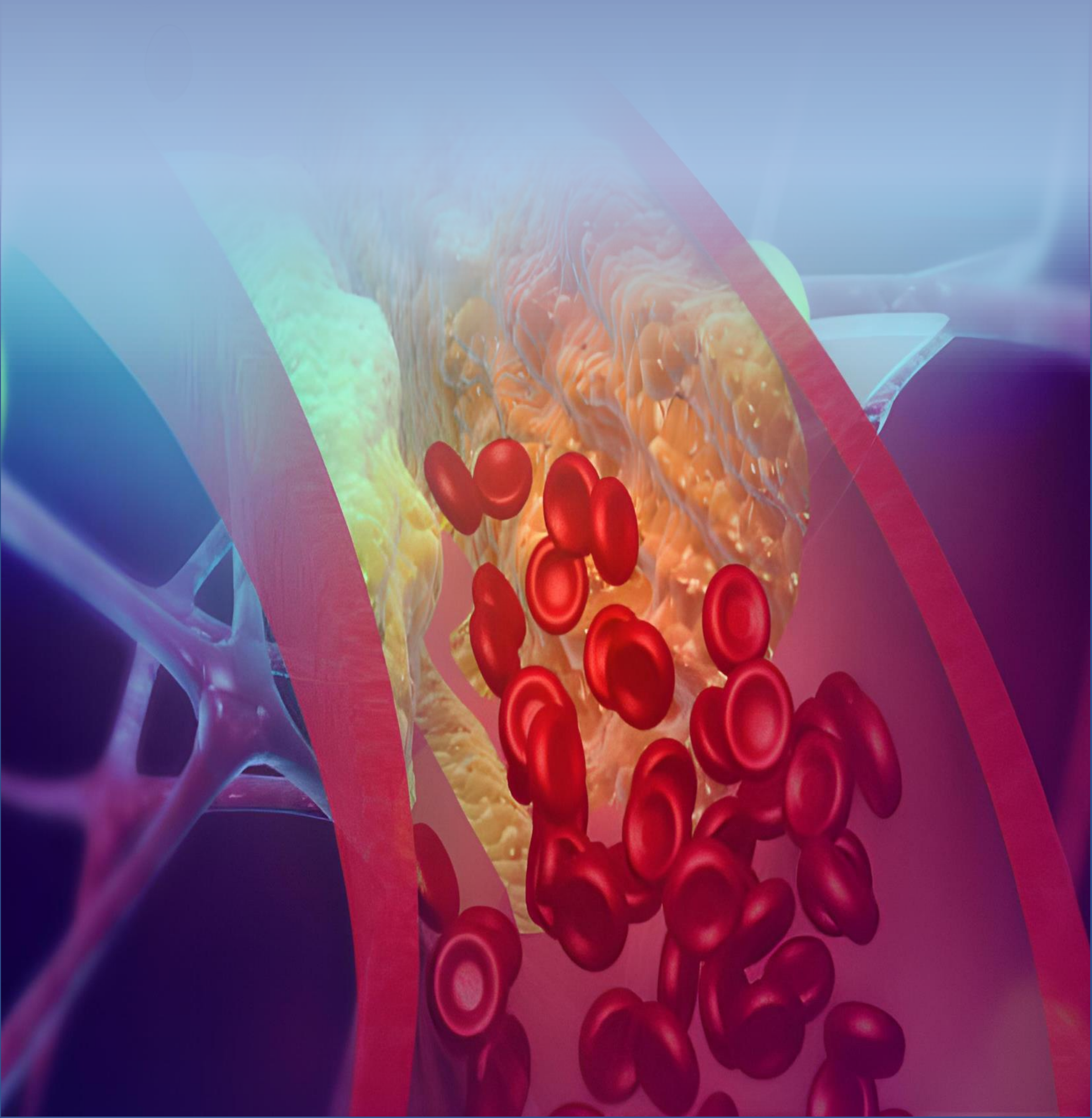
Artery size adjusted calcium score for contrast-enhanced CT scans in peripheral artery disease patients

Maikel Derksen



Master Thesis Technical Medicine – Department of vascular surgery, UMCG

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Abstract

Background: Patients suffering from peripheral artery disease (PAD) are at increased risk of major amputations and cardiac mortality. Identifying patients at risk is desired to optimize patient care and minimize the risk of these complications. Calcium scores, determined on non-contrast computed tomography (CT) scans in coronary arteries, have proven to be a strong tool in identifying patients at risk for future cardiovascular events.

Objectives: The objective of this study was divided into two parts. First, a reliable method is developed for determining the calcium score on contrast-enhanced CT scans in non-coronary arteries. Second, the developed contrast calcium score method determined in the iliofemoral arteries is associated with worse patient outcomes within the first year of an endovascular or surgical revascularization.

Methods: First, a volume adjusted calcium score (VACS) was proposed to compensate for variation in artery size between patients. Four-phase liver scans were used to compare the VACS for non-contrast and contrast CT scans. Patient-specific thresholds of two and three standard deviations (SD) above the mean contrast attenuation were analyzed. In addition, the inter-observer agreement and influence of slice thickness were investigated.

Second, in addition to the VACS, the length adjusted calcium score (LACS) was proposed and evaluated for patients with PAD. A complication and matched control group with similar characteristics were created, with the complication patients undergoing secondary revascularization, major amputation or all-cause mortality within the first year of a primary revascularization. Calcium scores were determined in three arterial segments: common iliac artery (CIA), external iliac artery (EIA) & common femoral artery (CFA) and proximal superficial femoral artery (SFA).

Results: The three SD above the mean contrast attenuation was best for distinguishing contrast and calcium. An excellent intra-class correlation (ICC) coefficient (0.97) was found between VACS determined on non-contrast and contrast scans after applying a correction factor of 1.95. The inter-observer agreement for VACS determined on the contrast CT scan was also excellent (0.99). Furthermore, the 0.75 mm slices were less suitable for determining the calcium score than the 2 mm slices due to an increase in noise.

No statistically significant difference was found between the complication and control group for any of the segments and complications. However, most high scores calcium scores were found in the complication group in the proximal SFA.

Conclusion: The proposed VACS determined on contrast-enhanced CT scans correlated excellently with non-contrast calcium scores. Furthermore, the VACS had an excellent inter-observer agreement. No statistically significant differences were found between patients with and without complications after a revascularization intervention. However, in future studies the distal SFA and popliteal artery should be included.

List of abbreviations

BKA	Below the knee arteries
CAD	Coronary artery disease
CFA	Common femoral artery
CIA	Common iliac artery
CLI	Chronical limb ischemia
CT	Computed tomography
CTA	Computed tomography angiography
DM	Diabetes mellitus
EIA	External iliac artery
EVAR	Endovascular aneurysm repair
FOV	Field of view
HU	Hounsfield unit
ICC	Intra-class correlation
IIA	Internal iliac artery
IQR	Interquartile range
LACS	Length adjusted calcium score
PAD	Peripheral artery disease
PFA	Profunda femoris artery
ROI	Region of interest
SD	Standard deviation
SFA	Superficial femoral artery
TASC	Trans-Atlantic Inter-Society Consensus
VACS	Volume adjusted calcium score
VNC	Virtual non-contrast

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1. Introduction

Peripheral artery disease (PAD) is a condition whereby the peripheral arteries, predominantly in the lower extremities, are stenosed or occluded caused by atherosclerosis. As a result, the blood flow in the peripheral arteries is reduced. [1] In western countries, approximately 15% of the population suffers from PAD, increasing up to 30% in older populations. [1] Major risk factors for developing PAD are smoking, diabetes mellitus (DM), hypertension, obesity, dyslipidemia and family history of vascular disease. [1], [2] The severity of PAD can be classified using the Fontaine or Rutherford classification systems, which both grades based on the symptoms of patients. The Rutherford classification also contains objective criteria to increase the reliability of patient classification. Despite these objective criteria, the Fontaine classification is often used in clinical practice. The stages with associated symptoms are shown in Table 1.1. [3], [4]

Table 1.1: Overview of the Fontaine and Rutherford classification systems.

Fontaine		**Rutherford**		
Stage	**Symptoms**	**Category**	**Clinical description**	**Objective criteria**
I	Asymptomatic	0	Asymptomatic	Normal treadmill
IIa	Claudication, walking distance >200m	1	Mild claudication	Completes treadmill exercise – AP* after >50 mmHg, at least 20 mmHg lower than at rest
		2	Moderate claudication	Between categories 1 and 3
IIb	Claudication, walking distance <200m	3	Severe claudication	Incomplete treadmill exercise – AP after <50 mmHg
III	Rest pain	4	Ischemic rest pain	Resting AP <40 mmHg, TP* <30 mmHg
IV	Ulcer, necrose or gangrene	5	Minor tissue loss – nonhealing ulcer, focal gangrene	Resting AP <60 mmHg, TP <40 mmHg
		6	Major tissue loss – foot no longer salvageable	Same as category 5

**: AP = ankle pressure; TP = toe pressure*

Treatment of PAD first consists of reducing risk factors, such as smoking cessation or with pharmacologic treatments, and supervised walking programs. Endovascular or surgical revascularization may be considered when these treatments do not provide the desired effect. [5] Chronic limb threatening ischemia (CLI) (Fontaine 3-4) or failed interventions can lead to major lower extremity amputations. The amputation rate for patients with claudication intermittent over a 5-year period is approximately 5%, up to 20% over a 1-year period for patients with CLI. Moreover, the mortality rate of patients undergoing major amputations (48% within 1 year) is nearly twice as high as hospitalized PAD patients without major amputations (24% within 1 year). [6] Identifying patients at risk for amputations or (cardiovascular) mortality may lower these numbers and is therefore a desired goal.

Calcium scores determined in coronary arteries have proven to be a strong tool in identifying patients at risk for cardiovascular events. [7], [8] A previous study conducted in the UMCG showed an independent association between aorto-iliac non-contrast calcium scores and all-cause and cardiovascular mortality in patients undergoing kidney transplantation. [9] In addition, studies have shown that calcium scores determined in peripheral arteries may potentially be used in addition to existing risk stratification systems for identifying patients at risk for major amputations or (cardiac) mortality. [10]–[12] However, calcium score methods, first developed by Agatston, were originally developed for non-contrast computed tomography (CT) scans, whereby calcium is identified using a fixed threshold of 130 Hounsfield units (HU). [7], [13] Contrast-enhanced CT scans are commonly made in clinical practice to assess the severity of the stenosis and to detect (non-calcified) plaques. [8], [14] In practice only contrast CT scans are made for vascular patients suffering from PAD. The radiation dose would increase considerably when both non-contrast and contrast CT scans would be performed for calculating calcium scores. [14], [15] Therefore, there is a need for a calcium score method that can be calculated from contrast-enhanced CT scans. Several methods for distinguishing calcium and contrast are already described, such as manual selection, a fixed (higher) threshold and patients-specific thresholds. [8], [14], [16]–[18] However, no standardized method for determine calcium scores on contrast CT scans is developed.

Coronary arteries, for which the calcium score was developed, have limited size variation between patients. When calcium scores in other arteries will be used, the variation in size between patients should be taken into account. The artery length and diameter will be greater in larger individuals. Other factors that are associated with larger artery diameters are older age and an increased body surface area. [19] Larger arteries may contain larger calcification resulting in higher calcium score. Therefore, the calcium score method should be adjusted for this, making comparisons between patients more reliable.

This thesis consists of two separate studies. In the second chapter, a method for calculating calcium score for contrast-enhanced CT scans is described. Subsequently, in the third chapter, the described method is used to associate artery size adjusted calcium scores with patient outcomes after revascularization interventions in patients with PAD. Finally, a general discussion and conclusion is provided for the calcium score determined on contrast CT scans and its use in patients with PAD.

2. Development and validation of a volume adjusted calcium score method for contrast-enhanced CT scans

Introduction

Atherosclerosis is a progressive systemic disease and the leading cause of death in westernized societies. [20], [21] Calcifications in coronary arteries, abdominal aorta and peripheral arteries have been associated with a higher risk of coronary heart disease or major adverse cardiac events. [22], [23] Coronary calcium scores, first developed by Agatston in 1990, have proven to be a strong predictor of future cardiovascular events. [13], [24] The Agatston score is calculated by identifying individual calcium deposits and multiply the volume of these deposits with a weighting factor determined by the maximum density of the deposit. Adding together all scores of the individual calcium lesions results in a total calcium score, which can be used to divide patients into four risk categories. An absolute Agatston score of 0, 1-100, 101-400 and >400 indicates very low risk, low risk, increased risk and increased likelihood of future coronary events, respectively. [7], [25]

The weighting factor that is used to calculate the Agatston score makes it less suitable for follow-up, as small changes in scan settings or noise can affect the maximum attenuation value of the lesion and therefore the Agatston score of a lesion. [7] An alternative calcium score method is the volume score, which is similar to the Agatston score, but without the weighting factor. Therefore, the volume score is better suited for follow-up as the interscan variability is lower. [7] Reproducibility may be increased by reducing the slice thickness, as thinner slices reduces the partial volume effect. [26] Thinner slices make it also possible to detect smaller calcium lesions, improving the accuracy of the calcium score. However, noise increases in thinner slices, affecting the calcium score negatively. [26], [27]

Calcium scores are currently used in the clinic in coronary arteries. However, abdominal aortic calcium scores may also have added value in identifying patients at risk, e.g. for cardiovascular events or mortality. [9], [28] Benjamens et al. have classified patients prior to kidney transplantation in low, medium and high Agatston scores and showed that patients in the medium and high categories suffered more cardiovascular events and all-cause mortality. [9] O'Connor et al. showed a higher mean and median Agatston score for asymptomatic patients suffering from cardiovascular events than patients with no cardiovascular events during the 13.5 years follow-up. [28] Implementing abdominal aortic calcium scores may therefore be used for risk stratification and used to optimize individual care.

Calcium scores have originally been developed for non-contrast CT scans, while contrast CT scans are required to assess the severity of the stenosis and to detect non-calcified plaques. [8], [14] Furthermore, in practice only contrast CT scans are made for vascular patients and the radiation dose would increase considerably when both non-contrast and contrast scans are performed. [14], [15] It is therefore desired to develop a method for performing calcium scores on contrast CT scans. However, the standard threshold of 130 HU used in the Agatston and volume score cannot be used in contrast scans because the attenuation of contrast-enhanced blood exceeds the threshold.

Two patient-specific thresholds were proposed by Mylonas et al. and Raggi et al. by adjusting the threshold to two and three times the standard deviation (SD) above the mean contrast or soft tissue attenuation, respectively. [14], [29] However, these patient-specific thresholds were only tested for coronary calcium scores and no translation was made to other arteries.

In this study both variations will be tested to calculate aortic calcium scores on non-contrast and contrast-enhanced CT scans. In addition, the influence of the slice thickness and observer variability on the calcium score will be investigated.

Method

A single-center, retrospective analysis of patients undergoing four-phase liver scans between 2017 and 2021 at the University Medical Center Groningen (UMCG) was performed. Four-phase liver scans were used as these scans provide non-contrast and contrast-enhanced CT-images of the same patient in quick succession. Furthermore, the delayed scan shows attenuation values close to the non-contrast CT scan, making it possible to better assess both patient-specific threshold for distinguishing contrast and calcium.

All patients included had to be over the age of 55 at the time of the scan as the chance of calcifications increases considerably above this age. Allison et al. used multiply public domain datasets to investigate the ethnic-specific prevalence of PAD in the United States and found that from the age group of 50-59 the prevalence increased considerably. [30] In addition, the Framingham study also showed an increase in prevalence in the age group 55-64 for both males and females. [31] The patients in this study were not vascular patients and the age limit was therefore set at 55 to ensure that the majority of patients had calcifications.

Other inclusion criteria were a field of view (FOV) from the celiac trunk to the aortic bifurcation on all scan phases and availability of reconstruction with a slice thickness of 2.0 mm with increments of 1.5 mm for all scan phases. Exclusion criterion was the presence of artifacts in or surrounding the abdominal aorta, e.g., by stents or protheses. Patient outcomes were not taken into account, as these were not relevant for this study. This study was approved (study nr: 202200343) and informed consent was waived by the UMCG Institutional Ethical Review Board.

CT protocol

Four-phase liver scans were obtained with the Somatom Force, Somatom definition Flash, Somatom definition AS and Somatom definition Edge of Siemens Healthineers (Siemens Healthcare, Erlangen, Germany). Scans were performed using a spiral acquisition, with a pitch of 0.8 sec and a collimation of 128x0.6 mm. Scan parameters were adjusted for patient body types and set in the range of 70-140 kVp, with 84% at 100 kVp, 36-551 mA and a FOV of 296-500 mm. After a non-contrast scan, 100 cc contrast medium (Iomeron 350, Bracco Imaging, Milan, Italy) was administered with a flow rate of 4.0 cc/sec. The arterial phase was scanned with bolus timing, whereby the trigger was set at a threshold of 120 HU in the descending aorta at the top of the liver. The portal venous phase was scanned 75 seconds after injection and the delayed phase 220 seconds after the portal venous phase. Scans were reconstructed with a slice thickness of 2.0 mm and slice increments of 1.5 mm. For the image reconstruction, either the B40f (20% of the times) or the I30f (80%) kernel was used.

Non-contrast versus contrast calcium scores

Volume scores were calculated using Aquarius iNtuition software (Version 4.4.13.P6, TeraRecon, Inc., San Mateo, CA, USA). Volume scores were calculated on non-contrast scans as described by McCollough et al., using thresholds of 130 HU and four adjacent pixels to avoid false noise classification. [32] The abdominal aorta was manually circled in axial slices throughout the region of interest (ROI). The upper slice of interest was chosen where the celiac trunk originated from the aorta and the lower slice where the common iliac arteries (CIA) branched from the aortic bifurcation. These slices were selected using the arterial scan and corresponding slices on the other scans were visually selected based on landmarks, such as calcifications or the spine. The option *visible slice only* was used to avoid selection of calcium outside the ROI. Patient-specific thresholds were used to calculate the volume score in the arterial and delayed scans. Both two and three SD above the mean attenuation of the contrast in the abdominal aorta were used, as previously described by Mylonas et al. and Raggi et al., respectively. [14], [29] The mean attenuation and SD were determined by selecting an area in the abdominal aorta without calcium. In Figure 2.1, a visual overview is provided of the measurements conducted in the software program.

The length and diameter of the abdominal aorta varies between patients. To better assess the severity of atherosclerosis, comparing patients and translating the results to other blood vessels, a modified scoring method called the volume adjusted calcium score (VACS) was developed. The VACS was calculated by dividing the volume score by the volume of the artery in which this score was determined (*Volume score (mm^3)/Volume ROI (cm^3)*). The ROI volume was approximated using the length, determined by a center lumen line, and the mean diameter of the center slice for each patient. The VACS of the delayed scan were compared to the non-contrast scan scores to determine the best method for distinguishing contrast and calcium. The arterial scan VACS was than compared with the non-contrast scores, as these images most closely resemble computed tomography angiography (CTA) images. A second observer repeated the measurements for all patients on the 2 mm arterial scans to determine the inter-observer agreement.

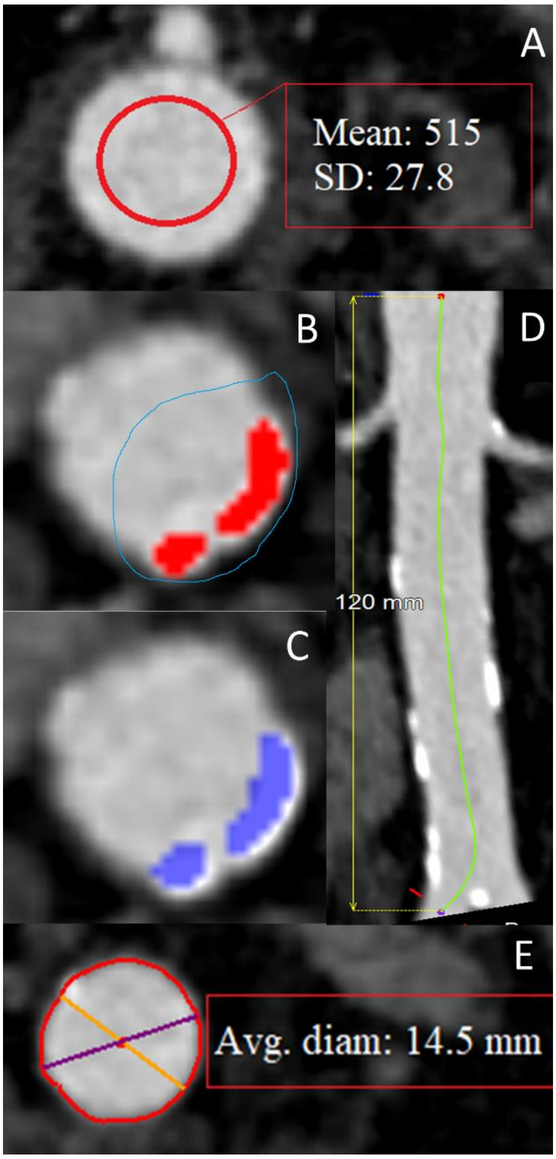

Figure 2.1: Steps for determination of the VACS. ***(A)*** *Determination of the patient-specific threshold using the contrast HU (e.g., mean+3*SD);* ***(B)*** *Manual selection of calcified region using the overlay;* ***(C)*** *Classified calcium;* ***(D)*** *Measurement of ROI's length using center lumen line;* ***(E)*** *Determination of average diameter of artery using ROI's middle slice and center lumen line.*

In addition to the evaluation of the two patient-specific threshold variations, the influence of the slice thickness was also evaluated. The arterial scan provided 0.75 mm slices for twenty-eight of the thirty patients, with increments of 0.5 mm. The thresholds had to be adjusted for the 0.75 mm slices, as the increase in noise resulted in higher standard deviations.

Statistical analysis

Statistical analyses were performed using open-source software R (Version 1.4.1106). Continuous variables were expressed as median with interquartile range (IQR). Wilcoxon signed rank test was used to compare continues variables, with *p<0.05* considered statistically significant. In addition, the intra-class correlation (ICC) absolute agreement estimates were used to compare the calcium scores determined on the delayed scan and the non-contrast scan to assess which patient-specific threshold is best to distinguish calcium and contrast. The ICC and 95% percent confidence interval were calculated based on a single rating and 2-way mixed effects model. ICC values of less than 0.5 indicates poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and greater than 0.9 excellent reliability. [33] A correction factor to convert the arterial calcium scores to non-contrast calcium scores was determined using a linear regression model through the origin. For evaluating the corrected arterial VACS, a Bland-Altman plot and the ICC absolute agreement were used.

VACS determined on 0.75 mm and 2.0 mm slices were compared with different threshold, i.e., the calcium scores were determined on the 0.75 mm and 2.0 mm slices with the threshold determined in that image series. In addition, a comparison was made between the two different slice thicknesses with the threshold determined on the 0.75 mm images. The inter-observer agreement was calculated by comparing the VACS determined by two observers. Again, all results were evaluated using the ICC agreement and Bland-Altman plots.

Results

Patient characteristics

A total of 333 patients who underwent a four-phase liver CT scan between 2017 and 2021 were identified. Of these 333 patients, 303 were excluded, which is summarized in Figure 2.2. After exclusion thirty patients remained (50% male, age 62.5 ± 6.1 years) who met the established inclusion and exclusion criteria.

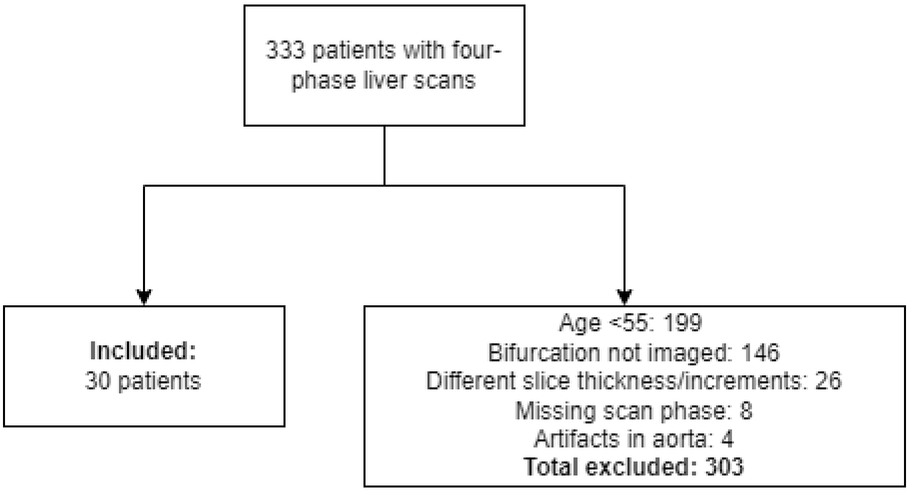

Figure 2.2: Overview of included and excluded patients.

Non-contrast vs. delayed calcium scores

The median two and three SD threshold for the delayed contrast CT scan were 156 HU (IQR: 147-168 HU) and 182 HU (IQR: 172-195), respectively. The differences between the VACS determined on the delayed CT scan with the two and three SD thresholds compared to the VACS on the non-contrast CT scan can be seen in Figures 2.3a and 2.3b, respectively. The mean difference between calcium scores determined on the delayed scans with two SD threshold and non-contrast scans was 13.55. The mean difference between calcium scores determined on the delayed scans with three SD threshold and non-contrast scans was -4.96. In addition, the mean number of calcium lesions on the non-contrast scans was 111 ± 54, which was significantly lower than the delayed two SD threshold (135 ± 72 lesions, $p = <0.001$) and not significantly higher than the delayed three SD threshold (89 ± 52 lesions, $p = 0.11$). The ICC agreement of the number of lesions determined on the two and three SD scans compared with the non-contrast scans were 0.68 (0.27-0.85) and 0.99 (0.98-0.99), respectively. Therefore, the three SD method was used instead of the two SD method in the remainder of the analysis.

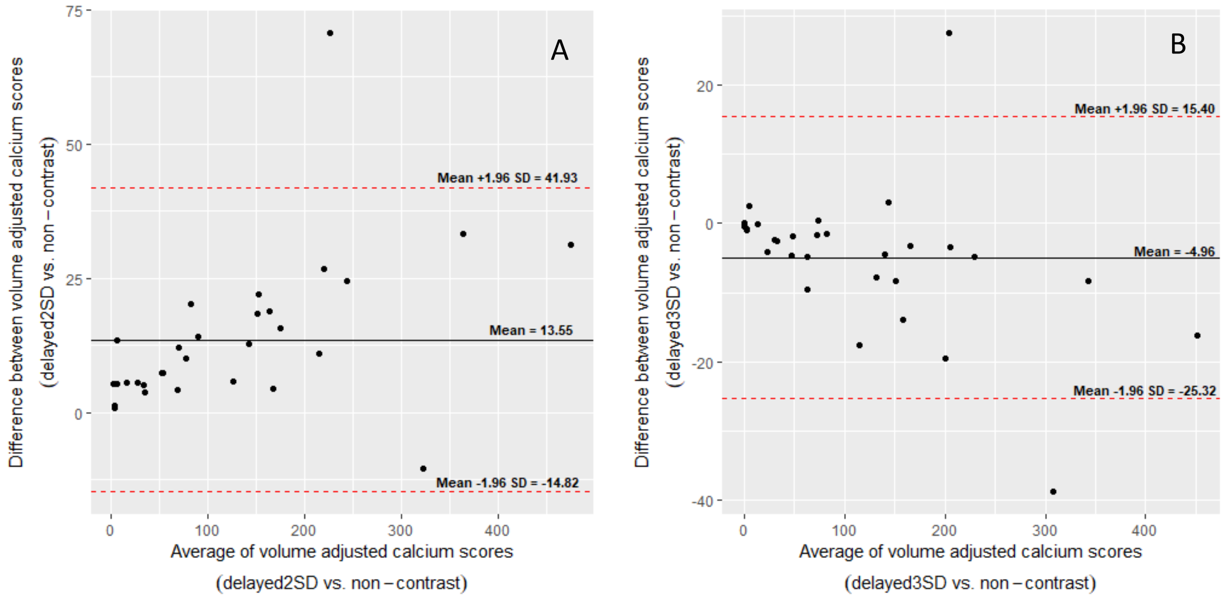

Figure 2.3: (A) Bland-Altman plot comparing the volume adjusted calcium scores determined on delayed scans phase with thresholds determined by two times the standard deviation and non-contrast scans. (B) Bland-Altman plot comparing the volume adjusted calcium scores on delayed scans with thresholds determined by three times the standard deviation and non-contrast scans.

Non-contrast vs. arterial calcium score

The median patient-specific threshold used for the arterial scans was 500 HU (IQR: 416-560 HU). The median abdominal aorta volume was 31 cm^3 (IQR: 25-37 cm^3). The ICC absolute agreement between the non-contrast VACS and arterial VACS before correction was moderate (0.65, 95%: 0.056-0.86). The correction factor derived from linear regression to convert the arterial VACS was 1.95, as can be seen in Figure 2.4a. The Bland-Altman plot with the corrected arterial VACS and non-contrast VACS, shown in Figure 2.4b, showed no consistent bias after correction. Some random errors above and below the 95% limits of agreement are shown for higher calcium scores. None of the type of CT scanners showed a consistent bias, as can be seen in Figure 2.4b. Overall, an excellent ICC agreement was found after correction (0.97, 95%: 0.94-0.99).

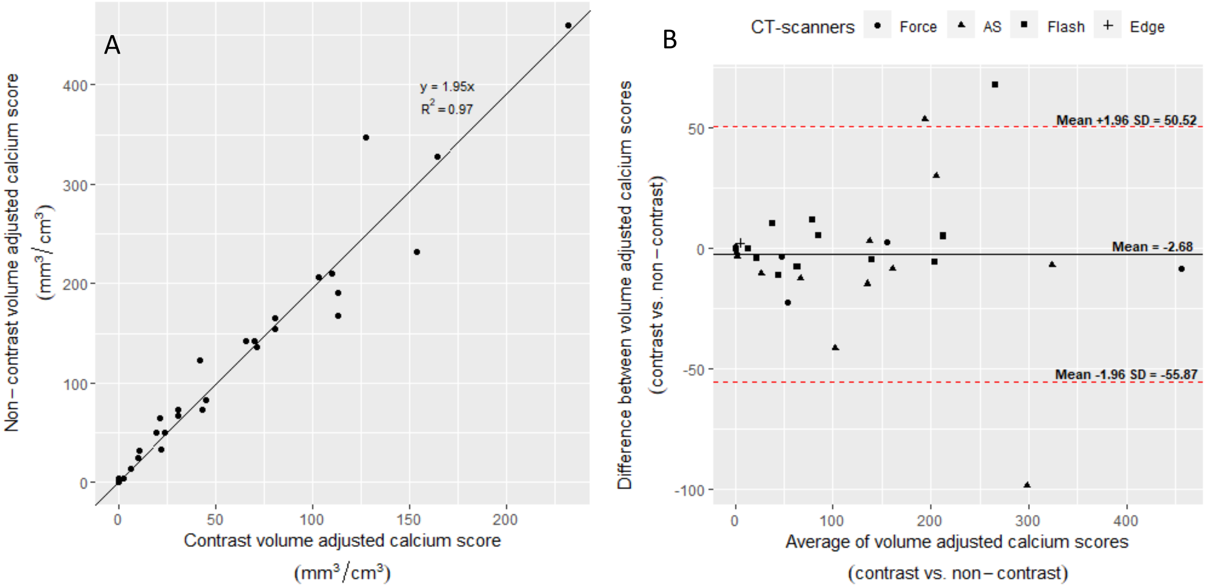

Figure 2.4: (A) Correlation between volume adjusted calcium scores determined on the arterial scan with the three SD threshold and the non-contrast volume adjusted calcium scores. (B) Bland-Altman plot comparing the corrected arterial volume adjusted calcium scores with the non-contrast volume adjusted calcium

Inter-observer agreement

The median patient-specific threshold on the arterial CT scans determined by the second observer was 484 HU (406-568 HU). This was significantly lower compared to the threshold determined by the first observer (*p = 0.008*), which as mentioned before was 500 HU (416-560 HU). However, the Bland-Altman plot showed a minimal difference between the VACS determined by both observers, as can be seen in Figure 2.5. One large outlier is visible, caused by a considerably higher threshold used by the first observer (713 vs. 683 HU). The ICC agreement between both observers was excellent (0.99, 95%: 0.98-1.0).

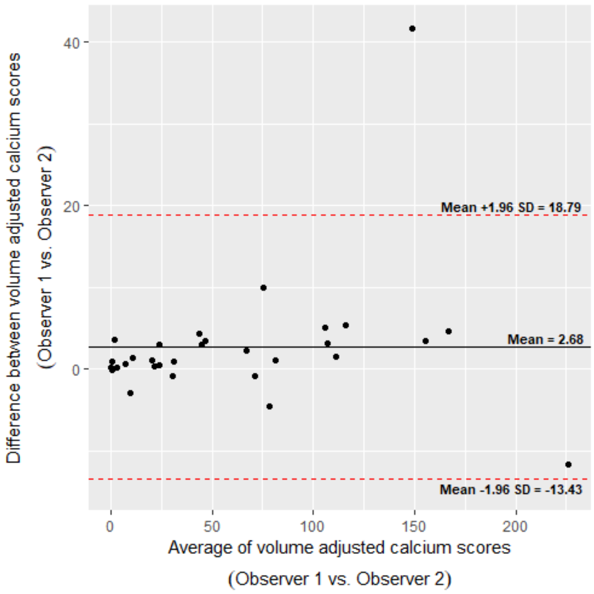

Figure 2.5: Bland-Altman plot comparing the volume adjusted calcium score determined by two observers.

Influence of slice thickness

The median threshold on the 0.75 mm slices was 541 HU (459-625 HU), which was significantly higher (*p = <0.001)* than the median threshold on the 2.0 mm slices. The VACS ICC agreement between 2.0 mm and 0.75 mm slices with different thresholds was excellent (0.98, 95%: 0.82-0.99). However, the Bland-Altman plot shown in Figure 2.6a shows an increased difference between the VACS in the higher calcium scores. When the same threshold was used on the 2.0 mm slices as on the 0.75 mm slices the agreement improved to 1.0 (95%: 1.0). In addition, the Bland-Altman plot shown in Figure 2.6b shows minimum difference between both slice thicknesses.

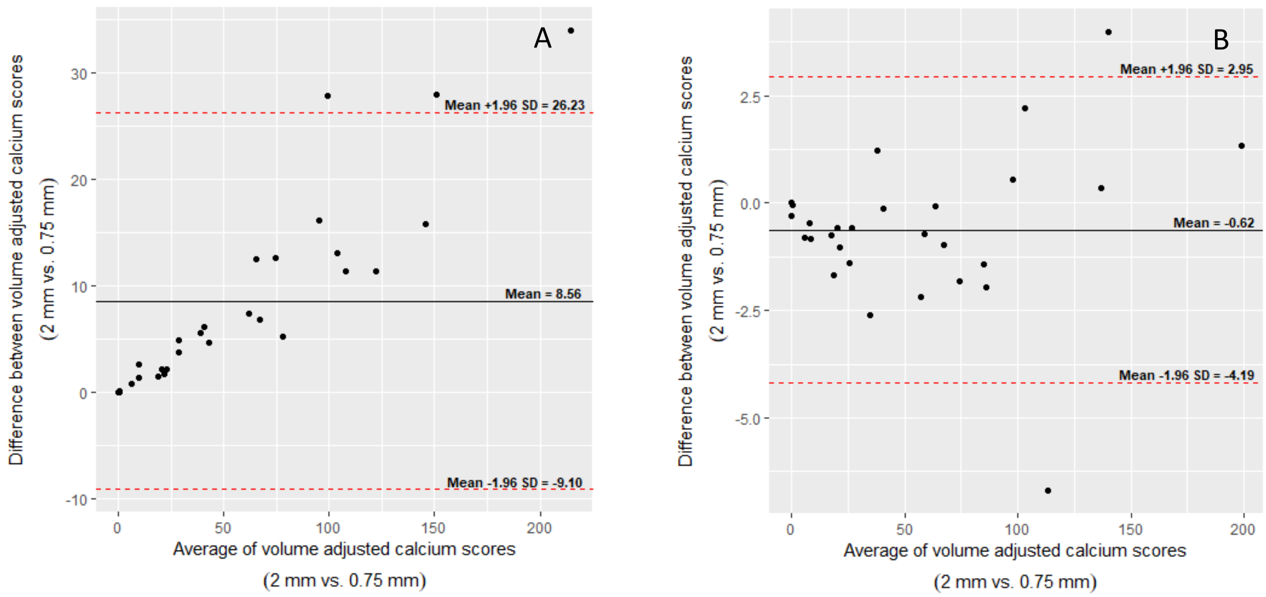

Figure 2.6: (A) Bland-Altman plot comparing the volume adjusted calcium scores determined on 2.0 mm and 0.75 mm slices with different thresholds. (B) Bland-Altman plot comparing the volume adjusted calcium scores determined on 2.0 mm and 0.75 mm slices with the same threshold

Discussion

In this study, two patient-specific threshold variations for distinguishing calcium and contrast were evaluated. It was found that the three SD threshold had a higher agreement with the non-contrast gold standard compared to the two SD above the mean contrast attenuation, indicating that a patient-specific threshold of three SD should be considered when calcium scores are determined on contrast CT scans. The higher VACS determined on the delayed scan with a threshold of two SD compared to the non-contrast VACS indicated that contrast was falsely classified as calcium, as the higher threshold should lead to a lower VACS. The VACS, using the patient-specific threshold of three SD and correction for the volume of the aorta determined on the arterial scan, showed excellent ICC agreement with the non-contrast calcium scores after applying the correction factor of 1.95. For clinical purposes, the correction factor can be rounded to 2.0. The inter-observer agreement was excellent, with small deviations in the thresholds determined by both observers. The 0.75 mm slices resulted in higher SDs because of more variation in HU values within the slices and therefore significantly higher thresholds compared to the 2.0 mm slices. These higher thresholds resulted in lower calcium scores. When equal thresholds were used on both slice thicknesses, the differences were negligible, indicating that the improved detection of small calcium lesions on 0.75 mm slices does not improve the calcium score.

Patient-specific thresholds were previously described for contrast-enhanced coronary and abdominal aortic calcium scoring. [8], [14], [34] Mylonas et al. used a patient-specific threshold of two SD above the mean contrast attenuation, as the authors believed that the three SD method described by Raggi et al. would exclude to many lower attenuating calcifications. However, in this study it was shown that a threshold of two SD above the mean contrast attenuation cannot sufficiently distinguish between calcium and contrast. Mylonas et al. also calculated a correction factor of 2.74 to correlate Agatston scores determined on contrast and non-contrast scans. The ICC agreement between both scores after correcting was excellent (0.93; 95%: 0.86-0.99) and 92% of the scores were classified into the same risk category. [14] The correction factor found by Mylonas et al. was higher than the correction factor in this study, possibly caused by the difference in slice thicknesses in that study. Non-contrast scans were reconstructed with a slice thickness of 2.5 mm and contrast scans with a slice thickness of 0.625 mm, which may lead to unnecessary higher thresholds due to a higher SD, as was shown in this study. As a result, the difference between the calcium scores determined on contrast and non-contrast scans is larger, resulting in a higher correction factor.

Other patient-specific thresholds were proposed by Bischoff et al. and Buijs et al. for contrast-enhanced coronary and abdominal aortic calcium scoring, respectively. [8], [34] Bischoff et al. used a patient-specific threshold of 150% of the mean contrast attenuation. A high correlation (r = 0.95) between Agatston scores determined on contrast and non-contrast CT scans was found after applying a correction factor, including the threshold, and 90% of the patients were classified in the same risk category. [8] Despite the good correlation, this method seems less suitable due to the higher threshold. The median threshold in the current study would increase from 500 HU (IQR: 416-560 HU) to 606 HU (IQR: 489-728 HU), which may result in more missed calcium. Buijs et al. used four-phase liver scans to compare the volume score determined on contrast and non-contrast scans. Patient-specific thresholds were calculated using the global thresholding principle, which distinguishes calcium and contrast using a histogram. No correction factor was calculated and therefore it was concluded that volume scores determined on contrast CT scans were not reliable enough for clinical use. [34] The mean patient-specific threshold was 230 ± 23 HU, which was much lower than the thresholds used in this study and the studies of Mylonas et al. and Bischoff et al.

The accuracy of the volume score, used to calculate the VACS, may be affected by interscan variability. The slice thickness and inter-observer variability were investigated in this study. Previous studies showed that coronary volume scores determined on thinner slices are significantly higher compared to volume scores determined on thicker slices. Higher scores might be caused by an improved detection of small lesions on thinner slices due to the partial volume effect. [26], [35], [36] However, an increase in noise can be seen in thinner slices, resulting in lower signal-to-noise ratios (SNR) and making it more difficult to distinguish contrast and calcifications. [37] The increase in noise resulted in higher threshold in the current study. Using 0.75 mm slices is therefore not recommended in contrast CT scans, as more calcium is missed. However, thick slices, e.g. 5 mm, can also cause inaccuracies due to overestimation of calcium or by missing calcium due to the partial volume effect. [26] Therefore, a trade-off must be made between better detection of small lesions on thinner slices and an increase in SD and thus threshold on thinner slices and the time saved by performing the calcium score on thicker slices.

The inter-observer variability in this study was mainly caused by different thresholds determined by both observers. Threshold calculations were not standardized in the aorta because the highest attenuation of contrast was not consistently located in the same area across patients. Little variation is expected in manually selecting the calcium in the aorta as an overlay was used. Mylonas et al. found an excellent inter-observer agreement for Agatston scores determined with a patient-specific threshold on contrast CT scans (ICC = 0.97). [14] In addition, Bijl et al. also reported an excellent inter-observer agreement for CTA-derived Agatston scores (ICC = 0.94) where calcium was visually identified and manually selected. [16] Finally, Ghadri et al. reported excellent inter-observer agreements for both Agatston scores and volume scores. [38]

Factors not investigated in this study, but described in previous studies, are variabilities caused by different scanners, scanning and reconstruction parameters and different software programs. [7], [38]–[41] None of the four different CT scanners used in this study showed consistent outliers.

However, no patients were scanned on two different scanners and therefore no comparison can be made. Ghadri et al. found a good inter-scanner agreement for volume scores determined on multislice and dual source CT scanners. [38] In addition, Mao et al. found an excellent linear correlation and inter-scanner variability of 17.6% between an electron beam CT scanner and multidetector CT scanner. [39] The inter-scanner variability reported by Mao et al. was similar to previous reported interscan variability of the volume score (9 to 16%). [7]

Changing scan and reconstruction parameters can affect the attenuation values. Decreasing the tube potential results in an increase of attenuation values. [14], [40] However, the impact is minimized as both calcium and contrast are affected by changing tube voltages and a dynamic threshold is proposed in this study. In addition, de Jong et al. did not find a change in volume scores when two different tube currents were used for scanning human fresh-frozen legs. [36] Finally, Mantini et al. showed a significant difference and moderate correlation between volume scores determined with a sharper kernel compared to a reference kernel. However, a third kernel used in this study showed an excellent correlation with the reference kernel. Indicating that differences in calcium scores may occur due to different types of kernels used, but some kernels are interchangeable without negatively affecting the results. [41] Furthermore, Komen et al. showed no significant difference between two kernels, but only eight patients were used. [42]

Finally, Ghadri et al. found that volume scores determined with two different software programs differed significantly. Siemens Syngo.via software highly overestimated phantom calcifications compared the GE SmartScore software and the ground truth. [38] In addition, Ajlan et al. found a significant discordance between high Agatston scores determined with two different software programs. [43] However, Ajlan et al. and also Weininger et al., who used three different software programs, both found high correlation between these software programs. [43], [44] These results show that the correction factor determined in this study cannot simply be used to adjust VACS determined with other software programs.

Limitations

The volume of the aorta was approximated by assuming a cylindrical shape. However, the diameter of the aorta can vary over the length. It was tried to minimize the error by using the mean diameter of the center of the aorta. However, determining the exact volume would improve the VACS method against the cost of considerable measurement time. In addition, the contrast attenuation was not determined in a standardized place, as no good place was found in this patient group. In some patients the highest attenuation values were measured at the top of the ROI and in other patients in the center, making it difficult to standardize the measurements with the used software. The overlay available in the software was used to determine whether the threshold could distinguish contrast and calcium in the entire ROI. Standardizing the threshold determination would increase the interobserver agreement.

Only a small number of the total available patients were included in this study. Many four-phase liver scans did not contain the aortic bifurcation and were therefore excluded. The aortic bifurcation was desired as most calcifications are located around the bifurcation. [45] Furthermore, as the slice thickness influences the volume score, it was desired to only include patients with 2.0 mm slices and 1.5 mm increments. Also, patients with stents in or surrounding the ROI were excluded, as these objects may be misclassified as calcium or cause artifacts that would make the calcium score unreliable. Therefore, only a small sample size was used. However, the excellent correlation between non-contrast and contrast calcium scores indicated a sufficient number of patients were included.

Future perspectives

As described above, several factors can influence the reproducibility. The effect of these factors on the variability in the VACS has yet to be determined. However, first VACS should be correlated with patient outcomes to determine how much variability is acceptable before patient risk stratification would be unreliable. In coronary arteries the Agatston score can be used to classify patients into four risk categories and is used to identify patients at risk for future cardiovascular events. [7], [25] New risk categories should be created for the proposed VACS in both coronary and non-coronary arteries.

Conclusion

In this study, a modified calcium score method was proposed that corrects for artery size with two different patient-specific threshold variations, which should make it possible to better compare the calcium score of vascular patients who have a contrast-enhanced CT scan. It was shown that a patient-specific threshold of three SD above the mean successfully distinguishes contrast and calcium. The correlation between calcium scores determined on non-contrast and corrected contrast CT scans was excellent. In addition, an excellent inter-observer agreement was found. It was shown that 0.75 mm slices influenced the calcium score negatively due to the increase in noise and therefore require a higher threshold. Future research should focus on correlating volume adjusted calcium scores with patient outcomes.

3. Association of iliofemoral calcium score and major cardiovascular events within the first year after lower limb revascularization

Introduction

Patients suffering from PAD have an increased risk of all-cause mortality. [2], [46] Ness and Aronow showed an incidence of 68% and 42% of coronary artery disease (CAD) and stroke, respectively, in patients suffering from PAD. [47] First steps to reduce the risk of cardiovascular events or mortality and improve quality of life involves risk factor modification, best medical treatment and supervised exercise. [5], [46] When these treatments does not provide the desired improvement regarding symptomology or quality of life, revascularization may be considered. [5] Untreated or unsuccessfully treated limb ischemia can lead to major limb amputations, resulting in loss of quality of life and increased risk of mortality. [6]

Severe calcifications are associated with worse intervention outcomes and therefore worse patient outcomes. [48], [49] Non-contrast calcium scores, determined in peripheral arteries, have already been associated with an increased severity of PAD and risk of (cardiac) mortality. [10]–[12] Guzman et al. showed that patients suffering from CLI have an significantly increased tibial calcium score compared with patients suffering from claudication. [10] In addition, Chowdhurry et al. divided patients into four groups based on the lower limb arterial calcium score, with nearly all cardiac morbidity and mortality occurring in the highest quartile during the follow-up period. [12] Finally, Huang et al. also divided patients in two groups based on the median lower limb calcium score and showed that the number of amputations and all-cause mortality was significantly higher in the high calcium score group. [11]

The abovementioned studies all showed that higher calcium scores, determined on non-contrast scans, can be associated with worse patients' outcomes. However, these studies used non-contrast CT scans and did not correct for artery sizes. Furthermore, patients were divided based on calcium score or a comparison was made between patients suffering from claudication and CLI. The aim of this study was to investigate whether the previously proposed volume adjusted calcium score (VACS) and a new proposed length adjusted calcium score (LACS) determined on CTA scans are independent risk factors for complicated recovery after revascularization in patients with CLI.

Methods

A single-center, retrospective, observational study including patients suffering from PAD was performed. 589 patients who underwent endovascular or surgical revascularization between 2005 and 2017 with a pre-intervention CTA scan in the UMCG were identified for a previous study. [50] Exclusion criteria in the current study were the presence of artifacts in or surrounding the peripheral arteries, e.g., caused by stents or protheses, and previous interventions. Patients with aneurysmal arteries were included, but dilated arteries were excluded from the analysis.

Patients suffering from CLI (Fontaine 3 and 4) who underwent a secondary revascularization, major amputation (above the ankle) or all-cause mortality in the first year after the primary revascularization were identified and included into the 'complication' group. Subsequently, patients who survived the first year without the above described complications were matched with the patients in the complication group and included into the 'control' group. Patients were primarily matched on type of intervention (PTA, PTA/stent, endarterectomy, stent/endarterectomy, bypass), treated artery and Fontaine classification. Secondary, diabetes mellites (DM) type 1 and 2, impaired renal function (defined as eGFR < 60), gender, age, BMI and smoking status were used to match both groups. This study was approved (study nr: 202200343) and informed consent was waived by the UMCG Institutional Ethical Review Board.

Scan protocol

CTA scans were obtained with the Somatom Force, Somatom definition Flash, Somatom definition AS, Somatom definition, Sensation 64 and Sensation 16 of Siemens Healthcare (Siemens Healthcare, Erlangen, Germany). Scans were performed with a pitch of 0.7 or 0.8 sec using spiral acquisition with a collimation of 128x0.6 mm. Scan parameters were adjusted for patient body types and set in the range of 100-120 kV (Sensation 64 and Sensation 16), 70-100 kV (Force, Flash and AS) or 70-120 (definition). The tube current and FOV ranged from 52-1268 mA and 303-485 mm, respectively. Iomeron 350 (Bracco Imaging, Milan, Italy) or Visipaque 320 (GE Healthcare, London, UK) was administered with bolus-triggering and a flow rate of 4.0 cc/sec to obtain contrast-enhanced images. Scans were reconstructed in 3 mm slices with increments of 3 mm.

Calcium score measurements

The calcium score was measured in every slice with increments of 3 mm over three arterial segments. The first segment included the common iliac artery (CIA), i.e., the area from the aortic bifurcation to the orifice of the internal iliac artery (IIA). The second segment included both the external iliac artery (EIA) and the common femoral artery (CFA), i.e., the area from the origination of the IIA to the orifice of the profunda femoris artery (PFA). The third segment included the first ten centimeters of the superficial femoral artery (SFA) measured from the orifice of the PFA, determined using a center lumen line. The total calcium score was determined by adding all three calcium scores.

As previously described in the second chapter, the VACS can be calculated by dividing the volume score (mm^3) by the volume of the artery (cm^3) in which the calcium score was determined. The volume score was calculated using Aquarius TeraRecon as previously described in chapter 2. The determination of the patient-specific threshold for distinguishing calcium and contrast was standardized by using the first and last slice of the ROI. If absence of contrast or too much calcium made the threshold determination unreliable, the closest slice in the ROI was used that gave a reliable attenuation value of the contrast-enhanced blood lumen. The highest of the two determined thresholds was then used to measure the volume score in all three arterial segments.

The volume of the three segments was calculated using the length and the radius of the arteries. The length of a segment was determined with a center lumen line. Using the center lumen line, the diameter of the artery was determined at a quarter, half and three quarters of the segment. The average of these three diameters was used to approximate the volume of the segment.

The absence of contrast, caused by occlusions, can make the diameter determination less reliable. The contours of the artery are less visible and may disappear into surrounding structures. Furthermore, calcified plaques may appear larger due to blooming artifacts, resulting in an overestimation of the artery volume, especially in smaller vessels. [51] Therefore, also a second modified calcium score method was used, the length adjusted calcium score (LACS). The LACS corrected the calcium score for the length of the artery (cm) instead of the volume of the artery (cm^3). The center lumen line was again used to determine the length of the arteries.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (Version 28.0.0.0). Continuous variables were expressed as means ± SD or median (IQR) and categorial data were described as frequencies (percentage). Group comparisons were performed using Mann-Whitney U test for continues variables and Fishers exact test for categorial variables, with $p<0.05$ considered statistically significant. The VACS and LACS were used as individual variables to compare the complication and control group for all patients. Subsequently, in the complication group, the total LACS for all three complications were compared using the Kruskal Wallis test. Patients with multiple complications were also included in multiple analyses, e.g., patients with secondary revascularization and major amputation were used in both analyses.

Results

A total of forty-eight patients who underwent a secondary revascularization, major amputations or died of all-causes were identified. Subsequently, forty-eight matched patients without these complications and who met the inclusion criteria were matched with the complication patients. Ten patients in the complication group underwent secondary revascularization, eight had a major amputation and eighteen died in the first year. In addition, four patients in the complication group underwent both a secondary revascularization and a major amputation, two died after a secondary revascularization, three died after major amputation and three patients died after secondary revascularization and major amputation. Three patients in the complication group suffered from an iliac aneurysm and these arterial segments were excluded from the analysis. Group characteristics are presented in Table 3.1, in which the aspects used to match both groups are outlined in orange. Significantly more patients in the complication group (24 vs. 13) had impaired renal function, all other characteristics did not differ significantly between both groups. An attempt was made to match based on renal function, but it was not possible to find matched patients in the control group.

Table 3.1: Group characteristics. Characteristics outlined in orange are used to match the groups

	Complication (n=48)	**Control (n=48)**	**p-value**
Age	68.7±12.3	67.1±10.9	0.51
Male	25 (52%)	24 (50%)	1.00
(former) Smoker	44 (0.92%)	43 (90%)	0.24
BMI	26.3±5.4	26.1±4.7	0.86
DM type 1 & 2	23 (48%)	23 (48%)	1.00
Hypertension	32 (67%)	33 (69%)	1.00
Impaired renal function[1]	24 (50%)	13 (27%)	0.03*
Hemodialysis	7 (15%)	3 (6%)	0.32
Fontaine III **Fontaine IV**	13 (27%) 35 (73%)	12 (25%) 36 (75%	1.00
CAD	16 (33%)	22 (46%)	0.30
Congestive heart failure	8 (17%)	11 (23%)	0.34
Hypercholesterolemia	38 (79%)	41 (85%)	0.59
Hyperhomocysteinemia	1 (2%)	0 (0%)	1.00
History of CVA	6 (13%)	3 (6%)	0.49
History of TIA	2 (4%)	4 (8%)	0.68
COPD	12 (25%)	13 (27%)	1.00
Malignity	12 (25%)	7 (15%)	0.31

DM: Diabetes mellitus; CAD: coronary artery disease; CVA: Cerebrovascular accident; TIA; Transient ischemic attack

[1] *Defined as eGFR < 60*

VACS and LACS all patients

The median patient-specific threshold to distinguish calcium and contrast was 552 (479-667) and 513 (400-639) for the complication and control group, respectively, which was not significantly different (*p = 0.40*). The VACS score for the complication group and control group per arterial segment in order from proximal to distal were 239 (98-469) vs. 334 (129-463), 140 (33-266) vs. 131 (37-350) and 64 (1-178) vs. 37 (7-109), respectively, with a total VACS of 528 (145-926) vs. 503 (270-1052). All arterial segments and the total VACS score did not differ significantly between both groups. The LACS did also not differ significantly between the complication and control group with median LACS scores per segment of 195 (69-441) vs. 269 (108-460), 45 (15-144) vs. 55 (17-127) and 14 (0-41) vs. 7 (1-22), respectively, and a total LACS of 292 (89-647) vs. 356 (200-505). The VACS and LACS with p-values are visualized in Figure 3.1 and 3.2. In Figure 3.2, three outliers are visible in the total LACS, which were caused by relatively more calcium compared to other patients in their group.

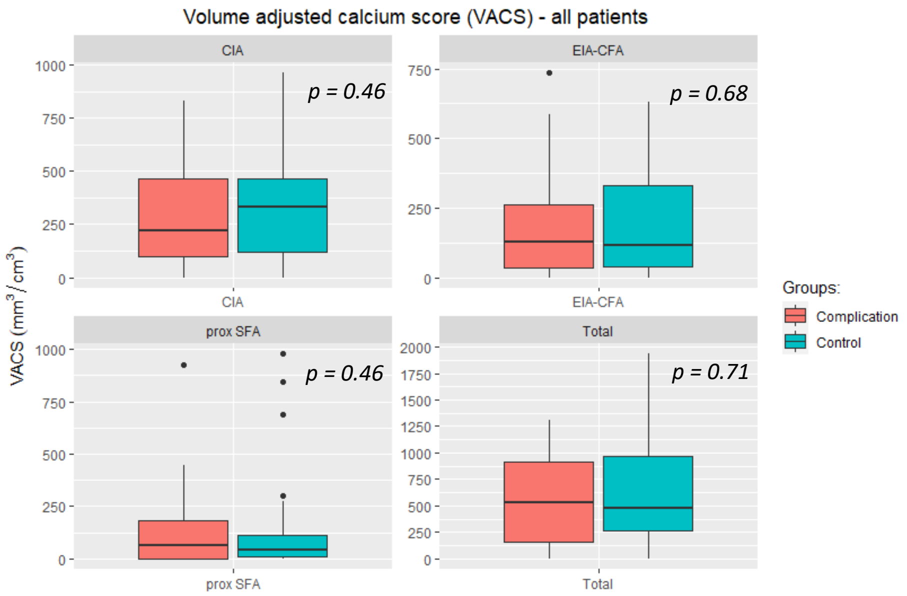

Figure 3.1: Comparison for the volume adjusted calcium score in all three segments measured and the total calcium score

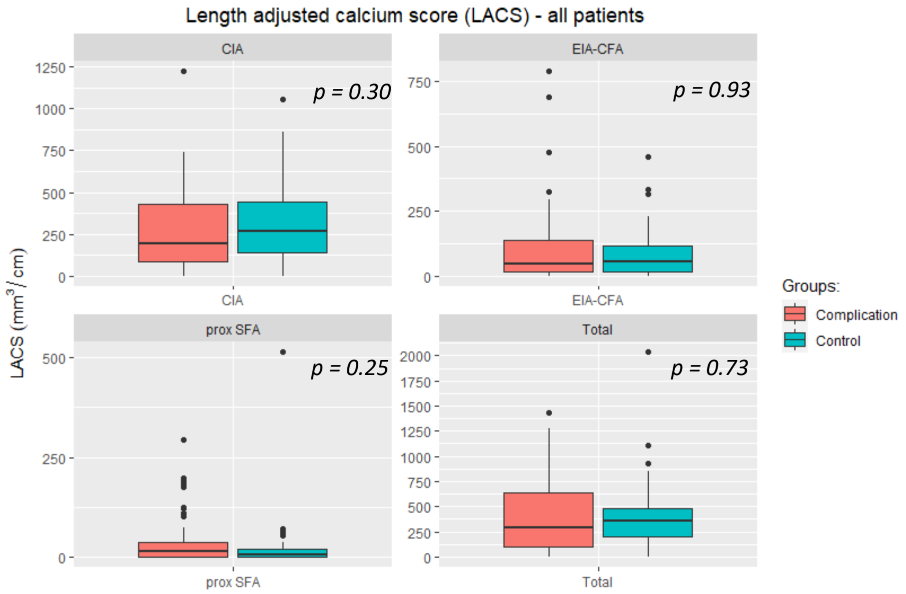

Figure 3.2: Comparison for the length adjusted calcium score in all three segments measured and the total calcium score

The total LACS for the secundary revascularization, major amputation and all-cause mortality patients in the complication group were 353 (55-654), 337 (269-532) and 315 (198-635), which did not differ significantly ($p = 0.97$).

Discussion

In this study, the VACS was used to compare patients with and without secondary revascularizations, major amputations or all-cause mortality within the first year of a primary revascularization. In addition, the LACS was also introduced, since an absence of contrast or blooming caused by calcium makes the diameter determination less reliable. It was expected that patients with complications would have higher calcium scores, indicating that more severe calcifications would lead to worse patients' outcomes. However, no statistically significant differences were found between the complication and control groups in any of the arterial segments or the total area. Nonetheless, the calcium score determined in the proximal SFA showed most high calcium scores in the complication group. The total LACS did not differ significantly between the patients who underwent a second revascularization, major amputations or died from all causes.

Other studies have shown that calcium scores can be used for risk stratification in patients suffering from PAD. [10]–[12], [52]–[54] Megale et al. used a patient-specific threshold of 130% of the average contrast attenuation to calculate Agatston scores from the infrarenal aorta to the infrapopliteal arteries on CTA scans, resulting in an almost significant difference between patients with and without amputations (small and major) in the first year after a revascularization. Furthermore, a significant relationship between calcium scores and all-cause mortality was found after 30 days and 6 months. [52] The method used by Megale et al. is similar to the method used in this study. However, no compensation was made for artery length or volume, resulting in potentially unfair comparison between patients. Taller patients are likely to have a higher calcium score, while this is probably due to the longer trajectory and may not be related to disease progression. The study also showed that the highest calcium scores were measured in the infrarenal aorta and decreased toward the distal vascular axis, most likely explained by the size of the arteries and subsequent higher calcium burden.

The relationship of calcium scores determined on non-contrast CT scans and the severity of PAD has been studied more frequently. [10]–[12], [53], [54] Higher calcium scores measured in the SFA and below the knee arteries (BKA) are associated with higher Fontaine or Rutherford classifications and thus with more severe PAD. [10], [53], [54] In addition, Huang et al. and Chowdhurry et al. divided patients based on the calcium score measured in the iliac-BKA region and infrarenal aorta-BKA region, respectively. It was shown that (all-cause) mortality and amputations were more frequent in the group with the highest calcium score. [11], [12] These studies used a different approach for dividing patients into groups and patient outcomes than in this study. Most importantly, a comparison was often made between patients suffering from CLI and claudication or even asymptomatic patients, resulting in higher odds of finding significant differences between groups.

Study limitations

Aspects not included in this study, or in calcium scoring methods in general, are the distinction between intima and media calcifications or the size and length of the diseased segment. Intima and media calcifications may lead to different complications and might therefore be valuable in treatment strategies. Intima calcifications may be associated with acute cardiovascular diseases caused by lumen narrowing or unstable plaques and media calcifications with hypertension, chronic cardiovascular diseases and heart failure caused by increased arterial stiffness. [55] However, the calcium score has proven to be a strong predictor when no distinction was made. [10] The Trans-Atlantic Inter-Society Consensus (TASC) classification system was created to measure the severity of the diseased segment based on the length and size of the stenoses. Using this classification system, the best treatment option can be chosen. [56] Since patients were primarily matched on the type of intervention, it also seems likely that there will be no significant difference between the two groups regarding the TASC score. However, this study and future studies would improve if the TASC scores were included in the analysis.

Due to the retrospective nature of this study only the Fontaine classification system could be used. The Rutherford classification or the WIfI classification might provide additional objective information, making patient comparison more accurate. In addition, improving the patient's lifestyle is a critical part in the treatment of PAD, e.g., patients who continue smoking have an increased risk of bypass graft failure compared to patients who stop smoking. [56] In this study no information about lifestyle improvements was available. In future studies it would be interesting to collect this data as it might provide additional insights into disease progression.

Future perspectives

In this study, calcium scores in the CIA, EIA, CFA and proximal SFA were measured. The results in this study and in other studies suggest that calcium scores determined in the SFA and BKA are better for identifying patients at risk for all-cause mortality or major amputations. Atherosclerosis is a systemic disease and therefore it was expected that calcium scores determined in the iliac-femoral arteries would also be an indicator of patient outcomes. In future studies it would be interesting to determine the calcium score in the distal SFA and possibly also include the popliteal artery or BKA. Measuring calcium scores in the BKA might provide technical difficulties due to the size of the arteries and the visibility due to absence of contrast. When these smaller arteries are included, it is recommended to use the LACS as volume determinations are probably unreliable due to blooming.

The follow-up period in this study was only 1 year. However, it is expected that some of the patients included in the control group will also suffer from complications after the first year. A retrospective study found that 61% of major amputations occurred within the first year after a revascularization intervention, increasing to approximately 75% after 5 years. [57] Furthermore, the 5 years mortality rate of patients suffering from CLI exceeds 50%. [58] By using a follow-up period of 1 year the worst cases of PAD were included, however it might be necessary to use a longer follow-up period to include all high-risk patients. Future studies could also examine the long-term prognosis of patients with intermittent claudication, as these are also at increased risk for cardiovascular or cerebrovascular events. [46]

Conclusion

This study compared patients with CLI who underwent secondary revascularization, major amputation or all-cause mortality and patients without complications within one year of primary revascularization. No significant difference was found between the groups using the adjusted calcium scores in the iliac-femoral tract. However, the proximal SFA showed most high calcium scores in the complication group and future studies should focus on calcium scores determined in the distal SFA and possibly popliteal artery and BKA.

4. General discussion

In this thesis adjusted calcium scores for non-contrast CT scans and CTA scans were developed and analyzed. Patient-specific thresholds should be used to distinguish contrast from calcium, with a threshold of three SD above the mean contrast attenuation was found to be best. Calcium scores determined on contrast CT scans were corrected with a correction factor of 1.95 after which an excellent correlation was found with non-contrast calcium scores. The calculated correction factor will probably rarely be used in practice, since vascular patients normally only have CTA scans. The inter-observer agreement for the volume adjusted calcium score (VACS) was excellent, with an ICC of 1.0. In addition, using 0.75 mm slices are not recommended, as the increase in noise resulted in higher thresholds. Furthermore, using 2 mm or 3 mm slices reduces the time needed to calculate the calcium score manually considerably and are therefore easier to implement in the clinic.

In the second chapter, the length adjusted calcium score (LACS) was introduced, as the diameter determination became unreliable in some patients due to a partial absence of contrast. Furthermore, blooming artifacts in especially smaller arteries would result in overestimations of the lumen diameter. [51] Peripheral artery disease (PAD) patients undergoing a reintervention, major amputation or all-cause mortality within the first year after a primary revascularization were matched and compared with patients who did not suffer from these complications. No statistically significant differences were found between the calcium scores determined in the iliac-femoral arteries for both the VACS and LACS. However, most high calcium scores determined in the proximal superficial femoral artery (SFA) were seen in the complication group. In addition, other studies have shown that calcium scores determined in the SFA and below the knee arteries (BKA) arteries can be correlated with more severe disease manifestations. [10], [53], [54] In future studies the LACS should be calculated in the entire femoropopliteal segment, as this area is most commonly affected. [5]

In this study, a second revascularization, major amputation or all-cause mortality were used as endpoints. However, PAD is strongly associated with coronary artery disease (CAD) and cerebrovascular disease. [1] In future studies the VACS or LACS should therefore also be correlated with other cardiovascular and cerebrovascular events. Follow-up using calcium scores after treatment is more difficult, for example, stents cause artifacts making calcium scores unreliable. Another aspect for which calcium score can potentially be used is the prediction of in-stent restenosis. Zheng et al. showed significantly higher risk of in-stent restenosis in patients with higher coronary calcium scores and peripheral artery calcium scores may also be correlated with the risk of in-stent restenosis in future studies. [59] Calcium scores may also be used for other patient groups, for example in patients undergoing an endovascular aneurysm repair (EVAR). Vaccarino et al. found that ilio-femoral calcium scores may have an added value in identifying patients at risk for mortality after an EVAR procedure. [60]

An excellent inter-observer agreement was found for the VACS. Some variation was seen between the patient-specific thresholds determined by both observers. Developments and more widespread use of dual-energy CT scanners might improve the inter-observer agreement. Using dual-energy CT, virtual non-contrast (VNC) images can be reconstructed from contrast scans, after which a fixed threshold can be used. Coronary calcium scores determined on VNC scans showed an excellent correlation with true non-contrast calcium scores. [61]–[63] Although, similarly to the calcium score determined on contrast CT scans in this study, a constant underestimation of plaque volume was seen on VNC scans and a correction factor was necessary to compare VNC and true non-contrast calcium scores. Furthermore, results were affected by the iodine suppression technique used and the best suppression technique has yet to be chosen. [61], [63] The UMCG has two dual-source CT scanners, however, vascular patients are currently not scanned with a dual-energy protocol and it was therefore not possible to include VNC images in this study.

Blooming artifacts cause an overestimation of calcified plaques and an underestimation of arterial lumen diameters. Thinner slices or sharper reconstruction algorithms can reduce blooming artifacts. However, this would also result in an increase in image noise, which would negatively affect the calcium scores, as seen in the second chapter. [51] Dual-energy CT scanners might reduce blooming artifact using virtual monochromatic images (VMI). [64] Using VMI, images can be reconstructed with different keV settings, with lower keV images increasing vascular contrast and higher keV images reducing artifacts. [65] Hedent et al. showed a significant decrease of blooming artifact and improved luminal detection in higher mono-energy levels. [66] On the other hand, Yunage et al. showed no significant difference for both stenoses and lumen diameters between various VMI reconstruction and the conventional CT scan. [67] These studies were both conducted in coronary arteries and contradict each other. Therefore, further research will need to be done on possible reduction of blooming artifacts using dual-energy CT scanners, especially in peripheral arteries.

The calcium score calculation for the PAD patients, including region selection and threshold determination, took approximately 15 to 20 minutes per patient. Time could be saved when an automatic method will be used. Achmed et al. and Eberberger et al. both developed a fully automatic method to determine calcium scores in coronary arteries on contrast CT scans using centerlines and vessel boundaries, respectively. Calcium was detected based on deviation of lumen attenuation values. Both studies showed an excellent correlation between automatic contrast calcium scores and manual non-contrast calcium scores. [68], [69] Both studies automatically detected the coronary arteries. However, in the current study automatic centerline determination was not possible due to an absence of contrast or the presence of calcium. Furthermore, in the software used in the current study also a region-grow algorithm is implemented to select calcium through multiple slices. This method was not used because in some patients it was not possible to automatically distinguish calcium from the spine and much of the spine was classified as calcium. Using an automatic method can therefore not easily be implemented in the abdominal aorta and peripheral arteries.

5. Conclusion

This study aimed to develop a modified calcium score method for patients suffering from peripheral artery disease using contrast-enhanced CT scans. It was shown that a patient-specific threshold of three SD above the mean contrast attenuation was the best method for distinguishing contrast and calcium compared with methods described in literature before. Furthermore, an excellent ICC was found after applying a correction factor of 1.95 between calcium scores determined on non-contrast CT scans using the standardized method and calcium scores determined on contrast CT scans using the VACS. Using the proposed volume adjusted and length adjusted calcium scores, no significant different in iliofemoral calcium scores were found between patients who suffered from complications after a revascularization and patients who survived the first year complication free. In future studies, calcium scores should be determined in the distal SFA and possibly popliteal artery, as the proximal SFA showed almost significant differences between both groups.

6. References

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