

   (ii) a distance which is a derivative of, a multiple of, or equal to the radius or diameter of the underlying vessel; or

   (iii) from 0.1mm to 3cm, preferably from 0.2mm to 2.5cm, more preferably from 0.3mm to 2.25cm, more preferably from 0.4mm to 2cm.

4. The method according to any preceding claim, wherein the output value determined in (b) provides a measure of the texture of the vascular region.

5. The method according to any preceding claim, wherein the output value determined in step (b) provides a measure of the inflammation of the vascular region.

6. The method according to any preceding claim, wherein the method is used to identify sub-clinical plaque, a pre-plaque state, and/or early atherosclerotic disease activity, in the blood vessel wall of an inflamed vascular region.

7. The method according to any preceding claim, further comprising the step of identifying inflamed plaque within the vascular region.

8. The method according to any preceding claim, further comprising the step of identifying inflamed portions of plaque within the vascular region.

9. The method according to claim 8, wherein areas of the plaque which are calcified are not classed as inflamed.

10. The method according to any of claims 6 to 9, further comprising the step of classifying the plaque as low risk, medium risk, high risk or very high risk.

11. A method of characterising a plaque in a blood vessel of a subject, said method comprising:

(a) providing medical imaging data gathered along a length of the blood vessel and;

(i) identifying voxels corresponding to plaque by their radiodensity;

(ii) determining a radial segment of the vessel comprising voxels corresponding to the plaque, wherein the radial segment extends from a point in the centre of the vessel to a distance extending beyond the outer wall of the vessel;

(iii) determining a value for the radiodensity and/or one or more radiomic features of the radial segment;

(b) comparing each value determined in (iii) to a pre-determined threshold value, or using the absolute value determined in (iii), in order to generate an output value that indicates inflammation of the plaque;

wherein at least one method step is computer-implemented.

12. The method according to claim 11, wherein step (ii) comprises determining the radiodensity of voxels corresponding to perivascular tissue in the radial segment, preferably wherein step (ii) comprises determining the radiodensity of voxels corresponding to perivascular adipose tissue (PVAT).

13. A method according to claim 11 or claim 12, wherein the radial segment is:

(i) a predefined geometry;

(ii) wherein the radii of the radial segment is defined by the physical limits of the voxels corresponding to plaque.

14. The method according to any of claims 11 to 13, wherein the subject is administered a therapy following determination of an inflamed plaque.

15. The method according to any of claims 11 to 14, wherein the plaque is characterised as inflamed, and wherein the inflamed plaque is fibrous plaque or non-fibrous plaque.

16. The method according to any of claims 11 to 15, wherein the inflamed plaque is classified as hot, unstable, high-risk or potential culprit.

17. The method according to any preceding claim, wherein the medical imaging data is computer tomography (CT) data.

18. The method according to any preceding claim, comprising determining a value for at least two radiomic features; wherein the value for each radiomic feature is included in step (b).

19. The method according to any preceding claim, wherein the vascular region comprises: the entire radial segment, the perivascular portion of the radial segment, or the vascular portion of the radial segment.

20. The method of any preceding claim, wherein the radiomic features are selected from the radiomic features of clusters 1 to 9, wherein:

cluster 1 consists of Short Run High Gray Level Emphasis, High Gray Level Emphasis, High Gray Level Run Emphasis, Autocorrelation, Sum Average, Joint Average, and High Gray Level Zone Emphasis;

cluster 2 consists of Skewness, Skewness LLL, Kurtosis, 90th Percentile, 90th Percentile LLL, Median LLL, Kurtosis LLL, and Median;

cluster 3 consists of Run Entropy, Dependence Entropy LLL, Dependence Entropy, Zone Entropy LLL, Run Entropy LLL, and Mean LLL;

cluster 4 consists of Small Area Low Gray Level Emphasis, Low Gray Level Zone Emphasis, Short Run Low Gray Level Emphasis, Low Gray Level Run Emphasis, Low Gray Level Emphasis, Small Dependence Low Gray Level Emphasis, Gray Level Variance LLL (GLSZM), Gray Level Variance (GLDM), Variance, Gray Level Variance (GLDM), Difference Variance LLL, Gray Level Variance LLL (GLRLM), Variance LLL, Gray Level Variance LLL (GLDM), Sum of Squares, Contrast LLL, Mean Absolute Deviation, Interquartile Range, Robust Mean Absolute Deviation, Long Run Low Gray Level Emphasis, Difference Variance, Gray Level Variance (GLSZM), Inverse Difference Moment Normalized, Mean Absolute Deviation LLL, Sum of Squares LLL, and Contrast;

cluster 5 consists of Zone Entropy, Gray Level Non Uniformity Normalized (GLRLM), Gray Level Non Uniformity Normalized LLL (GLRLM), Sum Entropy, Joint Energy, Entropy, Gray Level Non Uniformity Normalized (GLDM), Joint Energy, Gray Level Non Uniformity Normalized LLL (GLDM), Uniformity LLL, Sum Entropy LLL, and Uniformity;

cluster 6 consists of Zone Entropy HHH, Size Zone Non Uniformity Normalized HHH, and Small Area Emphasis HHH;

cluster 7 consists of Strength, Coarseness HLL, Coarseness, Coarseness LHL, Coarseness LLL, Coarseness LLH, Coarseness HHH, Coarseness HLH, Coarseness HHL, and Coarseness LHH;

cluster 8 consists of Cluster Tendency LLL, Cluster Tendency, Sum of Squares LLL, Mean Absolute Deviation LLL, Gray Level Variance LLL (GLDM), Variance LLL, Gray Level Variance LLL (GLRLM), Gray Level Variance (GLRLM), Robust Mean Absolute Deviation LLL, Gray Level Variance (GLDM), Variance, Mean Absolute Deviation, Cluster Prominence, Sum Entropy LLL, Interquartile Range LLL, Gray Level Variance LLL (GLSZM), Sum of Squares, Robust Mean Absolute Deviation, Sum Entropy, Interquartile Range, Cluster Prominence LLL, Entropy LLL, 10th Percentile LLL, 10th Percentile; and

cluster 9 consists of Size Zone Non Uniformity LLL, Dependence Non Uniformity HLL, Gray Level Non Uniformity HLL (GLSZM), Gray Level Non Uniformity (GLSZM), Run Length Non Uniformity HHL, Run Length Non Uniformity LHL, Dependence Non Uniformity LHL, Dependence Non Uniformity, Run Length Non Uniformity HLH, Busyness, Run Length Non Uniformity LLH, Dependence Non Uniformity LLH, Dependence Non Uniformity LLL, Size Zone Non Uniformity, Energy HLL, Run Length Non Uniformity LHH, Size Zone Non Uniformity HLL, Gray Level Non Uniformity LLH (GLSZM), Gray Level Non Uniformity LHL (GLSZM), Gray Level Non Uniformity LLL (GLSZM), Run Length Non Uniformity HLL, Gray Level Non Uniformity HLH (GLSZM), Gray Level Non Uniformity HHL (GLSZM), Run Length Non Uniformity, and Run Length Non Uniformity HHH;

preferably wherein at least two radiomic features are selected; preferably wherein the at least two radiomic features are each selected from different clusters.

21. The method according to any preceding claim, wherein the radial segment has a predefined geometry; preferably wherein the segment has an angle from the point in the centre of the vessel from 1 to 359°, preferably from 2 to 270°, more preferably from 10 to 180°C, more preferably from 30 to 150°.

22. A method according to any preceding claim, wherein the data was gathered from a computerised tomography scan along a length of a right coronary artery,

left anterior descending artery, left circumflex artery, aorta, carotid arteries or femoral arteries.

23. The method according to any preceding claim, wherein the threshold value is a distribution of attenuation values, preferably wherein the threshold value is vessel specific and/or specific to how proximal or distal along the vessel the attenuation value was derived.

24. The method according to any preceding claim, wherein the pre-determined threshold value is adjusted for biological factors, preferably wherein the biological factors are selected from one or more of the age of the subject, the gender of the subject, the ethnicity of the subject, the background adipocyte size, partial volume effects, and the type of blood vessel.

25. The method according to any preceding claim, wherein the pre-determined threshold value is adjusted for technical factors, preferably wherein the technical factors are selected from one more of the tube voltage of the CT scanner, reconstruction algorithms, iodinated contrast agent, contrast type, injection rate, aortic contrast opacification, left ventricular blood pool opacification, signal-to-noise, contrast-to-noise, milliamps, method of cardiac gating, single and multiple energy image acquisition, CT scanner type, heart rate, heart rhythm, or blood pressure.

26. The method according to any preceding claim, wherein the method is computed-implemented.

27. The method according to any preceding claim, wherein the method is used to monitor the development of plaques.

28. The method according to any preceding claim, wherein the method is used to predict cardiac mortality risk or risk of a subject suffering a cardiovascular event.

29. The method according to claim 20, wherein the output value is combined with other biomarkers to predict cardiac mortality risk or risk of a subject suffering a cardiovascular event.

30. The method according to any preceding claim, wherein the method is used to guide pharmacological treatment decisions and/or monitor responses to medical treatments.

31. The method according to any preceding claim, wherein the method is used to non-invasively monitor aortic aneurisms or carotid plaques.

32. The method according to any preceding claim, wherein the method is used to stratify subjects according to their risk of cardiac mortality or risk of suffering a cardiovascular event.

33. The method according to any preceding claim, wherein the method is used to quantify one or more of vascular inflammation, fibrosis, oedema and vascularity.

34. The method according to any preceding claim, wherein the output value is compared to an earlier scan of the same subject to compute a local change in inflammatory status.

35. A computer program product comprising executable instructions which, when executed by one or more processors, cause the one or more processors to perform the method of any preceding claim.

36. A system comprising one or more processors configured to perform the method of any preceding claim.